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Alexander E. Hramov • Alexey A. Koronovskii • Valeri A. Makarov • Vladimir A. Maksimenko • Alexey N. Pavlov • Evgenia Sitnikova

# Wavelets in Neuroscience

Second Edition



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Alexander E. Hramov · Alexey A. Koronovskii · Valeri A. Makarov · Vladimir A. Maksimenko · Alexey N. Pavlov · Evgenia Sitnikova

# Wavelets in Neuroscience

Second Edition



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## Foreword

Modern technologies have provided unexpected new dimensions of data in size and variety with a strongly increasing tendency. Their processing and analysis is one of the basic challenges in our era of digitalization. However, most conventional data analysis techniques were designed for much smaller data sets. Wavelets are one of the most important exceptions; they have a very strong potential for applications to big data even when the data are non-stationary, noisy and high-dimensional. Wavelets have been very successfully applied to solve various scientific and engineering problems in which conventional methods, as correlation and spectral techniques, are ineffective or even fail. In recent decades, wavelet analysis has become one of the most successful and widespread tools for analyzing and synthesizing multivariate and spatio-temporal measurements, performing efficient image processing, compressing large amounts of data, or recognizing patterns, etc.

There is a huge and rapidly growing amount of publications devoted to wavelet techniques and their application to various fields. Therefore, it is hard for newcomers or interested users from other disciplines to understand important modern methodological directions and learn how to use wavelet tools appropriate for their specific problems. In this monography, a group of outstanding and very active Russian scientists presents the second edition on modern wavelet techniques and their application to urgent problems in neuroscience. Modern neuroscience is characterized by a rapidly increasing amount of measurements. Making this great potential accessible for the study of the brain and even for clinical practice is indeed a challenging problem of highest actuality. It is clearly demonstrated here that wavelets are very appropriate for this task.

This book gives first a clear and concise mathematical introduction to wavelet theory and secondly discusses how to use wavelets efficiently in neuroscience. In this second edition, the selected neuroscientific problems are well subdivided into exemplary and basic topics from single neurons to real-time classification of EEG patterns. Based on their manifold experience with such data, the authors provide an excellent guidance how to treat such problems. This monography is a very useful introduction for starters in the field, but it provides also important information and suggestions for researchers applying advanced signal processing techniques in neuroscience as well as also for users from other fields.

Berlin/Potsdam, Germany

Jürgen Kurths

# Preface

If people do not believe that mathematics is simple, it is only because they do not realize how complicated life is John von Neumann

More than 30 years ago, Jean Morlet introduced for the first time the notion of a wavelet as a soliton-like function. At the beginning, he applied this function to the analysis of backscattered seismic signals, but soon he realized that wavelets have a significantly broader field of possible applications. In 1981, Alexander Grossmann interpreted wavelets as coherent states and gave an elegant proof of Morlet's reconstruction algorithm. Since then this technique has witnessed explosive growth and it now represents a universal mathematical tool with useful applications in many scientific and engineering studies.

Originally wavelets emerged as an alternative to the classical spectral analysis based on the Fourier transform, such as windowed Fourier analysis or the Gabor transform. In order to improve processing of transient components in complex signals, Morlet decided to replace Gabor functions, which have a fixed duration, by new building blocks or time—frequency atoms, which can have an arbitrarily small duration. Later this concept led to new insights and a mathematically rigorous foundation.

Nowadays, there is no doubt that the introduction of wavelets theory was one of the most important events in mathematics over the past few decades. This is probably the only concept that has been applied in practically all the fields of basic science. Moreover, wavelets are widely used for image recognition and compression, for analysis and synthesis of complex signals, in studies of turbulent flows and feature extraction from biological and medical data, etc.

This book is devoted to application of wavelet-based methods in neuroscience. We have attempted to illustrate how wavelets may provide new insight into the complex behavior of neural systems at different levels: from the microscopic dynamics of individual cells (e.g., analysis of intracellular recordings) to the macroscopic level of widespread neuronal networks (e.g., analysis of EEG and MEG recordings). Our main aim has been to show how and where wavelet-based tools can gain an advantage over classical approaches traditionally used in

neuroscience. We hope that the logical structure of the book as regards content (from micro to macro scale) represents a new approach to experiential data analysis and could be helpful in everyday use. The book describes several examples obtained by the authors in experimental neuroscience.

In the second edition of the monograph, we added new results of the development of wavelet-based methods for online processing of epileptic EEG for the creation system for prediction and prevention of epileptic events, which has been used for the closed-loop brain-computer interface to epilepsy control. We also considered, in the revised monograph, several new wavelet applications to analyze various neurophysiological processes associated with the processing of visual sensory information and the real and imaginary motor activity executions in humans. We mainly focus in the second edition on our results, which were obtained in the past few years on the study of multi-channel EEG. We consider the results obtained with the help of wavelets and leading to a deeper understanding of the human brain's processes during acts of sensorimotor integration. Moreover, we apply the discovered brain activity patterns to create brain-computer interfaces to monitor and improve a subjects' performance (brain-computer interface operators) under routine tasks (for example, prolonged classifying visual stimuli, increasing attention level, etc.)

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# Acronyms

ANN	Artificial neural networks
BCI	Brain-computer interface
CNS	Central nervous system
CSD	Current source density
CWT	Continuous wavelet transform
DWT	Discrete wavelet transform
EA	Eldery adult
ECoG	Electrocorticogram
EEG	Electroencephalogram
ERD	Event-related desynchronization
ERWP	Event-related wavelet power
FFT	Fast Fourier transform
GAERS	Genetic rats with absence epilepsy
HF	High frequency
HPF	High-pass filter
ICA	Independent component analysis
icEEG	Intracranial EEG
ISI	Interspike interval
LF	Low frequency
LFP	Local field potential
LH	Left hand
MBRT	Motor brain response time
MEG	Magnetoencephalogram
NN	Neuronal network
OSDS	On-line SWD detection system
PCA	Principal component analysis
PSTH	Peristimulus time histogram
PWAF	Parametric wavelet sorting with advanced filtering
RH	Right hand
RTN	Reticular thalamic nucleus

rWF	Representative waveform
SD	Standard deviation
sdEEG	Subdural EEG
SI	Somatosensory
SWD	Spike-wave discharge
TC	Thalamocortical
TSS	Time scale synchronization
VPM	Ventroposteromedial
WAG/Rij	Wistar Albino Glaxo/Rijswijk
WF	Waveform
wICA	Wavelet independent component analysis
WMSPC	Wavelet method with superparamagnetic clustering
WNN	Wavelet neuronal network
WPOD	Wavelet power over domain
WSAC	Wavelet shape-accounting classifier
WSC	Wavelet-based spike classifier
WT	Wavelet transform
YA	Young adult

# Chapter 1 Mathematical Methods of Signal Processing in Neuroscience



**Abstract** This chapter offers a brief introduction to the novel advanced mathematical methods of analysis and processing of neurophysiological data. First, we give the rationale for the development of specific mathematical approaches for decoding information from non-stationary neurophysiological processes with time-varying features. Second, we focus on the development of mathematical methods for automatic processing and analysis of neurophysiological signals, more specifically, in the development of brain-computer interfaces (BCIs). Finally, we give an overview of the main applications of wavelet analysis in neuroscience, from the *microlevel* (the dynamics of individual cells or intracellular processes) to the *macrolevel* (dynamics of large-scale neuronal networks in the brain as a whole, ascertained by analyzing electro- and magnetoencephalograms).

### 1.1 General Remarks

Neurodynamics is a contemporary branch of interdisciplinary neuroscience that examines mechanisms of the central nervous system based on the mutual experience of chemists, biologists, physicists, mathematicians, and specialists in the nonlinear theory of oscillations, waves, and dynamical chaos [1–6]. Practical applications of modern methods in neuroscience facilitate an interdisciplinary approach to brain functions and attract experts in experimental and theoretical neurobiology, psychophysiology, cognitive neuroscience, biophysics, physics, nonlinear dynamics, etc. This interdisciplinary collaboration provides unique methods for analyzing the functional activity of the central nervous system (CNS) that focus on the basic principles of the neuronal dynamics of individual cells and neural networks.

Recent progress in understanding molecular and ionic mechanisms of neuronal activity [7] encourages further investigation of certain key problems in modern physics, such as exploration of the functional properties and principles of infor-

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mation coding, as well as its representation and the processing of sensory data in the central nervous system. Perception and information processing are important functions of the CNS. Visual, acoustic, tactile, and gustatory stimuli are transformed by the sensory receptors of the first order neurons into a sequence of electrical pulses. These first-order sensory neurons are therefore involved in primary processing of sensory information [8–12]. Sensory information is then passed through relay stations (brain stem and thalamic nuclei) that transform and convolve the information code, until finally it reaches the cerebral cortex which shapes the "fingerprint" of the external world [13–15]. At each subsequent stage, the processes of information transfer become increasingly difficult to study. The question of how the totality of nervous impulses (action potentials or spikes) generated by single neurons can reflect the full complexity and diversity of the external world remains one of the biggest challenges in fundamental science [13, 16–18].

Experimental methods have recently been developed for registering the neuronal activity underlying processes of information encoding-decoding at different levels of the nervous system-from molecular changes in membrane properties of receptor cells to changes in the local (electrical) field potentials in the cerebral cortex. Traditional and noninvasive methods for registering electrical brain activity, such as electroencephalography (EEG) with electrodes arranged on the skin of the head, offer several advantages, and this method is still commonly used in neurophysiology and medicine. EEG is often used in various studies of brain functions in humans and animals [19, 20]. There are also invasive methods using implanted electrodes which provide better spatial resolution, and these are advantageous when examining neuronal activity in small groups of neurons in superficial (cortex) and deep (subcortical) structures. Another advantage of invasive recording techniques is that implanted electrodes can also be used for electrical stimulation with different research purposes, e.g., suppression of epileptic discharges [21-23]. The relatively new noninvasive recording technique known as magnetic encephalography (MEG) has become more popular over the last few years, because it provides better spatial resolution than EEG and better quality of signals reflecting brain activity [24–26].

### 1.2 Nonstationarity of Neurophysiological Data

Despite technical progress in developing new methods of data acquisition in experimental neurophysiology, mathematical methods of experimental data analysis could not be readily applied, and this may impede further progress. In the vast majority of experimental studies in neuroscience, only a few statistical methods of data analysis are used, e.g., calculation of the mean spike frequency, construction of various correlation characteristics and distribution functions, etc. Traditional methods of statistical analysis are undoubtedly useful, but most of them unable to evaluate the relevant information regarding complex processes in the CNS. In order to illustrate this fact, we give an example that demonstrates the response of a sensory neuron to periodic stimulation. From a mechanical point of view, the response of the neuron to a sequence of equal external stimuli could be identical, so periodic stimulation of a neuron with a series of impulses could elicit a periodic sequence of spikes (action potentials, for example, 2 or 3 spikes per stimulus). However, in the experimental situation, we often obtain time- and activity-dependent variations in the neuron's response (the neuron does not demonstrate an equal response to repeated identical stimuli) which reflect neuronal plasticity. The phenomenon of synaptic neuronal plasticity (the basic mechanism underlying memory and learning) reflects adaptation to external afferent activity modified by the internal characteristics of individual cells and the global dynamics of the wider neuronal network interactions [27, 28]. It is known that a neuron can even stop responding to the next stimulus from a certain moment.

Figure 1.1 illustrates the adaptive response of a neuron of the trigeminal complex to periodic stimulation. Maximum neuron activity (27 spikes/s) is observed at the onset of stimulation; it falls to an average of 10 spikes/s within a few seconds and varies thereafter, exhibiting a slow negative drift. On the one hand, such behavior of a living cell makes it extremely difficult to define characteristic forms/patterns of neural activity associated with the peculiar properties of a given stimulus. On the other hand, such complexity in neuronal activity encourages the development of more relevant (complex) methods of data analysis, in addition to the simple description of statistical characteristics of neuronal responses that is one of the tasks of neurodynamics. We conclude that more specific mathematical methods must be applied, such as wavelets



**Fig. 1.1** Illustration of adaptation reaction of neuronal firing activity to a repeated stimulation. This neuron was recorded in a rat in the trigeminal sensory nuclear complex which receives tactile information from vibrissae. Stimulation was performed by periodic mechanical deflection of one whisker by a series of short directed air puffs (duration of each air pulse 5 ms). *From top to bottom:* start and end of stimulation by the sequence of periodic impulses, firing activity of a single neuron (train of spikes), and dynamics of the mean spike frequency (averaging over a sliding time window of 500 ms duration)

[29–31], the Hilbert–Huang transform [32–34], and the Wigner–Ville transform [35–37], which are more suitable for decoding information about non-stationary processes with time-varying features.

### 1.3 Wavelets in Basic Sciences and Neuroscience

Wavelet analysis [29, 38–41] is unique in the sense that even the first practical application to neurophysiological data analysis produced prominent results [30, 42–46]. For this reason, it is considered a very powerful analytical tool for studying the dynamics of neural systems.

Wavelet terminology was introduced in the 1980s [38, 47, 48]. This mathematical approach was initially proposed as an alternative to classical spectral analysis based on the Fourier transform. Wavelet theory is considered to be one of the most important events in mathematics of the past decades. Indeed, it appears to be the sole new mathematical concept that was immediately recognized as a tool in practically all branches of basic science (first and foremost, in physics and related disciplines) and many technical fields [31, 49–56]. In fact, introduction of the wavelet theory itself was not entirely unexpected. It was developed to meet the very real needs of experimental investigations, particularly in geophysics and seismology. Contemporary wavelet transform algorithms are based on the subband coding ideology known from radio and electric engineering [57]. Some ideas were borrowed from physics (coherent states [58], etc.) and mathematics (studies on Caldéron–Zygmund integral operators [59]). Wavelet analysis is logically related to the theory of diffusion differential equations [60].

Today, wavelets are widely used for the analysis and synthesis of various signals, image processing and recognition, compression of large volumes of information, digital filtration, the study of fully developed turbulence, and the solution of certain differential equations. This list can certainly be extended [55, 60-68]. The new theory aroused great interest from the very beginning. According to well-known estimates [49], since the 1990s, the number of publications using wavelets in physics has been growing continuously. The number of references to Internet sources containing the term "wavelet" has reached several million. In fundamental science, this mathematical approach is mostly applied to study complex temporally non-stationary or spatially nonhomogeneous nonlinear processes. Wavelet analysis is well adapted for studying the complex structure of signals from living systems, since other traditional computation techniques can be applied only to processes with time (or space)constant parameters (i.e., stationary in time or spatially homogeneous). Despite the fact that wavelet analysis has long been regarded as a standard tool for studying complex processes and practical application of this method in neuroscience and medicine is just beginning, prognoses for its successful application are rather optimistic. In this monograph we highlight recent advances made by practical application of wavelet in neurodynamics and neurophysiology.

### **1.4 Automatic Processing of Experimental Data in** Neuroscience

An important field of wavelet applications in neurophysiology and neuroscience is the development of methods for automatic processing and analysis of brain signals. Electrical signals that can be recorded from the brain (EEG) represent a linear mixture of coexisting oscillatory components, i.e., nonlinear effects do not complicate the process of recognition. The development of expert systems for automatic EEG analysis is of particular interest for both fundamental neuroscience and clinical practice due to a wide spectrum of possible applications (classified in Fig. 1.2). One must distinguish between on-line and off-line analysis. Automatic (i.e., without the attention and control of an operator) analysis of pre-recorded EEG signals (*off-line* diagnostics) aims to reduce routine work, for example, to suppress artifacts in the recorded EEG. EEG analysis in real time (*on-line*) aims at fast detection of certain EEG events and the organization of closed-loop control systems. Clinically-oriented applications are the most effective field of on-line analysis of neurophysiological signals, including EEG monitoring with predictive diagnostic purposes, e.g., for the suppression of epileptic activity, the so-called spike-wave discharges [21].



Fig. 1.2 Wavelet-based methods of automatic EEG diagnostics, processing, and analysis

### **1.5 Brain-Computer Interfaces**

One of the most exciting applications of wavelets is to use it for *mental control* of brain functions, which, as a matter of fact, is a new form of human-computer interaction [69, 70]. The specific dynamics of electrical brain activity characterizes mental activity that includes compilation of imaginary commands ("mental action"). This "mental action" is associated with specific changes in the time–frequency characteristics and spatial structure of EEG [71–74]. In the brain-computer interface, mental control systems must perform the following steps (see Fig. 1.3):

- Recognize and select characteristic changes in the EEG (event-related *oscillatory patterns*).
- Decrypt their meaning (associated with a specific operation).
- Convert this meaning into commands for hardware control.

Mental control systems should be able to solve two main problems. First, the technical problem of precise recognition of an EEG pattern, subsequent formulation of a "command", and transmission to control. Second, cognitive and psychological tasks in which the operator (a person) should learn to keep specific mental states that can be recognized from analysis of the spatial-temporal structure of his/her EEG. An additional problem is that the system should work in real time. Earlier control systems were suggested to use information about complex physical activity expressed as



**Fig. 1.3** General scheme of a simple brain-computer interface. Modern IBC is a system that registers and analyzes signals of electrical brain activity (usually EEG) from the user and "converts" them into a "machine" command for external device control. The central point of such a system is the development of algorithms for real-time recognition of EEG patterns corresponding to certain cogitative operations. Note the importance of the feedback loop in the BCI. This is necessary to adapt the aforementioned algorithms to recognize the specific patterns of electrical brain activity based on EEG features. Also the operator (user) must learn to evoke and control the relevant mental state, which is impossible without the use of feedback

body movements of the operator, e.g., the trajectory when moving a hand in the process of equipment handling. These interfaces encountered many problems, including registration of complex information, isolation of relevant information from the general data stream, and correct interpretation. Besides that, such interfaces require a system of sensors for registration of motor activity and a wireless device for data transmission from operator to computer. Therefore, simple brain-computer interfaces (BCI) are of particular interest, such as interfaces that are able to monitor electrical brain activity and detect the mental intentions of the operator. For example, simple stimulus-symbol interfaces conceived by the operator [75, 76] open up new prospects for resolving the problem of mental control.

Thus, algorithms of automatic EEG pattern recognition associated with specific cogitative operations in real time help to effectively perform the first step (pattern recognition) in brain-computer interfaces. Wavelet-based methods are perfectly suited to pattern recognition tasks [77–80].

Note that brain-computer interfaces have already been used as an alternative to traditional devices for inputting information into the computer. So for certain categories of users, for example, people with motor function disabilities, this way of interacting with the computer can improve their quality of life, at least partly, opening the way to a full-fledged life in society [81–84]. One of the first successfully worked BCIs was developed at Emory University by Roy Bakay and Phillip Kennedy, who used implanted depth electrodes in the brain motor center of a paralyzed 53-year-old patient, who was able to move the cursor on a computer screen, and thus communicate with doctors (writing several simple sentences) [85]. Rapid progress in neuroscience and technology suggests that brain-computer interfaces could be widely used for control of artificial limbs, manipulators, and robot technical devices (for example, wheelchairs), and also in the gaming industry [86–89].

### 1.6 Topics to Consider

A mathematically rigorous description of wavelet analysis can be found in numerous textbooks and monographs (see, for example, [29, 54, 56, 61, 90–94]) as well as in reviews in scientific journals [17, 52, 53, 95]. This book focuses on the new possibilities provided by the wavelet approach for decoding information from signals recorded on the level of individual neurons and groups of neurons, as well as neural network activity. A large number of the aforementioned scientific publications aimed to identify the most important problems in the field of wavelet applications to neurodynamics and neurophysiology. On this topic, we distinguish the following three areas of wavelet applications in neuroscience:

- **Microlevel** (cellular/intracellular)—wavelet analysis of the dynamics of individual cells or intracellular processes.
- **Mesolevel** (groups of cells)—analysis of information processes in small neuronal ensembles.

• **Macrolevel** (brain activity)—analysis of macrodynamics in widespread neural networks (EEG/MEG, neuroimaging data).

This monograph discusses the progress made on each of these levels in a consistent manner. The book contains eight chapters:

• Chapter 2 provides a mathematical introduction to wavelet analysis, including the basic concepts and definitions of wavelet theory, and considers practically significant questions related to the effective numerical implementation of the wavelet transform (both discrete and continuous). Special attention is paid to the importance of the relationship between wavelet and Fourier analysis. This chapter explicitly addresses those readers who are not familiar with the mathematical concepts of complex signal processing.

The next two chapters describe methods for wavelet investigation of neurophysiological systems.

- Chapter 3 discusses the application of wavelets to analyze cellular dynamics at the microscopic level (individual cells or intracellular processes). This chapter also presents the principles for analyzing the information from a single cell using electrical signals of individual neurons.
- Chapter 4 describes the main aspects of the wavelet analysis of the impulse shapes of individual neurons (action potentials) obtained by extracellular recordings of single-unit activity. We consider different approaches to classifying neuronal spikes, some based solely on wavelets and others involving combined methods, such as wavelet neural networks.
- Chapter 5 provides an introduction to the analysis of local field potentials (LFPs). LFPs are generated by synaptic currents excited by presynaptic neuronal assemblies in target cells. Thus, their study can shed light on the information processing on the circuit level. However, the multi-source nature of LFPs significantly complicates the analysis and requires advanced mathematical methods. We discuss how ongoing LFP activity can be disentangled into pathway-specific contributions. Then, we present wavelet-based methods that enable the identification and quantification of gamma waves (rhythmic patterns) generated by the CA3–CA1 pathways in the hippocampus while the compound LFPs are irregular.

The last four chapters of the book consider the macrodynamics of neuronal networks using wavelet analysis of electroencephalograms (EEGs).

• Chapter 6 considers the main definitions and principles of electroencephalography that are required for a better understanding of Chaps. 7, 8 and 9. We describe general physical and mathematical approaches to time–frequency analysis of rhythmic EEG activity using continuous wavelet transforms. We also review some recent achievements of wavelet-based studies of electrical brain activity, including (i) time–frequency analysis of EEG structure, (ii) automatic detection of oscillatory patterns in pre-recorded EEG, (iii) classification of oscillatory patterns, (iv) real-time detection of oscillatory patterns in EEG, (v) detection of synchronous states

### 1.6 Topics to Consider

of electrical brain activity, (vi) artifact suppression/rejection in multichannel EEG, and (vii) the study of cognitive processes.

- Chapter 7 considers basic problems of automatic diagnostics and processing of epileptic EEG. We discuss the wavelet-based techniques in order to fully automatize routine operations, such as visual inspection of EEG. In addition to that, we exemplify some practical applications of wavelet methods for automatic analysis of pre-recorded signals of neuronal activity (off-line diagnostics), and also some examples of wavelet-based EEG analysis in real-time (on-line). We also discuss principles of fast and precise detection of transient events in EEG and organization of close-loop control systems that can be used in brain-computer interface (BCI).
- Chapter 8 considers using wavelet analysis to study mechanisms of visual perception. First, we introduce an ambiguous visual stimulus, the Necker cube, a useful visual perception analysis tool. Second, we demonstrate how the waveletbased methods reveal the local and network properties of the percept-related brain activity. Then, we considered the effect of the human condition (motivation and alertness) on the perceptive process. Finally, we review the basic principles of the BCIs that use the wavelet-based algorithm to evaluate the human state in visual perception tasks.
- Chapter 9 describes wavelet analysis of the motor-related cortical activity. First, this chapter introduced real and mental motor activity in the young and the middleaged healthy subjects. The real motor acts, or motor execution (ME), enables interaction with the environment and induces the motor-related changes in 8– 12 Hz and 15–30 Hz wavelet power in the motor cortex. The mental motor acts, or motor imagery (MI), did not include muscle control but may have a motorplanning stage, similar to ME. Detecting the ME and MI brain states underlies the BCI for motor control. Second, we described two types of motor imagery: kinesthetic and visual. Visual imagery corresponds to the self-visualization of the subject moving a limb that does not require special training. Kinesthetic imagery is the feeling of muscle movement that can only be realized by athletes or specially trained persons. Finally, we considered how the ME brain states change with age representing criteria for an objective assessment of the motor abilities in elderly adults.

This book is based primarily on the fundamental results in neurodynamics obtained recently by the authors—physicists, mathematicians, and biologists in close collaboration with specialists in experimental neurophysiology. At the same time, the book contains a relatively complete bibliography (over 400 sources) characterizing the application of wavelets in neurophysiological research. In general, this book overviews theoretical and practical knowledge and, in our opinion, demonstrates the advantages of powerful analytical tools and novel mathematical methods of signal processing and nonlinear dynamics in order to address neurophysiological problems. Moreover, wavelet analysis helps to reveal important information and facilitates a deeper understanding of the investigated phenomena. More intensive studies in

this area can contribute to interdisciplinary interactions between physics, nonlinear dynamics, applied mathematics, and neurophysiology and promote further mutual research in these areas.

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# Chapter 2 Brief Tour of Wavelet Theory



**Abstract** In this chapter, the main definitions of wavelet theory are given. To explain the basic ideas of the continuous wavelet transform, we describe a transition from Fourier analysis to wavelets. Mother functions and numerical techniques for implementing the wavelet transform are described. The problem of visualising the results is considered. Finally, features of the discrete wavelet transform are discussed.

As already mentioned in Chap. 1, wavelet analysis constitutes a powerful tool for studying the nonstationary dynamics of nonlinear systems. Although it arose not so long ago [1-3], researchers are already widely using wavelets in different areas of modern science. At present, there are many monographs and reviews devoted to wavelets and their applications in different areas of science and technology, e.g., in physics, biology, medicine, economics, meteorology, etc. [4-11]. Thus, wavelet analysis has become an essential mathematical tool, providing effective solution for various problems related to the study and diagnostics of complex nonlinear processes, as well as digital signal processing. Over the past few decades, wavelet analysis has been widely considered as an interdisciplinary technique. One of the most impressive examples of such interdisciplinary cooperation is the application of wavelets to neurodynamics and neurophysiology, where wavelet analysis is increasingly used to examine neurophysiological data as well as to diagnose both normal and pathological processes in neural systems.

In the present chapter, we give a brief mathematical introduction to the wavelet theory. Here we try to explain the main principles of the wavelet transform (for both, the continuous and the discrete form), a method for numerical implementations of the transform, and the potential of wavelets for investigating complex signals associated with physiological processes. With a view to providing easier explanations, we restrict the discussion to simple mathematical examples and models.



Fig. 2.1 Signals (2.1) and (2.2) and the corresponding Fourier spectra (a) and (b), respectively

### 2.1 From Fourier Analysis to Wavelets

We begin our considerations with the well-known Fourier transform [5, 12], which to some extent provides the background for the wavelet theory. As a first example, let us consider a signal representing the sum of two harmonic functions with different angular frequencies  $\omega_1$  and  $\omega_2$ , viz.,

$$x(t) = \cos(\omega_1 t) + \cos(\omega_2 t) . \qquad (2.1)$$

The Fourier spectrum of this signal (see Fig. 2.1) is characterized by two sharp peaks corresponding to the frequencies<sup>1</sup>  $\omega_1$  and  $\omega_2$ . If both components exist permanently, the Fourier spectrum detects their frequencies, providing the researcher with full information about the signal under investigation.

Further, we consider another signal in which the harmonics appear and disappear with time:

$$x(t) = \left[1 - H(t)\right]\cos(\omega_1 t) + H(t)\cos(\omega_2 t) , \qquad (2.2)$$

where

$$H(t) = \begin{cases} 0, & t < 0, \\ 1/2, & t = 0, \\ 1, & t > 0 \end{cases}$$

<sup>&</sup>lt;sup>1</sup>Note that hereafter we will consider only the positive range of frequencies, since the negative frequency region is the "mirror image" of the positive one and does not provide any additional useful information.



**Fig. 2.2** Signal  $x(t) = \cos[\omega(t)t]$  with linearly increasing frequency  $\omega(t) = \omega_1 + a(\omega_2 - \omega_1)t$  and its Fourier spectrum. Having examined only the spectrum  $|S(\omega)|$ , one can suppose that the signal contains all frequencies in the range  $[\omega_1, 2\omega_2 - \omega_1]$ 

is the Heaviside function.

Comparing the Fourier spectra<sup>2</sup>  $|S(\omega)|$  of the considered signals (2.1) and (2.2), one can see that they are quite similar (see Fig. 2.1a and b). In other words, the Fourier spectrum is unable to provide enough information about frequencies that can be recognized in the analyzed signal at a given moment of time. The spectrum  $|S(\omega)|$  of the signal does not allow one to say whether the signal is a superposition of two harmonic functions or whether it consists of two distinct components existing during clearly different time intervals. In other words, spectral analysis reveals the occurrence of different harmonic components, but it does not provide information related to their time localization. Nevertheless, the Fourier transform is a powerful tool for examining time series produced by systems with constant parameters. The spectral composition of such signals remains unchanged during the whole observation period. On the other hand, if the frequency components appear and disappear with time or if the frequency changes smoothly (see, e.g., Fig. 2.2), another spectral technique is required.

This circumstance is brought about by the core mechanism of the Fourier transform, which performs integration over the whole available signal. From the mathematical point of view, the time interval of integration is infinite<sup>3</sup>:

$$S(\omega) = \int_{-\infty}^{+\infty} x(t) e^{-i\omega t} dt , \qquad (2.3)$$

and each frequency component makes a contribution to the spectrum. Thus, using spectral analysis, we can detect characteristic rhythms in the signal, but we are unable to reveal their time localization. In other words, infinite oscillating harmonic functions sine and cosine used within the Fourier transform cannot be applied for localized spectral analysis [13, 14].

<sup>&</sup>lt;sup>2</sup>More precisely, amplitude spectra of the Fourier transform.

<sup>&</sup>lt;sup>3</sup>Of course, in the case of experimental signals or data from numerical simulation, researchers deal with finite time series.

As a consequence, if we are going to localize the frequency components in time, we have to pass from integration over the infinite time interval  $(-\infty, +\infty)$  to a certain time "window"<sup>4</sup> with duration 2*T*, viz.,  $[t_0 - T, t_0 + T]$ , where  $t_0$  is the time at which we are (locally) defining frequency components in the signal:

$$S(\omega, t_0) = \int_{t_0-T}^{t_0+T} x(t) e^{-i\omega t} dt .$$
 (2.4)

To evaluate the dynamics of the frequency components over time, we must shift the observation window along the time series. In this case we obtain the instantaneous spectrum depending on  $t_0$ . This spectrum changes as the observation window is moved along the time axis. Since  $t_0$  is a variable in (2.4), the spectrum  $S(\omega, t_0)$  should be considered as a two-dimensional function (Fig. 2.3).

However, this approach with the rectangular window, known as the short-time Fourier transform, also has several limitations [15]. Indeed, the spectrum of a harmonic signal is the  $\delta$ -function only in the case when the signal is infinite and the integration is performed over the whole infinite time interval. If the signal is finite (or if the integration is performed over a finite time interval), the spectral image of the signal is characterized by the finite width, and the shorter the duration of the signal, the broader its image in the Fourier space. So, using the short-time Fourier transform, one has to operate with the shortest length 2T of the observation window to localize the appearance (or disappearance) of the frequency components of the signal more precisely. On the other hand, however, this decreases the resolution of the method in the frequency domain. In other words, the more precisely we define the frequency of the spectral components, the less exactly we can localize this component in time, and vice versa.

If we wish to maintain the possibility of tracing the modifications of the signal with time, but also to reduce the lack of precision in frequency detection, the transform (2.4) needs to be modified. Note also that the short-time Fourier transform performed only once does not give full information about the signal under consideration. A set of transformations performed for the same signal and different widths 2T of the observation window is more informative. Indeed, the transformation with a narrow window may be used to localize modifications of the signal in the time domain, whereas the transformation with a broad window can provide information about the frequencies. Of course, this approach is inconvenient, since one has to consider a function  $S(\omega, t_0, T)$  depending on three variables instead of two,  $\omega$  and  $t_0$ , and this requires representation in a space of at least four dimensions.

To reduce the number of the variables, one can link the frequency  $\omega$  of the harmonic filling with the length of the observation window *T*, e.g., for each value of *T* one can use  $\omega = \omega_n = 2\pi n/T$ , where  $n \in \mathbb{N}$  is the number of filling periods fitted into the window length. Then, the short-time Fourier transform may be written in the form

<sup>&</sup>lt;sup>4</sup>Here, for simplicity, a rectangular window is used. In a more general case (known as the Gabor transform), we use a window function g(t) that is localized in both the time and frequency domains.



**Fig. 2.3** Spectrum  $S(\omega, t_0)$  of the signal (2.2) consisting of two consecutive parts of harmonic signals with the different frequencies  $\omega_1$  and  $\omega_2$ . Five locations of the observation window (rectangle) are shown. Shifting the window along the time series results in a transformation of the spectrum (see bottom of figure)





$$S(T, t_0) = \int_{t_0 - T}^{t_0 + T} x(t) \exp\left(-i\frac{2\pi n}{T}t\right) dt , \quad n > 0 .$$
 (2.5)

In fact, in the 3D space  $(\omega, t_0, T)$ , where the function  $S(\omega, t_0, T)$  is defined, a surface  $\sigma$  is introduced and further consideration is carried out at the points belonging to this surface. Obviously, some information is lost in this case, but the remaining data allow us to understand the particularity of the time series under study, since the surface  $\sigma$  covers both the frequency and the time domain (see Fig. 2.4).

Moreover, the length of observation window that is optimal to detect different frequency components of the signal is defined by the corresponding time scales. To pick out the low-frequency components, a longer part of the time series should be used than for analysis of high-frequency oscillations. The relation  $\omega_n = 2\pi n/T$  provides a reasonable ratio between the analyzed frequency and the length of the observation window.

Transforming (2.5) for the time series  $x(t) = \sin(\omega t)$  results in

$$S(T, t_0) = \frac{2T\sin(\omega T)}{\omega^2 T^2 - 4\pi^2 n^2} \left[\omega T\sin(\omega t_0) - i2\pi n\cos(\omega t_0)\right] \exp\left(-i2\pi n \frac{t_0}{T}\right).$$
(2.6)

As for the spectral analysis, the result of this transformation is characterized by both real and imagine parts. By analogy with the Fourier transform, there is a reason for considering the square of the absolute value of *S*, i.e.,

$$|S(T, t_0)|^2 = \frac{4T^2 \sin^2(\omega T)}{(\omega^2 T^2 - 4\pi^2 n^2)^2} \Big[ \omega^2 T^2 \sin^2(\omega t_0) + 4\pi^2 n^2 \cos^2(\omega t_0) \Big] .$$
(2.7)

One can see that in this case the quantity of  $|S(T, t_0)|^2$  takes its maximal value  $4\pi^2 n^2/\omega^2$  for  $T_{\rm m} = 2\pi n/\omega$  (Fig. 2.5), i.e., as for the Fourier transform, the transfor-


**Fig. 2.5** Transformation (2.5) of the signal  $x(t) = \sin(\omega t)$  ( $\omega = \pi$ ,  $t_0 = 0$ ) for **a** n = 2, **b** n = 4

mation (2.5) allows detection of the time scale  $T_{\rm m}$  (related to the frequency  $\omega$  of the signal) corresponding to the main rhythm of the analyzed signal.

There are several important points to be made here. Firstly, for the same signal  $x(t) = \sin(\omega t)$  and different values of the parameter n (which is determined as the number of periods of the harmonic function with the corresponding frequency that would fill the integration window of length 2T), the values  $T_m$  corresponding to the maximal magnitude of  $|S(T, t_0)|^2$  are different (see Fig. 2.5a and b). This becomes clear when one takes into account the fact that the quantity  $|S(T, t_0)|^2$  reaches its maximum when the harmonic filling is characterized by the same frequency  $\omega$  as the main frequency of the signal under study x(t) (Fig. 2.6). In other words, the quantity  $|S(T, t_0)|^2$  is maximal when  $T = T_m = 2\pi n/\omega$ , where  $\omega$  is the frequency of the signal x(t) under investigation. In fact, the same situation is also observed for Fourier analysis. Note that the value of  $T_{\rm m}$  (when the quantity  $|S(T, t_0)|^2$  becomes maximal) depends on the integration window and, in general, does not coincide with the corresponding time scale of the signal. Note also that the more periods are considered within the integration window, the more clearly the corresponding harmonic in  $|S(T, t_0)|^2$  is defined (compare Fig. 2.5a and b). Nevertheless, as a consequence, the length of the integration window corresponding to the maximal value of  $|S(T, t_0)|^2$ also increases with the growth of the period number n. As mentioned above, this results in the deterioration of the resolution of the transformation (2.5) in the time domain.

Secondly, one should note that the quantity  $S(T, t_0)$  that results from the transformation (2.5) is a function of two variables, i.e., T and  $t_0$ . The parameter T defines the time interval used for the integration and the frequency of the harmonic filling. So the frequency of the analyzing harmonic filling is closely related to the length 2T of the window. The variable  $t_0$  determines the time moment associated with the transformation. In fact, it defines a shift of the integration window along the time axis. At the same time, the harmonic filling remains fixed when the integration window is shifted (see Fig. 2.6d and e). In other words, the phase of the filling changes continuously when the integration window is moved along the time axis. To avoid this problem the filling phase should be fixed relative to the observation window by



**Fig. 2.6** a Time series  $x(t) = \sin(\pi t)$  and several integration windows **b**-**d** with different lengths 2*T* and the analyzing harmonic filling  $\exp(-i2\pi n/T)$ . The real part of the filling is shown by the *solid line*, and the imaginary part by the *dashed line*. The maximal value of  $|S(T, t_0)|^2$  is observed for T = 4 (**c**), when the frequency of the filling coincides with the signal frequency  $\omega$ . **e** Shift of the integration window by the value determined by the second variable  $t_0$ 

means of the following modification of (2.5):

$$S(T, t_0) = \int_{t_0-T}^{t_0+T} x(t) \exp\left[-i\frac{2\pi n}{T}(t-t_0)\right] dt .$$
 (2.8)

Clearly, changes in the phase of the harmonic filling do not influence the value of  $|S(T, t_0)|^2$ . For the harmonic signal  $x(t) = \sin(\omega t)$ , the transform (2.8) gives

$$S(T, t_0) = \frac{2T\sin(\omega T)}{\omega^2 T^2 - 4\pi^2 n^2} \Big[ \omega T\sin(\omega t_0) - i2\pi n \cos(\omega t_0) \Big].$$
(2.9)



It is easy to see that the difference between (2.6) and (2.9) consists only of the factor  $\exp(-i2\pi nt_0/T)$ .

Thirdly, one has to take into account the fact that different frequency components of the signal with equal amplitude are detected by the transformation (2.8) in different ways. The corresponding maxima are characterized by different magnitudes. The squares of these maxima are related to each other by

$$\frac{|S_1|^2}{|S_2|^2} = \left(\frac{\omega_2}{\omega_1}\right)^2 , \qquad (2.10)$$

which may be obtained directly from (2.7). In other words, the lower the frequency, the larger its contribution to the signal spectrum, under the condition that the amplitudes of the considered spectral components are equal (see Fig. 2.7). This means that, if there are two or more components in the signal whose frequencies differ sufficiently from each other, the components with higher frequencies may be missed.

Equation (2.8) may be written in the more general form

$$S(T, t_0) = \int_{-\infty}^{+\infty} x(t) \psi^* \left(\frac{t - t_0}{T}\right) dt , \qquad (2.11)$$

where  $\psi(\xi)$  is the analyzing function (see Fig. 2.8)

$$\psi(\xi) = \left[ H(\xi+1) - H(\xi-1) \right] e^{i2\pi\xi} , \qquad (2.12)$$

and the star hereafter indicates complex conjugation. In fact, (2.11) may already be considered (with some corrections) as the wavelet transform. So we have gone in stages from the Fourier transform to the wavelet analysis.

The transformation (2.11) consists in the expansion and shift of the function  $\psi(\xi)$  as described above and shown in Fig. 2.6. In this case the quantity *T* describes the expansion of the analysing function  $\psi(\xi)$ , whereas the variable  $t_0$  corresponds to the shift of  $\psi(\xi)$  along the time axis. The function  $\psi(\xi)$  is known as the mother wavelet,

Fig. 2.8 The real (*solid line*) and imaginary (*dashed line*) parts of the sine wavelet (2.12)

and all other functions  $\psi((t - t_0)/T)$  used for other time scales are obtained from it by expansions and shifts. For convenience, a normalization condition is imposed on the mother wavelet:

$$\|\psi\|_{L^2} = \left[\int_{-\infty}^{+\infty} \psi(\xi)\psi^*(\xi)d\xi\right]^{1/2} = 1.$$
 (2.13)

Taking into account the requirement (2.13), the mother wavelet (2.12), denoted by  $\psi_0$ , should be written in the form

$$\psi_0(\xi) = \frac{H(\xi+1) - H(\xi-1)}{\sqrt{2}} e^{i2\pi\xi} .$$
(2.14)

The wavelet functions  $\psi_0((t - t_0)/T)$  obtained for other time scales by means of the expansion and shift of the mother wavelet  $\psi_0$  do not satisfy the requirement (2.13). To satisfy the normalization condition for every time scale *T*, a normalization factor depending on the time scale *T* should be introduced. Then the function  $\psi_0(\xi)$  with normalization coefficient  $T^{-1/2}$  should be used instead of  $\psi(\xi)$  in (2.11):

$$\psi_{T,t_0}(t) = \frac{1}{\sqrt{T}} \psi_0\left(\frac{t-t_0}{T}\right) \,. \tag{2.15}$$

Finally, (2.11) takes the form

$$S(T, t_0) = \frac{1}{\sqrt{T}} \int_{-\infty}^{+\infty} x(t) \psi_0^* \left(\frac{t - t_0}{T}\right) dt .$$
 (2.16)

Equation (2.16) is the standard form of the continuous wavelet transform introduced in the scientific literature [7, 12, 14, 16–20]. At the end of this section we need also to compare the notation in this section with the one used traditionally in the literature. For the continuous wavelet transform, the time scale is traditionally denoted by s (so



in the above consideration,  $T \equiv s$ , whereas for the wavelet surface that results from the transformation, the symbol W is used, i.e.,

$$W(s, t_0) = \frac{1}{\sqrt{s}} \int_{-\infty}^{+\infty} x(t) \psi_0^* \left(\frac{t - t_0}{s}\right) dt .$$
 (2.17)

Often, the notion of "frequency" f is considered instead of the "time scale" s since it is more suitable in many studies. In fact, the frequency f used in the wavelet analysis carries the same meaning as the frequency of the Fourier transform. In particular, this approach is commonly used in neuroscience and neurophysiology. At the same time, researchers have to be very careful using the term "frequency" for wavelets, since in general the relationship between the time scale s of the wavelet analysis and the frequency f of the Fourier transform differs from the equation f = 1/s, which becomes correct only for special choices of the mother wavelet and its parameters.

So we have moved gradually from the Fourier transform to the wavelet analysis, aiming to expose the underlying ideas of wavelets. By analogy with the Fourier transform, the wavelet analysis expands the given signal x(t) in terms of a certain functional basis. At the same time, the functional bases used for the Fourier and wavelet transforms are not the same. While the infinite-in-time harmonic functions sine and cosine are used in classical spectral analysis, functions  $\psi_{s,t_0}$  that are well-localized in both time and frequency (obtained by expansion and shift of the mother wavelet  $\psi_0$ ) are used in wavelet analysis. These localized functions (wavelets) allow us to examine processes with statistical characteristics that vary in time (or in space), and provide a two-dimensional representation of the signal x(t) when the time and frequency are interpreted as independent variables.

We shall refer to the mother wavelet (2.14) obtained by the gradual transition from the Fourier transform shown in Fig. 2.8 as the sine wavelet. The sine wavelet is not widely used in practical applications (in particular, due to the low level of localization in the frequency domain), but it brings out the main ideas and methodology of continuous wavelet analysis. An important particularity of the wavelet transform is the possibility of using an arbitrary function satisfying certain conditions (which will be discussed in Sect. 2.2) as the mother wavelet.

Finally, note that, besides the continuous wavelet transform, the discrete wavelet transform is also used in many applied problems. General information concerning these two counterparts of the wavelet transform is given below.

# 2.2 Continuous Wavelet Transform

# 2.2.1 Main Definitions. Properties of the Continuous Wavelet Transform

In the following, we restrict the class of mother functions to  $f \in L^2(\mathbb{R})$ . The function space  $L^2$  contains signals with limited energy, i.e., with finite norm  $||f||_{L^2}$ . The continuous wavelet transform (CWT) is performed by convolution of the examined function f(t) with the two parameter wavelet function  $\psi_{s,t_0}(t)$ , viz.,

$$W(s, t_0) = \int_{-\infty}^{+\infty} f(t) \psi_{s, t_0}^*(t) dt .$$
 (2.18)

The wavelet function is obtained from the mother wavelet  $\psi_0(t)$  by means of an expansion and a shift:

$$\psi_{s,t_0}(t) = \frac{1}{\sqrt{s}} \psi_0\left(\frac{t-t_0}{s}\right) .$$
(2.19)

The parameter *s*, known as the time scale of the wavelet transform ( $s \in \mathbb{R}^+$ ), determines the width of the wavelet in the time domain, whereas the parameter  $t_0 \in \mathbb{R}$  specifies the wavelet location on the time axis. The factor  $1/\sqrt{s}$  in (2.19) provides the constant unit norm of the wavelets in the function space  $L^2(\mathbb{R})$ , i.e.,

$$\|\psi_{s,t_0}\|_{L^2} = \|\psi_0\|_{L^2} = 1 , \qquad (2.20)$$

where the norm in the space  $L^2(\mathbb{R})$  is defined by

$$\|f\|_{L^2} = \left[\int_{-\infty}^{+\infty} |f(x)|^2 \,\mathrm{d}x\right]^{1/2} \,. \tag{2.21}$$

Below, we will use the following notation for the wavelet functions:

- $\psi_0$  for the mother wavelet.
- $\psi_{s,t_0}$  for the wavelet function obtained from the mother wavelet  $\psi_0$  by (2.19).
- $\psi$  for the wavelet function obtained from the mother wavelet  $\psi_0$ , for which the normalizing factor is not yet defined, i.e.,  $\psi = a\psi_0$ , where *a* is unknown.
- $\Psi$  for the wavelet function used in the calculation of the wavelet surface using the fast Fourier transform.

By the Parseval formula, the condition (2.20) implies that

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$$\frac{1}{2\pi} \int_{-\infty}^{+\infty} |\hat{\psi}_0(\omega)|^2 \, \mathrm{d}\omega = 1 \,, \qquad (2.22)$$

where  $\hat{\psi}_0(\omega)$  is the Fourier image of the mother wavelet function

$$\hat{\psi}_0(\omega) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \psi_0(t) \mathrm{e}^{-\mathrm{i}\omega t} \,\mathrm{d}t \;. \tag{2.23}$$

Analogously,

$$\frac{1}{2\pi} \int_{-\infty}^{+\infty} |\hat{\psi}_{s,t_0}(\omega)|^2 \,\mathrm{d}\omega = 1 \;, \tag{2.24}$$

where  $\hat{\psi}_{s,t_0}(\omega)$  is the Fourier image of the wavelet function  $\psi_{s,t_0}(t)$ .

So the continuous wavelet transform maps the space of one-dimensional functions into the two-dimensional (in general, complex) space.

$$W: L^2(\mathbb{R}) \to \mathbb{C}(\mathbb{R} \times \mathbb{R}^+)$$
,

and as a consequence, information contained in the wavelet coefficients is abundant. This fact results, e.g., in the presence of a correlation in the wavelet spectrum of a random signal (noise), although this correlation is not actually present in the signal (so this is a consequence of the wavelet transform). This may be considered as a significant disadvantage of the wavelet transform that must be taken into account when wavelet spectra are interpreted.

The mother wavelet can be chosen rather arbitrarily, e.g., as in Sect. 2.1, but it must fulfill several requirements. First of all, we should mention the *boundedness condition* 

$$\int_{-\infty}^{+\infty} |\psi_0(t)|^2 \mathrm{d}t < \infty .$$
(2.25)

Then there is the *localization condition*, according to which the mother wavelet function  $\psi_0$  must be localized in both the time and frequency domains. This condition is satisfied if the function  $\psi_0$  decreases rapidly and is quite regular. As an estimate for good localization and boundedness, the conditions  $|\psi_0(t)| < 1/(1 + |t|^n)$  or  $|\hat{\psi}_0(\omega)| < 1/(1 + |\omega - \omega_0|^n)$  may be used, where  $\omega_0$  is the dominant frequency of the wavelet and the parameter *n* should be as large as possible [21].

According to the *admissibility condition*, the Fourier image  $\hat{\psi}_0(\omega)$  of the mother wavelet  $\psi_0(t)$  must obey the condition

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$$C_{\psi} = \int_{-\infty}^{+\infty} \frac{|\hat{\psi}_0(\omega)|^2}{\omega} d\omega < \infty .$$
(2.26)

Since in practice only positive frequencies are usually considered, (2.26) can often be replaced by

$$\int_{0}^{+\infty} \frac{|\hat{\psi}_{0}(\omega)|^{2}}{\omega} d\omega = \int_{0}^{+\infty} \frac{|\hat{\psi}_{0}(-\omega)|^{2}}{\omega} d\omega < \infty .$$
(2.27)

Note also that, for practical purposes, the condition (2.26) is analogous to the condition of zero mean as a consequence of (2.22):

$$\int_{-\infty}^{+\infty} \psi_0(t) \mathrm{d}t = 0 , \qquad (2.28)$$

or

$$\hat{\psi}_0(0) = 0$$
, (2.29)

whence the mother wavelet  $\psi_0(t)$  must be an oscillatory function.

Sometimes this requirement may be important not only for the zero moment (2.28), but also for the *m* first moments, i.e.,

$$\int_{-\infty}^{+\infty} t^k \psi_0(t) dt = 0 , \quad k = 0, 1, \dots, m .$$
 (2.30)

Such *m* th order wavelets may be used to analyse small-scale fluctuations and high order features by ignoring quite regular (polynomial) components. Indeed, expanding the function f(t) in (2.18) in a Taylor series at  $t_0$ , one obtains

$$W(s, t_0) = \frac{1}{\sqrt{s}} \left[ f(t_0) \int_{-\infty}^{+\infty} \psi_0^* \left( \frac{t - t_0}{s} \right) dt + f'(t_0) \int_{-\infty}^{+\infty} (t - t_0) \psi_0^* \left( \frac{t - t_0}{s} \right) dt + \dots + \frac{f^{(n)}(t_0)}{n!} \int_{-\infty}^{+\infty} (t - t_0)^n \psi_0^* \left( \frac{t - t_0}{s} \right) dt + \dots \right].$$
 (2.31)

By (2.30), the first *m* terms of (2.31) vanish, and as a consequence, they do not contribute to  $W(s, t_0)$ . Note that it may be enough for practical purposes if (2.30) is approximately satisfied.

If the admissibility condition (2.26) is satisfied, *the inverse wavelet transform* exists (see, e.g., [22] for details):

$$f(t) = \frac{1}{C_{\psi}} \int_{0}^{+\infty} \frac{\mathrm{d}s}{s^2 \sqrt{s}} \int_{-\infty}^{+\infty} \psi_0\left(\frac{t-t_0}{s}\right) W(s,t_0) \mathrm{d}t_0 .$$
(2.32)

By analogy with the Fourier power spectrum  $P(\omega) = |\hat{f}(\omega)|^2$ , the distribution of instantaneous energy over the time scales of the wavelet transform can be introduced by

$$E(s, t_0) = |W(s, t_0)|^2 , \qquad (2.33)$$

along with the time-averaged integral wavelet spectrum or scalogram

$$\langle E(s) \rangle = \frac{1}{T} \int_{0}^{T} |W(s, t_0)|^2 dt_0 .$$
 (2.34)

Since the distribution of the wavelet energy is related to the Fourier power spectrum [16] by

$$\langle E(s) \rangle \sim s \int P(\omega) |\hat{\psi}_0(s\omega)|^2 \,\mathrm{d}\omega \,,$$
 (2.35)

this means that  $\langle E(s) \rangle$  is a smoothed Fourier power spectrum, defined by the Fourier image  $\hat{\psi}_0$  of the mother wavelet  $\psi_0$ .

One important point is the ability of the wavelets to pick out information concerning local properties of a signal. As discussed above (Sect. 2.1), in order to obtain precise information about high-frequency components with good temporal resolution, rather short time intervals must be used. However, extracting information about low-frequency spectral components requires relatively long fragments of time series.

Figure 2.9 illustrates the ability of different transformations to extract localized information. Figure 2.9a shows a segmentation of the time *t*-frequency  $\omega$  space for discrete samples of the signal values, when the  $\delta$ -function plays the role of the basis function (Shannon transform). One can see that this transform provides excellent time resolution, but no frequency information at all can be extracted. In contrast, the Fourier transform is characterized by perfect frequency resolution, but there is no localization in time (see Fig. 2.9b). Figure 2.9c corresponds to the short-time Fourier transform, where the resolution on short and long time scales is determined by the length of the integration window. In the case of the wavelet transform (Fig. 2.9d), the time resolution determined by the width of the wavelet  $\psi(t/s)$  decreases with the growth of the time scale *s*, whereas the frequency resolution determined by the



width of the Fourier image of the wavelet  $\hat{\psi}(s\omega)$  increases. It provides good time localization for small scales and good frequency resolution for large scales (see Fig. 2.9d).

So the *main feature* of the wavelet transform which is extremely important when analyzing complex nonstationary processes is the ability to respect the locality of the signal representation, and as a consequence, the ability to reconstruct the signal locally. Importantly, the continuous wavelet transform allows us to determine the contribution of a certain scale at a given moment of time. It also provides the possibility to reconstruct only a part of the signal. In fact, there is a relationship between local properties of the signal and local behavior of the wavelet surface related to this signal. This means that, in order to reconstruct a part of the signal, one has to use the values of the wavelet surface W(s, t) belonging to a certain region called the influence angle (see Fig. 2.10a).

When the wavelet function  $\psi_0$  is well localized in the time interval  $\Delta T$  for the time scale s = 1, the values of the wavelet spectrum corresponding to the time  $t'_0$  are contained in the influence cone bounded by the straight lines  $s = 2(t'_0 - t_0)/\Delta T$  and  $s = 2(t_0 - t'_0)/\Delta T$ . At the same time, the value  $W(s', t'_0)$  at point  $(t'_0, s')$  depends on the fragment of the time series contained in the same influence cone (see Fig. 2.10b).

The longer the analyzed time scale *s*, the longer the fragment of time series, i.e., high-frequency (or, what comes to the same, short-scale) information is determined by short fragments of the time series, whereas longer fragments of time series should be used for low-frequency components. If the wavelet function  $\psi_0$  provides good localization in the Fourier space, i.e., the Fourier image  $\hat{\psi}_0$  of the mother function is concentrated in the frequency band  $\Delta\Omega$  around the dominant frequency  $\omega_0$  for time scale s = 1, the values of the wavelet transform corresponding to the frequency  $\omega'$  are located in the range of time scales  $s \in [(\omega_0 - \Delta\Omega/2)/\omega', (\omega_0 + \Delta\Omega/2)/\omega']$ . If f(t) is a locally smooth function, the corresponding values of the wavelet surface are fairly small. When f(t) has a singularity, the magnitude of the wavelet surface increases in its vicinity. Note also that, if the wavelet surface contains artifacts at certain points, they are influenced on the reconstructed signal only locally, in the vicinity of these positions, whereas the inverse Fourier transform spreads these errors over the whole reconstructed signal.

## 2.2.2 Mother Wavelets

One important problem when using the wavelet transform is the choice of appropriate mother wavelet  $\psi_0$  for analysis of the signal. This choice depends on both the aim of the study and the characteristics of the analyzed signal. Thus, to detect phases of an oscillatory process by means of the wavelet transform, *complex wavelets* are used. In contrast, to reveal self-similarity on different time scales, there is a good reason to use *real wavelets*. Existing traditions as well as intuition and the experience of the researcher may also play an important role when choosing the mother wavelet. This section discusses the main wavelets used in practical applications.

The actual choice of mother wavelet depends on what information is to be extracted from the analyzed signal. Each wavelet function  $\psi_0$  is characterized by different properties that allow us to reveal distinct features of the signal f(t). Figure 2.11 shows the most commonly used wavelets  $\psi_0(\eta)$ , together with their Fourier images  $\hat{\psi}_0(\eta)$ . Important characteristics of these wavelets (discussed in detail later) are given in Table 2.1.

One of the most popular complex wavelets used to reveal the time-frequency structure of signals is the Morlet wavelet [3] (see Fig. 2.11)

$$\psi_0(\eta) = \pi^{-1/4} \left( e^{i\omega_0 \eta} - e^{-\omega_0^2/2} \right) e^{-\eta^2/2} , \qquad (2.36)$$

where  $\omega_0$  is the wavelet parameter (often taken as  $\omega_0 \sim 2\pi$ ). The second term in the brackets performs a correction of the wavelet transform for signals with nonzero mean values. When  $\omega_0 \gg 0$ , the term  $e^{-\omega_0^2/2}$  may be neglected, whereas the central frequency (the global maximum of the Fourier image of the wavelet) is conventionally taken to be  $\omega_0$ .



**Fig. 2.11** Most commonly used wavelets (*left*) and their Fourier images (*right*). The real part of each wavelet function is shown by a *solid line*, while the *dashed line* illustrates the imaginary part. **a** Morlet wavelet with main frequency  $\omega_0 = 2\pi$ . **b** Morlet wavelet with  $\omega_0 = 16$ . **c** MHAT wavelet (DOG wavelet with m = 2). **d** Paul wavelet with m = 4. **e** FHAT wavelet

**Table 2.1** Commonly used wavelets and their main properties. Here H(x) is the Heaviside function, f is the frequency of the Fourier transform,  $f_s$  is the frequency of the wavelet transform ( $f_s = 1/s$ ), and  $\tau_s$  is the width of the region of boundary effects

Wavelet	$\psi_0(\eta)$	$\hat{\psi}_0(s\omega)$	$\tau_s$	$f/f_s$
Morlet	$\pi^{-1/4} \mathrm{e}^{\mathrm{i}\omega_0\eta} \mathrm{e}^{-\eta^2/2}$	$\pi^{-1/4}H(\omega)\mathrm{e}^{(s\omega-\omega_0)^2/2}$	$\sqrt{2}s$	$\frac{\omega_0+\sqrt{2+\omega_0^2}}{4\pi}$
Paul	$\frac{2^m i^m m!}{\sqrt{\pi (2m!)}} (1 - i\eta)^{-(m+1)}$	$\frac{2^m}{\sqrt{m(2m-1)}}H(\omega)(s\omega)^m \mathrm{e}^{-s\omega}$	$s/\sqrt{2}$	$\frac{2m+1}{4\pi}$
DOG	$\frac{(-1)^{m+1}}{\left[\Gamma\left(m+\frac{1}{2}\right)\right]^{1/2}}\frac{\mathrm{d}^m}{\mathrm{d}\eta^m}\mathrm{e}^{-\eta^2/2}$	$\frac{\mathrm{i}^{m}}{\left[\Gamma\left(m+\frac{1}{2}\right)\right]^{1/2}}(s\omega)^{m}\mathrm{e}^{-(s\omega)^{2}/2}$	$\sqrt{2}s$	$\frac{\sqrt{m+1/2}}{2\pi}$
FHAT	$\begin{cases} 1, &  \eta  < 1/3, \\ -1/2, & 1/3 <  \eta  \le 1, \\ 0, &  \eta  > 1 \end{cases}$	$3H(s\omega)\left[\frac{\sin(s\omega)}{s\omega}-\frac{\sin(3s\omega)}{3s\omega} ight]$	$\sqrt{2}s$	3/4

In fact, the Morlet wavelet is an analog of the sine wavelet described in Sect. 2.1. Indeed, the Morlet wavelet is a plane wave modulated by a Gaussian function, whereas the sine wavelet is the same plane wave modulated by a rectangular impulse. The functional set obtained on the basis of the Morlet wavelet is well localized in both the time and frequency domains. With growing value of the parameter  $\omega_0$ , the resolution in Fourier space increases, whereas the time localization is reduced. This is easily seen from the comparison of Fourier images of the Morlet wavelet obtained for  $\omega_0 = 2\pi$  and  $\omega_0 = 16$  (see Fig. 2.11a and b). For  $\omega_0 = 16$ , the Fourier image is narrower, attesting to the better resolution in the frequency domain. However, the time resolution decreases for  $\omega_0 = 16$ .

Another example of a complex wavelet is the Paul wavelet [23] (Fig. 2.11d)

$$\psi_0(\eta) = \frac{2^m \mathrm{i}^m m!}{\sqrt{\pi (2m!)}} (1 - \mathrm{i}\eta)^{-(m+1)} , \qquad (2.37)$$

where *m* is the wavelet order corresponding to the number of zero moments.

Among real wavelet functions, the DOG wavelets are widely used (DOG stands for difference of Gaussians) [24]. DOG wavelets are constructed on the basis of derivatives of the Gaussian function (see Fig. 2.11c):

$$\psi_0(\eta) = \frac{(-1)^{m+1}}{\left[\Gamma\left(m + \frac{1}{2}\right)^{0.5}\right]} \frac{d^m}{d\eta^m} \exp\left(\frac{-\eta^2}{2}\right) \,. \tag{2.38}$$

The mother wavelet corresponding to m = 1 is called the WAVE wavelet, viz.,

$$\psi_0(\eta) = \eta \mathrm{e}^{-\eta^2/2} , \qquad (2.39)$$

while m = 2 corresponds to the MHAT (Mexican hat) wavelet, viz.,

$$\psi_0(\eta) = \left(1 - \eta^2\right) e^{-\eta^2/2} . \tag{2.40}$$

Another real mother wavelet is the discrete FHAT (French hat) wavelet shown in Fig. 2.11e, viz.,

$$\psi_0(\eta) = \begin{cases} 1, & |\eta| < 1/3, \\ -1/2, & 1/3 < |\eta| \le 1, \\ 0, & |\eta| > 1. \end{cases}$$
(2.41)

The simplest discrete wavelet used in many technical applications is the Haar wavelet [25]

$$\psi_0(\eta) = \begin{cases} 1, & 0 \le \eta < 1/2, \\ -1, & 1/2 \le \eta < 1, \\ 0, & \eta < 0, & \eta \ge 1, \end{cases}$$
(2.42)

which will be discussed in detail in Sect. 2.3 on the discrete wavelet transform.

The set of mother wavelets is not restricted to the functions considered here. Other functions are also applied in practice and successfully used in various areas of research. The reader can find additional examples of the mother wavelets as well as ways to construct them, e.g., in [16, 26–30]. In the following chapters of this book, we shall discuss examples of wavelets constructed especially to analyze neurophysiological signals.

# 2.2.3 Numerical Implementation of the Continuous Wavelet Transform

Since the analytical form of wavelet spectra can be obtained only for the simplest cases such as, e.g.,  $f(t) = a \sin(\omega t)$ , analysis of experimental time requires numerical implementation of the wavelet transform.

When we carry out numerical analysis, we are dealing with time series of a variable x(t) whose values are known only at specified time moments. Typically, the values of x(t) are recorded with equal time span.<sup>5</sup> Therefore, we shall further consider a time series  $\{x_n\}$ , where each value  $x_n$  is acquired with an equal time interval h, i.e.,  $x_n = x(hn), n = 0, ..., N - 1$ , where N is the number data points in the time series.

<sup>&</sup>lt;sup>5</sup>This is the most typical case in experimental studies. However, data can be acquired in such a way that each data point is related to an arbitrary instant of time. This happens, e.g., for point processes represented by RR intervals of the electrocardiogram [31, 32]. In such a case, the relevant algorithms must be modified [31, 32].

#### 2.2 Continuous Wavelet Transform

The continuous wavelet transform of the sequence  $\{x_n\}$  is defined as the discrete counterpart of the convolution of the analyzed signal and the basis function  $\psi(\eta)$  (2.18) which is normalized by the corresponding time scale *s* and shifted along the time axis by the interval *nh*. One can then write

$$W(n,s) = \sum_{n'=0}^{N-1} x_{n'} \psi^* \left(\frac{(n'-n)h}{s}\right) , \qquad (2.43)$$

where the normalization coefficient for the discrete analogue of the continuous wavelet transform will be discussed later [see (2.59)]. Changing the scale coefficient and the time shift nh, one can localize the dynamics of any particularities of the process  $\{x\}$  in the time domain s.

# 2.2.3.1 Effective Numerical Method for the Continuous Wavelet Transform

Direct calculation of the wavelet transform using (2.43) is not optimal. The simplest and most universal way to optimize the numerical procedure of the wavelet transform is to consider the local nature of the wavelet function (see Fig. 2.10). Indeed, the wavelet function  $\psi_{s,t_0}$  is localized within the time interval  $t \in [t_0 - T(s), t_0 + T(s)]$ . As the function  $\psi_{s,t_0}$  is normalized for different time scales, the time localization interval 2T(s) depends on the time scale *s*. Since the wavelet function is supposed to be close to zero with high precision outside this interval, (2.18) may be replaced by

$$W(s,t_0) \simeq \int_{t_0-T(s)}^{t_0+T(s)} f(t)\psi_{s,t_0}^*(t)\mathrm{d}t \ .$$
(2.44)

The quantity T(s), which also depends on the selected mother wavelet, can be found experimentally for the preassigned precision of numerical calculations. Of course, the higher the value of T, the more accurate the result of the wavelet transform. For the Morlet wavelet, for instance, the optimal length of the time interval related to a reasonable compromise between time duration and accuracy of the performed calculations is estimated as T(s) = 4s.

In the discrete form, (2.44) should be rewritten as

$$W(n,s) = \sum_{n'=n-[T(s)/h]}^{n+[T(s)/h]} x_{n'} \psi^* \left(\frac{(n'-n)h}{s}\right) .$$
(2.45)

One can see that, for arbitrary values of the analyzed discrete sequence  $\{x_n\}$ , the values of the wavelet function are invariable for all time moments *n*, and as a consequence, they can be calculated once and for all in the interval [-T(s), T(s)] with time span *h* as

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$$y_{sn} = \psi^* \left(\frac{nh}{s}\right) , \qquad (2.46)$$

keeping this thereafter as the matrix.

So the problem of calculating the wavelet transform is reduced to multiplying two matrixes, viz.,

$$W(n,s) = \sum_{i=-[T(s)/h]}^{[T(s)/h]} x_{n+i} y_{si} , \qquad (2.47)$$

which may be done rather quickly.

To perform direct numerical realization of the wavelet transform using (2.43), the sum should be estimated N times for every time scale s, where N is the number of data points. Assuming that  $\{x_n\}$  is a complex sequence and the wavelet function has already been calculated in the whole region of possible values,  $M = \mathcal{L} \times 8N^2 + O(N)$  arithmetic iterations must be carried out, where  $\mathcal{L}$  is the number of time scales s for which the wavelet transformation is applied. Indeed, according to (2.43), N complex multiplications (6 arithmetic operations) and N - 1 complex additions (2 arithmetic operations) must be performed at each point of the discrete space with dimension  $N \times \mathcal{L}$ .

Using (2.47) considerably reduces the required operations, since only

$$M = 8N \times \sum_{i=[s_{\min}/\Delta s]}^{[s_{\max}/\Delta s]} [T(i\Delta s/h)] + O(N)$$
(2.48)

operations must be carried out, where  $s_{\min}$  and  $s_{\max}$  are the minimal and maximal boundaries of the analyzed time scales, and  $\Delta s$  is the discretization step. If  $T(s)/h \ll N$ , a considerable efficiency gain is obtained. For the Morlet wavelet, the number of required iterations is estimated as

$$M = 64N \times \sum_{i=[s_{\min}/\Delta s]}^{[s_{\max}/\Delta s]} (i\Delta s/h) + \mathcal{O}(N) . \qquad (2.49)$$

# 2.2.3.2 Numerical Method for the Continuous Wavelet Transform Based on the Fast Fourier Transform

Considering the Fourier images for the initial signal  $\hat{x}_k$  and wavelet  $\hat{\psi}$  also reduces the number of required operations [8, 16]. By the convolution theorem, one can simultaneously compute all values of W(n, s) (n = 0, ..., N - 1) in the Fourier space for the fixed time scale *s* using the discrete Fourier transform.

For the sequence  $\{x_n\}$ , the discrete Fourier transform is estimated as follows

#### 2.2 Continuous Wavelet Transform

$$\hat{x}_k = \sum_{n=0}^{N-1} x_n \mathrm{e}^{-2\pi \mathrm{i} k n/N},$$
(2.50)

where  $k/(Nh) \subset (0, ..., (N-1)/(Nh))$  forms the frequency set of initial signal  $x_n$  given by the sequence consisting of N points with the time step h.

With a known Fourier image  $\hat{\psi}_0(\omega)$  of the mother wavelet  $\psi_0(t)$  [see (2.23)], one can easily compute the Fourier image of the function  $\psi(t/s)$ :

$$\begin{cases} \psi(t) \to \hat{\psi}(\omega) ,\\ \psi(t/s) \to \hat{\psi}(s\omega) , \end{cases}$$
(2.51)

i.e., renormalization of the wavelet function in the Fourier space is taken into account by multiplying the frequency by the scale factor *s*.

Similarly, using the discrete Fourier transform<sup>6</sup> one can obtain

$$\hat{\Psi}(\omega_k) = \sum_{n=0}^{N-1} \Psi(nh) e^{-i\omega_k nh} ,$$

$$\hat{\Psi}(s\omega_k) = \sum_{n=0}^{N-1} \Psi(nh/s) e^{-is\omega_k nh/s} ,$$
(2.52)

where the frequence  $\omega_k$  is given by

$$\omega_k = \frac{2\pi k}{Nh} . \tag{2.53}$$

In the Fourier space, the wavelet transform is written as a simple multiplication of the Fourier image of the signal  $\hat{x}$  by the complex conjugated Fourier image  $\hat{\Psi}^*$  of the wavelet function. The wavelet surface W(n, s) is obtained by the inverse Fourier transform

$$W(n,s) = \frac{1}{N} \sum_{k=0}^{N-1} \hat{x}_k \hat{\Psi}^*(s\omega_k) e^{i\omega_k nh} . \qquad (2.54)$$

When using the approach based on the Fourier images  $\{\hat{x}\}$  and  $\hat{\psi}$ , the wavelet function  $\psi$  should be renormalized for each time scale *s* to correctly compare the wavelet spectra of different signals (and, moreover, the same signal for different time scales *s*). The aim of this renormalization is to provide the unit energy at each time scale:

$$\hat{\Psi}(s\omega_k) = \left(\frac{s}{h}\right)^{1/2} \hat{\Psi}_0(s\omega_k) .$$
(2.55)

<sup>&</sup>lt;sup>6</sup>Notice the difference between  $\psi$ ,  $\hat{\psi}$  and  $\Psi$ ,  $\hat{\Psi}$  used for the continuous and discrete transforms, respectively.

Finally, the equation for the wavelet surface W(n, s) is written as

$$W(n,s) = \left(\frac{s}{h}\right)^{1/2} \frac{1}{N} \sum_{k=0}^{N-1} \hat{x}_k \hat{\Psi}_0^*(s\omega_k) e^{i\omega_k nh} .$$
 (2.56)

Fourier images of different wavelet functions  $\psi_0(\eta)$  are shown in Fig. 2.11 and Table 2.1. Constant factors for each function are chosen according to the normalization condition (the condition of the unit energy)

$$\int_{-\infty}^{\infty} \left| \hat{\psi}_0(\omega) \right|^2 \, \mathrm{d}\omega = 1 \; . \tag{2.57}$$

The analogous condition for the discrete form is

$$\sum_{k=0}^{N-1} \left| \hat{\Psi}(s\omega_k) \right|^2 = N , \qquad (2.58)$$

where N is the number of data points.

