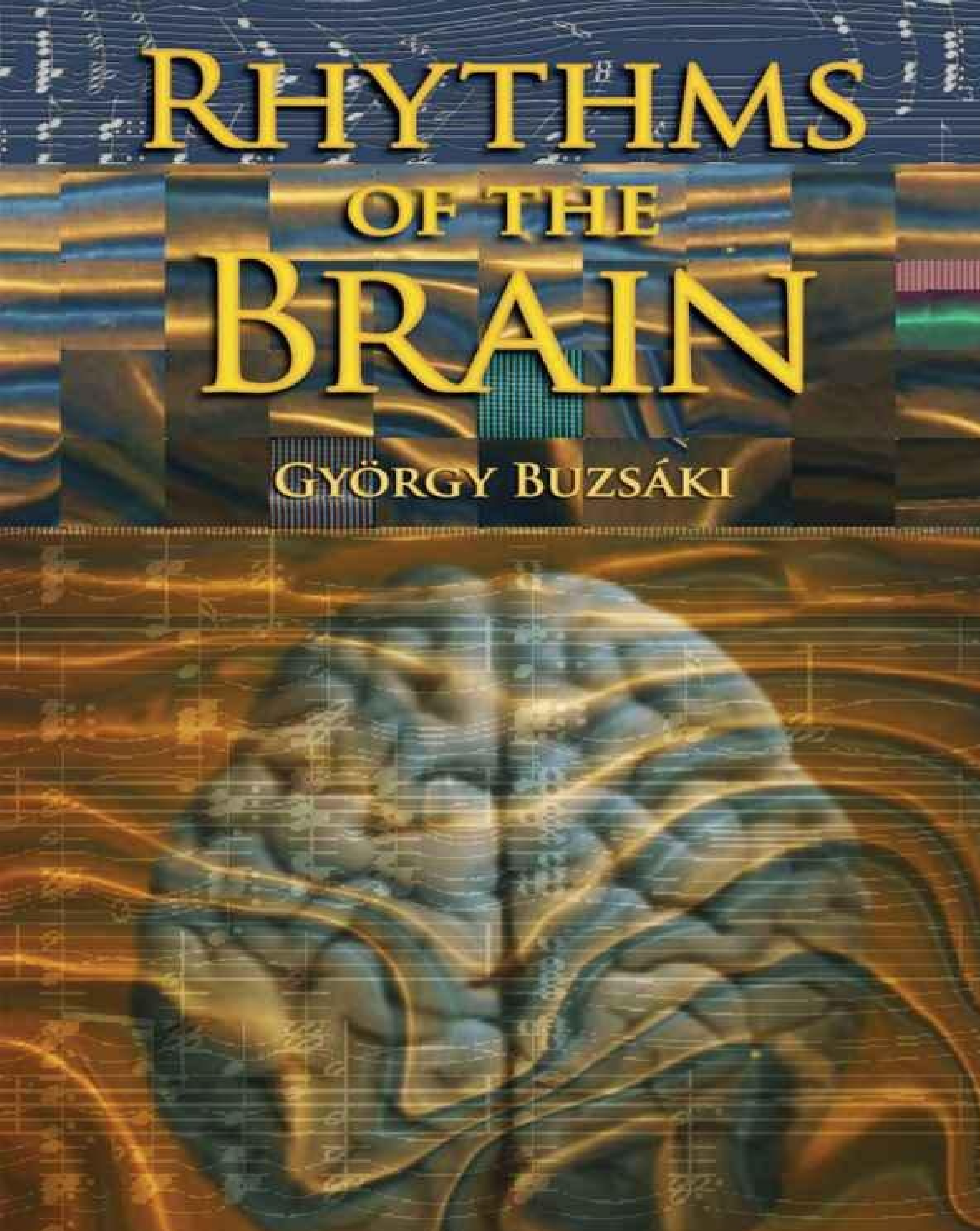
RHYTHMS OF THE BRAIN

GYÖRGY BUZSÁKI



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To my loved ones.

Prelude

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

The short punch line of this book is that brains are foretelling devices and their predictive powe emerge from the various rhythms they perpetually generate. At the same time, brain activity can b tuned to become an ideal observer of the environment, due to an organized *system* of rhythms. Th specific physiological functions of brain rhythms vary from the obvious to the utterly impenetrable. simple but persuasive example is walking. Bipedal walking is a periodic series of forward fal interrupted regularly by alternate extensions of each leg. It is almost as natural to us as breathing. Th effortless exercise is made possible by the predictive nature of spinal cord oscillators. On smoo terrain, the alternation of leg movements can take us any distance. Perturbation of the clocking, on t other hand, signals a change in the terrain. This general mechanism is the same in all animal including eight-legged scorpions and centipedes. The notion that oscillators or “central patte generators”[1] are responsible for the coordination of motor patterns, such as breathing and walking, old and well accepted in neuroscience. But the tantalizing conjecture that neuronal oscillators can b exploited for a plethora of other brain-generated functions, including cognition, is quite new an controversial. And it is the latter topic, the contribution of oscillations to the invisible, inferre operations of the brain, that this book is mostly about.

