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Imaging Brain Function With EEG

Advanced Temporal and Spatial Analysis of Electroencephalographic Signals

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To our wives, who have inspired us,
and to our children and grandchildren,
whom we aim to inspire.

Preface

This book is about temporal and spatial patterns that we find in the electric fields on the scalp (electroencephalogram, EEG) and cerebral cortex (electrocorticogram, ECoG) (Lopes da Silva 1993; Basar 1998). The patterns are enigmatic, ephemeral, easily dismissed as noise, and by most accounts epiphenomenal (Freeman and Baird 1989). Yet, some of the patterns are neural correlates of intentional actions, specifically the perception and discrimination of sensory stimuli by alert, aroused human and animal subjects. For this reason, they have become a focus of our experimental and theoretical investigations. What can they tell us about how brains work? What tools do we need to record and analyze them? Which related disciplines of science, mathematics, and engineering do we turn to for guidance in simulating them with computational models of cortical dynamics?

We begin with a brief overview of electroencephalography. Temporal analysis predominated in the first two decades after the discovery of EEG by Hans Berger (1873–1941). Thereafter, two main breakthroughs advanced the analysis of temporal signals. The first was the use of ensemble averaging – that is, the average over several stimulus presentations – to better visualize evoked responses (Dawson 1954), and the second was the introduction of personal computers in the analysis of EEG signals, especially after the implementation of the fast Fourier transform (FFT) by Cooley and Tukey (1965), which enabled a rapid and reliable representation of the frequencies in EEG signals. More recent advances include the study of time-frequency patterns and the introduction of wavelets in the analysis of EEGs and evoked responses (Quian Quiroga et al. 2001; Majumdar et al. 2006). Pioneers undertook spatial analysis with racks of primitive amplifiers. W. Gray Walter (1953) focused on the "toposcopy" of alpha waves in the EEG. John Lilly (Lilly 1954) recorded spontaneous and evoked potentials in the ECoG. Large, dense electrode arrays for scalp EEG were introduced by Donald W. DeMott (1970), Dietrich Lehmann (1971), M. N. Livanov (1977), and Konrad Maurer (1989), mainly to analyze the topography of alpha waves. The systematic study of beta and gamma patterns in the ECoG at high spatial resolution in the ECoG was introduced by Freeman and Schneider (1982). High temporal and spectral resolutions were later achieved by introduction to brain studies of the Hilbert transform (Freeman and Rogers 2002).

In this book, we pursue EEG and ECoG patterns as we would study the natural history of a new species, like searching for elusive forest animals, trying to catch and hold them for description without damaging or distorting them. We ask the following questions: Where are they found in brains? What behaviors are they correlated with and when? How large are they? How long do they last? Can we group them into recognizable categories? How often do samples that can be categorized recur? What are their internal structures and textures that constitute their features? What frequencies appear in their temporal and spatial spectra? Beyond empirical description, how do they form? Are they transmitted? If so, where do they go, by what means, and with what delays? Are they epiphenomenal or do they play an active role in the genesis and control of behavior? Do other parts of the brain detect and respond to them, and if so, how? Can we find meanings in the patterns? Are the meanings only for objective observers like ourselves or do the patterns reflect the construction and deployment of subjective meanings within the brains for the subjects?

In our book, we propose answers to these questions by showing examples of the textured patterns both in time and space and the contexts of recording. We describe the optimal conditions and methods for their measurement and present hypotheses on how they form and why they are significant. Our results give first glimpses of these patterns, which may already seem primitive but nevertherless provide prescriptions on how our results can be replicated, improved, and extended. What makes the work so difficult is that the electric potential differences we observe are samples from extracellular fields of very weak electric energy. They are signs of the transmembrane electric currents that give shape and texture to great clouds of cortical action potentials. The fields emerge because every neuron interacts with many thousand others in the cortical tissue that anatomists call laminar neuropil (from a Greek word for *felt*). It is the textured fabric of axons (Gr., *axis*), dendrites (Gr., *tree*), glia (Gr., *glue*), and capillaries (Latin, *hairs*) that generates and regulates its own spontaneous background activity. The pulse clouds emerging from the neuropil do the work of cortex (Gr., *tree bark*) by forming vector fields, which are manifested in scalar fields of electric potential. We cannot at present record enough pulse trains simultaneously to see the textures directly; so we infer them through the potentials that we can record, and confirm them when we can by simultaneously recording spikes from representative single cells in the population (Sect. 3.3.3 and Sect. 4.5 in Freeman 1975). The mixed activity of axons and dendrites is robust and resilient; yet, it resembles the bubbling of a pan of boiling water. Finding and extracting self-organized patterns emerging in such noise is not a trivial undertaking.