If (2.43) is used, the normalization of the wavelet function for the time scale *s* takes the form

$$\psi\left(\frac{(n'-n)h}{s}\right) = \left(\frac{h}{s}\right)^{1/2}\psi_0\left(\frac{(n'-n)h}{s}\right) , \qquad (2.59)$$

where  $\psi_0(\eta)$  is the wavelet function obeying the condition  $\|\psi\|_{L^2(R)} = 1$ , i.e., the wavelet function  $\psi_0$  is also characterized by unit energy. Taking into account (2.59), Eq. (2.43) should be written in the final form

$$W(n,s) = \left(\frac{h}{s}\right)^{1/2} \sum_{n'=0}^{N-1} x_{n'} \psi_0^* \left(\frac{(n'-n)h}{s}\right) .$$
 (2.60)

Taking into account (2.56), one can simultaneously obtain the results of the wavelet transform W(n, s) for the fixed value of *s* and all *n*, using the fast Fourier transform (FFT) to determine all sums in (2.50) and (2.56). Since the FFT requires only  $N \log_2 N$  iterations [33] to calculate the sums (2.50) or (2.56), the whole wavelet surface W(n, s) (for all considered time scales *s*) is computed with  $\mathcal{L} \times N \log_2 N$  iterations.<sup>7</sup> For a large number of points *N*, it gives sufficient gain in comparison with the use of (2.60).

An important aspect of the wavelet transform is the set of time scales  $\{s\}$  used to calculate the wavelet spectrum (2.56). If the mother function represents one from orthogonal wavelets [19, 34], this set of time scales is strongly restricted, whereas

<sup>&</sup>lt;sup>7</sup>Here we do not consider iterations for calculation of the Fourier image of the signal  $\hat{x}$ , since this transform should be performed only once.

for nonorthogonal wavelets the set  $\{s\}$  can be arbitrarily chosen in order to acquire more detailed information about the signal. When the FFT procedure is used, the set of time scales is typically considered to be some power of 2:

$$s_l = s_0 2^{l\Delta s}$$
,  $l = 0, \dots, \mathscr{L}$ ,  $\mathscr{L} = \frac{\log_2(Nh/s_0)}{\Delta s}$ . (2.61)

Here  $s_0$  is the minimal time scale distinguished when the wavelet transform is applied and  $\mathscr{L}$  is the maximal number of time scales used to calculate the wavelet spectrum. The minimal time scale  $s_0$  should be used in such a way that the Fourier period corresponding to this time scale is about 2h (see below). The optimal value of  $\Delta s$ is determined mainly by the width  $\Delta \Omega$  of the Fourier image of the mother wavelet  $\hat{\Psi}_0$ . If  $\Delta s$  exceeds  $\Delta \Omega / (2\omega_0 - \Delta \Omega)$ , the scale resolution of the wavelet transform decreases, since some time scales are excluded from consideration. On the other hand, the choice of a small  $\Delta s$  does not provide essential improvements in the resolution of the wavelet transform (due to the finite width of the wavelet function in the Fourier space). However, it does increase the time required for the calculation.

In the case of the Morlet wavelet with  $\omega_0 = 2\pi$ , the maximal value of  $(\Delta s)_{\text{max}}$  allowing acceptable resolution is about 0.5, whereas for other wavelet functions, e.g., the Paul wavelet, the maximal value of  $\Delta s$  may increase, e.g.,  $(\Delta s)_{\text{max}} \approx 1.0$  for the Paul wavelet.

The FFT procedure used for the continuous wavelet transform in (2.50) and (2.56) also constrains the length of the considered time series  $\{x_n\}$ , since for the FFT procedure the number of points in the time series must obey the requirement  $N = 2^p$ , where *p* is a natural number. Typically, it is not too difficult to obtain time series with the required number of points. Nevertheless, in several cases, the number of data points is limited and cannot be easily enlarged (e.g., in the case of climatic or geological data).

If the length of such time series is roughly (but less than)  $2^p$ , the properties of the wavelet transform allow one to effectively analyze this data using  $2^p$  points instead of  $2^{p-1}$ . This may be done by forming a surrogate time series in which the first and last  $(2^p - N)/2$  points are set equal to constant values, e.g., mean values of the initial time series ( $\overline{x} = \sum_n x_n/N$ ) or zeros. In this case the region of edge effects on the plane (n, s) becomes broader (see next section).

### 2.2.3.3 Influence of Edge Effects

When a finite time series is used to obtain the wavelet spectrum, the errors in W(n, s) appear near the boundaries of the time axis (i.e., near n = 0 and n = N - 1) and this results in a distortion of the time-frequency representation of the signal. Firstly, this is due to the fact that, for the considered time scale *s*, the wavelet function shifted along the time axis starts going beyond the analysed time series. As a consequence, the W(n, s) values in the vicinity of the time series boundaries become incorrect. Obviously, the region of influence of edge effects becomes broader for longer time

scales *s* (smaller frequencies). Secondly, use of the FFT procedure supposes that the analysed data  $\{x\}$  is periodic with period *Nh*, whereas the considered time series does not usually have this property.

The width  $\tau_s$  of the edge effect region is determined by the time interval T(s) introduced earlier [see (2.44)]. For the Morlet wavelet, the width of the region where edge effects influence the results of the wavelet transform is given by

$$\tau_s = T(s) = 4s . \tag{2.62}$$

There are different ways to suppress unwanted edge effects [8, 16, 35]. One of the most effective solutions of this problem is the formation of a surrogate time series  $\{x'_n\}$  with length 2N in which the first N points are taken from the initial time series  $\{x_n\}$ , whereas the next N points starting from n = N are filled by zeros. The resulting surrogate time series  $\{x'_n\}$  is further used for the wavelet transform (2.56). Since  $N = 2^p$ , the FFT procedure can be applied, but for a time series with length  $2^{p+1}$ . This approach reduces the influence of edge effects, and in addition, it is rather fast due to the use of the FFT procedure.<sup>8</sup>

The use of a surrogate time series  $\{x'_n\}$  results in the appearance of a large heterogeneity on the boundary of the initial time series  $x_n$ . Nevertheless, because half of the surrogate time series consists of constant values (e.g., zeros), the perturbations induced this heterogeneity are in the region of very long time scales, whereas the spectrum of the initial heterogeneity (being sufficiently less than added one from the formal point of view) connected with the influence of the boundaries of the time series is related to the region of time scales of the signal. As a consequence, introducing this kind of heterogeneity results in a decrease in the amplitude |W| of the wavelet spectrum in the vicinity of the boundaries of the time series. Obviously, the longer the part of the surrogate time series filled by zeros, the less the influence of edge effects. The use of surrogate time series with equal lengths of fragments filled by initial values and zeros seems to be an optimal solution in terms of the balance between speed of calculation, internal memory consumption, and accuracy of the wavelet transform in the vicinity of the boundaries of the initial time series  $x_n$  [8, 16].

The region of the wavelet spectrum W(n, s) on the plane (n, s) where edge effects are important and cannot be neglected will be referred to as *the region of influence of edge effects*. According to [8], the region of influence of edge effects can be defined using the effective width  $\tau_s$  of the autocorrelation function, which is calculated for the wavelet power at each time scale *s*. The value of  $\tau_s$  is equal to the shift relative to the boundary when the power of the wavelet transform of a time series with edge heterogeneity is halved on the logarithmic scale, i.e., on a linear scale, it corresponds to a power decrease by a factor of  $e^2$ . Such a choice for the boundary of the region associated with edge effects guarantees that these effects can be neglected for times *nh*, where  $(N - n)h > \tau_s$  and  $nh > \tau_s$  for the corresponding scales *s*.

<sup>&</sup>lt;sup>8</sup>For time series with length N, only  $\mathscr{L} \times 2N(1 + \log_2 N)$  arithmetic operations are needed to obtain the wavelet surface with the described technique for reducing edge effects.

Estimates of the widths  $\tau_s$  for different mother wavelets are given in Table 2.1 when using the technique of surrogate time series. Comparing the value of  $\tau_s$  obtained for the Morlet wavelet with the widths of the region of influence of edge effects obtained for the case when these effects have not been suppressed (2.62), one finds that this approach is reasonably effective, allowing effective suppression of the influence of edge effects.

Note also that the value of  $\tau_s$  characterizing the region of edge effects determines the characteristic time of influence of an isolated peak of large amplitude in the time series on the form of the wavelet power spectrum. Considering the width of the peak in the power spectrum, one can separate, e.g., large-amplitude artifacts in the time series from a permanent harmonic component with the same period.

## 2.2.3.4 Time Scales of the Continuous Wavelet Transform Versus Frequencies of Fourier Analysis

From Fig. 2.11 one can see that maximum of the Fourier image  $\hat{\psi}(s\omega)$  of  $\psi(s\omega)$  does not correspond to the frequency  $\omega_s = 2\pi f_s$  (where  $f_s = 1/s$ ). In other words, there is no equivalence between frequencies of the Fourier transform (f) and those of the wavelet transform ( $f_s$ ). Moreover, each mother wavelet is characterized by its own relationship between f and  $f_s$  (see Table 2.1). Thus, the Morlet wavelet with  $\omega_0 = 2\pi$  is characterized by  $f \approx f_s$ , and in this case the time scale of the wavelet transform is almost equivalent to the Fourier period. At the same time, for  $\omega_0 = 16$ , the frequencies f and  $f_s$  are already related to each other by  $f/f_s = 2.5527$ . A similar situation occurs for the MHAT wavelet ( $f/f_s = 0.2518$ ) and the Paul wavelet with m = 4 ( $f/f_s = 0.7166$ ). So these relations must be taken into account when the results of the wavelet analysis are compared with the results of the Fourier transform. This is also very important when the wavelet power spectra obtained for different mother wavelets are compared with each other.

A relationship between the frequencies  $f_s$  and f may easily be obtained either analytically by substituting the Fourier image of a harmonic signal with known frequency  $\omega_0$ , i.e.,  $\delta(\omega - \omega_0)$  into (2.54) and determining the corresponding time scale *s* (which may be found as a maximum of the wavelet power spectrum), or numerically, with only one difference, namely that the power spectrum in this case must be calculated with the technique described earlier.

### 2.2.3.5 Normalization of Wavelet Spectrum

In the framework of classical Fourier analysis, the total power of oscillations is equal to the area under the curve of spectral density  $|S(f)|^2$ , while the magnitude of the peak can be used to determine the amplitude of oscillations with the corresponding frequency. For wavelet analysis, this situation is more complicated. When the total power of the wavelet spectrum is considered, the amplitude cannot be estimated correctly and vice versa. Therefore, depending on the quantity to be obtained, different



Fig. 2.12 Spectra of two harmonic functions with unit amplitudes and different frequencies, calculated using the Morlet wavelet with  $\omega = 2\pi$ 

normalizations of the wavelet spectrum should be used. To illustrate this point, we consider the evaluation of the wavelet spectrum of a harmonic function for different frequencies of oscillation (see Fig. 2.12, where the Morlet wavelet with  $\omega_0 = 2\pi$  is used). One can see that the peak in the wavelet spectrum becomes "blurred" with increasing frequency, while its magnitude decreases.

If one needs to calculate the energy associated with a certain frequency band, this effect is not significant, since the increased width of the peak is accompanied by contraction of its amplitude, and the total power of oscillations, i.e., the area under the curve E(f) (see Fig. 2.12), remains unchanged. At the same time, estimating the amplitudes of each sine curve as the square root of the power related to the considered frequency gives different results, and the amplitude decreases with growing frequency f (see also Fig. 2.7 and the corresponding discussion in Sect. 2.1).

To estimate correctly the relationship between the amplitudes of oscillations, a special normalization should be used. For this purpose, the factor  $1/\sqrt{s}$  in (2.19) should be replaced by 1/s. This allows us to determine correct amplitudes for rhythmic processes with different periods (with a certain constant factor as compared with Fourier analysis), although energy characteristics are preserved. Below (in Fig. 2.15c and d), both normalizations of the wavelet spectrum are given. We thus conclude that the power in a certain frequency band and the amplitudes of characteristic peaks should be considered separately using appropriate normalizations.

#### 2.2.3.6 Signal Reconstruction Based on Wavelet Spectrum

The wavelet transform (2.18) or (2.43) can be considered as a band-pass filter with known frequency characteristic (wavelet function  $\psi$ ). Therefore, the initial signal can be reconstructed from the wavelet spectrum W(n, s) either through inversion of the convolution product (2.18) or by designing the inverse filter. Such manipulations are relatively easy when one deals with an orthogonal wavelet transform. However, for the continuous wavelet transform, reconstruction of the initial signal x(t) is a serious problem due to the redundancy of information contained in the wavelet surface W(s, t). A simple procedure for signal reconstruction based on knowledge of the wavelet surface for a certain function (the simplest case is the  $\delta$ -function) is described in [24, 36]. In this case, the time series  $x_n$  can be represented by the sum of all coefficients of the wavelet transform on all considered time scales [8, 16]:

$$x_n = \frac{\Delta s \sqrt{h}}{K_\delta \psi_0(0)} \sum_{l=0}^{\mathscr{L}} \frac{W(n, s_l)}{\sqrt{s_l}} , \qquad (2.63)$$

where the coefficients  $\psi_0(0)$  and  $1/\sqrt{s}$  are introduced to obtain the unit energy on each time scale *s*. For a real signal  $\{x_n\} \subset \mathbb{R}$ , the inversion formula (2.63) takes the form

$$x_n = \frac{\Delta s \sqrt{h}}{K_\delta \psi_0(0)} \sum_{l=0}^{\mathscr{L}} \frac{\operatorname{Re} \left\{ W(n, s_l) \right\}}{\sqrt{s_l}} .$$
(2.64)

The coefficient  $K_{\delta}$  in (2.63) and (2.64) is estimated from the reconstruction of  $\delta$ -function obtained from its wavelet spectrum, which has been calculated with the mother wavelet  $\psi_0(\eta)$ . To obtain  $K_{\delta}$  one has to construct the time series  $x_n = \delta_{n0}$ . In this case, the amplitudes of harmonics in the Fourier spectra are constant for all k,  $\hat{x}_k = 1/N$ . Having substituted  $\hat{x}_k$  into (2.54), one finds that the wavelet spectrum at n = 0 takes the form

$$W_{\delta}(s) = \frac{1}{N} \sum_{k=0}^{N} \hat{\psi}^*(s\omega_k) .$$
 (2.65)

In this case, the relation for  $K_{\delta}$  follows from the inverse formula (2.64)

$$K_{\delta} = \frac{\Delta s \sqrt{h}}{\psi_0(0)} \sum_{l=0}^{\mathscr{L}} \frac{\operatorname{Re} \left\{ W(n, s_l) \right\}}{\sqrt{s_l}} .$$
(2.66)

Therefore, the parameter  $K_{\delta}$  does not depend on the time scale *s* and remains constant for each mother function  $\psi_0$ . The values of  $K_{\delta}$  for commonly used mother wavelets  $\psi_0$  are given in Table 2.2.

Obviously, the total energy of the signal must remain unchanged after the direct and inverse wavelet transforms. This requirement results in an analogue of Parseval's theorem for the wavelet transform, which (in the discrete form) can be written as

Wavelet	$K_{\delta}$	$\psi_0(0)$
Morlet ( $\omega_0 = 2\pi$ )	0.776	$\pi^{-1/4}$
Paul $(m = 4)$	1.132	1.079
DOG(m=2)	3.541	0.867
DOG (m = 6)	1.966	0.884

 Table 2.2 Characteristics of mother wavelets for the reconstruction of the initial signal from its wavelet spectrum

$$\sigma^2 = \frac{\Delta sh}{K_\delta N} \sum_{n=0}^N \sum_{l=0}^{\mathscr{L}} \frac{|W(n, s_l)|^2}{s_l} , \qquad (2.67)$$

where  $\sigma^2$  is the standard deviation of the time series. The  $\delta$ -function is used in (2.67) to reconstruct the initial signal.

Equations (2.63) and (2.67) can be applied to check upon the accuracy of the numerical realization of the wavelet transform. Having obtained information about the accuracy of the numerical calculation of the wavelet spectrum, the minimal time scale and the step along the time axis can be selected to achieve the required accuracy of analysis.

# 2.2.4 Visualisation of Wavelet Spectra. Wavelet Spectra of Model Signals

In general, the wavelet spectrum  $W(t_0, f_s) = |W(t_0, s)|e^{-i\varphi_W(t_0,s)}$  of a 1D signal x(t) can be considered as two surfaces, viz., the surfaces of amplitudes |W(t, s)| and phases  $\varphi_W(t, s)$  of the wavelet transform, in the three-dimensional space of time–time scale *s*/frequency *f*-amplitude |W|/phase  $\varphi_W$ . In the case where both the mother wavelet and the analysed signal, are real functions, the wavelet spectrum is also a real function. In this section we shall consider only the amplitude spectrum of the wavelet transform  $|W(t_0, s)|$ , while questions related to the phase of the wavelet transform will be considered in the next.

As the simplest model, let us consider the harmonic function  $x(t) = \sin(2\pi f t)$ , with all calculations performed with the MHAT wavelet. For simplicity, the frequency of the signal is fixed as f = 10. The wavelet transform of this function is shown in Fig. 2.13.

In Fig. 2.13a, the wavelet spectrum is shown in the form of a three-dimensional surface. However, this kind of visualization is not often used due to the poor clarity and complicated qualitative interpretation of the results. It is more typical to represent the amplitude wavelet spectrum as the projection of the wavelet surface on the plane  $(t_0, s)$  [or  $(t_0, f_s)$ ] either in the form of contour curves or with shades of gray (see Fig. 2.13b and c, respectively).



**Fig. 2.13** Methods for visualising wavelet spectra. Results of the wavelet transform of a harmonic signal with frequency f = 10 for the MHAT wavelet. **a** Three-dimensional representation, **b** projection, and **c** contour curves of the wavelet surface  $W(f_s, t)$ . **d** Distribution of the total energy  $\langle E(f_s) \rangle$  over the wavelet frequencies  $f_s$ 

The distribution of the energy  $\langle E \rangle$  (2.34) over the time scales *s* (or over the wavelet frequencies  $f_s$ ) is also very informative. This distribution  $\langle E(f_s) \rangle$  is shown for the considered harmonic function x(t) in Fig. 2.13d. Note that the maximum of the distribution corresponds to  $f_s \approx 40$ , which is in good agreement with the relationship (see Sect. 2.2.3) between the frequency *f* of the Fourier transform and the wavelet frequency  $f_s$  for the MHAT wavelet.

Visual analysis of the wavelet surface provides detailed information concerning the particularities of the signal structure. There is only one characteristic time scale which is constant during the whole time of observation. For multiple-frequency and non-stationary signals, analysis of wavelet surfaces becomes more complicated. The alternation of light and dark spots in the vicinity of each local maximum or minimum overloads the wavelet spectrum by a large number of details which may be insufficient for understanding the time–frequency structure of the signal under study.

The results are analogous to those shown in Fig. 2.13 and can be obtained with the help of other mother wavelets. For clarity of analysis, complex wavelet functions are preferable [besides eliminating phase information by considering the modulus of the wavelet surface  $|W(t_0, s)|$ ]. In particular, the complex Morlet wavelet (2.33) is very useful for analyzing multiple-frequency and non-stationary signals.

Different representations of the corresponding wavelet spectrum of the harmonic signal with the same frequency f = 10 are shown in Fig. 2.14. One can see that use of the Morlet mother wavelet gives a clearer wavelet surface than would real wavelets.



**Fig. 2.14** Wavelet transform of the harmonic signal with frequency f = 10 for the Morlet wavelet. **a** Three-dimensional representation, **b** projection, and **c** skeleton of the amplitude surface  $|W(f_s, t)|$ . **d** Distribution of the total energy  $\langle E(f_s) \rangle$  over the wavelet frequencies  $f_s$ 

Indeed, the maximum of the wavelet surface corresponds to the unique rhythm of the signal with frequency f = 10. Obviously, contour curves are not convenient in this case. An alternative way of visualizing the wavelet surface, the so-called *skeleton*, may then be used.

The skeleton is a way to vizualize results of the wavelet transform by local maxima or minima of the wavelet surface at each time moment. In other words, the skeleton is the plane (t, s) [or  $(t, f_s)$ ] containing only the peaks of the wavelet energy distribution. This form of information representation is clearer than the 3D representation. For the considered sinusoidal signal, the skeleton gives the time dependence of the instantaneous frequency shown in Fig. 2.14c. Thus, using the approach described above, one can move from consideration of initial signals to study of the instantaneous frequencies (or time scales) and the instantaneous amplitudes of rhythmic processes, and we shall show in the following chapters that this facilitates analysis of neurophysiological signals.

Note also that the ordinate axis (s or  $f_s = 1/s$ ) is usually shown on a logarithmic scale to represent the data over a wide range of time scales or frequencies.

Since the simple example considered here does not allow us to demonstrate conclusively all the advantages of wavelet analysis, we shall consider in the next few sections several examples of nonstationary signals which are characterized by features that are typical of real neurophysiological signals.

### 2.2.4.1 Signals with Frequency Switchings

Analysis of oscillations with a frequency of about 0.01 Hz is important when studying the complex dynamics of many physiological processes in living systems. Many rhythms in biology and medicine correspond to the range  $10^{-2}$ – $10^{-1}$  Hz, and special methods allowing the detailed analysis of signal structure are important, especially for diagnosing the state from experimental data. As mentioned in Sect. 2.1, classical spectral analysis based on the Fourier transform allows us to detect the presence of different rhythms. However, it is impossible to track the time evolution of instantaneous characteristics of these rhythmic processes. Wavelet analysis provides various ways to examine the local properties of signals, including the case of fast changes in the instantaneous frequencies of rhythmic processes. This kind of behavior is typical, e.g., for electroencephalograms, which are characterized by the fast occurrence/disappearance of different rhythms.

A model signal for which the frequency of oscillations changes suddenly is shown in Fig. 2.15. Note that the amplitude of the harmonic function is equal to unity, both before and after switching. Wavelet analysis with the Morlet mother function allows us (with good enough accuracy) to localize time moments when the signal structure is altered. Figure 2.15c and d illustrate the instantaneous distributions of the wavelet energy, both before and after the frequency switches. The maximum of the wavelet power spectrum is shifted after the signal frequency has changed.

Figures 2.15c and d differ only in the type of normalization. The "classical" wavelet transform (Fig. 2.15c) fixes the energy  $E(f_s) = |W(f_s, t = t_{fix})|^2$ , whereas the normalization used in Fig. 2.15d ensures the equivalence of the amplitudes in the wavelet power spectrum  $|W(f_s, t = t_{fix})|^2/s$  if the harmonics are characterized by equal amplitudes. For a detailed discussion of this aspect see the previous section and Fig. 2.11.

Wavelet analysis allows us to correctly localize the moments of switching for series with rather fast frequency variation. Figure 2.16 shows the case when the frequency changes twice during one period of oscillation.

#### 2.2.4.2 Signals with Varying Frequency (Chirps)

When we consider neurophysiological signals, frequency variations are typically smooth (in contrast to the sudden frequency switchings of Sect. 2.2.4.1). As a model example, let us consider a chirp signal, i.e., a signal whose frequency changes linearly or, more generally, monotonically in time. Figure 2.17a illustrates the results of the wavelet transform (with the Morlet mother wavelet) of the signal consisting of two "parallel" chirps, viz.,

$$x(t) = \sin \left[ 2\pi (f_1 + \Delta f_1 t/2)t \right] + \sin \left[ 2\pi (f_2 + \Delta f_2 t/2)t \right]$$

where  $f_1 = f_2/2 = 0.02$ ,  $\Delta f_1 = \Delta f_2 = 1.33 \times 10^{-4}$ . For clarity, only the signal x(t) and the corresponding skeleton of the wavelet surface are shown. As one can see,



**Fig. 2.15** Analysis of a signal with frequency switchings. **a** Projection of the wavelet spectrum obtained using the Morlet mother wavelet. **b** Skeleton (time dependence of the instantaneous frequency). **c** and **d** Instantaneous distributions of the wavelet power spectrum (compare with Fig. 2.11) for time moments shown by the *arrows A* and *B*, for a normalization that fixes the energy  $E(f_s) = |W(f_s, t = t_{fix})|^2$  and a normalization ensuring equivalence of the amplitudes in the wavelet power spectrum  $|W(f_s, t = t_{fix})|^2/s$ , respectively

**Fig. 2.16** Analysis of a signal with fast evolution of the frequency of the harmonic signal. Analyzed signal and skeleton of the wavelet surface





Fig. 2.17 Analysis of chirps. **a** Two parallel chirps. **b** A chirp whose frequency is approximately doubled during one period of oscillation. Only the skeletons of the wavelet surfaces are shown

the variations of the instantaneous frequencies described by the linear dependence can easily be identified using the wavelet transform. Thus, wavelet analysis can obtain information concerning the structure of the given signal. This analysis reveals the presence of two chirps in this example.

Although the complex wavelet basis makes it possible to perform local spectral analysis, all characteristics are evaluated within a certain time range corresponding to the wavelet function  $\psi_{s,t_0}(t)$ . This means that these characteristics are not found absolutely locally, but are obtained as a result of some averaging. Indeed, the averaging procedure leads to decreased accuracy in the estimated instantaneous characteristics, and this accuracy will be less for fast frequency variations. Nevertheless, even for fast variation of the signal properties, the wavelet analysis provides correct results. To illustrate this aspect, a chirp whose frequency is approximately doubled during one period of oscillation is considered in Fig. 2.17b. As one can see, the wavelet analysis with the Morlet wavelet resolves this extremal case with good precision.

#### 2.2.4.3 Processes with Complex Spectral Structure

Wavelet analysis is also a powerful tool for studying complex multiple-frequency signals [16]. To illustrate this aspect of the wavelet transform, we consider a signal representing a multiple-frequency process. Results of the wavelet transform (with the Morlet wavelet) for such a (sawtooth) signal are shown in Fig. 2.18a. The period of the impulses is T = 0.1 s. The spectrum of this signal is characterized by higher harmonics of the main frequency, as can be seen from Fig. 2.19.

The wavelet transform nicely reveals the higher harmonics of the main frequency. Indeed, the wavelet spectrum has several stripes corresponding to the frequencies 10, 20, 30 Hz, etc. The skeleton can represent the structure of the signal in a more obvious



Fig. 2.18 Analysis of signals with complex spectral structure. Model of a sawtooth signal. Wavelet surface and its skeleton for the signal with constant main frequency f = 10 GHz (a) and main frequency varying from 10 to 5 GHz (b)



Fig. 2.19 Fourier spectrum of the sawtooth signal shown in Fig. 2.18. One can clearly see the harmonics nf (where n = 2, 3, 4, ...) of the main frequency f = 1/T = 10 Hz

way, since only the first harmonics can be clearly seen by considering the wavelet surface. Starting from a certain number n, one cannot distinguish higher harmonics of the signals that are caused by their decreasing magnitudes. This example perfectly illustrates differences in the frequency resolution between the Fourier and wavelet analysis. As one can see, Fourier analysis is a more sensitive tool than wavelet analysis for frequencies with small amplitudes.

Note also the growth in the magnitude of the wavelet surface in the region of higher frequencies at times when the initial signal is changing quickly. This kind of

behavior is typical and so can be used to localize and select different artifacts of the experimental data. The application of this feature of wavelet analysis to neurophysiological data will be discussed in detail in the following chapters.

Figure 2.18b illustrates the application of the wavelet analysis to a more complicated case where the period of the sawtooth signal grows with time. As one can see from the skeleton estimated for this case, the dynamics of both the main frequency and its higher harmonics can also be precisely estimated. As the main frequency of the sawtooth signal decreases, the skeleton lines come closer together with time. Alternatively, if the main frequency increases, the skeleton lines diverge. These particularities of the wavelet spectra must be taken into account when experimental data are examined.

## 2.2.5 Phase of the Wavelet Transform

In Sect. 2.2.4, attention was focused on the amplitude and power characteristics of the wavelet spectra. At the same time, if complex wavelets are used, the wavelet surface is also complex, and the quantity W(s, t) is therefore characterized by both the amplitude and the phase

$$\varphi(s,t) = \arg(W(s,t)). \qquad (2.68)$$

Typically, the phase of the wavelet surface is eliminated from consideration and only the amplitude |W(s, t)| is taken into account, in the same way as was done in Sect. 2.2.4. Nevertheless, the phase contains important information about the signal and, roughly speaking, the phase dynamics involves approximately half the information contained in the signal, with phase information being different from information about the amplitude part of the wavelet spectrum.

Indeed, it is more customary to use the amplitude and it is more convenient to deal with, allowing a simple and clear interpretation. Moreover, for many tasks, analysis of amplitudes is quite sufficient to solve research problems. At the same time, this does not mean that the phase does not play an important role, i.e., that it does not deserve attention. There are a broad range of problems in which phase dynamics is extremely important, e.g., problems involving synchronization phenomena. In this section, we consider the phase and discuss problems where phase analysis can prove useful. We begin our considerations with the phase of the Fourier transform (2.3), in the same way as when the wavelet transform was introduced in Sect. 2.1.

### 2.2.5.1 Phase of the Fourier Transform

Let us imagine, that the signal under study f(t) is shifted along the time axis by some time interval  $f_1(t) = f(t + \tau)$ . In this case the result of the Fourier transform of new signal  $f_1(t)$  is

$$S_{1}(\omega) = \int_{-\infty}^{+\infty} f_{1}(t) e^{-i\omega t} dt = \int_{-\infty}^{+\infty} f(t+\tau) e^{-i\omega t} dt$$
$$= e^{i\omega \tau} \int_{-\infty}^{+\infty} f(\xi) e^{-i\omega \xi} d\xi = S(\omega) e^{i\phi(\omega)}, \qquad (2.69)$$

where  $S(\omega)$  is the Fourier transform (2.3) of the initial signal f(t) and  $\phi(\omega) = \omega \tau$ . One can see that the same signal in other reference systems is characterized by Fourier images that are related to each other by (2.69). The amplitudes of these Fourier images are identical, i.e.,  $|S(\omega)| \equiv |S_1(\omega)|$ , but the phases are different:

$$\varphi_1(\omega) = \varphi(\omega) + \omega\tau , \qquad (2.70)$$

where  $\varphi(\omega) = \arg S(\omega)$ ,  $\varphi_1(\omega) = \arg S_1(\omega)$ . Thus, the phase of the signal contains information about the positioning of the signal relative to the time axis, while information about the presence of a certain harmonic and its intensity is completely included in the amplitude part of the Fourier spectrum.

Since the characteristics of the signal are the main subject of interest (but not its position on the time axis), the amplitude part of the Fourier spectrum is used for this kind of task. On the other hand, the question of the position of the signal relative to the coordinate origin of the time axis is very specific and seldom arises in practice.

The situation changes radically when one begins to consider interactions between systems. Since in this case the states of the systems should be considered relative to each other (but not relative to the coordinate origin), the phase difference  $\Delta \varphi(\omega)$  of the Fourier spectra must be used rather than the phases:

$$\Delta \varphi(\omega) = \varphi_1(\omega) - \varphi_2(\omega) . \qquad (2.71)$$

Consideration of the phase difference has been proposed to study synchronization of chaotic oscillators [37–40]. The phase difference between spectral components can be found either directly (see, e.g., [37]) or using the cross-spectrum [41].

### 2.2.5.2 Phase Synchronization

The wavelet transform with a complex mother function becomes a more useful and effective tool for studying the phase dynamics of the given systems. Besides giving access to the spectral composition of the signal, this approach allows one to track the phase evolution with time. Note that the phase of the oscillations can be obtained without the wavelet transform. For periodic oscillations, the definition of the phase is quite obvious (see, e.g., [42]). But for chaotic oscillations, the definition of the phase becomes more complicated. The concept of chaotic phase synchronization involves consideration of the phases of chaotic interacting systems and we shall discuss it

here, since it is closely related to the analysis of phases introduced using wavelet analysis and will be considered below.

Oscillating chaotic systems are widespread in nature [43, 44], but they are characterized by complicated irregular behavior that makes it difficult to study them. Neurophysiological systems are also characterized by intricate dynamics whose characteristics often coincide with, or at least resemble, the characteristics of chaotic systems. Although it is impossible in general to prove that neurophysiological systems are deterministic with chaotic dynamics (moreover stochastic or random behavior must be taken into account), the prospects for studying them from the standpoint of dynamical chaos look quite promising. A wide range of phenomena typical of chaotic oscillators are observed in neurophysiological systems.

One of the most widespread phenomena is the synchronous dynamics of interacting systems. When the systems under study are chaotic, this type of behavior is called *chaotic synchronization*. The concept of the chaotic synchronization is fundamental and deals with different types of synchronous behavior. Several types of chaotic synchronization are known: complete synchronization [45], lag synchronization [46], generalized synchronization [47], noise induced synchronization [48–50], phase synchronization [42], time scale synchronization [51–54], synchronization of spectral components [40], etc.

One of the most important and commonly occurring types of synchronous dynamics is phase synchronization. As pointed above, phase synchronization is based on the concept of the instantaneous phase  $\varphi(t)$  of a chaotic signal [42, 55–57]. In addition, the instantaneous phase is also used to detect the coupling direction of interacting oscillators, which is useful for neurophysiological systems. Note, however, that there is no universal method for defining the phase of a chaotic signal which would be correct for every dynamical system.

The concept of the *attractor* plays an important role in the phase definition. Typically, the oscillating behavior of the system under study is presented in the form of a time series when the observable quantity is shown as a time function. There is another way to represent the oscillating dynamics when the variables characterizing the system state are plotted as coordinates along axes in a certain space called the *phase space*,<sup>9</sup> while the time is not shown at all. Although this type of representation of the system dynamics is unusual in biological studies, it is quite useful for solving certain tasks. Each point in the phase space corresponds to a specific state of the system state and the point in the phase space. The point corresponding to the current state of the system is referred to as the *representation point* and the curve along which the representation point moves is called the *phase trajectory*. A set attracting the representation points as time goes to infinity is an *attractor* of the dynamical system. When the system dynamics is represented in the plane, one speaks of the

<sup>&</sup>lt;sup>9</sup>The dimension of the phase space is equal to the number of quantities required to fully characterize the state of the system under study.



**Fig. 2.20** Projections of phase coherent (**a**) and phase incoherent (**b**) attractors on the plane (x, y). The dynamics of the chaotic Rössler system is shown

*projection* of the phase space (the phase trajectory, attractor) on the corresponding plane.<sup>10</sup> Examples of the projections of chaotic attractors are shown in Fig. 2.20.

There are various ways of defining the phase of a chaotic signal. All these ways can be effectively used when the chaotic attractor of the system has simple topology. Such systems are called *systems with well-defined phase* or *systems with phase coherent attractor*. The chaotic attractor for these systems is characterized by the topology when the projection of the phase trajectory on a certain plane of states, e.g., (x, y), winds around the coordinate origin but does not cross and envelop it (see Fig. 2.20a). In this case the phase  $\varphi(t)$  of the chaotic signal may be defined as the angle in the polar coordinate system (x, y) [46, 58], whence

$$\tan\varphi(t) = \frac{y(t)}{x(t)} . \tag{2.72}$$

Since the projection of the phase trajectory does not cross and envelop the coordinate origin, the mean frequency  $\overline{\Omega}$  of the chaotic signal, defined as the mean frequency of the phase variation

$$\overline{\Omega} = \lim_{t \to \infty} \frac{\varphi(t)}{t} = \langle \dot{\varphi}(t) \rangle , \qquad (2.73)$$

coincides with the main frequency of the Fourier spectrum S(f) of the system oscillations. If the projection of the phase trajectory envelops or crosses the coordinate origin at certain times, the origin of the coordinate plane is smeared by pieces of the phase trajectory. This kind of chaotic attractor is said to be *phase incoherent* and the system is referred to as a *system with ill-defined phase* (see Fig. 2.20b).

<sup>&</sup>lt;sup>10</sup>Of course, if one deals with a system dimension of 3 or higher.

Another way to define the phase of a chaotic signal is to construct the analytical signal [42, 55]

$$\zeta(t) = x(t) + i\tilde{x}(t) = A(t)e^{i\phi(t)} , \qquad (2.74)$$

where the function  $\tilde{x}(t)$  is the Hilbert transform of x(t), viz.,

$$\tilde{x}(t) = \frac{1}{\pi} \operatorname{PV} \int_{-\infty}^{+\infty} \frac{x(\tau)}{t - \tau} \,\mathrm{d}\tau , \qquad (2.75)$$

and PV indicates that the integral is taken in the sense of the Cauchy principal value. The instantaneous phase  $\phi(t)$  is defined from (2.74) and (2.75).

The third way to define the instantaneous phase of a chaotic signal is the Poincaré secant surface [42, 55]

$$\phi(t) = 2\pi \frac{t - t_n}{t_{n+1} - t_n} + 2\pi n , \quad t_n \le t \le t_{n+1} , \qquad (2.76)$$

where  $t_n$  is the time of the *n* th crossing of the secant surface by the trajectory.

Finally, the phase of a chaotic time series can be introduced by means of the continuous wavelet transform [59], but an appropriate wavelet function and parameters must be chosen [60].

The regime of phase synchronization of two coupled chaotic oscillators means that the difference between the instantaneous phases  $\phi(t)$  of chaotic signals  $\mathbf{x}_{1,2}(t)$  is bounded by some constant, i.e.,

$$|\phi_1(t) - \phi_2(t)| < \text{const}.$$
 (2.77)

As mentioned above, it is possible to define a mean frequency (2.73), which should be the same for both coupled chaotic systems, i.e., phase locking leads to frequency entrainment. Indeed, according to (2.77) and (2.73), the main frequencies of the synchronized chaotic oscillators must coincide with each other.

Note that, independently of the method used to define it, the phase of a chaotic signal may be located in both the region  $\varphi \in (-\infty, \infty)$  and a band of width  $2\pi$ , e.g.,  $\varphi \in [-\pi, \pi)$  or  $\varphi \in [0, 2\pi)$ . To examine the phase-locking condition (2.77), the values  $\varphi_{(-\infty,\infty)} \in (-\infty, \infty)$  are more useful. However, in certain circumstances, the bounded phases, e.g.,  $\varphi_{[0,2\pi)} \in [0, 2\pi)$ , can be used. The two cases are related by

$$\varphi_{[0,2\pi)} = \varphi_{(-\infty,\infty)} , \mod 2\pi .$$
 (2.78)

All these approaches provide correct and similar results for "good" systems with well-defined phase [58]. Indeed, the behavior of the instantaneous phase for the methods (2.72) and (2.76) is very similar within any time range that is less than the characteristic recurrence time. Furthermore, the instantaneous phase defined using the Hilbert transform (2.75) is known to behave for the phase coherent attractor in

just the same way as the phases introduced by (2.72) and (2.76) (see, e.g., [58]). These methods involve certain restrictions [61], in particular, for oscillators with ill-defined phase (see, e.g., [61, 62]).<sup>11</sup>

Obviously, if the examined system is characterized by a well-defined main frequency in the Fourier spectrum and by low background noise, the phase of the signal introduced using one of the above methods will be close to the phase of the corresponding harmonic signal. This is the case when good results can be achieved using the approach of chaotic phase synchronization. If the spectral composition of the signal becomes more complicated, e.g., there are several spectral components with similar amplitudes, the dynamics of the system cannot be correctly described by means of only one phase. In such cases, an approach based on continuous wavelet analysis and the associated concept of time-scale synchronization [52, 53, 65] can be used.

### 2.2.5.3 Phase of the Wavelet Transform

Since the wavelet surface is complex (if a complex mother wavelet is used), so that

$$W(s, t_0) = |W(s, t_0)| e^{i\varphi(s, t_0)} , \qquad (2.79)$$

and since it characterizes the system behavior at each time scale s at the arbitrary time  $t_0$ , the instantaneous phase of the wavelet transform is also automatically defined at each time scale s by

$$\varphi(s,t) = \arg W(s,t) . \tag{2.80}$$

In other words, the behavior of each time scale *s* can be described by means of its own phase  $\phi(s, t)$ , this being a continuous function of the time scale *s* and the time *t*. Thus, a set of phases  $\phi(s, t)$  characterizes the dynamics of the system and can be used to study its behavior.

As in the case of a chaotic signal, the phase defined through the wavelet transform can also be presented in both the range  $\varphi \in (-\infty, \infty)$  and a band of width  $2\pi$ , viz.,  $\varphi \in [-\pi, \pi)$  or  $\varphi \in [0, 2\pi)$ . When (2.80) is used, the phase takes values in the  $2\pi$  band, but there is no problem representing the phase in the infinite range of values.

We begin our considerations of the wavelet phase with a simple signal of the form  $f(t) = \sin(\omega t + \phi)$  and transforming it using the Morlet wavelet. In this case the wavelet surface is given by

$$W(s,t) = \sqrt{2\pi s} \pi^{1/4} \sin(\omega t + \phi - i\omega\omega_0 s) e^{-(s^2\omega^2 + \omega_0^2)/2}$$
  
$$\approx \pi^{1/4} \sqrt{\frac{s}{2}} e^{-(\omega s - \omega_0)^2/2} e^{i(\omega t + \phi - \pi/2)} , \qquad (2.81)$$

<sup>&</sup>lt;sup>11</sup>Nevertheless, the phase synchronization of such systems can usually be detected by means of indirect indications [58, 63] and measurements [64].


Fig. 2.21 Modulus of the wavelet spectrum for each component of the signal (2.82), showing them separately (a) and for the whole signal (b). The wavelet spectrum of the harmonic function with frequency  $\omega_1 = \pi$  is shown in a by the *dashed line*, and the function with frequency  $\omega_2 = 2\pi$  by the *dotted line* 

where  $\varphi(s, t) = \omega t + \phi - \pi/2$ . As one can see from (2.81), the phase of the wavelet transform does not depend on the time scale and repeats the phase of the initial harmonic signal ( $\varphi_{sin} = \omega t + \phi$ ) with time lag  $-\pi/2$ . Note that, in the case of a harmonic signal, the evolution of the phase  $\varphi(s, t)$  is the same *for all* time scales. As for the Fourier spectrum, shifting the signal relative to the time reference point changes the phase  $\varphi(s, t)$ .

Consider now a signal consisting of two harmonic functions

$$f(t) = \sin \omega_1 t + \sin \omega_2 t , \qquad (2.82)$$

where  $\omega_1$  is assumed to be  $\pi$  and  $\omega_2 = 2\pi$  (see Fig. 2.21). Due to the linearity of the wavelet transform, the wavelet spectrum of the signal (2.82) is defined by

$$W(s,t) = \sqrt{2\pi s} \pi^{1/4} \sin(\omega_1 t - i\omega_1 \omega_0 s) e^{-(s^2 \omega_1^2 + \omega_0^2)/2} + \sqrt{2\pi s} \pi^{1/4} \sin(\omega_2 t - i\omega_2 \omega_0 s) e^{-(s^2 \omega_2^2 + \omega_0^2)/2} \approx \pi^{1/4} \sqrt{\frac{s}{2}} \left[ e^{-(\omega_1 s - \omega_0)^2/2} e^{i(\omega_1 t - \pi/2)} + e^{-(\omega_2 s - \omega_0)^2/2} e^{i(\omega_2 t - \pi/2)} \right],$$
(2.83)

and this spectrum is obviously more complicated.

Figure 2.21a shows the absolute value of the wavelet spectrum of each component of the signal (2.82) separately, while Fig. 2.21b shows the modulus of the wavelet surface of the whole signal (2.82). One can see that each frequency component is characterized by its own maximum of the wavelet surface |W(s, t)|, and that the amplitudes of these maxima are different due to the factors discussed in Sect. 2.2.3.5, despite the equivalence of the amplitudes of the sinusoidal functions.

It is intuitively clear that the presence of several spectral components results in the time dependence of the phase dynamics on the time scale of the observation. This statement is illustrated by Fig. 2.22, where the time dependence of the phase  $\varphi(s, t)$ 



Fig. 2.22 Time dependence of the phase  $\varphi(s, t)$  of the wavelet surface W(s, t) for different time scales s: **a**  $s_1 = 2.0$ , **b** s = 1.35, **c**  $s_* = 1.325$ , **d**  $s_2 = 1.0$ 

of the wavelet surface W(s, t) is shown for different time scales *s*. Figure 2.22a illustrates the time dependence of the phase  $\varphi(s, t)$  for the time scale  $s_1 = 2.0$  (see also Fig. 2.21b) corresponding to the lower frequency  $\omega_1 = \pi$ . Similar dynamics (but with different frequency) is observed for the second time scale  $s_2 = 1.0$ , corresponding to the second frequency  $\omega_2$  (Fig. 2.22d). Obviously, for intermediate time scales from the range  $s \in (s_2, s_1)$ , a transition from the behavior shown in Fig. 2.22d to the dynamics shown in Fig. 2.22a should be observed.

This transition is shown in Fig. 2.22b and c. One can see that the amplitude of the wavelet surface decreases with decreasing time scale, namely, in the transition from the time scale  $s_1$  corresponding to the main frequency  $\omega_1$  to the time scale  $s_2$  corresponding to the frequency  $\omega_2$ . The time dependence of the phase exhibits decreasing segments (Fig. 2.22b) due to the influence of the second harmonic of the signal f(t) (with frequency  $\omega_2$ ), but the harmonic with frequency  $\omega_1$  plays the dominant role as before. The time scale  $s_*$  separates regions where the phase dynamics is determined by the harmonic with frequency  $\omega_1$  or  $\omega_2$ , and as a consequence, on this time scale  $s^*$ , both harmonics provide equivalent contributions to the phase dynamics (see Fig. 2.22c). Finally, in the range of time scales  $s \in (s_1, s_*)$ , the phase dynamics is determined by the harmonic with frequency  $\omega_1$ .

Thus, considering the phase of the wavelet transform, we have to keep in mind the following:

- For each time scale *s* of the signal under study, the time-dependent instantaneous phase (2.80) is naturally defined.
- For the selected time scale s', the dynamics of the phase is defined not only by the frequency component corresponding to this time scale, but also by other harmonics

located nearby in the spectrum of the signal and characterized by a large enough amplitude. In other words, on the fixed time scale s', the phase dynamics can be determined by several components of the Fourier spectrum from a certain frequency band.

It is important to note that one can detect the presence of several frequency components by considering only the amplitude spectrum |W(s, t)| of the wavelet transform, and then defining these frequencies as well (see Fig. 2.21b). However, there are several cases where this cannot be done. Indeed, the wavelet spectrum of the two-frequency signal

$$f(t) = A_1 \sin \omega_1 t + A_2 \sin \omega_2 t$$
, (2.84)

where  $A_1 = 0.5$ ,  $\omega_1 = 0.9\pi$ ,  $A_2 = 1.25$ , and  $\omega_2 = \pi$ , is characterized by a single maximum exactly in the case of a signal with a single frequency (Fig. 2.23a). This form of the wavelet spectrum is caused by (i) the finite resolution of the wavelet transform in the time space and (ii) the closeness of the coexisting frequency components in the Fourier spectrum of the signal (2.84), as well as the difference between their amplitudes.

Consideration of the phase dynamics allows rather easy detection of nonharmonic dynamics since, in the time scale ranges  $s < s_*$  and  $s > s_*$ , the phase dynamics is different (see Fig. 2.23b). On the time scale  $s_2 = 2$ , this phenomenon is connected with the dominance of the spectral component with frequency  $\omega_2$  (dashed line in Fig. 2.23b) (the phase dynamics thus corresponds here to this component), whereas on the time scale  $s_1 = 3$ , the main role is played by the spectral component with frequency  $\omega_1$  (which thus determines the behavior of the phase in this case).



**Fig. 2.23** a The moduli of the wavelet spectra for each component of the signal (2.84) are shown separately (the wavelet spectrum of the sinusoidal function with frequency  $\omega_1 = 0.9\pi$  is shown by the *dotted line*, and that of the function with frequency  $\omega_2 = \pi$  by the *dashed line*) and for the whole signal (*solid line*). **b** Time dependences of the phase  $\varphi(s, t)$  for the time scales  $s_1 = 3$  (*dotted line*) and  $s_2 = 2$  (*dashed line*)

#### 2.2.5.4 Time-Scale Synchronization

To end this section let us briefly discuss the concept of time scale synchronization [51-54], based on the examination of the phase dynamics of interacting systems on different time scales. An important feature of the concept of time-scale synchronization is the unification of all types of synchronous behavior of chaotic systems, since all known types of chaotic synchronization (phase synchronization, generalized synchronization, lag synchronization, complete synchronization) can be considered from a unified point of view.

Let us consider the dynamics of two coupled oscillators with complex dynamics. If the time series  $\mathbf{x}_{1,2}(t)$  generated by these systems contain the range  $s_m \le s \le s_b$  of time scales *s* for which the condition of phase locking

$$|\phi(s_1, t) - \phi(s_2, t)| < \text{const.}$$
 (2.85)

is satisfied, and if also a part of the wavelet spectrum energy within this range is not equal to zero, viz.,

$$E_{\text{sync}} = \int_{s_{\text{m}}}^{s_{\text{b}}} \langle E(s) \rangle \,\mathrm{d}s > 0 \;, \qquad (2.86)$$

we say that time-scale synchronization (TSS) takes place between the oscillators.

It is obvious that the classical synchronization of coupled periodic oscillators corresponds to TSS because all time scales in this case are synchronized according to the time scale *s*, instantaneous phase  $\phi_s(t)$ , and TSS definitions. The case of chaotic oscillations is more complicated. Nevertheless, if two chaotic oscillators demonstrate any type of synchronized behavior, the time series  $\mathbf{x}_{1,2}(t)$  generated by these systems contain time scales *s* which are correlated with each other for which the phase-locking condition (2.85) and the energy condition (2.86) are satisfied. Therefore, time-scale synchronization is also realized. In other words, complete synchronization, lag synchronization, phase synchronization, and generalized synchronization are particular cases of time-scale synchronization. To detect time-scale synchronization, one can examine the conditions (2.85) and (2.86), both of which should be satisfied for synchronized time scales.

Note that the phase-locking condition (2.85) may be generalized to the case of m: n synchronization. To study this kind of regime, the more general relation

$$|m\varphi_1(s_{n1},t) - n\varphi_2(s_{m2},t)| < \text{const.}$$
 (2.87)

should be examined in different ranges of time scales  $s_{n1} \in I_1 = [s_{11}, \le s_{1h}]$  and  $s_{m2} \in I_2 = [s_{21}, \le s_{2h}]$  instead of Eq. (2.85). For (m : n) synchronization, the time scale  $s_{m1}$  of the first system and correspondingly the time scale  $s_{n2}$  of the second system must obey the relation  $s_{m2}/s_{n1} = m/n$ . The energy condition (2.86) remains unchanged, but different ranges of time scales  $I_1$  and  $I_2$  should be used.

Finally, synchronous dynamics may take place on a time scale changing with time. In this case one, has to check for fulfillment of the condition

$$\left|\varphi_1(s(t),t) - \varphi_2(s(t),t)\right| < \text{const.}$$
(2.88)

This problem is important when investigating systems whose main rhythm changes with time. In particular, this kind of behavior is typical for physiological systems (see, e.g., [31, 32] where the human cardiovascular system was considered).

A measure of synchronization can also be introduced. This measure  $\gamma(t)$  can be defined as that part of the wavelet energy associated with the synchronized time scales:

$$\gamma(t) = \frac{E_{\text{sync}}(t)}{\int_{0}^{+\infty} E(s, t) \, \mathrm{d}s} \times 100\% \,, \tag{2.89}$$

where the numerator is the energy corresponding to the synchronous time scales and the denominator is the total energy of the wavelet spectrum. The value of this measure  $\gamma = 100\%$  corresponds to regimes of complete and lag synchronization, while  $\gamma = 0$  is evidence of completely asynchronous dynamics. Intermediate values of  $\gamma$  are manifestations of phase synchronous dynamics in a certain range of time scales, when the amplitudes of oscillations may remain uncorrelated. Increasing  $\gamma$ values attest to the expansion of ranges related to synchronous time scales. Thus, the synchronization measure  $\gamma$  can be used, not only to distinguish between synchronized and nonsynchronized oscillations, but also to characterize the degree of TSS synchronization. Since the synchronization measure depends on time, it can be used to analyze processes leading into or out of the synchronous state.

As a consequence, besides the amplitudes of the wavelet spectrum, the phases (on different time scales) also inform us about the behavior of these complex systems. However, detailed consideration of synchronization theory (in particular, time-scale synchronization based on the continuous wavelet transform) is beyond the scope of this book. The reader can find a detailed description of different aspects of synchronization theory and its applications in [31, 32, 40, 51–54, 65–70].

### 2.3 Discrete Wavelet Transform

# 2.3.1 Comparison of the Discrete and Continuous Wavelet Transforms

Section 2.2 focused on the continuous wavelet transform, which allows a clear visual representation of the results of signal processing. In contrast to scientific research, many technical applications deal mainly with the discrete wavelet transform. Although it is inferior to the continuous wavelet transform from the viewpoint

of visualizing results, the discrete wavelet transform has considerable advantages, such as computational speed, a simpler procedure for the inverse transform, etc. It is important to keep in mind that the discrete wavelet transform is not the discretization of the formula for the continuous wavelet transform (in contrast to the discrete Fourier transform). Differences between the continuous and the discrete wavelet transforms are sufficient to consider them as two different ways for for analyzing signal structure.

In the context of the continuous wavelet transform, infinitely differentiable functions represented in analytical form are considered as mother wavelets.<sup>12</sup> As a consequence, these functions are characterized by exponential decay at infinity, and the basis constructed from these wavelets is not orthonormal. Therefore, the continuous wavelet transform provides excessive information, and the values of the wavelet coefficients are correlated. Nevertheless, in several cases, this feature plays a positive role, allowing one to obtain a clearer interpretation of the results, e.g., in the form of skeletons or contour curves [13]. Information obtained from the continuous wavelet transform are more easily analyzed than other ways of studying non-stationary processes (see, e.g., [12, 72]).

Using complex functions, the continuous wavelet transform can be used to study the evolution of such characteristics as the instantaneous amplitude, frequency, and phase of rhythmic processes identified in the signal structure. One may also consider the set of phases corresponding to different spectral components of the signal [51–53, 65]. For these reasons, the continuous wavelet transform is a promising tool for solving many neurophysiological problems. Thus, the continuous wavelet transform is useful in the case when analyzing the synchronous dynamics between neurons or groups of neurons, or diagnosing the presence/absence of rhythmic components in the activity of a neuron group [73].

Although the discrete wavelet transform can use non-orthogonal basis functions (e.g., frames) [19], orthogonal (or almost orthogonal) bases are most commonly used since this allows one to represent the signal more precisely and simplifies the inverse transformation. In contrast to the continuous wavelet transform, the wavelets used in the framework of the discrete wavelet transform have no analytical expression, with the exception of the Haar wavelet (2.42) [18]. The wavelets are specified in the form of matrix coefficients obtained by solving certain equations. In practice, the concrete form of the wavelet function in the explicit form is not considered, and only sets of coefficients are used to define the wavelet. This results in a series of elementary operations that allow the realization of fast algorithms for the discrete wavelet transform. The basis is created using an iterative algorithm that varies the scale and shifts the single function. However, the detailed description of the essential differences between the discrete and continuous wavelet transforms is a mathematical problem that goes beyond the subject of our book, and is discussed, e.g., in [74].

The absence of an analytical expression for wavelets used in the discrete wavelet transform leads to a certain inconvenience with the discrete wavelet transforma-

 $<sup>^{12}</sup>$ For practical purposes, mother wavelets can also be constructed from tabulated segments of time series (see [30, 71]).

tion. However, this inconvenience is compensated by many useful properties of the discrete wavelet transform. For example, it provides the possibility of using fast algorithms (see, e.g., [75]), which is important for practical purposes, e.g., for coding and transmitting information, or for compressing data. The discrete wavelet transform is used, for instance, in the framework of the JPEG graphic format and the MPEG4 video format, in computer graphics for editing three-dimensional images, etc. The algorithms of the fast discrete transform are applied when processing experimental data.

An important feature of the wavelet transform is shift invariance. This means that, if the signal is shifted along the time axis, the wavelet coefficients are also shifted and, after relabeling, one can find a relationship between the new coefficients and those prior to the shift. This feature is easily illustrated for the continuous wavelet transform, but the relationship between the coefficients on different time scales is more complicated for the discrete wavelet transform. Estimating the wavelet coefficients provides a way to solve the problem of image identification. More efficient algorithms can also be created using a combination of wavelet analysis and neural networks.

The majority of wavelet functions used in the framework of the discrete wavelet transform are irregular. For practical purposes, such properties as the regularity, the number of zero moments, and the number of wavelet coefficients exceeding a certain value are important when selecting the wavelet function. A large number of zero moments makes it possible to realize effective data compression, since wavelet coefficients at small scales tend to be zero at those points where the function is rather smooth, and as a consequence, these coefficients may be neglected without significant loss of information. In this case, however, the wavelet function becomes broader and this results in a decreased speed of computing. Thus, the choice of basis function is determined by specific features of the problem to be solved. Typically, the discrete wavelet transform is used to solve technical problems (signal coding, computer graphics, image recognition, etc.), whereas the continuous wavelet transform is applied in scientific studies related to the analysis of complex signals.

Wavelet analysis, as applied to neurodynamics and neurophysiology tasks, provides many possibilities for effective recognition (or identification) of signal shapes. Additionally, wavelets are able to filter noise, artifacts, and random distortions from experimental data. Indeed, neurophysiological data often contain artifacts such as rapid changes in the amplitude and other local variations of the signal, which may be caused by the neurophysiological processes themselves or by equipment failures, external factors, etc. Filters based on the Fourier transform are useless for eliminating artifacts, since information about them is contained in all coefficients of the transform. Filtration with wavelets is more effective, since it is possible (perhaps in automatic regime) to detect, localize, identify, and eliminate artifacts, having analyzed the wavelet coefficients on small scales. Digital filtration based on wavelets can be used to clear noisy signals from experimental data at the preprocessing stage. Wavelets are also widely used to recognize signals with similar shapes in the presence of noise. In neurophysiology, such problems arise in the tasks of EEG pattern recognition, identification of impulse activity of single neurons from extracellular recordings of electric potentials, etc. In other words, the reason for the active use of wavelets in modern studies is that similar problems arise in the digital processing of different signals.

### 2.3.2 General Properties

The continuous wavelet transform discussed in Sect. 2.2 deals with the expansion of the signal f(t) when the basis is obtained from a soliton-like function  $\psi(t)$ . In this approach, the scale transformation is carried out for only one function (the mother wavelet). The multi-scale analysis is based on a different concept. It uses orthonormalized wavelet bases to characterize the 'increment of information' required for the transition from the rough description to the more detailed one [18]. This approach was used for the first time in problems relating to image analysis. It provides successive approximations of the given signal f(t) at different scales. In fact, the signal is approximated for certain intervals, and deviations from the approximating functions are analyzed. The approximating functions are related to each other on different scales and orthogonal to each other with the shift along the time axis. This means that only specific functions can be used for the approximation. To explain the ideology of multi-scale analysis, we introduce the necessary definitions using the Haar wavelet as the most simple example.

To analyze the successive approximations for the signal on different scales, the approximating functions should be chosen to satisfy an additional requirement imposed by the relationship between the approximating functions on different scales. In the ideal case, it is better to use a single function  $\varphi(t)$  to approximate the signal on both the large and small scales. Further, the detailed analysis of the signal structure is carried out at the selected scale with the wavelet  $\psi(t)$ . The function  $\varphi(t)$  is called the *scaling function* or *father wavelet*. For the scaling function, the following property is fulfilled:

$$\int_{-\infty}^{\infty} \varphi(t) \mathrm{d}t = 1 , \qquad (2.90)$$

i.e., its mean value is not equal to zero as for the mother wavelet  $\psi(t)$ . The functions  $\varphi(t)$  and  $\psi(t)$  of the Haar wavelet are shown in Fig. 2.24. Scaling of the functions  $\varphi(t)$  and  $\psi(t)$  results in the equations

$$\varphi(t) = \varphi(2t) + \varphi(2t - 1) , 
\psi(t) = \varphi(2t) - \varphi(2t - 1) ,$$
(2.91)

from which the difference between these functions is clear. When the signal is analyzed, the functions  $\varphi(t)$  and  $\psi(t)$  play the role of high-pass and low-pass filters, respectively.



By analogy with the basis of the continuous wavelet transform, we introduce the notation

$$\varphi_{j,k}(t) = \frac{1}{2^{j/2}} \varphi\left(\frac{t}{2^j} - k\right) . \tag{2.92}$$

For the given values of the scale and shift, characterized by the parameters j and k, the approximation coefficients of the signal x(t) are

$$s_{j,k} = \int_{-\infty}^{\infty} x(t)\varphi_{j,k}(t)\mathrm{d}t \ . \tag{2.93}$$

For the selected scale the resulting coefficients are referred to as the *discrete approximation* of the signal on the scale j. Summing the scaling functions with the corresponding coefficients provides the so-called *continuous approximation* of the signal x(t) at the selected scale [76]:

$$x_j(t) = \sum_{k=-\infty}^{\infty} s_{j,k} \varphi_{j,k}(t) . \qquad (2.94)$$

On small scales, this continuous approximation is very close to the initial signal x(t).

As an illustration, let us consider the approximation of one period of the harmonic function shown in Fig. 2.25. Using the Haar scaling function means that on different scales the signal is replaced by the averaged values. For large j, it results in a very rough representation of the harmonic function, but for the maximum possible resolution level j = 0 (determined by the discretization step), the continuous approximation tends to the initial signal x(t).

Using the Haar wavelet, we thus have a simple illustration of the main idea of multi-scale analysis, namely the construction of a set of approximating function spaces. In fact, we are dealing with the histogram approximation of the signal, with the orthogonal complements adding more details on the smallest scales [76]. Figure 2.26 shows examples of the calculation of two successive approximations and the complement to the second of these.





Fig. 2.25 Approximation of the harmonic function on different levels of resolution j



**Fig. 2.26** Approximations of a half period of the harmonic function on the scales j = 2 and j = 3, together with the complement to the approximation on the scale j = 3, allowing one to move to the next scale



Wavelets and the corresponding scaling functions used in practice are usually characterized by a more complicated form (see, e.g., Fig. 2.27). However, all equations written for Haar wavelets remain applicable with other bases. We thus pursue our discussion of the simplest case, assuming that the results can be extended to other wavelets.

The concept of continuous approximation can reveal a trend in the analysed process at the selected scale, with further detailed wavelet-based analysis of fluctuations relative to this trend. On a certain arbitrary scale, any function  $x(t) \in L^2(\mathbb{R})$  can be expanded in a series

$$x(t) = \sum_{k} s_{j_n,k} \varphi_{j_n,k}(t) + \sum_{j \le j_n} \sum_{k} d_{j,k} \psi_{j,k}(t) , \qquad (2.95)$$

where

$$d_{j,k} = \int_{-\infty}^{\infty} x(t)\psi_{j,k}(t)\mathrm{d}t$$
(2.96)

are the wavelet coefficients. The first sum is the approximation of x(t), whereas the second sum provides the details of this function on different scales.

For the selected scale  $j_n$ , one can write

$$x(t) = x_{j_n}(t) + \sum_{j \le j_n} \mu_j(t) , \qquad (2.97)$$

whereas the function

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$$\mu_{j}(t) = \sum_{k} d_{j,k} \psi_{j,k}(t)$$
(2.98)

characterizes the detailed structure of the signal on the scale j. According to (2.97), one obtains

$$x_{j-1}(t) = x_j(t) + \mu_j(t) , \qquad (2.99)$$

i.e., if the detailing function  $\mu_j(t)$  of the signal is added to the approximation on the selected scale *j* (this characterizes fluctuations relative to the approximated trend), the approximation on the next, more precise level of resolution (j - 1) is obtained. This is the main idea of multi-scale analysis.

In general, the relationship between the functions  $\varphi(t)$  and  $\psi(t)$  and their scaled and shifted modifications can be written in the form

$$\varphi(t) = \sqrt{2} \sum_{\substack{k=0\\2M-1}}^{2M-1} h_k \varphi(2t-k) , \qquad (2.100)$$
  
$$\psi(t) = \sqrt{2} \sum_{\substack{k=0\\k=0}}^{2M-1} g_k \varphi(2t-k) ,$$

where the factor  $\sqrt{2}$  is connected with the traditional form of the fast algorithms and normalization of the functions  $\varphi_{j,k}(t)$  and  $\psi_{j,k}(t)$ , whereas the parameter M determines the wavelet length, e.g., M = 1 for the Haar wavelet. Note also the relationship between the coefficients  $h_k$  and  $g_k$  [76]:

$$g_k = (-1)^k h_{2M-k-1} . (2.101)$$

These coefficients are determined from general properties of the scaling functions and wavelets.

As an example, let us consider calculation of the coefficients for the case M = 2. Since the relatively shifted scaling functions are orthogonal, we have

$$\int_{-\infty}^{\infty} \varphi(t)\varphi(t-l)\mathrm{d}t = \delta_{0l} \ . \tag{2.102}$$

Using (2.100), a first restriction on the coefficients  $h_k$  is obtained:

$$\sum_{k} h_k h_{k+2l} = \delta_{0l} \ . \tag{2.103}$$

The condition

$$\int_{-\infty}^{\infty} t^n \psi(t) \mathrm{d}t = 0 , \qquad (2.104)$$

excluding slow nonstationarity (the polynomial trend) for n = 0, ..., M - 1 gives

$$\sum_{k} k^{n} g_{k} = \sum_{k} (-1)^{k} k^{n} h_{k} = 0 .$$
(2.105)

Finally, from the normalization condition (2.90), one obtains

$$\sum_{k} h_k = \sqrt{2} . \tag{2.106}$$

In the particular case (M = 2), the last 3 equations written in explicit form result in the system

$$\begin{array}{c}
h_0h_2 + h_1h_3 = 0, \\
h_0 - h_1 + h_2 - h_3 = 0, \\
-h_1 + 2h_2 - 3h_3 = 0, \\
h_0 + h_1 + h_2 + h_3 = \sqrt{2}.
\end{array}$$
(2.107)

Solution of these equations [74] gives the coefficients

$$h_{0} = \frac{1}{4\sqrt{2}}(1+\sqrt{3}) ,$$

$$h_{1} = \frac{1}{4\sqrt{2}}(3+\sqrt{3}) ,$$

$$h_{2} = \frac{1}{4\sqrt{2}}(3-\sqrt{3}) ,$$

$$h_{3} = \frac{1}{4\sqrt{2}}(1-\sqrt{3}) ,$$
(2.108)

which determine the Daubechies wavelet  $D^4$  (the upper index corresponds to the number of coefficients  $h_k$ ). For wavelets of higher order, the coefficients  $h_k$  can be obtained only numerically, but with any required accuracy. The resulting set of coefficients is typically represented in the form of a vector. As already mentioned, in practice, the functions  $\varphi(t)$  and  $\psi(t)$  are not considered in the explicit form. With the pyramidal expansion algorithm and the vector  $h_k$ , it is easy to estimate the coefficients  $s_{j,k}$  and  $d_{j,k}$ .

The procedure of the pyramidal algorithm is shown in Fig. 2.28. In the case of the Daubechies wavelet  $D^4$ , the discrete wavelet transform with time series x(i) may be represented as multiplication of the vector of the analyzed data by the matrix constructed from the vector  $h_k$  by its translations, viz.,

**Fig. 2.28** Schematic representation of the pyramidal expansion algorithm



$$\begin{bmatrix} h_0 & h_1 & h_2 & h_3 \\ h_3 & -h_2 & h_1 & -h_0 \\ & h_0 & h_1 & h_2 & h_3 \\ & h_3 & -h_2 & h_1 & -h_0 \\ \vdots & \vdots & \ddots & & \\ & & & h_0 & h_1 & h_2 & h_3 \\ & & & & h_3 & -h_2 & h_1 & -h_0 \\ h_2 & h_3 & & & h_0 & h_1 \\ h_1 & -h_0 & & & h_3 & -h_2 \end{bmatrix},$$
(2.109)

where empty matrix elements correspond to zero values.

For the sequence x(i) consisting of 8 elements, the pyramidal expansion is implemented as follows. First, after multiplying the vector

$$\begin{bmatrix} x_1 \ x_2 \ x_3 \ x_4 \ x_5 \ x_6 \ x_7 \ x_8 \end{bmatrix}^{\mathrm{T}}$$
(2.110)

corresponding to the scale j = 0 by the  $8 \times 8$  matrix (2.109), the set of coefficients *s* and *d* are obtained:

$$\left[s_{11} d_{11} s_{12} d_{12} s_{13} d_{13} s_{14} d_{14}\right]^{\mathrm{T}} .$$
 (2.111)

The coefficients  $d_{j,k}$  are not used in the following transformations and they should therefore be separated by reorganizing the vector elements

$$\left[s_{11} \ s_{12} \ s_{13} \ s_{14} \ | \ d_{11} \ d_{12} \ d_{13} \ d_{14}\right]^{\mathrm{T}} \ . \tag{2.112}$$

Secondly, the 4  $\times$  4 matrix (2.109) multiplies the vector of *s*-coefficients to give the vector

$$\begin{bmatrix} s_{21} \ d_{21} \ s_{22} \ d_{22} \ | \ d_{11} \ d_{12} \ d_{13} \ d_{14} \end{bmatrix}^{\mathrm{T}} .$$
 (2.113)

Rearranging the coefficients, one obtains

$$\left[s_{21} s_{22} \mid d_{21} d_{22} \mid d_{11} d_{12} d_{13} d_{14}\right]^{\mathrm{T}} . \tag{2.114}$$

Thus, the wavelet coefficients characterizing the signal at different scales are separated. The resulting coefficients can be used for signal recognition, e.g., to recognize the impulse activity of single neurons from the common activity of the neuron ensemble which is considered in the next chapter.

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# Chapter 3 Analysis of Single Neuron Recordings



**Abstract** In this chapter, we consider several problems where wavelets provide information about the dynamics of neuronal systems that cannot be obtained with ordinary frequency or time domain methods. We discuss the possibility of studying intracellular dynamics and information encoding by individual neurons. We characterize the dynamical stability of the neuronal response and propose an approach to quantify wavelet coherence.

# 3.1 Introduction

The central nervous system (CNS) of living beings processes a large amount of sensory information that is received through interaction with the external world. A study of how this information is encoded, represented, and processed is one of the most important problems in the natural sciences.

Visual, auditory, tactile, gustatory, and olfactory stimuli are encoded by the corresponding receptors into sequences of electrical pulses (spikes) that are transferred to the first neurons, i.e. to the areas of the CNS that carry out preprocessing. Sensory information passes through several other processing stages before reaching the cortex, where an internal representation (or image) of the external world is formed.

The complexity of experimental studies of the corresponding processes increases significantly with each subsequent stage. Though the molecular and ionic mechanisms underlying encoding are rather well understood [1, 2], the properties of spike trains as information carriers remain less clear: How do these trains reflect the enormous complexity and variety of the external world? There are many open questions regarding the principles of information encoding by individual neurons and their networks, even at the initial information processing stage.

In Chap. 2 we provided a short introduction to the theory and practice of wavelet analysis. Let us now apply this knowledge to several problems in which wavelets can offer information about the dynamics of neuronal systems that would be inaccessible to ordinary frequency or time domain methods.

In general, these problems can be separated into groups depending on the chosen mathematical approach, i.e., either the continuous or the discrete wavelet transform.

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However, as already mentioned, both approaches can provide useful information about the object under study, although this information may differ. Therefore, a better choice is to separate tasks according to the subject of research. In our case it is reasonable to sort out problems according to the spatial scale and complexity of the analyzed signals. In this chapter we deal with single neuron recordings, i.e., signals recorded from one neuron, even if it is a part of a network. We also consider different types of recording: in studies of intracellular dynamics we analyze continuous signals (data from interference microscopy), whereas for the investigation of information processing we use spike trains (point processes) extracted from extracellular single unit recordings.

### 3.2 Wavelet Analysis of Intracellular Dynamics

At the single neuron level, cell activity includes a large number of biochemical processes that occur on different time scales in the membrane and in the cell cytoplasma. Traditional experimental approaches such as, e.g., fluorescent microscopy, intracellular recordings of the membrane potential, and patch-clamping provide ways to analyze features of biochemical, metabolic, and electrical processes. Often, however, they are highly invasive and may have a significant impact on the intracellular dynamics.