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

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

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

Like many of us at a young age, in his twenties Grastyán could not quite make up his mind abo his future. Finding nothing too interesting or challenging initially, he decided to train for th priesthood to get some orientation in philosophy. But his mind, far too curious and questionin prevented him from becoming a preacher. He ended up in medical school during the stormy yea after World War II and became the assistant of Professor Kálmán Lissák. Lissák, a student of Ott Loewi in Graz, Austria, and subsequently Walter Cannon's assistant at Harvard, had returned t Hungary to become Chair of Physiology just before the war. Grastyán's pairing with Lissák wa fortunate because Lissák, of course, knew quite a bit about rhythms from his years with Loewi, wh provided the first evidence that a chemical—a neurotransmitter—is released at the junction (synaps between the vagus nerve and the heart muscle.[2] Although Grastyán was perhaps Lissák's close friend, the two were as different as can be. Lissák was a reserved man, and his lectures were scarce attended. In contrast, Grastyán was a performing artist whose seminars were carefully composed an choreographed. The huge lecture room in the medical school was always packed, and even studen from the neighboring law school came over to listen to his mesmerizing lectures. He generated s much enthusiasm that we students became convinced that the topics he discussed were among th most important in the whole universe.

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

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

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

As I have repeatedly discovered in my career, the informal lunch-seminar approach to science hard to substitute with formal lectures or the reading of dense scientific papers. Seminars are tailore for an average group of people with the naive assumption that the audience retains all the details ar follows and accepts the fundamental logic of the lecturer. In contrast, the essence of lunc conversations is to question the fundamental logic, a quest for clarification and simplification, search for explanations and answers without a rigid agenda, where the focus is not on covering larg chunks of material but on fully understanding even the smallest details. Of course, one can follow up lecture by finding and reading the relevant published papers on the topic. However, most of th exciting findings in neuroscience are hidden in the small print of specialty journals, often written in specialized and arcane language comprehensible to, at most, a handful of specialists. Overwhelme with new and important discoveries in the various subsubspecialties, the practicing neuroscientis such as myself, tends to forget that neuroscience is of startling relevance to a contemporary socie wrestling with complex issues such as social behavior, depression, and brain aging. It is hard predict which of the numerous fundamental discoveries could alter the face of such large issues, ar unless they are conveyed to others, they might be overlooked without making an impact. This mainly so because the explanations we provide in papers to the superspecialists may be impenetrab to the uninitiated. Without attempting to place our work into a larger context from time to time, v deprive ourselves of the chance to be able connect to the more macroscopic and microscopic levels research. Yet, discoveries and insights realize their power only when understood by other Understanding this important connection is what mostly motivated me to write this volume.

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

Parallel with the amazing progress in neuroscience, another discipline has emerged: comple systems, a new science that cuts across many fields. During the past decade, I have learned as muc about the brain by reading about novel branches of physics, engineering, mathematics, and comput science as I did from studying papers directly dealing with the nervous tissue. Rest assured, the huma brain is the most complicated machinery ever created by nature. Nevertheless, it is truly excitin looking for concepts, mechanisms, and explanations that are common among many different systen and cut across the living/nonliving dichotomy. Seemingly unlikely sources such as fractals ar Internet communication have provided novel clues for understanding neuronal networks. My goal is illustrate how this new knowledge is being incorporated into neuroscience at a breathtakingly hig speed and to convey fascinating discoveries to neuroscientists, psychiatrists, neurologists, and th ~~growing group of computational scientists, physicists, engineers, and mathematicians interested~~ complex systems. A covert agenda is that, along the way, describing these new discoveries wi encourage outsiders to become brain rhythm enthusiasts.

Deciphering the code of the brain will have a lasting impact on our society. It is not simply a intellectual exercise for a handful of esoteric individuals anymore. It is also more than a “just” brain-health–related issue, which affects millions in the United States and many more worldwide. A Robert Noyce, the co-inventor of the integrated circuit, once put it: “In order to understand the brai we have used the computer as a model for it. Perhaps it is time to reverse this reasoning. T understand where we should go with the computer, we should look to the brain for some clues.” No that our economy, financial institutions, education system, research programs, distribution system human interactions, politics, and defense have all become computer and Internet dependent, this que is more acute than ever. The hope is that the new knowledge about the brain will not only inspi novel designs for computer architectures and a more efficient and safer electronic communication b also, at the same time, provide a better understanding of ourselves. Books, computers, and Intern communication have *externalized* brain functions and provided virtually unlimited storage space f the accumulated knowledge of humankind. However, this externalized information is only as useful a its accessibility. Currently existing search engines, such as Google and Yahoo, that provide access t this externalized knowledge are very inefficient (even though they are the best available at presen compared to the brain’s ability to retrieve episodic information, because neuronal networks utiliz fundamentally different strategies for the reconstruction of events and stories from fragments than o search engines. Understanding the brain’s search strategies may allow us individuals to have bett access to the cumulative knowledge of humankind.