Laminar neuropil, in other words, is an active medium that embeds the sensory, cognitive, and motor systems and serves as a massive axodendritic channel of communication among them. We propose that the spatiotemporal patterns manifest the forms taken by *macroscopic* perceptual and cognitive information, carried by dense pulse clouds in the neuropil, in parallel with the *microscopic* sensory and motor information, carried by sparse pulse trains of neurons singly in local networks. We suggest that the large-scale patterns, which are the focus of our book, can convey the relevant context and meaning of the information, in a word, the knowledge that

the subject has about the received information, because the laminar neuropil provides the neural mechanisms for constructing and storing knowledge during sensation, and for mobilizing the knowledge for transmission during perception. It is the massive quantity of integrated information that supports our experience and feeling of recognition in perception, variously described as "metastable coordination dynamics" (Kelso and Tognoli 2006), "virtual associative networks" (Yufik 1998), "mind force" (Orsucci 1998, 2009), "holographic brain" (Pribram 1999), "global work space" (Baars et al. 2003), and others (Jordan 2008; Koch and Tononi 2008; Tononi 2008; Seth 2009; Tallon-Baudry 2009).

The large-scale patterns from the neuropil, measured using EEG, ECoG, or local field potentials (LFP), constitute the first method of imaging brain activity in awake subjects, going back to Berger in the 1920s (see Chap. 1). Our knowledge about brain function has been greatly increased by the introduction of single-cell recordings in the 1950s, now advanced to high level of sophistication with the identification of *concept cells* (Quian Quiroga 2012) and, more recently, by imaging techniques of MEG, PET, fMRI and BOLD (blood oxygen level dependent), and fMRI. Why then do we focus on the predecessor of these methods? This is because EEG, ECoG, and LFP signals are the most challenging in terms of data processing, and in spite of being known for nearly a century, we still learn a lot from their analysis, especially when we use advanced signal-processing methods and bold experimental designs. Most prior research with EEG signals has been constrained to variations of a couple basic paradigms: the study of evoked responses and the study of EEG oscillations in given frequency bands in single channels or a judicious sample of channels. In our book, we provide some tools to go beyond these standard analyses and experimental designs. In particular, we propose two radical paradigm shifts. First, we argue that the ensemble averaging that is typically used to observe evoked responses imposes a large loss of information of systematic and nonsystematic changes of the trial-by-trial responses (Quian Quiroga 2000; Quian Quiroga and Garcia 2003). New powerful signal-processing tools, like wavelet denoising, indeed allow the visualization of the single-trial responses, thus opening a window to new types of analyses and experiments (Quian Quiroga et al. 2007). In fact, some of the most interesting cognitive processes (e.g., learning) are revealed by changes during an experimental session. The use of these new techniques requires new experimental designs, where trial-by-trial changes are sought in order to study their correlation with different cognitive processes, instead of being avoided in order to get cleaner averages. It is the tracking of this variability that allows us to study different cognitive processes and merge the spatial and temporal information from fMRI and EEG (Eichele et al. 2005; Eichele et al. 2008; Freeman et al. 2009). The second main paradigm shift we propose is to study the dynamics and propagation of spatial patterns of field potentials, as one can study the continuous evolution of waves in fields. So far, the information from different EEG or ECoG channels has been studied independently or at most by the use of topographic plots at precise times. However, both the single-channel temporal analysis and the multiple-channel topographic analysis are too limited because they do not display how spatial patterns of brain activity evolve in time.