Since intracellular dynamics can be extremely rich and manifests itself on different time scales, the wavelet approach is very useful. It can provide information about the interplay between different processes and help to achieve a deeper understanding of intracellular regulatory mechanisms. In this section we discuss a study of intracellular dynamics using interference microscopy and wavelet-based techniques.

### 3.2.1 Interference Microscopy and Subcellular Dynamics

Interference microscopy measures the optical path difference between the beam transmitted through an object and a reference beam [3, 4]. The resulting value is normalized to the wavelength to estimate the so-called phase height of the object, which is given by

$$\Phi = \frac{\phi_0 - \phi_{\text{obj}}}{2\pi} \frac{\lambda}{2} - \Phi_0, \qquad (3.1)$$

where  $\phi_0$  is the initial phase,  $\phi_{obj}$  is the phase shift that occurs after the laser beam is transmitted through the analyzed object,  $\lambda$  is the laser wavelength, and  $\Phi_0$  is a constant shift of the phase height depending on the selected reference point.

For inhomogeneous objects characterized by a refractive index that varies along the vertical direction z, the phase height is estimated as



Fig. 3.1 Isolated pond snail neuron. a Optical photograph of the neuron. b Phase height landscape of the same neuron obtained by interference microscopy (wavelength  $\lambda = 532 \text{ nm}$ ). Bars in the x and y directions correspond to 10  $\mu$ m, and the bar in the z direction corresponds to a phase height of 200 nm (for details, see [5])

$$\Phi(x, y) = \int_0^Z \left[ n_{\rm obj}(x, y, z) - n_{\rm s} \right] dz - \Phi_0, \qquad (3.2)$$

where  $n_s$  is the constant refractive index of the physiological saline and  $n_{obj}(x, y, z)$  is the refractive index of the cell at a point (x, y, z) placed at the distance z from the mirror. The integration limit Z is selected to be above the whole object.

By scanning a cell in the horizontal (x, y) plane, the interference microscope measures the phase height landscape  $\Phi(x, y)$ . Figure 3.1 shows side-by-side an example of an optical photograph and a phase height landscape of an isolated pond snail neuron. Movements of, e.g., organelles in the cell change  $n_{obj}(x, y, z)$ , and hence the phase height in the corresponding place. By scanning a cell many times with constant time interval, we can obtain frames as in a movie. The resulting dynamics of the phase height  $\Phi(x, y, t)$  can then be used to monitor different intracellular processes.

Here we consider results obtained from experiments performed with isolated neurons from the buccal ganglia of the pond snail *L. stagnalis*. We measured the phase height at a single point (x, y) inside the cell. Figure 3.2a shows the power spectrum of such a signal. It exhibits a number of characteristic frequencies near 0.1, 0.3, 0.6, 1.2, and 3.0 Hz. These rhythms are caused by movements of protein macromolecules, changes in ion concentration near the membrane, fluctuations in the membrane potential, etc. Many of these intracellular processes interact with one other.



Fig. 3.2 Analysis of the phase height dynamics reflecting intracellular processes. **a** Energy spectrum exhibiting several peaks. Frequency peaks correspond to different rhythmic components in the intracellular dynamics. **b** Extracted ridges of the wavelet coefficients, obtained after the wavelet transform of the phase height

# 3.2.2 Modulation of High Frequency Oscillation by Low Frequency Processes

To reveal possible interactions between different rhythmic components, we applied the continuous wavelet transform with the Morlet mother function to the phase height signal. Then we identified instantaneous frequencies and amplitudes of rhythmic contributions.

Figure 3.2b illustrates a typical example of the dynamics of instantaneous frequencies. Rhythmic components in the range from 0.1 to 0.3 Hz have almost constant frequency, while instantaneous frequencies of rhythms near 1 and 3 Hz show slow oscillations [5, 6]. Thus, the processes characterized by long time scales modulate high-frequency oscillations of the phase height. This type of modulation is a known phenomenon in living systems. As an example, we can mention the modulation of the heart rate by breathing. The duration of beat-to-beat intervals varies at different stages of the breathing process.

There exist several types of low frequency modulation of a high-frequency process. During modulation, the amplitude A(t) and/or the frequency  $\omega(t)$  of a fast oscillation x(t) can vary with the frequency of a slow process z(t).

In the case of so-called amplitude modulation (AM), we can write

$$A(t) = A_0 + \Delta A_z(t), \qquad (3.3)$$

where  $A_0$  is the base-line amplitude of the fast oscillation and  $\Delta A$  is the maximal deviation of the amplitude (for convenience, we assume that  $|z(t)| \le 1$ ). A single-tone modulated signal (with single frequency  $\omega_0$ ) is given by

$$x(t) = A(t)\cos(\omega_0 t + \varphi_0) = A_0 [1 + m_a z(t)]\cos(\omega_0 t + \varphi_0), \qquad (3.4)$$

where  $m_a = \Delta A/A_0$  is called the amplitude modulation index or the modulation depth, and  $\varphi_0$  is the initial phase. The modulation depth is a bounded constant with  $m_a \in [0, 1]$ . If  $m_a = 0$ , then no modulation exists, whereas  $m_a = 1$  corresponds to maximal modulation.

Frequency modulation (FM) is another type of modulation. In this case the instantaneous frequency of the signal x(t) can be written as

$$\omega(t) = \omega_0 + \Delta \omega z(t) \tag{3.5}$$

where  $\omega_0$  is the base frequency and  $\Delta \omega$  is the maximal deviation of the frequency. Then an FM signal can be written as

$$x(t) = A_0 \cos\left[\Psi(t) + \varphi_0\right], \qquad \Psi(t) = \int_0^t \omega(s) \mathrm{d}s, \tag{3.6}$$

or using (3.5),

$$x(t) = A_0 \cos\left[\omega_0 t + \varphi_0 + \Delta \omega \int_0^t z(s) ds\right].$$
(3.7)

In the case of a single-tone FM-signal  $z(t) = \cos(\Omega t + \Phi_0)$  and therefore

$$x(t) = A_0 \cos\left[\omega_0 t + \varphi_0 + m_f \sin(\Omega t + \Phi_0)\right], \qquad (3.8)$$

where  $m_f = \Delta \omega / \Omega$  is the frequency modulation index, which characterizes the depth of modulation of the FM signal, which can take values exceeding 1.

In terms of modulation, slowly varying frequency ridges shown in Fig. 3.2b can be classified as FM processes.

### 3.2.3 Double Wavelet Transform and Analysis of Modulation

The nonstationary dynamics which is frequently observed in living systems always has multi-tone oscillations. Then the equations describing modulated processes become complicated and the values used to compute modulation indexes become time-dependent. To describe such phenomena and their structure, a double wavelet transform has been proposed [7].

First, we apply an ordinary wavelet transform to the analyzed signal. Then the second wavelet transform is applied to signals constructed from instantaneous frequencies (or amplitudes) of modulated rhythmic processes. Again, as in the first wavelet transform, CWT coefficients are estimated and the ridges of the wavelet energy are identified. Since the wavelet transform is applied twice, this method has been called the double-wavelet analysis [7]. A similar idea called the *secondary wavelet transform* has been proposed independently by Addison and Watson [8, 9].



**Fig. 3.3** Double wavelet analysis of the phase height dynamics of single cells. **a** Frequency modulation of 1 and 2–4 Hz rhythmic components by slow processes. Modulation depth vs frequency of the slow process. **b** The same as in (**a**), but for amplitude modulation. **c** Typical normalized spectra of the modulation processes

This approach allows one to obtain a time series for such characteristics as the amplitude (or frequency) deviation, time-varying modulation indexes, and local spectra of modulation [10].

In addition to the FM process shown in Fig. 3.2b, analysis of the phase height dynamics can reveal modulation of the amplitude of high-frequency oscillations by slower dynamics. To obtain statistical information about features of AM and FM phenomena in the dynamics of intracellular processes, we repeated the above described experiments 200 times [5]. Then for each measurement we estimated the modulation frequencies and modulation indexes (modulation depths) using the double-wavelet technique.

Figure 3.3a and b illustrate the distributions of the modulation indexes for FM and AM, respectively. In the FM case, there is clear difference between the two rhythms. The modulation depth is higher for the 2–4 Hz oscillation. In the AM case the 2–4 Hz rhythm generally has a higher modulation frequency. Figure 3.3c shows a typical example of the power spectra of the modulation processes for each rhythm. Thus, the rhythmic components near 1 and 3 Hz are modulated by different intracellular processes. The rhythm near 1 Hz is mainly modulated by a process with ultralow

frequency around 0.1 Hz, while the 3 Hz rhythm is modulated by a higher-frequency dynamics.

In conclusion, the double wavelet analysis revealed the presence of an interaction between slow and fast rhythmic intracellular processes. This interaction occurs in the form of modulation. We associate low-frequency dynamics with processes occurring in the plasma membrane, while high-frequency processes are associated with cytoplasmic events. Evidence for such an assumption is discussed in [11]. Thus, low-frequency oscillations are significantly more pronounced in the membrane region than in the centre of neurons, while the 20–25 Hz rhythms display the opposite behaviour [6]. Moreover, independent experiments on the same type of neurons demonstrated the existence of rhythmic dynamics. In particular, it has been established [12] that frequencies in the range of 0.2–0.4 Hz depend on the activity of  $Ca^{2+}$  channels. It has also been found [13] that neurons in invertebrates possess intrinsic electrical activity with frequencies 1 and 1.5–3 Hz. The suggestion about the origin of high frequencies (20–25 Hz) from cytoplasm processes accords with experimental data on vesicle movements in neurons (8–40 Hz) obtained by light-scattering measurements [14].

The double-wavelet approach allows a better understanding of neuron functions and features of intracellular dynamics, both under normal conditions and under different external influences. This approach provides quantitative measures characterizing the interplay among intracellular processes and allows one to diagnose changes in this interplay when there are external stimuli (see, e.g., [6]).

# 3.2.4 Modulation of Spike Trains by Intrinsic Neuron Dynamics

Neurons encode and exchange information in the form of spike trains. Figure 3.4a shows a typical example of the extracellular potential recorded in the vicinity of a projecting neuron in the gracilis nucleus. The trace has a number of spikes (short pulses) that are clearly distinguishable over the background activity. In Chap. 4, we will discuss the problem of spike identification and sorting in more detail. Here we just cross-check that all spikes belong to the same cell. This can be done by superposing spikes (Fig. 3.4b). We can verify that all of them have a similar shape and hence can be classified as emitted by only one neuron.

The first part of the recording corresponds to spontaneous neuron dynamics (no external stimulation), while the second represents the neuron response to stimuli (a slight pricking of the rat foreleg with frequency of 1 Hz). We observe that the stimulation drastically changes the firing rate of the neuron. Moreover, the structure of neural firing shows some signs of modulation. The analysis of modulation phenomena discussed in Sect. 3.2.3 can also be applied to this spike train. In general, this approach can lead to a deeper understanding of the information encoding used by neurons.



**Fig. 3.4** Experimental recording of spiking activity in a single neuron. **a** Extracellular potential with spikes generated by only one projecting neuron in the gracilis nucleus of a rat. The *arrow* marks the beginning of external (tactile) stimulus. **b** Superposed spikes exhibit the same shape, which confirms that they belong to the same neuron

The structure of interspike intervals without external stimulation is quite irregular, whereas under stimulation a well pronounced rhythm appears at the frequency of the external stimulation (Fig. 3.5a, b). To reveal the time dynamics of different rhythms in the spike train, we apply the wavelet transform (with the Morlet mother wavelet) to interspike intervals. The spontaneous neuron dynamics exhibits several rhythms. The two most powerful of these correspond to 8 and 20 s interspike intervals (Fig. 3.5a, c, peaks at 0.05 and 0.125 Hz). Under stimulation, a clear peak appears in the power spectrum at the driving frequency of 1 Hz and the ultralow frequency (0.05 Hz) disappears. However, the low-frequency dynamics observed under spontaneous conditions remains in the spectrum (Fig. 3.5b).

Figure 3.5c, d show the time–frequency spectrograms. Under control conditions (spontaneous firing), there are several rhythms whose frequencies "float" around certain mean values. The sensory stimulus excites a new oscillation at 1 Hz, which again shows some oscillations. Thus, the neuron has some intrinsic dynamics even under stimulation. This provides evidence for a nonlinear interaction between the rhythmic components in neuron dynamics and raises an open question: Is it possible to describe the process of information encoding in terms of frequency modulation?

Indeed, one possible interpretation of the oscillation observed in the main 1 Hz rhythm (Fig. 3.5d) can be given in terms of frequency modulation. The idea is that the intrinsic slow dynamics of the neuron modulates the stimulus driven frequency. Therefore, information encoding by this neuron is not trivial, but includes additional features describing the neuronal state, feedbacks, and even some temporal history of oscillations. On the basis of this hypothesis, modulation features such as the central frequency, depth index, etc., can be estimated using the double-wavelet technique (Sect. 3.2.3).

The instantaneous external frequency 1 Hz is considered as a new signal for the CWT. As a result, all rhythms occurring in the modulation will be revealed and the depth of modulation can be estimated separately for each rhythm. Figure 3.6



**Fig. 3.5** Analysis of interspike intervals in the neuronal spike train shown in Fig. 3.4. **a** and **b** Power spectra under spontaneous conditions and under stimulation, respectively. **c** and **d** Time–frequency dynamics of wavelet ridges under spontaneous conditions and under stimulation, respectively



shows that the structure of low-frequency modulating signals is quite similar to the spontaneous dynamics of the neuron. This indirectly confirms the hypothesis. However, physiological interpretation of the observed phenomena and direct ways of testing the hypothesis require more detailed analysis.

### 3.3 Information Encoding by Individual Neurons

In Sect. 3.2.4, we saw that neurons can encode sensory stimuli in a rather complex way. Besides extrinsic stimuli, some intrinsic neuronal dynamics enters the output spike train transmitted to further relay stations of the central nervous system. Let us now consider information encoding in more detail.

### 3.3.1 Vibrissae Somatosensory Pathway

The rodent vibrissae system is one of the most widely used experimental models for the study of sensory information handling. The rat perceives the main information by means of the vibrissal pad or "whiskers" (Fig. 3.7a). This is a highly specialized and sensitive piece of apparatus that conveys tactile signals via the trigeminal system to the animal's brain (Fig. 3.7b) [15].

The four longest vibrissae, called straddlers, are labeled by the letters  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ . The other vibrissae are placed on the upper lip in five rows labeled by letters A, B, C, D, and E. In each row, the vibrissae are numbered, e.g.,  $A_1$ ,  $A_2$ , etc. The length of the vibrissae varies from 30–50 to 4–5 mm, thus providing simultaneous contact of their tips with a tangible surface of an object during whisker movements. The different lengths and widths of wibrissae provide them with different oscillatory features. This allows them to cover the wide range of frequencies required for effective perception of objects with different tactile characteristics.

Rats actively use their whiskers to detect and localize objects, and also to discriminate surface textures. By sweeping the whiskers at rates between 5–20 Hz, they can localize and identify objects within a few whisking cycles or even with a single vibrissa [16]. Thus relatively short temporal, but not spatial mechanical information, dominates in the object detection.

Mechanical encoding of different textures is attributed to the whisker resonance. The vibration amplitude across the whisker array codifies the texture (see, e.g., [17]). It occurs also in awake rats and shapes natural whisker vibration. However, it seems that textures are not encoded by the differential resonance. Instead, slip-stick events contribute to a kinetic signature for texture in the whisker system, which suggests the presence of temporal structure in neural spike trains under these experimental conditions [18]. Thus the efficacy of the sensory information transmission and processing in the time domain resides in the possibility for multiple cells to generate coherent responses to a stimulus, which constitutes the neural code.

Although there has been much discussion about what type of neural code is employed by each individual neuron or neuron group, growing experimental evidence shows that the same neuron may use different coding schemes (see reviews in [19, 20]). The temporal correlation of multiple cell discharges has also been found important for information transmission to the cortex and its modulation by corticofugal feedback (see, e.g., [21–23]).



Fig. 3.7 Rat vibrissae system. **a** Illustration of vibrissae and their labeling. **b** Sketch of the main steps in the pathway of tactile information processing

Somatosensory information from the whiskers arrives at the trigeminal complex, organized into one motor and three sensory nuclei, including the principal nucleus or principalis (Pr5), the spinal nucleus (Sp5), and the mesencephalic nucleus (Fig. 3.7b). In turn, Sp5 consists of three subnuclei called oralis (Sp5o), interpolaris (Sp5i), and caudalis (Sp5c). Information from Pr5 and Sp5 goes to the contralateral thalamus (VPm) and then to the primary somatosensory (SI) cortex. There is also a feedback monosynaptic projection with an extremely precise somatotopy from SI to the trigeminal nuclei.

Over the whole pathway, primary afferents and neurons form spatial structures called barrelettes, berreloids, and barrels in the trigeminal complex, VPm, and SI, respectively. These spatial structures replicate the patterned arrangement of the whisker follicles on the snout (for details see, e.g., [24–27]).

### 3.3.2 Classification of Neurons by Firing Patterns

In electrophysiological studies, the classification of neurons according to their firing patterns for spontaneous activity and under stimulation is widely accepted. Neurons can be divided into three groups according to their mean firing rate (MFR) under spontaneous conditions: silent neurons (SN) with MFR < 0.1 spikes/s, low-frequency (LF) neurons with 0.1 < MFR < 1.5 spikes/s, and high-frequency (HF) neurons with MFR > 1.5 spikes/s.

For tactile whisker stimulation, short air puffs directed toward a single vibrissa are usually used. This kind of stimulation produces vibrations of the individual whisker similar to real behavioral conditions. In experiments, the duration of air puffs can be varied. We used three values: short 10 ms, intermediate 50 ms, and long 100 ms pulses. Trigeminal neurons fired from 1 to 8 spikes in response to each onset of tactile stimulation of 10 and 50 ms duration. For the long (100 ms) stimulus, some of the neurons produced from 20 to 40 spikes.

Taking into account the neural responses to the 100 ms stimuli, we can classify all neurons into tonic and phasic [28]. Figure 3.8 shows an example of each neuronal type. Phasic neurons (PhN) generate a few spikes under a change of stimulus phase, i.e., at the beginning and/or the end of the stimulus (Fig. 3.8a, c). Tonic neurons (TN) produce large spike trains lasting for the whole stimulation period (Fig. 3.8b, d).

According to the standard electrophysiological analysis, the three nuclei have a quite different percentage of SN, LF, and HF cells (Fig. 3.9a). There is also some



**Fig. 3.8** Classification of neurons into phasic and tonic types, according to their response to a long stimulus. **a** Typical response of a phasic neuron to a single stimulus. The extracellular potential recorded in the trigeminal nucleus is shown. The *upper bar* corresponds to the duration of the stimulus. **c** Peristimulus histogram of a phasic neuron made over 50 identical stimuli (2 ms bin). **b** and **d** The same as in (**a**) and (**c**), but for a tonic neuron



**Fig. 3.9** Statistical properties of neurons in Pr5, Sp5i, and Sp5o trigeminal nuclei. **a** Distribution of neurons according to spontaneous activity: SN silent, LF low frequency, and HF high-frequency neurons. **b** Mean spiking frequencies of S, LF, and HF cells. **c** Distribution of neurons according to the type of response to whisker stimulation: TN tonic and PhN phasic neurons. **d** Mean spiking frequencies for entire population, phasic, and tonic neurons

deviation in the mean firing frequencies among the nuclei (Fig. 3.9b). Thus there is a difference in the spontaneous neural activity among the nuclei.

The three nuclei have similar percentages of tonic and phasic cells (Fig. 3.9c), and hence no conclusions about dissimilarities among them can be drawn solely on the basis of the type of response to stimulation.

Nevertheless, the Sp5i nucleus appears to be different from the Pr5 and Sp5o, which in turn have some degree of similarity. Indeed, analysis of the firing rate reveals:

- Similarly low spiking frequency among neurons from Pr5 and Sp50 compared with Sp5i neurons for all (S, LF, and HF) groups (Fig. 3.9b).
- Ph cells from Pr5 and Sp50 nuclei have 2–3 times lower frequency than those from Sp5i (Fig. 3.9d). The opposite behavior is observed for T neurons.

# 3.3.3 Drawbacks of the Traditional Approach to Information Processing

In Fig. 1.1, we already gave an example of the firing dynamics of a Pr5 neuron under periodic stimulation of a vibrissa in its receptive field. Even under the condition of a completely repeatable stimulus, the neuronal response is far from being constant. During the first few seconds, the neuron exhibits a maximal firing rate (about 27 spikes/s), but the rate then quickly falls to about 10 spikes/s, and further fluctuates for more than 20 s. The neuron behavior is thus essentially nonstationary.

However, most traditional approaches, such as peristimulus histograms, ignore this observation.

Traditional analysis of neural spike trains has often been performed assuming that segments of the experimental time series are approximately stationary and that such segments can be studied by means of statistical techniques such as correlation measures or Fourier analysis (see, e.g., [29-31]). This approach is obviously useful if the nonstationarity has a time scale longer than the rhythms of interest. However, this is not always the case. Instantaneous frequencies of various rhythmic components can exhibit complex irregular fluctuations, that is, the nonstationarity may be associated with higher frequencies as well. Previous results [21] have shown that Fourier analysis is hardly applicable in such conditions. An alternative is to use the wavelet technique, which can be successfully applied to analyze the temporal structure of neuronal spiking over a wide range of time scales [10, 21].

### 3.3.4 Wavelet Transform of Spike Trains

For information processing it is reasonable to assume that neurons produce and exchange stereotypical events or spikes. Thus, only the timings of the spike occurrences carry a message. Consequently, before applying any analysis, spikes in experimental data should be identified and sorted among different neurons. This procedure will be discussed in detail in Chap. 4. Here we assume that this problem has already been solved.

Figure 3.10a illustrates a typical example of a high-pass filtered extracellular recording ( $f_{cut} = 300 \text{ Hz}$ ) made in a Pr5 nucleus. Four spikes coming from a single cell can be seen by the naked eye. However, in more complex situations, advanced spike sorting techniques must be used, including those based on the wavelet transform. The results of data preprocessing given in this section are based on the wavelet shape-accounting classifier (WSAC) (see Sect. 4.4).

Once spikes of a single cell have been identified, they can be represented as a series of  $\delta$ -functions,viz.,

$$n(t) = \sum \delta(t - t_i), \qquad (3.9)$$

where  $\{t_i\}$  is a set of time instants corresponding to spike firing (Fig. 3.10a). Then we can apply the continuous wavelet transform to the signal (3.9).

Let us consider the CWT with the Morlet function. The timescale *s* plays the role of the period of the rhythmic component. Given a characteristic timescale (e.g., the period) *s*, the resolution of the wavelet in the time and frequency domains is given by

$$\delta t = ck_0 s, \qquad \delta \omega = \frac{c}{k_0 s},$$
(3.10)

where *c* is a constant of the order of unity. There is a trade-off between the frequency and time resolutions: small values of  $k_0$  provide better time resolution, whereas large



(c) Time evolution of spectral ridges

**Fig. 3.10** Wavelet analysis of a spike train. **a** Conversion of extracellular recording into a spike train n(t). **b** Energy density E(f, t) of the spike train (*color from blue to red* corresponds to the spectrum magnitude). The *dashed black curve* defines the cone of influence where edge effects cannot be neglected. **c** Time evolution of spectral "ridges"  $F_k(t)$ . The *thick curve* corresponds to the main (most prominent and stable) ridge, whose central frequency oscillates in time at around 20 Hz

values of  $k_0$  improve frequency resolution. The commonly adopted value is  $k_0 = 1$  and the limit  $k_0 \to \infty$  corresponds to the Fourier transform. Sometimes, especially for the analysis of spike trains,  $k_0 = 2$  can be more suitable.

Equation (3.9) allows us to estimate the wavelet coefficients analytically:

$$W(s, t_0) = \frac{1}{\sqrt{s}} \sum_{i} e^{-i2\pi (t_i - t_0)/s} e^{-(t_i - t_0)^2/2k_0^2 s^2}.$$
 (3.11)

Using the wavelet transform (3.11), we can perform the time–frequency analysis of rhythmic components hidden in the spike train. The wavelet coefficients can be considered as a parameterized function  $W_p(t_0)$ , where  $t_0$  plays the role of time. It is convenient to introduce the following normalization of the energy density:

$$E(s, t_0) = \frac{1}{\sqrt{\pi} r k_0 s} |W(s, t_0)|^2, \qquad (3.12)$$

where *r* is the mean firing rate (the normalization of the energy spectrum per spike simplifies comparison of neurons with different firing rates). For biophysical convenience, instead of (3.12), its frequency counterpart E(f, t) is often considered. This is obtained by substituting s = 1/f ( $k_0 = 1$ ).

E(f, t) represents a surface in 3D space whose sections at fixed times provide information about the local energy spectra. Figure 3.10b is a 2D plot of the energy density of the spike train shown in Fig. 3.10a. Each spike produces a broad frequency spectrum. The existence of rhythms in the spike train leads to the appearance of "ridges" in the 3D energy surface, associated with the rhythmic contributions. These ridges, oriented along the time axis, identify the spectral content of the spike train at any given time moment.

Thus the dynamics of rhythmic components hidden in a spike train is reflected in the time evolution of spectral ridges. To construct spectral ridges, a search for local maxima of the energy spectrum  $E(f, t^0)$  at time  $t^0$  is performed (Fig. 3.10a), thus obtaining a set of 2D functions of time  $F_k(t)$ , where the subindex corresponds to the number of the ridge (Fig. 3.10c).

Spectral ridges can appear and disappear in time, and they can also oscillate (Fig. 3.10c). Oscillations indicate the presence of a given rhythm in the spiking dynamics of a neuron and its modulation by other rhythms (e.g., due to a high frequency jitter in the spike timings). If a neuron generates a stereotypic response to periodic stimulation (i.e., the same pattern for each stimulus event), then its instantaneous frequency associated with the stimulus rhythm remains constant. We thus obtain a "perfect" (continuous and straight) spectral ridge at the stimulus frequency.

Deviation from the stereotypic response associated with "missing" or "extra" spikes, or with changes in the interspike intervals, causes temporal variations in the instantaneous frequency and even disappearance of the ridge, as happens in Fig. 3.10c. Moreover, the greater the fluctuation of the instantaneous frequency, the more significant the differences in the neuronal response. Thus, following the time evolution of the instantaneous frequency of spectral peaks (i.e., the spectral ridge) enables one to study the stability and stationarity of neuronal responses to a tonic stimulus.

To quantify the stability of the neuronal response, the following measure can be considered:

$$St = \frac{1}{\sigma_0},$$
(3.13)

where  $\sigma_0$  is the standard deviation of the time evolution of the main spectral ridge  $F_0(t)$  found in the vicinity of the stimulus frequency.

To evaluate St for a spike train, its energy density (3.12) is estimated. Then for a fixed time  $t^0$  (changed with a 5 ms time bin), we search for the energy maximum in the frequency range  $f_{stim} \pm 5\%$ . The resulting frequency is assigned as  $F_0(t^0)$ . Finally, the standard deviation of  $F_0$  yields St.

### 3.3.5 Dynamical Stability of the Neuronal Response

In this section we test the methodology proposed in Sect. 3.3.4 on simulated neuronal responses to external stimuli. To do so, we consider three neurons embedded in a network and receiving the same periodic (1 Hz) sequence of 50 stimuli. Depending on the current network state and its dynamics, the neuronal responses may have different variability, i.e., the firing patterns provoked by each stimulus event may have different degrees of repeatability.

We simulated neuronal responses under three different conditions:

- N1: Constant in time strong variability. The neuron responds to each stimulus by generating 3–5 phasic spikes  $(3.9 \pm 1.2 \text{ std})$  with fluctuating spike timings (8 ms std).
- N2: Changing (small) variability. The neuron generates a spike train similar to N1, but the firing rate decays linearly (from 5 spikes per stimulus at the beginning to about 2.5 at the end).
- N3: Increasing (intermediate) variability. The spike train is similar to N2, but the fluctuation in spike timings increases from 0 at the beginning to about 40 ms std at the end.

The response pattern of the first neuron has a stationary distribution, whereas those of the second and third neurons are similar to the experimentally observed adaptability to the stimulus (Fig. 1.1). Their firing rates decay in time. The difference between the neurons N2 and N3 is in the variability of the spike timings. The neuron N2 has constant fluctuations, whereas the magnitude of the fluctuations for N3 increases with time.

Figure 3.11a shows a 5 s epoch of the stimulus and spike trains of the three neurons. Applying the traditional peristimulus time interval analysis, we obtain roughly the same peristimulus time histograms (PSTHs). All histograms have three peaks at latencies 20, 50, and 90 ms, corresponding to the neuronal phasic response to the stimulus, and are hardly distinguishable. Thus, PSTH fails to quantify the differences in behavior exhibited by the neurons, as expected. Not much additional information is provided by the raster plot (not shown).

The wavelet energy spectrum of the first spike train differs significantly from the spectra of N2 and N3, which are very similar (Fig. 3.11b). Fluctuations in the spectral magnitude of the 1 Hz rhythm reflect changes in the strength of the neuronal response at that frequency. Loosely speaking, it is proportional to the number of spikes generated per stimulus. The spectral magnitude of the train N1 fluctuates around the mean value, which agrees with the stationary nature of the firing patterns of this neuron. The energy magnitude of N2 and N3 decays in time, again as expected from the decaying firing rate of these neurons.

Figure 3.12a shows the time evolution of the main spectral ridges  $F_0(t)$  (corresponding to  $f_{\text{stim}} = 1 \text{ Hz}$ ) for the three neurons. This provides information about the phase (temporal) relationships between spikes in the firing patterns and reveals differences in the three cases. The instantaneous frequency of N1 displays large



**Fig. 3.11** Quantification of the dynamical stability of the stimulus response patterns for three neurons. **a** Stimulus and spike trains of three neurons (only 5 s epoch is shown). The three neurons have almost the same PSTHs, but their firing dynamics is significantly different (see the main text). **b** Wavelet energy spectra of the spike trains in the stimulus frequency band (*color from blue to red* corresponds to the spectrum magnitude)

stationary deviations from 1 Hz due to the constant variability of spike timings and "missing" spikes. The ridge of N2 has smaller deviations, especially in the first half of the recording, where the neuronal response was more consistent (in the number of generated spikes). N3 shows the smallest ridge variability (close to zero by construction) at the beginning of the stimulation, but growing progressively toward the end. The difference with N2 is explained by the temporally increasing variability of the N3 spike timings.

It is noteworthy that the time evolution of the spectral magnitude (Fig. 3.11b) and the ridge dynamics (Fig. 3.12a) provides complementary information about the firing



**Fig. 3.12** Quantification of the dynamical stability of the stimulus response patterns for three neurons. **a** Time evolution of the main spectral ridges for the three spike trains. *Shaded areas* correspond to the envelopes of  $F_0(t)$  (obtained by the Hilbert transform). **b** Different response stability measures. *Left*: Reciprocal of the standard deviation of the number of spikes. *Center*: Reciprocal of the standard deviation of the energy density at 1 Hz. *Right*: Dynamical stability factor S. The latter characteristic reveals distinctions in the stimulus responses of the neurons

patterns. Indeed, a strong neuronal response with a similar number of spikes produces a quite stable, high magnitude spectral ridge. If the variability of spike timings is much lower than the reciprocal of the ridge frequency (interstimulus intervals), then it makes little contribution to the ridge height. However, this high-frequency dynamics will affect the instantaneous ridge frequency and, consequently, will be visible in the  $F_0(t)$  plot.

Let us now check the different measures of the response stability of the neurons N1–N3 that can be derived from the spike trains and their wavelet analysis. First, the standard deviations of the number of spikes elicited by each stimulus were calculated. Similar characteristics have been used for quantification of the frequency-dependent response in VPm and SI neurons [32]. Figure 3.12b (left inset) shows that the reciprocal of the standard deviation (i.e., 1/std number of spikes) is the same for all neurons, whence this measure cannot distinguish dynamical differences in their responses.

Figure 3.12b (middle inset) shows the reciprocal of the standard deviation of the magnitude of the energy density (corresponding to Fig. 3.11b) at the stimulus frequency. This measure differentiates the responses of N1 from those of N2 and N3. The lower value for N2 and N3 is mostly due to the trend in the energy magnitude in these cases. Detrending the energy density functions raises the measure to 74 for N2 and N3 and does not affect its value for N1. Thus the energy magnitude-based
measure can be a good predictor of a neural rate code, but it cannot pick up the variability in the spike timings.

Finally, Fig. 3.12b (right inset) shows the dynamical stability measure (3.13) evaluated for the three neurons. This measure correctly quantifies the differences in stability of the firing patterns among all three neurons.

# 3.3.6 Stimulus Responses of Trigeminal Neurons

The examples described in this section are based on experiments performed on anesthetized (urethane, 1.5 g/kg) Wistar rats of either sex weighing 200–250 g. The experimental procedure is similar to that described in the work by Moreno et al. [33]. Animals were placed in a stereotaxic device that allowed easy access to the vibrissae. Recordings were obtained using tungsten microelectrodes directed vertically into the Pr5, Sp5i, and Sp5o nuclei.

Once an electrode had been put in place, the vibrissae were manually stimulated by means of a thin brush to determine their receptive fields. The vibrissa maximally activating a neuron near the electrode was further used for mechanical stimulation. Free whisker movements were generated by air puffs directed at one vibrissa only and signals were not recorded when other vibrissae exhibited any vibration. Air pulses were generated by a pneumatic pressure pump (Picospritzer III, Parker Inst. TX) and delivered via a silicon tube of diameter 0.5 mm, positioned at 10–12 mm perpendicularly to the vibrissa:

- Stimulus protocol S1: Three separate sequences of 50 air puffs lasting 10, 50, or 100 ms each with 1 s interpuff intervals were delivered at the neuron's receptive fields.
- Stimulus protocol S2: Air puffs of fixed duration (10 ms), but with different stimulation frequency, ranging from 1 to 30 Hz, were delivered at the neuron's receptive fields. During the course of individual experiments, the frequency was randomly changed. The whole duration of stimulation at a given frequency was 50 s.

The extracellular potential was amplified, sampled at 20 kHz, passed through the band-pass filter (0.3–3.0 kHz), and then analyzed using the special software Spike 2 and custom packages written in Matlab. For the wavelet analysis, we selected only those neurons whose extracellularly recorded spikes were well isolated from the activity of the other neurons.

#### **3.3.6.1** Effect of Stimulus Duration (Protocol S1)

The stability parameter St was calculated for all selected neurons and the three stimulus durations. In addition, we determined the stimulus duration (10, 50, or 100 ms) that provides the maximally stable response pattern for each neuron. To describe quantitative changes in the stability parameter when the stimulus duration



**Fig. 3.13** Population analysis of the dynamical stability of the neuronal response patterns under variation of the air puff duration (stimulus protocol S1). **a** Percentage of cells showing maximal stability for 10, 50, or 100 ms stimuli. Neurons from Pr5 and Sp5i "prefer" 50 ms, whereas Sp5o shows better stability for shorter (10 ms) stimuli. **b** Percentage of neurons showing an increase (*left*) or decrease (*right*) in the response stability under increasing stimulus duration

**Table 3.1** Comparative analysis of the stability of neural response patterns evoked by tactile whisker stimulation by air puffs of different duration (10, 50, and 100 ms) for neurons from Pr5, Sp5i, and Sp5o nuclei

	Maximal S (%)			Increase in S	Decrease in S
				(%)	(%)
	10 ms	50 ms	100 ms	$(S_{50} > S_{10})$	$(S_{50} > S_{100})$
Pr5	20	53	27	73	73
Sp5i	8	67	25	92	75
Sp5o	50	17	33	33	67

increases  $(10 \rightarrow 50 \rightarrow 100 \text{ ms})$ , the neurons satisfying the conditions  $St_{50} > St_{10}$ and  $St_{50} < St_{100}$  were counted. Figure 3.13 and Table 3.1 summarize the results.

In the case of Pr5 neurons, the stability parameter St is likely to be maximal for the middle stimulus duration (50 ms, Fig. 3.13a). The most stable response is observed for 53% of all cells with the 50 ms stimulus. The remaining 27 and 20% of cells respond stably to 100 and 10 ms stimuli, respectively.

Quite similar behavior occurs for Sp5i neurons. Here even more cells (67%) "prefer" stimuli of intermediate duration. This is achieved mostly by decreasing the cell population showing a better response to the shortest 10 ms stimuli (8%).

Sp5o neurons typically behave differently. The maximally stable response pattern for 50 ms stimulation was observed for only 17% of the cells. Meanwhile, half of the neurons showed better stability for the shortest stimulation (10 ms). The proportion

of the cells with better response to the 100 ms stimuli was about 33%, a little bit higher than for Pr5 and Sp5i neurons.

Figure 3.13b shows differential stability characteristics. For 73% of Pr5 neurons, responses to 50 ms stimulation are more stable than those to air puffs of 10 ms duration. In the case of Sp5i neurons, the value of St increases at the transition  $10 \rightarrow 50$  ms for about 92% of cells. Thus, Pr5 and Sp5i neurons are characterized by a rather similar type of reaction to variation of the stimulus duration. However, different behavior is observed for Sp5o neurons. Only for 33% of cells did St increase with the stimulus duration (from 10 to 50 ms). If the stimulus duration increases further (50  $\rightarrow$  100 ms), about 70% of neurons from all nuclei display a decrease in their response stability.

Thus the protocol S1 allowed us to conclude that:

- The stability of response patterns depends on the stimulus duration, that is, neurons process stimuli of different duration in different ways.
- There exist significant changes in the types of responses for Pr5, Sp5i, and Sp5o neurons. The most reliable responses are achieved in Pr5 and Sp5i for 50 ms stimulus and in Sp5o for 10 ms.

#### 3.3.6.2 Effect of Stimulus Frequency (Protocol S2)

Let us now discuss effects of the stimulation frequency (protocol S2). It has been found that all trigeminal neurons can be subdivided into three groups by their type of response to the frequency content of the stimulus. Figure 3.14 shows the stability measure as a function of the stimulus frequency  $St(f_{stim})$  for three representative cells. By analogy with the filter terminology, we will refer to the three basic types of neuronal response as low-pass, band-pass, and no dependence.

In all nuclei, band-pass is the most frequent cell behavior. It occurs in 58, 59, and 53% of neurons in Pr5, Sp5i, and Sp5o, respectively (Fig. 3.15a). The low-pass reaction is observed for 33, 31, and 35% of neurons from Pr5, Sp5i, and Sp5o, respectively. Finally, 9, 10, and 12% of cells in the corresponding nuclei are characterized



**Fig. 3.14** Three main types of behavior of the dynamical stability of neuronal responses to the frequency of a tonic stimulus  $St(f_{stim})$ : low-pass (**a**), band-pass (**b**), and no dependence (**c**)



**Fig. 3.15** Population analysis of the dynamical stability of neuronal responses under variation of the stimulus frequency (stimulus protocol S2). **a** Percentage of cells showing different "filtering" characteristics in Pr5, Sp5i, and Sp5o nuclei. **b** Mean central frequencies of band-pass neurons

by the no-dependence reaction. Thus, there are small population distinctions in the frequency filtering properties of Pr5, Sp5i, and Sp5o nuclei.

For band-pass type responses, the mean central frequency was determined (mean  $\pm$  s.e.): 5.1  $\pm$  0.9 Hz (Pr5), 5.2  $\pm$  0.8 Hz (Sp5i), and 4.0  $\pm$  1.3 Hz (Sp5o) (Fig. 3.15b). Thus, neurons in Pr5 and Sp5i nuclei have the same central frequency, whereas cells in Sp5o typically show a smaller value of the stabilization frequency.

#### 3.3.6.3 Biophysical Interpretation

For effective stimulus perception, information specific to the object should be invariant to the details of the whisking motion. Therefore, flexibility and adaptability in the processing of the whisker vibrations are required. Experiments in vitro [34] demonstrated that neurons in the barrel cortex do indeed adapt their input-output function, in such a way that the gain rescales, depending on the range of the current stimulus distribution. In this section, it has been shown that in vivo accommodation of firing patterns to stimulus characteristics can be quantified by the stability measure St, which was used to study neuronal responses in the trigeminal nuclei evoked by tactile whisker stimulation.

Analysis of the time evolution of frequency ridges in the wavelet space can be used to identify the variable frequency content in a neural spike train under essentially nonstationary conditions of sensory information processing. The method allows an integral quantification of the variability in the number of phasic spikes and in the spike timings. It takes into account changes at the stimulus time scale and also at significantly shorter time scales. The validity of the method has been cross-checked using simulated spike trains resembling properties of real recordings (Fig. 3.11).

A fundamental issue in neural coding is the role of variation of spike timings in information processing. Indirectly, this can be tested by an artificial jittering of the spike timings and its influence on the derived measures (see, e.g., [35, 36]). The stability measure St can be used to provide a direct answer to the question: how stable or repeatable are the firing patterns produced by a neuron for each stimulation. If the stability measure is high, then the spike patterns are highly repeatable during the whole recording, and consequently, such a neuron is likely to be using a kind of temporal code. Conversely, low stability suggests high variability in the spike patterns and points to a rate code or the presence of a complex dynamics, for example, involving local and global feedback and fast adaptation.

Recent results [35] demonstrate that the trigeminal ganglion neurons use temporal code. Here, using the dynamical stability measure, it has been shown that neurons in Pr5, Sp5i, and Sp5o nuclei can vary their response stability according to the stimulus characteristics, for example, the stimulus duration (Fig. 3.13). Thus the trigeminal neurons adapt their coding scheme to the stimulus characteristics, and there is a continuous oscillation between the two extremes, the temporal and rate codes. This conclusion is indirectly supported by the presence of an extensive network locally connecting neurons in the trigeminal nuclei and the global corticofugal projections, so that the global network dynamics can modify the stimulus-evoked patterns of each individual neuron.

It is known that the frequency of whisker movements plays an important role in effective perception (see, e.g., [37, 38]). Previous results showed the presence of resonance properties in the firing of thalamic and cortical neurons (see the review in [17]). Indeed, the stimulation of a vibrissa at a given frequency can be related to its vibration during perception. Then the surface discrimination requires fine-tuning of the system and a series of impulses deflecting the vibrissa can be considered as a single entity. Therefore, we expect an effective band-pass amplification (or filtration) of the stimuli in a given frequency band by some cells. It was found that more than half (about 57%) of neurons in the trigeminal nuclei have this property. Finally, the remaining 10% of cells have no pronounced dependence on the stimulus frequency, and these neurons probably perform a different task, not directly linked to stimulus codification and transmission. Besides, their stability factors are usually extremely low (e.g., in Fig. 3.14, St<sub>low</sub>  $\approx 500$ , St<sub>band</sub>  $\approx 150$ , whereas St<sub>nodep</sub>  $\approx 18$ ), which also suggests that stimulus processing is not their primary role.

The percentage of neurons showing low-pass, band-pass, and no-dependence behavior is quite similar across different nuclei (Fig. 3.15a). This suggests that the number of neurons specializing in different tasks (e.g., border or texture detection) is also similar in Pr5, Sp5i, and Sp5o nuclei. The mean "optimal" stimulation frequencies of the band-pass neurons is about 5 Hz for Pr5 and Sp5i and about 4 Hz in Sp5o. These frequencies are close to the lower end of the frequency scale for whisker movements in active exploration (4–12 Hz) [39]. These results correlate with studies of the amplitude of averaged neuronal responses in the somatosensory cortex, where similar filtration properties have been found [32]. Thus, we can suppose that

at least some the filtration properties observed for neurons in the somatosensory cortex can be influenced by analogous responses generated by neurons in the trigeminal complex.

# 3.4 Wavelet Coherence for Spike Trains: A Way to Quantify Functional Connectivity

A very common method to track temporal coupling or functional association between stimulus and neural response is the peristimulus time histogram, which characterizes the cross-correlation between two point processes, i.e., stimulus events and the neural spike train [29]. On the one hand, the PSTH examines temporal changes in the amount of generated spikes triggered by the stimulus. On the other, analyses in the frequency domain can provide a more concise description of the temporal correlation of the oscillatory patterns in spike trains.

In the frequency domain, spectral coherence is a well-established standard tool to analyze the linear relationship between two (usually continuous) signals by determining the correlation between their spectra. A high spectral coherence suggests the presence of a functional association between, e.g., the stimulus and the neural response in the corresponding frequency band. Starting from this concept, several modifications of the coherence measure have been suggested (see e.g., [40-42]).

Although the above-mentioned measures have been shown to be very useful for different problems in neuroscience, they suffer from the assumption of stationarity of the neural response and do not account for dynamical changes in associations (coupling) between stimulus and neural response. Indeed, any analysis based entirely on time averaging (PSTH) or on the Fourier transform (spectral coherence) ignores all temporal variations in the functional coupling between tactile stimulation and neural response. An additional temporal resolution is essential and demands replacement of the classical Fourier (spectral) coherence by other methods. There have been successful attempts to adapt Fourier-based methods to short time signals, for example, by means of orthonormal sliding windows [43–45], which are similar to the classical Gabor transform [46].

Wavelet analysis is a significantly more powerful tool that offers a reasonable compromise between temporal and frequency resolutions. The wavelet transform has been used to analyze brain signals from the very beginning in neuroscience. Most of its applications have been to electroencephalographic recordings (see, e.g., [47–54]).

The first studies of wavelet coherence go back to the beginning of this century [55–58]. In a similar way to spectral coherence, wavelet coherence informs about the functional coupling between, e.g., the stimulus and neural response, but it also provides the temporal structure of the coupling. The use of the wavelet transform for analysis of neural spike trains recorded in the trigeminal nuclei under tactile whisker stimulation is illustrated in [10, 59].

In this section, we quantify the wavelet coherence (i.e., functional association) of the gracile neural response to tactile stimulation, and show that activation of the SI cortex leads to a dynamical (i.e., time-varying) alteration of the neuronal response characteristics mediated by the corticofugal pathway. For this purpose, we shall consider how wavelet coherence can be used to investigate the dynamical properties of neural spike trains and to evaluate dynamical changes in the neural response to tactile stimulation in the gracilis nucleus provoked by activation of the corticofugal feedback from the SI cortex.

# 3.4.1 Wavelet Coherence of Two Point Processes

PSTH and ordinary spectral coherence usually provide little information about the time-frequency contents of a spike train. Some insight can be obtained by the traditional dot-raster display. Although the raster display can capture important temporal characteristics of the neural stimulus response, it is merely a visual tool, i.e., no measure of stability of the neural response can be derived directly. Moreover, a correct comparison of raster displays generated by several neurons with essentially different firing rates is difficult, if not impossible. This leads eventually to a problem in generalizing results over the neuronal population. Meanwhile, the wavelet technique offers a natural way to study the temporal structure of neural stimulus response coherence.

A spectral representation of a spike train can generally be obtained by the Fourier transform. However, this transformation is known to have difficulties in dealing with point processes [30]. To overcome some of these difficulties, the multitaper Fourier transform has been advocated in the literature [31]. Although the multitaper transform usually provides a good estimate of the power spectrum, in the case of excessively periodic spike trains (e.g., under experimental conditions of periodic stimulation), it may fail to represent the spectral density consistently. The wavelet transform can be used as an alternative way to perform spectral analysis.

As we saw in Sect. 3.3.4, a spike train can be represented as a sum of delta functions (3.9). Then the wavelet power spectrum of the spike train can be defined by (3.11) and (3.12). The global wavelet spectrum can be obtained from (3.12) by time-averaging the local (time-dependent) spectrum:

$$E_{\rm G}(s) = \frac{1}{T} \int_0^T E(s, t_0) dt_0, \qquad (3.14)$$

where T is the time length of the spike train. The global spectrum (3.14) provides an unbiased and consistent estimate of the true power spectrum [60].

This approach ensures that the mean energy in a random spike train is homogeneously distributed over all interspike intervals  $E_G(s) = 1$ . This is similar to the spectrum of white noise. Consequently, we quantify the power distribution in the train under study in units of the power of the random spike train with the same mean firing rate. Energy below (above) 1 means that the probability of spike patterns with the given scale *s* is below (above) the probability of such a pattern in the random spike train.

When dealing with two spike trains N and M, by analogy with the Fourier cross-spectrum, we can introduce the following wavelet cross-spectrum:

$$W_{NM}(s, t_0) = \frac{W_N W_M^*}{k_0 \sqrt{\pi r_N r_M}},$$
(3.15)

where  $W_N$  and  $W_M$  are the wavelet transforms of the trains N and M, respectively. Then a normalized measure of association between the two spike trains is the wavelet coherence [55]

$$C_{NM}(s, t_0) = \frac{\left| S \left[ W_{NM}(s, t_0) / s \right] \right|^2}{S \left[ E_N(s, t_0) / s \right] S \left[ E_M(s, t_0) / s \right]},$$
(3.16)

where *S* is a smoothing operator (for details see [55, 61]). The coherence definition (3.16) may give artificially high values for the coherence in the case of infinitesimally small values of the power spectrum of either signal or both signals, i.e., when  $E(s^*, t_0^*) \approx 0$ . To avoid this problem in numerical calculations, a thresholding procedure can be used, setting the coherence to zero when either of the power values is below a certain threshold.

# 3.4.2 Measure of Functional Coupling Between Stimulus and Neuronal Response

#### 3.4.2.1 Coherence in the Stimulus Frequency Band

To study the functional coupling between the stimulus and the neuronal response we can use (3.16) with N the train of stimulus events and M the neuronal spike train. Because we are interested in studying the functional coupling with stimulus events, which are periodic, we will focus on the frequency band corresponding to the stimulus frequency, i.e., on f = 1 Hz, which is associated with the scale s = 1 s. To successfully resolve the stimulus-induced frequency contents in the neural response with minimal loss in time resolution, we set  $k_0 = 2$ . Then from (3.10),  $\delta \omega \approx 1/2$  and  $\delta t \approx 2$ . Although the wavelet transform uses the time scale (period) *s* as a parameter, to address the frequency contents, we shall use the frequency as the parameter, defined formally by f = 1/s.

To quantify the variation of the functional coupling among stimuli and neural response, we average the neural stimulus coherence over scales in a narrow band around the stimulus frequency. An estimate of the band limits can be obtained from (3.10), viz.,  $f \in [(1 - c/2\pi k_0), (1 + c/2\pi k_0)]$ , which gives 0.83–1.16 Hz for c = 2. We shall refer to this frequency band as the stimulus frequency band. Obtained this

way, the coherence is a function of time

$$C(t) = \frac{1}{s_2 - s_1} \int_{s_1}^{s_2} C_{NM}(s, t) \mathrm{d}s, \qquad (3.17)$$

which is then used to evaluate the power spectrum by the conventional Fourier transform.

#### 3.4.2.2 Statistical Significance

Two linearly independent spike trains have insignificant coherence  $C_{NM}(s, t_0) \approx 0$ , whereas  $C_{NM}(s, t_0) = 1$  indicates a perfect linear relationship between the spike trains at the scale *s* and localization  $t_0$ .

Although a large coherence amplitude usually indicates the presence of a consistent phase relationship (coupling) between two spike trains in a given time interval, it is also possible that this is a random variation in the spike trains. One should therefore cross-check the statistical significance of the observed coherence.

The statistical significance of the wavelet coherence can be assessed relative to the null hypotheses that the two spike trains generated by independent stationary processes with given distributions of interspike intervals (ISIs) are not coherent. To evaluate the significance level, we use a surrogate data test [62, 63] with Monte Carlo simulation to establish a 95% confidence interval. The surrogate spike trains are obtained from the original one by randomizing phase relations, keeping other first-order characteristics intact. We shuffle the ISIs and evaluate coherence among the surrogate spike trains. To conclude positively about the connectivity between the stimulus train and the neuronal response, their coherence should be higher than the resulting significance level.

#### 3.4.2.3 Mean Characteristics Describing Effects of Cortical Stimulation

To examine the effect of cortical stimulation on the coherence of neural response to stimulus, we average the local coherences over time and the stimulus frequency band

$$C_{\text{cntr}}^{\text{m}} = \left\langle C_{\text{cntr}}(t) \right\rangle_{t}, \qquad C_{\text{AESC}}^{\text{m}} = \left\langle C_{\text{AESC}}(t) \right\rangle_{t}, \qquad (3.18)$$

where  $C_{\text{cntr}}(t)$  and  $C_{\text{AESC}}(t)$  are the coherences in the stimulus frequency band in the control and after the SI cortex stimulation conditions, respectively. For convenience we also introduce the overall mean coherence  $C^{\text{m}} = (C_{\text{AESC}}^{\text{m}} + C_{\text{cntr}}^{\text{m}})/2$ . First, we recall that  $C_{\text{cntr}}(t)$  and  $C_{\text{AESC}}(t)$  are bounded functions of time and thus the maximal increment  $\delta C^{\text{m}} = C_{\text{AESC}}^{\text{m}} - C_{\text{cntr}}^{\text{m}}$  depends on the overall mean coherence and cannot exceed the value  $2(1 - C^{\text{m}})$ . Thus the higher the overall mean coherence, the lower the coherence increment can be. Then we guess a linear model

$$|\delta C^{\mathrm{m}}| = \alpha (1 - C^{\mathrm{m}}), \qquad (3.19)$$

where  $\alpha$  is a constant to be identified from the data.

Then for a given value of the wavelet coherence, by using (3.19) we can evaluate the expectation of the absolute value of the coherence increment. If the observed increment is much smaller than the expectation, we can question its significance (i.e., no effect). To decide positively on the presence of an effect on the stimulus coherence provoked by the SI cortex stimulation, we require the experimentally observed increment  $\delta C^m$  to be at least 50% of the expectation value, i.e.,  $|\delta C^m| \ge$  $0.5\alpha(1 - C^m)$ . Then we have a coherence increase or I-effect for positive  $\delta C^m$  and a decrease or D-effect for negative values.

# 3.4.3 Functional Connectivity of Gracilis Neurons to Tactile Stimulus

The analyzed data set consisted of 29 extracellular recordings (spike trains) of unitary neuronal activity from the gracilis nucleus measured at three different epochs:

- Spontaneous firing.
- Responses to periodic stimulation (1 Hz rate) of the neuronal receptive field (control conditions).
- Responses to periodic stimulation (1 Hz rate) of the neuronal receptive field after electrical stimulation of the SI cortex (AESC conditions).

All neurons were identified as projecting to the thalamus [21]. The analyzed neurons showed a low spontaneous activity with mean firing rate  $1.1 \pm 0.4$  spikes/s (range 0–10 spikes/s) whose pattern coincided with the firing characteristics of projecting neurons described previously [64, 65].

#### 3.4.3.1 Example of Wavelet Analysis

First, let us illustrate the wavelet analysis of a representative neural spike train. Figure 3.16a shows the spike train during three different experimental epochs (for illustration purposes, we selected a neuron with a considerable spontaneous activity). Under spontaneous conditions, the neuron exhibits an irregular spiking pattern with a slight peak at 70 ms, manifested in the autocorrelation histogram (ACH, Fig. 3.16b, left). Mechanical stimulation under the control conditions elicited a well-pronounced neuron response with 25 ms peak latency, followed by a weakly rhythmic firing with 120 ms period (Fig. 3.16b, middle). Electrical stimulation of the SI cortex facilitated the neural response to the tactile stimulation. The response in the PSTH became more prominent (Fig. 3.16b, right). However, neither the response latency nor the mean firing rate (21.1 vs. 23.7 spike/s) varied much relative to the control conditions.



**Fig. 3.16** Wavelet spectral and coherence analysis of experimental spike trains. **a** Stimulus events and neural spike trains during three experimental epochs: spontaneous activity, control 32 s tactile stimulation delivered to the neuron receptive field at 1 Hz rate, and the same tactile stimulation repeated after electrical stimulation of the somatosensory (SI) cortex (AESC). **b** Autocorrelation (ACH) and peristimulus time histograms (PSTHs) for the corresponding epochs. **c** Wavelet power spectra of the neural spike train for the corresponding epochs. The *x*-axis corresponds to the localization *z* (time), whereas the oscillation frequency from 0.5 to 15 Hz is plotted along the *y*-axis on a logarithmic scale. *Gray intensity* is equivalent to wavelet spectral power. *Dashed lines* define the cone of influence and *horizontal dotted lines* delimit the stimulus frequency band 0.83–1.16 Hz. **d** Level of statistical significance for the wavelet coherence obtained by the surrogate data test. Coherence above the curve is deemed significant. The *gray region* is the frequency band of interest (around the stimulus frequency). **e** Wavelet coherence of the neural spike train to tactile stimulation events for the control epoch and after SI cortex stimulation. *Solid black lines* delimit islands of statistically significant coherence (the stripe between two dotted lines is of interest). *Gray intensity* corresponds to the stimulus coherence of the neural response

Furthermore, the weak oscillatory behavior observed in the tail of the PSTH under control conditions disappeared.

The wavelet power spectrum (Fig. 3.16c, left) confirms the irregularity of spontaneous firing observed in the ACH. There are many oscillatory rhythms localized in both the time and frequency domains with essentially erratic distribution. Thus spiking activity has no well-defined dominant periodic activity (although there is

a feeble and not-persistent-in-time power peak at 14 Hz). The distribution of the power under control conditions (Fig. 3.16c, middle) shows a consistent peak in the stimulus frequency band (from 0.83 to 1.16 Hz, between the two dotted horizontal lines). This peak indicates the presence of the stimulus-evoked rhythm in the neural firing. We also note that the peak amplitude (power) is not persistent in time, but instead exhibits a low-frequency oscillation (<0.3 Hz). This oscillation of the spectral power suggests that the neural response to the same tactile stimulation is not stable (identical) throughout time, but instead has some variability, i.e., the neuron fires essentially different numbers of spikes with different ISIs in response to the same stimulus events during the stimulation epoch. We also observe some increase in the spectral power around 8 Hz, consistent with the oscillations (120 ms period) observed in the corresponding PSTH (Fig. 3.16b, middle). In accordance with the stimulus response facilitation observed in the PSTH after electrical cortex stimulation, the power peak at the stimulus frequency band became even more pronounced (Fig. 3.16c, right). Now we have a continuous practically black island going through the whole stimulation epoch in the stimulus frequency band. Notice, however, that the ultralow-frequency oscillation of the power is weaker, but still exists. Besides, there is a significant increase in the power of harmonics of the 1 Hz rhythm and, on average, a greater presence of oscillations in the domain of higher frequencies.

To quantify how coherent (reliable) the neural response to the stimulus events is, we evaluated the wavelet coherence of the neural spike train and stimulus events. To decide on the statistical significance of the observed coherence level, i.e., on the presence of functional associations (coupling) between the stimulus and neural response, we performed a surrogate data test by randomizing phase relationships between two signals. Figure 3.16d shows a statistical significance curve (P value 0.05) for the frequency range observed in the neural spike train. Coherence above the curve is deemed statistically significant, although if the area of the significant islands is small enough (5%), then the conclusion regarding the coherent response should be made carefully.

Figure 3.16e illustrates the wavelet coherence of the tactile stimulus events and evoked neural response. Because the tactile stimulation is periodic (i.e., has only one frequency), we shall refer to the stimulus frequency band only (delimited by dotted lines in Fig. 3.16e) when speaking about the response coherence. During the control stimulation epoch, we observe three islands of significant coherence in the stimulus frequency band (Fig. 3.16e, left). This provides evidence for the presence of the stimulus–response association previously observed in the corresponding PSTH. However, we also find that the association or stimulus response coupling is not constant, but an oscillatory function of time. Notice also that the neural power spectrum in the corresponding frequency band was not very strong (Fig. 3.16c, middle). However, the coherence clearly reveals the functional coupling between the neural firing dynamics and stimulus events. The stimulus coherence of the neural response becomes stronger after electrical stimulation of the somatosensory cortex (Fig. 3.16e, right). As we observed earlier in the wavelet power spectra (Fig. 3.16c, middle and right), the stimulus coherence also suffers from ultralow-frequency oscillations.

Thus for a given neuron we observed two phenomena:

- The strength of the functional stimulus-neural response coupling is amplified by the electrical stimulation of the SI cortex.
- The coupling strength is a dynamical quantity, slowly oscillating in time, that can temporarily fall below the significant level.

The latter implies that the stimulus–response association may be temporarily lost for a single neuron.

#### 3.4.3.2 Pitfalls of Fourier Spectrum and Wavelet Spectral Analysis

To illustrate possible pitfalls in the interpretation of the Fourier power spectrum, we first evaluated the power spectrum through the multitaper Fourier transform of the neural spike train shown in Fig. 3.16a. In accordance with the irregularity of firings under spontaneous conditions, the Fourier spectrum (Fig. 3.17a) is essentially flat with a peak at 14 Hz corresponding to the periodicity observed earlier in the ACH (Fig. 3.16b, left). However, for the control stimulation epoch, the overall spectral distribution is quite similar to that of the spontaneous spectrum, and it lacks a peak at 1 Hz corresponding to the neural response at the stimulus frequency. In contrast, due to the excessive periodicity of the neural response, after the electrical stimulation of the SI cortex, we observed an unreasonably wide peak around 1 Hz, followed by many strong harmonics contaminating the high-frequency range. Thus the Fourier transform of a spike train may fail to consistently represent its spectral density.

We then used the wavelet transform as an alternative way to perform spectral analysis. Figure 3.17b shows the global wavelet power spectra of the neuron-firing counterpart to the Fourier spectra. The wavelet spectra are much more consistent with the oscillatory rhythms suggested by the previous analysis of spike trains by the ACH and PSTHs. According to the normalization used in (3.12), the unit power density corresponds to the power spectrum of a spike train with randomly distributed ISIs, which we refer to briefly as a random spike train. Then a spectral power above (or below) unity indicates the presence (or absence) of the corresponding rhythm in the spike train with statistical power higher than just a random ratio.

During spontaneous activity, the power spectrum of the neuron firing only slightly deviates from the spectrum of the random train across all frequency bands (Fig. 3.17b, dotted line). In agreement with the weak rhythm observed in the ACH (Fig. 3.16b, left), the global wavelet spectrum also has a small peak at 14 Hz. We also detected peaks at about 0.7 and 1.9 Hz. Going back to the complete wavelet spectrum (Fig. 3.16c, left), we find that the latter peaks are due to strong episodic events localized between 4 and 7s and between 10 and 16s from the beginning, respectively. Thus spontaneous firing can be characterized as random, showing no strong persistent specific frequencies. Under the control tactile stimulation, we observed a dramatic peak in the stimulus frequency band (Fig. 3.17b, solid line). Note that the peak is quite narrow and has a harmonic at 2 Hz. Stimulation of the SI cortex boosts the amplitude of the power peak in the stimulus frequency band, and we also observed an important enhancement of the power in the band ranging from about 5



to 15 Hz. For higher frequencies (>15 Hz), there is no significant deviation of the power density from 1, whereas for the range <5 Hz, the harmonics of the stimulus frequency rhythm are manifested in the power spectrum. Accordingly, we define the second frequency band of interest (5–15 Hz), which we shall refer to briefly as the alpha frequency band. Thus at the single-neuron level used in this study, we found that the frequency band corresponding to the evoked neural spiking activity is localized in the stimulus and alpha frequency bands.

#### 3.4.3.3 Population Properties of Spectral Power

To assess statistical properties of the observed changes in the spectral power of the neuronal firing, we compared the global wavelet power spectra under spontaneous conditions and under tactile stimulation in the control and after the SI cortex stimulation conditions. Figure 3.18 summarizes the results.

The overall mean power under spontaneous conditions corresponds to the power of the random spike train, in both the stimulus and the alpha frequency bands (Fig. 3.18a, b, spontaneous). This confirms that the firing pattern of projecting neurons in the gracilis nucleus is essentially random. Stimulation of the neuron receptive fields boosts the mean power concentrated in both the alpha and the stimulus frequency bands (Fig. 3.18a, b, control), although the increase in the stimulus band is much



**Fig. 3.18** Spectral characteristics of gracile projecting neurons in the stimulus and alpha frequency bands. **a** Mean power of the global wavelet spectrum and its SE in the stimulus frequency band for spontaneous conditions and during response to tactile stimulation under control conditions and after electrical stimulation of the SI cortex (AESC). **b** Same as **a**, but for the alpha frequency band. **c** Statistics of the types of spectral effect of the electrical stimulation of the SI cortex for 2 frequency bands. I, No, and D stand for increase, no effect, and decrease in the spectral power, respectively. *Black* and *gray bars* correspond to the stimulus and alpha frequency bands, respectively

stronger (7 vs. 2.5 times). Electrical stimulation of the SI cortex raises the power concentrated in these frequency bands even higher (Fig. 3.18a, b, AESC). However, on average, the latter enhancement is not so drastic. The effect of electrical stimulation lasted between 15 and 30 min, after which the neurons recovered their activity.

A balanced one-way ANOVA ensures that the mean spectral powers in three different epochs are significantly different with  $\alpha$  values 2.5E–5 for the stimulus frequency band and 2.7E–5 for the alpha band. A multiple-comparison test shows that the values of the power during tactile stimulation under control conditions and after SI cortex stimulation conditions differ significantly from the power of spontaneous firing in both frequency bands, and that they are statistically indistinguishable from each other.

Although the mean spectral power across both frequency bands does not differ significantly between tactile stimulations under control conditions and after electrical stimulation of the SI cortex (Fig. 3.18a, b), in the majority of experiments we observed an increase in the power provoked by cortex stimulation. This result agrees with the previously reported facilitation of the stimulus response provoked by SI cortex stimulation [66–69]. To quantify the percentage of neurons exhibiting different types of effects of stimulation of the SI cortex, we evaluated the number of increases in the spectral power (I-effects), the number of cases when the difference was negligible (no-effects), and the number of decreases (D-effects). To decide on the type of the effect we used the relative increment of the power in the given frequency band, viz.,

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$$\Delta E = \frac{E_{\text{AESC}} - E_{\text{cntr}}}{(E_{\text{AESC}} + E_{\text{cntr}})/2},$$
(3.20)

where  $E_{cntr}$  and  $E_{AESC}$  are the spectral power under control conditions and after SI cortex stimulation conditions. If the absolute increment was <5%, we assigned no-effect, otherwise, according to the sign of the increment, we decided on an I- or D-effect.

Figure 3.18c shows that, after stimulation of the SI cortex, in the majority of cases (66 and 69% for the stimulus and alpha frequency bands, respectively), the power of firing does indeed increase in both frequency bands, i.e., we have an I-effect of cortex stimulation. In 17% of cases for the stimulus band and 14% for the alpha band, cortex stimulation had no effect on the spectral characteristics of the neural response. Finally, in 17% of cases, for both bands, the spectral effect of cortex stimulation was negative, i.e., the power diminished.

Thus tactile stimulation leads to a significant enhancement of the power of neuron firing, in both the alpha and the stimulus frequency bands. In addition, electrical stimulation of the SI cortex amplifies the spectral power in these bands for about two thirds of the neurons in the gracilis nucleus. We also conclude that facilitation of the neural response by the corticofugal pathway occurs not only through an increase in the number of spikes elicited by the stimulus, but also through the ordering of the response pattern.

#### 3.4.3.4 Effect of Cortex Stimulation on Response Coherence

Let us recall that coherence is a normalized measure of the cross-spectrum of two signals. It thus has meaning in the frequency bands presented in both the neural spike train and the stimulus. The latter has the fixed frequency of 1 Hz (up to small variations due to the experimental setup). Accordingly, we study the wavelet coherence of the neural response to tactile stimulation in the stimulus frequency band only, whose limits were set to 0.83–1.16 Hz.

To study the effect of cortex stimulation on the neural response coherence in the gracilis nucleus, we evaluate the mean stimulus coherences in the control  $C_{cntr}^{m}$  and after electrical stimulation of the SI cortex  $C_{AESC}^{m}$ . Figure 3.19a shows the absolute value of the coherence increment  $|\delta C^{m}| = |C_{AESC}^{m} - C_{cntr}^{m}|$  as a function of the mean overall coherence  $C^{m} = (C_{AESC}^{m} + C_{cntr}^{m})/2$  for the experimental data set. Not surprisingly, the plot shows a strong linear tendency of the coherence increment to be smaller for higher values of the overall mean coherence. By fitting the model (3.19) to the data in the least-squares sense, we obtain  $\alpha = 0.41$  (solid straight line in Fig. 3.19a). Thus for a given value of the wavelet coherence increment and define the effect (No, I, or D) provoked by cortical stimulation (Fig. 3.19a).

Figure 3.19b shows the percentage of different types of effects of electrical stimulation of the SI cortex on the tactile stimulus coherence of neuron firing in gracile projecting neurons. In the majority of cases (59%), electrical stimulation of the SI



**Fig. 3.19** Effect of the electrical activation of the SI cortex on the wavelet coherence (reliability) of the response of projecting neurons in the gracilis nucleus to tactile stimulation of their receptive fields (RFs). **a** The absolute value of the coherence increment  $\delta C^m$  as a function of the mean overall coherence  $C^m$  shows a strong linear tendency. The *solid straight line* is the best fit of the data to the model (3.19). The *gray region* delimits the no-effect region (data points shown by *triangles*), where the experimentally observed value of the coherence increment is <50% of the expectation. *Circles* and *squares* correspond to I (increase) and D (decrease) effects of electrical cortex stimulation on the stimulus response coherence. **b** Percentage of neurons exhibiting I, No, and D types of effect. **c** Relative changes (increase or decrease) in the coherence for I and D effects

cortex facilitates a more reliable (higher coherence) neural response to the tactile stimulus. In 24 and 17% of cases, we had no effect or a decrease in coherence, respectively. The observed relative increment of the coherence value for I- and D-effects was about the same, namely, 13 and 15%, respectively (Fig. 3.19c).

We note that the positive increment in the coherence (reliability of the neuron response to tactile stimulation) was observed in a slightly lower number of cases than the increment of power in the stimulus frequency band (59% in Fig. 3.19b vs. 66% in Fig. 3.18c), which confirms the statement made earlier that an increase in the spectral power is not necessarily accompanied by an increase in the coherence. Moreover, this suggests possible subtle changes occurring in the stimulus response pattern due to the corticofugal pathway, instead of a simple increase in the firing rate.

To cross-check whether the increment in the wavelet stimulus coherence correlates with conventional characteristics of neural activity, we plotted an increment in the mean firing rate  $\delta FR = FR_{AESC} - FR_{cntr}$  and an increment in the amplitude of the



**Fig. 3.20** Increment in the mean neural firing rate (**a**) and the amplitude of the PSTH peak (**b**) vs. the increment in the neural stimulus response coherence. Quadrants I and III correspond to positive correlation between two characteristics (i.e., increase or decrease of one characteristic is accompanied by the same effect in the other), whereas quadrants II and IV correspond to negative or anticorrelation (i.e., when the effect in one characteristic is contrary to the effect in the other). *Dashed straight lines* and *gray regions* containing them show the best linear fits of the data and their 95% confidence limits. The direction and position of the fits imply the absence of correlation between the firing rate and coherence measures, and a positive correlation of the amplitude of the PSTH peak and coherence measures. However, note the presence of cases where changes in the PSTH amplitude do not correspond to changes in the coherence

response peak in the PSTH  $\Delta A_{PSTH} = A_{AESC} - A_{cntr}$  versus  $\delta C^m$  (Fig. 3.20). In these plots, a data point belonging to quadrant I or quadrant III corresponds to a positive correlation between the corresponding measures, i.e., an increase or decrease in coherence is associated with an analogous effect in the other characteristic, whereas quadrants II and IV establish the contrary effect or anticorrelation. According to the above-described findings, we expected that an enhancement of the reliability of the neural response to tactile stimulation (i.e.,  $\delta C^m > 0$ ) would not necessarily be reflected in the neuron firing rate, but it seems reasonable to expect a better peaking of the PSTH and consequently  $\Delta A_{PSTH} > 0$ .

Indeed, Fig. 3.20a shows that the data points in the case of the mean firing rate are distributed quite arbitrarily over the plane—the linear fit of the data confirms this. The straight line and its 95% confidence interval are essentially horizontal, showing no significant correlation between the measures. A different picture is observed for the increment in the amplitude of the PSTH peak (Fig. 3.20b). The best-fit line and its 95% confidence interval have a notably positive slope. Thus, as expected, we have a positive correlation for the changes provoked by electrical stimulation of the SI cortex between the coherence and the amplitude of the PSTH peak. However, we note that an enhancement (or reduction) of the stimulus coherence is not always

accompanied by an increase (or decrease) in the PSTH amplitude. This means that, for a considerable number of experiments the PSTH measure fails to predict the effect of changes in the coherence of the neural response to the tactile stimulus.