Writing to a general audience interested in neuroscience is a much more arduous exercise tha writing scientific papers. Scientists, rather than just the science they have produced, and metapho that are deliberately absent in specialty journals come to the fore. This process inevitably impli oversimplification from the experts’ viewpoint, occasional redundancies, and some rugged transitio for the novice. To alleviate the inevitable, I have written a simplified main story, which I hope to be relatively easy read in most Cycles. Each Cycle ends with a brief summary, which highlights th primary message of the Cycle. The main story is supplemented by extensive footnotes, which serv partly to define novel terms. In most cases, however, they provide further critical information for th more sophisticated reader, along with links to the appropriate literature. I have deliberately chose this format because it allowed me to interweave the main story and its more complex ramificatio without breaking the flow of thought. The additional comments and citations in the footnotes give ri 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 wa to survey and conquer the New York City art market. Yet, after a month or so, he plainly declared t us that every painting has already been painted and the art dealers are aware of all potential innovato in case the market is in need of such redundancy. He returned to Europe the next day. This is how felt while writing this book. Clarity, critical details, and giving proper credit compete for space, an achieving the appropriate balance is the most difficult thing in writing a book. The more I explore the mysteries of brain oscillators and neuronal functions, the more I realized that the fundament ideas (some which I thought were genuinely mine) have already been expressed, often repeatedl Many times the ideas have come up in studying systems other than the brain, or they were express in a different context. But they existed. The deeper I ventured into the problems, the further back 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 th past decade that during the previous history of humankind. This may be true regarding the volume ~~factual knowledge. But discoveries are not (just) facts. They are ideas that simplify large bags~~ factual knowledge. Such fundamental ideas rarely pop up suddenly. Typically, they slowly emerg after appropriately long incubation periods and are shaped by numerous proponents and critic Fundamental ideas are rare, and probably as many have been conceived prior to modern neuroscien as in the past few decades. One just has to recognize and adapt the old thoughts to the new lingo ar the findings we have recently generated. My dear mentor advised me in my student days, “do n publish when you have only data but when you have a novel idea.” If I followed his advice strictly, would perhaps still be writing my first paper and this volume would not exist. Although I honest attempted to reach a balance between summarizing large chunks of work by many, and crediting th deserved ones, I am aware that I did not always succeed. I apologize for those whose works unintentionally ignored or missed. To claim innocence, I shall simply shift the responsibility on 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 Kail Christof Koch, Nancy Kopell, Rodolfo Llinás, Stephan Marguet, Edvard Moser, Denis Paré, Ma Raichle, Wolf Singer, Anton Sirota, Paula Tallal, Jim Tepper, and Roger Traub. My dear frien Mircea Steriade took the trouble of reading the entire manuscript and provided invaluable feedbac My special thanks to Mary Lynn Gage for her attempts to transpose my Hungarian-Zombi idioms in comprehensible English. This may not have always succeeded, and I would like to publicly apologi 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 who examples, support, and encouragement sustained me in difficult times and whose collaboration inspiring discussions, and criticism have served as constant reminders of the wonderful collegiality our profession—David Amaral, Per Andersen, Albert-László Barabási, Reginald Bickford, Yehezke Ben-Ari, Anders Björklund, Brian Bland, Alex Borbely, Ted Bullock, Jan Bures, Gábor Czéh, Jáno Czopf, Eduardo Eidelberg, Jerome (Pete) Engel, Steve Fox, Walter Freeman, Fred (Rusty) Gage, M Goodale, Charlie Gray, James McGaugh, Michale Fee, Tamás Freund, Helmut Haas, Michael Häusse Walter Heiligenberg, Bob Isaacson, Michael Kahana, George Karmos, Nancy Kopell, Lóránd Kellény Gilles Laurent, Joe LeDoux, Stan Leung, John Lisman, Rodolfo Llinás, Nikos Logothetis, Fernan Lopes da Silva, Jeff Magee, Joe Martinez, Bruce McEwen, Bruce McNaughton, Richard Miles, Istv Mody, Robert Muller, John O’Keefe, Marc Raichle, Jim Ranck, Menahem Segal, Terry Sejnowsk Larry Squire, Wolf Singer, David Smith, Peter Somogyi, Mircea Steriade, Steve Strogatz, Kar 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 o these outstanding colleagues—Bob, Bruce, David, Gábor, Helmut, István, Karel, Mircea, Pete Rodolfo, Roger, Rusty, Ted, Tamás, and Wolf—became my trusted, close friends. Most importantly, would like to thank my students and post-doctoral fellows without whose dedication and hard work th 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 takes time, precious time that I had to steal from somewhere, mostly from my family. My dear wif Veronika, and my sweet daughters, Lili and Hanna, forgive me for the many weekends you had t spend without me and for my frequent mental absences at dinners and family events when only m body was present. How fortunate I am to have you as my supporters. Without your understanding ar encouragement, this venture would have been worthless.

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

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

2. Loewi called the chemical “Vagusstoff,” which Henry Hallett Dale from Cambridge, Englan identified later as acetylcholine, the first neurotransmitter. They received the Nobel Prize for the discoveries in 1936. I have heard various versions of the story behind the Vagustoff experiment fro 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 few notes on a tiny slip of thin paper. Then I felt asleep again. It occurred to me at six o’clock the morning that I had written down something most important, but I was unable to decipher th scrawl. The next night, at three o’clock, the idea returned. It was the experiment to determi whether or not the hypothesis of chemical transmission that I had thought about years ago w correct. I got up immediately, went to the laboratory, and performed a simple experiment on 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, th same chemical is released in all the other synapses made by the same neuron.