Without getting into deep philosophical issues, we can say that knowledge is an immense collection of fragments of information, each fragment being interrelated with every other so as to form a pattern. The laminar neuropil provides the dense grid of neurons that can store and express the massive information and the connectivity required for each to share it with others in the field. These operations constitute the exercise of intelligence, which is defined as the ability to acquire and apply knowledge and skills. It is noteworthy that the laminar neuropil is most fully developed in the brains of the most intelligent animals of three phyla: Vertebrata (mammals), Arthropoda (bees), and Mollusca (cuttlefish). Intelligent life has emerged and evolved independently three times in the earth's geological history, each branch with very different brain architectures but similar neuropil and neural dynamics. Clearly, the neuropil is an electrochemical system made of the same atoms as all matter. It is also a thermodynamic system that uses metabolic energy to construct knowledge from information. By study of cortical temporospatial activity patterns, their neural mechanisms of construction and transmission prior to termination, we might aspire to better understand human mechanisms of intelligence and brain disorders and, perhaps, even construct intelligent machines that, in some useful sense, know what they are doing.

We find it profitable to look for concepts and tools in physics, mathematics, and engineering that we can use to design our experiments and simulate our observations of the properties of laminar neuropil. We rely most heavily on techniques for digital signal processing, by which we decompose EEG and ECoG time series into frequency bands and components (Chap. 2). We analyze frequency modulation by using time-frequency analysis (Chap. 3) and by using wavelets (Chap. 4). We adapt the filters to single-trial, single-channel evoked potentials in order to avoid ensemble averaging and reveal how trial-by-trial changes correlate with different brain processes (Chap. 5).

We also rely heavily on techniques from systems control theory (Chap. 6) and from digital imaging (Chap. 7). We show that, during normal cognitive operations, the cortical neuropil holds itself in a range we can characterize as linear, Gaussian, and time-invariant. Having done so, we can then simulate the major dynamic operations of the neuropil by using matrices of linear differential equations in piecewise linear approximations. The solutions of the equations give a family of linear basis functions – exponentials, sines, cosines, ramps, etc. – with which to measure the evoked potentials and the waves of spontaneous and induced cortical activity. Then we can use changes in the parameters and coefficients of the equations to represent the changes in cortical dynamics caused by intrinsic nonlinearities as well as the time-varying state changes that underlie arousal, learning, and the exercise of experience. We illustrate the categorization of spatiotemporal images with respect to behavior in the primitive allocortex in the olfactory system (Chap. 8), the more complex sensory neocortices (Chap. 9), and higher cognitive functions correlated with patterns in the ECoG and EEG (Chap. 10). We finish with a synthesis of our data in the context of the brain viewed as an open thermodynamic system operating far from equilibrium (Chap. 11), which uses the cortex to extract relevant sensory information and condense it into knowledge stored in widespread synaptic

modifications that are retrieved for use, as revealed in macroscopic patterns and microscopic firing of multiple types of category cells (Chap. 6).

The greatest value of piecewise linear analysis is in the application of feedback control theory to the calculation of the strengths of functional synaptic connectivity. We define the various types of synaptic interaction strengths as the forward and feedback gains of the multiple neural loops formed by populations of excitatory and inhibitory neurons. The calculations of gain values are based on models of the topology of the types of connections in a hierarchy, called Katchalsky sets (K-sets, Freeman 1975; Kozma and Freeman 2001; Freeman and Erwin 2008). We evaluate the gains from measurements of the frequencies and rates of increase or decrease in the envelopes of oscillatory components of the EEG, ECoG, and evoked potentials. We use the gains to define the stable states of cortical neuropil, each with its attractor, the boundaries of each basin of attraction, and the state transitions that enable the temporospatial pattern of each attractor to emerge, flourish, and dissolve.