#### 3.4.3.5 Variable Functional Coupling to Stimulus

In Fig. 3.16e, we observed qualitatively that tactile stimulus coherence oscillates slowly in time, both for the control experimental conditions and after electrical stimulation of the SI cortex. Let us now quantify these oscillations and study their possible functional role.

Figure 3.21a shows two strips cut out of the corresponding coherence functions in the stimulus frequency band that is shown in Fig. 3.16e between two horizontal dotted lines. To examine the mean coherence and its modulation in time, we average the local coherence over the stimulus frequency band. The resulting time series for the control  $C_{\text{cntr}}(t)$  and after SI cortex stimulation  $C_{\text{AESC}}(t)$  give a measure of the reliability of the neuron response to stimulation events throughout the corresponding stimulation epoch (Fig. 3.21a, bottom). At the beginning of the stimulation epochs (up to ~20 s), the stimulus response coherence is higher after electrical cortex stimulation than under the control conditions. The two characteristics then both exhibit some decay (i.e., the neuron firing becomes less stimulus coherent) and no substantial difference between the coherence values is observed. Over all the stimulation epochs, we observed a slow oscillation of relatively large amplitude. We note that the period of slow oscillation is much longer than the wavelet temporal resolution (about 10–15 vs. 2 s), which ensures correct identification of the coherence oscillatory behavior.

The observed oscillation may have a functional role. Indeed, for the control stimulation epoch the coherence falls temporarily below the significance level (Fig. 3.16e, left and Fig. 3.21a, bottom). We can thus define time windows (segments) with coherence above or below the level of statistical significance. In Fig. 3.21a, these windows are shown by white and gray boxes, so that the total length of the significant and nonsignificant segments is the same. Obviously, in windows with high coherence, the neuron should exhibit a strong functional stimulus-response relationship. However, when the stimulus coherence is not significant, this functional association may be lost. The "raw" PSTH (Fig. 3.16b, middle) does not provide evidence for this phenomenon. However, by splitting the spike train into two parts according to the significance of the observed coherence, we do indeed observe an essential difference in the PSTHs (Fig. 3.21b). In regions with significant coherence, the neuron exhibits a well-pronounced stimulus response (Fig. 3.21b, left), whereas its firing becomes practically uncorrelated with the stimulus in the time windows of nonsignificant coherence (Fig. 3.21b, right). We can interpret this behavior as a temporal loss of functional connectivity between the tactile stimulus and the neuron. We also note that electrical stimulation of the SI cortex increases the stimulus-response coherence and that it stays above the level of significance during practically the whole stimulation epoch. Only after about 27 s does the coherence become nonsignificant. In such



**Fig. 3.21** Oscillatory behavior of the wavelet coherence of the neural response to tactile stimulation events in the stimulus frequency band. **a** *Top strips* show coherences evaluated in the stimulus frequency band 0.83–1.16 Hz (corresponding to those shown in Fig. 3.16e between horizontal dotted lines) for the control and after electrical stimulation of the SI cortex (AESC) for the representative neuron. *Gray intensity* corresponds to the local coherence value. Zero on the time axis corresponds to the beginning of each epoch. *Bottom: Thick curves* show the integral (averaged over the stimulus frequency band) wavelet stimulus coherence of the neuron response throughout the stimulation epochs. The *thin dash-dotted horizontal line* defines the level of statistical significance for coherence under control stimulation conditions. According to the statistical significance, we define time windows of significant (*gray boxes*) and nonsignificant (*white boxes*) coherence. **b** PSTHs of the neural response under control conditions, evaluated over time windows with coherence above (*left*) and below (*right*) the significance level. In the windows of coherent response, the neuron shows a pronounced peak, whereas it loses the stimulus correlation outside the coherence windows. **c** Fourier power spectra of the oscillation of the wavelet coherences under control conditions and after SI cortex stimulation (AESC)



**Fig. 3.22** Statistical properties of the ultraslow oscillations of the stimulus response coherence of projecting neurons in the gracilis nucleus under control conditions and after electrical stimulation of the SI cortex (AESC). **a** Mean oscillation frequency. **b** Mean oscillation power

an "alerted" state, the neuron maintains functional coupling to the sensory stimulus, sending coherent spikes to the thalamus.

Figure 3.21c shows Fourier power spectral densities for the ultralow-frequency oscillation of the stimulus coherence in the control and after cortex stimulation. In the first case, the spectrum has a peak at 0.09 Hz, whereas after SI cortex stimulation, the peak shifts to a lower frequency (0.06 Hz) and becomes smaller.

Figure 3.22 shows the mean frequency and power of the coherence oscillations averaged over the neuron population during tactile stimulation under control conditions and after electrical cortex stimulation. The mean frequency under control conditions was 0.065 Hz, which is slightly lower than the oscillation frequency of 0.068 Hz after cortex stimulation. However, there is no statistically confirmed significant difference between the two means. Similarly, the mean oscillation power is slightly (but not significantly) higher in the case of tactile stimulation preceded by electrical stimulation of the SI cortex. The mean frequency and amplitude of the ultralow-frequency oscillations averaged over the neural population are not affected by the electrical stimulation of the SI cortex.

Thus, the possibility of studying the temporal structure of the stimulus–response coherence allowed us to describe ultraslow fluctuations in the tactile responses of single projecting neurons. We note that such oscillations are not directly observable either in the Fourier spectrum or in the PSTH of the neural response. Instead, they represent slow modulation of the coherence (or reliability) of the neural response to the tactile stimulation over a long timescale, i.e., the neuron fires essentially a different number of spikes with different ISIs for the same stimulus events during the stimulation epoch. Besides observing a facilitation of the tactile stimulus–neural response functional coupling by the electrical stimulation of the SI cortex, we have provided evidence that the functional coupling between the sensory stimulus input and neural response oscillates slowly in time. During this oscillation, the stimulus coherence can temporarily fall below the significant level. This means that the stimulus–response association may be temporarily lost for a single neuron. This phenomenon suggests that information processing in the gracilis nucleus occurs on the network level, which may be "energetically" beneficial for the system. The mean frequency of the observed coherence oscillation was about 0.07 Hz. Oscillations in the same frequency band (0.02–0.2 Hz) have been reported in studies of human EEG [70]. The authors showed that large-scale ultraslow oscillations in widespread cortical regions may represent a cyclic modulation of cortical gross excitability. This ultraslow oscillation of cortical activity might be transferred to the gracilis nucleus through the corticofugal projections, thus modulating tactile responses.

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# **Chapter 4 Classification of Neuronal Spikes from Extracellular Recordings**



**Abstract** In this chapter, we consider the problem of spike separation from extracellularly recorded action potentials, which is important when studying the dynamics of small groups of neurons. We discuss general principles of spike sorting and propose several wavelet-based techniques to improve the quality of spike separation, including an approach for optimal sorting with wavelets and filtering techniques. Finally, we consider the application of artificial neural networks to solve this problem.

# 4.1 Introduction

Most of the neurons in the brain communicate by sending and receiving short-lasting electrical pulses, so-called action potentials or spikes. When analyzing the cooperative behavior of a neuronal ensemble or studying the neural code, spikes are thought to be stereotypical events. Hence it is not the shape of each spike waveform but the precise timing of spike firing that matters for this analysis. Then we can speak about spike trains generated by neurons as of a multivariate binary process. Many contemporary studies of neuronal activity rely on the analysis of spike trains. One may seek different correlations among neurons or behavioral correlates, spatial and temporal patterns, firing synchronization phenomena, etc. For example, this is especially relevant for the analysis of neuronal responses in the first relay stations of the brain to external tactile stimuli, i.e., the way neurons process different external inputs and the temporal sequences of spikes they generate [1, 2]. In particular, it has been shown that spiking of single neurons in the gracilis nucleus in response to a stimulus may not always be faithful, while the neuronal group does reliably transmit the stimulus to the next neural nuclei.

Spiking activity can be recorded by a single microelectrode or microelectrode array immersed in a nervous tissue. The vast majority of in vivo electrophysiological experiments use so-called extracellular recordings, i.e., an electrode (inside the nervous tissue) detects electrical activity of neurons from a distance. Then several neurons near the electrode tip can produce spikes of different amplitude and shape (for more detail see, e.g., [3]). Consequently, one experimental recording (extracellular electric potential) may contain a mixture of spikes generated by different neurons.

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Then the experimentalist must identify and sort or separate spikes due to different neurons. Ideally all spikes produced by a single neuron should be assigned to one group or cluster. Errors occur when spikes belonging to other neurons are grouped together with the spikes of the target neuron (so-called false positives) or when some spikes emitted by that neuron are not included in its group (false negatives).

Finally, the quality and reliability of any subsequent analysis of spike trains, cooperative neuronal behavior, or single neuron activity depends on the quality of solution of the spike sorting problem. It has been shown that the quality of spike sorting by a human operator is significantly below the estimated optimum [4]. Besides, the amount of data generated by modern experimental setups is truly enormous and continues to grow. In a typical experiment one can easily get more than 10<sup>4</sup> spikes recorded by a single electrode tip. Modern multielectrode arrays can have hundreds of tips, which multiplies the amount of information to be processed. For all these reasons, there is a growing demand to develop automatic techniques for spike sorting.

It is typically assumed that each neuron generates spikes of the same shape and amplitude, while signals from different cells have some individual peculiarities (even though their signatures may be quite similar). Although this assumption may be significantly compromised (e.g., in a burst, each subsequent spike is usually smaller than the previous one), it is reasonably reliable for many practical cases and we shall accept it throughout this chapter.

Nowadays, there exist a number of numerical tools for spike sorting (see, e.g., [3, 5, 6, 8–14], and references therein). In this chapter we shall provide a brief overview, while paying attention to methods involving the wavelet transform and comparing them to the standard techniques most widely used in experimental labs. Although existing methods show good performance on preselected data sets [15–22], the best procedure for spike feature extraction is still a challenging issue.

# 4.2 General Principles of Spike Sorting

Figure 4.1a sketches a typical setup with a linear multi-electrode lowered to the rat hippocampus along the main axis of the pyramidal neurons. The electrode spans several hippocampal subfields, including CA1 and CA3 regions. As we mentioned above, in vivo electrophysiological experiments usually provide recordings of the extracellular field potential that contains multi-unitary activity coming from nearby neurons. This activity, besides spikes, contains low-frequency oscillations (<1 kHz), so-called local field potentials (LFPs) produced by synaptic currents in principal cells (Fig. 4.1b). LFPs can have significantly higher amplitude than the spikes. These oscillations can be considered as a *noise* from the standpoint of spike sorting. However, LFPs have great importance when studying information processing (see, e.g., [23, 24] and references therein). Figure 4.1c shows a short epoch of a recording where we see low-frequency oscillations and fast spikes. LFPs generally have a broad-band spectrum, which significantly overlaps with the spectrum of a typical spike. How-



**Fig. 4.1** Example of extracellular recordings in the CA1–CA3 regions of the rat hippocampus. **a** Sketch of the recording setup. A linear micro-electrode with 16 tips is lowered into the hippocampus along the main cell axis. **b** Epoch of electrical potentials recorded by the electrode (16 traces). **c** Zoomed trace from the electrode tip #14. Several neuronal spikes can be observed with the naked eye (*arrows*)





ever, even with the naked eye, we can distinguish at least high amplitude spikes and conclude that they may not be the same.

Although details of different spike sorting techniques may differ significantly, the vast majority of known methods go through a number of common steps. These steps can be independent, or some of them can be included in a single procedure for improving the quality of spike sorting. Some methods can also skip some steps. However, to obtain a good understanding of the problem of spike sorting, it is useful to separate it into four steps (Fig. 4.2).

Steps I) and III) are the most challenging. In Sect. 4.10, these two problems will be solved together. Concerning step III, there are two types of method: empirical and model-based. In step IV, the researcher should determine the number of different groups (neurons) and the membership of the spikes in these groups.

There are also many clustering algorithms (see, e.g., [25, 26]) showing different performances on different data sets. As a matter of fact, the final performance of spike sorting is largely defined by the quality of the extracted spike features. Currently available methods for feature extraction may be divided into groups, including:

- Naive, threshold based.
- Principal component analysis (PCA).
- Wavelet transform (WT).

The first two methods are the most widely used now, but the third technique has been shown to be superior and is becoming more popular [10-12].

# 4.3 Spike Detection Over a Broadband Frequency Activity

In the spike sorting procedure mentioned above (Fig. 4.2), step I (filtering the extracellular potential) is usually intended to suppress noise and facilitate step II (detection of spiking events). A straightforward way to identify spikes is then to apply a highpass filter (HPF) to the raw recording. However, this may significantly distort spike waveforms and create additional difficulties for the ensuing spike sorting. Besides, the operator must set the cutoff frequency, which is not always obvious (we shall discuss this problem in detail in Sects. 4.9 and 4.10). Figure 4.3a, b, and c show an example application of HPF with different cutoff frequencies to a recording containing high amplitude low frequency activity. Obviously, filtering reduces the noise: the more aggressive the filter, the lower the noise. However, the spike amplitude is also reduced, so we may even decrease the signal-to-noise ratio (Fig. 4.3c). More importantly, the spike shape may be significantly distorted.

A better choice in the case of linear multi-electrode recordings (Fig. 4.1) may be the so-called current source density (CSD) analysis. This is based on modeling the field potential using Maxwell's equations [27]. In its simplest form, the CSD can be written as

$$J(t,x) = -\sigma \nabla^2 V(t,x) , \qquad (4.1)$$

where V(t, x) is the extracellular (recorded) potential,  $\sigma$  is the (ohmic) conductivity of the extracellular space, and J(t, x) is the CSD. Since spikes are local events, while LFPs usually have large spatial extent, evaluation of the CSD from experimental data can spotlight spikes over LFPs.

For practical reasons we can approximate the second spatial derivative in (4.1) at the *j*th electrode by finite differences (this is especially useful in laminar brain structures like the hippocampus):



**Fig. 4.3** Attenuation of low-frequency oscillations in extracellular recordings. **a** Original electric potential with strong low-frequency oscillation (*red dashed curve*). **b** High-pass filtering with cutoff frequency  $F_{\text{cut}} = 300$  Hz. Spiking activity stands out above the noise. However, spike amplitudes decrease and spike shapes are distorted. **c** Same as in **b**, but with more aggressive filtering,  $F_{\text{cut}} = 800$  Hz. **d** CSD-based method emphasizing local currents corresponding to spikes without disturbing their shapes

$$J_{j}(t) = -V_{j+1}(t) + 2V_{j}(t) - V_{j-1}(t) , \qquad (4.2)$$

where  $V_j(t)$  is the voltage recorded at the *j*th electrode [without loss of generality, we assumed  $\sigma = 1$  in (4.2)]. Then  $\tilde{J}_j$  can be used for spike detection and sorting. Figure 4.3d shows the currents produced by spiking activity. Note that we now avoid the need to adjust any filter parameters and obtain the true shape of the spikes, but in terms of the CSD.

Let x(t) be the preprocessed signal containing spikes [either high-pass filtered V(t) or CSD-like  $\tilde{J}(t)$ , Fig. 4.3]. Once x(t) has been obtained, we have to select events corresponding to spikes. In other words, we aim to distinguish spikes from the background activity. This is often done by amplitude thresholding. If x(t) crosses

Fig. 4.4 Detection of spikes by thresholding. Events that go through the threshold (*red dashed line*) are marked as spikes ( $x_{\text{th}} = -3\sigma_x$ ). The detected spikes are then used for sorting



a threshold  $x_{\text{th}}$  (in one selected direction), we mark this event as a spike. More complex detection algorithms are sometimes applied. For example, power detection, in contrast to x(t), uses the quadratic quantity

$$y(t) = \int H(t-\tau)x^2(\tau) \,\mathrm{d}\tau \;, \tag{4.3}$$

where *H* is some smoothing kernel [in the simplest case  $H(t) = \delta(t)$ ].

Changing the threshold level  $x_{th}$  allows us to regulate the trend between missed spikes (so-called *false negatives*, going undetected) and the number of events occurring due to random fluctuations (*false positives*, which are non-existent spikes). Ideally, the threshold should be selected in such a way as to minimize the total error. As a rule of thumb  $x_{th} \approx -3\sigma_x$ , where  $\sigma_x$  is the standard deviation of x(t) (Fig. 4.4).

Finally, we obtain a set of spikes:

$$\Omega = \left\{ \left( t_j, x_j(t) \right) \middle| t \in [t_j, t_j + T] \right\},$$
(4.4)

where  $t_j$  are the times of the spikes and T is a time window or duration of spikes (usually  $T \approx 1-2$  ms). For correct spike sorting, all spikes should be aligned in the set  $\Omega$ . This is usually done in such a way that the maxima (or minima) of all spike waveforms are at the same distance from the beginning of the corresponding spike.

In experimental recordings, each spike waveform  $x_j(t)$  is discretized with the time step  $\Delta t = 1/F_s$ , where  $F_s$  is the sampling rate. For adequate spike sampling,  $F_s$  should be sufficiently high.  $F_s = 20$  kHz is usually acceptable. Then the discretized spikes can be considered as vectors in an m-dimensional space:

$$x_j = (x_{j1}, \dots, x_{jm})^{\mathrm{T}} \in \mathbb{R}^m , \qquad (4.5)$$

where  $m = T/\Delta t$  is the length of the spikes. Finally, we can construct a data matrix

$$X = [x_1 \ x_2 \ \dots \ x_N] \in \mathscr{M}_{m \times N}(\mathbb{R}) \tag{4.6}$$

containing all spikes. Each column of X describes one spike waveform and the column number corresponds to the number of the spike in the set  $\Omega$ . Hence we can work with the set

$$\Omega = \left\{ X, \{t_j\}_{j=1}^N \right\} \,. \tag{4.7}$$

## 4.4 Naive Spike Sorting

Once a set of events (spikes)  $\Omega$  (4.7) has been obtained, we must decide how many classes (neurons) there are and separate spikes between them. Comparing spike waveforms, one can resolve this problem with some degree of reliability. However, in practice, spike sorting represents a complicated task due to the high level of background noise, variability of spike waveforms, the fact that distinctions between spikes of different neurons are frequently not well-pronounced, and so on. For example, in Fig. 4.5, at least two groups of spikes are observable by the naked eye, but a reliable inference needs more careful investigation.

Mathematically speaking, each spike is a point in an *m*-dimensional space (4.4). Since *m* is quite big (usually m = 30-70), the curse of dimensionality is the major obstacle for clustering spikes in such a multidimensional space. Hence some method is required to reduce the dimension of the representation space. In this section, we describe the simplest (but sometimes very useful) approach to the dimension reduction problem.

Extracellularly recorded signals can be treated as a mixture of spikes produced by several neurons and different sources of fluctuations or noise. Figure 4.6 illustrates a model of this process. The recorded signal is then given by

$$V(t) = \sum_{n=1}^{N} v_n(t) + \sum_{k=1}^{K} \xi_k(t) .$$
(4.8)

The simplest approach to the problem of spike sorting is amplitude thresholding. The amplitude is one of the most important characteristics of spikes. It is assumed a priori that each neuron generates signals of the same shape, and that this shape does not change significantly over time. If the electrode is placed near one neuron,

Fig. 4.5 A typical example of the extracellular potential recorded from the rodent hippocampus. The simplest way to sort spikes (marked by *arrows*) is by amplitude thresholding (two *dashed lines*)





then its spikes will be significantly higher than spikes of distant neural cells and the background activity. In this case it becomes possible to identify at least one type of spike with amplitude thresholding (e.g., spikes B in Fig. 4.5). Spikes of different heights can be separated by selecting different thresholds (spikes A and B in Fig. 4.5). The advantage of this method is that it requires minimal equipment and can be implemented on-line during recordings. In some cases this approach provides quite precise information, adequate for the research at hand, and no further improvements are required. One obvious disadvantage is that the amplitude is not the only feature of a spike. Spikes of different neurons may have similar amplitudes but, e.g., different widths. Then the quality of spike sorting by amplitude thresholding decays drastically.

To test the quality of spike sorting one can use a superimposed plot of all spikes belonging to a single cluster (Fig. 4.7). If the spikes belonging to one class have basically the same form (up to small variations induced by noise), then we can conclude that the sorting is good enough (Fig. 4.7a). The existence of a spike class with clearly different spike shapes (Fig. 4.7b) means that the method is unable to accurately resolve spikes and other techniques should be applied. However, this method usually works when the number of spikes is relatively small. In the case of big data sets (thousands of spikes), other methods based on electrophysiological and anatomical criteria should be applied (for details see, e.g., [7]).

Besides the background noise, which can be considered as a normally distributed process (or sometimes a Poisson distribution), the amplitude can vary due to possible overlapping if two different neurons fire simultaneously or within a small time window. When the maximum of one spike coincides with the minimum (or, more



generally, with the negative phase) of another spike, then the resulting signal may not reach the threshold (Fig. 4.8a). The number of such events can be estimated approximately as follows:

$$N_{\rm missed} \sim \nu \tau^-$$
, (4.9)

where  $\nu$  is the mean firing rate of neurons and  $\tau^-$  is the mean duration of the negative phase.

Another possible error occurs when two independent spikes with small amplitudes add together and the threshold is crossed by the resulting signal (Fig. 4.8b). Denoting the firing rates of spikes as  $v_1$  and  $v_2$ , we can estimate the error rate in this case as

$$N_{\rm wrong} \sim \nu_1 \nu_2 \tau_1 \tau_2 , \qquad (4.10)$$

where  $\tau_1$ ,  $\tau_2$  are the spike durations.

These two types of error are typical for amplitude thresholding. Besides the possibility of doubled spikes, one can also consider noisy events with high enough amplitudes to affect the amplitude of spikes. The shape-accounting techniques discussed in the remaining part of this chapter are more robust against these errors. Nevertheless, false positive and false negative errors appear for any spike-sorting technique, but their number is typically much lower than for amplitude thresholding.

In order to perform a more detailed description of spike features, besides amplitude, additional characteristics such as duration, height of local extrema, etc., can also be used. Such an ad hoc approach based on the geometrical description of spikes was widely used in spike-sorting techniques developed early on [28–30]. As a rule, the more characteristics are employed for spike description, the better the spike sorting that can be achieved. However, these techniques are subjective and usually provide suboptimal spike sorting. In the following sections, we discuss spike-sorting techniques based on an integral analysis of spike waveforms.

# 4.5 Principal Component Analysis as Spike-Feature Extractor

Principal component analysis (PCA) is a simple but significantly more powerful tool for spike sorting [31–35]. This approach can be considered as a particular case of factor analysis [36]. It is widely used for image recognition [37], noise reduction [38], reduction of dimensions in dynamical models without significant loss of information, e.g., for mathematical description of turbulent flows [39], and so on.

### 4.5.1 How It Works

PCA estimates a set of orthogonal vectors for the matrix (4.6), the so-called principal components  $\{c_i\}_{i=1}^N$ . These are eigenvectors of the covariance matrix constructed from the data  $c_i = (c_{i1}, \ldots, c_{im})^T \in \mathbb{R}^m$ . Then each spike  $x_j$  can be represented as a weighted sum of the principal component vectors with the corresponding weights or scale factors, so called scores  $S_{ij}$ , which are evaluated by the scalar product

$$S_{ij} = (c_i^{\mathrm{T}}, x_j) \equiv \sum_k c_{ik} x_{jk} .$$
 (4.11)

Thus we decompose each spike into an orthogonal set of principal components:

$$x_j = \sum_{i=1}^{N} S_{ij} c_i . (4.12)$$

Then the scores  $S_{ij}$  can be considered as features describing the *j*th spike.

To illustrate the use of PCA for spike sorting, we generated an artificial set of spikes that consisted of a series of 3 repeated waveforms extracted from experimental data (with random order of the waveforms), corrupted by noise with Poisson distribution. By analogy with Lewicki [3], we consider the standard deviation of the scores in the direction of each principal component (Fig. 4.9). If  $\lambda_1, \lambda_2, \ldots$  are the variances in the directions of the principal components, we can estimate the percentage of the data variation that is accounted for by the first *k* components as  $100(\lambda_1 + \lambda_2 + \cdots +$ 



Fig. 4.9 Principal component analysis of spikes of three different classes. a Standard deviations of the scores versus the number of the principal component. b Plane of the first two principal components. Three clusters are easily distinguishable

 $\lambda_k$ )/ $\sum_i \lambda_i$ . Figure 4.9 illustrates the standard deviation of scores versus the number of the principal component. The first three components characterize the main changes in the spike shapes. They account for about 80% of the variance in the data. This suggests that, for reasonably faithful description of spikes, one can use just the first few principal components.

There are different approaches for selecting the number of principal components to retain, i.e., deciding which components are important and which can be excluded without losing important information (see, e.g., [40, 41]. For instance, the method proposed by Cattel [41] examines the explained variance (Fig. 4.9a) and searches for the point where the decrease in the standard deviation versus the number of the principal component becomes the slowest (the so-called elbow criterion). Components to the right of this point can be excluded without loss of important information.

In practice, using the first two [N = 2 in (4.12)] or sometimes three components turns out to be optimal. These components have eigenvalues larger than the background noise. Consequently, they account for the most important information about the shapes of the action potentials, while higher components are usually very noisy and provide no information about the shape of the spikes. Other components provide either an insignificant improvement or even decrease the accuracy of spike sorting. The score of the first two components typically enables acceptable spike sorting with much better performance than the method of amplitude thresholding (or at least equivalent). For instance, in the case shown in Fig. 4.9b, the performance of the method is 100%, i.e., all 'recorded' spikes are correctly assigned to three neurons.
**Fig. 4.10** Original spike waveforms used to generate two data sets (sets #1 and #2). We use three clearly different waveforms (WFs 1–3) and two similar waveforms (WFs 4 and 5). The difference between the similar WFs appears on short time scales for set #1 and on longer time scales for set #2



# 4.5.2 Possible Pitfalls

In contrast to the amplitude approach, disadvantages with the PCA-based method are less obvious and can be revealed only in comparative analysis of different techniques for spike sorting. For illustrative purposes, we generated two semi-simulated data sets (Fig. 4.10), both consisting of 500 spikes of five different waveforms. The original spike waveforms where selected from electrophysiological recordings. The two sets have three clearly different waveforms (WFs 1–3) and two similar ones (WFs 4, 5). Similar waveforms in set #1 exhibit differences only on short time scales, while WFs 4 and 5 in set #2 show a more pronounced difference on longer time scales. To simulate the noisy background, we mixed a colored noise, band-pass (300 Hz–3.0 kHz) filtered Poisson process, with the noise-free spike waveforms.

Spike sorting of set #1 by PCA reveals four different clusters (Fig. 4.11a). Three clusters correspond to spikes of WFs 1–3, thereby confirming the potential of the PCA approach. However, the fourth cluster contains a mixture of spikes of the two similar waveforms (WFs 4 and 5). Analysis of the first principal components proves that the difference between WFs 4 and 5 is not reflected by them. Thus a problem with the PCA method may occur when, among different spike waveforms, there are two types with similar shapes and clearly expressed distinctions appearing only on small time scales (set #1 in Fig. 4.10). Such distinctions are not usually reflected in the first principal components, and consequently the method fails to separate such spikes.

In order to confirm this conclusion, we considered the other test data set, i.e., data set #3, consisting of 500 spikes of five different waveforms (Fig. 4.12a) corrupted by noise. Application of the PCA to this data set again reveals four different clusters.



**Fig. 4.11** Sorting of the data sets shown in Fig. 4.10 by PCA and wavelet techniques. **a** The waveletbased approach outperforms the spike separation by PCA for set #1. In the PCA feature space, the spikes of WFs 1–3 are clearly clustered, but WFs 4 and 5 (*open* and *solid circles*, respectively) are mixed together. The wavelet space provides five well separated clusters for all spikes (WFs 1–5). **b** The PCA method provides better separation of set #2, than the WSC method. The chosen suboptimal wavelet coefficients exhibit multi-modal distributions allowing separation of clearly different spikes (WFs 1–3), but not similar WFs 4 and 5

First, three clusters correspond to spikes of the WFs 1–3, thereby demonstrating the potential of the PCA approach. However, the fourth cluster contains a mixture of spikes of two similar waveforms: WFs 4 and 5 (Fig. 4.12b). Analysis of the principal components confirms that the difference between WFs 4 and 5 is not reflected in the first of them. Thus PCA-based methods may fail to separate spikes with differences appearing on small scales.



**Fig. 4.12** An example where the wavelet-based approach outperforms the spike separation by the PCA. **a** Original spike waveforms used for generation of the data set (set #3). We use three clearly different waveforms (WF 1–3) and two similar waveforms (WF 4 and 5). The difference between the two similar WFs appears on small time scales. **b** Feature space of the first two principal components. A zoomed region corresponding to the fourth cluster is shown. Spikes of two waveforms (*open* and *solid circles* for WFs 4 and 5, respectively) are mixed, and an acceptable separation is impossible. **c** The "Wave", i.e., the function chosen for wavelet analysis. **d** Zoomed region corresponding to the fourth and fifth clusters (WFs 4 and 5) in the wavelet space. Two clearly distinct clouds are formed, and separation is possible with high fidelity

# 4.6 Wavelet Transform as Spike-Feature Extractor

The wavelet approach [10–12] represents the spike waveform  $x_j(t)$  by coefficients of the WT. In the case of the continuous wavelet transform [13, 14], the coefficients are associated with selected values of the time localization  $t_0$  and the scale *s*. In its most general form, the continuous WT of a spike waveform reads

$$W_j(s, t_0) = \frac{1}{\sqrt{s}} \int_0^T x_j(t) \psi_{s, t_0}(t) \,\mathrm{d}t \,\,, \tag{4.13}$$

where T is the spike duration (typically 1-3 ms), and

$$\psi_{s,t_0}(t) = \psi\left(\frac{t-t_0}{s}\right)$$

is a translated and scaled mother wavelet.

The main wavelet-based techniques for spike sorting (e.g., [10-12]) use the discrete wavelet transform, since this provides a quick decomposition of a spike with fewer coefficients. Let us consider, e.g., an approach proposed by Letelier and Weber [10].

# 4.6.1 Wavelet Spike Classifier

The WT of a spike can be considered as a set of filters with different bandwidth. Then the value of the energy found in a specific frequency band for each spike is considered as its feature. This idea was first adopted in the framework of the wavelet-based spike classifier (WSC) [10]. This approach is based on the standard pyramidal expansion algorithm (see Fig. 2.28, Sect. 2.3). The coefficients of the spike decomposition in the basis of Daubechies wavelets are used as features for spike sorting.

For illustrative purposes, we can consider a more general case, namely, application of both the continuous and the discrete wavelet transform, depending on the researcher's choice. We shall consider here the continuous WT, because it is simpler and allows for a detailed representation of the results. In particular, it becomes possible to discuss the problem of optimization of spike features in terms of a surface of the wavelet coefficients, which is a more illustrative approach.

With the tuning parameter *s* in (4.13), one can successfully resolve the multi-scale structure of the data sets #1 (Fig. 4.10a) and #3 (Fig. 4.12a). Indeed, the WSC technique finds all five clusters, including those corresponding to WFs 4 and 5 (Figs. 4.11a and 4.12d).

In the case where spike waveforms have a multi-scale structure with significant characteristics appearing on small scales, as in the data sets #1 and #3 used in Figs. 4.10a and 4.12a, the wavelets are able to resolve these features. Indeed, application of the wavelet technique to the data set of Fig. 4.11a shows that this approach finds all five clusters. Figure 4.12d also illustrates a good separation of WFs 4 and 5 into two clusters, where the PCA had difficulties (Fig. 4.12b).

# 4.6.2 Potential Problems

Although the WT is potentially more powerful than PCA, there are a number of inherent problems restricting its broader application for spike sorting. Here we discuss the main ones among them: an arbitrary choice of mother wavelet and selection of the best wavelet coefficients:

- Apparently, the results of the analysis, e.g., the wavelet coefficients, depend on the mother wavelet ψ. Generally, there is no standard answer about how to choose the mother wavelet in a particular case. Thus the performance of the method for a given mother wavelet may vary considerably from one data set to another. For spike separation, different mother wavelets have been advocated: Daubechies [10], Coiflet [11], and Haar [12]. Possible advantages of one or the other depend on the particular spike waveforms of the analyzed data set, and no a priori recommendation can be given about which mother wavelet will perform better. Successful classification can be achieved by selecting a mother wavelet similar in shape to the spike waveforms. For instance, in the example shown in Fig. 4.12, to obtain a good separation, we used the Wave wavelet (Fig. 4.12c), which is visually very similar to WFs 4 and 5 (Fig. 4.12a).
- Let us assume that the mother wavelet has been selected somehow. Then the WT of spike waveforms is performed, thus obtaining a number of different wavelet coefficients for each spike (usually 64 in the case of the DWT and even more for the CWT). In contrast to PCA, these coefficients are not ordered, and making the right choice among them for spike sorting is a challenging problem. Different authors have suggested different procedures for coefficient selection. Among others, we can list: large standard deviation, large mean values, and multi-modal distribution [10]. There is also a more complicated, but at the same time mathematically better justified method based on information theory [11]. However, there is no single universal approach for the choice of WT features capable of providing the best classification in every case, and a counterexample can always be found. Difficulties occur especially when the analyzed data contains spiking activity of many neurons, and among them there are both clearly different and rather similar types of spike waveforms.

To illustrate the kind of problems that may be encountered, we again generated test data sets #2 and #4 (Figs. 4.10b and 4.13a) with more pronounced differences between the WFs 4 and 5 and with no clear distinctions on small scales. This helps the PCA to separate all spike groups, including those of similar waveforms (Figs. 4.11b and 4.13a). According to one of the wavelet coefficient selection procedures [10], the features used for classification should show a multi-modal distribution. However, in many practical cases, a multi-modal distribution is obtained for many different wavelet coefficients and there is no clue about how to perform an automatic comparison in order to select the most informative ones. An example of such a quasi-arbitrary (unsuccessful) choice of coefficients is illustrated in Fig. 4.13b. Although the chosen wavelet coefficients have multi-modal distributions (Fig. 4.13d), allowing separation of the first three clearly different spike waveforms, the wavelet approach gives a worse classification of two similar waveforms than the one provided by the PCA (Fig. 4.13a and c).



**Fig. 4.13** A case where the PCA provides better separation than the wavelet technique. As in Fig. 4.12, we use a data set with spikes of three clearly different and two similar waveforms. However, the difference between similar spikes is not so pronounced now, and is not on small scales (set #4). **a** Principal components show a good separation of spikes of WF4 and WF5 (*open* and *solid circles*, respectively). **b** Wavelet classification. The chosen wavelet coefficients exhibit multi-modal distributions allowing separation of clearly different spikes. However, separation of WF4 and 5 is not achieved. **c** and **d** Histogram of spike density along the first component score (**c**) and one of the wavelet coefficients (**d**). The wavelet coefficient exhibits a multi-modal distribution, but the number of peaks [four in (**d**)] corresponding to clusters is less than in the PCA case [five in (**c**)]

# 4.7 Wavelet Shape-Accounting Classifier

With a view to improving the wavelet-based extraction of discriminative spike features, let us consider a three-step approach based on a combination of the PCA and wavelet techniques [13, 14]. This algorithm, which we shall refer to as the wavelet shape-accounting classifier (WSAC), works as follows:

- Find representative waveforms (rWFs).
- Search for wavelet parameters (*s*, *t*<sub>0</sub>) maximizing the distances between the rWFs in the wavelet space.
- Evaluate the wavelet coefficients for the resulting parameter sets for all neuronal spikes  $W_i(s^*, t_0^*)$ .

To demonstrate the method we start with a typical situation frequently encountered when processing real electrophysiological recordings. A conventional method of spike feature extraction, e.g., PCA, gives two poorly separated overlapping clouds (Fig. 4.14a). For the sake of simplicity, we suppose that these clouds consist of spikes of two neurons (or spikes of one neuron and other possibly noisy spike-like pulses).



**Fig. 4.14** Working principle of the WSAC method. **a** Two overlapping clouds correspond to spikes of different types on the PCA plane. *Insets* show representative spike waveforms obtained by averaging over neighborhoods of the cloud centers. **b** Difference between wavelet coefficients for the representative spikes as a function of scale. *Circles* mark the coefficient pairs (s = 4.8,  $t_0 = 18$  and s = 7.1,  $t_0 = 32$ ) that correspond to the most prominent distinctions between rWF1 and rWF2. **c** New spike feature space. The resulting coefficients are used. **d** Spike density along the clouds. Peaks correspond to the centers of the clouds. The *dashed line* corresponds to the PCA space and the *solid line* shows the results obtained in the wavelet space. The later distribution shows better separated and more prominent peaks resulting in a better localization of spikes of different waveforms in feature space [compare the clouds in (**a**) and (**c**)]

Our goal is to improve the separability of the two clouds and hence to reduce the number of wrongly classified spikes.

First, we localize the cloud centers  $S_k$  (k = 1, 2), i.e., the positions of the spike density maxima in the PCA space (step 1). Then we average the spike waveforms over spikes falling in a small neighborhood of each cloud center (insets in Fig. 4.14a):

$$x_{\text{rWFk}} = \overline{x}_{j\in\omega} , \qquad \omega = \left\{ j \in [1, N] : \|S_j - S_k\| < \varepsilon \right\}.$$

$$(4.14)$$

The mean or representative waveforms (rWFs) thus obtained approximate noise-free spike waveforms of the two neurons. Here we assume that each neuron emits spikes of the same shape that are linearly mixed with noise at the electrode, so that the noise impact near the cloud centers is minimal and gets canceled by averaging.

Second, we apply the WT to  $x_{rWF1}$ ,  $x_{rWF2}$  and search for a set of parameters  $(s^*, t_0^*)$  that maximizes the distance  $|W_{rWF1}(s^*, t_0^*) - W_{rWF2}(s^*, t_0^*)|$  (step 2). Figure 4.14b shows the distance between rWFs in the wavelet space as a function of the scale *s* for different values of  $t_0$ . Frequently, crucial differences between spike waveforms occur at the beginning and the end of firing. To better account for the spike morphology, we search separately for the maximal distance in the first and second halves of the spike time window. Circles in Fig. 4.14b mark two points (one for each half window) where the distance between the representative waveforms is maximal.

Third, we apply the WT for all spikes  $x_j$ , using the parameter sets  $(s^*, t_0^*)$  found above (step 3). The resulting coefficients are the new spike features (Fig. 4.14c). Visually, the clouds corresponding to two neurons are better delimited in the wavelet plane than in the PCA space (compare Fig. 4.14a and c). Indeed, the histogram of the distribution of spike features in the wavelet spaces (WSAC method) exhibits significantly more pronounced peaks than the PCA method (Fig. 4.14d). This means that one can now better delimit clouds and considerably reduce classification errors arising from misclassification of spikes in the overlapping part of the clouds.

# 4.8 Performance of PCA Versus WT for Feature Extraction

We tested the proposed approach on three different data sets (S1, S2, and S3). Each data set is obtained in the following way. We take two experimental electrophysiological recordings. One of the recordings is selected in such a way that spikes of one type can be easily separated from the rest by the conventional thresholding method (Sect. 4.4). These spikes are then mixed with another experimental recording displaying complex spiking activity. On the one hand, this procedure allows one to keep all characteristics essential to a real electrophysiological experiment (level and type of noise, spike waveform variation, etc.), and on the other hand, we possess a priori information about the membership of spikes for one target cluster formed by the "additional" spikes. Hence, we can estimate the classification error for the given cluster.

The generated data sets were used as an input to three feature extraction algorithms discussed above: PCA, WSC, and WSAC. Then clustering was performed using the superparamagnetic method [42], and the number of misclassified spikes was estimated.

Figure 4.15 illustrates results obtained for the data set S1 consisting of 16568 spike waveforms, including 3069 "additional" spikes. The PCA gives 2 clusters (Fig. 4.15a) shown in black and gray, corresponding to the additional (targeting) and the original action potentials, respectively. Squares mark unclassified spikes that are not related to either of the clusters. Classification of spikes by the three first PCs gives 290 misclassified spikes: 24 false negative and 266 false positive, i.e., 0.8% and 8.6% of the total number of spikes in this cluster. The histograms of spike densities for each coordinate in the feature space show a bimodal distribution for the PC1, and a unimodal distribution for the PC2. The former allows separation of different



Fig. 4.15 Results of spike separation by different methods for the data set S1. **a** Projection of the feature space for the PCA onto its first two components, and corresponding histograms of spike densities. *Black points* correspond to spikes classified as belonging to the targeting cluster. **b** The same as in **a**, but for the WSC method. **c** The same as in **a**, but for the WSAC method. **d** Number of misclassified spikes for the different methods and for different spike feature subsets used for classification

waveforms into two clusters, while the latter does not actually provide additional information for spike classification.

Figure 4.15b illustrates the results of spike sorting performed by the WSC method [10]. Following the authors' recommendations, we chose for classification the wavelet coefficients showing the largest standard deviations, the largest values, and the bimodal distributions. Note that, in contrast to the PCA, the histograms in Fig. 4.15b are both bimodal, so they actually provide useful information for spike sorting. However, for the considered example, we obtain a higher classification error: 410 misclassified spikes (5.2% of false negative and 8.1% of false positive). Thus a quasi-arbitrary choice of wavelet coefficients satisfying the given recommendations did not lead to an improvement in spike sorting as compared with the PCA method.

Figure 4.15c shows the results of the spike classification obtained using the WSAC method. We found that three pairs of coefficients ( $s^*$ ,  $t^*$ ), namely, (6.8, 31), (8.6, 51), and (6.2, 20), maximize the difference between the characteristic spike shapes. These sets were used for spike sorting, which provided the best results: 185 or 2.8% of false negatives and 3.1% of false positives.

	S1				S2				\$3			
	FN	FP	Sum		FN	FP		Sum	FN	FP	Sum	
PCA	0.8	8.6	9	0.5	41.6	11	0.8	53.4	0.1	2.6	2	0.7
WSC	5.2	8.1	13	0.3	34.2	13	0.8	48.0	6.7	2.9	9	0.6
WMSPC	7.5	8.9	16	0.4	28.7	0	0.8	29.5	9.5	4.4	13	0.9
WSAC	2.8	3.1	5	0.9	26.4	8	0.2	34.6	1.8	0.3	2	0.1

 Table 4.1
 Classification error rates for all data sets and different methods (percentage of misclassified spikes out of the total number of spikes in the cluster). FN and FP denote false negative and false positive errors

Figure 4.15d shows the results of spike classification using the three methods for different combinations of features used in each particular technique. For instance, classification performed using the first two principal components gives 364 errors (first bar in Fig. 4.15d), whereas the same done with PC1 and PC3 results in 296 errors. This means that, in this case, PC3 describes the variation in the data set better than PC2. Using all three components slightly improves the classification, resulting in 290 errors. Considering WSC, we note that each coefficient improves the results of classifications, but the overall performance is the worst among all the methods. On average, the WSAC approach gives the minimal classification error for any combination of spike features.

Table 4.1 summarizes the results obtained for all data sets. We also include classification errors obtained by the WMSPC method based on the approach proposed by Quian Quiroga et al. [12]. This approach performs considerably better for the set S2, while showing poor performance for S1 and S3.

Hence, regarding the question of when wavelet-based methods outperform the PCA, we have shown that the main advantage of WT techniques reveals itself when dealing with the detailed structure of experimental signals over a broad range of scales. Considering the WT approach as a *mathematical microscope*, the following interpretation can be given: wavelets can resolve fine details of a signal structure, but we need to choose the focal point and resolution of this "microscope" appropriately. From the mathematical viewpoint, this means that the selection of wavelet parameters responsible for resolution and focusing is of crucial importance. If they are selected successfully, the "microscope" can elucidate the differences in spike waveforms.

This is why the problem of selecting the optimal wavelet coefficients is an important trend in the problem of spike separation. In contrast to PCA-based methods, where the first principal component scores are used as spike features due to their natural order, optimal selection of features within the framework of WT techniques is a significantly more complicated procedure.

There are at least two cases where wavelet-based techniques are potentially preferable to PCA:

• When there is small-scale structure in the waveforms that is not reflected in the first principal components.

• When there is strong enough low-frequency noise, since this significantly diminishes the performance of the PCA method, whereas noise statistics are less critical for wavelets.

In other situations, the considered WT-based approaches give comparable results to PCA.

# 4.9 Sensitivity of Spike Sorting to Noise

Sensitivity of spike sorting to noise statistics is an important problem for any approach. Extracellular recordings of neural activity contain different kinds of noise, from Johnson noise in the electrode and electronics, through the background activity of distant neurons and electrode micromovement, to variation of action potentials due to physiological processes in the cell dynamics.

Obviously, the quality of the spike separation is degraded by increasing noise intensity, although robustness against the noise level may be different for different methods. Another, more important question we address here is how the efficacy of the method depends on the frequency band of the noise. Indeed, when the noise frequency band lies far outside the frequency band of a spike spectrum (about 300–3000 Hz), the noise can be easily filtered out by applying high-pass and/or low-pass filters, thus eliminating the impact of the noise on spike separation. However, when the noise frequency band overlaps with the spike spectrum, the use of filters becomes worthless, and the advantages of one or another method can become significant. This kind of overlap can happen, for example, when recording certain neurons from a densely populated brain region and spikes from more distant neurons (far enough away and consequently of low enough amplitude to be included as spikes for separation, but close enough that their effect is noticeable) are confused with noise.

In this section, we study and compare the performance of the PCA and the wavelet technique with regard to the noise statistics, assuming an overlap between the spike spectrum and the noise frequency band. We discuss how the quality of spike separation depends on the frequency band of the experimental noise.

# 4.9.1 Impact of High/Low Frequency Noise on PCA and WT

Quantities used as features for spike separation in the PCA and WT techniques are often related to rather different time scales. This suggests that PCA and WT may show different degrees of robustness against noise with different statistics.

The wavelet coefficients  $W(s, t_0)$  used for spike classification are typically related to rather small values of the scale parameter *s*. Therefore we expect the coefficients to be distorted mainly by fluctuations in the frequency band associated with the scale parameter value. Relatively slower or faster fluctuations should not have an essential



**Fig. 4.16** PCA feature space of spike waveforms contaminated by noise. **a** Low-frequency noise,  $f_{\text{noise}} = 500 \text{ Hz}$ . **b** High-frequency noise,  $f_{\text{noise}} = 2500 \text{ Hz}$ 

influence (in the case of additive noise). The latter means that separation of several types of spikes by the WT approach should have a maximal classification error for noise with high-frequency dynamics.

Another situation is expected for PCA. This approach quantifies spike features on large scales for entire waveforms. The low-frequency noise appearing on the time scales of the first principal components disperses spikes in the PCA feature space. The high-frequency noise mainly affects high principal components that are not considered for spike separation. As a result, the PCA method should exhibit an error that decreases with the frequency band of the presented fluctuations.

To check these conjectures, we generated data sets consisting of 2000 spikes of two different types (two neurons). Then we mixed spike waveforms with colored noise of a certain frequency band, and finally we performed spike sorting on the resulting data sets.

The colored noise was obtained by band-pass filtering of a Poisson random process. Choosing different values of the central frequency  $f_{\text{noise}}$  of the band-pass filter, which defines the base noise frequency, and fixing the filter width ( $\Delta f_{\text{noise}} = 700 \text{ Hz}$ ), we estimated the classification error for each spike-sorting technique. Noise with base frequency lower than the main frequency of the spike spectrum (about 1 kHz) was considered to be low frequency, while fluctuations with  $f_{\text{noise}} > 1 \text{ kHz}$  were considered to be the high-frequency noise. For wavelet sorting, we used the WSC method [10], but other methods show qualitatively similar results.

Figure 4.16 shows that the presence of slow fluctuations is more critical for PCA than the high-frequency dynamics. In the case of high-frequency noise, clusters are well distinguished ( $f_{noise} = 2500$  Hz, Fig. 4.16b), whereas they are less pronounced for a slower random process ( $f_{noise} = 500$  Hz, Fig. 4.16a). In contrast, spike sorting using the wavelet technique shows good performance in the case of low-frequency noise (Fig. 4.17a,  $f_{noise} = 500$  Hz), but performance is diminished for high-frequency noise (Fig. 4.17b,  $f_{noise} = 2500$  Hz).



**Fig. 4.17** WT feature space of spike waveforms contaminated by noise. **a** Low-frequency noise,  $f_{\text{noise}} = 500 \text{ Hz}$ . **b** High-frequency noise,  $f_{\text{noise}} = 2500 \text{ Hz}$ 



Fig. 4.18 Classification error versus base noise frequency for PCA (a) and the WT technique (b)

We repeated spike sorting for a different base noise frequency. Figure 4.18 summarizes our results. The error of spike sorting using PCA clearly decreases with the base noise frequency (Fig. 4.18a). Spike separation using the wavelet technique shows a bell-like resonance curve. The worst classification is achieved for an intermediate noise frequency (around 2 kHz). Thus, the spike classification error is sensitive to the noise statistics.

# 4.9.2 Proper Noise Filtering May Improve Spike Sorting

The results shown in Fig. 4.18 provide a clue that the quality of spike sorting may be increased by smart data preprocessing, i.e., noise filtering. In particular, when the noise frequency band lies far outside the frequency band of the spike spectrum,



Fig. 4.19 Classification error versus cutoff frequency of a high-pass filter in the case of nonoverlapping (a) and overlapping (b) power spectra of noise and spikes. The noise intensity is higher in (b)

the noise can be easily filtered out by applying high- and/or low-pass filters, thereby eliminating the noise impact on the spike separation. Figure 4.19a illustrates this simple situation.

In order to choose an optimal value for the filter cutoff frequency, one must estimate the power spectra of noise and spikes. But in order to provide a better separation of action potentials, rather than the latter spectrum, it seems to be even more useful to evaluate the spectrum of the difference between the typical (averaged) spike waveforms. Choosing the cutoff frequency of the high-pass filter higher than the range of fluctuations, we obtain clear spike sorting (Fig. 4.19a). Note that the classification error remains the same here, even when the cutoff frequency lies inside the spike spectrum: the filtering changes the waveform shapes, but these changes are the same for each type of spike, so the waveforms can be well separated. Similar results can be obtained if the frequency band of the noise is higher than the frequency band of the spike dynamics. The noise intensity does not have a crucial impact on the selection of the optimal cutoff frequency here.

In practice, however, a significantly more complicated situation is typically encountered. Usually the noise spectrum overlaps significantly with the spike spectrum and the choice of filter parameters becomes less obvious.

In order to seek for the best filtering strategy, we filtered waveforms using elliptic IIR zero-phase filter. Figure 4.19b illustrates an example of how the classification results depend on the cutoff frequency of a high-pass filter for overlapping power spectra. In contrast to the previous case (Fig. 4.19a), we cannot take bigger values of the cutoff frequency here due to the increasing classification error. An optimal value of the given frequency probably depends on both the noise intensity and the strength of spectrum overlap. In particular, this optimum may not be well expressed for rather low noise intensity (Fig. 4.20a), while the choice of filter parameters becomes more critical in the case of intense noise. According to Fig. 4.20b, a cutoff frequency around 400 Hz provides the best spike separation here.



Fig. 4.20 a Classification error of the PCA and WT techniques versus the cutoff frequency of a high-pass filter in the case of overlapping power spectra of noise and spikes (low noise intensity). b The same, but for low-pass filtered spikes

Let us now consider how the use of a low-pass filter influences the quality of spike sorting. Figure 4.20b shows the dependence of the total classification error on the cutoff frequency of the low-pass filter. Indeed, the classification error for the WT technique has a minimum at frequencies around 2.2 kHz and then rapidly increases. For the PCA, the error first decreases gradually to 2 kHz, then remains almost constant. This suggests that low-pass filtering of spikes is worthless for PCA, and is essential for the WT, where to be on the safe side we recommend a cutoff frequency in the range 2.5-3 kHz.

# 4.10 Optimal Sorting of Spikes with Wavelets and Adaptive Filtering

In the vast majority of spike sorting methods, experimental noise is reduced by a standard filtering prior to extraction of spike features. This procedure does not account for the noise statistics, nor for the spike signatures. Standard techniques like amplitude thresholding and PCA have a long history, and well established recipes for optimal filtering. Their performance usually reaches a maximum for a high-pass filter at 0.3–1 kHz. However, this may not be the case for the WT technique (Fig. 4.20). Then a different filtering approach may be superior.

As we shall see in this section, the performance of the WT method can be significantly improved by incorporating the filtering step into the problem of selecting the optimal feature set. In other words, signal filtering and spike feature extraction can be done in a single step. The parametric wavelet sorting with advanced filtering (PWAF) approach was proposed to exploit this idea [43].



### 4.10.1 Noise Statistics and Spike Sorting

To illustrate how the noise statistics affects the spike-sorting performance, we generated semi-artificial data sets. Each data set consisted of (1000+1000) spikes of two different neurons. The original spike waveforms where selected from electrophysiological recordings in the hippocampus. To simulate the effect of the noisy background, we mixed colored noise (a band-pass filtered Poisson process) of a certain frequency band with spike waveforms. We used these data sets for spike sorting and then estimated the performance through the error rate, i.e., the ratio of misclassified spikes to the total number of spikes.

Figure 4.21a shows the error rate as a function of the base noise frequency. In accordance with previous results (Sect. 4.9), the PCA method gives a high error rate for low-frequency noise and then progressively increases performance for high-frequency noise.

As a representative approach for wavelet-based methods, we use the WSC technique. This method exhibits significantly different behavior. The error rate has a well-pronounced peak at an intermediate noise frequency (about 2 kHz). Compared with PCA, the wavelet technique is a better option for sorting spikes contaminated by low-frequency noise ( $f_{noise} < 800 \text{ Hz}$ ).

In order to find the best filtering strategy, we filter waveforms, varying the cutoff frequency of the LPF, and then perform spike classification on the filtered data. Here we use white noise passed through the LPF with a varying cutoff frequency. Filtering generally reduces the error rate. However, it affects the PCA and WT methods differently (Fig. 4.21a). Indeed, the classification error for the WT technique has a

minimum at a filter frequency around 2.2 kHz and then increases rapidly. For PCA, the error begins by gradually decreasing to 2 kHz and then remains practically constant. This suggests that low-pass filtering of spikes is worthless for PCA, but it may be essential for WT methods, where the cutoff frequency should be appropriately selected.

# 4.10.2 Parametric Wavelet Sorting with Advanced Filtering

We now discuss the details of optimal spike sorting using the wavelet technique.

### 4.10.2.1 Derivation of PWAF Method

We start from a data set of N + M spikes of two different neurons, contaminated by noise. Denoting the original noise-free spike waveforms by  $w_A(t)$  and  $w_B(t)$ , the recorded spikes can be written as

$$x_{j}(t) = \xi_{j}(t) + \begin{cases} w_{A}(t) , & j = 1, 2, \dots, N , \\ w_{B}(t) , & j = N+1, \dots, N+M . \end{cases}$$
(4.15)

where we have assumed without loss of generality that the spikes are ordered. Here,  $\{\xi_j\}$  are colored noise sources, mutually uncorrelated and with the same statistics (i.e., spectrum).

Applying the WT (4.13) to the spike waveform  $x_j(t)$  for a selected parameter set  $(s, t_0)$ , we obtain

$$W_j(s, t_0) = \eta_j + \begin{cases} W_A, & j = 1, 2, \dots, N, \\ W_B, & j = N+1, \dots, N+M, \end{cases}$$
(4.16)

where we have put

$$\eta_j(s, t_0) = \frac{1}{\sqrt{s}} \int_0^T \xi_j \psi_{s, t_0} \,\mathrm{d}t \,\,, \tag{4.17}$$

$$W_{A,B}(s,t_0) = \frac{1}{\sqrt{s}} \int_0^T w_{A,B} \psi_{s,t_0} \,\mathrm{d}t \;. \tag{4.18}$$

In (4.16), the  $\eta_i(s, t_0)$  represent a kind of measurement noise and  $W_{A,B}$  are the WT coefficients of the corresponding noise-free spikes.

The coefficients  $W_j$  can now be used for sorting. The aim is to separate them blindly into two clusters or groups with the lowest possible error rate. In our case, the sorting is achieved by selecting a threshold  $W_{\text{th}}$  and assigning spikes with  $W_j < W_{\text{th}}$ to neuron A, and the others to neuron B (Fig. 4.22). This makes sense if the  $\{W_j\}$ 



have a bimodal distribution, otherwise when, e.g., the noise is too strong or the parameters  $(s, t_0)$  are not optimal and no bimodal distribution exists, spike sorting is meaningless.

Let us now assume that the measurement noise is approximately Gaussian with standard deviation  $\sigma$ . We denote the half distance between the noise-free spikes in the wavelet space by

$$\widehat{W} = \frac{W_B - W_A}{2} = \frac{1}{2\sqrt{s}} \int_0^T (w_B - w_A) \psi_{s,t_0} \,\mathrm{d}t \;. \tag{4.19}$$

Without loss of generality, we can shift the origin and set  $\widehat{W} \equiv W_B = -W_A$ . Then the probability density distribution of  $\{W_i\}$  reads

$$h(W) = \frac{M}{\sqrt{2\pi\sigma}} \left\{ \gamma \exp\left[-\frac{(W+\widehat{W})^2}{2\sigma^2}\right] + \exp\left[-\frac{(W-\widehat{W})^2}{2\sigma^2}\right] \right\} , \qquad (4.20)$$

where  $\gamma = N/M$  is the ratio of the numbers of spikes emitted by the neurons. Then the minimum of the total number of misclassified spikes is attained for

$$W_{\rm th} = \frac{\sigma^2}{2\widehat{W}} \ln \gamma \ . \tag{4.21}$$

Note that the optimal threshold value ( $\gamma \neq 1$ ) does not generally correspond to the position of the minimum in the histogram. Finally, the theoretical minimum of the error rate is given by

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$$R_{\min} = \frac{\gamma \operatorname{erfc}\left(\Delta + \frac{\ln\gamma}{4\Delta}\right) + \operatorname{erfc}\left(\Delta - \frac{\ln\gamma}{4\Delta}\right)}{2(1+\gamma)} , \qquad (4.22)$$

where erfc is the complimentary error function, and

$$\Delta = \frac{\widehat{W}}{\sqrt{2}\sigma} \tag{4.23}$$

is the *discriminability coefficient*. Accordingly, the error rate is a two-parameter function of  $\gamma$  and  $\Delta$  that decays with an increase in  $\Delta$  (Fig. 4.22b). The ratio  $\gamma$  of the spike numbers is fixed by experiment, so the only remaining freedom is the discriminability  $\Delta$ .

Let us now explore ways to improve the discriminability. Selecting  $(s, t_0)$  appropriately, we can maximize the value of  $\widehat{W}$  which, for constant  $\sigma$ , increases  $\Delta$ . However, as we shall show, the scaling parameter *s* has a nontrivial effect on the standard deviation  $\sigma$  of the noise, and consequently also on  $\Delta$ .

The experimental noise  $\xi(t)$  of a limited frequency band  $\Omega_{noise}$  can be represented by a sum of harmonics:

$$\xi_j = \sum_{\Omega_{\text{noise}}} A(\omega_k) \cos(\omega_k t + \phi_{kj}) , \qquad (4.24)$$

where  $\omega_k$  and  $\phi_{kj}$  are the frequency and random phase of the corresponding harmonic, and  $A(\omega)$  defines the noise amplitude spectrum. Using the Haar wavelet (advocated for spike sorting in [12]), we obtain the WT of the experimental noise (4.24):

$$\eta_j = -\frac{4}{\sqrt{s}} \sum_k \frac{A(\omega_k)}{\omega_k} \sin \phi_{kj} \sin^2 \frac{s\omega_k}{4} .$$
(4.25)

Note that the statistical properties of  $\eta$  do not depend on the localization parameter  $t_0$ . Then the standard deviation of the measurement noise reads:

$$\sigma^2(s, \Omega_{\text{noise}}) = \frac{8}{s} \sum_k \frac{A^2(\omega_k)}{\omega_k^2} \sin^4 \frac{s\omega_k}{4} .$$
(4.26)

Thus the discriminability may depend nontrivially on the parameters  $(s, t_0)$ , the spike waveforms, and the spectral characteristics of the experimental noise. A natural way to change the noise spectrum is to filter the signal. Denoting the cutoff frequency of the filter by  $f_c$ , we finally reduce the problem of optimal spike sorting to *searching for the parameter set*  $(s, t_0, f_c)$  *which maximizes the discriminability*:

$$\arg \max_{s,t_0,f_c} \frac{\widehat{W}}{\sqrt{2\sigma}} . \tag{4.27}$$

Note that our problem statement is more general than conventional methods relying on a search for the best parameter set for the WT alone. By including spike filtering in the problem of optimal spike sorting, we account for the specific noise of the individual experiment and potentially provide the best possible spike classification. Moreover, other methods of WT parameter selection are based on empirical analysis of the experimental distribution of the WT coefficients, while the PWAF method is parametric.

#### 4.10.2.2 Implementation of the PWAF Method

Under experimental conditions, we have no a priori knowledge of the noise-free spikes, nor the spectrum of the experimental noise. To estimate these and optimally sort spikes, we propose the following algorithm:

- 1. Estimate the noise-free spike waveforms. Applying a conventional algorithm, e.g., PCA, we find peaks in the distribution of spike features and average spike waveforms in the vicinity of each peak, thus estimating  $w_{A,B}$ .
- 2. Estimate the spectrum of the experimental noise  $P(\omega)$ . A good approximation is the spectrum of the whole extracellular signal.
- 3. Find an optimal parameter set  $(s^*, t_0^*, f_c^*)$  maximizing the discriminability. For a given  $(s, t_0, f_c)$ :
  - Filter the signal representing the waveform difference  $(w_B w_A)$  and evaluate  $\widehat{W}$ .
  - Evaluate

$$A^{2}(\omega) = P(\omega)H^{2}(\omega) ,$$

where H is the filter magnitude response, and then  $\sigma$ .

• Evaluate the discriminability,  $\widehat{W}/\sqrt{2}\sigma$ .

Find the maximum

$$(s^*, t_0^*, f_c^*) = \arg \max_{s, t_0, f_c} \Delta(s, t_0, f_c)$$

- 4. Filter spikes with  $f_c^*$  and calculate  $W_i(s^*, t_0^*)$ .
- 5. Sort spikes according to the coefficients  $W_i$ .

Note that the proposed method can be very efficient for large data sets. Steps 1-3 do not depend on the number of spikes and the WT of the whole data set is evaluated only once. Moreover, the algorithm allows the use of more than one feature set for sorting. At step 3, we can obtain more than one extremum, and then perform step 4 for all of them. In this way, we describe each spike with more than one feature (wavelet coefficient) and can use them together for spike sorting in step 5.

Fig. 4.23 Sorting of data set #1. a Discriminability  $\Delta$  vs cutoff frequency of an LPF. For the maximal  $\Delta = 2.39$ , the theoretical minimum of the error rate is 0.3%. *Inset*: Superposed experimental spike waveforms and noise free spikes (*white*). b Distributions of spike features for different methods: PCA, exhaustive wavelet, and PWAF



#### 4.10.2.3 Algorithm Performance

To test the algorithm, we employ simulated data sets differing by noise statistics and spike waveforms. Figure 4.23 shows an application of the algorithm to the data set #1. The discriminability has a strong peak at a surprisingly low frequency  $f_c = 100$  Hz (Fig. 4.23a). With such aggressive filtering, the difference  $\widehat{W}$  between the noise-free spikes in the wavelet space is small, but at the same time, we almost completely filter out the noise, thereby gaining in performance.

Figure 4.23b shows histograms of the distribution of spike features (see also Fig. 4.22a). The PCA method involves a significant overlap of the spikes of two neurons and the resulting error rate is 5.5%. To find the best possible classification with the conventional WT, we *search exhaustively* through all pairs (s,  $t_0$ ) for a set

Data set	PCA		Exhaustive wavelet (%)	PWAF (%)
Simulated #1	5	0.5%	4.5	0.7
Simulated #2	28	0.0%	5.5	1.7
Experiment #1	11	0.1%	7.0	3.4
Experiment #2	12	0.2%	7.3	6.8

 Table 4.2
 Error rate for spike sorting by different algorithms with simulated and experimental data sets

minimizing the error rate. Note that this is not possible in any real situation without a priori knowledge of the spike clusters. This procedure yields the absolute minimum of classification errors that can be achieved by any empirical WT-based method. The exhaustive wavelet gives a bit better classification than PCA, achieving a 4.5% error (Fig. 4.23b).

The PWAF method is significantly superior, with an error rate of 0.7%, which is quite close to the theoretical minimum. This confirms the hypothesis that intelligent filtering is essential for wavelet methods.

We performed the same procedure for another data set (Table 4.2) that was selected to exhibit differences between noise-free spikes at small time scales. This is a case where the wavelet technique has an advantage over the PCA method. Indeed exhaustive wavelet and PWAF yield a much better classification than PCA.

We now test the PWAF method on real measurements. Extracellular recordings were made using tetrode electrodes. Their design permits recording of the same neuron by two electrode tips (for details see [4]). In rare cases, two electrode tips captured high-amplitude spikes generated by a single neuron in addition to simultaneous multi-neuronal activity. Among many experimental recordings, we selected two data sets where these conditions were satisfied. For these data sets relating voltage traces of the two channels, we sort spikes manually with high fidelity. Then using this information, we estimate the error rate of the automatic methods. Table 4.2 summarizes the results, showing once again that the PWAF method is superior.

# 4.11 Spike Sorting by Artificial Neural Networks

We now discuss applications of artificial neural networks [44–48] for spike sorting, including combined approaches based on wavelets and neural networks.



Fig. 4.24 Multilevel decomposition of a typical spike waveform using the  $D^4$  wavelet

## 4.11.1 General Approach

Here we use the wavelet multiscale decomposition of spikes as an input to a neural network. For spike decomposition, the discrete wavelet transform is used as a tool to characterize the structure of complex signals over a broad range of time scales. Figure 4.24 depicts an example of a three-level DWT of a typical spike waveform x(t). The series of coefficients  $s_1-s_3$  correspond to the approximation of x(t) at three levels, whereas  $d_1-d_3$  represent details. Then the set  $[s_3, d_1, d_2, d_3]$ , used as input to a neural network, uniquely represents the original spike waveform x(t) in the wavelet space.

In general, DWT provides quite a large number of coefficient features for each spike (equal to the spike length, e.g., 64). Not all of them are relevant for spike sorting, others may contain duplicated information. Thus for efficient spike sorting, a dimension reduction is required, and for this purpose we use neural networks.

Let us assume that some multilayer feedforward neural network receives as input spike waveform features extracted by the wavelet technique described above (Fig. 4.25). The network should be trained in such a way that, at the output, we can read out a *few compound* features best discriminating the spikes [44]. Then the problem of spike sorting becomes trivial and simple clustering algorithms, e.g., *k-means*, can be used. We thus formulate the following algorithm for spike sorting:

• Detect spikes that exceed the level of experimental noise by thresholding the high-pass-filtered recorded potential [Fig. 4.5,  $f_{cut} = 100-300$  Hz,  $V_{th} = 3*MAD$  (mean absolute deviation)].



**Fig. 4.25** General scheme for spike sorting using the wavelet transform and neural networks. Different spikes are wavelet transformed and the resulting coefficient features are fed into a network which finally represents the spikes in a low-dimensional space. The network should be trained in such a way that spikes of different neurons are grouped into clusters located far away from each other

- Apply DWT to the selected waveforms (Fig. 4.24). We assume that each waveform has 64 data points and use the  $D^4$  orthonormal Daubechies wavelet, performing a pyramidal decomposition of the waveforms.
- Remove wavelet coefficients fluctuating around zero mean value, since these coefficients are strongly influenced by noise.
- Process the remaining wavelet coefficients by a 3-layer feedforward neural network.

After applying the algorithm, we expect to obtain several clusters grouping spikes in the low-dimensional feature space (Fig. 4.25). The most challenging problem in this algorithm is how to select an appropriate network and how to train it [45–48].

In general, training algorithms can be subdivided into two groups: supervised and unsupervised learning. Supervised learning, i.e., with a "teacher", usually gives better results. However, within this framework, the learning procedure requires a priori knowledge of all standard spikes, i.e., denoised typical spikes generated by all neurons, which is hardly going to be available in a real experiment.

At the present time, there exist different algorithms for unsupervised learning (without a "teacher") [46, 47]. These algorithms have been shown to be successful in image recognition, but their reliability depends significantly on the noise level and the data set. Consequently, their use for spike sorting may not be effective. In the present approach, we thus use a kind of supervised learning algorithm, which we shall describe later.

Setting the network structure for a recognition problem is often simply a matter of experience on the part of the researcher. The selected three-layer network in Fig. 4.25 is just one among many. However, several circumstances should be taken into account. The feedforward network representing a multilayer perceptron [49] is one of the most studied in the literature. The choice of the number of layers and units in each layer is a compromise between network stability and plasticity. More complex networks possess better adaptation, but they may be unstable in the recognition process. Concerning the number of units (neurons), we use 64, 32, and



Fig. 4.26 Block diagram for the proposed method of spike sorting

2 units in the first, second, and third layers, respectively. The number of units in the first layer is fixed by the number of data points available for each waveform, whereas the output layer has only two units, corresponding to the lowest useful dimension for clustering (clustering in 1D usually has much lower performance) (Fig. 4.26).

# 4.11.2 Artificial Neural Networks

Following on from the brief sketch given in Sect. 4.11.1, let us now discuss approaches based on ANN in more detail. We continue to use a 3-layer perceptron (Fig. 4.27). In the theory of ANNs, neuron nodes are typically described by the McCulloch–Pitts equations [50]. The state of the neuron j in layer k, denoted by  $y_{jk}$ , is given by

$$y_{jk} = F(v_{jk}), \quad v_{jk} = \sum_{i=1}^{M_k} \omega_{ijk} y_{ik-1} - \theta_{jk}, \quad j \in [1, N_k], \quad (4.28)$$



**Fig. 4.27** Artificial neural network in the form of a 3-layer perceptron

where F(x) is the activation function, and in fact, usually  $F(x) = \alpha \tanh(\beta x)$ , while  $\omega_{ijk}$  are the synaptic weights defining connections of the neuron with other neurons in the previous layer, and  $\theta_{jk}$  is the threshold for activation of the neuron. Finally,  $M_k$  and  $N_k$  are the numbers of synapses and neurons, respectively, in layer k.