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

Contents

Rhythms of the Brain

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. Vanderwo

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

After returning to Jena from active military duty, Berger was promoted to the Chair of th Department of Psychiatry and Neurology in 1919 and devoted the rest of his career to the study of th brain’s electrical activity. Berger reasoned that the electromagnetic forces generated by the huma brain could be the carrier waves of telepathy, his true interest. Since even in that day telepathy wa regarded as an “occult” subject, his experiments were conducted in utter secrecy in a laborato located in a small building on the grounds of the clinic. Most of his initial recordings were done o himself, his son Klaus, and patients with skull defects. He performed numerous experiments an importantly, eliminated the possibility that the voltage changes measured by his string galvanomet were an artifactual consequence of blood pressure changes; nor did they arise from the scalp ski After five years of experimentation, he concluded that the most prominent electrical activity could b recorded from the occipital (lower rear) part of the skull when the subject’s eyes were closed. In h groundbreaking 1929 paper he wrote, “The electroencephalogram represents a continuous curve wi continuous oscillations in which… one can distinguish larger first order waves with an avera duration of 90 milliseconds and smaller second order waves of an average duration of 35 millisecon The larger deflections measure at most 150 to 200 microvolts….”[2] In other words, the electrical fie generated by millions of discharging neurons in the cerebral cortex is 10,000 times smaller than th 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 observe this rhythm first. He named the faster, smaller amplitude waves, present when the eyes were ope “beta” waves. Paradoxically, Berger’s recordings provided firm physical evidence *against* his ide that waves generated by one brain could somehow be detected by another brain. The voltage chang that emerge from the cooperative activity of neurons in the mammalian brain are just too small, an current propagation requires a low-resistance conductor, so it cannot cross air, for example. Althoug he failed to prove his hypothesis of telepathic communication between brains, his research created 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 behavior and cognition is quite another. Ever since Berger's early observations, three questions hav ~~haunted neuroscientists: how are EEG patterns generated, why are they oscillatory, and what~~ is the content? Providing answers to these questions is a major goal of this volume. I introduce the topic Cycles 2 and 3 by discussing the important issue of how the speed of communication in the cerebr cortex can be preserved despite the great size differences of the brains of small and large mammal Cycle 4 can be skipped by those who have had an introductory class on methods in neurophysiology. discusses the major methods currently available for investigating brain activity patterns in livi tissue and the mechanisms that give rise to the field EEG. Cycles 5 and 6 serve as an introduction the different types of oscillators and discuss the large family of oscillations in the mammalian corte Cycles 7 and 8 are devoted to the "default" states of the brain: sleep and early brain developme Tying the macroscopic features of oscillations to neuronal mechanisms requires large-scale recordin of numerous single neurons. Such techniques allow us to gain some insight into the content oscillations, which is described in Cycles 9–12. In Cycle 13 I examine the structural and function requirements of awareness by contrasting brain structures that can and cannot support self-generat 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 periodicity.[4] This law governs all manifestations of living and nonliving. In its broadest definitio periodicity refers to the quality, state, or fact of being regularly recurrent: a repeating pattern structure in time or space. What goes up must come down. The sun rises and sets, and the days wa and wane. Without periodicity, there is no time; without time, there is no past, present, or future. living systems, the periodicity of individual lives gives rise to the continuity of life on Earth. O existence has meaning only when experienced in time. The essence of music and dancing is rhyth An important part of human culture is the celebration of the periodicity of life. The Jewish a Muslim religions are attuned to the lunar cycle. Christians adopted a solar calendar. Periodicity can seen in the monthly windows of opportunity for conception of human life.

Periodicity, oscillation, rhythm (from Latin meaning to flow), and cyclic process are synony that refer to the same physical phenomenon. Historically, different academic disciplines have adopt a preferred term to describe these related phenomena. Periodicity is the term of choice in social a earth sciences. Oscillation is the preferred term in physics, and engineers talk about cyclic or peri generators. Until recently, neurologists and neuroscientists used the term "brain rhythms" almo exclusively when referring to the various brain patterns. Reference to oscillations is quite recent.[5] T avoidance of the term "oscillator" in brain research for so long perhaps reflected the tacit view th brain rhythms may be qualitatively different from the oscillators discussed in physics textboo Assuredly, neuronal oscillators are quite complex. Nevertheless, the principles that govern the operation are not fundamentally different from those of oscillators in other physical systems. Today, is widely recognized that the brain's ability to generate and sense temporal information is prerequisite for both action and cognition. This temporal information is embedded in oscillations th exist at many different time scales. Our creativity, mental experiences and motor performance a modulated periodically both at short and long time scales. But how are oscillatory states broug about, especially if they occur in the absence of external influences? In Cycles 5 and 6 I propose so 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 “real” and that brains have mechanisms for tracking it. Since time is a major concept in this book, attempt to provide a working definition without getting lost at the nebulous boundary between physi and philosophy.[6]Newton held that time flows in absolute intervals, independent of the physic universe. According to Immanuel Kant, space and time are irreducible categories through whic 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 th could be interpreted as its “property”; space and time disappear along with the things. An opposi view is that time is a subjective abstraction and does not exist in any physical substrate and has more reality than a mathematical axiom. In a broad sense, time is a *measure of change*, a metric succession, a parameter that distinguishes separate events. One practical definition is that “time is th which is measured by a clock,” a pragmatic description adequate for most branches of physics ar neuroscience.[7]