The mathematical details of the digital signal processing and systems control theory we use have been described in many textbooks and monographs. In our book, we present an overview of the main features and dynamics of spatiotemporal patterns, with only a minimum of the mathematics on which our analyses and conclusions rest. We cite suitable references for readers from clinical and biological domains to go beyond our qualitative descriptions. There is also an extensive literature on the theory of electric potentials and their applications to the study of the brain electrophysiological signals, serving particularly to locate the sources and sinks of evoked potentials and epileptic spikes in EEGs and ECoGs. In order to maintain focus and ensure brevity, we introduce only a bit of this theory in describing the limits of the spatial resolution of the high-density arrays of electrodes we use to reveal the textures of EEG and ECoG. For readers from mathematics, physics, and engineering, we also describe briefly the main physiology principles involved in the generation and interpretation of EEG and ECoG signals. For more details, we recommend introductory texts on neurobiology. We refer readers who propose to replicate our experimental results to our original reports for technical details. We have in mind also readers from psychology, psychiatry, cognitive science, and philosophy, and we hope that we have made a judicious selection of arcane details needed by anyone who seriously addresses the mind-body problem.

There is still more extensive literature on the interactions of the cortex with subcortical structures: the thalamus, striatum, cerebellum, and the modulatory aminergic and peptidergic nuclei in the brain stem. We refer to these mechanisms whenever we find it necessary to do so, but our focus is on the intracortical mechanisms that form and maintain spatiotemporal images, particularly those with frequencies in the theta, beta, and gamma ranges. We emphasize that the greater part of our understanding of cortical dynamics comes from sampling the fields with electrode arrays of unprecedented high density, spaced at intervals one tenth those of conventional clinical arrays (Chap. 7).

Exploration of the properties of high-resolution spatiotemporal images related to cognition opens enticing new avenues for the development of new brain theory by experts in physics and for the devising of new forms of machine intelligence by

experts in robotics. Examples of exploration of the dynamics of very large systems are already emerging in other areas of knowledge that are being applied to brain imaging, include models of neuropil implemented in VLSI analog hardware (Principe et al. 2001); the use of random graph theory (Kozma 2007; Freeman et al. 2009); the use of many-body physics and quantum field theory (Vitiello 2001; Freeman and Vitiello 2010); and the use of nonequilibrium thermodynamics (Freeman et al. 2012), which is especially attractive for the possibility of combining EEG/ECoG/LFP imaging with recordings from concept cells and with the several measures estimating the oxidative metabolism of brains (Logothetis 2008; Freeman et al. 2009) into a unified science (Chap. 11). However enticing these new avenues may be, the business at hand is to describe the existence and detailed properties of macroscopic neural electrical activity patterns now known in order to acquire new data at even higher resolutions in the spatial, temporal, and spectral dimensions.

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Acknowledgments

I was inspired by my father, Walter Freeman, to embark upon a career in brain science by applying my training in engineering and wartime electronics. My teachers at Yale included John Fulton in neurophysiology, inspired by his mentor Sir Charles Sherrington; Rafael Lorente de Nó in neuroanatomy, inspired by his mentor Santiago Ramón y Cajal; Warren McCulloch in neural networks; and Paul Yakovlev, Paul Maclean, and Karl Pribram in neuropsychiatry. At Berkeley I learned behaviorism from Frank Beach, linear control systems theory from Otto J M Smith, multivariate statistics from Lucien LeCam, probability theory from Michelle Loève, differential equations from Morris Hirsch, phenomenology from Hubert Dreyfus, and chaos theory from Leon Chua. The names of my students and colleagues who have taught me so much are listed as coauthors in the chapters. Prominent among them are Robert Kozma, who introduced me to random graph theory; Giuseppe Vitiello, who shared with me elements of quantum field theory; Terence Barrett, who engaged me with electromagnetic field theory; and Ichiro Tsuda, who showed me how far one can go with the mathematics of chaos theory.

<div align="right">Walter J. Freeman</div>

Toward the end of my studies in physics, I had the fortune to meet Horacio Garcia, an Argentinean neurologist, who introduced me to the fascinating realm of brain function. Horacio was my first mentor, the one that passed me his enthusiasm in trying to understand how the brain works and spent endless hours explaining me the art of reading EEG recordings and evoked potentials. Peter Grassberger shaped my knowledge on dynamical systems, chaos theory, statistical mechanics, and signal processing, a baggage of extremely useful tools to study the brain. The big jump to neuroscience was during my time at Caltech thanks to my two mentors, Christof Koch and Richard Andersen, who gave me the foundations to start a career in neuroscience. I have also been very lucky to have excellent collaborators and students, too many to be named, who have made this quest to understand the brain truly a joy.