The learning of such a multilayer structure assumes an appropriate tuning of the thresholds  $\{\theta_{jk}\}\$  and synaptic coefficients  $\{\omega_{ink}\}\$ , in such a way that input vectors  $\mathbf{x}^s$  would be mapped to predefined output vectors  $\mathbf{y}^s$ . As the learning technique, we shall consider algorithms based on the backward propagation of errors. This approach uses minimization of the error functional over the parameters  $\omega_{ijk}$  and  $\theta_{jk}$ , viz.,

$$E = \frac{1}{2} \sum_{j=1}^{N_k} (y_{jk} - y_j^s)^2 , \qquad (4.29)$$

where  $y_{j3}$  represents the vector of output values obtained in the process of recognition of the input vector  $\mathbf{x}^s$  using the neural network, and  $\mathbf{y}^s$  is the known vector. The minimization procedure is based on the convex property of *E*. In order to reach a minimum of the function, one can move against the gradient of *E*. Let  $\mathbf{P} = \{\dots \omega_{ijk} \dots; \dots \theta_{jk} \dots\}$  be the vector whose components are the synaptic coefficients and threshold levels of the neural network. Then we have to find arg min<sub>P</sub> *E*(**P**). This can be done by the following iterative procedure:

$$\mathbf{P}^{(1)} = \mathbf{P}^{(0)} - \mathbf{e}_j h \frac{\partial E(\mathbf{P}^{(0)})}{\partial P_j^{(0)}} , \qquad (4.30)$$

where h > 0 is a small constant known as the learning rate (the learning is performed for one component at a time). Then the minimum of the scalar error function (4.29), using all components  $\{\omega_{ijk}\}, \{\theta_{jk}\}$ , corresponds to

$$\frac{\partial E}{\partial \omega_{ijk}} = \frac{\partial E}{\partial y_{jk}} \frac{\partial y_{jk}}{\partial v_{jk}} \frac{\partial v_{jk}}{\partial \omega_{ijk}} = 0 ,$$
  

$$\frac{\partial E}{\partial \theta_{jk}} = \frac{\partial E}{\partial y_{jk}} \frac{\partial y_{jk}}{\partial v_{jk}} \frac{\partial v_{jk}}{\partial \theta_{jk}} = 0 ,$$
  

$$y_{ik} = \alpha \tanh(\beta v_{ik}) .$$
(4.31)

The coefficients of the neural network (Fig. 4.27) are corrected using (4.28), (4.29), and (4.31):

$$\frac{\partial E}{\partial \omega_{ij3}} = y_{i2} \frac{\beta}{\alpha} (y_{j3} - y_j^s)(\alpha - y_{j3})(\alpha + y_{j3}) ,$$
  
$$\frac{\partial E}{\partial \theta_{j3}} = (-1) \frac{\beta}{\alpha} (y_{j3} - y_j^s)(\alpha - y_{j3})(\alpha + y_{j3}) ,$$

$$\frac{\partial E}{\partial \omega_{ij2}} = y_{i1} \frac{\beta}{\alpha} (\alpha - y_{j2}) (\alpha + y_{j2}) \sum_{n=1}^{N_3} \omega_{jn3} \frac{\beta}{\alpha} (y_{n3} - y_n^s) (\alpha - y_{n3}) (\alpha + y_{n3}) ,$$
(4.32)
$$\frac{\partial E}{\partial \omega_{ij2}} = (-1)^{\beta} (y_{n3} - y_{n3}) (\alpha + y_{n3}) \sum_{n=1}^{N_3} (y_{n3} - y_n^s) (\alpha - y_{n3}) (\alpha + y_{n3}) ,$$

$$\frac{\partial E}{\partial \theta_{j2}} = (-1)\frac{\beta}{\alpha}(\alpha - y_{j2})(\alpha + y_{j2})\sum_{n=1}\omega_{jn3}\frac{\beta}{\alpha}(y_{n3} - y_n^s)(\alpha - y_{n3})(\alpha + y_{n3}),$$

$$\frac{\partial E}{\partial \omega_{ij1}} = x_i \frac{\beta}{\alpha} (\alpha - y_{j1}) (\alpha + y_{j1}) \\ \times \sum_{m=1}^{N_2} \omega_{jm2} \frac{\beta}{\alpha} (\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3} \frac{\beta}{\alpha} (y_{n3} - y_n^s) (\alpha^2 - y_{n3}^2) ,$$

$$\begin{aligned} \frac{\partial E}{\partial \theta_{j1}} &= (-1)\frac{\beta}{\alpha}(\alpha - y_{j1})(\alpha + y_{j1}) \\ &\times \sum_{m=1}^{N_2} \omega_{jm2}\frac{\beta}{\alpha}(\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3}\frac{\beta}{\alpha}(y_{n3} - y_n^s)(\alpha^2 - y_{n3}^2) \\ \omega_{ijk}^{(1)} &= \omega_{ijk}^{(0)} - h_k \frac{\partial E}{\partial \omega_{ijk}} \Big|^{(0)} , \qquad \theta_{jk}^{(1)} &= \theta_{jk}^{(0)} - h_k \frac{\partial E}{\partial \theta_{jk}} \Big|^{(0)} .\end{aligned}$$

# 4.11.3 Training the Artificial Neural Network

Let us now describe the supervised network training. We denote the input and output vectors by w and y, respectively. In our particular case  $w \in \mathbb{R}^{64}$  represents a spike waveform in the DWT space and  $y \in \mathbb{R}^2$  is the reduced set of discriminating spike features. We then construct a set of vector pairs  $(w_j, y_j)$ , (j = 1, ..., n) for n spikes, and say that the network is trained if, when presenting vector  $w_j$  at the input, we receive  $y_j$  at the output for any  $j \in [1, n]$ . To achieve this we have to adjust the synaptic weights of the interneuron couplings.

#### 4.11.3.1 Delta Rule

The simplest learning algorithm for a two-layer network consists in several steps and uses iterative adjustment of weights for each neuron in the network. In the first step all weights are randomly initialized. In the second step we present a vector  $w_j$  to the input of the network and receive some vector  $z_j$  at the output. Then the error of the network response is

$$\delta_j = y_j - z_j \ . \tag{4.33}$$

In the third step the coupling weights are modified proportionally to the obtained error. We employ the following delta-rule learning:

$$V_{t+1} = V_t + \nu w_j \delta_j^{\mathrm{T}} , \qquad (4.34)$$

where  $V_t$  is the weight vector at the learning step t and v > 0 is a small constant defining the learning rate. The learning is performed until convergence is achieved. The learning contains several epochs and is deemed finished if either (a) the weights do not change, or (b) the full absolute error (a sum over all vectors) becomes less than some fixed value.

#### 4.11.3.2 Back Propagation of Errors

When training a multilayer network, the delta-rule described above is not applicable, since the outputs of the internal layers are unknown. In this case the method of back propagation of errors is usually used. This method allows one to obtain the errors for the internal layers. In the learning process, information is passed from the input layer to the output layer, while the error propagates in the opposite direction.

The method estimates the gradient of the error within the network and performs a correction on the coupling weights. It consists of two stages. In the first stage, forward propagation of the input signal is performed to estimate output activations. Then, differences between output activations and the teacher output are estimated to obtain deltas for all neurons in the hidden layers. In the second stage, the gradient for each weight is computed by multiplying its output delta and input activation. Further, the weight is reduced by analogy with (4.34).

Details of the method are given in [44–48]. We shall illustrate this approach for different examples of neural networks.

### 4.11.4 Algorithm for Spike Sorting Using Neural Networks

When sorting experimental spikes, the main problem is lack of information about the number of clusters and about the noise-free standard spikes. Thus we cannot apply the above algorithm for network training directly. To overcome this difficulty, we use the algorithm for finding representative waveforms discussed in Sect. 4.7. Finally, the spike-sorting algorithm is as follows (Fig. 4.26):

- Detect spikes that exceed the level of experimental noise.
- Obtain information about the noise statistics and perform preliminary spike sorting using PCA or the wavelet transform.

- Select regions in the feature space with a high density of spikes and obtain the mean spike shapes.
- Apply the wavelet transform to the mean spike waveforms.
- Train the neural network using the wavelet coefficients computed in the previous step.
- Sort the experimental spikes with the resulting network parameters.

Thus for network training, we use spike waveforms corresponding to the centers of the clusters obtained using preliminary spike clustering by a conventional method, e.g., PCA or wavelet transform. As the standard output of the network, we use vectors obtained in the feature space of the mean waveforms [51].

In order to test the spike-sorting abilities of this approach, we created a semisimulated data set. Two different but rather similar spike waveforms (Fig. 4.25, spikes A and B) were selected from a real extracellular recording. We then generated a series consisting of 946 spikes for each repeated waveform and added colored noise to the data. The noise characteristics were similar to those observed experimentally. As a result, we obtain a signal similar to a real extracellular recording, but with a priori knowledge about the membership of each spike in one or the other group.

The use of preselected standard spikes without experimental noise enables the simplest supervised learning using the back propagation of errors algorithm. We used 64 wavelet coefficients as the learning sequence  $w_j$  for the first spike waveform and the same number for the second spike waveform. As a result, the learning algorithm contained 64 epochs. As mentioned above, the network should provide the most effective spike clustering, so the standard output vectors  $y_i$  associated with the two waveforms should be markedly different. They can be appropriately chosen. Here we used  $y_1 = [0.1, 0.1]$  and  $y_2 = [0.5, 0.5]$ . Once the learning procedure has been finished, the network can be used to separate noisy data. DWTs of all spike waveforms are used as input to the trained network, thus providing pairs  $(y_1, y_2)$  for each spike. For the final data clustering, we used the k-means algorithm. Then the clustering error is the number of wrongly classified spikes relative to the total number of spikes.

Figure 4.28 illustrates the performance of the proposed approach for spike sorting in the presence of color noise with a fixed bandwidth of 500 Hz and varying central frequency. The classification error grows slightly from 0.7% for low-frequency noise  $(f_c = 250 \text{ Hz})$  to about 1.5% for noise for the central frequency 1 kHz, and then it remains constant.

We now test the approach with real electrophysiological recordings. Following the proposed algorithm, we performed preliminary spike sorting using the wavelet spike classifier. Figure 4.29a illustrates the clustering results in the wavelet space. The data are organized into three partially overlapping clusters. For each cluster, we selected 50 points located closest to the spike density peaks in the feature plane. Averaging over 50 spikes provided the representative spike waveforms for three neurons. Using these waveforms, we trained the neural network. Then the full set of spikes was passed through the neural network. Figure 4.29b shows the network output, i.e., the plane ( $y_1$ ,  $y_2$ ). Again all spikes formed three clusters. However, in the network output



**Fig. 4.28** Sorting of semi-simulated spikes. **a**  $(y_1, y_2)$ -planes representing spikes for different central noise frequencies. **b** Classification error vs central noise frequency (noise band 500 Hz)

space, cluster overlapping was significantly reduced. This facilitates clustering (e.g., using k-means), and presumably reduces the number of misclassified spikes.

In conclusion, the considered approach combines the wavelet transform and artificial neural networks. The wavelet analysis allows us to reveal characteristic features in the shapes of spike waveforms. As we have shown in previous sections, WT is potentially a more powerful technique than PCA. However, the selection of the most informative features and rejection of noisy ones in WT approaches is a challenging problem. The use of neural networks provides an automatic solution to this problem (through training). The trained network automatically selects appropriate combinations of the most discriminative features from the whole set. It effectively projects



Fig. 4.29 Clustering of electrophysiological spikes by a conventional wavelet method (a) and by the proposed combined approach (b)

wavelet coefficients into a low dimensional space (2D in our case), significantly improving the separability of spikes generated by different neurons.

We tested the proposed approach with semi-simulated and real electrophysiological data. We showed that the use of neural networks can significantly improve the preliminary classification obtained using PCA scores or wavelet coefficients. Reliability of the spike clustering also has been shown for the case of several clusters in the feature space of wavelet coefficients. The considered examples demonstrate the superior performance of the present approach over conventional PCA and wavelet techniques.

# 4.12 Artificial Wavelet Neural Networks for Spike Sorting

In Sect. 4.11, we showed that the approach based on a combination of the wavelet transform and artificial neural networks can reduce errors in automatic spike sorting. However, it also has some limitations.

On the one hand, this approach can outperform standard neural networks because the integration of a time–frequency representation (using wavelets) into the structure of the recognition algorithm allows an initial preprocessing of the data used as input for the neural network. In this context, the wavelets used in the data preprocessing stage provide a way to select characteristics that can be used by the neural network to better distinguish signals of different types. On the other hand, this method assumes no variation of wavelet parameters in the learning phase. For this reason, the efficacy of the method depends on the initial selection of the parameters, i.e., the results of the data preprocessing.

In the learning phase, there is a loss of connection with the selection of WT parameters since, in the approach considered here, these parameters are not adjusted in the course of the learning procedure. If these parameters are selected sub-optimally, then the situation cannot be further improved. It has been shown that this circumstance

strongly influences the final result of image recognition (and consequently of spike sorting), because the personal experience of a researcher becomes one of the key factors. In order to reduce the influence of subjective factors, one can extend the learning phase and include additional tuning of the wavelet parameters, depending on the quality of recognition. This approach is used with the so-called *wavelet neural networks* (WNN) (see, e.g., [52–56]).

### 4.12.1 Structure of Wavelet Neural Networks

The structure of WNN and its analytic description is similar to standard neural networks. A WNN can be treated as an extended perceptron that includes two parts: a wavelet transform for revealing typical features of signals and an artificial neural network for image recognition using the selected features.

The first part includes wavelet nodes where wavelet functions (e.g., the Morlet function) are used instead of the classical logistic function. These wavelets reveal features of signals on different independent scales. The procedure begun with obtaining of wavelet coefficients from native data that reflect typical features of the analyzed signal. These coefficients represent an input for the second part of the algorithm when final recognition is performed. One feature of WNN is the possibility of selecting wavelet coefficients in the course of learning, besides correcting the synaptic coefficients. WNNs constitute one of the most promising approaches for recognition of spike waveforms. We shall thus discuss this approach in more detail. Since WNN is an extension of standard ANN (Fig. 4.27), we shall briefly discuss some aspects of image recognition with different variants of WNNs (Figs. 4.30, 4.31 and 4.32).

# 4.12.2 Wavelet Neural Networks

Figure 4.30 shows the first and simplest variant of WNN. It does not require one to include the wavelet part of the WNN in the learning process. To obtain a mathematical description of this WNN, we shall consider discretization of the CWT and the basic functions WAVE and MHAT.

When computing the continuous wavelet transform of a function x(t), we shall use the discrete values of the scale parameter  $s = 2^{j}$  and the WAVE function as mother wavelet, written in the form

$$\psi(\rho, q, t) = (\rho t - q) \exp\left[-\frac{(\rho t - q)^2}{2}\right].$$
 (4.35)

The process of computing wavelet coefficients will be rewritten as follows:



Fig. 4.30 First type of WNN



Fig. 4.31 Second type of WNN

$$C_{jk} = W\left(\frac{1}{2^j}, \frac{k}{2^j}\right) \approx 2^{j/2} \Delta t \sum_{n=0}^{N-1} x(n\Delta t) \psi(\rho_j n - q_k) , \quad \rho_j = 2^j \Delta t , \quad q_k = k\rho_j .$$

$$(4.36)$$

The signal decomposition over the wavelet basis can be treated as the formal inclusion of an additional layer of NN nodes that will contain wavelet coefficients in the synapses. Thresholds of such nodes are switched off, and the activation function is a simple linear function. For the neuron l of the first wavelet layer, we obtain



Fig. 4.32 Third type of WNN

ı

$$y_{l1} = \alpha v_{l1} - \beta , \quad v_{l1} = \sum_{n=0}^{N-1} x_n w_{nl1} ,$$
$$v_{nl1} = \psi(\rho_j n - q_k) = (\rho_j n - q_k) \exp\left[-\frac{(\rho_j n - q_k)^2}{2}\right] , \quad (4.37)$$

for

$$1 \le l \le NN_{\rm f}$$
,  $j = \left[\frac{l}{N}\right]$ ,  $k = \left[\left\{\frac{l}{N}\right\}N\right]$ ,

where  $y_{l1}$  is the reaction of neuron l from the first layer after receiving the vector **x**,  $N_{\rm f}$  corresponds to the maximal frequency in the power spectrum, and the integer values j, k quantify the scale and translation parameters. In Eq. 4.37 square and curly brackets denote the integer and fractional parts of the number, respectively. According to (4.37), each neuron of the first layer is associated with the given parameters of the wavelet transform. If the neural network (Fig. 4.27) is added to this layer, one of the simplest variants of the WNN of the first type is obtained (Fig. 4.30). This variant does not require differentiation of the wavelets, and its practical realization is quite simple.

The second type of WNN (Fig. 4.31) assumes a more complex computing algorithm within the framework of which the wavelet function is used in the synaptic part of the first layer and should satisfy the differentiation condition for including wavelet nodes in the learning algorithm. Coefficients of the wavelet transform carry information about the relation between the input vector and a given type of signal,

and this is why an additional layer with wavelet functions integrated into the synaptic part seems to be useful. According to the model neuron (4.28), mathematical operations in the synaptic part are analogous to the discretized version of the wavelet transform (4.36), but the decomposition is provided using another basis of functions. If the wavelet function  $\psi$  is included in both the recognition and the learning cycles, then a layer of "wavelet nodes" is obtained, where synaptic coefficients are given by the translation and scale parameters of the corresponding function  $\psi$ .

Let us show how the procedure of learning and recognition will be written for the WNN shown in Fig. 4.31. The first layer includes a decomposition of the input vector in the basis of wavelet functions. The following layers are organized according to the standard scheme shown in Fig. 4.27. The additional layer of this WNN is described by the following equations:

$$y_{j1} = \alpha \tanh\left[\beta\left(\sum_{i=1}^{M_1} x_i w_{ij1} - \theta_{j1}\right)\right], \quad w_{ij1} = (\rho_j i - q_j) \exp\left[-\frac{(\rho_j i - q_j)^2}{2}\right],$$
$$y_{j2} = \alpha \tanh\left[\beta\left(\sum_{i=1}^{M_2} y_{i1} \omega_{ij2} - \theta_{j2}\right)\right], \quad y_{j3} = \alpha \tanh\left[\beta\left(\sum_{i=1}^{M_3} y_{i2} \omega_{ij3} - \theta_{j3}\right)\right].$$
$$(4.38)$$

Two variants can be considered for the functioning of the wavelet layer, namely, the cases of linear and nonlinear activation function, where (4.38) corresponds to the latter. The learning procedure for this WNN assumes correction of the following parameters: the translation parameter  $\rho_j$  and the scale parameter  $q_j$  of the wavelet function  $\psi(t)$  in the first layer, the thresholds  $\theta_{j1}$  of formal neurons in the first layer, the synaptic coefficients  $\omega_{ij2}, \omega_{ij3}$ , and the thresholds  $\theta_{j2}, \theta_{j3}$  of the remaining neural layers. The learning process follows the scheme

$$\frac{\partial E}{\partial \rho_j} = \frac{\partial y_{j1}}{\partial \nu_{j1}} \frac{\partial \nu_{j1}}{\partial \rho_j} \sum_{m=1}^{N_2} \omega_{jm2} \frac{\beta}{\alpha} (\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3} \frac{\beta}{\alpha} (\alpha^2 - y_{n3}^2) (y_{n3} - y_n^s) ,$$
  
$$\frac{\partial E}{\partial q_j} = \frac{\partial y_{j1}}{\partial \nu_{j1}} \frac{\partial \nu_{j1}}{\partial q_j} \sum_{m=1}^{N_2} \omega_{jm2} \frac{\beta}{\alpha} (\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3} \frac{\beta}{\alpha} (\alpha^2 - y_{n3}^2) (y_{n3} - y_n^s) ,$$

$$\begin{aligned} \frac{\partial E}{\partial \theta_{j1}} &= (-1) \frac{\beta}{\alpha} (\alpha - y_{j1}) (\alpha + y_{j1}) \\ &\times \sum_{m=1}^{N_2} \omega_{jm2} \frac{\beta}{\alpha} (\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3} \frac{\beta}{\alpha} (\alpha^2 - y_{n3}^2) (y_{n3} - y_n^s) , \end{aligned}$$

 $\frac{\partial E}{\partial \omega_{ij2}} = y_{i1} \frac{\beta}{\alpha} (\alpha - y_{j2})(\alpha + y_{j2}) \sum_{n=1}^{N_3} \omega_{jn3} \frac{\beta}{\alpha} (y_{n3} - y_n^s)(\alpha - y_{n3})(\alpha + y_{n3}) ,$ 

$$\begin{aligned} \frac{\partial E}{\partial \theta_{j2}} &= (-1)\frac{\beta}{\alpha}(\alpha - y_{j2})(\alpha + y_{j2})\sum_{n=1}^{N_3}\omega_{jn3}\frac{\beta}{\alpha}(y_{n3} - y_n^s)(\alpha - y_{n3})(\alpha + y_{n3}) , \\ \frac{\partial E}{\partial \omega_{ij3}} &= y_{i2}\frac{\beta}{\alpha}(y_{j3} - y_j^s)(\alpha - y_{j3})(\alpha + y_{j3}) , \\ \frac{\partial E}{\partial \theta_{j3}} &= (-1)\frac{\beta}{\alpha}(y_{j3} - y_j^s)(\alpha - y_{j3})(\alpha + y_{j3}) , \\ \rho_j^{(1)} &= \rho_j^{(0)} - h_1 \left.\frac{\partial E}{\partial \rho_j}\right|^{(0)} , \qquad \theta_{jk}^{(1)} &= \theta_{jk}^{(0)} - h_k \left.\frac{\partial E}{\partial \theta_{jk}}\right|^{(0)} , \\ q_j^{(1)} &= q_j^{(0)} - h_1 \left.\frac{\partial E}{\partial q_j}\right|^{(0)} , \qquad \omega_{ijk}^{(1)} &= \omega_{ijk}^{(0)} - h_k \left.\frac{\partial E}{\partial \omega_{ijk}}\right|^{(0)} . \end{aligned}$$

The values of derivatives  $(\partial y_{j1}/\partial v_{j1})(\partial v_{j1}\partial \rho_j)$  are estimated depending on the selection of the activation function and the wavelet. Let us consider the WAVE and MHAT wavelets as activation functions:

$$\psi(t) = \begin{cases} t \exp\left(-\frac{t^2}{2}\right), & \text{WAVE}, \\ (1-t^2) \exp\left(-\frac{t^2}{2}\right), & \text{MHAT}. \end{cases}$$
(4.40)

The general structure of the WNN constructed on the basis of the 3-layer neural network with the WAVE wavelet in the first layer is shown in Fig. 4.31.

The third type of WNN (Fig. 4.32) includes the wavelet functions as activation functions in the first layer. Let us consider a 3-layer neural network with the activation function  $\psi(t)$  in the first layer (Fig. 4.32). The coefficients of this WNN are corrected according to the following equations:

$$\frac{\partial E}{\partial \omega_{ij3}} = y_{i2} \frac{\beta}{\alpha} (y_{j3} - y_j^{s})(\alpha - y_{j3})(\alpha + y_{j3}) ,$$
$$\frac{\partial E}{\partial \theta_{j3}} = (-1) \frac{\beta}{\alpha} (y_{j3} - y_j^{s})(\alpha - y_{j3})(\alpha + y_{j3}) ,$$

$$\frac{\partial E}{\partial \omega_{ij2}} = y_{i1} \frac{\beta}{\alpha} (\alpha - y_{j2}) (\alpha + y_{j2}) \sum_{n=1}^{N_3} \omega_{jn3} \frac{\beta}{\alpha} (y_{n3} - y_n^s) (\alpha - y_{n3}) (\alpha + y_{n3}) ,$$
$$\frac{\partial E}{\partial \theta_{j2}} = (-1)\frac{\beta}{\alpha}(\alpha - y_{j2})(\alpha + y_{j2})\sum_{n=1}^{N_3} \omega_{jn3}\frac{\beta}{\alpha}(y_{n3} - y_n^s)(\alpha - y_{n3})(\alpha + y_{n3}),$$
(4.41)

$$\frac{\partial E}{\partial \omega_{ij1}} = x_i \frac{\partial \psi(\rho_j v_{j1} - q_j)}{\partial v_{j1}} \sum_{m=1}^{N_2} \omega_{jm2} \frac{\beta}{\alpha} (\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3} \frac{\beta}{\alpha} (\alpha^2 - y_{n3}^2) (y_{n3} - y_n^s) ,$$

$$\frac{\partial E}{\partial \theta_{j1}} = (-1) \frac{\partial \psi(\rho_j v_{j1} - q_j)}{\partial v_{j1}} \sum_{m=1}^{N_2} \omega_{jm2} \frac{\beta}{\alpha} (\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3} \frac{\beta}{\alpha} (\alpha^2 - y_{n3}^2) (y_{n3} - y_n^s) ,$$

$$\frac{\partial E}{\partial \rho_j} = \frac{\partial \psi(\rho_j v_{j1} - q_j)}{\partial \rho_j} \sum_{m=1}^{N_2} \omega_{jm2} \frac{\beta}{\alpha} (\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3} \frac{\beta}{\alpha} (\alpha^2 - y_{n3}^2) (y_{n3} - y_n^s) ,$$

$$\frac{\partial E}{\partial q_j} = \frac{\partial \psi(\rho_j v_{j1} - q_j)}{\partial q_j} \sum_{m=1}^{N_2} \omega_{jm2} \frac{\beta}{\alpha} (\alpha^2 - y_{m2}^2) \sum_{n=1}^{N_3} \omega_{mn3} \frac{\beta}{\alpha} (\alpha^2 - y_{n3}^2) (y_{n3} - y_n^s) ,$$

$$\omega_{ijk}^{(1)} = \omega_{ijk}^{(0)} - h_k \left. \frac{\partial E}{\partial \omega_{ijk}} \right|^{(0)} , \quad 1 \le i \le M_k , \quad 1 \le j \le N_k , \quad k = 1, 2, 3 ,$$

$$\rho_{j}^{(1)} = \rho_{j}^{(0)} - h_{1} \left. \frac{\partial E}{\partial \rho_{j}} \right|^{(0)}, \quad \theta_{jk}^{(1)} = \theta_{jk}^{(0)} - h_{k} \left. \frac{\partial E}{\partial \theta_{jk}} \right|^{(0)}, \quad q_{j}^{(1)} = q_{j}^{(0)} - h_{1} \left. \frac{\partial E}{\partial q_{j}} \right|^{(0)}$$

The learning rules for all considered WNNs (Figs. 4.30, 4.31 and 4.32) are generalized as the following computing algorithm:

- Select initial values of the synaptic coefficients and thresholds of the neural network and wavelet coefficients.
- Recognition based on testing data sets that contain signals of several types is provided for a random sequence of signals of different type. After recognition, the error is estimated and the coefficients of NN and WNN are corrected.
- Recognition and correction are repeated in several stages ("epochs"). The number of stages is chosen depending on the features of the recognized objects.

#### 4.12.2.1 Performance of WNNs

To compare the efficacy of different types of WNNs and to analyze spike-sorting errors, we used two types of waveforms produced by real neurons. Two different waveforms were extracted from extracellular recordings of electrical activity of neural ensembles. The quality of spike identification was controlled using tetrode microelectrodes that allow registration of extracellular potentials in four closely located



Fig. 4.33 Fragment of a test signal used to compare the efficiency of different recognition approaches

#	Parameter	Description
1	Number of layers	3
2	Number of neurons in the 1st layer	16
3	Number of neurons in the 2nd layer	250
4	Number of neurons in the 3rd layer	2
5	Activation function	$F(x) = \alpha \tanh(\beta x), \alpha = 6.0, \beta = 0.45$
6	Number of learning epochs	1000
7	Number of types × spikes	$2 \times 250$
8	Learning step of neurons from layer i	$h_1 = 0.0003, h_2 = 0.0002, h_3 = 0.0001$
9	Initial values of coefficients	Random values equally distributed in the range $[-0.001, 0.001]$
10	Maximal $\times$ minimal value of the output vector	$-6.0 \times 5.0$

Table 4.3 Parameters of the neural network (Fig. 4.27)

points (about 30  $\mu$ m apart) thus providing multichannel recordings of neural activity. A more detailed description of the experimental data can be found in [14, 43]. Further, test signals were generated, including a random sequence of impulses of both types with added noise. Figure 4.33 shows an example of the corresponding test signal. A 3-layer perceptron (Fig. 4.27) contained a number of parameters indicated in Table 4.3. Parameters of the WNNs are given in Table 4.4.

In the course of learning, the considered neural networks solved the problem of signal identification in the presence of fluctuations within different frequency bands.

#	Parameter	Description	
1	Wavelet function	$\psi(t) = t e^{-t^2/2}, \psi(t) = (1 - t^2) e^{-t^2/2}$	
2	Type of WNN	<ul> <li>WNN of the first type (not including learning procedure for the wavelet layer)</li> <li>WNN of the second type (including learning procedure for the wavelet layer) with linear and nonlinear activation function</li> <li>WNN of the third type (including wavelet function as activation function)</li> </ul>	
3	Number of layers used for learning (in general case)	3	
4	Number of neurons in the 1st layer	16	
5	Number of neurons in the 2nd layer	250	
6	Number of neurons in the 3rd layer	2	
7	Activation function	$F(x) = \alpha t h(\beta x)$	
8	Number of epochs	1000	
9	Number of types $\times$ spikes	2 × 250	
10	Learning step of neurons from layer <i>i</i>	$h_i \in [0.000001, 0.005]$	
11	Initial values of coefficients	Random values equally distributed in the range [-0.001, 0.001]	
12	Maximal × minimal value of the output vector	$-6.0 \times 5.0$	

**Table 4.4** Parameters of the WNNs (Figs. 4.30, 4.31 and 4.32)

As the first test, a narrow-band noise (1/20 from the maximal frequency in the power spectrum) was applied because, according to Sect. 4.4, the efficiency of techniques for image recognition strongly depends on the spectral properties of the presented fluctuations. Experiments were performed using ANN (Fig. 4.27) by changing the frequency band of the presented noise added to the signal (Fig. 4.33). The results are shown in Fig. 4.34. According to this figure, the quality of recognition depends heavily on the frequency band of the fluctuations. The error is maximal for the central frequency of the noise, viz., 600–700 Hz. In general, the classification error takes larger values in the low-frequency area compared with the central frequency of the analyzed signal (about 1.0–1.5 kHz) and approaches zero in the high-frequency area. The test was performed using a series of 3 610 000 generated spikes (each consisting of 32 data points) with frequency band 250 Hz.

Another situation is observed for fluctuations in the middle and high frequency range. The identification error is small and an increase in the noise intensity (at least, up to the value 0.6 of the signal energy) does not lead to any remarkable increase in the error. This allows us to conclude that the NN can be treated as a filter with characteristics that are adjusted in the course of learning. According to Fig. 4.34a, effective filtering and further recognition are able only when fluctuations



**Fig. 4.34** Estimation of the identification error for a standard neural network [(**a**) and (**b**)] and WNN of the second type [(**c**) and (**d**)] with the MHAT function and nonlinear activation function for different values of the ratio of energies  $E_{\text{noise}}/E_{\text{signal}}$ : 0.1 (1), 0.2 (2), 0.3 (3), 0.4 (4), 0.5 (5), 0.6 (6). Dependencies of the recognition error [(**a**) and (**c**)] on the central frequency of narrow-band noise and of the mean error versus the relative intensity of fluctuations [(**b**) and (**d**)]

are associated with the middle and higher frequencies as compared with the mean frequency of the recognized signal. Figure 4.34b illustrates an increase in the mean error (as a result of averaging over the whole range of  $f_c$ ). The mean error increases for higher noise intensities, but the rate of this increase and absolute values of the error depend on the type of NN used. Thus, application of WNNs typically improves recognition accuracy.

Analogous test experiments were performed for WNNs. All variants of wavelet neural networks (Figs. 4.30, 4.30 and 4.32) were analyzed using the two basic functions WAVE and MHAT. Additionally, for WNN of the second type (Fig. 4.31), both linear and nonlinear activation functions were considered (Table 4.5). Testing was performed using the same example (Fig. 4.33) to compare the errors of the various methods under identical conditions.

This investigation showed that results obtained with WNNs correspond to the results obtained for the classical ANN (Fig. 4.27), but that wavelet nodes enable error recognition in the presence of noise. Let us consider the corresponding results for the WNN of the second type. Application of the linear activation function within this

#	Type of the used network	
1	Standard NN	
2	WNN of the first type with WAVE function	
3	WNN of the first type with MHAT function	
4	WNN of the second type with WAVE function and linear activation	
5	WNN of the second type with WAVE function and nonlinear activation	
6	WNN of the second type with MHAT function and linear activation	
7	WNN of the second type with MHAT function and nonlinear activation	
8	WNN of the third type with WAVE function	
9	WNN of the third type with MHAT function	

 Table 4.5
 Neural networks used for spike recognition





WNN simplifies computations and does not use thresholds, i.e., it provides a much quicker learning procedure as compared with the nonlinear activation function. The more nonlinear elements are included in the WNN, the more time is required for learning.

According to Fig. 4.34, application of WNNs reduces the maximal error by about 5% (for the case  $E_{noise}/E_{signal}$ =0.6) and the mean error by about 1%. These results are obtained for the case of narrow-band noise. With an increased frequency band of fluctuations, the quality of recognition with WNN may be significantly improved, and the dependence of the error on the frequency band changes. As another test, the case of noise with a broader frequency band (1 kHz) was considered. This test was performed using a series of 3 040 000 generated spikes (each consisting of 32 data points).

Instead of visual comparison between the graphics (similar to Fig. 4.34), we use two numerical measures: error at fixed signal-to-noise ratio and the coefficient of the increase in the mean error with the noise intensity. Nine NNs (see Table 4.5) were compared using these measures (Fig. 4.35).

According to the results obtained, we can conclude that the most effective recognition techniques are WNN of the second type with nonlinear activation function (variants 5 and 7 in Table 4.5). Let us note that this conclusion is based on the processing of a large number of experiments performed in vivo with the trigeminal complex of rats. Less effective results are obtained for WNNs 6 and 9. In the latter case, the accuracy is less than for the standard approach (variant 1). Likewise, for WNNs 2, 3, 4, and 8, no essential improvement was revealed in the results compared with the standard NN. This may be explained by the nonlinearity of WNN, which requires appropriate adjustment using special techniques. The less effective results for some WNNs (e.g., 6 and 9) confirm that the adjustment of WNNs with linear activation functions requires special techniques or complicating the NN structure.

We considered in more detail the WNN of the second type, which is typically not considered in practical applications due to the more complicated learning procedure. They require a learning process about 7 times larger compared with the standard NN. However, they provide better recognition in the presence of noise (by about 16% compared with the classical NN), which easily counterbalances the extra computing time.

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## Chapter 5 Analysis of Gamma-Waves in Multielectrode LFP Recordings



**Abstract** Neuronal activity in different brain regions is predominantly irregular. Nevertheless, the coordinated firing in cell assemblies is responsible for at least part of the information flow at the circuit level. The synchronization of the synaptic bombardment promotes sizable transmembrane currents in target neurons that give rise to extracellular local field potentials (LFPs). Thus, LFPs provide convenient access to information processing at the circuit level. However, the LFP analysis requires the solution of complex mathematical problems. This chapter offers a brief introduction to mathematical methods that enables the separation of raw LFPs into pathway-specific components and their in-depth analysis. In particular, we discuss two wavelet-based methods for quantifying gamma waves induced in the CA1 region of the hippocampus by the synchronized firing of functional clusters of CA3 pyramidal cells. We show how gamma waves' analysis helps establish causal relationships between the firing of individual CA3 and CA1 cells. We also address the problem of integrating information parsed by gamma waves in the two bilateral CA3-CA1 circuits.

## 5.1 Introduction

Information processing and transfer between higher brain nuclei are primarily based on the coordinated firing of functional groups of neuronal assemblies. Yet, little is known about how much of the neural code resides in units or assemblies activities [1, 2]. Although spike trains of single neurons in different brain regions are predominantly irregular, it has been proposed that synchronous activity in cell assemblies is responsible for at least part of the information flow [3-5].

Thus, many studies have focused on the search for synchronization in an irregular activity. However, this task applied to the firing of single units is technically demanding [6]. At the circuit level, the synchronous firing of neuron assemblies promotes the summation of synaptic currents in tissue volume surrounding the target neurons. These currents may give rise to measurable extracellular local field potentials (LFPs), which provide a link between neuronal activity and behavior [7–9].

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LFP is a mesoscopic variable. It contains accurate spatiotemporal information of the synaptic activity generated by converging neuronal populations [10]. LFPs can be easily monitored by intra-cranial multi-electrode matrices. The multiple presynaptic origins of LFPs have, however, limited their use to a few macroscopic events and oscillations mostly in architectonically simple regions as the hippocampus [7].

This chapter discusses a novel approach to extract pathway-specific ongoing synaptic activity from irregular hippocampal LFPs [11, 12]. The pathway-specific activity can be used to investigate the ongoing dynamics of one presynaptic population, e.g., the CA3 region. We can quantify its contribution to the elaboration of spike trains in postsynaptic CA1 units. Pyramidal cells in the CA1 region receive excitatory inputs from several presynaptic nuclei, all of which can themselves initiate postsynaptic firing when sufficient synchrony occurs (e.g., following electrical stimulation) [13]. Although CA3 pyramidal cells usually fire within functional assemblies [14, 15], it is unknown whether the degree of synchronization is enough to fire CA1 pyramidal neurons during ongoing activity.

The independent component analysis (ICA) has a spatiotemporal resolution sufficient to separate different generators in irregular LFPs [16]. Hippocampal LFPs are particularly suited for ICA as the stratification of afferent axons from diverse presynaptic populations along principal cell dendrites facilitates spatial discrimination of the electrical current sources. Recently, a successful decomposition of irregular hippocampal LFPs into several generators with a subcellular spatial definition has been obtained [11, 12]. Specifically, we identified the so-called Schaffer generator corresponding to the ipsilateral input from the CA3 to CA1.

To get a more in-depth insight into synchronization processes, we develop two wavelet-based methods that allow the identification of separate micro-events in the ongoing activity of the CA3-CA1 pathways. The low firing rate and functional clustering of CA3 pyramidal cells [17] allows us discriminating elementary synaptic events in the Schaffer generator, which we term micro-field EPSPs ( $\mu$ fEPSPs).

We use the identified  $\mu$ fEPSP events to find correlated spikes between presynaptic and postsynaptic CA3-CA1 pairs of units within long spontaneous epochs. Paradoxically, during irregular hippocampal LFPs, the Schaffer  $\mu$ fEPSPs constitute a regular oscillatory succession of excitatory packages involving a variable contribution from individual presynaptic CA3 units. These  $\mu$ fEPSPs appearing at gamma rate can effectively fire CA1 pyramidal cells revealing the pathway-specific origin of some spikes as proposed in synfire chains [18]. Further, we study the bilateral integration of gamma-parsed information in the two hippocampal lobes. First, we show that under irregular activity, the probability of generating asynchronous (one side) events is about the same as the probability of synchronous (two sides) events. On average, the amplitude of the asynchronous left and right events is significantly smaller than that of synchronous  $\mu$ fEPSPs. Second, synchronous events exhibit variable time lag between left and right lobes. Moreover, the right side leads more often, and  $\mu$ fEPSP events have significantly higher amplitude on the right side. We show that initial asynchrony in bilateral events is compensated by adjusting their durations.

## 5.2 Disentanglement of Raw LFP Recordings into Pathway-Specific Generators

This section shows a step-by-step procedure allowing obtaining from LFPs recorded by a multielectrode array the pathway-specific electrical activity produced in a target domain by projecting neurons from other brain regions.

## 5.2.1 LFP Recordings and Current-Source-Density Analysis

For recording LFPs, we used linear multisite silicon probes with 32 recording tips, lowered into the hippocampus of an anesthetized rat (see cartoon in Fig. 5.1a). Surgical and stereotaxic procedures were standard, and their detailed description can be found elsewhere [19, 20]. For orthodromic activation of the CA1 region, a concentric bipolar stimulating electrode was used in the ipsilateral CA3 area.

The multi-electrode array recorded the electrical activity in 50  $\mu$ m steps along the principal axis of the CA1 pyramidal cells, also spanning the DG/CA3 regions. The acquisition frequency was 20 kHz, which enables recording both LFPs and spike waveforms. The firing activities of pyramidal cells and putative interneurons were isolated, and units were classified (for details on the problem of spike sorting, see Chap. 4). After the spike analysis, the sampling rate was decreased to 2 kHz to analyze LFPs, which have the frequency band limited from above by 500 Hz.

Our goal is to study the CA3-CA1 pathway, which is represented by the Schaffer collaterals in the ipsilateral part of the hippocampus (Fig. 5.1). Axons from CA3 pyramidal neurons bifurcate and pass through the CA1 area in parallel (Fig. 5.1b). Neurons in the CA3 region can form temporal clusters and synchronize their firing. Thus, a CA1 cell receives spikes from a group of CA3 neurons, whereas each



**Fig. 5.1** Schaffer pathway in the hippocampus. **a** The laminar organization of the CA3 and CA1 areas in the hippocampus facilitates multiple parallel synaptic contacts between neurons in these areas through Schaffer collaterals. A multi-electrode array can record the LFP activity along the principal axis of pyramidal neurons. **b** Axons from CA3 pyramidal neurons bifurcate and pass through the CA1 area in parallel (left), giving rise to the convergence-divergence of the information content (right). Multiple CA1 neurons receive multiple synaptic contacts from CA3 neurons



**Fig. 5.2** Retrieval of pathway-specific generators from raw LFP recordings. **a** *Right panel*: A typical segment of LFPs (right panel) recorded across the CA1 and CA3 fields (black and gray traces, respectively). The vertical red line marks the time of a subthreshold stimulus applied to the ipsilateral CA3. *Left panel*: Zoom from the right panel corresponding to the evoked Schaffer-specific field potential. **b** The current source density plot obtained from the LFPs shown in (**a**). **c** ICA of LFPs provides four LFP-generators, each defined by a curve of spatial weights (top panel) and a time course (bottom traces). The Schaffer generator (blue curves) captures the Schaffer-evoked activity (stimulus arrows). **d** The reconstructed virtual LFPs corresponding to the activity of the Schaffer pathway taken separately. **e** The CSD map of the virtual Schaffer LFPs provides the precise spatiotemporal distribution of inward/outward currents

CA3 neuron has a synaptic contact with multiple CA1 cells, which gives rise to the convergence-divergence of the information content.

Figure 5.2a (right panel) shows a typical segment of LFPs recorded simultaneously along a linear track spanning the CA1 and CA3 fields of the rat hippocampus (see also Fig. 5.1a). The segment consists of a bulk subthreshold stimulation of the ipsilateral CA3 region. The stimulus produces evoked potentials. Their topographic analysis allows identifying the electrode's position up to tens of micrometers and location of the soma layers [20]. The spontaneous activity (Fig. 5.2a, right panel, after stimulation) exhibits irregular oscillations without strongly correlated rhythmic activity as, e.g., during theta rhythm.

Current source density (CSD) analysis [21, 22] determines the magnitude and location of the net transmembrane current generated by neuronal elements within a small tissue region. The transmembrane current i(x, y, z, t) is a spatiotemporal function depending on various factors. It is determined by the synaptic currents produced by the converged inputs from presynaptic neuronal assemblies. Assuming a purely ohmic conductive medium, the CSD can be related to the field potential [23, 24]:

$$i(x, y, z, t) = \nabla \big( \sigma(x, y, z) \nabla u(x, y, z, t) \big), \tag{5.1}$$

where  $\sigma$  is the conductivity tensor of the medium, *u* is the electric field potential, i.e., LFPs, and  $\nabla$  is the standard gradient operator. For simplicity, we can assume that the medium is homogeneous and the conductivity is a constant  $\sigma(x, y, z) = \sigma$  (but see discussion in [25]). Therefore, the CSD reduces to

$$i(x, y, z, t) = -\sigma \Delta u(x, y, z, t), \qquad (5.2)$$

where  $\Delta$  is the Laplacian operator.

Next, we observe that the hippocampus consists of monolayer structures with principal cells oriented along the main (vertical) *z*-axis. Hence u(x, y, z) has little variations along *x* and *y* directions. Accordingly, to estimate the CSD, we can use the one-dimensional approach, which evaluates the CSD from the voltage gradients along the cells axis [26]:

$$i(x, y, z_k, t) \approx i(z_k, t) = -\sigma \frac{\partial^2 u(x, y, z_k)}{\partial z^2},$$
(5.3)

where  $z_k = z_0 + kh$  are the location of electrode tips. The partial derivative along *z*-axis can be approximated by 3-point formula:

$$i(z_k, t) \approx i_k(t) = -\sigma \frac{u_{k-1}(t) - 2u_k(t) + u_{k+1}(t)}{h^2},$$
 (5.4)

where  $u_k(t)$  is the LFP recorded at time t by electrode tip k, and h is the distance between recording tips.

Admittedly, the spatial extent of CSD may not be large enough to fulfill the criterion of homogeneous activation in the (x, z)-plane parallel to anatomical strata or laminae during an asynchronous synaptic bombardment. Thus, tangential currents may introduce error in the amplitude of sinks and sources [27]. Conveniently, the spatial distortion introduced by unbalanced tangential currents is effectively canceled out by time averaging of myriads microscopic currents as if they all were synchronously activated [16]. Thus, the curve of spatial weights for each LFP-generator is accurate to the subcellular level. Although there is also a notable heterogeneity of tissue resistivity at the level of the stratum pyramidale [28], it introduces a negligible spatial distortion of depth profiles when active currents are located in distant dendritic loci. Thus, we can assume homogeneous resistivity and use arbitrary units instead of [A m<sup>-2</sup>].

The CSD analysis of the recorded LFPs [employing Eq. (5.3)] shows the standard Schaffer-specific evoked field potentials (Fig. 5.2b, left panel) with the subcellular spatiotemporal pattern of the transmembrane current along the main axis of pyramidal cells. As expected [26], active inward synaptic currents or sinks (blue color) are surrounded by passive outward currents or sources (red color), corresponding to the CA1 field EPSP produced by the stimulation of the CA3 region.

However, the CSD map for the ongoing spontaneous LFPs (Fig. 5.2b, right panels, after the stimulus) shows a poorly informative spatiotemporal mixture of sources and

sinks induced by the co-activation of several different afferent inputs converging on principal cells. Thus, in such a spontaneous mixture, we cannot distinguish the activity produced by different synaptic inputs from different neuronal nuclei, including from the CA3 region through the Schaffer collaterals. In Sect. 5.2.2, we will address this issue.

## 5.2.2 Decomposition of LFPs into Pathway-Specific Generators

#### 5.2.2.1 Independent Component Analysis of Raw LFPs

Independent component analysis (ICA) is routinely used to elucidate functional connectivity either in multisite scalp recordings or in functional magnetic resonance imaging. It provides spatially stable components of coherent activity [29–32].

The attribution of the independent components to their source populations and pathways is difficult when recording from a distance (e.g., for EEG). Nevertheless, the in-source recording of intrahippocampal LFPs allows the thorough spatial inspection of active neurons down to the subcellular resolution and direct matching with the evoked potential profiles [12].

A detailed procedure of the ICA of LFPs can be found elsewhere [11, 33]. Both the mathematical validation and the interpretation of ICA components in laminated structures, such as, e.g., the hippocampus, were performed using realistic LFP modeling [16]. There is also a freely available Matlab package for performing different analyses of LFPs, including the decomposition into pathway-specific components by ICA (Fig. 5.3).

Briefly, let  $u(t) = (u_1(t), u_2(t), \dots, u_M(t))^T \in \mathbb{R}^M$  be a vector representing M recorded LFP signals at a discrete-time instant t ( $t = 1, 2, \dots, L$ ). The ICA model assumes that the observed data matrix  $U = (u(0)|u(1)| \cdots |u(L)) \in \mathbb{R}^{M \times L}$  can be represented as the weighted sum of the activities of N neuronal sources or the so-called LFP-generators:

$$U = VS, (5.5)$$

where  $V = (\mathbf{v}_1 | \mathbf{v}_2 | \cdots | \mathbf{v}_N) \in \mathbb{R}^{M \times N}$  is the mixing matrix composed of the so-called voltage loadings or spatial distributions of all LFP-generators  $(\mathbf{v}_n = (v_{1n}, \dots, v_{Mn})^T$  is the voltage loading of the *n*th generator) and  $S = (s_1 | s_2 | \cdots | s_N)^T \in \mathbb{R}^{N \times L}$  is the matrix of time courses of the LFP-generators  $(s_n = (s_n(1), \dots, s_n(L))^T)$  is the time course of the *n*th generator). Thus, the raw LFP observed at the *m*th electrode tip is a linear mixture of the electrical activity of several independent LFP-generators describing oscillations of the transmembrane currents in principal cells:

$$u_m(t) = \sum_{n=1}^{N} v_{mn} s_n(t).$$
 (5.6)



**Fig. 5.3** The front panel of the software ICAofLFPs. It shows an example of five LFP-generators: *Top panel:* A segment of time courses of the generators; *Bottom panels:* Spatial distributions of voltage and CSD loadings (see also Fig. 5.2c). The software is freely available at http://www.mat.ucm.es/~vmakarov/downloads.php

The LFP observed in all electrodes at a time instant t is given by

$$\boldsymbol{u}(t) = \sum_{n=1}^{N} \boldsymbol{v}_n \boldsymbol{s}_n(t).$$
(5.7)

Then, the CSD is

$$\dot{\boldsymbol{i}}(t) = -\sigma \sum_{n=1}^{N} \tilde{\Delta} \boldsymbol{v}_n \boldsymbol{s}_n(t).$$
(5.8)

where  $\tilde{\Delta}$  represents the discrete second order spatial derivative, which in the simplest case can be approximated by the 3-point formula (5.3). We can now introduce the CSD loading (spatial weights) for the *n*th LFP generator:

$$\boldsymbol{j}_n = -\sigma \tilde{\Delta} \boldsymbol{v}_n, \tag{5.9}$$

and obtain the formula for CSD equivalent to (5.7):

$$i(t) = \sum_{n=1}^{N} j_n s_n(t).$$
 (5.10)

As recording sites' location is known, the curve of spatial weights of the *n*th LFP generator  $v_n$  equals the instant depth profile of voltages recorded during a predominant activation of the corresponding single pathway. Such a situation happens, e.g., during the laminar recording of standard pathway-specific evoked potentials.

#### 5.2.2.2 Technical Considerations on ICA of LFPs

When dealing with ICA of LFPs, some technical considerations should be taken into account. In general, ICA allows separating up to M LFP-generators, where M is the number of electrode tips in a multielectrode array. However, usually, only a few ICA components exhibit significant variance and distinct spatial distributions. Our experience suggests that 4–7 stable LFP-generators out of possible 32 can be identified [12, 34].

Such a low number of sizable LFP-generators in raw LFPs permits further optimization of the algorithm by pre-processing raw LFPs before performing the ICA. In particular, the dimension reduction of the data matrix U by the principal component analysis (PCA) efficiently diminishes weak, noisy generators [16]. The PCA also stabilizes and accelerates the subsequent convergence of ICA algorithms [11].

By assuming that U has been previously centered (i.e., row mean values have been subtracted), we can find the covariance matrix of the data:  $C = \frac{1}{L}UU^{T}$ . Then, the covariance matrix can be factorized:

$$C = W D W^T, (5.11)$$

where  $D = \text{diag}(\lambda_1, \ldots, \lambda_M)$  is the matrix of eigenvalues sorted in descending order  $(\lambda_1 \ge \lambda_2 \ge \cdots \lambda_M \ge 0$ , note that *C* is symmetric semi-positive) and  $W = (w_1 | \cdots | w_M)$  is the matrix of the corresponding eigenvectors. When dealing with LFPs, the eigenvalues decrease rapidly, which means that the effective data dimension is less than *M* (about 4–7 compared to M = 32).

We now can project the data matrix U into a reduced PCA space:

$$Y = \tilde{W}^T U, \quad \tilde{W} = (w_1 | \cdots | w_N) \in \mathbb{R}^{M \times N}, \tag{5.12}$$

where  $N \le M$  is the number of principal components we want to retain. Finally, the ICA is applied to the reduced data matrix *Y*, and we get its factorization:

$$Y = Q\tilde{S},\tag{5.13}$$

where  $Q \in \mathbb{R}^{N \times N}$  is the squared matrix of loadings describing the spatial dynamics and  $\tilde{S} \in \mathbb{R}^{N \times L}$  is the matrix of activations describing the time dynamics. We thus have the following data representation:

$$\tilde{U} = \tilde{V}\tilde{S},\tag{5.14}$$

where  $\tilde{V} = \tilde{W}Q$  is the mixing matrix (or the matrix of voltage loadings) and  $\tilde{U}$  approximates the original data matrix U. We now have to select N in such a way that the approximation error  $||U - \tilde{U}||$  would be reasonably small.

The optimal choice of N is 2–3 more than the number of components that attain significant variance in the ICA. We routinely disregard the ICA components with a total compound variance below 1% (i.e., always keeping 99% of the original LFP variance) unless their spatial and temporal accuracy can be ensured through other means. Algorithmically, to select N, we use the following equation:

$$N = \arg\min_{m \in \overline{1,M}} \left| \sum_{n=1}^{m} \lambda_n - 0.99 \sum_{n=1}^{M} \lambda_n \right|.$$
(5.15)

#### 5.2.2.3 Schaffer LFP-Generator: CA3 Ipsilateral Input to CA1

Figure 5.2c shows the results of ICA separation of the ongoing raw LFPs into the contribution of pathway-specific LFP-generators. The analysis of the component variance [see Eq. (5.15)] reveals the existence of four significant LFP-generators with specific spatial patterns and time dynamics (top and bottom panels in Fig. 5.2c, respectively). Thus, these four major LFP-generators contribute to the epoch of LFPs shown in Fig. 5.2a.

Each of the four generators is described by its distribution of spatial weights along the principal axis of pyramidal cells and by its temporal dynamics, given by matrices  $\tilde{V}$  and  $\tilde{S}$  in Eq. (5.14), respectively. The cross-animal stability, pathway specificity, and quantitative properties of these LFP generators have been described elsewhere, both experimentally [11, 12, 33] and by using realistic simulations of the field potentials generated by the multicompartmental model of pyramidal neurons aggregated in monolayers [16].

One of the generators (colored in dark blue in Fig. 5.2c) corresponds to the activation of the Schaffer collaterals conveying packets of spikes from the ipsilateral CA3 region of the hippocampus to CA1 (Fig. 5.1). We derive this observation from the following facts: (i) This generator exclusively captures the evoked activity produced by subthreshold stimulation of CA3 (pulse followed after "stimulus" arrows in the time course, Fig. 5.2c); (ii) The characteristic spatial profile matching the Schaffer-evoked field EPSPs.

Disentanglement of raw LFPs into four LFP-generators enables the reconstruction of virtual LFPs produced by each pathway taken separately. Figure 5.2d shows the virtual LFPs contributed exclusively by the activity of the Schaffer pathway. Subsequent CSD analysis of the reconstructed Schaffer-LFPs produces a clean spatiotemporal map of the transmembrane currents with a characteristic source-sink-source distribution, both for the evoked and ongoing activities (Fig. 5.2e). We then can compare the distribution of the CSD maps of evoked potentials over raw LFPs and clean Schaffer LFPs (Fig. 5.2b and e left panels, respectively).

# 5.3 Localization and Quantification of Gamma Waves in the Schaffer-Generator by Wavelet Analysis

In Sect. 5.2, we described the method of isolation of a pathway-specific activity from raw LFPs. In particular, we separated the synaptic contribution induced by the Schaffer pathway activated by the ipsilateral CA3 input to the CA1 region (Fig. 5.2). More details on the characteristics and pharmacological studies of this pathway can be found elsewhere [33, 35]. Below, we will study the time course (activation dynamics) of this LFP-generator.

### 5.3.1 Method for Detecting Gamma Waves

Figure 5.4 shows a short epoch of the activation of the Schaffer generator. The baseline activity of this generator is composed of a series of discrete field events excited by packets of spikes coming from the CA3 region to pyramidal cells in CA1. We term such elementary synaptic events as micro-field EPSPs or  $\mu$ fEPSPs. Paradoxically, during irregular hippocampal LFPs, the Schaffer  $\mu$ fEPSP events constitute a rather regular succession of excitatory packages produced by a variable contribution of individual presynaptic CA3 units. The rhythmic excitatory packages appear at gamma frequency, the histogram peaks at 45 Hz. We now aim at detecting and quantifying individual  $\mu$ fEPSP events. To this end, let us first model a succession of  $\mu$ fEPSP.



Fig. 5.4 The ICA-separated Schaffer generator exhibits typical micro-field EPSP events appearing at a gamma rate

#### 5.3.1.1 Model of the Schaffer Generator Time Course

A short packet of spikes reaching pyramidal neurons in CA1 evokes local active synaptic currents surrounded by passive transmembrane currents (Fig. 5.2e). These currents generate Schaffer LFPs. Figure 5.2c (bottom subplot, left panel, dark blue trace) shows a typical time course of a single field EPSP in the form of a short pulse. As discussed above, single  $\mu$ fEPSP events have the same electric nature.

For the description of  $\mu$  fEPSP, we use the alpha function [36]:

$$\alpha(t) = H(t)te^{1-t}, \qquad (5.16)$$

where H(t) is the Heaviside step function, which makes  $\alpha(t)$  casual ( $\alpha(t) = 0$  for t < 0). This alpha function reaches a maximum at  $t_{\text{max}} = 1$ , and  $\alpha(t_{\text{max}}) = 1$ . The effective duration of the alpha function measured at level  $e^{2-e} \approx 0.5$  is equal to *e*. The alpha function describes a change in the conductance of the postsynaptic membrane with a characteristic time-course.

Then, the time course of the Schaffer generator in a specific time interval can be modeled as a sum of *K* individual  $\mu$ fEPSP events:

$$s(t) = -\sum_{i=1}^{K} A_i \alpha \left(\frac{t - t_i}{\tau_i}\right), \qquad (5.17)$$

where  $t_i$  is the time instant of the beginning of the *i*th event,  $A_i$  and  $\tau_i$  are the amplitude and time scale of the event. Figure 5.5a, b (top panels) show examples of simulated activations of the Schaffer generator consisting of one and five  $\mu$ fEPSP events with different parameters.

Equation (5.17) describes a direct problem, i.e., how to build the time course of the Schaffer generator by using a known number of  $\mu$ fEPSP events with known parameters. However, we are instead interested in the inverse problem: how to infer on the number of events *K* and their parameters {*A<sub>i</sub>*,  $\tau_i$ , *t<sub>i</sub>*} from the time course *s*(*t*). Although in the modeled situations shown in Fig. 5.5a, b, this problem can be resolved by employing a nonlinear curve-fitting method, in experimental conditions (Fig. 5.4) such a direct approach fails. Indeed, even in a short time interval of 1 s, we have about 45 events, each described by three parameters, and hence, we get an optimization problem in 135-dimensional space. Then, the curse of dimensionality makes it untreatable [37]. Besides, inferring on the number of events *K* is also a big issue.

#### 5.3.1.2 Wavelet Measure for Identification and Quantification of μfEPSP Events

To approach the inverse problem, we use the continuous Wavelet Transform of the Schaffer activation s(t) (for details, see Chap. 2):



Fig. 5.5 Identification and quantification of  $\mu$ fEPSP events in simulated epochs of the Schaffer generator. **a** *Top*: Single event (alpha function) with unit amplitude and unit time scale. *Bottom*: Measure *C*(*a*, *b*) and its maximum (cyan dot) defining the event parameters. **b** Same as in **a** but for five events with different parameters. **c** Comparison of the parameters of the events shown in (**b**) with those found by the wavelet method

$$W(a,b) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} s(t)\psi\left(\frac{t-b}{a}\right) dt, \qquad (5.18)$$

where a is the time scale, b is the localization in time, and

$$\psi(t) = \begin{cases} 1, & \text{if } -\frac{1}{2} \le t < 0\\ -1, & \text{if } 0 < t \le \frac{1}{2}\\ 0, & \text{otherwise} \end{cases}$$
(5.19)

is the Haar mother wavelet function. As we will see below, such a mother wavelet, in the form of two successive pulses of different polarity, is well suited for detecting short pulses in a signal.

We then rectify the wavelet coefficients and introduce the following wavelet measure for quantifying gamma events:

$$C(a,b) = \frac{1}{\sqrt{a}} \max\{0, W(a,b)\}.$$
 (5.20)

The two-dimensional surface C(a, b) describes the local linear fit of the Schafferspecific LFP by the Haar wavelet at scales *a* and localizations *b*. Peaks of C(a, b)correspond to abrupt pulse-like transitions in s(t). Thus, we can associate such points in the (b, a)-plane with single pulse-like events. Consequently, we identify the local maximums of C(a, b) evaluated as global maximums over a set of small enough, non-overlapping open domains  $\{\omega_i\}$ :

$$(a_i, b_i) = \underset{a, b \in \omega_i}{\operatorname{arg\,max}} \{ C(a, b) \}.$$
(5.21)

As we show below, the time instants of  $\mu$ fEPSPs are given by  $\{b_i\}$ , their durations by  $\{a_i\}$ , and amplitudes by  $\{C(a_i, b_i)\}$ . We also note that the factor  $\frac{1}{\sqrt{a}}$  in Eq. (5.20) is essential, since it ensures the existence of local maximums in (5.21).

Let us now study the properties of the surface C(a, b) in more detail. We consider the signal  $s(t) = -\alpha(t)$  consisting of a single  $\mu$ fEPSP event generated at t = 0 with the unit amplitude and time scale (Fig. 5.5a, top). We can now apply the wavelet transform (5.18), (5.19) to the signal and obtain:

$$W_{\alpha}(a,b) = \frac{e^{1-b}}{\sqrt{a}} \times \begin{cases} 0 & b < -\frac{a}{2} \\ e^{b} - (1+b+\frac{a}{2})e^{-\frac{a}{2}} & b \in [-\frac{a}{2},0) \\ 2(1+b) - e^{b} - (1+b+\frac{a}{2})e^{-\frac{a}{2}} & b \in [0,\frac{a}{2}) \\ 2(1+b)(1-\cosh\frac{a}{2}) + a\sinh\frac{a}{2} & b \ge \frac{a}{2}. \end{cases}$$
(5.22)

We observe that  $W_{\alpha}(a, b) \in C^1$ . This function attains a global maximum over localizations *b*, given that *a* is a constant, at

$$b_{\max} = \frac{a/2}{2e^{a/2} - 1}.$$
(5.23)

Assuming that *a* is big enough, we can approximate  $b_{\text{max}} \approx 0$ , i.e., the maximum of W(a, b) (and hence of C(a, b)) coincides rather precisely with the time instant of the event beginning. Nevertheless, in a computer algorithm the correction (5.23) can be easily taken into account, i.e.,  $t' = t - b_{\text{max}}(a_{\text{max}})$ .

The maximum of C(a, b) over time scales a satisfies to

$$(a_{\max}+1)^2 = 4e^{a_{\max}/2} - 3, \tag{5.24}$$

which for a > 0 has a unique solution, although it cannot be written in a closed form. We note that W(a, b) has no maximums in a.

Figure 5.5a (bottom panel) shows the measure C(a, b) for the simulated event. A numerical analysis yields:

$$a_{\max} \approx 2.94, \ b_{\max} \approx 0.19, \ C(a_{\max}, b_{\max}) \approx 0.43.$$
 (5.25)

Let us now assume that the event has an arbitrary amplitude and time scale,  $s(t) = -A\alpha(t/\tau)$ . Then, the wavelet transform (5.18) of s(t) and the wavelet measure (5.20) can be written as:

$$W(a,b) = \sqrt{\tau} A W_0(a',b'), \quad C(a,b) = A C_0(a',b'), \quad (5.26)$$

where  $a' = a/\tau$ ,  $b' = b/\tau$ ;  $W_0$  and  $C_0$  are the wavelet transform and the wavelet measure of the unitary event  $-\alpha(t)$ . Thus, the magnitude of *C* scales linearly with *A*, whereas the time scale and localization *a* and *b* scales linearly with  $\tau$ .

Therefore, we can use the constants (5.25) to express the event duration, time instant, and amplitude:

$$d_{i} = \frac{a_{i}}{a_{\max}}e, \quad t_{i} = b_{i} - \frac{b_{\max}}{a_{\max}}a_{i}, \quad A_{i} = \frac{C(a_{i}, b_{i})}{C(a_{\max}, b_{\max})}, \quad (5.27)$$

where  $a_i$  and  $b_i$  are the coordinates of the *i*th local maximum given by (5.21).

To illustrate the approach, we simulated the activity of the Schaffer generator consisting of five  $\mu$ fEPSP events (Fig. 5.5b). Then, we evaluated C(a, b), found its maximums, and calculated the parameters of each event by using (5.27). The number of local maximums in C(a, b) provides the number of  $\mu$ fEPSP events in the signal *K*. Figure 5.5c shows the comparison of the found parameters with the original characteristics used to generate the signal s(t). One can observe the good precision of the detection method.

#### 5.3.2 Elementary Micro-fEPSPs in Ongoing Schaffer Activity

Oscillatory gamma patterns, formed by small pulse-like events of variable amplitude and duration, dominates the basal activity of the Schaffer generator (Fig. 5.4). This temporal pattern is exclusive for the Schaffer generator, which can also include occasional sharp-wave events that emerge from the baseline during non-theta epochs [33].

Figure 5.6a illustrates an epoch of the Schaffer-generator activity isolated by ICA and a typical spike train of a CA3 pyramidal neuron recorded simultaneously. Some Schaffer events are time-locked to neuronal spikes. Then, we can assume that this neuron participates in the firing activity of a cluster of CA3 neurons that provokes some of the Schaffer events.

To crosscheck this assumption, we evaluated the spike-triggered activity of the Schaffer generator (Fig. 5.6b). The confidence intervals (dashed red lines) were evaluated using surrogate data (spikes in the train were randomly shuffled). The significance level was set to 0.05, and we also used the Bonferroni correction [38]. The activity of the Schaffer generator exhibits a statistically significant coupling with the spiking of the CA3 neuron. Moreover, the coupling is causal, i.e., firing of the neuron, presumably involved in synchronous firing of a cluster of CA3 neurons, causes a



**Fig. 5.6** Decomposition of Schaffer LFPs into elementary  $\mu$ fEPSPs triggered by CA3 pyramidal cells. **a** A representative epoch (6 s out of a 10 min recording and its zoom) of a spike train of a pyramidal neuron in the CA3 region of the hippocampus (dark red) and the activity of the Schaffer generator (black and blue traces). **b** Averaged (over 10 min) Schaffer activity triggered by spikes of the CA3 pyramidal neuron. Dashed red lines mark the confidence interval (the significance level of 0.05 and the Bonferroni correction were used). **c** The wavelet-measure *C*(*a*, *b*) corresponding to the zoomed region of the Schaffer generator. Cyan dots mark locations of local maximums (see also Fig. 5.5). **d** Schematic representation of the micro-field EPSPs composing the Schaffer activity. The width and height of the bars codify the duration and amplitude of the detected  $\mu$ -fEPSP events. **e** The distributions of the duration (top) and amplitude (bottom) of the detected  $\mu$ -fEPSP events (10 min recording)

sizable response in the Schaffer generator. Therefore, we assess whether elementary postsynaptic events from single CA3 principal cells or their functional clusters could be discriminated in ongoing CA1 LFPs by studying the fine temporal structure of the Schaffer generator.

When considering an epoch of the Schaffer-specific activity (Fig. 5.6a), we observe a sequence of pulses corresponding to individual  $\mu$ LFP events. To detect these elementary events, we use the wavelet-based method described in Sect. 5.3.1. Figure 5.6c shows the wavelet-measure C(a, b) calculated for a short segment of the activity of the Schaffer generator. The measure has local maximums similar to those shown in Fig. 5.5. The positions of the maximums (cyan dots) correspond to the time instants and durations of elementary  $\mu$ fEPSPs, while the amplitudes of the local maximums provide the amplitudes of the elementary  $\mu$ fEPSPs [see Eq. (5.27)].

Figure 5.6d illustrates the identified and quantified single  $\mu$ fEPSP events as rectangles of the width and height corresponding to the duration and amplitude of the events and with the left side located at the beginning of the event. The found events

exhibit substantial amplitude variability and moderate fluctuations in the event durations. The rate of the detected events (about 42 Hz) falls within the gamma band.

Figure 5.6e shows histograms of the distribution of the duration and amplitude of  $\mu$ LFP events identified over a 10 min recording period. Both parameters have a right-skewed distribution with modes at 11.6 ms (mean 14.5) and 114  $\mu$ V (mean, 156). These parameters are similar to the spike-averaged Schaffer activity shown in Fig. 5.6b. The absence of the baseline explains the amplitude discrepancy due to the hardware high-pass filtering of the recordings (AC-recordings, for more details, see [39]). Note that the wavelet-based method is insensitive to the presence of the DC-part and hence enables better estimation of the event parameters (the Haar wavelet canceles the DC part).

## 5.3.3 Detected Gamma Events Help to Establish Causal Relations Between CA3 and CA1 Pyramidal Cells

Let us now get a deeper insight into the properties of  $\mu$ fEPSPs. A *mu*fEPSP can be considered as an intermediate event between spikes of a presynaptic CA3 neuron and a postsynaptic CA1 cell. Thus, identification of time series of elementary  $\mu$ fEPSPs permits a detailed study of information transfer from CA3 to CA1. We can test whether an ongoing input from a single afferent pathway is strong enough to fire postsynaptic units in the CA1 region.

Figure 5.7a shows spike trains of CA3 and CA1 pyramidal neurons and an intermediate train of  $\mu$ fEPSP events (a point process consisting of the identified starting time instants  $t_i$ ). Presumably, the CA3 neuron is coupled with the CA1 (Fig. 5.7a, cartoon) and thus can participate in its excitation. However, the cross-correlation analysis of the spike trains of these neurons shows no significant peaks (Fig. 5.7b). Therefore, we could conclude that the neurons are uncoupled, or at least only a few spikes of the CA3 cell participate in the excitation of CA1, and hence their contribution to the histogram is negligible. Nevertheless, we will show how the knowledge on the  $\mu$ fEPSP events composing the activity of the Schaffer generator helps in establishing causal relations between the CA3 and CA1 neurons.

Figure 5.7c illustrates the histogram of cross-correlation among  $\mu$ fEPSP events and firings of the CA3 pyramidal cell. By analogy with the latency of evoked subthreshold fEPSPs [26], we consider that  $\mu$ fEPSP events can be monosynaptically related with firings of the presynaptic unit within a postspike time window of 2– 6 ms. Notably, the obtained latency of 4.9 ± 2.2 ms (mean ± std) falls within this interval (orange bars in Fig. 5.7c, dashed line shows the Holm–Bonferroni statistical significance interval [40]). Moreover, all CA3 principal cells, which exhibited a correlation with the Schaffer generator, displayed statistically significant peaks within this time window [33].

We thus separated all spikes of the CA3 pyramidal neurons into two groups: (i) Spikes time-locked with  $\mu$ fEPSP events (about 50% of spikes fall within a 10 ms time



Fig. 5.7 Wavelet analysis reveals functional couplings between spontaneous firing of CA3 pyramidal cells and spikes of CA1 neurons. **a** *Left:* A cartoon of the information transfer from CA3 to CA1 regions through Schaffer collaterals. *Right:* A five second epoch showing spikes of a pyramidal presynaptic CA3 neuron (bottom train),  $\mu$ fEPSP events created by Schaffer collaterals (middle train), and spikes of a pyramidal postsynaptic CA1 neuron (top train). **b** Direct cross-correlation of spikes of the CA3 and CA1 cells exhibits no temporal relation. Blue dashed line marks the level of statistical significance. **c** Step by step identification of the functional CA3-CA1 coupling. *Left:* Identification of CA3 spikes time-locked to Schaffer  $\mu$ fEPSP events. Orange bars show significant correlation, and we thus define Type I spikes in CA3 firing. *Middle:* Significant correlation of  $\mu$ fEPSP events and firing of the CA1 cell enables identification of CA1 neuron exhibits a significant peak (orange bar)

window, orange bars in Fig. 5.7c) and (ii) Other remaining spikes. The spike-locked Schaffer time course constitutes a subpopulation of the monosynaptic  $\mu$ fEPSPs, which are probably elicited by the CA3 neuron or the functional cluster to which it belongs.

We then performed cross-correlation analysis of  $\mu$ fEPSPs and spikes of the CA1 neuron. The cross-correlation exhibits a significant peak (Fig. 5.7d) with the latency 2.6  $\pm$  1.5 ms, which corresponds to the time lag between the initiation of a  $\mu$ fEPSP and firing of the CA1 cell. We note that only 2.3% of  $\mu$ fEPSPs excite the cell, and about 24% of spikes of the CA1 neuron are time-locked with  $\mu$ fEPSPs. We now

separate spikes of the CA1 cell into (i) spikes caused by  $\mu$ fEPSP events and (ii) all the other.

The introduced classification of spikes of the CA1 and CA3 neurons allows us to identify the following temporal relations:

- *Type I: Spikes driving Schaffer.* A presynaptic CA3 spike participates in excitation of a μfEPSP event but no time-locked CA1 spike appears (green ticks in Fig. 5.7c).
- *Type II: Shaffer driven spikes.* A  $\mu$ fEPSP excites a postsynaptic CA1 spike, but no CA3 time-locked spike is recorded (blue ticks in Fig. 5.7c).
- *Type III: Triple coincidences.* A presynaptic CA3 spike participates in exciting a  $\mu$ fEPSP event and, in turn, it excites a CA1 spike (red ticks in Fig. 5.7c).