How we approach the problem of time largely determines our view of the outside world arour us. First, we need to distinguish two aspects of time. Absolute time is clock time, referring to particular point in a time series, for example, your birth date. Absolute time is a fundamental eleme of existence since everything exists in time. Duration refers to the change of time, the interv 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 relativ distinction in space as well, when we talk about position and distance. However, while distance ca refer to many directions (vector) in space, time has only one direction (scalar).

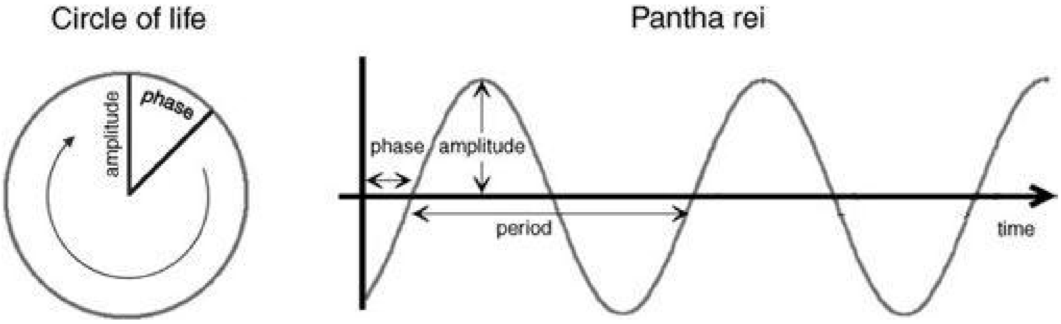

Figure 1.1. Oscillations illustrate the orthogonal relationship between frequency and time ar space and time. An event can repeat over and over, giving the impression of no change (e.g., circle life). Alternatively, the event evolves over time (*pantha rei*). The forward order of succession is main argument for causality. One period (right) corresponds to the perimeter of the circle (left).

The intimate relationship between space and time is packaged into the concept of “spacetime” (y, z, t dimensions). Oscillations can be conceived of and displayed in terms of either space or tim The phase-plane of a sinusoid harmonic oscillator[8] is a circle. We can walk the perimeter of the circ once, twice, or billion of times and yet we always get back to our starting point. “What has been what will be, and what has been done is what will be done; and there is nothing new under the sun 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 si

waves. Now we can walk along the troughs and peaks of the line without ever returning to the startin
~~point (figure 1.1, right). Time here is a continuum with the cycle as its metric. The cycles are identic~~
in shape, and the start and end points of the cycles form an infinite path into the seemingly endle
universe. This meandering line illustrates the basis of our time concept: *linear change* and a *forwa*
order of succession, features that are often used in arguments of causality. A moment never repea
itself. *Pantha rei*—everything flows—according to the ancient Greek saying. “Upon those who ste
into the same rivers, different and ever different waters flow down.”[10] Whichever model we choos
the circle or the meandering line, in periodically changing systems the past can predict the futu
(position or moment).

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

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

Time, Prediction, and Causation

Causality among world events is linked to our perception of time.[13] Prediction, inference, forecas
and deduction are used as synonyms in the context of proposed causality. They refer to an inductiv
process, which integrates information about the past and present to calculate the following mo
probable outcome.[14] Brains help their owners to survive and prosper by predicting and decipherin
events in the world, including consequences of their own actions. Predictions and relationships a
constructed by ordering the succession of events according to elapsed subjective time. We are usual
able to say which of two events happened before the other, with decreasing precision as time elapse
Causal-explanatory relationships are usually considered a one-way process because such relationshi
are embedded in the context of time and time is asymmetric and unidimensional. The cause preced
the effect in time. If the discharge of neuron *a* consistently and reliably precedes the discharge
neuron *b*, and after destruction of neuron *a* neuron *b* ceases to discharge, a causal relationship
suspected. Linear causation works most of the time, and it is the foundation of many essenti
operations from catching a ball to solving a mysterious murder case. Causation can also fail. F

example, in an oscillatory system, most or all neurons with reciprocal, one-way connections or ~~direct connections may discharge with a zero time lag (i.e., simultaneously), making linear causatio~~ impossible, as illustrated in several subsequent Cycles. Oftentimes, the reason for causation failin can be explained by the discrepancy between objective or external time and subjective time registere by the brain.