<div align="right">Rodrigo Quian Quiroga</div>

Contents

Chapter 1
Electroencephalography

1.1 Introduction

Our knowledge about brain function increased dramatically in the last decades due to the development and refinement of several recording techniques. Such advances flourished at different levels, ranging from the study of synaptic activity at the microscopic level to the refinement of brain imaging techniques at a macroscopic level. Modern data acquisition systems and new electrode designs enabled the simultaneous recording from dozens of neurons at a larger scale, and powerful computers allowed more complex simulations and data analysis, thus giving rise to the field of computational neuroscience. A somewhat less spectacular but also remarkable and steady progress has been made at an intermediate mesoscopic level (Freeman 1975, 1999) in the analysis of electroencephalograms (EEGs).

The EEG measures the electrical activity of the brain at different sites of the head, typically using electrodes placed on the scalp. Its main advantages over other recording techniques are its high temporal resolution and the fact that it can be recorded noninvasively (i.e., without the need of a surgery). Due to their relatively low cost, EEG recordings are widely used both in clinical settings and research laboratories. This makes the EEG a very accessible and useful tool, which is particularly interesting for the analysis of high-level brain processes that arise from the group activity of large cell populations. Such processes can be well localized in time or they can be correlated to time varying patterns, like brain oscillations, which are beyond the time resolution of imaging techniques as functional magnetic resonance imaging (fMRI). The caveat of noninvasive EEGs is the fact that they reflect the average activity of a large number of sources far from the recording sites and, therefore, they do not have an optimal spatial resolution.

Although the way of recording EEG signals did not change as much as in the case of microscopic and macroscopic recordings (though in later chapters, we will describe basic guidelines for electrode designs that improve the spatial analysis of the EEGs), there have been significant advances in the methodology for analyzing

EEG data. In fact, EEG recordings have been an ultimate challenge for most methods of signal processing due to their high complexity, low signal to noise ratio, nonlinearity, and nonstationarity. As we will describe in this book, the development and implementation of new algorithms that are specifically designed for complex signals such as the EEGs will allow us to get much more information than has been accessible with previous methods and the conventional visual inspection of the recordings, as done by trained electroencephalographers. These methods open a new window to the study of high-level cognitive processes in humans with noninvasive techniques and at no great expense.

1.2 Brief History of EEG

The history of human EEG recordings goes back to Hans Berger (1873–1941), a professor of psychiatry at the University of Jena, Germany. Following the work of Richard Caton (1842–1926), a surgeon from Liverpool who successfully recorded the electrical activity of exposed cerebral hemispheres from monkeys and rabbits in 1875, Hans Berger was the first one able to record electrical activity from the human scalp in 1924. After 5 years collecting data and reexamining his results, he finally published in 1929 "Über das Elektroenkephalogramm des Menschen." In this seminal work, Berger already reported the presence of brain oscillations of about 10 cycles per second, what he called alpha waves, seen with the subject in a relaxed state with eyes closed. When opening the eyes, these waves disappeared (alpha blocking) and oscillations of higher frequencies (beta waves) were observed (Fig. 1.1). A similar type of beta oscillations was also observed with eyes closed when the subjects performed mental arithmetic tasks.