Type I temporal relationships were observed in all CA3 pyramidal cells, although only about 23% of the spikes had a monosynaptic association to  $\mu$ fEPSPs. This index is interpreted as the recruitment rate of individual CA3 pyramidal cells into functional clusters responsible for  $\mu$ fEPSPs. Thus, time-variable clustering of presynaptic CA3 neurons is behind sizable  $\mu$ fEPSPs in the CA1 region. This indicates that CA3 pyramidal neurons can organize into functional clusters to effectively transmit information to the CA1 output and the cortex.

Statistically significant Type II temporal relationships were found in about 70% of CA1 pyramidal cells. The cross-correlation histogram of  $\mu$ fEPSP-CA1 shows a statistically significant peak at a 2 ms time lag, corresponding to the Schaffer-driven spikes (Fig. 5.7c, left). Such spikes constitute about 11% of the firing of CA1 cells. Thus, a significant share of the CA1 output is driven by the local Schaffer input.

Some spontaneous  $\mu$ fEPSPs fulfill both Types I and II temporal relationships. We then assume that  $\mu$ fEPSPs can be considered as a selector of time instants when the information transmission from a CA3 cell to a CA1 neuron is likely. Thus, the  $\mu$ fEPSP events can be used for searching for functional coupling between individual CA3 and CA1 cells. Figure 5.7c (right) shows such a situation of monosynaptically connected CA3-CA1 cell pairs. The cross-correlation histogram, in this case, was build by taking into account only spikes of Types I and II of the CA3 and CA1 neurons, respectively. We observe a significant peak at the time lag of 7.3 ms (compare to the raw cross-correlation in Fig. 5.7b), which reveals a functional connection between these neurons, i.e., some spikes fired by a CA3 cell actively participates in the firing of a CA1 spike.

#### 5.4 Improved Identification of Micro-fEPSP Events

#### 5.4.1 Distortion of Micro-fEPSP Events by Wavelet Method

In Sect. 5.3.1, we have introduced the wavelet-based method for the identification of  $\mu$ fEPSP events in the irregular activity of the Schaffer LFP generator. It enables computationally efficient isolation and quantification of individual gamma waves

induced in the CA1 region by firing of pyramidal cells in the CA3 area. However, we noticed that due to the frequent overlap of successive events, the method could introduce some distortions in the identified parameters of the  $\mu$ fEPSP events, given by Eq. (5.27).

To quantify the distortions, we simulated a random sequence of 2000 overlapping gamma events on a 50 s time interval (mean event rate 40 Hz). The parameters of gamma events were chosen to reproduce the experimental distributions of the event duration and amplitude shown in Fig. 5.6e. To do that, we evaluated the experimental cumulative distribution functions for the amplitudes and durations,  $F_A(u)$  and  $F_d(u)$ , and then generated a set of random event durations and amplitudes by:

$$d_i = F_d^{-1}(\xi_i), \quad A_i = F_A^{-1}(\eta_i), \quad i = 1, \dots, 2000,$$
 (5.28)

where  $\xi_i$  and  $\eta_i$  are independent random variables uniformly distributed on the interval (0, 1). These parameters have been used for simulating Schaffer activation by using Eq. (5.17). Finally, we added a small (-25 dB) Gaussian white noise to the obtained signal.

Figure 5.8a shows an epoch of the simulated Schaffer activity composed of a sequence of randomly chosen gamma events. We then applied the wavelet method described in Sect. 5.3.1, blindly identified the  $\mu$ fEPSP events in the simulated signal, and determined their parameters: starting times, durations, and amplitudes (Fig. 5.8b). Finally, we quantified the distortions obtained during the identification of the parameters.

Figure 5.8c shows the histograms of deviations of the event parameters from the original values. We observe that the wavelet method tends to delay the starting time of the identified event on average by 1.0 ms, although time lags up to 3 ms have been detected. The event duration and amplitude could be underestimated by 4.1 ms and 17  $\mu$ V, respectively. In Sect. 5.4.2, we describe a modification to the wavelet method that significantly improves the precision of the identified characteristics of  $\mu$ fEPSP events, although on the expenses of time-consuming calculations.

#### 5.4.2 Likelihood Enhanced Wavelet (LeW) Method

#### 5.4.2.1 Probabilistic Mixture Model of Micro-fEPSP Events

Let us consider an epoch of the Schaffer activity composed of  $K \ \mu \text{fEPSP}$  events modeled by Eq. (5.17) with some arbitrary parameters  $\{A_i, t_i, \tau_i\}_{i=1}^K$ . Then, such a model can be rewritten in terms of a weighted mixture of the probability density functions:

$$p(t) = \sum_{k=1}^{K} w_k f(t - t_k; \tau_k), \qquad (5.29)$$



**Fig. 5.8** Distortion of the parameters of  $\mu$ fEPSP events by the wavelet analysis. **a** Composition of simulated Schaffer activity (*bottom*) from single  $\mu$ fEPSP events (*top*) of different amplitude and durations appearing at gamma rate (40 Hz). The distributions of amplitude and durations repeat the experimental ones (Fig. 5.6e). The simulated activity also includes Gaussian noise (-25 dB). **b** The wavelet analysis of the signal shown in (**a**). Cyan dots mark the locations of local maxima of the wavelet measure C(a, b), and thus determine features of detected events. See also Fig. 5.5. **c** Probability densities of deviations of the event parameters determined by the wavelet analysis from the original values: *Left*: Starting times of  $\mu$ fEPSP events, *Middle:* Durations of events, and *Right:* Amplitudes of events. **d** Correlations between pairs of deviations:  $\Delta T$  starting times,  $\Delta D$  durations, and  $\Delta A$  amplitudes

where

$$f(x;\tau) = \frac{1}{e\tau} \alpha\left(\frac{x}{\tau}\right) = \frac{x}{\tau^2} e^{-\frac{x}{\tau}} H(x), \qquad (5.30)$$

is the probability density function (scaled  $\alpha$ ) and  $w_k$  is the relative magnitude of the *k*th event. The latter can also be interpreted as a prior probability of the *k*th  $\mu$ fEPSP. One can check  $\int_{-\infty}^{\infty} f(x; \tau) dt = 1$ . Besides, the relative magnitudes must satisfy the condition  $\sum_{k=1}^{K} w_k = 1$ . Thus, we set

#### 5.4 Improved Identification of Micro-fEPSP Events

$$w_k = \frac{A_k}{\sum_{j=1}^{K} A_j}.$$
 (5.31)

We note that in experimental conditions, one can obtain p(t) from the recorded signal by applying an appropriate scaling:

$$p(t) = \frac{s(t)}{s_0}, \quad s_0 := \int_0^T s(t) \, \mathrm{d}t,$$
 (5.32)

where *T* is the working time interval. In the case of an AC-recording, special attention should be given to satisfy  $p(t) \ge 0$  [41]. Using definition (5.32) and Eqs. (5.17), (5.29)–(5.31), we can find the inverse relation for the amplitudes of  $\mu$ fEPSP events:

$$A_{i} = \frac{|s_{0}|w_{i}}{e\sum_{k=1}^{K} w_{k}\tau_{k}}.$$
(5.33)

Thus, knowing the parameters of the probabilistic mixture model and the area limited by the Schaffer signal s(t), we can evaluate the amplitudes of the  $\mu$ fEPSP events.

Figure 5.9a illustrates an example of p(t) made up by 22  $\mu$ fEPSP events of different magnitude and duration (colored curves). Overlapped oscillations are added and produce a higher magnitude signal, which also includes some small noise (black curve).

#### 5.4.2.2 Inverse Problem: Estimation of the Presynaptic Content

Given the parameter set  $\theta = \{w, \tau, t\}$ , where

$$\mathbf{w} = (w_1, \dots, w_K)^T, \ \mathbf{\tau} = (\tau_1, \dots, \tau_K)^T, \ \mathbf{t} = (t_1, \dots, t_K)^T,$$
 (5.34)

one can easily build the compound Schaffer signal (in Fig. 5.9a  $s(t) = s_0 p(t)$ ). However, in experimental conditions, we rather deal with the inverse problem, i.e., we have to estimate the parameter set  $\theta$  from the observed activation s(t) or, which is the same, from the corresponding probability p(t). To accomplish this task, we will use a combination of the wavelet approach described in Sect. 5.3.1 and the method of maximization of a likelihood function. Let us now describe the maximization of likelihood.

Given the parameter set  $\theta$ , we can define

$$p(\mathbf{x}|\boldsymbol{\theta}) = \prod_{n=1}^{N} p(x_n|\boldsymbol{\theta})$$
(5.35)

where  $\mathbf{x} = (x_1, \dots, x_N)^T$  are time samples,  $x_n \in [0, T]$ ,  $n = \overline{1, N}$ . In general,  $\mathbf{x}$  can be taken independently from the experimental distribution p(t). However, such an



**Fig. 5.9** Improved identification and quantification of  $\mu$ fEPSP events by the LEW method. **a** A probabilistic mixture model of a sequence of 22  $\mu$ fEPSP events. The obtained signal p(t) is considered as a probability density function, and hence the total probability (gray area) is scaled to 1. **b** The LeW method works in two stages. First, we apply the wavelet approach described in Sect. 5.3.1 and find the number of gamma events *K* and estimate their parameter values. The obtained estimate (blue curve) deviates from the original signal p(t) (gray curve). Second, the estimate is optimized by maximizing the likelihood function (red curve). The detected events correspond faithfully to the original events shown in (**a**). **c** Quantification of the deviation of the parameters of  $\mu$ fEPSP events from the original ones found after the Wavelet step (blue triangles) and Likelihood step (red circles)

approach is extremely resource-demanding and we will rather use equidistant samples  $(x_n = \delta(n-1))$ , where  $\delta = T/(N-1)$  together with the experimental probability distribution:

$$\boldsymbol{p} := (p_1, \dots, p_N)^T, \quad p_n = \int_{\delta(n-1)}^{\delta n} p(t) \, \mathrm{d}t, \quad n = \overline{1, N}.$$
(5.36)

This distribution is naturally obtained from an experimental sampling of the Schaffer activation s(t).

Thus, to solve the inverse problem, we aim at maximizing the log-likelihood:

$$\mathscr{L}(\boldsymbol{\theta} \mid \boldsymbol{x}, \boldsymbol{p}) = \sum_{n=1}^{N} p_n \log \left[ \sum_{k=1}^{K} w_k f(x_n - t_k; \tau_k) \right] + \left( 1 - \sum_{k=1}^{K} w_k \right).$$
(5.37)

The first term in (5.37) is the log-likelihood (log  $p(\mathbf{x}|\boldsymbol{\theta})$ ), whereas the second one accounts for the constraint  $\sum_{k=1}^{K} w_k = 1$ . Since the sum over components (single events) appears inside the logarithm, there is no closed-form solution maximizing the likelihood. Thus, to maximize  $\mathcal{L}$ , we use the expectation-maximization algorithm adapted for the given likelihood function.

#### 5.4.2.3 Optimization of the Likelihood Function: E-Step

In general, any data point  $x_n$  can be sampled from one of the *K* components (gamma waves) satisfying the condition  $x_n > t_k$  (where  $t_k$  is the starting time of the component). Thus, we can introduce a set of latent variables  $z_n \in \{1, 2, ..., K\}$ ,  $n = \overline{1, N}$ . If  $z_n = k$ , then the data point  $x_n$  has been drawn from the *k*th component. To describe these variables, we introduce the conditional probability that a given data point  $x_n$  has been generated by the *k*th event:

$$r_{kn} := p(z_n = k | x_n). \tag{5.38}$$

This posterior probability is frequently called *responsibility* of the component k for generating the observation  $x_n$ .

Using the Bayes theorem, we get

$$r_{kn} = \frac{p(z_n = k)p(x_n | z_n = k)}{\sum_{j=1}^{K} p(z_n = j)p(x_n | z_n = j)} = \frac{w_k f(x_n - t_k; \tau_k)}{\sum_{j=1}^{K} w_j f(x_n - t_j; \tau_j)}$$
(5.39)

Therefore, we define the responsibility matrix:

$$R(\boldsymbol{\theta}) = (r_{kn}) \in \mathbb{R}^{K \times N}.$$
(5.40)

Thus, for a given parameter set  $\theta$ , we can evaluate the expectation of the responsibilities for all data points, or perform the E-step.

#### 5.4.2.4 Optimization of the Likelihood Function: M-Step

A maximum of the likelihood satisfies:

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$$\frac{\mathscr{L}(\boldsymbol{\theta})}{\partial w_k} = \frac{\mathscr{L}(\boldsymbol{\theta})}{\partial \tau_k} = \frac{\mathscr{L}(\boldsymbol{\theta})}{\partial t_k} = 0, \quad k = \overline{1, K}.$$
(5.41)

We will now use it to perform the maximization of the likelihood or M-step. *Optimization of weights.* Evaluating the first derivative in (5.41), we get:

$$\frac{1}{w_k} \sum_{n=1}^{N} \frac{p_n w_k f(x_n - t_k; \tau_k)}{\sum_{j=1}^{K} w_j f(x_n - t_j; \tau_j)} - N = 0.$$
(5.42)

Using the definition of the responsibilities (5.39), (5.40), we obtain:

$$\boldsymbol{w} = \boldsymbol{R}\,\boldsymbol{p}.\tag{5.43}$$

*Optimization of time scales.* Calculating the partial derivative of (5.37) with respect to  $\tau_k$  and by using similar arguments as above, we obtain:

$$\sum_{n=1}^{N} \frac{p_n r_{kn} (y_{kn} - 2\tau_k)}{\tau_k^2} = 0,$$
(5.44)

where  $y_{kn} := x_n - t_k$ . Then, we denote by  $Y = (y_{kn}) \in \mathbb{R}^{K \times N}$  the data matrix and get

$$\boldsymbol{\tau} = \frac{1}{2} (Y \odot R) \boldsymbol{p} \oslash R \boldsymbol{p}, \qquad (5.45)$$

where  $\odot$  and  $\oslash$  stand for the Hadamard product and division, respectively. To simplify notation, we also assume that the standard product has higher priority than the Hadamard operations.

*Optimization of starting times.* Similarly to the cases discussed above, the partial derivative of (5.37) with respect to  $t_k$  is:

$$\sum_{n=1}^{N} p_n r_{kn} \left( \frac{1}{\tau_k} - \frac{1}{y_{kn}} \right) = 0.$$
 (5.46)

Thus, we get the following equation:

$$F(t) := (R \oslash Y) p - R p \oslash \tau = 0.$$
(5.47)

Equation (5.47) is nonlinear with respect to t (a polynomial of order N in general case). We can solve it numerically by, e.g., using the Newton method:

$$t^{j+1} = t^{j} - F(t^{j}) \oslash F'(t^{j}),$$
(5.48)

where *j* is the method's step and the derivative of *F* is given by

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$$F'(t) = (R \oslash (Y \odot Y))p.$$
(5.49)

The numerical scheme (5.48) converges rapidly (in a few steps), given a good initial approximation  $t^0$ . As an initial approximation, we can take the value of t found at the previous step of the algorithm but see below.

#### 5.4.2.5 The LeW Algorithm

Above, we discussed the expectation-maximization approach to maximize the likelihood. It is iterative and alternates E and M steps while the likelihood grows reasonably fast. One of the difficulties to start the calculation is to provide the initial conditions for the first E-step. To start the numerical scheme and facilitate the convergence, at the beginning, we perform an initial estimation of the parameters by the wavelet method (Sect. 5.3.1). The wavelet method requires no a-priory knowledge and provides reasonably good results. Besides estimating the starting times *t*, durations  $\tau$ , and amplitudes *w*, it automatically finds the number of sizable events *K* in the Schaffer activity (see, e.g., Fig. 5.5).

**LeW algorithm:** *Likelihood-enhanced Wavelet method for identification and quantification of gamma events.* 

- (a) Rescale signal s(t) into the probability representation [Eq. (5.32)] and evaluate the probability vector p.
- (b) Evaluate for p the wavelet measure C(a, b) [Eq. (5.20)].
- (c) Detect local maximums of C(a, b) and find the number of gamma events K, and estimate their parameters  $t^W$ ,  $w^W$ , and  $\tau^W$  [Eqs. (5.21), (5.27)].
- (d) Set the initial parameter values  $\theta$  to those found in step (c).
- (e) Evaluate the responsibility matrix *R* (E-step) [Eq. (5.40)] and the weights *w* (M-step) [Eq. (5.43)]. Evaluate the likelihood  $\mathscr{L}$  [Eq. (5.37)], and if it was increased, update the value of *w*.
- (f) Evaluate the responsibility matrix *R* (E-step) [Eq. (5.40)] and the durations  $\tau$  (M-step) [Eq. (5.45)]. Evaluate the likelihood  $\mathscr{L}$  [Eq. (5.37)], and if it was increased, update the value of  $\tau$ .
- (g) Evaluate the responsibility matrix R (E-step) [Eq. (5.40)] and numerically approximate the starting times t (M-step) [Eqs. (5.47)–(5.49)]. Evaluate the likelihood  $\mathscr{L}$  [Eq. (5.37)], and if it was increased, update the value of t.

Loop steps (e)–(g) until a convergence criterion is reached. Calculate the amplitudes and durations of the events:  $A_i$  [Eq. (5.33)],  $d_i = e\tau_i$ .

Figure 5.9 illustrates the algorithm. Step (a): we rescale the Schaffer signal s(t) and find the probability vector p (Fig. 5.9a). Steps (b)–(c): we evaluate the wavelet measure C(a, b), search for local maximums and use them to define the number of events K, and estimate their parameters  $t^W$ ,  $w^W$ , and  $\tau^W$  (Fig. 5.9b, Wavelet step). At this point, we already can approximate the signal s(t) by the sum of gamma waves.

Method	Deviations from original values			
	Starting time, $\Delta T$ (ms)	Centering Duration,	Amplitude, $\Delta A (\mu V)$	
		$\Delta D$ (ms)		
Plain wavelet	0.95	5.15	21	
LeW	0.22	0.55	3	

 Table 5.1 Deviations of the main parameters of gamma waves identified by two methods relative to the original values

However, such an approximation (Fig. 5.9b, Likelihood step, blue curve) exhibits a relatively strong discrepancy with the original signal (gray curve), especially when several events overlap strongly.

Next, we use the results of the wavelet approach for the expectation-maximization algorithm (Steps (d)–(g)). Maximizing the likelihood function yields a significantly better approximation of the original signal. Both curves practically coincide (Fig. 5.9b, Likelihood step, red and gray curves). We then can plot the identified gamma waves (Fig. 5.9b, Detected events) and compare them with the original events used for building signal s(t) Fig. 5.9a, Original events).

Finally, to confirm the method validity, we compared the parameters of gamma waves found by the Wavelet approach and the LeW method with the original parameters (Fig. 5.9c, blue triangles and red circles, respectively). The LeW method provides a significant reduction of the deviation of the evaluated parameters from the original ones. Table 5.1 summarizes the main results. As expected, the Wavelet approach estimates  $\mu$ fEPSP events with good but not optimal precision. The most significant discrepancy is observed in the duration of events. The LeW method improves this first estimate by 4, 9, and 7 times for the starting times, durations, and amplitudes.

## 5.5 Bilateral Integration of Gamma-Parsed Information

The hippocampus is a paired structure consisting of two anatomically similar lobes. It is thus interesting to study the lateralization of information processing. Do the two hippocampal lobes convey similar or complementary activities, and how do they cooperate?

Lateralization of certain neural functions in vertebrates is thought to bear evolutionary advantages [42]. Many studies have focused on finding anatomical correlates to behavioral asymmetries. For example, fMRI studies have shown bilateral or lateral activation of the same structures when a subject performs different tasks [43, 44]. But there has been little insight into the functional mechanisms underlying the differential routing and integration of activity in bilateral networks.

The existence of important bilateral connections between hippocampal subregions suggests some degree of integration and cooperation. In rodents, hippocampal lateralization is observed during specific memory tasks [45, 46], in the expression



Fig. 5.10 Analysis of bilateral LFPs. a Cartoon illustrating the CA3-CA1 pathways. Intrinsic gamma oscillations in each CA3 region produce gamma output. Pyramidal cells in the left and right CA3 are coupled through the ventral hippocampal commissure (VHC), enabling the coupling of gamma waves. The excitatory outputs of CA3 from both sides converge in each CA1 through Schaffer (ipsilateral) and Commissural (contralateral) pathways. LFPs were recorded simultaneously by multielectrode matrices in the left (L) and right (R) hippocampal lobes (blue and red traces on the top). The contribution of CA3 neurons to CA1 LFPs was isolated by the independent component analysis. b *Left:* Traces of activations of the LFP-generators in the left and right CA1 regions (in black) and traces obtained by the LeW method after reconstruction from individual  $\mu$ fEPSP events (in blue). *Right:* Detected  $\mu$ fEPSP events composing the traces of activation in the left (top) and right (bottom) CA1 regions. Synchronous and asynchronous  $\mu$ fEPSP events ( $\omega_0 = 0.5$ )

of synaptic plasticity [47], or following environmental enrichment [48]. In humans, lateralization was reported during sequence disambiguation [49] and in cognitive navigation [50, 51].

The hippocampal CA3 region is an important hub for ascending and cortical pathways [52], and its output is conveyed to numerous brain regions. The left and right CA3 are connected reciprocally, and they also send excitatory inputs to the CA1 on both sides of the brain (Fig. 5.10a). Thus, this system represents an ideal model to explore the flow of activity and its integration in bilateral networks. In this section, we provide some results of the analysis of electrophysiological data with the LeW method described above (additional data can be found in, e.g., [53]).

## 5.5.1 Experimental Recordings and Retrieval of Bilateral Micro-fEPSP Events

Recordings were obtained from two multielectrode linear probes lowered at homotopic sites of the dorsal hippocampus across the CA1 region, and that also spanned the DG/CA3 (Fig. 5.10a, raw LFPs). Then, we processed the raw LFPs and isolated the contribution of CA3 regions into the activity in CA1 zones in the same way as it was described in Sect. 5.2. Figure 5.10b (left, black traces) illustrates a typical epoch of the obtained traces corresponding to the left (L) and right (R) regions of the hippocampus.

Once the traces of the activity in CA1 regions induced by ipsi- and contra-lateral CA3 neurons were obtained, we have proceeded to their analysis by the LeW method (Sect. 5.4.2). The analysis revealed individual  $\mu$ fEPSP events (Fig. 5.10b, right) composing the traces of the corresponding LFP-generators (Fig. 5.10b, left, blue traces). As it was observed above (Fig. 5.9), the theoretical traces built from individual  $\mu$ fEPSP events faithfully reproduce the original experimental signals. In the next step, we will deal with individual  $\mu$ fEPSP events.

Since now we have events recorded from the left and right hippocampal lobes, we can analyze their possible synchronization. Such a synchronization occurs due to the synchronous spiking activity of functional clusters in ipsi- and contra-lateral CA3 regions promoted through the ventral hippocampal commissure (Fig. 5.10a, VHC). Thus, we expect that packets of spikes codifying information can propagate from CA3 to CA1 (left and right) and excite similar micro field potentials.

Accordingly, we consider two  $\mu$ fEPSP events detected in different CA1 regions synchronous if they have similar durations and considerable overlapping in time. We now introduce a formal criterion for the detection of synchronous events.

Let  $t_{1,2}$  and  $d_{1,2}$  be the staring times and durations of two  $\mu$ fEPSP events. Then, the interval of their overlapping in time is

$$\Delta = \max\left\{0, \min\{t_1 + d_1, t_2 + d_2\} - \max\{t_1, t_2\}\right\} \in [0, \min\{d_1, d_2\}].$$
(5.50)

We now introduce the ratio of the durations and overlapping coefficient:

$$\delta = \frac{d_1}{d_2} \in (0, \infty), \quad \omega = \frac{\Delta}{\max\{d_1, d_2\}} \in [0, 1], \tag{5.51}$$

and define:

**Definition 5.1** Two  $\mu$ fEPSP events are synchronous, if  $\omega \ge \omega_0$ , where  $\omega_0 \in (0, 1)$  is a threshold.

Such a one parametric definition yields the region delimited by  $\omega_0 \le \omega \le \delta$ , and  $\omega \le \delta^{-1}$ . In particular, it implies that  $\delta \in [\omega_0, \omega_0^{-1}]$  and hence we can satisfy the qualitative conditions imposed on the synchrony of  $\mu$ fEPSP events. Indeed, without loos of generality, we can assume that  $d_1 \le d_2$ , then the condition  $\omega \ge \omega_0$  yields:
$$\omega_0 d_2 \le \Delta \le d_1 \le d_2,\tag{5.52}$$

and hence the duration  $d_1$  and the overlapping interval  $\Delta$  are bounded from below by  $\omega_0 d_2$  and from above by  $d_2$ . Figure 5.10c shows the regions in the parameter space corresponding to synchronous and asynchronous events for  $\omega_0 = 0.5$ .

By applying this criterion to the events detected in the left and right generators, we can classify them into synchronous and asynchronous. Figure 5.10b (right) illustrates synchronous events by colored curves and asynchronous (i.e., appearing on one or another side) by gray areas. We observe that there are synchronous and asynchronous events of different amplitudes and durations.

#### 5.5.2 Analysis of Bilateral CA3-CA1 Pathways

To test the bilateral complementariness, we detected and classified into synchronous and asynchronous  $\mu$ fEPSP events in the time courses of the left and right Schaffer generators over a recording of 160 s long. Setting  $\omega_0 = 0.67$ , we found 47% of synchronous and 53% of asynchronous events. This percentage was the same for the right and left hippocampal lobes.

We found a notable bilateral asymmetry. In particular, waves on the right side were significantly larger in amplitude  $A_R = 0.210 \pm 0.003$  mV (mean  $\pm$  confidence interval) vs  $A_L = 0.133 \pm 0.002$  mV. Figure 5.11a (left plot) shows the mean amplitudes for synchronous and asynchronous events on the left and right sides. In general, asynchronous events are smaller on both sides, but the right lobe exhibits significantly stronger events. Even asynchronous events on the right side are larger than synchronous ones in the left lobe. The difference between synchronous and asynchronous events can be explained by summation of ipsilateral and contralateral inputs during synchronized spiking of clusters in bilateral CA3 regions.

The duration of gamma waves was relatively stable and did not change much between left-asynchronous (La), left-synchronous (Ls), and right-synchronous (Rs) events (Fig. 5.11a, middle plot). The only significant difference was observed for right-asynchronous events, which were shorter on average. We then also cross-checked the crosscorrelation between the starting times of events of different types (Fig. 5.11a, right plot). In general, synchronous events are highly correlated with their twins on the contralateral side, as expected. Then, there was a silence in asynchronous events on both sides (blue and red curves) in the interval [-20, 20] ms. It is also expectable since, in the interval [0, 20] ms, we have synchronous events excited on both sides, which last about 27 ms. Silence in [-20, 0] interval is less obvious. It indicates a relatively strong periodicity (due to gamma rhythm) of synchronous and asynchronous events excited on both sides. Secondary peaks at  $\pm 23$  ms support this conclusion. We found no other peaks at larger time lags, which indicates the absence of coupling at time scales larger than gamma rhythm. This result is compatible with the experimental recording of spontaneous irregular activity under anesthesia.



**Fig. 5.11** Quantification of main characteristics of bilateral  $\mu$ fEPSP events. **a** *Left:*. Mean amplitudes of events. L<sub>s</sub>, L<sub>a</sub>, R<sub>s</sub>, and R<sub>a</sub> stand for left-synchronous, left-asynchronous, right-synchronous, and right-asynchronous. *Middle:* Mean durations of events of different types. *Right:* Cross-correlations between starting times of synchronous events on the right side and asynchronous events on the right side (blue), asynchronous events on the left (red), and synchronous events on the left side (yellow). **b** Covariance analysis of increments in left events respective to right events of starting times  $\Delta T$ , amplitudes  $\Delta A$ , and durations  $\Delta D$ . The value of *r* shows the crosscorrelation coefficient

We now quantify the synchronous events. In this case, one  $\mu$ fEPSP event appears on one side, and with a small enough time lag (the limit is defined by  $\omega_0$ ), there arises another event on the contralateral side. Although either side may lead, waves in the right side appear earlier in 57% of the pairs vs 43% of the left leading waves. Overall, the time lag between right and left waves was  $0.43 \pm 0.07$  ms. We also observed that left waves were longer by 0.61 ms but smaller by 0.076 mV on average (Fig. 5.11a). We then studied possible covariances between these parameters.

Figure 5.11b shows plots of the increments of amplitudes ( $\Delta A = A_L - A_R$ ), durations ( $\Delta D = d_L - d_R$ ), and starting times ( $\Delta T = t_L - t_R$ ) of left events in respect to right ones. We observe no correlation between pairs ( $\Delta T$ ,  $\Delta A$ ) and ( $\Delta D$ ,  $\Delta A$ ). The corresponding correlation coefficients were r = -0.03 and r = -0.004, respectively. However, there is a strong negative correlation between the time lag and the increment of the duration of left event events (r = -0.45). Fitting a linear model by the principal component analysis (it takes into account errors in both axes; Fig. 5.11b, middle plot, red line) yields:

$$\Delta D - \mu_D = K(\Delta T - \mu_T), \qquad (5.53)$$

 Table 5.2 Effect of compensation of initial asynchrony of synchronous  $\mu$ fEPSP events in the left and right CA1

Case	Initial Asynchrony, $\Delta T$ , (ms)	Final Asynchrony, $\Delta E$ , (ms)
Left lead	-2.91	0.06
Right lead	2.96	1.89



Fig. 5.12 Schematic representation of bilateral information processing in CA3-CA1 pathways

where  $\mu_D = 0.61$  ms,  $\mu_T = 0.43$  ms, and K = -2.06.

Equation (5.53) suggests that synchronous events can tune their durations in such a way that if the right side leads (i.e.,  $\Delta T > 0$ ), then the difference in the event durations becomes negative (i.e.,  $\Delta D < 0$ ). Thus, for a given pair of events, we can have  $\Delta T + \Delta D \approx 0$ . In other words, the events compensate the initial asynchrony ( $\Delta T$ ) and synchronize their ends ( $E_L - E_R = \Delta T + \Delta D$ ). The same effect occurs for left side-leading events. If  $\Delta T < 0$ , then  $\Delta D > 0$ . The data analysis confirms the hypothesis (Table 5.2). For the left side-leading events, the asynchrony practically vanishes, while for the right-leading ones, it is reduced significantly.

Figure 5.12 schematically summarizes our results. First, we note that under irregular activity, the probability of generating asynchronous (one side) events is about the same as the probability of synchronous (two sides) events. On average, the amplitude of the asynchronous left and right events is significantly smaller than that of synchronous  $\mu$ fEPSPs. Such a difference can be explained by either the cumulative contribution of ipsi and contra-lateral inputs for paired events or by stronger recruitment of ipsilateral CA3 cells into a cluster provoking  $\mu$ fEPSP under synchronous activity. A direct contralateral driving of gamma waves in the CA1 via commissural fibers is less likely. The commissural pathway contributes little to field potentials due to anatomical and geometrical factors [41]. Curiously, the duration of asynchronous and left asynchronous events.

Second, synchronous events exhibit variable time lag between left and right lobes. Moreover, the right side leads more often (57% vs 43%), and  $\mu$ fEPSP events have significantly higher amplitude on the right side.

Since the fate of Schaffer waves is to excite CA1 units where they integrate with input from the contralateral side, it is crucial to optimize the temporal overlap of the respective excitatory envelopes. Therefore, the short mean lag between paired bilateral waves indicates that the system is so finely adjusted.

A significant finding is that both CA3 are required for short-term memory. Yet, inactivation of the left CA3 impairs performance in an associative spatial long-term memory task and plasticity [46]. Along with the present observations of independent gamma strings upon the VHC blockade [53], it becomes clear that the left and right sides do not convey equivalent information. Whether lateralization is devoted to different sensory modalities, features of a scene, or perceived/recalled nature remains unknown.

## 5.6 Conclusions

This chapter has introduced two methods for quantifying gamma waves in the activity of micro-field potentials excited by CA3 pyramidal cells in the CA1 region of the hippocampus. To isolate the contribution of the CA3 neurons to the common LFPs recorded in CA1, we have used the independent component analysis, previously adapted to the use with LFPs [11] and further theoretically tested [16, 54] and experimentally validated [12, 55, 56].

The ICA approach represents each pathway's activity as a product of the spatial part (weights on individual electrodes) and time activation. The time activation of the isolated Schaffer generator (ipsilateral CA3-CA1 pathway) exhibits an ordered succession of micro field excitatory postsynaptic potentials,  $\mu$ fEPSPs, at gamma frequency rate (40–50 Hz). Each  $\mu$ fEPSP appears to be generated by a functional cluster of CA3 pyramidal neurons, to which individual cells are recruited variably. Thus, we assumed that the observed gamma pattern in CA1 is composed of individual  $\mu$ fEPSPs created by spike packets coming to CA1 neurons from the CA3 region.

To investigate such packets, we have developed two wavelet-based methods. The first method processes gamma waves by the Haar continuous wavelet transform, and the output is further rectified. The obtained wavelet measure represents a two-dimensional surface in the coordinates: time localization-scales. We have described how local maximums of this surface can be used to detect individual  $\mu$ fEPSP events and quantify their time instants, durations, and amplitudes.

Then, we observed that the proposed method tends to underestimate the durations and amplitudes of  $\mu$ fEPSP events, while the starting times appear to have a positive time lag. To overcome this problem, we have introduced the second method. It uses as an initial approximation the results provided by the first method. Then, the parameters of the  $\mu$ fEPSP events are optimized by maximizing a likelihood function. The optimization process employs the expectation-maximization approach. In simulations, we have shown that this method approximates the parameters of the  $\mu$ fEPSP events significantly better than the first method, although it requires additional computational resources. Both methods have been used for the analysis of real electrophysiological data.

We have shown that  $\mu$ fEPSP events can reveal causal relations between spikes of individual CA3 and CA1 pyramidal cells. It is improbable that a single CA3 spike depolarizes a target cell in CA1 beyond threshold since CA3 cells form a few contacts on each of the CA1 neurons [57, 58]. Our results support the hypothesis that a functional cluster of synchronously firing CA3 neurons generates an elementary  $\mu$ fEPSP, in agreement with previous findings [15, 59]. For example, only a fraction of spikes of a single CA3 pyramidal cell is related to  $\mu$ fEPSPs. Therefore, if the firing of a CA3 cell is not in synchrony with the other cells in the ensemble, no  $\mu$ fEPSP will be generated. Overall, functional clusters of CA3 neurons are synchronized in a chain of one-at-a-time activations under supra-cluster oscillatory gamma dynamics.

Earlier studies of spike trains showed no significant correlation between CA3 and CA1 pyramidal cells [60, 61]. Such observations favor a stochastic model of spike initiation whereby the synaptic noise details define the output code. However, the availability of the mediating  $\mu$ fEPSPs allowed us to narrow the output of individual CA1 pyramids to spikes specifically driven by the Schaffer input. The entire synaptic chain (triple correlations) thus revealed cell-to-cell specific impact to be explored in nonstimulated conditions. We have shown that CA3 pyramidal neurons contribute to monosynaptic  $\mu$ fEPSPs in CA1, and about 10% of spikes in CA1 are fired in response to input from CA3.

We then investigated the bilateral integration of gamma-parsed information in the two lobes of the hippocampus. Electrophysiological recordings were simultaneously obtained from the left and right sides. We processed raw LFPs by the ICA approach and identified  $\mu$ fEPSPs on both sides by the likelihood enhanced wavelet (LeW) method. We have shown that gamma waves are generally larger and lead from the right hemisphere. Synchronous (two sides) events drive CA1 pyramidal units more strongly than asynchronous unilateral waves.

In general, synchronous bilateral events exhibit a variable delay between the initiation of  $\mu$ fEPSPs on the left and right sides. We then observed the effect of compensation of the initial asynchrony. The event durations are "tuned" in such a way that if one side leads, then the duration of the event on this side is larger than that of the contralateral event. Thus, both events tend to finish synchronously. Summarizing, our findings support the hypothesis that inter-hippocampal connections integrate different aspects of information that flow through the left and right lobes.

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# Chapter 6 Wavelet Approach to the Study of Rhythmic Neuronal Activity



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**Abstract** This chapter considers the main definitions and principles of electroencephalography (EEG) that are needed to get a good grasp of next chapters. We describe the general physical and mathematical approaches to time–frequency analysis of rhythmic EEG activity using the continuous wavelet transform. Besides that, we review some recent achievements of wavelet-based studies of electrical brain activity, including (i) time–frequency analysis of EEG structure, (ii) automatic detection of oscillatory patterns in pre-recorded EEG, (iii) classification of oscillatory patterns, (iv) real-time detection of oscillatory patterns in EEG, (v) detection of synchronous states of electrical brain activity, (vi) artifact suppression/rejection in multichannel EEG, (vii) the study of cognitive processes.

## 6.1 Introduction

Let us take the next step in the application of wavelet analysis to neurophysiology and consider practical aspects of this mathematical tool for retrieving information about rhythmic brain activity. From a physical viewpoint, the brain is an extremely complex object, consisting of a huge number of elements (neurons) with their own oscillatory dynamics, organized in networks with complex topologies [1–8]. The traditional and highly effective method for studying electrical brain activity is based on registration of electroencephalograms (EEG), which sum the average electrical fields of synaptically interconnected neuronal ensembles located in the vicinity of the recording electrode. In humans, EEG is usually recorded by small metal disks (electrodes or sensors), placed on the scalp. In rats, EEG is usually recorded by intracranial electrodes implanted at the cortical surface or in deep subcortical structures, and this approach can procure more detailed information about electrical activity in relatively small groups of neurons.

Chapters 7–9 will discuss different aspects of time–frequency characteristics of EEG and the main results from continuous wavelet analysis of EEG as regards automatic processing of EEG recordings, i.e., the development of new techniques to remove the need for routine visual inspection of EEG and diminish subjective factors. Nowadays, advanced practical methods for automatic processing of multi-

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channel EEG data are given a high priority in modern neuroscience. For example, wavelet-based EEG analysis can be used to identify functional relationships between various brain areas, to explore underlying mechanisms of different types of rhythmic brain activity, and to better understand the fundamental principles of brain function. Moreover, EEG comprises a wide variety of rhythms and periodic oscillations, whose frequencies are important characteristics of the functional activity of neuronal structures [3, 9–11]. The frequency content of the EEG recorded in the local brain area depends on the functional activity of this area and its interactions with other areas. New mathematical approaches have important theoretical significance for the study of rhythmic brain activity, underlying, for example, integrative (cognitive) functions of the brain. In addition to that, these new approaches can be widely applied in practical work, for example, in developing effective diagnostic tools and monitoring systems in clinics, in specific brain–computer interfaces, etc. [12–18].

This chapter provides a brief introduction to wavelet analysis of EEG. It starts with the basic definitions and principles of electroencephalography in order to give the reader a better understanding of subsequent chapters. In general, this chapter describes the physical and mathematical bases of the wavelet transform used to investigate rhythmic brain activity.

### 6.2 Basic Principles of Electroencephalography

EEG is an acronym for electroencephalogram (*electro* = electrical signals, *encephalo* = the brain, graph = a recording).

**Electroencephalogram**. Record of electrical activity of the brain taken by means of electrodes placed on the surface of the head, unless otherwise specified [19].

**Electroencephalogram**. Electrical potentials recorded from the brain, directly or through overlying tissues [20].

Electroneurophysiology has a history of more than a hundred years [21]. In 1875, a Liverpool physician and medical school lecturer Richard Caton first demonstrated that electrical signals could be measured directly from the surface of the animal brain. The father of clinical electroencephalography, the German psychiatrist Hans Berger, recorded electrical activity from human brain and introduced the term 'electroencephalogram'. The first published EEG data from humans appeared in 1929, when Hans Berger published a paper in which he presented 73 recordings [22].

Between Caton and Berger, Adolph Beck in 1890 found that sensory stimuli (flashes or sounds) induced slow changes in electrical brain activity (slow wave response, evoked potentials). Fleischl von Marxow (1890) made a similar observation. A Russian scientist, Vasili Yakovlevich Danilevsky, in his doctoral thesis (1877), described electrical brain activity in dogs. Another Russian physiologist, Nikolai Evgenjevich Wedensky, recorded electrical activity from peripheral nerves and the central nervous system using a telephone (the results were published in his

master's thesis in 1884). In 1913, Vladimir V. Pravdich-Neminsky published photographic recordings of electrical brain activity in dogs and introduced the term *electrocerebrogram*.

From that time, electroencephalographic investigations have led to major advances in studying sleep and epilepsy. Electroencephalography is the most popular method for the analysis of spontaneous brain oscillations and evoked (event-related) potentials, and changes in electrical brain activity during anesthesia and sleep, during sensory perception, and during voluntary activity, etc. Nowadays, EEG investigation has become a necessary part of clinical practice for the diagnosis and prognosis of various neural disorders, especially in epileptic patients.

Several spontaneous rhythms are encountered in EEGs of animals and humans during different behavioral states, whereas peculiar (paroxysmal) patterns appear in EEG during epileptic seizures. Mechanisms that underlie spontaneous rhythmic activity in the brain were studied by V. V. Danilevski (1875) and A. Beck (1890), who described EEG desynchronization in animals, by I. M. Sechenov, who found spontaneous rhythms in medulla oblongata in the frog, and by H. Berger, who described alpha and beta rhythms in human EEGs.

#### 6.2.1 Electrical Biopotential: From Neuron to Brain

According to the traditional viewpoint, brain functions are associated with continuous processes of integration and disintegration of functional associations within neuronal circuits. These neural associations are temporary and they represent synchronized network activity of neuronal assemblies located in different parts of the brain. Although neural associations are functional, they have an anatomical substrate, viz., synaptic contacts between neurons. Neural connections can be readily reorganized, so different neural circuits can be linked together into a single unit, a so-called functional system. A functional system is a neuronal entity that accomplishes specific functions [23] and disintegrates when the result has been successfully achieved. One of the signs of neuronal integration is synchronization of local electrical field potentials. Synchronized neuronal activity can be recorded locally in the brain, for instance, at the surface of the cerebral cortex, by means of an invasive intracranial electrocorticogram, or on the scalp by non-invasive extracranial EEG [9]. An EEG contains a variety of rhythms and periodic oscillations whose frequencies provide important information about functional activity of the neural system. The state when different brain areas sustain oscillations with the same frequency is called the neuronal synchronization state. It accounts for the processes of neuronal association and information exchange between these brain areas [24, 25]. Synchronization of rhythmic activity in multi-channel EEG can manifest the binding processes (active associations) between neurons and neuronal ensembles [26].

Synchronization between some cortical areas characterizes normal cognitive brain functions. Pathological processes in the central nervous system can selectively increase the level of synchronization between interconnected brain structures. Abnormally high synchronization can underlie seizure activity that can be recorded in EEG as hypersynchronized rhythms. In particular, absence epilepsy, which is analyzed by means of wavelets in Chap. 7, results from hypersynchronization of the thalamo-cortical network. Up to now, thalamo-cortical interactions have not been fully explored because they require invasive implantation of electrodes in the thalamus (intracranial EEG). This operation could not be performed on patients with absence epilepsy for ethical reasons (the patients do not have clinical indications for this operation).

During the last decade, non-invasive neuro-imaging and neuro-mapping techniques, such as magnetic resonance imaging (MRI), positron emission tomography, and photoemission computer tomography have been widely used in patients with absence epilepsy. These modern methods have several disadvantages, the main one being that the time resolution is too low and there is no reliable procedure for processing the resulting data. An additional problem with neuro-imaging data comes from the fact that reconstruction of neuronal activity is based on indirect measurements, such as changes in the hemodynamic response, tissue metabolism, blood flow, and blood oxygen saturation, etc. These processes are influenced by many factors, besides neuronal processes. The absence of effective tools for analysis of neuro-imaging data and the high probability of errors in reconstruction of neuronal activity often lead to false conclusions. Thus, two different approaches to analysis of MRI signals during absence epilepsy may lead to different results [27].

In this situation, EEG is preferable in humans as a reliable, cheap, and easily available technique, and application of EEG in animals can be extended by implanting intracranial electrodes in deep structures. Chapter 7 presents the results of time–frequency wavelet analysis (continuous wavelet transform) of electrical activity in the cortex and thalamus during absence epilepsy in animals with a genetic predisposition to this disease.

## 6.2.2 Application of EEG in Epilepsy Research

Since this monograph focuses on features of the wavelet-based analysis of brain dynamics in animals and patients with epilepsy, we briefly discuss the practical application of EEG in epileptology. Fifteen years before H. Berger published his landmark report (1929), in which he described spontaneous electrical activity in the human brain, N. Cybulski and S. Jelenska-Macieszyna (1914) at the University of Krakow in Poland published the first photographs of paroxysmal activity during experimental focal seizures in dogs (cited in [21]). In 1931, H. Berger demonstrated the first recordings of spike-and-wave activity obtained in epileptic patients (Fig. 6.1). Two years later, in 1933, he published an EEG recording during a brief episode of "simple automatic activity with no other movement" (cited in [21]). Note that it was H. Berger who first suggested applying EEG in clinical practice (cited in [28]).



Fig. 6.1 EEG record made by H. Berger in an 18-year-old girl during a seizure. High voltage spike-and-wave complexes appear with a frequency of about 3 per second. From [21]

In 1935, Frederick Gibbs, Hallowell Davis, and William G. Lennox at Boston City Hospital demonstrated spike-and-wave complexes in EEG that manifested clinical absence seizures [29]. Since that time, clinical application of EEG has increased rapidly and the EEG recording technique has been profoundly improved. Over the years, EEG has helped in making short- and long-term prognoses of various neurological and psychiatric disorders. EEG investigation is necessary for the diagnosis of epilepsy (especially in patients with atypical epileptic syndromes), and it also offers important prognostic information.

In clinical practice, EEG is recorded with open and closed eyes using special techniques to provoke epileptic activity (such as photo-stimulation, hyperventilation). Comparative analysis of EEG shape during the states with open and closed eyes provides the most important information. Some paroxysmal activity appears only when the eyes are open, and some under closed eye conditions or immediately at the moment of opening/closing the eyes (alpha rhythm can mask the abnormal activity that can be seen in EEG, when the eyes are open and the alpha rhythm is suppressed). Only in about 50% of adult patients with epilepsy can photo-stimulation and hyperventilation provoke epileptic activity in EEG during the waking state. This percentage can be increased up to 92% if 4 consecutive EEG sessions are used. EEG monitoring during sleep increases the chances of identifying epilepsy in patients (from 50% up to about 80%).

The area of clinical application of EEG is rather broad. Changes in EEG structure can be used to evaluate the effectiveness of drug medication. Changes in EEG may also carry prognostic information and can be for short- or long-term prediction of neurological diseases.

Routine non-invasive EEG studies provide an opportunity to localize sources of epileptic activity and to determine which areas of the brain could benefit from surgical correction. In complicated cases, localization of pathological brain areas requires intracranial recordings with deep electrodes placed under the dura mater. Electrical activity recorded intracranially from the surface of the cortex is called an electrocorticogram (ECoG), or alternatively, a subdural EEG (sdEEG), or an intracranial EEG (icEEG). An advantage of ECoG over EEG is its high spatial resolution (ECoG reflects the local electrical field potential). Furthermore, high-frequency components are present in ECoG, but they are reduced in EEG, since the electrical current passes

through high-resistance structures, such as meninges, bone, soft tissue, and the scalp. Despite the harmful effect of the invasive procedure, ECoG still remains a standard for the localization of epileptic focus, and it is often used before surgical treatment of epilepsy, when pharmacological treatment appears ineffective. We hope that, in the future, invasive methods will be excluded from clinical practice, to be replaced by new effective noninvasive brain imaging techniques. These new noninvasive methods should provide a high quality of data (spatial resolution and information content), whilst remaining as simple and cheap as possible, and should be easily combined with subsequent data processing techniques.

## 6.3 General Principles of Time–Frequency Analysis of EEG

## 6.3.1 The Need for Mathematical Analysis of EEG

Since the days of Hans Berger, the method for recording the EEG has improved substantially. Progress in this area was achieved by development of engineering and computer technologies. The ink recorder was replaced by the digital recording system, which was able to record multi-channel EEG with high temporal resolution. In fact, the availability of analog EEG data made it necessary to find a new approach to the analysis of digital recordings, where the EEG signal is represented as a sequence of discrete values of the electric potential measured in the millisecond range. [In this book, we usually operate with the sample rate 1024 Hz, i.e., a discretization step of 1/(1024 Hz), or approximately 1 msec.] Digital recording systems with high-capacity and digital memory meant that one could operate with large volumes of information and perform the subsequent analysis of the EEG. Nowadays, it is necessary to find better ways to store, share, and analyze EEG data.

New computer technologies promote an interdisciplinary approach to the investigation of brain functions under normal conditions and in pathological cases. EEG studies are still attractive for experts in experimental and theoretical neurobiology, psychophysiology, cognitive neuroscience, biophysics, physics, nonlinear dynamics, etc. There is an interdisciplinary field of knowledge called neuroinformatics and computational neuroscience that combines mathematical methods of neural network modeling, time–frequency and structural analysis of neuronal signals, the theory of dynamic chaos, and nonlinear dynamics. The interdisciplinary approach to EEG analysis led to the development of unique methods which helped to unravel certain mechanisms of perception and sensorimotor integration (see, e.g., [30–32]), and to understand some fundamental aspects of sleep, epilepsy (e.g., [7, 33]) and cognitive functions [34]. It is profitable to apply powerful tools of physics and mathematics to EEG analysis. However, interpreting the results of mathematical analysis in the context of neurobiology is often a complex and ambiguous matter. Any result derived from the mathematical analysis of EEG, which may look obvious to the mathematician, can appear meaningless to the physiologist. Difficulties in interpreting the results of mathematical analysis may be caused by a considerable gap in understanding between the biological and mathematical sciences. We believe that new knowledge resulting from cooperation between these disciplines will help to solve many mysteries about brain functions. But success in this venture is only possible through close cooperation (despite all the difficulties) between theory and practice, i.e., between experts in the exact sciences (applied mathematics, physics, nonlinear dynamics, etc.) and practitioners in neurophysiology. Without a deep understanding of the physiological basis of the problem, it would be impossible to develop adequate mathematical tools for further processing and analysis of the relevant experimental EEG records, at least such as would be easily acceptable to physiologists [35].

An interdisciplinary approach is beneficial for any research, but in neurophysiology it is particularly important, because the subject of study—the brain—is an extremely complex one. A better understanding of brain functions requires the cooperation of biologists, physicists, chemists, mathematicians, information specialists, and even the humanities—philosophers, linguists, and so on. One thing is certain: the key to the success of such an interdisciplinary trend in modern neuroscience is the clarity and meaningfulness of the statements of physiological problems.

## 6.3.2 Time–Frequency Analysis of EEG: From Fourier Transform to Wavelets

The main difficulty with the practical application of physical and mathematical approaches in neuroscience is the strict compliance with the conditions under which the mathematical operations can be considered to be correct and justified with regard to the answers they provide to the relevant questions.

In terms of physics and mathematics, an EEG record is a time series which appears as a sequence of amplitude values for a certain quantity (in the case of EEG, it is a measure of electrical potential), measured at discrete points of time. This representation allows one to take advantage of the considerable theoretical basis of time series analysis developed in mathematics, physics, and nonlinear dynamics, as well as the powerful mathematical tools of statistical analysis.

Among the methods widely used for EEG analysis, we should note the methods of time domain measurements. This concerns primarily auto- and cross-correlation analysis, which should be considered as statistical methods. In the frequency domain (Fourier space), attention should be paid to spectral or Fourier analysis and wavelet analysis (applicable in both the time and frequency domains). The latter approach is of particular interest in the this book. It is relatively new and has been successfully applied in neurodynamics and neurophysiology.

In contrast, the spectral (frequency) analysis of EEG recordings is still widely used in clinical practice, as well as in neuroscience. The fast Fourier transform (FFT) or its modifications are typically used for neurophysiological signals [36–38]. EEG spectral analysis results are usually presented in the form of a power spectrum, in which the frequency content of EEG is depicted as the power value of each frequency component.

The Fourier transform can only be applied to stationary signals, which are infinite in time. The term "stationary" means that the spectral composition and statistical characteristics of the signal do not change over time. However, EEG is essentially a non-stationary signal, whose characteristics change over time.<sup>1</sup> In particular, certain rhythms constantly appear and disappear in EEG. Each of them is characterized by its own frequency in Fourier space and by a typical form in the time domain.

In order to illustrate all the characteristic mentioned above, Fig. 6.2 gives an example of an electrical activity record from the frontal cortex of a WAG/Rij rat with a genetic predisposition to absence epilepsy.<sup>2</sup> Large variations can observed in both the amplitude and the frequency parameters of EEG, even in this short fragment. Firstly, one can select the segments of background activity, so-called desynchronized EEG (area F in Fig. 6.2). Secondly, in this EEG segment, the periods that differ from the background EEG by the amplitude, shape, and characteristic frequency can be easily distinguished. Hereinafter we will refer to such EEG fragments as oscillatory patterns. The oscillatory patterns can be classified by shape and by frequency composition. These two classifications are traditionally used by neurophysiologists for analysis and "decoding" of EEG [37, 42]. Taken together, they represent an accurate formal tool for analysis and classification of EEG rhythms. In the signal shown in Fig. 6.2, several oscillatory EEG events are highlighted, such as sleep spindles, short episodes of 5–9 Hz oscillatory activity, K-complexes (delta waves followed by a sleep spindle), and spike-wave discharges (SS, TR, K, SWD, respectively).

Thus, different rhythmic and oscillatory patterns can be distinguished in EEG. In other words, EEG is characterized by a complex time–frequency structure [1]. Traditional electroencephalography subdivides the frequency content of EGG in several bands from about 0.5 to 200–500 Hz (Fig. 6.3a). The presence of EEG oscillations with certain frequencies (frequency bands) is associated with certain states of vigilance (specific brain activity), so the frequency characteristics of EEG correspond roughly to specific brain functions [43–45]. EEG oscillations with different frequencies can co-exist in one structure or present the same time in different brain structures [44, 46, 47].

<sup>&</sup>lt;sup>1</sup>Although the non-stationarity of EEG signals causes difficulties for spectral analysis, Fourier transform algorithms have been successfully adapted to EEG analysis (see, e.g., the technical manual [39]).

 $<sup>^{2}</sup>$ WAG/Rij rats are a special inbred line with a genetic predisposition to absence epilepsy [40, 41]. This animal model of epilepsy will be discussed in Sect. 6.3.3, and also in the following chapters of the book.



**Fig. 6.2** A typical fragment of EEG recorded in the frontal cortex in a WAG/Rij rat, illustrating the non-stationarity of the signal. Selected areas are: spike-wave discharge SWD, sleep spindle SS, short episode of 5–9 Hz activity (in the theta range) TR, K-complex denoted by K, and background activity denoted by F

The spectral power density P of an EEG signal is inversely proportional to the frequency f (see Fig. 6.3b). The observed 1/f law of the spectral power suggests that the system exhibits self-organized critical dynamics [1, 48, 49], where disturbances at low frequencies result in sequential transmission of oscillation energy at high frequencies [50, 51]. So high-frequency EEG events superimpose on low-frequency oscillations in EEG [44, 46, 52].

These properties of oscillations are determined by the physical architecture of the neuronal network, as well as by the limited propagation speed of electrical signals between neurons due to synaptic delay [53]. Since the majority of neuronal connections are local (small in size [54]), the period of oscillation depends on the size of neuronal ensembles involved in the oscillatory activity. High-frequency oscillations in EEG (which often manifest cognitive processes [55]) are underlain by synchronous activity in relatively small neural networks that occupy a limited region of space,



**Fig. 6.3 a** EEG frequency bands distinguished by traditional electroencephalography. **b** Power spectrum of an EEG recorded from the human right frontal lobe during sleep. Figures are based on the data from [1]

while relatively widespread neural networks are involved in low-frequency oscillatory activity [44, 56]. Considering spatial and temporal scales of neuronal network activity, the relationship between network anatomy and frequency of oscillations (which reflects brain activity) should be taken into account.

It is obvious that analysis of complex non-stationary signals, such as electroencephalograms, requires specific methods with good resolution in both the frequency and time domains. Before the introduction and development of wavelet analysis, the only method to study the time–frequency structure of non-stationary signals was the short-time Fourier transform (2.4) considered in Sect. 2.1. In practice, two types of short-time Fourier transform procedure were used to analyze neurophysiological signals.

The first approach was based on the decomposition of the non-stationary EEG signal into fragments of length 2T, where signal parameters did not change with time, i.e., the EEG fragments were treated as stationary. These EEG fragments overlapped in order to minimize the undesirable effect of boundary artifacts. This procedure could provide the power spectrum at any given time. The second method was based on multiplying the EEG signal by a given window function, e.g., Gauss function, Hamming window, Hann window, etc., which takes a nonzero value for some short period of time. In fact, the Fourier transform (2.3) was performed in a short time interval corresponding to the width of the selected window function. Then the window function was shifted along the time axis, and the next interval of EEG provided the major contribution to the resulting spectrum. The fixed time window is the main disadvantage of the short-time Fourier transform (as already discussed in Chap. 2). Furthermore, the window size could not be adapted to the local properties of the signal.

The mathematical apparatus of the wavelet transform provides a better alternative to the Fourier transform which is free from the above-mentioned shortcomings. From the various physical applications of wavelets, it is well known (see, e.g., [57–63]) that wavelet analysis is well suited for studying non-stationary signals. It is characterized by the following important features:

- It decomposes the signals in the time and frequency domains, which allows us to localize the particularities of a signal in both domains.
- It is suitable for short intervals. One can effectively analyze a short time series containing a small number of characteristic periods of oscillatory activity.
- It is flexible. One can choose the wavelet basis that best takes into account the peculiarities of the analyzed data.
- It is less sensitive to noise. Wavelets are highly effective for analyzing "noisy" data, i.e., signals in which important information is superposed with additive noise.

These advantages make wavelet analysis attractive for studying EEG signals, which are characterized by non-stationarity, the simultaneous presence of oscillatory activity with different shapes and frequencies (which requires an adaptive approach to examining the EEG structure), a high level of noise, and a relatively short length (either due to the limited time of registration or short duration of fast processes in the brain) [64–67].

The significant advantage of wavelets is that the analysis is not limited to the selected time scale of the observation. Indeed, since the frequency of a signal is inversely proportional to its period, the information about high-frequency components could be obtained from the relatively small time intervals, whereas information about low-frequency components could be obtained from the longer periods of time.

## 6.3.3 Time–Frequency Analysis of Spike-Wave Discharges by Means of Different Mother Wavelets

Here we discuss the application of wavelet analysis to the description of the structure of the spike-wave discharges in EEG. As pointed out above, in the structure of the EEG, one can distinguish different forms of rhythmic activity and oscillatory patterns which reflect the nature of the neural activity and hence the functional state of the brain. Importantly, many pathological processes in the brain may also be manifested in EEG. For example, during epilepsy, which is characterized by the hypersynchronous activity of brain neurons [40, 68], there are high-amplitude EEG discharges of characteristic shape [69, 70].

There are many types of epileptic disorder (more than 30), and each of them corresponds to a specific epileptic EEG pattern. At the same time, there are difficulties in the diagnosis of certain types of epilepsy, and as a consequence, these diseases remain unnoticed. According to World Health Organization data, about 1% of the world's population suffers from epilepsy and more than 30% of patients do not receive health care [70, 71]. In this section we focus on absence epilepsy (petit mal or childhood absence epilepsy), which is a common neurological disease, the main clinical manifestation of which is a brief loss of consciousness with the absence of the convulsive component (the automatisms of the mimic muscles may be observed) [69, 71]. The attack of absence epilepsy (lower level of consciousness) can last from a few seconds to tens of seconds. Epileptic seizure is accompanied by high-amplitude spike-wave discharges in EEG [70, 71]. Spike-wave discharges (SWD) consist of a relatively high-frequency component (the spike) with peak amplitude significantly exceeding the background activity and the low-frequency "wave" [72].

There are several rat lines with a genetic predisposition to absence epilepsy [40], such as the WAG/Rij rats used in our study. Electroencephalographical and clinical signs of absence epilepsy can be observed in 90% of WAG/Rij rats [40], and epileptic activity is known to increase progressively with age. Despite some differences in the manifestation of absence epilepsy in WAG/Rij rats and human patients (such as different age-related dynamics and the main frequency of SWD), the WAG/Rij rat model is recognized as reliable, since the clinical manifestations and response to drugs in WAG/Rij rats is similar to that in patients with absence epilepsy [40].

Figure 6.4 shows typical EEG fragments with spontaneous SWD, as recorded in a symptomatic WAG/Rij rat (Fig. 6.4a) and for a human patient suffering from absence epilepsy (Fig. 6.4b). In the WAG/Rij rat (1 year old), EEG was recorded intracranially



Fig. 6.4 EEG fragments with typical spike-wave discharges as recorded in a WAG/Rij rat (a) and in a human patient with absence epilepsy (b)

by means of an electrode implanted at the surface of the frontal cortex. In the male patient (23 years old), EEG was recorded extracranially with skin electrodes attached to the frontal cortex (F4 electrode in the right hemisphere in the system 10–20 [73]). Enlarged fragments at the bottom of each EEG illustrate the detailed structure of spike-wave discharges with the typical fast (spike) and slow (wave) components. In the human EEG, the spikes are not pronounced, mainly because the signal was recorded at the surface of the skull, and hence relatively far from the source of electrical brain activity.

In the rest of this section, we consider in depth the wavelet analysis of spike-wave discharges in humans and the WAG/Rij rat by means of different types of mother wavelets (see Sect. 2.2.2). We start by considering the use of the *complex* Morlet wavelet for the continuous wavelet analysis of the SWD. Equation (6.1) gives the formula for the complex mother wavelet:

$$\psi_0(\eta) = \pi^{-1/4} \mathrm{e}^{\mathrm{i}\omega_0 \eta} \mathrm{e}^{-\eta^2/2} , \qquad (6.1)$$

where the second term in the brackets of (2.33) is neglected and  $\omega_0 = 2\pi$ .

Figures 6.5a and 6.6a show the wavelet spectra of a spike-wave discharge as computed with the aid of the Morlet wavelet in the WAG/Rij rat and in a human patient with absence epilepsy, respectively. In the wavelet spectrum of the rat SWD, the complex frequency dynamics during an epileptic event is clearly visible. In order to identify the frequency dynamics of the SWD, Fig. 6.7a displays the skeleton of the wavelet surface shown in Fig. 6.5a. Typically, the frequency of spontaneous SWD is approximately 12–15 Hz at the beginning, but it decreases rapidly to  $\sim$ 10 Hz during the first 300 ms and becomes stable at  $\sim$ 10 Hz with fluctuations of 1–3 Hz, while the period of fluctuations lasts approximately 0.7 s. In general, there is a steady trend towards a decrease in frequency to 7–8 Hz at the end of the SWD [74, 75].

Analysis of the skeletons of the wavelet surface reveals that there are three first harmonics of the SWD fundamental frequency (shown in Fig. 6.7a) located in the range of 7–15 Hz, and that they tend to decrease in time. This kind of spectrum with higher harmonics is typical for signals with complex shape and sharp peak components (compare with Fig. 2.18, which shows a model pulse signal whose spectrum contains higher harmonics, and see also the discussion in Sect. 2.2.4). It should be noted that the frequency composition of a spike-wave discharge changes very quickly (during one or two oscillation periods). As a consequence, the methods given in [75] could not be used effectively to detect the time–frequency structure of SWDs.

The wavelet spectrum of the SWD in a patient with absence epilepsy is similar to what was found in a rat (see Fig. 6.6). The wavelet spectra of SWDs in humans and in animals differ quantitatively, since the frequency of the human SWD lies in the range 3–4 Hz, which is lower than the frequency in a rat. However, the tendency for a rapid decrease of the main frequency from the beginning to the end of the SWD, and further stabilization of the frequency in the middle of the discharge, is observed in both rats and humans. This can be seen clearly in the skeleton of wavelet spectrum (see Fig. 6.7b). Note also that, in humans, the wavelet spectrum and its skeleton display less pronounced higher harmonics of the main frequency in comparison with the rat. Therefore, in the skeleton of the wavelet spectrum in humans, only the dynamics of the second harmonic can be traced (Fig. 6.7b). This can be accounted for by a *smoother* form of SWD in humans, i.e., low spike amplitudes, which contribute mainly to the dynamics of high frequencies in EEG (the appearance of higher harmonics) during SWD.

It should be noted that the complex Morlet wavelet provides the optimal relationship between resolution in the frequency and time domains, and can be successfully used to analyze the fine time–frequency structure and dynamics of the fundamental frequency of complex non-stationary neurophysiological signals. For example, wavelet analysis has been successfully used to identify and describe the dynamics of the intrinsic SWD frequency. The dynamics of EEG frequencies described in this way reflects the functional activity of widespread neuronal networks during the process of initiation and termination of the SWD, which is important for understanding epileptogenesis mechanisms.

We turn now to the analysis of spike-wave discharges by means of *real mother* wavelets. Figures 6.5 and 6.6 illustrate the modulus  $|W(f_s, t)|$  of wavelet spectrum





**Fig. 6.6** Wavelet spectra of a typical spike-wave discharge in a person with absence epilepsy, as computed with the aid of different mother wavelets: complex Morlet wavelet with  $\omega_0 = 2\pi$  (**a**), real MHAT wavelet (**b**), WAVE wavelet (**c**), and modified Morlet wavelet (**d**)







coefficients obtained with the help of the standard real mother MHAT (2.40) and WAVE (2.39) wavelets. The figures show the EEG with SWD in a WAG/Rij rat (Fig. 6.5b and c) and in a human (Fig. 6.6b and c). In order to convert the wavelet frequencies  $f_s$  into the frequencies f of the Fourier transform, we determine the relationship between f and  $f_s$  in the way discussed in Sect. 2.2.3 (see the ratio  $f/f_s$  in Table 2.1).

Indeed, the wavelet spectra obtained by means of the MHAT or WAVE wavelets are characterized by the low-frequency resolution and, as a consequence, the higher harmonics and their frequency dynamics are not clearly distinguished from the background dynamics of the main frequency. At the same time, the characteristic features of these real wavelets lead to sharp peaks in the wavelet spectrum, so any EEG event with a sharp waveform produces intense amplitude bursts in the frequency range of interest in the wavelet spectrum. The disadvantage of real wavelets is the complexity involved in determining the main frequencies in the wavelet spectrum, because the maxima and minima of the wavelet surface correspond to an increase/decrease in the EEG amplitude. Obviously, this form of wavelet spectrum of the SWD does not properly display the particularities of the signal, nor the dynamics of its frequency and amplitude. An advantage of the WAVE and MHAT wavelets is good time resolution, which allows one to track the rapid increase in amplitude of the wavelet spectrum and the moment when the examined rhythm appears in the EEG. However, due to the poor frequency resolution, sharp changes in amplitude of the wavelet spectra could be missed, and that complicates the analysis of the time–frequency structure of the signal. The above remarks concerning real wavelets are valid for the analysis of both animal and human epileptic EEG.

As an example application of real wavelets in EEG analysis, we mention the paper [76], which proposed a real wavelet mother function constructed on the basis of the Morlet wavelet, especially for the analysis of spike-wave discharges in WAG/Rij rats. This modified Morlet wavelet zeroizes the amplitude of the wavelet transform coefficients corresponding to the fundamental EEG frequency in the time and frequency domains.

The modified real Morlet wavelet used in [74, 76] has the form

$$\psi_0(\eta) = \eta \cos(\Omega \eta) \mathrm{e}^{-\eta^2/2} , \qquad (6.2)$$

where the parameter  $\Omega = 5$ . It can be shown [77] that the particularity of this mother wavelet is that the frequencies  $f_{s \max}$  corresponding to the maximum of the wavelet surface |W| built with the classic wavelet basis satisfy the condition  $|W(f_{s \max}, t)| = 0$  when the modified basis (6.2) is used. So in this case the dynamics of the fundamental frequencies in the EEG is not determined by the presence of local maxima as we saw earlier (Chap. 2), but by the zero values of the wavelet surface (see Figs. 6.5d and 6.6d). The modified real Morlet wavelet (6.2) was used to analyze the dynamics of frequency characteristics of typical SWD in patients with child absence epilepsy, juvenile absence, or juvenile myoclonic epilepsy, as well as to study the effect of various pharmacological substances on the time–frequency structure of epileptic discharges.

Comparative analysis of results obtained with the modified real Morlet wavelet (6.2) and standard complex Morlet wavelet (6.1) did not reveal any advantages with the modified wavelet basis. Moreover, application of the real Morlet wavelet in the continuous wavelet transform may just obscure features in the wavelet spectrum, especially when the amplitude of the fundamental frequency was close to its maximum or did not reach the maximum. In this case, the wavelet coefficients were close to zero, which was not convenient for digital signal processing and introduced undesirable difficulties in the automatic processing of the wavelet spectra. Modification of the mother wavelet function is potentially beneficial for signal analysis, because it helps to adjust the method to solve specific problems and expands the area of

practical application of the wavelet transform. However, considering the ambiguities associated with real wavelet basis functions, we will modify the complex (not real) wavelet basis function in this book, and demonstrate some profitable features of the modified Morlet wavelet constructed on the basis of the standard complex mother Morlet wavelet function (6.1), which provides good resolution in both the time and frequency domains.

The effects of pharmacological treatment on the structure of spike-wave discharges in WAG/Rij rats, as observed by means of wavelet analysis with a modified real Morlet wavelet, are presented in [77, 78]. This study led to the following conclusions, which could be taken into account in clinical practice (antiepileptic drug treatment).

*Haloperidol* (an antipsychotic drug) in small doses reinforces absence epilepsy and causes numerous short spike-wave discharges in EEG. Rats under low doses of Haloperidol had an SWD of mean duration of 5 s, characterized by a rapid change



**Fig. 6.8** Short-lasting SWD in WAG/Rij rat under the influence of ketamine (from [78]). The SWD has a specific waveform in EEG (*top*) with two parts, namely a "head" with frequency 6–7 Hz and "tail" with a frequency of about 9 Hz. The corresponding wavelet surface obtained with the modified Morlet wavelet (*bottom*) shows the time–frequency profile of this phenomena

in intrinsic frequency from 15 Hz at the beginning to 5 Hz at the end of the SWD. In high doses, Haloperidol induces long-lasting spike-wave discharges with relatively low frequency, which varied between 6 and 9 Hz with two types of modulation with periods 0.5-0.6 s and 3-6 s.

*Vigabatrin* (drug of choice for antiepileptic medication, anticonvulsant) in small doses greatly increases the duration of SWDs (up to 20–45 s). Under vigabatrin treatment, the SWD started with short bursts of oscillatory activity with frequency 17–20 Hz, and then the frequency decreased to 5 Hz, and gradually reached a plateau of 8–9 Hz. The main frequency of spike-wave discharges fluctuated between 4.5–5 Hz and 8–9 Hz, and the major changes in frequency occurred approximately every 2 s.

*Ketamine* (a drug with an anesthetic and analgesic action) caused a biphasic effect on spike-wave discharges. In the first phase, the number of discharges was reduced, and during the second phase, short and long spike-wave discharges were usually observed. The short-lasting discharges had a head-tail waveform (see Fig. 6.8). The "head" consisted of high-amplitude spike-wave complexes with frequency 6-7 Hz and a duration of 1-1.5 s, whereas the "tail" was formed by low-amplitude oscillations with a frequency about 9 Hz and duration 1-3 s.

In general, antiepileptic drug therapy altered the frequency characteristics of SWDs, which are associated with changes in the neuronal network mechanisms of absence epilepsy. These changes underlie the basic mechanisms of absence epilepsy and, in particular, mechanisms involved in suppression of seizure activity.