According to the second law of Newtonian mechanics, a body tends to remain in its state of re or motion unless acted upon by an external force.[15] The force is the cause, an agent responsible for t motion of the body. When a moving billiard ball hits a stationary one, the latter begins to move. Th happens because the kinetic energy of the moving ball exerts force on the stationary ball, causing it move. Now consider the following psychophysical experiment. A ball is moving toward another on this time not on a pool table but on a computer screen. If the second ball starts moving in the sam direction after the arrival of the first ball, we conclude from the timing of the events that the first ba caused the second one to move. However, derivation of such a conclusion depends critically on t exact timing of the events. We make the inference of causality only if the second ball begins to mov within 70 milliseconds after the first ball reaches it. If at least 140 milliseconds elapse between t halting of the first ball and movement of the second ball, no causality is suspected. Between 70 a 140 milliseconds of delay, the two disks appear to stick together but some indirect causality is sti deducted.[16] Thus, temporal context is critical for perception, including the perception of causatio The brain “chunks” or segregates perceived events according to its ability to package information 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 ord of events. You are driving on a highway and a deer crosses the road. You slam on the brakes and avoi a collision. The mental reconstruction of the events is as follows. You noticed a deer (cause) an realized that it would be dangerous to hit the animal. So you decide to avoid it, push the brakes, a turn the steering wheel (effects). Laboratory replication of such real-world actions offers a differe explanation. A deer appeared (first event), you braked (second event), and *then* you recognize t animal (third event). This sequence is proposed because reaction time to an unexpected event is le than half a second, whereas conscious recognition requires the recruitment of a large number neurons in a large, distributed complex brain circuit, which takes longer than half a second.[17] T 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 exist mental reconstruction offers a different cause. The brain takes into consideration the conducti velocities of its own hardware and compensates for it. For example, touching your nose and toe at t same physical time (or touching your nose with your toe) feels simultaneous even though neuron events in the cerebrum, representing the touch of two body parts, are delayed by several tens milliseconds. The conclusion that follows from this discussion is that our time reconstruction is consequence of an accumulation of past experience rather than a truthful representation of real tim Nevertheless, despite the difficulty in deducting causality, the above examples are simple becau they involve a single well-defined cause. In many cases, the causes are multiple and so pointing to single cause or agent is not possible. Deducing causality is particularly difficult when the cau involves a reciprocal relationship between parts and wholes, as is often the case for neuron 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. fact, ~~a main argument put forward in this book is that most of the brain’s activity is generated~~ fro within, and perturbation of this default pattern by external inputs at any given time often causes only minor departure from its robust, internally controlled program.[18] Yet, these perturbations ar absolutely essential for adapting the brain’s internal operations to perform useful computation Without adjusting internal connectivity and computations to the spatial and temporal metrics of th external world, no constructive, “real-world” functions can be generated by the brain.[19] In engineerin terms, this process can be referred to as “calibration.” The self-reliance of brain circuits increases 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 proce information but also *generates* information. As a result, the world outside is not simply “coded” b meaningless “bits” of neuronal spikes but gets embedded into a context, an important part of which time. “Representation” of external reality is therefore a continual adjustment of the brain’s sel generated patterns by outside influences, a process called “experience” by psychologists. From th 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 t defend if one subscribes to Aristotle’s thesis that nothing moves or changes itself. The novel idea of “self-cause”–governed principle has emerged in several disciplines and is referred to by numerou synonyms, such as spontaneous, endogenous, autogenous, autochthonous, autopoietic, autocatakineti self-organized, self-generated, self-assembled, and emergent. Systems with such features are ofte called complex.[20] The term “complex” does not simply mean complicated but implies a nonline relationship between constituent components, history dependence, fuzzy boundaries, and the presen of amplifying–damping feedback loops. As a result, very small perturbations can cause large effec or no effect at all. Systems in balance are simple and hard to perturb. Complex systems are open, an information can be constantly exchanged across boundaries. Despite the appearance of tranquility an stability over long periods, perpetual change is a defining feature of complex systems. Oftentimes, n only does complexity characterize the system as a whole, but also its constituents (e.g., neurons) a complex adaptive systems themselves, forming hierarchies at multiple levels. All these features a present in the brain’s dynamics because the brain is also a complex system.

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

Emergence, Self-Causation, and Adaptation

The fundamental assumption of classical thermodynamics is destruction of structure, an inevitab temporal progression from organized to disorganized, characterized by the monotonic increase entropy.[24] In the framework of classical physics, order in nature must be created through extern forces. When designing a car, many rational considerations, such as power, size, appearance, cost, ar other *goals*, are first evaluated. Prior to the car’s physical existence, its designers can envision mar of its characteristics. Such top-down effort requires an extraordinary a priori knowledge of mat physics, engineering, computer graphics, esthetics, marketing, and other complicated stuff. Can ord 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, clos systems, things are different in open, complex systems that exist far from a state of equilibrium. complex systems, the direction is typically from disorganized to better organized, according physicists. Indeed, extremely complicated protein structures with multiple uses can be built b following stunningly simple algorithmic steps dictated by the variation of just four nucleic acids th form DNA. Could the “smartness” of brain organization and performance be traced back to similar 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 fro thermodynamic equilibrium, so that the system can exchange energy, matter, or entropy with i environment. Typical examples include avalanches, earthquakes, galaxies, and, in fact, the evolutic of the whole universe. The Belgian-American chemist Ilya Prigogine introduced the term “dissipativ structures,” which refers to patterns that self-organize in far-from-equilibrium states. The expressic “far from equilibrium” means that the system cannot be described by standard linear mathematic methods. Characterization of dissipative systems requires nonlinear differential equations becau there are no universal solutions. These complex systems live by the rules of nonlinear dynamic better known as chaos theory.[25] The immediate link between problems of neuronal communicatic and dynamical theory is that both are concerned with the fundamental aspects of change and the tin context within which the change occurs. In complex systems, the evolution of the system is describe as a motion vector in a multidimensional space. The sequentially visited points in tl multidimensional state space are called a “trajectory.” Applying this idea, for example, to visu perception, the trajectory corresponds to the ordered assemblies of neurons set into motion, from tl retina to higher visual and memory systems. The spatiotemporal trajectory of neuronal activi depends not only on the constellation of light impinging on the retina but also on the perceiver’s bra state and past experience with similar physical inputs. Hence, each time the same stimulus presented, it generates a somewhat different and unique trajectory in the neuronal space.