The importance of Berger's work was not recognized until 1934 when Lord Edgar Adrian (1889–1977), at Cambridge, confirmed his results. From then on, the EEG technique triggered a revolution in the way to study normal and pathological brain processes (Fig. 1.2). Just to mention some of the major achievements, in the 30s Grey Walter, first in London and then at the Burden Neurological Institute in Bristol, reported slow oscillations (delta waves) over hemispheric brain tumors and introduced the concept of EEG topography to localize brain lesions. Immediately after, EEG research spread to the USA. At Harvard, Hallowell Davis, Frederic Gibbs, Erna Gibbs, and William Lennox started to study paroxysmal EEG patterns related to epilepsy. These abnormal patterns, such as spikes or spike-waves, are still used to help the diagnosis of epilepsy. The 1940s saw the beginning of sleep studies. At the end of this decade, the first human intracranial recordings were performed. In our days, these types of recordings are mainly used in patients that are candidates to epilepsy surgery in order to determine the origin of the seizures. In the 1950s, Wilder Penfield and Herbert Jasper, at McGill University in Montreal, used electrical stimulation, with open brain surgeries under local anesthesia, to localize areas involved in different brain processes. In the same decade, a major advance in the field was
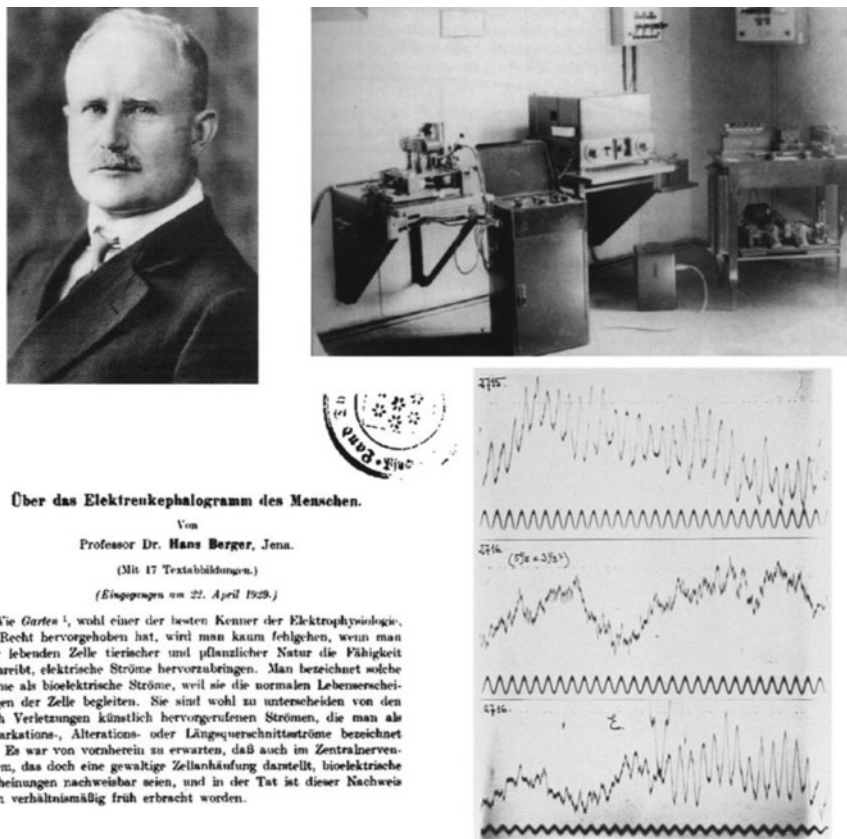
Fig. 1.1 Hans Berger and his laboratory at the University of Jena (*top*). Berger's seminal paper describing the EEG for the first time, and one of his recordings of alpha and beta oscillations (*upper traces*) and the appearance of alpha oscillations when closing the eyes (*lower trace*)

introduced by George Dawson, in London, who developed a summation technique to visualize average EEG responses to stimuli. Later on, a major breakthrough was the introduction of computers in the analysis of EEG signals, especially with the use of the fast Fourier transform developed by Cooley and Tukey (1965).

A significant slowdown in EEG research resulted as a consequence of the introduction of other methodologies for measuring brain activity, such as single neuron recordings in the 1950s and especially the emergence of imaging techniques and magnetoencephalography in the 1980s. In our days, EEG recordings are generally used for clinical diagnoses, like head injuries, brain tumors, and epilepsy. Neuroscientists also study different types of EEG activity during controlled behavior in human subjects and animals.

Fig. 1.2 Grey Walter (*top*), Lord Edgar Adrian and a picture of his laboratory in Cambridge (*bottom*)

What is the future of electroencephalography given the advances of the new recording techniques? There are three main advantages of EEG over other methods: (1) it is noninvasive and it is therefore possible to do experiments with normal human subjects; (2) it has very high time resolution – of the order of milliseconds – which permits to follow up the temporal dynamics of brain processes; and (3) it is relatively inexpensive. On top of that, there have been significant advances in the development of methods to study complex signals, and most of them are only starting to be used in EEG recordings. As we will see in later chapters, some of these methods offer a new perspective to study EEGs and brain processes in general.