#### 6.4 Applications of Wavelets in Electroencephalography

An EEG contains many different rhythmic components whose frequencies provide important information about functional activity in different brain structures. As already discussed, wavelet analysis is well suited to study complex processes with time-varying characteristics, and it is widely used for time–frequency analysis of EEG data (non-stationary signals that include a variety of oscillatory patterns with significantly different waveforms and frequencies). Furthermore, the presence of a high level of noise and the short duration of EEG recordings cause additional difficulties in EEG analysis [20, 63–65, 67].

Careful attention should be paid to the specific forms of rhythmic activity associated with specific brain and behavioral functions (episodes of epileptic activity, sleep, etc.). It is known that rhythmic components in EEG reflect the synchronous dynamics of a huge number of neurons integrated into ensembles [33, 72, 79], and studies of rhythmic brain activity using wavelets are closely related to an important task of nonlinear dynamics, viz., the study of synchronous behavior in networks with complex topology [4–6, 80].

Sections 6.4.1-6.4.7 overview the most important and actively developed applications of wavelets in studies of electrical brain activity and in diagnostics based on EEG. In the heading of each part, we indicate the first and most important works

from our point of view, but the bibliography given here is obviously incomplete due to the large number of publications.

## 6.4.1 Time–Frequency Analysis of EEG Structure

One of the most obvious applications of wavelets in neurophysiology and electroencephalography is identification of certain EEG patterns and analysis of the time-frequency structure of EEG signals. This application takes into account the basic properties of wavelets and the main areas of their use. The first wavelet-based studies in neurobiology aimed to analyze characteristic time-frequency features of various patterns in EEG [38, 81, 83]. Subsequently, specific methods were developed to estimate different statistical characteristics of non-stationary signals such as timevarying wavelet coherence, wavelet entropy, etc. [103-108]. Wavelet-based studies were directed towards determining particular interactions between the cardiovascular system and the CNS using experimental data (ECoG and EEG) [109–111]. One of the most effective applications of wavelets could be found in papers [76, 77, 85, 87, 98] with close attention to pathological electrical brain activity characterized by short duration and complex frequency content (see Sect. 6.3.3), such as spontaneous epileptic spike-wave discharges in EEG. Wavelet analysis has also been used to identify the influences of medication on the time-frequency structure of SWDs [78] and to describe the structure of characteristic "precursors" of epileptic activity [95]. Wavelet-based methods were also used to study other forms of oscillatory activity (oscillatory patterns) in EEG, in particular, sleep spindles and 5-9Hz oscillations [101].

# 6.4.2 Automatic Detection of Oscillatory Patterns and Different Rhythms in Pre-recorded EEG

Simple methods of automatic pattern recognition in EEG (e.g., the threshold method, method of templates, simple neural networks, etc.) often failed to be successful because of high noise levels, nonstationarity of EEG signals, and/or the highly variable time–frequency structure of oscillatory EEG events [119].

The following properties of wavelet analysis benefit its application in the automatic processing of EEG data:

- 1. A representation of the time-frequency structure of signals that enables one to localize signal features simultaneously in the time and frequency domains.
- Effective analysis of short time series containing small numbers of characteristic oscillations, as required for automatic diagnostics of short-lasting events in EEG.

- Flexibility in the choice of basis function for signal decomposition, a prerequisite for successfully adjusting the mathematical apparatus of wavelet analysis to the signal properties.
- 4. Highly effective analysis of noisy data, i.e., processes comprising a sum of useful signals and additive noise.

Currently, there is a quite general approach to automatic processing of pre-recorded EEG data using estimates of wavelet energy in characteristic frequency bands (with standard mother wavelets and adaptive wavelet bases) [101, 114]. This method has been successfully used to analyze the structure of sleep spindles in EEG, i.e., short episodes of rhythmic activity in the EEG.

Automatic data processing methods facilitated further progress in the study of the time-dependent dynamics of various rhythmic components in EEG. For instance, it was shown that epileptic brain activity in WAG/Rij rats is an intermittent process corresponding to on-off intermittency [114]. A similar intermittent dynamics was also found in sleep spindles [101]. This type of dynamical behavior was observed in coupled chaotic oscillators and in networks of nonlinear units at the boundary of the synchronization region [120–125]. On-off intermittent behavior in neuronal networks and applications of combination of wavelet and extreme events theory can provide a deeper understanding of the dynamics of epileptic activity and, in particular, the underlying mechanisms of epilepogenesis [126–128].

#### 6.4.3 Classification of Oscillatory Patterns

The development of standardized databases of characteristic electroencephalograph patterns is an important fundamental and applied problem [135–137]. A relatively new approach to classification and standardization of oscillatory EEG patterns, similar to the *template matching technique*, constructs complex adaptive wavelet bases from original EEG segments [75]. This procedure was effective for identification and classification of spindle-like oscillatory events in EEG. In particular, this method was used to describe "spike-wave spindles" that occurred during desynchronization of EEG and were considered as an immature form of epileptic spike-wave discharges that combined some properties of sleep spindles and SWD [75]. More details will be given in Sect. 7.4.3.

#### 6.4.4 Real-Time Detection of Oscillatory Patterns in EEG

Online identification of characteristic oscillatory patterns in EEG is one of the most interesting and intensively studied problems. Further progress in this area is impor-

tant for monitoring human brain activity, and also for the development of special brain-computer interfaces. One difficulty in identification of EEG patterns relates to the problem of selectivity (different EEG patterns have similar spectra). It is difficult to develop a universal method for online diagnostics of oscillatory patterns in EEG due to the nonstationarity of experimental data. Application of wavelets for online diagnostics in EEG may help to overcome this problem of nonstationarity, and we shall discuss examples of how a wavelet-based method provides a way to monitor seizure activity in the brain [141]. Let us note that current methods for extracting characteristic EEG patterns using wavelets are increasingly used in developing prototypes of brain-computer interfaces [134, 140, 143]. An advantage and at the same time a disadvantage of these approaches is the use of the discrete wavelet transform. Although it provides quick signal processing, allowing online analysis of a large amount of experimental data, it is less appropriate for flexible recognition of different patterns in EEG. Approaches like those described in [141] which use the continuous wavelet transform can improve the quality of recognition. Section 7.6 describes an algorithm for automatic online detection of spike-wave discharges.

# 6.4.5 Multichannel EEG Analysis of Synchronization of Brain Activity

It is known that different areas of the cerebral cortex often exhibit synchronous activity in both normal states (e.g., during cognitive activity) and pathological states (Parkinson's disease, epilepsy, paranoid schizophrenia, etc.). As shown in Sect. 2.2.5, the corresponding synchronous dynamics can be analyzed using continuous wavelet analysis with complex mother functions in an approach known as the *time-scale synchronization* [152, 153]. This has been used to study synchronization phenomena in different kinds of system [154–159].

Application of the continuous wavelet transform for analysis of multichannel EEG revealed periods of synchronization in short and noisy data. Besides, synchronization of time scales is quite stable to errors when estimating the characteristic frequencies of analyzed processes and this is important for automatic processing of experimental neurophysiological data during cognitive and motor processing in the brain (see Chaps. 8 and 9 for detail).

## 6.4.6 Artifact Suppression in Multichannel EEG Using Wavelets and Independent Component Analysis

Analysis of EEG essentially becomes complicated due to the presence of different artifacts, in particular high-amplitude EEG components associated with eye move-

ments, blinking, muscle activity, etc. Currently, wavelets have become a popular technique for artifact suppression [63, 166, 167]. For example, a new approach known as wavelet-enhanced independent component analysis (wICA) [164] has been applied to suppress artifacts caused by blinking eyes and heart beats. It is important to note that wICA resulted in a tenfold reduction of movement artifacts in EEG without significant influence on neuronal signals. This advantage can be used to develop algorithms for automatic artifact rejection in EEG.

## 6.4.7 Study of Cognitive Processes

In addition to analysis of pathological dynamics in EEG, the wavelet transform is widely used in studies of cognitive processes. Thus, interactions between different areas of the cerebral cortex were investigated during cognitive tasks in [168]. This study aimed to assess the strength of intracortical interactions using the degree of synchronization of electrical EEG activity expressed in different brain areas. It used a wavelet-based correlation method to measure the degree of synchronization during short time intervals (comparable with the duration of mental operations, i.e., up to 100 ms).

The discrete wavelet transform with Daubechies functions was used in [170] to study spectral powers in the alpha and beta frequency bands in different brain areas of healthy subjects who were solving simple arithmetic tasks. The continuous wavelet transform of EEG data has been intensively used to study rapid cognitive processes underlying the process of human face recognition. Short fragments of EEG (800 ms) were analyzed in [171] after emotionally valenced stimuli (expression of angry and neutral faces). Analysis was performed using the Morlet function with estimation of wavelet coefficients in the frequency range  $\Delta f = 1-30$  Hz, reflecting the amplitude dynamics of cortical potentials in the corresponding frequency range  $\Delta f$ . Statistical analysis of rhythmic components in the evoked EEG activity was carried out in the alpha and theta frequency bands. It was shown that individual differences in the perception of facial expressions correlated with wavelet coefficients in the above-mentioned frequency ranges. Thus, changes in the alpha and theta bands were important at the stage of stimulus perception. Emotional reaction is associated with theta activity. Based on wavelet analysis, Yakovenko et al. [171] suggested that emotional expressions are accompanied by different cortico-subcortical interactions among different humans and at different stages of the experiment.

Finally, cognitive processes of human brain activity, accompanied by changes in the waveform of evoked potentials in the EEG, were analyzed in [151] using wavelets. Let us consider this work in more detail. The *evoked potential* represents a structured fluctuation of electrical brain activity in response to external stimulus [172]. Eight components of the evoked potential are traditionally introduced, taking into account their polarity (*P* positive, *N* negative) and the latency, i.e., the time delay from the onset of the stimulus. It is important to note that the evoked potential of a certain modality (visual, auditory, somatosensory) is recorded at the corresponding



**Fig. 6.9** Waveform of acoustically evoked potential and ranges of the "cognitive" components *N*1, *N*2, and *P*300. From [151]

projection area of the neocortex. Potentials at other brain regions are secondary (associative) and may differ in waveform, latent period, and amplitude. For example, the spatial organization of an acoustically evoked potential reflects the following stages of cognitive processes:

- non-arbitrary perception—component N1,
- transition from non-arbitrary to arbitrary perception—component N2,
- information processing and decision regarding significance—component P300.

The purpose of the paper [151] was to develop an effective method for evaluating phase synchronization to analyze acoustically evoked potentials in healthy human subjects. It was shown that, in situations that do not require concentration (e.g., listening to sounds), spatial organization of the components of acoustically evoked potentials had a diffuse character. Phase synchronization indexes fluctuated over the range 0.5–0.8 and took similar values in all components N1, N2, and P300 (see Fig. 6.9, reproduced from [151], which shows a typical waveform of the acoustically evoked potential and variation of the "cognitive" components N1, N2 and P300). Higher phase synchronization indexes in the studied components were found in the frontal or temporal areas of the right hemisphere. Concentration (elicited by auditory stimuli) increased this index up to 0.9 in components N1 and P300 (see Fig. 6.10). The highest degree of synchronization was observed between associative areas of the cortex (frontal, central, and parietal), between the hemispheres (often diagonally), with a shift in the direction of the left hemisphere.

The described changes in the phase synchronization reflect the process of selective involvement of the above-mentioned areas of neocortex in cognitive (acoustic) tasks. Romanov et al. [151] used the good temporal resolution of the wavelet transform in order to extract information about quick changes in the shape of the electric potential



**Fig. 6.10** Changes of phase synchronization (**a**) and wavelet power (**b**) while listening to sounds (1) and while counting auditory stimuli (2) in the same subject. From [151]

(evoked potential) during mental activity. Wavelet analysis is thus in demand in psychophysiology, where it is often necessary to analyze short fragments of EEG and rapid processes of human brain activity.

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# **Chapter 7 Wavelet-Based Diagnostics of Paroxysmal Activity in EEG and Brain-Computer Interfaces for Epilepsy Control**



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**Abstract** This chapter considers basic problems of automatic diagnostics and processing of epileptic EEG. We discuss the wavelet-based techniques in order to fully automatize "routine" operations, such as visual inspection of EEG. In addition to that, we exemplify some practical applications of wavelet methods for automatic analysis of pre-recorded signals of neuronal activity (off-line diagnostics), and also some examples of wavelet-based EEG analysis in real-time (on-line). We also discuss principles of fast and precise detection of transient events in EEG and organization of close-loop control systems that can be used in brain-computer interface.

#### 7.1 Introduction

The electroencephalographic signal (EEG) reflects synchronous synaptic activity generated by brain areas located close to the recording electrode (sensor). Information obtained from EEG signals is widely used in cognitive and clinical studies and other technologies such as automatic systems for detecting abnormal EEG patterns (i.e., epileptic spikes or sharp waves) [1], interactive systems based on brain-computer interfaces [2], etc. Considering that EEG recording technique is non-invasive, lowcost and readily available in clinical and research centers, it has a large number of medical and technological applications. Therefore, development of advanced methods and expert systems for the analysis of EEG signals is an important trend in basic neuroscience and in clinical practice. In this chapter we consider the continuous wavelet transform as an appropriate method for time-frequency analysis of EEG signal. It is advantageous that the CWT does not require stationarity, and therefore it is an ideal tool for accurate analysis of short-lasting non-stationary events in EEG of animals and humans, especially in subjects with epilepsy. Epilepsy is a chronic disease that usually develops slowly in parallel with gradual changes in EEG-from normal to epileptiform activity. At the preclinical stage, subjects often show transitory pro-epileptic EEG activity that includes some epileptiform components, but could not be considered as a fully blown seizure. This has been very well demonstrated in developmental studies of absence epilepsy in aging rats [3, 4]. Development of absence epilepsy in rat models is known to be associated with partial substitution of

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normal sleep spindle oscillations by epileptic spikewave discharges [4, 120, 122]. We demonstrate that this process results to the occurrence of pro-epileptic activity in EEG characterized by spindle-like waveform and spikewave elements (Sect. 6.3.3).

In this chapter we also discuss several automatic and semi-automatic methods for wavelet-based processing of EEG signals. In the past few decades, the waveletbased approach has proven to be efficient tool for EEG data analysis. This is partly explained by a certain degree of linearity in EEG signals that can be considered as a linear mixture of coexisting oscillatory components generated by different sources. Therefore, nonlinear effects can be neglected in the first approximation, thus allowing linear models of EEG. This in turn facilitates decomposition of EEG by linear methods (such as wavelet transform or independent component analysis) into spectral and/or temporal components with the anticipated properties. For example, in Sect. 7.3, we use a wavelet decomposition of EEG to identify specific patterns of absence epilepsy in the gamma frequency band. It appears that this band, which is not the most powerful in the spectrum of spikewave discharges, is in fact the most representative due to the maximum differences in this range with other EEG patterns.

Advanced automatic methods could significantly improve systems monitoring brain activity. In Sect. 7.4, we consider automatic detection and discrimination of sleep spindles and 5–9 Hz oscillations by means of standard Morlet-based and adaptive wavelet analysis. Then we demonstrate the application of the methods to long-term EEGs. Such methods significantly reduce the time of EEG analysis and errors when dealing with large amounts of data. The identification of spikewave discharges and sleep spindles in long recordings offers the possibility of studying their temporal dynamics.

When speaking about automatic or semi-automatic methods, one must distinguish *off-line* and *on-line* processing of EEG. For off-line processing of previously recorded EEG, we have an access to the full data set. Thus, for a given time point  $t = t_0$ , we know not only the "past" ( $t < t_0$ ), but also the "future" ( $t > t_0$ ) data samples. This allows one to compute the wavelet transform normally. In the case of on-line or real time processing, we have two additional difficulties. First, the "future" data samples are not available, which forces special adaptation of the wavelet transform. Second, real time calculations impose strong limitations on algorithm complexity. It must be fast enough to carry out the necessary calculations within the time window between two consecutive data samples.

The use of on-line algorithms is a must in the study of BCIs [43, 49, 70, 75, 76]. In particular, the spectral characteristics of the activity of the sensorimotor cortex are related to movements of the limbs [47, 99]. This finding underlies apparatus improving the life quality of paralyzed patients and can be used for selection of letters or phrases on a screen [20, 44, 94]. Methods capable of diagnosing pathological brain activity in real-time are equally important [93]. In particular, on-line detection of spike-wave discharges could be used to trigger the presentation of external stimuli to study information processing during periods of reduced consciousness [30], or to trigger automatic electrical brain stimulation upon appearance of spikewave discharges [10]. In Sect. 7.6, we provide an algorithm for real-time diagnostics of epileptic seizures and discuss its experimental implementation.

In Sect. 7.7, we consider a real-time absence seizure prediction algorithm, evaluated and implemented in an on-line, closed loop stimulation system aimed to prevent the for absence epilepsy typical SWDs in a genetic absence rat model. The proposed wavelet-based algorithm correctly predicted 88% of SWD while the remaining ones were quickly detected, but with a high number of false positives mainly during light sleep. Implementation of the wavelet-based method into a closed loop brain stimulation system resulted in a 72% decrease of seizure activity. In contrast to long standing beliefs, these results demonstrate that absence seizures can be predicted and that the development of closed loop seizure prediction and prevention systems is an interesting and feasible future direction to strive for seizure freedom.

# 7.2 Mother Wavelet Function in the Continuous Wavelet Transform

The continuous wavelet transform has several advantages over traditional FFT for representing non-periodic and non-stationary signals that have sharp peaks or other kinds of fast events. One limitation of FFT is that it characterizes the EEG signal only in the frequency and not in the time domain, i.e., information regarding the dynamic changes of spectral components. In wavelet space, the EEG signal power is simultaneously represented as a function of time *t* and frequency  $f_s$ . In the case of a real mother wavelet function, the wavelet coefficients *W* represent the degree of correlation of a prototype wavelet function  $\psi_0$  with the EEG signal on the given time scale *s* (wavelet frequency  $f_s = 1/s$ ). The wavelet transform with complex mother wavelet can be regarded as a bandpass filter whose transfer characteristic is determined by the mother wavelet, and which also carries information about phase relationships.

The wavelet prototypes (mother wavelets) are wave-like scalable functions which are well localized in both the time and frequency domains [55]. Some mother wavelets provide better resolution in the time domain, and others in the frequency domain. The choice of mother wavelet is of great importance and it is crucial for accurate representation of the EEG signal in the wavelet space  $(t_0, f_s)$ . Important characteristics that were taken into account before making a choice of mother wavelet were complex/real, width, and shape of the candidate wavelets  $\psi_0$ .

First, complex or real mother wavelet function. A real wavelet  $\psi_0 = \text{Re } \psi_0$  returns information about the amplitudes of the EEG signal and it may be sufficient for isolating EEG spikes or other discontinuities (for example, various artifacts and interferences during EEG registration), but not sufficient for detecting sustained oscillatory processes. A complex wavelet returns information about both amplitudes and phases (see Sect. 2.2.5) and this is more suitable for time-frequency analysis and for representing oscillatory EEG phenomena in wavelet space [55, 62].

Second, the shape of mother wavelet function. Accurate results from the wavelet decomposition are dependent on the shape of the chosen wavelet function, which

should be similar to the shape of the analyzed EEG signal [69]. Rectangular functions such as the Haar (2.42) or FHAT (2.41) wavelets are better for representing EEG spikes (and other sharp events in the EEG), while the real Mexican hat (MHAT) wavelet (2.40), which has a smoother shape than the non-smooth Haar and FHAT wavelets, is particularly suitable for detecting epileptic spikes and spike-wave discharges in EEG [5, 69]. Meanwhile, oscillatory EEG patterns can be more accurately represented with complex wavelet functions which are based on smooth harmonic functions, and the Morlet wavelet (2.36) in particular is better suited for the detection of delta, theta, and alpha events, as well sleep spindles, because it mimics the characteristic spindle waveform [14, 69, 124]. Although the Morlet wavelet has no sharp elements equivalent to spikes in SWDs and its shape does not mimic SWDs, it provides the best time–frequency representation and resolution of spike–wave discharges (as well as other oscillatory EEG patterns) in comparison to other mother wavelets (including the sharp-looking Mexican hat wavelet) [35, 124].

Third, width of mother wavelet function. If a candidate wavelet in Fourier space is too narrow, the frequency resolution will be poor, and if it is wide, the time localization will be less precise. It is also important to take into account the reverse relationship between time and frequency resolution. The higher the frequency resolution, the lower the time resolution and vice versa. The time-frequency resolution can be defined by the shape and width of the mother wavelet function in the frequency domain. In the case of the complex Morlet wavelet, properties of the time-frequency resolution of the wavelet transform can be controlled by changing the main frequency  $\omega_0$ , which affects the width and position of the Fourier image of the Morlet wavelet in Fourier space (see (2.36) and (6.1), Fig. 2.11, and Table 2.1). Actually, in the complex Morlet wavelet family the parameter provided by the central frequency  $\omega_0$  determines the shape and the width of the wavelet function in the frequency domain. When  $\omega_0 < \pi$ , the temporal resolution is high, but little information is available about the frequency content of EEG events (the frequency resolution is low). When  $\omega_0 > 4\pi$ , the frequency resolution is high, but the time resolution is low. As the Morlet wavelet central frequency  $\omega_0$  increases, the properties of the wavelet transform approach the characteristics of the window Fourier transform. We chose the complex Morlet wavelet with  $\omega_0 = 2\pi$  as the most appropriate basis, providing optimal time-frequency resolution for the majority of observed EEG phenomena. This basis function was particularly good in localizing the abrupt onset of SWD, as well as gradual amplitude changes during the seizure train. A further advantage in choosing this parameter value  $\omega_0 = 2\pi$  is that the frequency  $f_s$  of the wavelet transform is equal to the frequency f of the Fourier transform, viz.,  $f_s = f$ , which facilitates the explication and comparison of results.

# 7.3 Detection of Spike-Wave Discharges (Absence Epilepsy) in WAG/Rij Rats

Around 20 percent of all epileptic seizures have a genetic background and classified as genetic generalized epilepsies (formerly known as idiopathic generalized epilepsies [114], including childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone (reviewed by Ratcliffe et al. [107]). An important hallmark of this type of epilepsy on the electroencephalogram (EEG) is bilateral synchronous, symmetrical and generalized 3 Hz spike-wave discharges. Typical absence epilepsy or spike-wave epilepsy is associated with brief and sudden lapses of consciousness that may be misinterpreted as daydreaming or inattention (i.e., the state of "absence") [11, 114, 116].

Rodents are widely used as models of human diseases. Apart from thousands of genetically engineered strains, rat strains with natural genetic predisposition to certain diseases. In particular, the inbreed Wistar-Albino-Glaxo from Rijswijk (WAG/Rij) rat strain is genetically prone to develop absence epilepsy and it has been validated as a reliable animal model of absence epilepsy [21, 23, 110].

EEG manifestation of absence epilepsy in WAG/Rij rats were described as "spikewave complexes" [138]: "a discharge of this type lasts at least 1 s and is characterized by a train of sharp spikes and slow waves. The spikes are directed upwards with an amplitude (mean  $300 \mu$ V; range  $100-450 \mu$ V) of at least twice the background EEG activity. The spike-wave complexes are asymmetric, the repetition of spikes within a burst varies from 7.5 to 9.5 Hz with a mean frequency of 8.7 Hz. The mean duration of the complexes is about 5s (range 1–30s) whereas the mean number of discharges per hour is 18 (range 4–33)" (p. 395). Nowadays the term "spikewave complexes" with reference to rat's EEG was replaced by the term "spike-wave discharges" (SWD). SWD in WAG/Rij rats occurred during passive wakefulness, drowsiness and light slow wave sleep [22]. During EEG seizures rats stay immobile and sometimes demonstrating vibrissal twitching, myoclonic jerks of the eyelids and facial muscles [23, 89, 138]. The electroencephalographic profile of SWD in WAG/Rij rats is similar to that in human patients with absence epilepsy [126].

Spike-wave discharges (SWD) represent a complex of two components—the spike and the wave (see Sect. 6.3.3 and Fig. 6.4). At first glance, the problem of automatic detection of spikewave discharges may seem trivial. Indeed, one solution arises directly from the definition of SWD since their amplitude significantly exceeded the amplitude of background EEG. Thus one could monitor the oscillation amplitude and simply detect events when it overcomes certain threshold. However, this straightforward approach has poor performance due to three reasons. First, besides SWD, the EEG contains other patterns with high amplitude, such as sleep spindles and 5–9 Hz oscillations [124] (see Fig. 6.2). Second, the amplitude of the background EEG considerably changes during different vigilance states (e.g., during sleep or wakefulness, and low-amplitude brain electrical activity appeared to only in wake state—desynchronized EEG), therefore, it is difficult to define the threshold value in background EEG. Third, some SWD-like pattern contain spike-wave elements, but does not match the definition of SWD, and should be excluded [125]. These difficulties could be solved by means of computational techniques.

A great variety of different methods for recognition of spikewave discharges that has been described in the literature can be divided in three classes. The first class uses the nonlinear dynamics approach and quantifies different features of EEG signals, such as Lyapunov exponents [6] or entropy [57]. The second class uses artificial neural networks and learning algorithms for data classification [48]. The third class of methods attempts to formalize the definition of the SWD and compares statistical features of different typical epochs in the EEG [38, 87]. These methods have the following drawbacks:

- They are not applicable for real-time signal processing, e.g., methods based on the calculation of Lyapunov exponents or entropy.
- They provide low accuracy of detections, e.g., methods estimating statistical properties of different epochs.
- Their performance is unstable, and they require adjustment of parameters for each individual EEG, e.g., methods based on artificial neural networks.

Applications of the discrete wavelet transform (DWT) to detection of epileptic events in EEG [133] has serious limitations in comparison to the continuous wavelet transform (CWT). Below we introduce the principles of CWT-based method for the automatic detection of SWD applied for off-line and on-line recordings.

Let us consider an off-line method for automatic detection of epileptic spikewave discharges in a previously recorded EEG [50, 124]. A practical implementation of this method has been used to detect SWDs in long-term EEG recordings in WAG/Rij rats with a predisposition to absence epilepsy. We used a single-channel EEG recorded from the frontal cortex (the detailed experimental procedure can be found in [124]).

In WAG/Rij rats, the duration of SWD ranges from 1 to 30 s, and their average number in adult animals vary from 0 to more than 30 seizures per hour. Based on the analysis of a large number of SWD, we defined some particular features in their time frequency structure, namely, a sharp increase in the spectral power in the gamma frequency range (20–50 Hz). Importantly, such an increase did not appear during high-amplitude regular normal EEG patterns, like sleep spindles. Therefore, a sharp increase in the gamma spectrum can be considered as a marker for SWD.

CWT is an optimal tool to define an increase in gamma power. It allows to estimate the instantaneous energy of the wavelet spectrum in gamma frequency band and to compare it with a threshold. SWD is detected when the energy exceeds a certain threshold value [42, 50, 64]. Figure 7.1 shows a typical energy distribution of wavelet spectrum E(f) (see Eq. (2.33)) of SWD, sleep spindle, and background EEG. The fundamental frequency of the SWD is about 8 Hz, which corresponds to the major peak in the wavelet spectrum. However, at low frequencies (f < 15 Hz), this peak overlaps with the spectral peak of spindle waves, whence SWD and spindle events may be confused. Nevertheless, SWD epochs show high power at higher frequencies  $f > 15 \div 20$  Hz, i.e., in the gamma frequency band, due to the presence of the second and third harmonics of the fundamental SWD frequency (see Figs. 6.7 and 7.1, harmonics of SWD fundamental frequency are marked by arrows). Thus each



individual peak, a part of the spike-and-wave complex, is displayed in the wavelet spectrum as a local burst in the wavelet power (see, for example, Fig. 6.5 for epileptic rats and Fig. 6.6 for human patients).

Let  $F_{SWD} = 30 \div 50 \text{ Hz}$  be the characteristic frequency range of apparent structural differences between spikewave discharges and other oscillatory patterns. Since we expect an increase in the energy in this frequency range during SWD, it is convenient to consider the following integral energy:

$$w_{F_{\rm SWD}}(t) = \int_{F_{\rm SWD}} |W(t, f)|^2 \,\mathrm{d}f \;. \tag{7.1}$$

If a spike-wave discharge occurs at a certain time *t*, then the following relation holds:

$$w_{F_{\rm SWD}}(t) \ge E_k , \qquad (7.2)$$

where  $E_k$  is the experimentally determined threshold energy.

For automated delimitation of epileptic events, we used the method of threshold sorting. Time instants at which the value of  $w_{F_s}$  (7.2) exceeded the threshold  $E_k$  and did not decrease within the following 1 s were regarded as onsets of epileptic activity. Time instants when the energy level dropped below the threshold were considered as the ends of SWDs.

Figure 7.2a shows an EEG epoch with five spike-wave discharges (grey rectangles) corresponding to epilepsy paroxysms. Figure 7.2b and c illustrate the modulus |W(f, t)| of the wavelet spectrum obtained with the Morlet wavelet with central frequency  $\omega_0 = 2\pi$  and the corresponding integral energy  $w_{F_{SWD}}(t)$ . Identification of SWDs is carried out using the criterion (7.2). The threshold level  $E_k = 0.5$  is indicated by the dashed line in Fig. 7.2c. Thus in the integral wavelet spectrum, SWDs (highlighted in grey) are easily recognized by simple thresholding.



**Fig. 7.2** Typical results from automatic recognition of SWDs using a wavelet-based method with a Morlet wavelet with central frequency  $\omega_0 = 2\pi$ . **a** EEG fragment with spike-wave discharges marked by *grey rectangles*. **b** Modulus |W(f, t)| of the wavelet spectrum corresponding to this EEG. The *dome-shaped curve* in the wavelet spectrum outlines a confidence (upper) area in which boundary effects are significant (see Sect. 2.2.3.3). **c** Time-dependence of the instantaneous energy w(t) (7.1) averaged over the characteristic frequency range  $F_{SWD} = 30-50$ Hz. SWDs were recognized automatically using the value of the wavelet energy w(t) when  $w(t) > E_k$ , where  $E_k$  is the threshold level (*dashed line*)

The performance of the above-described method has been evaluated by measuring the percentage of true positive/negative and false positive/negative detections. We also computed the sensitivity and specificity of the method. True positives (TP) are defined as the number of correctly detected SWD. True negatives (TN) are the number of correctly rejected SWD-like events. Then false positives (FP) and false negatives (FN) represent the numbers of events wrongly identified as SWD and SWD missed by the method, respectively. Primarily the accuracy of the automatic recognition of absence epileptic oscillatory patterns was computed as

$$\rho_{\rm SWD} = \frac{\rm TP}{N_{\rm expert}} \times 100\% , \qquad (7.3)$$

Rat #	Visual detections N <sub>expert</sub>	Automatic detections			Performance of automatic detections		
		TP	FP	FN	Accuracy ρ <sub>SWD</sub> (%)	Sensitivity β (%)	Specificity δ (%)
1	105	105	0	0	100.0	100.0	100.0
2	81	79	2	1	97.5	98.8	97.5
3	249	247	1	2	99.2	99.2	99.6
4	120	117	1	3	97.5	97.5	99.2
5	66	65	2	1	98.5	98.5	97.0
Mean $\pm$ SD					$98.5 \pm 1.1$	$98.8 \pm 0.9$	$98.7 \pm 1.3$

**Table 7.1** Results of automatic identification of SWD using the CWT with the complex Morlet wavelet ( $\omega_0 = 2\pi$  rad/s)

where  $N_{\text{expert}}$  is the number of SWD events selected by an operator, expert in SWD neurophysiology. Table 7.1 summarizes the main results for the automatic identification of spike-wave discharges.

Almost all SWD in all animals were selected with  $F_{SWD} = 30 \div 50 \text{ Hz}$  and  $E_k = 0.5$ . The obtained accuracy was 97.5  $\div$  100% (mean 98.5%, n = 5 rats). The percentage of the incorrect detections or false positives did not exceed 1.8%. Therefore, SWD events can be faithfully distinguished from the non-epileptic background EEG using the described method. Noteworthy is that SWD in all animals were automatically recognized with the same parameters (FSWD and Ek). Thus the parameter choice is quite robust and requires no further tuning.

The quality of the algorithm's performance, i.e. correctness of the "binary" solution on the presence/absence of an epileptic event (SWD) was statistically analyzed using a criterion that provided false result with a certain degree of probability: the sensitivity  $\delta$  and specificity  $\sigma$  [18] using the formulae

$$\delta = \frac{\text{TP}}{\text{TP} + \text{FN}} \times 100\% , \qquad (7.4)$$

$$\beta = \frac{\text{TP}}{\text{TP} + \text{FP}} \times 100\% . \tag{7.5}$$

The sensitivity  $\delta$  is used to estimate the sensitivity of the method, i.e., the percentage of recognized spikewave discharges out of the total number of SWDs in the analyzed EEG fragment. The specificity  $\beta$  estimates the percentage of correct detections of SWD out of the total number of events identified as SWD. These characteristics also exceed 98% (see Table 7.1 for details), which is acceptable for automatic processing methods of neurophysiologic signals. In general, this CWT-based automatic method for recognition of SWD has advantage over other standard techniques in terms of accuracy and simplicity of application (no additional adjustments required). Moreover, this method can also be used for detection of other oscillatory patterns in EEG.

#### 7.4 Spindle-Like Oscillations and Spike-Wave Epilepsy

Sleep spindles are the hallmark of non-REM sleep in humans and animals (reviewed in [25, 27, 37]. The name "spindle" refers to its characteristic waxing and waning envelope. Sleep spindles were first described by Loomis et al. [73, 74]. The first commonly accepted definition was given by Rechtschaffen and Kales [109]: waxing and waning oscillations of 12–14 Hz and of at least 0.5 s duration. In animals, the frequency of sleep spindles tends to be slightly lower, 7–14 Hz, than in humans [130]. Similarly to humans, there are two topographically specific types of sleep spindles in rats: anterior and posterior [134]. However, anterior sleep spindles in rats only partially resemble anterior spindles in humans, but posterior spindles seem to be rather specific.

The idea that both sleep spindles and epileptic spike-wave discharges (EEG manifestation of absence epilepsy) are produced by the thalamus has been proposed time long. Initially, both spontaneous spindle waves and SWD were found to be "recruiting" response evoked by repetitive stimulation of intralaminar thalamic nuclei [53, 91, 92]. Latter on, spindle waves appeared to be more similar to the "augmenting" response (e.g. a pattern evoked by repetitive simulation of sensorimotor thalamic nuclei) [90, 128, 129]. In 1968, Pierre Gloor introduced a cortico-reticular theory of primary generalized absence epilepsy assuming that sleep waves could be transformed into epileptic spike-and-wave activity in the neocortex due to cortical hyperexcitability [40]. A variety of experimental and theoretical studies have further supported the idea that sleep spindles are functionally related to SWDs [8, 65, 131, 137]. First, sleep spindles typically appear during slow-wave sleep and they are more numerous at sleep onset similarly to spike-and-wave discharges that could usually be recorded during drowsiness and the initial stages of sleep [29, 77]. Second, sleep spindles and spike-and-wave discharges are generated in the same thalamocortical circuit (Fig. 7.3).

Sleep spindles and spike-wave discharges share a common thalamocortical mechanism, but originate from different neuronal sources (Fig. 7.3) (reviewed in [71]). Sleep spindles are triggered by thalamic neurons, whereas spike-wave discharges are initiated locally in the neocortex as in human patients [141] as well as in genetic rat models in (facial projection area in the somatosensory cortex, layers 5/6) [88, 106]. Recently it was found that the posterior thalamic nucleus (Fig. 7.3) was involved in the initiation of spontaneous spike-wave discharges in WAG/Rij rats [81, 82]. The posterior thalamic nucleus is a higher order thalamic nucleus of the somatosensory system, which receives its main driving input from epileptic source in the cortex and sends widespread projections to the neocortex and to the reticular thalamic nucleus



**Fig. 7.3** Thalamocortical network mechanisms of sleep spindle and spike-wave discharges as established in rat models of absence epilepsy. **a** Examples of the frontal EEG recorded in 8 months old WAG/Rij rat. **b** The neocortical part of the network includes epileptic focus in the somatosensory cortex (in orange); the thalamic part includes reticular, relay and posterior thalamic nuclei. The posterior thalamic nucleus (orange) is a high order nucleus that specifically involved in generation of spike-wave discharges, but its role in sleep spindles has not been investigated yet. VPm/VPl ventroposterior medial and lateral nuclei; MGN—medial geniculate nucleus; LGN—lateral geniculate nucleus. From [118]

[reviewed in Ref. [81]]. The role of higher order thalamic nucleus, including the posterior nucleus, in sleep spindles has not been explored.

A common thalamo-cortical network mechanism of sleep spindles and spike-andwave discharges suggests that some changes of spindle activity might appear due to epileptogenic processes in the neuronal network. Only a few studies investigated sleep spindles in patients with absence epilepsy. Myatchin and Lagae [95] found fewer sleep spindles in stage 2 sleep in patients with childhood absence epilepsy. Similarly, Kellaway at al. [60] demonstrated that the average rate of sleep spindles was lower and their duration was shorter in patients with generalized absence seizures (3 Hz spike-and-wave discharges in EEG) as compared to the control group. Medical treatment (ethosuximide or valproate) was found to change sleep spindles, but contradictory [60, 95]. Sleep spindles appeared to be altered even after the successful treatment of childhood absence epilepsy. As it was found in 11-years boy with a history of childhood absence epilepsy, sleep spindles were distorted three years after cessation of his treatment (valproate monotherapy) [61]. In this boy, sleep spindles were completely absent throughout the NREM period of the first sleep cycle; during the following sleep cycles, the mean rate of occurrence and mean amplitude were below the normal expected values for the boy's age; and only during the brief ascending branches of NREM stage II sleep spindles were found to be normal. Considering ethical and methodological limitations in human EEG research, investigations of sleep spindles in genetic animal models with spontaneous absence seizures is highly beneficial. During the last few decades, sleep spindles has been intensively explored in vivo in WAG/Rij rats with genetic predisposition to absence epilepsy [40, 79, 89, 118, 124].

It is well known that sleep spindles and spontaneous SWDs (but not pharmacologically induced seizures, see, e.g., [40, 65, 132] are characterized by a similar temporal distribution across the sleep waking cycle. In particular, both EEG events are predominant in the drowsy state and in the transition from wakefulness to sleep (see, e.g., [29, 79, 130]). Sleep spindles are abundant during slow-wave sleep, and the circadian dynamics of SWDs also correlates positively with the dynamics of slowwave sleep, as was demonstrated in the WAG/Rij rat model of absence epilepsy [29]. In human patients, absence epilepsy is sometimes dismissed as simple "daydreaming". Absence epilepsy might be considered as a sleep-related disorder, inasmuch as SWDs appear more often when the level of vigilance is low, e.g., passive wakefulness, drowsiness, and light slow-wave sleep in animal models [23, 29, 68], as well as in epileptic patients [59, 111]. Absence seizures may be initiated by wakerelated processes (see [46, 101]). In particular, in Genetic Rats with Absence Epilepsy (GAERS), "SWDs develop from wake-related 5–9 Hz oscillations, which are distinct from spindle oscillations (7-15 Hz)" [102, p. 209]. Five to nine hertz oscillations originate from the cortex ("launched by corticothalamic neurons" [102]), in contrast to sleep spindles, whose pacemaker is well known to be located in the thalamus [132]. Spontaneous medium-voltage 5–9 Hz oscillations are usually present in EEG during waking immobility, but they do not always lead to spike-and-wave discharges [103]. In addition to that, 5–9 Hz oscillations can be recorded in nonepileptic rats and never give rise to SWDs [103].

Wavelet analysis provides very effective approach to accurate differentiation of epileptic, nonepileptic and intermediate (pro-epileptic) oscillations in EEG. As it has been shown in Chap. 5, spontaneous spike-wave discharges (SWDs) are the electroencephalographic hallmark of generalized idiopathic epilepsies, such as absence epilepsy and other syndromes. Occurrence of SWDs in EEG is accompanied by brief and sudden lapse of consciousness, i.e. the state of "absence" in human patients and by similar absence-like state in rats with genetic absence epilepsy (i.e., immobility and behavioral arrest). It is well known that SWDs are generated by the thalamo-cortical neuronal circuit, which normally produces sleep spindles [28, 56, 130, 132]. Sleep spindles are abundantly present in electroencephalograms during non-REM sleep in

humans and animals. They can be recorded at the cortical surface, and also in the thalamus as brief episodes of 9–14 Hz oscillations (e.g., [7, 26, 132]).

Inasmuch as SWDs and sleep spindles originate from the same neuronal circuitry, they seem to be functionally related [65, 132] and therefore SWDs have long be considered as pathologic alterations of sleep spindles [40, 71, 89, 113, 118]. More recent data did not confirm genuine relationship between SWDs and sleep spindles [67, 102]. It is likely that absence seizures might be initiated by wake-related mechanisms [45, 68, 79]. In particular, in Genetic Rats with Absence Epilepsy (GAERS), SWDs are known to develop from wake-related 5–9 Hz oscillations, which are distinct from spindle oscillations (7-15 Hz) [102]. Five-9 Hz oscillations originate from the cortex ("launched by corticothalamic neurons" [23]), in opposite to sleep spindles, whose pacemaker is well known to be located in the thalamus [28]. Spontaneous medium-voltage 5-9 Hz oscillations usually present in EEG during awake immobility, but they do not always lead to spike-and-wave discharges [59]. In addition to that, 5–9 Hz oscillations can be recorded in non-epileptic rats and never give rise to SWD [59]. In this Section we consider the characteristics and peculiarities of the time frequency structure of sleep spindles and epileptiform spindle-like EEG events in WAG/Rij rats with genetic predisposition to absence epilepsy.

## 7.4.1 Time–Frequency Analysis of Spindle-Like Oscillatory Patterns

In the preliminary stage, we tested several mother wavelet functions for the continuous wavelet transform of sleep EEG and identified the advantages and disadvantages of each of them. We focused our attention on the real MHAT (2.40), and complex Paul (2.37) and complex Morlet (6.1) mother wavelets. It is noteworthy that the wavelet transform with each wavelet basis resulted in wavelet surfaces with specific frequencies  $f_s$  that differ from Fourier frequencies f which are commonly used in neurophysiology (see Sect. 2.2.3). More specifically, for the MHAT wavelet,  $f_s \approx 3.97 f$ , for the Paul wavelet with parameter m = 4,  $f_s \approx 0.71 f$ , and for the Morlet wavelet with central frequency  $\omega_0 = 2\pi$ ,  $f_s \approx f$ .

The results of wavelet analysis of the EEG recorded in the frontal cortex during sleep with numerous sleep spindles are shown in Fig. 7.4. This figure shows a typical EEG epoch (Fig. 7.4a) containing several sleep spindles and the corresponding amplitude wavelet spectra  $|W(f_s, t)|$ , obtained with the mother MHAT (Fig. 7.4b), Paul (Fig. 7.4c), and Morlet (Fig. 7.4d) wavelet functions. The dashed frames indicate the sleep spindles in the EEG and the corresponding regions of the wavelet spectra. Taking into account the fact that the main frequency of sleep spindle oscillations varied between 10 and 15 Hz (alpha range), this frequency range was selected to analyze the amplitude distribution of the wavelet coefficients.

Analysis and comparison of different mother wavelet functions showed that the complex Morlet wavelet is the optimal mother wavelet function to identify the time-



Fig. 7.4 Fragment of EEG during sleep with numerous sleep spindles (marked by *dotted frames*) as recorded at the frontal cortex in a WAG/Rij rat (**a**) and continuous wavelet spectra obtained with different mother wavelets: real MHAT (**b**), complex Paul (**c**), and complex Morlet (**d**). The *dome-shaped curve* on the wavelet surfaces marks the area of boundary effects (see Sect. 2.2.3)

frequency structure of sleep spindles in EEG. The complex Morlet wavelet was therefore used in an automatic system for identification of the sleep spindles [124]. In the wavelet spectrum obtained by means of the real MHAT wavelet (see Fig. 7.4b), the frequency resolution is low. Correspondingly, the frequency range of sleep spindles in the wavelet spectra is broad and it overlaps with the other types of oscillatory activity in the EEG. At the same time, the real MHAT-based wavelet transform, spikes, and other sharp components in the EEG corresponded to a robust increase in the amplitude  $|W(f_s, t)|$  of the wavelet coefficients in the alpha frequency band of interest. The latter feature impedes analysis of oscillatory activity in this range. Furthermore, the shape of the MHAT-based wavelet spectrum does not allow one to track dynamic frequency and amplitude changes in the spindle oscillations. The advantage with the MHAT wavelet is the good temporal resolution, which determines a sharp increase in the amplitude of the wavelet spectrum coefficients when the corresponding oscillatory event appears in the EEG. However, it is a complex matter to classify the sharp jumps in the wavelet spectrum amplitude due to the low-frequency resolution.

A similar situation is observed in the case of the wavelet transform with the Paul mother function (m = 4), the results of which are shown in Fig. 7.4c. Likewise, its frequency resolution does not permit precise determination of the dynamical features of the EEG oscillations in the alpha band. In this frequency range in the wavelet surface, we observed many high-amplitude components that are not sleep spindles and complicate sleep spindle analysis.

At the same time, the Morlet mother wavelet with central frequency  $\omega_0 = 2\pi$  combines a good resolution both in the frequency and time domains of the EEG signal (see Fig. 7.4d). In the time-frequency wavelet spectrum obtained in the alpha band, we can easily localize patterns corresponding to sleep spindle events, both in the time and the frequency domains. This gives an opportunity to track the variations of frequency and amplitude of the EEG oscillations which are typical for sleep spindles, including the parameter identification in automatic mode.

Wavelet analysis of a large number of sleep spindles has shown that, in the EEG recordings of WAG/Rij rats, two typical kinds of spindle-like patterns can be picked out using the criterion provided by the fundamental frequency of their wavelet spectrum. As already mentioned above, the fundamental frequency of typical sleep spindles lies in the 10–15 Hz range, and the shape of their oscillations exhibits extreme variability, so the fundamental frequency varies considerably in this frequency range from spindle to spindle. Simultaneously, in the wavelet spectra we found spindle-like oscillatory events, whose shape was close to the that of sleep spindles, but whose fundamental frequencies were in the low-frequency range (5–9 Hz).

Figures 7.5 and 7.6 show EEG epochs, typical wavelet spectra obtained with the Morlet mother wavelet function, and instantaneous energy distributions over frequencies for several typical sleep spindles (10–15 Hz) and 5–9 Hz spindle-like oscillations, indicating that peak frequencies of these phenomena lie in two clearly distinctive frequency bands.

Indeed, according to Morlet-based wavelet analysis, sleep spindles in WAG/Rij rats showed a markedly increased wavelet power in the range 10–15 Hz (see Fig. 7.5, where illustrations of typical sleep spindles are shown). The wavelet spectrum of



**Fig. 7.5** EEG examples of sleep spindles (10–15 Hz) and corresponding Morlet-based wavelet spectra (**a**), (**c**), (**e**). *Right plates* show the distribution of instantaneous wavelet energy  $E(f_s)$  (2.33) measured in sleep spindles (**b**), (**d**), (**f**)



**Fig. 7.6** EEG examples of 5–9 Hz oscillations and corresponding Morlet-based wavelet spectra (**a**), (**c**), (**e**). *Right plates* show the distribution of instantaneous wavelet energy  $E(f_s)$  (2.33) measured in 5–9 Hz oscillations (**b**), (**d**), (**f**)

Rat #	Sleep spind	lle		Five–9Hz oscillations			
	N	T (s)	f (Hz)	N	T (s)	f (Hz)	
1	3312	0.8	14.1	1378	0.73	7.2	
2	5440	0.58	12.6	869	0.84	6.4	
3	2776	0.69	13.2	974	0.85	6.1	
4	2007	0.7	12.8	1096	0.76	8.3	
5	3145	0.66	14.0	1511	0.86	7.4	
6	4421	0.64	12.1	1827	0.81	7.8	
Mean ± SD	3517 ± 1227	$0.68 \pm 0.07$		1276±363	$0.81 \pm 0.05$		

**Table 7.2** Main time-frequency characteristics of sleep spindles and 5-9 Hz oscillations in EEG registered in the frontal cortex during sleep. *N*, *T*, and *f* are the number, average duration, and mean frequency of analyzed events in the EEG, respectively

sleep spindles was often contaminated with additional low-frequency components and high-frequency bursts (occasional spikes). There were substantial frequency fluctuations within one spindle train (i.e., intra-spindle frequency variation) and the mean frequency of different sleep spindles also varied (i.e., inter-spindle frequency variations). The average sleep spindle frequency per rat varied from 12.1 to 14.1 Hz (inter-subject variations).

Five–9 Hz oscillations (see Fig. 7.6) are characterized by a spindle-like waveform. The frequency of these oscillations was lower than that in sleep spindles and matched the frequency of epileptic spike-wave discharges, i.e., peaks of wavelet power spectra are in the 7–9 Hz range.

The main time–frequency characteristics of sleep spindles and 5–9 Hz oscillations in EEG registered during sleep are presented for 6 rodents in Table 7.2. It can be seen that sleep spindles appear in the EEG more frequently in comparison with 5–9 Hz spindle-like oscillations. Note that the number of spike-wave discharges observed in the 6 h EEG recordings under study is estimated to be on average approximately 300 events.

Comparing the instantaneous wavelet spectra  $E(f_s)$  obtained with the help of different mother wavelets and presented in Fig. 7.7, we can conclude that only the Morlet wavelet allows one to identify and distinguish between the two kinds of spindle-like activity (sleep spindles and 5–9Hz oscillations). It is clearly that the use of real MHAT and complex Paul mother wavelets as basis functions does not provide the required frequency resolution (the large width of the corresponding peak in the averaged wavelet spectra in Fig. 7.7), so the peaks corresponding to the 8 and 12 Hz frequencies merge and are not distinguishable using the wavelet analysis. Note that the wavelet energy of the 5–9 Hz oscillations is significantly lower (in fact, 2–3 times lower) than the energy of a typical sleep spindle, so it is difficult to select the low-frequency spindle-like activity in the background EEG and to distinguish it from the more frequent typical sleep spindles. This additionally impeded the process of



Fig. 7.7 Comparison of energy distributions of the wavelet spectra obtained with the MHAT, Paul, and Morlet mother wavelets ( $\omega_0 = 2\pi$ ) for sleep spindles (10–15 Hz) (**a**, *solid lines*) and 5–9 Hz oscillations (**b**, *dashed lines*) in the frontal cortex

automatic detection of sleep spindle oscillations using the real MHAT and complex Paul mother wavelets.

At the same time, the wavelet analysis with the complex Morlet mother wavelet was effective for selective detection of spindles and 5–9 Hz oscillations. There are several reasons for this. First, good frequency resolution of the Morlet wavelet, therefore, the peaks in the wavelet spectra corresponding to each oscillation type did not overlap. Second, in the Morlet-based wavelet spectrum, the amplitude of both oscillatory patterns was comparable to each other. This approach allowed selective recognizing these two types of oscillatory patterns in the EEG using the Morlet mother wavelet.

## 7.4.2 Wavelet-Based Approach for Detecting Sleep Spindles and 5–9 Hz Oscillations in EEG

Sleep spindles and 5–9 Hz oscillations can be automatically detected in EEG using method described in [120]. The method based on comparing the wavelet powers,  $E_{F_1}(t)$  and  $E_{F_2}(t)$ , which were computed in the frequency range of 5–9 Hz oscillations  $F_1 \in [5, 9]$  Hz and in the range of sleep spindles  $F_1 \in [10, 15]$  Hz (see Eq. (2.33)):

$$E_F(t) = \int_F |W(f,t)|^2 df.$$
 (7.6)

Some EEG episodes with rhythmic activity in the frequency bands  $F_1$  and  $F_2$  were neither associated with sleep spindles, nor with 5–9 Hz oscillations. This EEG activity corresponded to short-term increase of instantaneous wavelet energy and sometimes caused false detections. In order to prevent incorrect detections, instantaneous wavelet energy,  $E_F(t)$ , was averaged across the empirically defined time window T = 0.5 s

$$w(t) = \frac{1}{T} \int_{t-T/2}^{t+T/2} E_F(\tau) \, d\tau.$$
(7.7)

Selective detection of sleep spindles and 5–9 Hz oscillations in EEG was based on the value of the averaged wavelet energy w(t) as measured in the above-mentioned frequency bands,  $F_1$  and  $F_2$ , correspondingly,  $w_1(t)$  and  $w_2(t)$  (Fig. 7.8). In each subject, the two threshold levels were determined individually:  $w_{1c}$  for  $w_1(t)$  and  $w_{2c}$ for  $w_2(t)$ . The value of  $w_{1c}$  varied between 0.06–0.12 and  $w_{2c}$ —0.07–0.14 depending on the stability of amplitude-frequency characteristics of EEG over time. Sleep spindles were detected if the value of wavelet power in the frequency range 10–15 Hz,  $w_2(t)$ , exceeded the threshold value  $w_{2c}$ , and the value of  $w_2(t)$  was greater than the value of wavelet power in 5–9 Hz,  $w_1(t)$ :

$$w_2(t) > w_{2c} \land w_2(t) > w_1(t).$$
 (7.8)

Five-9 Hz oscillations were recognized based on the following condition:

$$w_1(t) > w_{1c} \wedge w_2(t) < w_1(t),$$
 (7.9)

i.e., the value of wavelet power in 5–9 Hz,  $w_1(t)$ , exceeded the threshold value  $w_{1c}$ , and the value of wavelet power in 10–15 Hz,  $w_2(t)$ , was lower than the value of wavelet power in 5–9 Hz.

The algorithm for selective identification of sleep spindles and 5–9 Hz oscillations is shown in Fig. 7.9. It was based on the "floating" thresholds method for identification of EEG pattern introduced by Grubov et al. [42]. Briefly, the detection started at the initial threshold levels of wavelet power,  $w_{c1}$  and  $w_{c2}$ . When the criterion  $w > w_{cr}$ 



**Fig. 7.8** An illustrative scheme of wavelet-based detection of sleep spindles, 5–9 Hz oscillations and their slow wave precursors. **a** The frontal EEG as recorded during sleep in WAG/Rij rat and **b** corresponding continuous wavelet transform, in which arrows indicate high power in the frequencies around 4 Hz before the onset of sleep spindles and 5–9 Hz oscillations. **c** Distribution of wavelet power,  $w_1(t)$  and  $w_2(t)$ , in the characteristic frequency bands  $F_1$  and  $F_2$ , correspondingly. Vertical lines outline automatically identified sleep spindles and 5–9 Hz oscillations. **d** Distribution of wavelet power, w3(t) in the frequency band  $F_p \in [2, 7]$  Hz that was used for detecting slow wave precursors. Based on data from Ref. [120]

was fulfilled, the threshold value wc was reduced to  $w_c$  (i.e.,  $c = 0.4w_c$ ), and on next steps the value of wavelet energy was compared with this new threshold value (i.e., the criterion was changed to  $w_c > w_c$ ). When the value of wavelet energy did not reach the lowered threshold value  $w_c$ , the threshold level was returned to the initial value  $w_c$ .

The quality of detection method was evaluated after the visual inspection of the automatically recognized sleep spindles and 5–9 Hz oscillations in 1h EEG epochs. The true positive (TP) was computed as the percentage of correct detections of sleep spindles (or 5–9 Hz oscillations). The true negative (TN)—the percentage of correct rejections of sleep spindles (or 5–9 Hz oscillations). False positive (FP)



represented the percentage of incorrect automatic detections of sleep spindles (or 5-9 Hz oscillations). The false negative (FN)—the percentage of events missed by the automatic wavelet-based method. In sleep spindles, the sensitivity (7.4) of the automatic recognition was  $\delta = 87.4\%$  and specificity (7.5)— $\beta = 95.3\%$ . In 5–9 Hz oscillations, the sensitivity was 91.2% and specificity-93.6%.

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# 7.4.3 Classification of Normal and Abnormal Spindle Oscillations by Means of Adaptive Wavelet Analysis

The classification of different kinds of oscillations in the EEG and the creation of databases for the reference electroencephalographic patterns are very important and actively investigated problems associated with fundamental research on brain functions [63, 112, 115], and with applied tasks such as the development of brain–computer interfaces (BCI) [58, 72, 98]. Nowadays various methods have been proposed for solving these problems, based on different mathematical and cybernetic approaches to pattern recognition and classification [9, 31, 66, 115].

#### 7.4.3.1 Construction of Adaptive Wavelet Basis ("Spindle Wavelet")

Sleep spindles in subjects with absence epilepsy are characterized by a variety of waveforms, including normal spindle-like oscillations and abnormal spindles by epileptic transformation (i.e., pro-epileptic oscillations or aberrant sleep spindles) [113]. Therefore, the shape of sleep spindles and their electroencephalographic pattern appear to be less stereotypic from normal to pro-epileptic spindle-like oscillations. This embarrassed the automatic detection of sleep spindles. In [124], we developed a new approach to examine the waveform of EEG using so-called adaptive continuous wavelet analysis. This analysis employed specifically selected EEGsignal epoch as a mother wavelet function. This EEG-signal showed the highest affinity for the analyzed pattern and it was used as a tool for the extraction and recognition of non-standard complex shape oscillations. This strategy may be referred to as an adaptive wavelet matching, is somewhat comparable with the matching pursuit technique [16, 32–34, 144], in which a template function was chosen from a stochastic library that contains a set of Gabor, Dirac, and Fourier basis waveforms. In adaptive wavelet analysis, we did not use preset templates, but our spindle wavelet basis functions were adopted directly from the EEG signal. This approach can be used both for effective automatic identification of sleep spindles and for standardizing the EEG structure and creating a database of reference electroencephalographic patterns.

For the standardization of sleep spindle patterns, an adaptive wavelet basis function (spindle wavelet) was built using a sleep spindle prototype extracted from the native EEG. Figure 7.10 illustrates this approach to adaptive wavelet construction. The EEG signal was represented by the function S(t). The signal g(t) with eliminated mean value was considered, viz.,

$$g(t) = S(t) - \frac{1}{\Delta T} \int_{\Delta T} S(t) dt , \qquad (7.10)$$

and subsequently transformed into the complex form



**Fig. 7.10** Algorithm used for constructing adaptive *spindle wavelets*. Sleep spindle prototypes g(t) are selected in the native EEG, converted into the complex form and normalized with a Gaussian function. **a** Spindle wavelet type 1 and **b** type 2. The *black line* corresponds to the real part of the spindle wavelets and the *grey line* to the imaginary part

$$\hat{g}(\eta) = g(\eta) + ig(\eta + T/4) , \quad i = \sqrt{-1} ,$$
 (7.11)

where T denotes the typical period of a sleep spindle oscillation. The time shift between the real and imaginary parts was T/4.

In order to construct a localized-in-time wavelet basis  $\psi^{S}(\eta)$ , the function  $\hat{g}(\eta)$  was normalized with a Gaussian function:

$$\psi^{S}(\eta) = \alpha \hat{g}(\eta) \exp\left[-\frac{(\eta - T/2)^{2}}{2}\right], \qquad (7.12)$$

were  $\alpha$  is the parameter determined from the normalization condition

$$\alpha^{2} \int_{-\infty}^{+\infty} |\hat{g}(\eta)|^{2} \exp\left[-\frac{(\eta - T/2)^{2}}{2}\right] \mathrm{d}\eta = 1.$$
 (7.13)

Both *spindle wavelets* fulfilled the requirements for wavelet bases, i.e., continuity, zero mean amplitude, and finite or near finite duration (see Sect. 2.2.1). Note that the same computational procedure is used for the harmonic function, e.g.,  $sin(\omega_0 t)$  [or  $cos(\omega_0 t)$ ], in order to construct the complex Morlet wavelet [see (6.1)].

In order to select a typical spindle template, about 100 candidate spindle templates were chosen in five WAG/Rij rats (15–25 spindles per rat). Each spindle template was tested as a wavelet basis (spindle wavelet) which was used to calculate and analyze the wavelet spectra of sleep spindles. We considered the dependencies of the wavelet spectrum energy E(t) on time t, for a time scale s = 1.0. Peaks  $E(t) = E_{\text{max}}$  in the wavelet energy dependencies E(t) correspond to sleep spindles with shape similar to the shape of the considered spindle wavelet. Introducing a certain threshold  $E_k$ , we could pick out the sleep spindles for which the characteristic energy value exceeded the threshold:  $E_{\text{max}} > E_k$ . Sleep spindles showed different degrees of conformity to two types of spindle wavelets, e.g., spindle wavelets type 1 and type 2.

#### 7.4.3.2 Normal (Type 1) and Abnormal (Type 2) Sleep Spindles

Spindle wavelets type 1 and type 2 were adopted from sleep spindle events in the raw EEG (i.e., spindle prototypes) and therefore they embraced the typical (or generic) features of sleep spindles. The spindle wavelet type 1 had the highest affinity to the maximum number of sleep spindles (85–90%) in EEG recorded in all WAG/Rij rats with absence epilepsy (n = 9 rats). Therefore, the spindle wavelet type 1 was considered as universal adaptive wavelet representing typical sleep spindle EEG pattern with the fundamental frequency 10–14 Hz in rats with absence epilepsy (Fig. 7.10a). The remaining 10–15% of sleep spindles were selected using the spindle wavelet type 2 (Fig. 7.10b). A basis function for type 2 spindle wavelet had to be selected in each rat individually. These type 2 spindles characterized by an increased power in frequencies between 12 and 25 Hz, exhibited a deviant spindle waveform and were considered as pro-epileptic events (i.e., a transitory waveform between sleep spindles and spikewave discharges) [124].

In order to understand the physiological implication of these two spindle prototypes, we performed a power spectrum analysis. It was found that spindle wavelet type 1 had a fundamental frequency of 12.2 Hz (see Fig. 7.11) that corresponds precisely to the mean frequency of sleep spindles in rats [130], and in addition, it had a spectral peak at around 7 Hz and elevations around 2 and 26 Hz. In contrast to the spectrum of spindle wavelet type 1, the spectrum of spindle wavelet type 2 was more complex with the main peak at the frequency of  $21 \pm 3$  Hz. Typically, spindle wavelet type 2 showed several sharp peaks at the frequency of 1, 3, 16.7, and 21.3Hz, and moderate elevations at 8.5, 11, 24.5, and 27 Hz (see Fig. 7.11). In conclusion, atypical sleep spindles (type 2) were distinguished from sleep spindles type 1 by (i) a higher individual variation (ii) more powerful beta component that might be considered as a hallmark of type 2 spindles.

Our data indicated that sleep spindles represented a very heterogeneous group of oscillations. The strong variability of sleep spindles between- and within-subjects



**Fig. 7.11** EEG waveforms of sleep spindles in WAG/Rij rats. *Top*: Native EEG in which the majority of sleep spindles comprise characteristic repetitive elements that match spindle type 1. Spindle wavelet type 1 is universal for all the animals. This type of oscillatory activity is a typical sleep spindle. However, 10-15% of sleep spindles are not recognized by the adaptive wavelet type 1, and their recognition requires one to construct new wavelet bases separately for each animal. This wavelet (referred to as the type 2 spindle wavelet) is characterized by a very complex form which is specific to each animal. Type 2 sleep spindles display larger inter-subject variability and complex structure and can be associated with pro-epileptic activity on the EEG. *Bottom*: Frequency power spectra of spindle wavelets types 1 (*left*) and 2 (*right*). The type 1 spindle wavelet is characterized by a predominant 8–14 Hz frequency component (spindle range). The type 2 spindle wavelet frequency spectrum consists of several frequency to mage the spindle and non-spindle range

causes problems with spindle detection using traditional methods [13, 52, 108, 135, 143]. Adaptive wavelet analysis helped us to overcome difficulties with extraction, recognition, and classification of spindle events in EEG. In all our rats, almost all sleep spindles (95.5%) are extracted with joint application of two different types of adaptive spindle wavelets. Spindle wavelets are adopted from spindle prototypes, i.e., from sleep spindle events in the EEG, and therefore they embrace the most typical (or generic) features of sleep spindles. The frequency profile of these two types of sleep spindles is crucially different.

The occurrence of type 2 sleep spindles with the powerful 16–25 Hz component might be accounted for by processes of epileptogenesis in rats with genetic predis-

position to absence epilepsy. Interestingly is that recent study [19] demonstrated that epileptiform activity in four rat models of epilepsy characterized by a remarkably similar profile of EEG power spectrum. In particular, kainic acid induced poststatus epilepticus, the traumatic brain injury induced posttraumatic epilepsy. Genetic Absence Epilepsy Rats from Strasbourg (GAERS) and Wistar Albino Glaxo from Rijswijk (WAG/Rij) showed seizure activity with spectral peak within the frequency range of 17-25 Hz. These frequencies are surprisingly close to abnormal elevation of 16–25 Hz in the spindle wavelet type 2 [124]. Our previous data [125] showed that frequency spectrum of SWDs characterized by the fundamental frequency (1012 Hz) and its second harmonic (20-24 Hz), while the onset of SWD was associated with a profound increase of bilateral synchronization in 15–16 Hz. In type 2 sleep spindles, the spectral peaks appeared to have the similar frequencies (16.7 and 21.3 Hz) and they might relate to an increased neuronal synchrony at 16.7 and 21.3 Hz that is in common to SWDs. So the type 2 sleep spindles might be considered as a transitory oscillatory waveform between spindle and SWD in the EEG of WAG/Rij rats [119, 124].

#### 7.4.3.3 Intra-Spindle Frequency Dynamics in Epileptic and Non-epileptic Rat Strains

We emphasize that balanced time frequency resolution provided by the complex Morlet wavelet ( $\omega_0 = 2\pi$ ) allows for effective analysis of frequency dynamics within sleep spindles that would not be possible with the other mother functions. Figure 7.12 shows the EEG epoch (and its wavelet spectrum obtained with the help of the Morlet wavelet (Fig. 7.12b), and the instantaneous amplitude distributions of the wavelet spectrum at different times (Fig. 7.12c), which correspond to the times 1–3 indicated by arrows in Fig. 7.12a. In the given time interval of the EEG, we observe two sleep spindles, but the first one that appears at time t = 4 s is short and poorly visible in the EEG signal. Therefore, the analysis was carried out for the second sleep spindle, occurring in the time interval t = 9-11 s as indicated by arrows.

The main frequency during spindle oscillations varied significantly and usually increased from beginning to the end of sleep spindle. This can be seen in the wavelet surface  $|W(f_s, t)|$  and the instantaneous wavelet energy distributions E(fs) plotted at the three different times. In particular, the frequency of the sleep spindle was close to 7.5 Hz at the beginning (curve 1 in Fig. 7.12c). Then there was an increase in amplitude of oscillations and a shift from slow to higher frequencies (curve 2). Simultaneously, oscillatory components with smaller amplitude and frequency close to 14 Hz were present in the wavelet spectrum. At the end of the sleep spindle, there was a rapid increase in the frequency of spindle oscillations to about 12 Hz (curve 3). Noteworthy that 7.5 Hz component was present at the beginning of the spindle and remained in the wavelet spectra during the spindle yet with a reduced amplitude.

Time frequency characteristics of sleep spindles were studied in EEG recordings using CWT described in the previous section. For the time–frequency analysis and observation of the dynamics of the dominant frequency during oscillatory events



**Fig. 7.12** Dynamics of oscillation frequencies during sleep spindle event at different time moments (indicated by arrows 1, 2 and 3). EEG signal recorded in the frontal cortex (**a**); wavelet spectrum obtained using the complex Morlet wavelet (**b**); the instantaneous amplitude distributions of wavelet coefficients (**c**)

in EEG we used the numerical method of construction of "skeletons" of wavelet surfaces. In this case we analyzed the instantaneous wavelet energy distribution  $E_i(f_s) = |W(f_s, t_0)|^2$  for the fixed time moments  $t = t_0$  and found all the local maxima of the  $E_i(f_s)$ :

$$E_{\max, k}(f_s) = \max[E_i(f_s)].$$
 (7.14)

After this we found the largest peak in wavelet energy distribution at the considered time moment  $t = t_0$  and determined the main frequency,  $f_b$ , which is corresponded the greatest maximum. This frequency was considered as the basic main frequency of oscillations in EEG and plotted in skeletons of wavelet surfaces. Let us note, that in each moment of time there is only one dominate frequency,  $f_b$ , which is presented on skeletons in Fig. 7.12. In fact, the skeleton is the dependence of the instantaneous basic frequency on the time and allows conveniently representing and tracking the dynamics of instantaneous frequency,  $f_b(t)$ , in the EEG recordings. In this paper, for



**Fig. 7.13** Wavelet spectra and corresponding skeletons of sleep spindles in EEG illustrating dynamics of instantaneous intra-spindle frequency. Local maximum of the instantaneous frequency was measured at the beginning  $(f_1)$  and the end  $(f_2)$  of a spindle. **a** Sleep spindle, in which instantaneous frequency increases from the beginning to the end  $(f_{mean} = 13.8 \text{ Hz})$ , and (**b**)—instantaneous frequency decreases  $(f_{mean} = 13.1 \text{ Hz})$ 

the time-frequency analysis we exploited only skeletons of wavelet surfaces and did not use the wavelet spectra that are allowed automated data processing. Using the skeleton we can easy define both extreme frequency values at the beginning ( $f_{start}$ and the end ( $f_{end}$ ) of spindle train and mean frequency,  $f_{mean}$ , as

$$f_{mean} = \frac{1}{h} \int_{t_1}^{t_1+h} f_b(t) dt, \qquad (7.15)$$

where *h* is the duration of the sleep spindle,  $t_1$  is the time of the beginning of sleep spindle.

In Fig. 7.13 the wavelet spectra and corresponding skeletons of wavelet surfaces are shown for the sleep spindles with typical dynamics of basic frequency: (a) with increasing frequency from the beginning to the end of spindle, and (b) with diminishing frequency. One can easily see that the skeleton plot is very effective tool for analyzing time–frequency peculiarities of oscillatory events in EEG.

Rapid changes of the dominant frequency during sleep spindles in EEG signals recorded in non-epileptic and epileptic rat strains were examined using skeletons of wavelet surfaces [4, 119, 121]. Age-related and epilepsy-related changes of intraspindle frequency dynamics was examined in a group of six male WAG/Rij rats. In each subject, EEG signals were recorded at the age of 5, 7 and 9 months [121]. Epileptic activity in these rats significantly increased between the age of 5 and 9 months: the number of SWD increased from 3 to 38 discharges as counted in 6-h interval, as well as the total duration of seizure activity—from  $34 \pm 20$  s to  $439 \pm 281$  s. At



the preclinical age (5-m), WAG/Rij rats showed significantly lower value of spindle frequency at the beginning ( $f_{start}$ ) as compared to that in older ages (7 and 9 months), when epileptic discharges became more numerous and epileptic activity became longer (Fig. 7.14).

#### 7.4.3.4 Slow-Wave Precursors of Spindle-Like Oscillations in Rats with Spike-Wave Epilepsy

Detection was conducted after the automatic recognition of sleep spindles and 5–9 Hz oscillations using the algorithm described in Sect. 7.4.2. The analysis was performed in 2 s time periods  $(T_t)$  immediately before the onset of spindles/oscillations. Short intervals (<1 s) between the consequent oscillations were excluded from the analysis. If the interval between oscillations was between 1 and 2, this very interval was analyzed. The value of wavelet power  $w_3(t)$  was computed during the time epoch  $T_t$  in the frequency band  $F_p \in [2, 7]$  Hz using the formula (Eq. 7.7) as shown in Fig. 7.8. The averaging time window T = 1 s was applied, taking into account the low amplitude of the analyzed precursor frequency.

The onset of slow wave precursors was determined based on the condition:

$$w_3(t) > t_{tc},$$
 (7.16)

where  $w_{tc} = 0.5w_{2c}$ . If the condition (7.16) was satisfied for several successive events, the precursor was selected as the closest (in time) to sleep spindle/Five–9 Hz oscillations. The instantaneous frequency of the slow wave precursor varied between 2 and 7 Hz and partly overlapped with the frequency of 5–9 Hz oscillations. In fact, the low frequency component (2–7 Hz) did not disappear with the onset of the automatically detected oscillations. At the moment when 5–9/10–15 Hz rhythm appeared to be dominant, this low frequency component became subdominant as it was described in Ref. [123]. The abovementioned study also indicated that the

majority of sleep spindles and 5-9 Hz oscillations contained <5 Hz as subdominant slow frequency component.