Complexity can be formally defined as nonlinearity, and from nonlinear equations, unexpecte solutions emerge. This is because the complex behavior of a dynamic system cannot easily l predicted or deduced from the behavior of individual lower level entities. The outcome is not simp caused by the summation of some agents. The emergent order and structure arise from the manifo interactions of the numerous constituents. At the same time, the emergent self-organized dynamic, fo example, a rhythm, imposes contextual constraints on its constituents, thereby restricting their degre of freedom. Because the constituents are interdependent at many levels, the evolution of comple systems is not predictable by the sum of local interactions. The whole is based upon cooperation ar competition among its parts, and in the process certain constituents gain dominance over the other

This dominance, or *attractor* property, as it is called in chaos theory, can affect other constituen ~~such that the degrees of freedom in the system decrease. Such compression of the degrees of freedo~~ of a complex system, that is, the increase of its entropy, can be expressed as a collective variabl These ideas have a profound effect on the interpretation of spontaneously organized brain patterns (discussed in Cycles 5–7).

Hermann Haken, a German laser physicist, refers to the relationship between the elements a the collective variable as synergy (he also calls it the "order parameter"), the simultaneous action emergence and downward causation. In Haken's system of synergetics, emergence through sel organization has two directions. The upward direction is the local-to-global causation, through whi novel dynamics emerge. The downward direction is a global-to-local determination, whereby a glob order parameter "enslaves" the constituents and effectively governs local interactions. There is supervisor or agent that causes order; the system is self-organized. The spooky thing here, of cours is that while the parts do cause the behavior of the whole, the behavior of the whole also constrains t behavior of its parts according to a majority rule; it is a case of circular causation. Crucially, the cau is not one or the other but is embedded in the configuration of relations. In fact, Haken argues that synergetic systems the cause is always circular. Perhaps a better term would be "nonsymmetric reciprocal causality."[26]

Putting the philosophical issues aside for a moment, nonlinear dynamics brought with it a nov kind of thinking about systems—not as mere aggregates of parts but as a bidirectional interacti between parts and the whole.[27] Systems that can be perturbed from outside and incorporate extern influences in their future behavior possess a remarkable capacity for learning and growth even thou they live within boundaries defined by simple rules. By adhering to these low-level rules, somethi greater than the sum of parts can emerge. The emergent level is thus qualitatively different from t level it springs from. If the component relationships within the system become optimized for particular task as a result of external perturbations, the system is called adaptive. The brain is such adaptive complex system.[28]

Today's systems neuroscience is an offspring of general systems theory, a sort of moderniz Gestalt concept in a quantitative disguise. Instead of looking at discrete moments in time, the syste methodology allows us to see change as a continuous process, embedded in a temporal conte Systems thinking and especially explorations in chaos have quickly identified an importa application in neuroscience by investigating the bioelectrical activity in the brain and have claim (premature) victory by stating that brain activity, and at times behavior, reflects chaos. How does th claim relate to our introductory discussion that the brain operates in an oscillatory mode, whose ma task is prediction? cycle 5 covers this important topic, followed by further discussion in subseque Cycles about the relationship between the internal complexity of neuronal networks and the reliab 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 should adapt to the outside world. The brain has to be calibrated to the metrics of the environment lives in, and its internal connections should be modified accordingly. If the statistical features of t environment reflect one particular constellation, the evolving brain should be able to adapt its intern structure so that its dynamics can predict most effectively the consequences of the extern perturbation forces. A great deal of this adaptive modification for each individual brain (i.e., i ~~“smartness”) comes from interactions with conspecifics, that is, other brains. In other words~~, t functional connectivity of the brain and the algorithms generated by such continuous modificatio are derived from interactions with the body, the physical environment, and to a great extent, oth beings.

One can ask a similar question at the single-component level of the brain, as well: how smart is neuron? The answer depends on the baseline of the comparison and on the size of the brain the neur is embedded in, because smartness is a relative judgment. In a very small neuronal network, ea neuron is critical, and discernible functions can be assigned to each. In larger brains, the complexi of single neurons tends to be underestimated largely because the relative contribution of a single c to the complex operation of the network appears small. The ratio of individual and collecti “intelligence” decreases radically as the brain size grows. But it is not simply the number of neuro that matters. Instead, it is the connectivity and the connectivity-confined communication that large determines the share single neurons have in brain computations. It is much like the smartness iss with us humans. Prior to our cultural evolution, as is the case in other animals, there was not mu difference between individual and species knowledge. However, with the invention of book computers, and the Internet, an ever-increasing portion of knowledge has become externalized fro individual brains. As a result, the primary carrier of species knowledge is no longer the individual the collective wisdom of tribe elders (i.e., their brains). Because of technology-enhanc externalization of information, the cumulative knowledge of humankind is constantly growin whereas the *relative* share of the average individual, sadly enough, is steadily decreasing. Similarl the relative smartness of individual neurons decreases with brain growth, despite their preserved even improved biophysical properties. The reason is that single neurons develop their smartne through their interactions with local peers. With growing brain size, single cells get less and le informed about system level and global decisions. In a strongly interconnected system, such as t mammalian cerebral cortex, changes in a single neuron or neuronal assembly can ripple througho the entire cortex. However, the impact of the distant effects decreases rapidly as brain size grows d to the expense of maintaining distant connections. The selective and specific response of a single ce that is, the degree of its “explicit” representation, is not a function of its biophysical or morphologic properties but depends largely on its functional connectivity in the network. Thus, there are no sma neurons; their explicitness derives simply from being at the right place at the right time. A speci challenge, therefore, is to explain how brain complexity scales with the size of growing networ while still preserving the useful functions of simpler brains. Cycles 2 and 3 dealing with t anatomical architecture of the brain and Cycles 5–11 addressing the statistical features of its glob activity attempt to illuminate these issues.

Causation and Deduction

An objection can be raised that the entire project of “dynamical systems” is guilty of vicio circularity. It just explains away the real problem, the cause–effect relationship. Self-emergence spontaneous activity is indeed a difficult conception because there is always an element of a “goal” “will.” One can adopt the practical view that this implication is primarily verbal rather th philosophical and perhaps need not be taken very seriously. Nevertheless, everyday experien dictates that logic should follow the path of linear causation and avoid circularity. But linear causati is not foolproof, either, as is amply illustrated by the fundamental deductive error made by the gre master of logic himself, Aristotle. He flatly denied that the brain has anything to do with cognitive ar ~~motor functions: “The seat of the soul and the control of voluntary movement—in fact of nervou~~ functions in general—are to be sought in the heart. The brain is an organ of minor importance, perhap necessary to cool the blood.” This declaration was a major attack on the correct view, expresse almost a century earlier by Hippocrates: “Men ought to know that from the brain and from the bra only arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tear Through it, we think, see, hear and distinguish the ugly from the good, the pleasant from t unpleasant…. To consciousness the brain is messenger.”[29] Aristotle’s linear causation managed t suppress the correct view for more than a millennium. His revisions were based on several *deducti* arguments. The heart is affected by emotion (the brain does not react). All animals have a heart, ar blood is necessary for sensation (he thought the brain was bloodless). The heart is warm (he thoug the brain was cold). The heart communicates with all parts of the body (he was ignorant of the crani nerves). The heart is essential for life (the brain is not essential, he thought). The heart is the fir organ to start working and last to stop (the brain develops later—this is somewhat true). The heart sensitive (the brain is not). The heart is in the middle of the body and is well protected (the brain exposed). However, Aristotle was not unique in his views. The kings of Egypt were prepared for th afterlife with virtually all body parts preserved, but the brain was scooped out and tossed away. Th Bible never mentions the brain and relates emotional and moral behaviors foremost to the heart, th bowels, and the kidneys. Interestingly, similar ideas about the importance of various organs occurre in other cultures, as well. According to the Talmud, one kidney prompts man to do good, and the othe 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” exampl cited above?[31] Surely facts are needed, but facts are always interpreted in context. Is the prop context linear time, brain-reconstructed time, or something else? Of course, similar skepticism can b expressed within the framework of dynamic complex systems. What does it mean to conjecture th the brain is a pattern-forming, self-organized, nonequilibrium system governed by nonline dynamical laws, and how should we prove or disprove this? The intuitively simple concept of sel organization or spontaneous activity has proven notoriously difficult to pin down formally.[32] It h remained a challenging task for systems neuroscience to go beyond the most general types explanations and elucidate the brain-specific mechanisms. General systems theory and nonline dynamics have provided useful concepts and novel paths for thinking, but the mechanism-lev research is left for neuroscience.[33]

Adopting the systems view poses difficulties for an experimentalist; it is already a daunting tas to understand the neurons and neural circuits in isolation. Examining the relationship between th collective-order parameters and activity of individual neurons in sufficiently large numbers, ar taking into account their past patterns—and doing it all at the same time—make the problem eve 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 onc Even if we are aware that interactions at multiple levels subserve a physiological function, oftentim progress can be made only after simplifying either the hardware (by looking at small pieces of th brain) or the operations (by anesthetizing the brain or keeping its environment constant). Th paramount importance of nonlinear dynamics notwithstanding, it is fair to say that, to date, most what we know about the brain in general, and about its physiological operation in particular, has bee discovered using simplified preparations and linear methods. Not surprisingly, the relationsh between the parts and the whole has been a much-debated topic in neuroscience, as well. Because mo studies in the past were carried out within either a top-down or bottom-up framework, we should fir