In order to avoid false detections due to brief and abrupt changes in EEG power, we used the "floating" threshold method. With this approach, the end point was determined after comparison between the value of wavelet power of precursor activity and the averaged value of wavelet power  $w_0$  in background EEG based on the condition:

$$w_3(t) < 1.2w_0. \tag{7.17}$$

In the detected slow wave precursors, the averaged power,  $R_i$ , and averaged frequency,  $f_i$ , was computed by averaging their wavelet spectra and skeletons:

$$R_{i} = \frac{1}{t_{end} - t_{start}} \int_{t_{start}}^{t_{end}} E(f_{max}(t), t) dt, \qquad f_{i} = \frac{1}{t_{end} - t_{start}} \int_{t_{start}}^{t_{end}} f_{max}(t) dt,$$
(7.18)

where  $t_{start}$  and  $t_{end}$  are the beginning and end time points of precursor event,  $f_{max}(t)$  is the frequency corresponding to the maximum energy in the frequency band F at each time moments.

Slow-wave precursors were recognized in the frontal EEG in two rat strains, Wistar and WAG/Rij, in 1-h sleep EEG. These animals were examined for the presence of spike-wave discharges, i.e. EEG manifestation of absence epilepsy, and were recognized as having "epileptic" and "non-epileptic" phenotypes.

WAG/Rij and Wistar rats showed the same portion of spindles with slow wave precursors (56% and 44%, correspondingly). The higher percentage of spindles with slow wave precursors (67%) was detected in "epileptic" subjects compared with "non-epileptic" (41%, p < 0.001). In "epileptic" subjects, no correlations were found between the SWDs number and the percentage of spindles with slow-wave precursors (Spearman's rank test, R = 0.08, p = 0.86). The intrinsic frequency of spindle precursors in "epileptic" rats (4.8 Hz) was higher than in "non-epileptic" (3.8 Hz, p < 0.05). The portion of slow-wave precursors of 5–9 Hz oscillations in WAG/Rij rats (18%) was significantly lower than in Wistar rats (63%, p < 0.0001). The intrinsic frequency of slow wave precursors of 5–9 Hz oscillations in WAG/Rij rats was higher than in Wistar rats (4.2 and 3.1 Hz correspondingly, p < 0.005). In "epileptic" subjects, the percentage of slow-wave precursors of 5–9 Hz oscillations did not differ from that in the "non-epileptic" subjects, but the intrinsic frequency of precursors in "epileptic" rats was higher than in "non-epileptic" subjects, but the intrinsic frequency of precursors in "epileptic" rats was higher than in "non-epileptic" rats (4.6 and 3.1 Hz correspondingly, p < 0.00005).

Amplitude changes in transition between slow wave precursor and consequent oscillation:

$$r_a = \sqrt{\frac{f_{SS}}{f_p}} \frac{R_{SS}}{R_p},\tag{7.19}$$



**Fig. 7.15** Illustrative scheme of wavelet analysis of slow wave precursors and consequent oscillations. The upper graph show raw electroencephalogram (EEG) recorded in the frontal cortex in WAG/Rij rat. Wavelet power spectrum was obtained using continuous wavelet transform with complex Morlet wavelet basis function. Two inserted plots display wavelet power spectra as computed at the time moment t = 2.25 s (precursor) and t = 2.75 s (sleep spindle). From Ref. [120]

where index "*p*" referrers the the slow wave precursor, and "*SS*"—sleep spindle or 5–9 Hz oscillations. The normalized factor  $\sqrt{f_{SS}/f_p}$  takes into account the amplitude differences in different scales in wavelet spectrum (see Sect. 2.1).

Amplitude changes in transition from precursors to oscillations using the CWT demonstrated in Fig. 7.15. Statistical analysis indicated that "epileptic" rats showed a weaker amplitude growth during transition from precursor to oscillations (both types) in comparison to "non-epileptic" rats. The transition "precursor  $\rightarrow$  5–9Hz oscillation" was accompanied by a greater increase in amplitude than the transition "precursor  $\rightarrow$  sleep spindle" [120].
## 7.5 Pro-epileptic Activity and Undeveloped Spike-Wave Seizures in Genetically Prone Subjects

Absence epilepsy has a strong genetic predisposition in human patients (for review, see [24]), as well as in the WAG/Rij genetic rat model (for review, see [23, 139]). Despite a genetic predisposition to absence epilepsy, WAG/Rij rats are characterized by strong individual variations in EEG pattern of spike-wave seizures. Around one third of WAG/Rij rats housed at our laboratory in Moscow did not develop absence seizures throughout their entire life [120, 123]. Considering that non-epileptic phenotype in an inbreed WAG/Rij rat stain might result from a genetic drift, we started breeding the "non-epileptic" substrain of WAG/Rij and examined the waveform of underdeveloped seizures (or pro-epileptic activity) in their EEG.

In "non-epileptic" WAG/Rij rats, we distinguished intermediate waveforms which were transitional from normal oscillations to epileptic discharges: the so-called proepileptic activity that did not meet the criteria for SWDs [127]. Empirically we defined the pro-epileptic activity as an immature epileptic discharge (or embryonic SWD) which might develop into an epileptic discharge in epileptic rats or remain in an embryonic latent state in "non-epileptic" rats. Five 9 Hz oscillations appeared to be the most probable source of pro-epileptic activity on EEG in rat models, since they were epileptogenic (pro-epileptogenic) in nature and were found to directly preceded SWDs in Genetic Absence Epilepsy Rats from Strasburg [102, 103]. Spontaneous medium-voltage 5–9 Hz oscillations are usually present in EEG during waking immobility, but they do not always lead to spike-and-wave discharges. In addition to that, 5–9 Hz oscillations can be recorded in nonepileptic rats and never give rise to SWDs. Moreover, immature epileptic discharges in rat models have a frequency of 5–7 Hz and amplitude similar to that in normal sleep spindles [17, 121].

In this Section, we describe principles of automatic recognition of pro-epileptic activity in "epileptic" and "non-epileptic" WAG/Rij rats introduced using the CWT and construction of the skeleton of the wavelet surface. The outcomes of the CWT were used to establish the main criteria of pro-epileptic activity, and skeleton of the wavelet surface—to access the dynamics of instantaneous frequency and refine selected pro-epileptic patterns.

## 7.5.1 Time–Frequency Characteristics of Pro-epileptic Patterns in EEG in WAG/Rij Rats

Characteristic SWDs were recognized in the frontal EEG as a sequence of high-voltage repetitive spike-wave complexes with a frequency of 8-10 Hz and a minimum duration of 1.5 s (Fig. 7.16, segment **A**). Pro-epileptic activity appeared as immature/embryonic epileptic discharges (Fig. 7.16, segment **a**). Figure 7.16 (segments **b**, **c**) demonstrates the results of CWT of pro-epileptic patterns with slightly different time–frequency structure. The duration of each fragment is 6 s; wavelet sur-



**Fig. 7.16** Examples of epileptic spike-wave discharges **a** and pro-epileptic activity (**b**), (**c**) in EEG recorded at the surface of the frontal cortex with implanted epidural electrode in 7-months old WAG/Rij rat. Bottom plates show results of the CWT computed with complex Morlet wavelet

faces are plotted in the range of 2–30 Hz. In general, pro-epileptic patterns showed the following distinctive properties: (i) a sharp start; (ii) the main maximum frequency in the range from 5 to 10 Hz; (iii) the presence of occasional spikes or sharp waves associated with an increased wavelet power in the range of the 1st harmonic from 10 to 20 Hz. The following criteria of pro-epileptic activity were defined by means of the CWT:

- The mean intrinsic frequency is 5–9 Hz.
- Duration more than 1.5 s.
- The presence of epileptiform elements (spikes or sharp waves).
- Decrease of the instantaneous frequency from beginning to the end of the proepileptic pattern (optional).

## 7.5.2 Algorithm for the Automatic Detection of Pro-epileptic Patterns in EEG

The proposed algorithm is based on the results of Sects. 7.3 and 7.4.3 and rely upon the criteria of the fundamental frequency (5–9 Hz), duration (more than 1.5 s) and high power in the range of 10–20 Hz (harmonic of the fundamental frequency), indicating the presence of sharp "epileptiform" elements in the pattern (i.e., spikes

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Fig. 7.17 Block diagram of the proposed algorithm for the automatic identifiaction of pro-epileptic patterns in rat's EEG

or sharp waves). The algorithm consistent of four steps (three mandatory steps and one optional step, see the block diagram in Fig. 7.17).

Step 1. Calculation of the wavelet energy over full-length EEG and averaging in 5-9 Hz frequency band. The maximum wavelet energy was around 0.2–0.3. However, wavelet energy of EEG signals varied across subjects, and the threshold value in 5-9 Hz, Wcr, was fixed in each individual as 60-70% from the maximal value. Usually, the threshold was around 0.11–0.18 therefore only EEG patterns with high energy were selected (1st detection list).

Step 2. EEG patterns that lasted less than 1.5 s were removed (2nd detection list). In these EEG patterns, rhythmic activity in 5–9 Hz was stable and continuously present longer than 1.5 s.

Step 3. Examination of time-frequency properties of EEG patterns using the method of wavelet skeletons (i.e., skeleton criterion). For each EEG pattern from the 2nd detection list, two skeletons were constructed at each moment in time: skeleton 1,  $S_1 \in [5, 9]$  Hz for the fundamental frequency of the pro-epileptic pattern and skeleton 2,  $S_2 \in [10, 20]$  Hz for the harmonic of the fundamental frequency. Additionally, the energy in 5–9 Hz was greater than in 10–20 Hz ( $E_{S1} > E_{S2}$ ) at each moment in time. Only EEG patterns in which >70% of points met the above mentioned criteria were included in the 3rd detection list.

Step 4 (optional). Examination of instantaneous frequency and frequency dynamics during EEG patterns using the method of wavelet skeleton. The instantaneous frequency of the first skeleton ( $S_1 \in [5, 9]$  Hz) was reduced, i.e., its values at the current time moment was lower than at the previous moment. EEG patterns from the 3rd detection list in which >70% of points met the above mentioned criterion were included in the 4th detection list.

An example of the proposed algorithm is shown in Fig. 7.18. Pro-epileptic EEG patterns are highlighted by shaded rectangles (1, 2, 3) in Fig. 7.18a. Steps 1 and 2 of the proposed algorithm are demonstrated in Fig. 7.18b: wavelet energies averaged over 5–9 Hz for each EEG fragment (solid lines) and the threshold value of the wavelet energy  $W_{cr}$  (dashed horizontal line). Rectangular frames outline EEG patterns included in the 1st detection list (i.e., wavelet energy exceeded Wcr). On the Step 1 shown on Fig. 7.18b, a presumably pro-epileptic pattern was identified on each of the three



**Fig. 7.18** Application of the proposed algorithm for identification proepileptic patterns in rat's EEG. **a** Fragments of EEG signal containing presumed proepileptic EEG patterns 1, 2 and 3. **b** Distributions of wavelet power EF averaged in 5–9 Hz frequency band (*a*) with the threshold value of the wavelet energy Wcr (dotted horizontal line, *b*) and the signal part included in the 1st detection list (*c*). **c** The 1st and 2nd skeletons,  $S_1 \in [5, 9]$  Hz and  $S_2 \in [10, 20]$  Hz; rectangular frames outline the part of signal included in the 2st detection list

Age, months	3rd detection	on list	4th detection list			
	5 m		7 m		5 m	7 m
Parameters	W <sub>cr</sub>	N	W <sub>cr</sub>	Ν	Ν	Ν
"Epileptic" rats	$0.151 \pm 0.022$	55 ± 11	$\begin{array}{c} 0.138 \pm \\ 0.028 \end{array}$	$44 \pm 10$	37 ± 7	29 ± 8
"Non- epileptic" rats	$0.133 \pm 0.019$	$46 \pm 16$	$0.129 \pm 0.017$	$36 \pm 6$	29 ± 8	$24 \pm 5$

**Table 7.3** Parameters of pro-epileptic EEG patterns automatically detected in WAG/Rij "epileptic" and "non-epileptic" rats (mean  $\pm$  stand. dev.)

Here N is the number of events

EEG fragments shown on Fig. 7.18a. Duration of the pattern in fragment 1 was less than 1.5 s, therefore, only patterns in fragments 2 and 3 were included in the 2nd detection list (Step 2). Figure 7.18c demonstrates the results of the Step 2 (rectangular frame), skeletons  $S_1 \in [5, 9]$  Hz and  $S_2 \in [10, 20]$  Hz (marked with dots). Skeletons were built only for those EEG sections that were included in the 2nd detection list, therefore, no skeletons are shown for the fragment 1. Patterns on the fragments 2 and 3 met the criteria introduced on the Step 3, i.e., >70% of points of the first skeleton fell in the frequency 5–9 Hz, >70% of points the second skeleton—the frequency 10–20 Hz, and the energy in S1 is greater than in S2. However, pattern in fragment 3 does not meet the criterion introduced on the optional Step 4 (i.e., reduction of instantaneous frequency in >70% of points in the first skeleton); accordingly, only the pattern in fragment 2 is included in the 4th detection list.

This algorithm was applied to electroencephalographic signals (EEG) recorded in a group of 26 WAG/Rij rats. Analysis was performed in the frontal EEG channel for the 6 h time interval. SWD were detected in 17 rats ("epileptic" phenotype) and absent in 9 animals (i.e., less than 2 seizures during 6-h period, "non-epilpetic" rats). In "epileptic" rats, the mean number of SWD was 4.4 per hour at the age of 5 months and 7.4 per hour—at the age of 7 months. Table 7.3 shows the results of the automatic detection of pro-epileptic patterns in "epileptic" and "non-epileptic" rats. The value of  $W_{cr}$  in "epileptic" rats was higher than in "non-epileptic" rats, suggesting that the power in 5–9 Hz in "epileptic" rats was higher than in "non-epileptic".

Statistical analysis revealed that the number of pro-epileptic EEG patterns significantly decreased with age in both groups of rats. Interestingly that age-related reduction in number of proepileptic EEG patterns in "epileptic" rats accompanied by an increase in number of SWD. Perhaps pro-epileptic activity in these rats acquires epileptic features between 5 and 7 months of age and transformed into SWD. This suggests a certain "epileptization" of rhythmic activity in "epileptic" WAG/Rij rats. The same age-related reduction in number of proepileptic patterns in "non-epileptic" rats did not associate with the occurrence of SWD and this might be accounted for elimination of proepileptic activity. In human patients with absence epilepsy and in WAG/Rij rats, the instantaneous frequency of SWD is known to be maximal at the beginning, gradually decreases during the seizure and reaches minimum at the end [15, 39]. Around 50–83% of pro-epileptic patterns identified using the proposed algorithm in WAG/Rij rats characterized by the same decrease in the instantaneous frequency. These patterns were recognized on the optional Step 4 and were included in the 4th detection list. Mann-Whitney test statistical analysis indicated that the number of pro-epileptic patterns in which instantaneous frequency was reduced (i.e., included in the 4th detection list) in "epileptic" rats was higher than in "non-epilpetic" at the age of 5 months (p < 0.05). However, the number of patterns with other dynamics of instantaneous frequency was the same in "epileptic" rats and did not change with age.

In general, this section introduces the principles of automatic recognition of proepileptic activity on the EEG in WAG/Rij rats with a genetic predisposition to absence epilepsy by taking into account individual characteristics of paroxysmal oscillatory activity. This approach is based on the continuous wavelet transformation of EEG signal and construction of wavelet surface skeletons. The following criteria for detection of pro-epileptic EEG patterns were used: (i) the main frequency of 5–9 Hz, (ii) duration of more than 1.5 s, (iii) the presence of epileptiform elements in the pattern (i.e., spikes/sharp waves). It was found that the total number of pro-epileptic patterns in WAG/Rij rats significantly decreased from 5 to 7 months of age in both "epileptic" and "non-epileptic" subjects. This suggests that the pro-epileptic activity in "epileptic" rats might develop in mature spike-wave seizures (i.e., transformed into SWD), but in "non-epileptic" rats it might be eliminated (i.e., transformed into healthy oscillatory pattern). A decrease of the instantaneous frequency during spikewave seizures is known from the literature [15, 39], and this property was used as an additional criterion characterizing pro-epileptic EEG patterns in WAG/Rij rats. It was found that the number of pro-epileptic patterns in which instantaneous frequency decreased in "epileptic" rats was higher than in "non-epileptic" rats. Therefore, negative dynamics of instantaneous frequency during the pro-epileptic pattern relates to the presence of epileptic discharges, and it can be considered as a sign of bad prognosis.

## 7.6 Brain-Computer Interface for On-Line Diagnostics of Epileptic Seizures

In Sect. 7.3, we described an *off-line* method for automatic identification and delimiting of epileptic EEG epochs. It is restricted to use with complete (previously recorded) time series. Here we present a description and an experimental verification of a real-time algorithm for detection of SWDs in the EEGs of a genetic rodent model (WAG/Rij rats).

#### 7.6.1 On-Line SWD Detection Algorithm

Diverse EEG patterns belonging to different classes may have similar spectral composition [58, 98]. Therefore, a method used for pattern recognition should adequately distinguish among such patterns with similar frequency content and, in addition, must be numerically efficient to allow hardware or software implementation for on-line EEG analysis [86, 98, 140].

Another significant problem stemming from the on-line data processing is a lack of knowledge of the full time realization. Indeed, at a given time instant  $t_0$ , only the preceding time instants ( $t \le t_0$ ) are available for the analysis. Thus, the problem of developing a universal method for diagnosis of oscillatory patterns in real-time is extremely complex. Therefore, in this section we provide a brief description of an already existing and tested method for on-line detection of spike–wave discharges [63, 96, 97].

The first problem mentioned above can be reasonably solved by using a complex Morlet wavelet. This wavelet offers optimal selectivity in terms of time-spectral resolution and can distinguish similar oscillatory patterns. The second problem (data restriction to  $t \le t^*$ ) can be solved if we select a mother wavelet function  $\psi$  that decays rapidly in time. Then the definition (2.18) can be replaced by (2.44) with high enough accuracy (for details, see Sect. 2.2.3). In other words, to calculate the wavelet coefficients for a given time scale *s* at some fixed time instant  $t^*$ , we need to have a fragment of signal with  $t \in [t^* - T, t^* + T]$ . Therefore, we can only determine whether there was an SWD at  $t = t^*$  when we reach time  $t = t^* + T$ , i.e., with a time lag *T*, which is essentially unremovable using this method. The value of *T* depends on the mother wavelet and the time scale *s* (wavelet frequency  $f_s \approx 1/s$ ). In the case of the Morlet wavelet, we can take  $T \approx 4$  s.

Let us now discuss the key features of an on-line diagnostic algorithm for detecting oscillatory patterns in EEGs, as proposed in [96, 97]. The method is based on the approach considered in Sect. 7.3. First, the wavelet transform (2.44) is calculated using the Morlet wavelet with central frequency  $\omega_0 = 2\pi$  rad/s. Second, a measure of the spectral energy within the frequency range  $F_{\text{SWD}}$  is introduced [see also (7.1)]:

$$w_{F_{\rm SWD}}(t) = \int_{F_{\rm SWD}} |W(t, f)| \, \mathrm{d}f \, . \tag{7.20}$$

This is the integral measure of the absolute value of wavelet coefficients over the given frequency domain, i.e., the *wavelet power over domain* (WPOD).

As in Sect. 7.3, we selected the gamma frequency band  $F_{SWD} = 30-80$  Hz, since it is the most characteristic for distinguishing SWDs and spindle waves. The wavelet power  $w_{F_{SWD}}(t)$  in this frequency range can be calculated with a delay of about  $4 \text{ s} \approx 4 \times 1/30 \approx 0.14$  s. If  $w_{F_{SWD}}(t)$  shows a drastic growth, then we can mark this time instant as the beginning of an SWD. A similarly rapid decrease in the power marks the end of the SWD. Thus fulfillment of the condition  $w_{F_{SWD}}(t) > E_k$  is the basic guideline for detecting an SWD at time  $t = t_{\text{current}} - T$ .



**Fig. 7.19** a Fragment of an EEG containing a single pulse of high amplitude (*arrow* at 3 s) and a spike-wave discharge (5.5–12.3 s). **b** Instantaneous WPOD energy  $w_{F_{SWD}}(t)$  with an artificial peak (*arrow*) corresponding to the single pulse in the EEG ( $F_{SWD} = 30-80$  Hz). **c** The artificial peak is attenuated in the time-averaged measure  $\langle w_{F_{SWD}}(t) \rangle$  ( $\Delta = 0.2$  s)

We note that an EEG is a complex signal, which may have relatively short bursts provoked by motion artifacts, K-complexes, and other events [142]. Then the spectrum of bursting activity can overlap with  $F_{SWD}$  and we can observe a rapid growth of the WPOD measure  $w_{F_{SWD}}(t)$ , which may exceed the threshold  $E_k$ . Thus some bursting activity in EEG can lead to false detection of spike-wave discharges, i.e., *false positive errors* (FP). Figure 7.19a and b show an example of this situation. An EEG epoch has an SWD and an artifact (arrow). Then the WPOD  $w_{F_{SWD}}(t)$  calculated over this epoch shows a strong pulse corresponding to the artifact. The pulse amplitude is significantly higher than the background oscillations of  $w_{F_{SWD}}(t)$  and hence, during on-line processing, we could wrongly detect such a pulse as the marker of an SWD event.

To reduce the number of such false positive detections, we could use a higher value of the threshold  $E_k$ . However, this may not help (as in Fig. 7.19b), but merely increase the number of false negatives. Besides, a higher threshold would introduce an additional time delay into the onset of the SWD. Another way to reduce the number of false positives is to consider an averaged value of  $w_{F_{SWD}}(t)$  over some smoothing window  $\Delta$ :

$$\langle w_{F_{\text{SWD}}}(t) \rangle = \frac{1}{\Delta} \int_{t-\Delta/2}^{t+\Delta/2} w_{F_{\text{SWD}}}(\tau) \, \mathrm{d}\tau \;.$$
 (7.21)

Then the criterion for detecting a spike-wave discharge is



**Fig. 7.20** Flowchart of the on-line algorithm for detecting epileptic seizures (OSDS). w(t) is the WPOD,  $E_k$  is the threshold for the WPOD,  $x_i$  and  $y_i$  are the discrete values of the EEG signal and preliminary calculated mother wavelet function, respectively, and log 0 and log 1 are the logical zero (absence of SWD) and one (presence of SWD) of the algorithm output, respectively

$$\left\langle w_{F_{\text{SWD}}}(t) \right\rangle > E_k \ . \tag{7.22}$$

Figure 7.19c shows this new measure  $\langle w_{F_{SWD}}(t) \rangle$ . One can see that the artificial peak becomes much lower, so we can detect SWD events with higher accuracy and exclude incidental short EEG events. Increasing the averaging window  $\Delta$ , we can achieve more accurate detection (better smoothing of short artificial events). However, averaging introduces an additional delay of order  $\Delta/2 = 0.1$  s into the detection of SWD patterns. There is thus a tradeoff between detection accuracy and detection delay.

Figure 7.20 shows a flowchart for implementation of the on-line method for detecting SWDs, called OSDS. To compute the wavelet transform we used the fast method based on the vector product (2.47) discussed in Sect. 2.2.3.1. The program calculates the corresponding wavelet power for a given frequency range (30–80 Hz) each time a new data sample is acquired (e.g., every 2 ms for 500 Hz sampling rate). The calculated power is compared with a threshold and a binary output (presence/absence of SWD) is generated. More precisely, the program performs the wavelet transform for 15 scales (corresponding to frequencies equally distributed in the range 30–80 Hz). Our results show that increasing the number of scales above 15 provides no significant improvement in the algorithm sensitivity, but rather requires additional calculation resources (the calculation time must be kept within 2 ms). The sum of the calculated wavelet power values provides  $w_{F_{SWD}}(t)$ , which is further averaged and compared to the threshold  $E_k$ . The result of the comparison is assigned to the output logical variable

$$V_{\text{out}}(t) \in \left\{ \log 0, \log 1 \right\}.$$

At the beginning, it is set to logical zero, i.e.,  $V_{\text{out}} = \log 0$ . As soon as  $w_{F_{\text{SWD}}}(t)$  exceeds the threshold  $E_k$ , the output is set to logical one, i.e.,  $V_{\text{out}} = \log 1$ . The output is maintained until  $w_{F_{\text{SWD}}}(t)$  goes below  $E_k$ , at which point the output is switched to logical zero, i.e.,  $V_{\text{out}} = \log 0$ .

## 7.6.2 Experimental Verification of the Algorithm and On-Line SWD Diagnostics

To test the algorithm, we used differential recordings made in eight rats [97]. The EEG was continuously acquired over 5 h during the light phase (5-15h). In addition, two of the 8 rats were subject to continuous 24 h recording. Rats were connected to EEG recording leads attached to a swivel contact, which allows registration of the EEG in freely moving animals. Signals were recorded using the WINDAQ recording system (DATAQ Instruments, Akron, OH, USA, www.dataq.com) with a constant sample rate of 500 Hz. Before digitizing, the EEG signal was amplified and filtered by a band pass filter with cutoff frequencies set at 1 and 100 Hz. In addition, a 50 Hz notch filter was applied to reject power line hum. The digitized signal was sent to the OSDS (Fig. 7.20).

Figure 7.21 shows a typical example of on-line SWD detection. Whenever the WPOD  $w_{F_{SWD}}(t)$  exceeds the threshold  $E_k = 0.8$ , an SWD is detected (Fig. 7.21b). The threshold value  $E_k$  should be adjusted for each animal individually. A good initial guess is 2.5–3.5 times the mean WPOD value at normal activity (i.e., non-epileptic background). The algorithm output  $V_{out}(t)$  (Fig. 7.21c) is sent to an additional channel of the WINDAQ recording system. This channel has a digital-analog converter (DAC) with two possible levels: *high* (log 1 := +2.5 V) and *low* (log 0 := -2.5 V).

The output signal  $V_{out}(t)$  of the OSDS delimits SWD events and, in general, can also control some external device, such as a generator sending some stimuli to the animal's brain. Thus an organized feedback loop can be used, e.g., for studying the effect of external stimuli on epileptic focus, synchronized with the onset of the epileptic neuronal activity.

In experiments, we determined the most adequate individual threshold values  $E_k$  using off-line analysis of EEG traces for each rat. One hour EEG fragments were



**Fig. 7.21** On-line detection of SWDs. **a** Example of an EEG epoch containing SWDs. **b** WPOD averaged power in the 30–80 Hz band. **c** Output of the detection algorithm (OSDS)

Rat #	Threshold	Window size (data points)	No of visual detections	No of automated detections			Quality of on-line detections	
				ТР	FP	FN	Sensitivity $\beta$ (%)	Precision δ (%)
1	0.6	600	101	101	3	0	100	97.1
2	0.7	500	29	29	0	0	100	100
3	0.7	500	43	43	2	0	100	95.6
4	0.65	600	66	66	1	0	100	98.5
5	0.8	500	44	44	2	0	100	95.7
6	0.6	500	66	66	4	0	100	94.3
7	0.85	500	115	115	3	0	100	97.5
8	0.9	600	56	58	2	0	100	96.6
Mean±SD		65 ±29	65 ±29	$2.1 \pm 1.3$	$0.0 \pm 0.0$	$100 \pm 0$	$96.9 \pm 1.8$	

Table 7.4 On-line detection rates of spike-wave discharges in 8 WAG/Rij rats recorded for 5 h

analyzed and  $E_k$  was tuned.  $E_k$  varied between 0.6 and 1.0 for different animals. This approach allowed us to achieve perfect sensitivity to SWDs for all animals, that is,  $\delta =$ 100% (Table 7.4), i.e., there were no false negative detections. The mean precision was  $\beta = 96.9\%$  (range 94.3–100%, n = 8) in the 5 h data set. The average time needed for SWD detection was  $1.0 \pm 0.55$  s following the SWD onset (smoothing window size 500 data points and sample rate 500 samples/s). The SWD detection time is determined primarily by the length of the smoothing window and can be reduced. Let us now consider the errors in the OSDS algorithm. False negative (FN) errors (SWD events skipped by the algorithm) appear in the first place due to small variations in the dynamics of the brain in response to changes in environmental conditions. In relatively short experiments with properly chosen parameters, FN errors do not appear (Table 7.4). In long-term experiments, FN events are rare and can be observed when the physiological state of the animal changes significantly. The first missed events begin to appear 4–8h after the beginning of the EEG recording. Such events tend to group together, i.e., within a few hours after registration of the SWD with subthreshold WPOD value, the probability of finding another one becomes greater. At the same time, the total number of unrecognized SWD events remains small (<1% of all detected SWDs).



**Fig. 7.22** Illustrative examples of typical complexes in EEG (intermediate states) falsely detected as SWDs and corresponding dynamics of the averaged WPOD  $\langle w(t) \rangle$  versus time

Another class of errors is false positives (FP), i.e., events wrongly detected as being SWDs. Figure 7.22 illustrates detection of an underdeveloped SWD. Despite the fact that the increase in the WPOD in this case was not as large as during a genuine SWD, it was enough to exceed the threshold and hence lead to false detection of an SWD event. Visual inspection of FP events showed that they correspond to *intermediate states* or spiky phenomena [41]. It should be noted that, by increasing the size  $\Delta$  of the smoothing window, the number of false positives can be reduced significantly. However, this will be achieved at the cost of increasing the time lag required for reliable detection of SWD events. The results shown in Table 7.4 were obtained through a compromise between speed of detection and number of FP errors.

## 7.7 Brain Stimulation Brain-Computer Interface for Prediction and Prevention of Epileptic Seizures

The ultimate goal of epileptology is the complete abolishment of epileptic seizures. This might be achieved by a on-line seizure prediction system in combination with a way to interfere [36, 54, 93, 117]. A long standing opinion is, that SWDs generated within the cortico-thalamo-cortical network [12, 51, 101] are unpredictable and suddenly arise from a normal background EEG [117]. At the same time, off-line analysis of available EEG data sets with advanced signal analysis techniques including wavelet-based methods revealed that some changes in communication between cortex and some thalamic nuclei can already be seen up to 2 s before seizure onset [81, 83], generalized epileptic seizures are the extreme events emerging from instability accompanied by preictal noise amplification [38, 104], and that SWDs are preceded by delta/theta precursors in the cortico-thalamo-cortical network [80]. In the current work we present a new seizure prediction algorithm, which assesses in real-time the synchoronicity between brain structures and by this automatically predicts SWD. In this Section we consider the wavelet-based real-time absence seizure prediction algorithm and based on them absence seizure control by a closed-loop precursor detection [84].

#### 7.7.1 Precursor Wavelet-Based On-Line Detection

The algorithm's estimation of synchronicity between brain structures is based on the analysis of both the synchronization of the electrical activity of the neurons in the vicinity of the single electrode, local synchronization, and the synchronization between the neuronal ensembles of cortex and thalamus, global synchronization [85]. This is achieved via the investigation of a multichannel EEG from cortex and thalamus. Within the framework of the algorithm, each EEG recording was considered



**Fig. 7.23** a Schematic representation of the experiments with a rat. **b** The set of ECoG recordings taken from subgranular layers 4 (Ctx4) and 5 (Ctx5) of the somatosensory cortex and postero/lateral thalamus (Th) before and during onset of the epileptic spike-wave discharge (SWD). **c** Histological verification of the electrode location in the somatosensory cortex (S1) and postero/lateral thalamus (Th). Reprinted from [105]

as the macroscopic characteristic of the ensemble of interacting cells, located in the vicinity of the recording electrode.

The seizure prediction algorithm was based on the ECoG signals recorded by three electrodes in the cortex and the thalamus, as shown in Fig. 7.23. The obtained ECoG recordings were simultaneously processed with the help of CWT with the specially designed mother complex function

$$\psi_0(\eta) = \pi^{1/4} e^{2\pi i \eta} e^{-5\eta^4},\tag{7.23}$$

and the corresponding wavelet energies  $w_i(s, t)$  were considered at every moment of time. The used mother wavelet function (7.23) is the modification of the classical Morlet wavelet (2.36), which is characterized by a better localization in time in comparison with the standard Morlet wavelet and, therefore is more suitable for online diagnostics due to better temporal resolution of local peculiarities of the EEG signal [78]. Figure 7.24 illustrates the dependency of the window length on the value of frequency belonging to the analyzed frequency band (3, 20) Hz is shown both for Morlet wavelet  $\delta_1$  and modified wavelet  $\delta_2$ . It is seen that use of modified wavelet allows to significantly reduce the window length and, therefore the delay. It is also seen that the maximal window size, used for the calculation of the wavelet spectrum, is about 600 ms. The view of wavelet function of this case is shown for both Morlet wavelet and modified wavelet. The delay is shown to be reduced from 1.2 to 0.3 s which is enough to on-line detect precursor pattern.

With the proposed wavelet the distribution of the wavelet energy (2.33) was calculated during a 600-ms window for the frequency range (3, 20) Hz. The resulted



**Fig. 7.24** (Left)The dependencies of the window length  $\delta_1$  and  $\delta_2$  on the frequency within the analyzed frequency band (3, 20) Hz for the Morlet and modified wavelet (7.23), respectively. (Top) Illustration of the calculation of the wavelet coefficient for f = 3 Hz (largest window length) with the help of Morlet wavelet (top) and modified wavelet (bottom). Based on the data from [84]

measure of wavelet spectra of multichannel EEG, G(s, t), was found as a product of the spectra obtained for all EEG recordings of the set

$$G(s,t) = E_1(s,t) \times E_2(s,t) \times E_3(s,t)$$
(7.24)

at the every moment of time. Subscript 1, 2 and 3 represented two subgranual cortical signals from the somatosensory cortex and from the thalamic PO as shown in Fig. 7.23.

The analysis of the wavelet power spectra (Fig. 7.25b) of a single preictal EEG channel (Fig. 7.25a), shows that the early signs of synchronization, developing within each considered neural ensemble, occurred several seconds before SWD onset and represented itself by a local increase of the wavelet energy in the 5–10 Hz band. Along with local synchronization, interactions between the cortex and thalamus increased and considering the power G(s, t) (7.24) (Fig. 7.25c) an isolated pattern (circles in Fig. 7.25c) corresponding with preictal precursor activity was noticed. Indeed, considering the momentary distributions of the wavelet energy of each EEG, taken for 4 (I) seconds and for 1 second (II) before the onset of SWD, one can see in (Fig. 7.25d) that as the beginning of the SWD is approaching, the increase of wavelet energy takes place in the timescale region  $0.1-0.2 \text{ Hz}^{-1}$  (or equivalent frequency 5–10 Hz band), and the main spectral components of the considered EEG signals start to synchronize (II).

In order to automatically recognize the precursor the value  $G_{\Delta s_j}$ , corresponded to the spectral energy of the timescales  $\Delta s_j$ , were given by the equation



**Fig. 7.25 a** The set of EEG recordings taken from subgranular layers 4 (Ctx4) and 5 (Ctx5) of the somatosensory cortex and postero/lateral thalamus (PO). **b** The CWT energy, corresponded to the considered EEG, distributed over the range of the timescales s = 1/f. **c** The resulting surface *G* (7.24). The oscillatory pattern, which is considered as a precursor, is circled. **d** The momentary distributions of the wavelet energy, taken for the 4 s (I) and 1 s (II) before seizure onset. Based on the data from [84]

$$G_{\Delta s_j}(t) = \frac{1}{\Delta s_j} \int_{s \in \Delta s_j} \frac{1}{T} \int_{t-T}^{T} G(s,t) \, ds \, dt, \quad j = 1, \, 2, \, 3,$$
(7.25)

where the integration was performed both over the range of timescales and the time interval T = 500 ms chosen experimentally considering the minimal duration of the precursor.

At the first step the wavelet energy  $G_{\Delta s_2}$ , corresponded to the frequency band (5, 10) Hz, was considered. It was found that the value of  $G_{\Delta s_2}$  increased during the onset of the seizure. According to this, the threshold value  $G_{th}$  was taken into consideration. This value was determined for the individual rat according to the preliminary analysis of the wavelet energy, corresponded to the preictal state and to the different types of background activity. As the result the possibility to set the threshold energy which exceeded the energy of wakefulness states, but, at the same time remained less then the energy of the preictal state was found and the precursors were detected via the condition  $G_{\Delta s_2} > G_{th}$ . Unfortunately, such criterion caused the large amount of false alarms during the sleep due to the increase of the power of EEG signals. In order to reduce the number of false alarms caused by any other patterns of synchronized neuronal activity during sleep (first-of-all, the sleep spindles) the additional "sleep criterion" was introduced. This criterion included the simultaneous consideration of the three ranges of timescales corresponding to the common patterns of synchronic neuron activity preceded the seizure onset [80]:

- $\Delta s_1$ —the range 7–20 Hz of sleep spindles;
- $\Delta s_2$ —the range 5–10 Hz of theta/alpha precursors;
- $\Delta s_3$ —the range 3–5 Hz of low-frequency oscillations (delta precursors).

For these ranges  $\Delta s_j$  the values of mean energy  $G_{\Delta s_j}$  was calculated using integral (7.25).

According to Ref. [84] the using the threshold value  $G_{th}$  one can automatically detect the precursor with the help of three addition conditions: (i)  $G_{\Delta s_2}(t) > G_{th}$ , (ii)  $G_{\Delta s_2}(t) > G_{\Delta s_1}(t)$ , and (iii)  $G_{\Delta s_2}(t) > G_{\Delta s_3}(t)$ . The conditions (ii) and (iii) were used to distinguish the precursor events from sleep spindles and low-frequency delta activity. Similar to the seizure, these types of activities are also induced by synchronous neuronal dynamics, but have higher (up to 20 Hz) and lower (up to 5 Hz) frequencies, respectively.

#### 7.7.2 Absence Seizure Control by a Brain Computer Interface

The described in the previous Sect. 7.7.1 algorithm was subsequently implemented in a closed-loop deep-brain stimulation system. In this system the EEG of a freely moving WAG/Rij rats, recorded from two cortical and a thalamic site, were fed via an amplifier to an acquisition system where they were analyzed on its level of synchronicity in real time by the prediction algorithm. Whenever the level of



**Fig. 7.26** a The experimental setup of the brain-computer interface. The set of analog inputs 1–6 of the acquisition hardware correspond to the EEG recordings (1–3), the prediction marker (4), the stimulation pulse train of 1 s (5) and the signal from the passive infrared registration system monitor sensor (PIR) for movement detection (6), respectively. The dashed line corresponds to the digital input of the PC, the feedback is shown by the shadow. **b** The prediction (upper case) and prevention (lower case) of the absence seizure by delivering a pulse train of 1.0 s duration. Based on the data from [84]

synchronicity exceeded a preset threshold value, a marker was set in an additional channel of the recording system and a constant current stimulator was triggered to deliver a 1 s lasting pulse train of 130 Hz and low intensity to the rat (see Fig. 7.26a, b).

The pulse train of 130 Hz might prevent the predicted SWD. Previously it was established that this pulse train was rather effective (close to 90% in interrupting an ongoing SWD) [136]. Comparison of seizure activity between a 1 h baseline recording, in which no stimulation was applied, to seizure activity during a one hour stimulation session showed that seizure activity was significantly reduced by 72% ( $\pm 10\%$ ) (F(1, 5) = 48.52, p < 0.001) (Fig. 7.27a). The reduction in seizure



activity can be attributed to a combination of SWD prediction and prevention (in 45% of cases) and SWD detection and interruption. In support for the conclusion that the reduction was not only the result of pure detection and disruption of SWD we again refer to the individual data, where in two rats reduction levels of up to 98% and 100% were achieved demonstrating total prevention of SWD activity by prediction and stimulation.

In addition, inspection of corresponding wavelet energies, calculated for successful SWD prediction and prevention periods, depicted a strong, momentary, increase in wavelet energy within the 6–8 Hz frequency band signaling the development of an SWD in its preictal state, and triggering the delivery of an electrical pulse train. During and following high frequency stimulation the wavelet energy within this frequency band drastically drops, indicating that the electrical pulse train efficiently desynchronized the EEG and by this successfully prevented the generation of the hypersynchronous SWD (see Fig. 7.28).

To investigate whether the remaining false positive detections, which also triggered the delivery of an electrical pulse train might have affected behaviour of the animals, we compared the activity level of rats between baseline and stimulation hour, which was measured by a movement detection system. There was no difference between activity of the rats during baseline and stimulation session (Fig. 7.27b) (F(1, 5) = 0.476, p = 0.521), suggesting that the by stimulation induced decrease in SWD time cannot be explained by an increase in behavioural activity. Furthermore, no other type of apparent activity was observed in the EEG recordings of the animal, so that, given the low intensity stimulation provided to prevent and disrupt the SWD and given the relative short stimulation session, it can be regarded as a safe intervention strategy.

So, in contrast to the long standing opinions, SWD can be predicted to a substantial degree and that such a prediction algorithm can successfully be implemented in a closed-loop deep brain stimulation system which is able to greatly reduce seizure activity based on a combination of seizure prediction and prevention and seizure detection and disruption. The relative high number of false positive predictions indicates that synchronization between brain structures is not unique for the generation of



Fig. 7.28 The seizure prevention by means of electrical stimulation with the pulse duration: the EEG signals, taken from postero/lateral thalamus (PO) and cortex layers (a), the distributions of the wavelet energy G (b) and the pulse train (c) (the structure of pulse is also shown in detail). Based on the data from [84]

an SWD. Probably the brain also "tries" to generate an SWD at the periods indicated by false positive detections but fails to do so since another unknown requirement for SWD generation is not met. In line with this, 5–9 Hz oscillations have been reported to preceded SWD in GAERS, another rat model of absence epilepsy, while not all of these 5–9 Hz oscillations are followed by SWD [100, 102].

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## Chapter 8 Analysis of Visual Sensory Processing in the Brain and Brain-Computer Interfaces for Human Attention Control



**Abstract** This chapter describes using wavelet analysis to study mechanisms of visual perception. First, we introduce an ambiguous visual stimulus, the Necker cube, a useful visual perception analysis tool. Second, we demonstrate how the wavelet-based methods reveal the local and network properties of the percept-related brain activity. Then, we considered the effect of the human condition (motivation and alertness) on the perceptive process. Finally, we review the basic principles of the brain-computer interfaces that use the wavelet-based algorithm to evaluate the human state in visual perception tasks.

## 8.1 Introduction

Perception and processing of sensory information are essential brain functions, ensuring our interaction with the environment. Humans and animals receive sensory inputs of the different modalities (tactile, visual, auditory, etc.), process them, and use them in the decision-making process, a process known as *perceptual decision-making* [36]. When performing perceptual-decision-making tasks, the brain dynamically adjusts its functional network structure to maintain optimal behavioral performance under the increasing cognitive demand [20, 83, 101]. Modern neurophysiological studies emphasize the leading role of functional connectivity in human cognition, and behavioral performance [106]. According to the functional magnetic resonance imaging (fMRI) studies, the whole-brain network activity is generated through the interaction of multiple functional subnetworks during either a resting state or task accomplishing. These functional subnetworks include a dorsal attention network, a frontoparietal network, an executive control network, a default mode network, etc. [112]. Although functional networks have different anatomical locations, they interact with each other and overlap during task accomplishing [121].

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Performance and neural activity during the sensory-processing tasks depend on the person's internal state, attention, and fatigue. In particular, the rest-state functional connectivity can predict the subject's ability to maintain sustained attention during demanding tasks [89]. Next, fatigue causes reshaping the network structure, making the brain regions more segregated and their communication less effective [56]. Increased cognitive demands result in a decrease in network modularity; the default mode network enhances its connectivity with other networks, while the connectivity inside the network itself decreases [27].

These processes also induce changes in the time-frequency properties of noninvasive EEG signals. EEG is composed of various rhythms of neural activity, e.g.  $\delta$ -band (1–5 Hz),  $\theta$ -band (5–8 Hz),  $\alpha$ -band (8–12 Hz),  $\beta$ -band (15–30 Hz) and  $\gamma$ band (>30 Hz). According to neurophysiological studies, these rhythms contribute to the coordination of neuronal activity in remote brain regions [30, 60]. The lowfrequency  $\theta$ -rhythm modulates electrical brain activity at the high-frequency  $\gamma$ -band of the electrocorticogram (ECoG) [13]. Apart from the  $\theta$ -band, according to [30], the low-frequency  $\alpha$ - and  $\beta$ -band neuronal activity in the visual cortex controls the neuronal activity in the  $\gamma$ -band. The functional connectivity between neuronal ensembles causes correlation or synchronization between the recorded EEG signals in the different frequency bands [30, 60]. As stated in [65], neuronal populations in remote brain regions interact in the different frequency bands differently. Recent studies [10, 73] demonstrate that during the performance of visual tasks, neural populations in the visual cortex communicate at frequencies in the joint  $\alpha$ ,  $\beta$  (830 Hz) and  $\gamma$  (5070 Hz) ranges. Moreover, an analysis of the functional connectivity between regions of the parieto-occipital cortex performed on the EEG sensory level reveals a different connectivity structure in separated  $\alpha$ - and  $\beta$ -frequency bands. In contrast, the functional connectivity in the  $\beta$ -band is affected by visual information complexity [67]. Along with the neuronal communication in the visual cortex, accomplishing the visual task also requires communication between the remote cortical regions. Thus, during visual information processing,  $\delta$ -activity in the frontal area and  $\alpha$ -activity in the parieto-occipital area are functionally coupled and jointly guide visual perception to integrate sensory evidence with current task demands [37]. During a sustained attention task, long-range functional connectivity between different parts of the frontoparietal network is mediated by oscillations in the  $\theta$ -band and connectivity within these areas is subserved by  $\gamma$ -band oscillations [99]. The attention-related functional connectivity also presents in the frontoparietal cortex in different frequency ranges [17, 97].

Thus, perceptual decision-making task requires coordination of neural activity across multiple brain areas. Coordination of neuronal activity in particular regions is subserved by high-frequency rhythms, while the coordination of neural activity between remote areas relies on low-frequency oscillations. Functional interactions dynamically reconfigure the neuronal network structure to maintain sustained attention and avoid fatigue and distraction during task performance.

This chapter focuses on the recent results of the time-frequency EEG analysis during the perceptual decision-making task, which requires sustained attention. Generally, sustained attention refers to focusing on relevant stimuli with repeated presentation over extended periods. Following [74], sustained attention tasks often involve long series of exhibitions of target and non-target stimuli on computer screens. The participants must respond to the targets and refrain from responding to the nontarget stimuli. Here, we considered a perceptual decision-making task implying a binary classification of a large number of consistently presented ambiguous visual stimuli (Necker cubes) with different degree of ambiguity [1, 41, 68]. In line with Denison et al. [21], we suppose that processing each stimulus depends on attention at the moment of its presentation. If the stimuli are presented repeatedly with a brief interval, the subject must continuously maintain a high level of attention to respond to the stimuli. Usually, perceptual decision-making is not viewed as a classical cognitive domain like attention or memory. At the same time, this is mostly true for near-threshold stimuli [118] or unambiguous stimuli when the subject has to choose between two different stimuli. In turn, ambiguous stimuli cause uncertainty in decision-making when ambiguity is high [41], and their interpretation appears to be a cognitive decision process [41].

The neuronal activity in  $\alpha$ - and  $\beta$ -bands represents two stages: a sensoryprocessing and a decision-making [73, 98]. During the former stage,  $\alpha$ - and  $\beta$ band activity is involved in top-down stimulus processing and subserves the neural interaction within the visual cortex [73]. The  $\beta$ -band activity is also shown [98] to coordinate the neuronal activity in the occipital and prefrontal areas during visual stimulus processing. During the latter stage, the  $\beta$ -band activity subserves the neural interactions within the fronto-parietal network [15, 16]. The decision accuracy also correlates with the power of the frontoparietal  $\beta$ -band activity registered during the decision-making stage [103]. A wide body of literature shows that both  $\alpha$  and  $\beta$ -band activity is relevant to attention in general (i.e., not restricted to the visual stimuli processing [2, 5, 6, 31]). Attention modulates the prestimulus  $\alpha$ - and  $\beta$ -band power [6, 31, 59] and affects the decision accuracy. Thus, either medium or low  $\alpha$ - and high  $\beta$ -band power during the prestimulus period is beneficial for sensory perception [31, 113]. According to [35], not only the power but the prestimulus EEG phase coupling in the  $\alpha$ - and  $\beta$ -bands also affects visual perception performance. Namely, better performance is associated with low phase coupling in the  $\alpha$ -band and high phase coupling in the  $\beta$ -band.

Having summarized, the neural activity in the  $\alpha$ - and  $\beta$ -bands subserves perceptual decision-making process and reflects attentional modulation. Thus, we mostly focus on these bands and describe the wavelet-based methods to estimate neural activity in the single areas and analyze their functional interactions. We also review the wavelet-based algorithms to evaluate attention in the real-time domain. Finally, we discuss the possibility of using wavelets in the brain-computer interfaces that control attention in visual processing tasks.

#### 8.2 Ambigous Stimuli as a Tool to Study Visual Perception

A practical approach to study visual perception uses the stimuli whose intensity lies near a perception threshold. The threshold can reflect the value of stimulus intensity, at which each subject detects 50% of the presented stimuli [25].

Another approach includes more complex stimuli which along with simple detection, require their classification based on the brief analysis of their morphology. In this context the threshold parameter reflects the complexity of stimuli classification [68].

This chapter describes the wavelet-based studies of visual perception that use Necker cube as an ambiguous visual stimulus [43, 52]. Let us consider this stimulus in detail. A subject without perceptual abnormalities interprets the Necker cube as a left- or right-oriented 3D-object, depending on the inner edges' contrast. The contrast of three middle lines centered in the left middle corner serve as a control parameter *a*, where a = 1 and a = 0 corresponded to 0 (black) and 255 (white) pixels' luminance according to 8-bit gray-scale palette. Therefore, we defined the control parameter as a = g/255, where g was the brightness of the inner lines.

Figure 8.1a demonstrates the Necker cube images with eight different values of the control parameter. Half of them,  $a = \{0.15, 0.25, 0.4, 0.45\}$  correspond to the left-oriented and another half,  $a = \{0.55, 0.6, 0.75, 0.85\}$ —to the right-oriented cubes.

For  $a \approx 0$  and  $a \approx 1$ , the stimulus has a clearly identified left and right orientation. For  $a \approx 0.5$ , the stimulus became ambiguous. This chapter does not consider the Necker cube image with a = 0.5. In this situation, processing relies on the endogenous factors rather than on the stimulus features [24].



**Fig. 8.1** a Set of visual stimuli, Necker cubes, with different degrees of ambiguity, *a*. b Schematic illustration of the experimental sessions.  $\tau_i$  is the duration of *i*th stimulus presentation,  $\gamma_i$  is the time of the abstract image presentation between *i*th and (i + 1)th stimuli. RT is the response time



**Fig. 8.2** a Response time (RT) to LA and HA stimuli (\*\*\* p < 0.001, *t*-test). **b** Median presentation times of LA and HA stimuli. **c** Error-rate (ER) of LA and HA stimuli processing (\*\*\* p < 0.001, Wilcoxon test). Group data are shown as means±SD and individual values

Each Necker cube image is drawn by black and gray lines located at the center of the computer screen on a white background. Subjects usually get instructions to quickly define stimulus orientation and press the left or right key on the joystick.

The Necker cubes paradigm allows studying external (bottom-up) and the internal (top-down) effects on the perception. Figure 8.1 evidences that LA left- and right-oriented cubes have different edges structure. In the left-oriented stimuli, the observer sees three middle edges centered in the right upper corner, while in the rightoriented stimuli, they see mostly ones centered in the left lower corner. In contrast, in the HA left- and right-oriented cubes, all inner edges have the same contrast, and the observer sees them all simultaneously. Thus, perception of LA stimuli mostly relies on the bottom-up mechanisms and perception of HA stimuli—on the top-down mechanisms.

To study the effect of ambiguity on the perceptual process in the recent work [64] 400 Necker cube images appeared in random order, each stimulus with a particular ambiguity *a* was presented 50 times. The whole experiment lasted 40 min, including 150 s recordings of the resting-state EEG before and after the main part. The *i*th stimulus was presented during a time interval  $\tau_i$ , followed by the abstract image presentation for a time interval of  $\gamma_i$  (Fig. 8.1b). The duration of the stimulus exhibition varied in the range of 1–1.5 s. Lastly, to draw away the observer's attention and make the perception of the next stimulus independent of the previous one, different abstract pictures were exhibited for 3–5 s between subsequent demonstrations of the Necker cube images. The response time (RT), a time interval between the stimulus onset and key pressing, determines processing speed and serves as the behavioral response. Besides, response accuracy reflects a match between the actual stimulus orientation and the subject's response.

As a result, subjects responded faster to LA stimuli than HA stimuli (Fig. 8.2a). The stimuli were presented randomly, and the median presentation time of HA and LA Necker cubes was unchanged (Fig. 8.2b). The repeated measures ANOVA used to compare RT for the similar, and opposite orientation of the previous stimulus revealed

an insignificant effect of the previous stimulus orientation ( $F_{1,19} = 1.86$ , p = 0.188) and insignificant interaction effect of ambiguity×orientation ( $F_{1,19} = 0.434$ , p = 0.518). The results confirmed that the stimulus presentation times and the previous stimulus (ambiguity and orientation) are randomized between the conditions and, therefore, did not affect the RT bias between LA and HA stimuli.

Finally, there was no correlation between the age and RT to HA stimuli: r(20) =-0.24, p = 0.3 and LA stimuli: r(20) = -0.31, p = 0.17. RT was similar for males and females for both HA stimuli: t(18) = 0.79, p = 0.436 and LA stimuli: t(18) = 0.96, p = 0.348. ER was higher for HA stimuli (M = 8.95%, SD = 11.5) than for LA stimuli (M=1.65%, SD=2.6): Z = 3.5, p < 0.001 via Wilcoxon test (Fig. 8.2c). It confirmed that subjects' characteristics did not affect their response to the stimuli. At the same time, for a small group of subjects, there is a risk that the individual characteristics of the people (such as sex, age, psychological traits) will influence the perception of ambiguous stimuli and decision-making (See Ref. [96] for the literature review). Thus, the authors expected that another group of younger or older subjects might demonstrate different scores on both behavioral and brain activity levels. The subjects' personality traits also may affect cognitive processes and behavioral performance during cognitive tasks. In particular, the anxiety level is essential for the perception of ambiguous situations. Previous studies documented that people with anxiety tended to interpret ambiguous stimuli negatively (See Ref. [82] for the review). Although, the processing of emotionally neutral Necker cube may be less affected by anxiety. Furthermore, the presented stimuli are not wholly ambiguous; therefore, their interpretation relied not entirely on the endogenous factors but the processing of the stimulus morphology. The existence of objectively decisionrelevant features in the sensory information also reduces endogenous components, such as the observer's state. Nevertheless, to ensure that the observed effects are not affected by the personality traits, the authors recommended the personality traits assessment beforehand.

## 8.3 Local and Integrative Neural Activity During Visual Sensory Processing

The different parts of the cortex process the different types of sensory information. For example, visual stimuli are processed in the occipital and parietal regions, while auditory input is processed in the temporal areas. However, the spatial localization dominants mostly at the earlier (low-level) processing stages lasting for tens of milliseconds. In the latter (high-level) stages, sensory processing is an integrative process that combines various sensory modalities for decision-making.

Simultaneously, sensory processing is affected by top-down human factors such as expectations, memory, and attention. These influences result in the activation of neural assemblies of the prefrontal and parietal cortex. Along with the internal topdown factors, sensory processing may also involve different neuronal ensembles due to the external bottom-up factors. These factors reflect the features of the sensory input. When the sensory information becomes unexpected, complex, or ambiguous, its processing demands more resources and activates neuronal populations in the frontal cortex.

Earlier studies on perceptual decision-making in rodents and monkeys used implanted micro-electrodes and identified spatially localized neuronal activity correlated with their behavioral performance. Simultaneously, a limited number of recording sites precluded revealing the interaction between distinct brain regions coordinating perceptual decisions [34]. More recent work reported on recordings from the multiple units in sensory, parietal, prefrontal, and motor cortex during the perceptual decision-making task [102]. The authors demonstrated that perceptual decisions resulted from complex temporal dynamics, including the coupling between the frontal and posterior cortex. Large-scale cortical interactions play a critical role in human perceptual decision-making. After reviewing plenty of neuroimaging studies, Siegel et al. [103] concluded that perceptual decisions in humans relied on neuronal activity in the high-frequency  $\gamma$  (>50 Hz) and low-frequency  $\beta$  (15–30 Hz) bands. They specified that the localized  $\gamma$ -band activity in the sensorimotor cortex reflected information encoding and motor planning. In turn, large-scale  $\beta$ -band activity across widespread cortical areas coordinated these local networks' activity.

According to the review [103], perceptual decision-making includes two stages, sensory information processing and decision-making. Lange et al. [76] further demonstrated that these stages involved different brain areas in different timeintervals. While the sensory processing occurs in the occipital cortex during 130–320 ms post-stimulus onset, the decision-related process is more prolonged and activates parietal and frontal areas. The other studies [49, 86, 120] reported on temporal dissociation between the sensory processing and decision-making stages for different types of stimuli. Philiastides and Sajda analyzed the influence of sensory evidence quality on the neuronal activity during the processing stage [86]. The authors concluded that the evidence accumulation process began after early visual perception and lasted 290-440 ms depending on the evidence's strength. In the recent study [63], authors considered the decision-making stage of the ambiguous stimuli classification task. They observed that the emergence of a large-scale frontoparietal network in the  $\beta$ -band preceded the perceptual decisions. The authors supposed that the large-scale  $\beta$ -band network served to integrate decision-relevant sensory information into decisions. The extraction of decision-relevant features, in turn, relied on the earlier processing stages, and this process depended on the quality and strength of the sensory evidence.

#### 8.3.1 Local Activity

The local neural activity can be evaluated using wavelet power of the noninvasive EEG signals recorded in different positions on the skull [64]. As described earlier in the book, wavelet analysis provides a signal power with a reasonable resolution

in the time-frequency domain. In turn, wavelet power peaking at the particular EEG sensor may reflect that a neighboring neuronal ensemble participates in the information processing. According to recent works, the neurons communicate due to the phase synchronization of their spiking activity; thus, if their activity becomes phase-locked, the summarized electrical signal's wavelet power increases. We refer this phenomenon to as the local neuronal synchronization [65].

To analyze the wavelet power during the Necker cube processing task, the authors segmented EEG recordings into 400 trials. Each trial corresponded to a single presentation of the Necker cube, including a 1.5 s interval before the presentation and a 0.5 s interval after the button pressing. The wavelet power for each trial was calculated in the frequency range of 4-40 Hz using a Morlet wavelet. The number of cycles *n* for each frequency *f* was defined as n = f. The wavelet analysis was performed in Matlab using the Fieldtrip toolbox [79]. The 0.5 s intervals on each side of the trial were reserved for the wavelet power calculation. As a result, the wavelet power was considered in three time-intervals of interest (TOIs), including prestimulus baseline, TOI1 (from -1.0 to -0.5 s), the stimulus-related activity after the stimulus presentation, TOI2 (from 0 to 0.5 s), and the stimulus-related activity, TOI3 (from RT-0.3 s to RT) preceded the response time. For TOI1 and TOI2, the authors calculated the event-related spectral perturbations (ERSP) via the baseline.

To minimize the additional effect of stimulus orientation, including the lateralization effects associated with the motor response, they considered two conditions: low ambiguity (LA) stimuli, including the Necker cube images with  $a \in$ {0.15, 0.25, 0.75, 0.85} and high ambiguity (HA) stimuli, including the Necker cube images with  $a \in$  {0.4, 0.45, 0.55, 0.6} (See Fig. 8.1a). Each condition included 100 stimuli (25 per each ambiguity, 50 per each orientation).

Finally, each subject's wavelet power was averaged across the trials and contrasted between HA and LA stimuli in three TOIs. Contrasts between conditions were tested for statistical significance using the permutation test in conjunction with clusterbased correction for multiple comparisons.

# 8.3.1.1 A Time-Frequency Evolution of the Wavelel Power During the Visual Stimuli Processing

At first, let us illustrate the evolution of the wavelet power during the stimulus processing. For this reason, we can combine the trials corresponding to LA and HA stimuli. To test how the power change in time, we segmented the stimulus processing period (TOI2) into the 0.05 s intervals and applied the dependent-samples *F*-test to compare ERSP on these intervals. As a result, we observed two significant clusters in the frequency bands of 4–14 Hz and 15.5–21.25 Hz. Based on these results, we defined frequency bands of interest (FOI) as 4–8 Hz ( $\theta$ -band), 8–14 Hz ( $\alpha$ -band), and 15.5–21.25 Hz ( $\beta_1$ -band). For  $\theta$ -band, the observed cluster included EEG sensors in the occipital, parietal, bilateral temporal, parieto-central, central, fronto-central, and frontal areas (Fig. 8.3). For  $\alpha$ -band, cluster included the



**Fig. 8.3** Topograms show the *F*-value and the channel clusters reflecting the significant change of ERSP during 0.5 s post-stimulus onset in the  $\theta$ ,  $\alpha$ , and  $\beta$  bands. Colored lines show the ERSP (group means and 95% confidence interval) averaged over the  $\theta$ ,  $\alpha$ , and  $\beta$  bands during 0.5 s post-stimulus onset

occipital, parietal, temporal, parieto-central, central, right fronto-central, and left frontal sensors (Fig. 8.3). The  $\beta$ -band cluster included sensors in the parietal, right parieto-central, left-lateralized central, left fronto-central, left frontal areas (Fig. 8.3). Analysis of the wavelet power in these clusters revealed that  $\theta$ -band power increased, peaking at 0.35 s post-stimulus onset (Fig. 8.3). The  $\alpha$ - and  $\beta$ -band power decreased gradually over the considered time interval (Fig. 8.3).

The  $\theta$ -band activity characterizes the brain's ability to transfer and coordinate information over large distances [104] and prolonged periods [48]. Thus, high  $\theta$ -band power may confirm the critical role of large-scale networks in visual processing, providing evidence that perception depends not just on the external stimulus. Instead, the brain integrates sensory evidence with other internal constraints, including expectations, recent memories, etc. [116]. In this respect, increasing stimulus-related  $\theta$ -band power across the large-scale cortical regions is supposed to coordinate information in the brain networks, including visual sensory and higher-order areas [72].

The stimulus-related  $\alpha$ -band power decreased over the EEG sensors in the parietooccipital and sensorimotor areas (Fig. 8.3). Reduced stimulus-related  $\alpha$ -band power in the occipital (visual) and parietal (attentional) areas may reflect the primary visual processing, as well as cognitive processing and visual attention [85]. The most significant change of the  $\alpha$ -band power in the motor area was for C3 and C4 electrodes,
manifesting the motor preparation process. The  $\beta$ -band power started decreasing after 0.25 s post-stimulus onset in the fronto-parietal and sensorimotor areas (Fig. 8.3). The high  $\beta$ -band power may reflect a strong endogenous, top-down component [24]. In particular, parietal  $\beta$ -band power grows during the processing of ambiguous stimuli where the percept solely relies on endogenous factors, rather than stimulus features [78]. The fronto-parietal  $\beta$ -band activity during the stimulus processing is a marker of top-down attentional mechanisms that control the accumulation of the decision-relevant sensory information [11]. These top-down mechanisms probably guide the subject's attention to the Necker cube details (e.g., the contrast of the inner edges), supporting a correct decision about its orientation. The fact that  $\beta$ -band activity decreased after 0.25 s might evidence that the information accumulation process was complete and the perceptual ambiguity was unresolved. Finally, reduced sensorimotor  $\beta$ -band power usually reflects movement preparation in the decision-making tasks where the choices are to be communicated via a motor response (See Ref. [108] for the literature review).

In the 0.3 s interval preceding behavioral response (TOI3), there were two significant clusters in  $\theta$  (4–7 Hz) and  $\alpha$  (9.2–12.5 Hz) frequency bands. The observed  $\theta$ -band cluster included EEG sensors in the occipital and parietal areas (Fig. 8.4). The  $\alpha$ -band cluster had sensors bilaterally in the sensorimotor area (Fig. 8.4). The wavelet power in these clusters decreased monotonically within the considered time-interval (Fig. 8.4). The  $\theta$ -band activity waned in the right-lateralized parietal and occipital areas until the subject had pressed the button (Fig. 8.4). It might show that occipito-parietal areas remained activated over the entire processing period, unlike



**Fig. 8.4** Topograms show the *F*-value and the channel clusters reflecting the significant change of ERSP during 0.3 s before the response onset in the  $\theta$  and  $\alpha$  bands. Colored lines show the ERSP (group means and 95% confidence interval) averaged over the  $\theta$  and  $\alpha$  bands during 0.3 s before the response onset

the frontal sites whose activity peaked during the earlier processing stage and rapidly diminished. The  $\alpha$ -band power decreased bilaterally over the sensorimotor electrodes (Fig. 8.4). It allows supposing that the  $\alpha$ -band activity supported only the motor execution on this interval.

#### 8.3.1.2 Effect of the Stimulus Ambiguity

In the next step, we consider the changes in wavelet power induced by the increasing ambiguity (HA vs LA stimuli) following the methodology described in the work [64]. In TOI1, the wavelet power in the frequency range 4-40 Hz did not change between HA and LA stimuli.

In TOI2, there were three significant positive clusters (Fig. 8.5). The first cluster extended from the stimulus onset to 0.15 s in the upper  $\theta$ -frequency band 7.25–8.5 Hz and included midline central, right fronto-central, and right frontotemporal sensors (Fig. 8.5a). The second cluster extended from approximately 0.02 to 0.2 s in the  $\beta_1$ -



#### ERSP difference (HA - LA stimuli) at TOI2

**Fig. 8.5** The wavelet power in the frontal  $\theta$ -cluster (**a**), occipito-parietal  $\beta_1$ -cluster (**b**), frontoparietal  $\beta_2$  cluster (**c**) during HA and LA stimulus processing. Topograms reflect the *t*-value and the channel clusters as the result of the ERSP comparison between HA and LA stimuli during 0.5 s post stimulus onset. The legends display time-frequency region for each cluster

frequency band 23–23.8 Hz and included the midline occipital, right parietal, and parieto-central sensors (Fig. 8.5b). The third cluster extended from approximately 0.35 to 0.42 s in the  $\beta_2$ -frequency band 31–31.8 Hz and included the midline parietal, left central, midline frontal, and fronto-central sensors (Fig. 8.5c).

Obtained results show that increasing ambiguity induced higher  $\theta$ -band power over the anterior electrodes for 0.15 s post-stimulus onset. The previous studies reported that anterior  $\theta$ -band activity might control and influence posterior brain sites, including early visual areas in the task requiring the reliable top-down control [9, 19, 55]. Anterior  $\theta$ -band response exceded the posterior response during the ambiguous task [72]. The anterior maximum of the  $\theta$ -band power may evidence the prevalence of expectations and prior experience in ensuring coherent object perception when the sensory information is inconclusive and elicits an ongoing conflict between perceptual interpretations. In line with the Ref. [72], we conclude that on the earlier processing stage, ambiguous stimulus processing mostly relied on top-down processes in contrast to the unambiguous stimulus. These top-down processes might be related explicitly to expectations, memory, and perceptual conflict resolution.

Increasing stimulus ambiguity also caused higher  $\beta$ -band power on two different time intervals over the different brain areas. First,  $\beta$ -band power grew in the right occipito-parietal area for 0.02-0.2 s post-stimulus onset (Fig. 8.5b). The previous study of ambiguous Necker cube perception by Yokota et al. [122] revealed that the right-occipital  $\beta$ -band power increased for 0.1–0.15 s after the onset of the completely ambiguous stimulus only when its perception differed from that of the previous unambiguous stimulus. These results linked activity in the right occipital beta band with endogenous switching between rivaling percepts. The authors also related their findings with the visual feedback circuits affecting early visual processing within 0.1 s of stimulus onset [28]. They concluded that the enhancement of early  $\beta$ -band activity might reflect the interaction between the visual cortex and other occipital and parietal cortical regions necessary for stimulus disambiguation. Finally, they proposed that the disambiguation process was complete within 0.25 s after stimulus onset. In line with the Ref. [122], we supposed that high right occipitoparietal  $\beta$ -band power at the earlier processing stage subserved the disambiguation process.

Ambiguous stimuli processing also resulted in higher  $\beta$ -band power over the parietal and midline frontal areas for 0.35–0.42 s post-stimulus onset (Fig. 8.5c). The Ref. [122] also reported increased  $\beta$ -band power for 0.35–0.45 s during the ambiguous stimulus processing. According to [87], this late component might reflect the conscious processing of the perceptual information or maintenance of the percept in working memory. The other studies provided evidence that the working memory demands could alter the  $\beta$ -band activity in the fronto-parietal cortical areas (see Ref. [22] for the literature review). However, overall changes in oscillatory activity during working memory processing are also often found in frequency bands other than  $\beta$ , especially  $\theta$  (See Refs. [90] for the literature review). We did not simultaneously observe higher  $\theta$ -band power for the ambiguous stimuli. Therefore, we did not report enhancing working memory demands in the later stages of ambiguous processing. In turn, we supposed that high fronto-parietal  $\beta$ -band power might reflect the decision-making process. A traditional view is that  $\beta$ -band activity in decision-making reflects motor preparation only. The motor plan expresses the final step, following the higher-order areas, based on sensory input. However, several studies pointed to the more direct involvement of  $\beta$ -band activity in decision formation, regardless of a specific motor plan. Also, decision-related predictions in the  $\beta$ -frequency band can occur beyond sensorimotor regions, both within and between distributed cortical areas, including fronto-parietal circuits (See Ref. [108] for the literature review). In their recent work [16], Chand and Dhamala analyzed the neural interaction between the anterior cingulate-insula network and the fronto-parietal network during the decision-making tasks. They reported that the fronto-parietal network achieved control over the cingulate-insula network in  $\beta$ -band during a 0.22–0.42 s timeframe in the behaviorally more demanding decision-making tasks.

# 8.3.2 Functional Connectivity

The previous section shows how the wavelet power change over the separate sensors under the stimulus ambiguity. This section describes using the wavelets to analyze how ambiguity affects the interaction between the different brain regions. Let us consider the EEG signals recorded by five occipito-parietal electrodes (O<sub>1</sub>, O<sub>2</sub>, P<sub>3</sub>, P<sub>4</sub>, P<sub>z</sub>) placed on the standard positions of the ten-twenty international system [77]. The wavelet energy spectrum  $E^n(f, t) = \sqrt{W_n(f, t)^2}$  can be calculated for each EEG channel  $X_n(t)$  in the frequency range  $f \in [1, 30]$  Hz. Here,  $W_n(f, t)$  is the complex-valued wavelet coefficients calculated as

$$W_n(f,t) = \sqrt{f} \int_{t-4/f}^{t+4/f} X_n(t) \psi^*(f,t) dt, \qquad (8.1)$$

where n = 1, ..., N is the EEG channel number (N = 5 is the total number of channels used for the analysis) and "\*" defines the complex conjugation. The mother wavelet function  $\psi(f, t)$  is the Morlet wavelet often used for analysis of neurophysiological data is defined as [42]

$$\psi(f,t) = \sqrt{f}\pi^{1/4} e^{j\omega_0 f(t-t_0)} e^{f(t-t_0)^2/2},$$
(8.2)

where  $\omega_0 = 2\pi$  is the wavelet parameter.

Observation of the bistable Necker cube and its further interpretation as left or right-oriented induces the stimulus-related response of the brain network. Such response is usually accompanied by the decrease of the alpha-band power (8–12 Hz oscillations) and increase of the beta-band power (15–30 Hz oscillations). The changes in alpha-band power are associated with the visual [93] or auditory attention

[29], and changes of beta-band power relate to the stimuli processing [98] and shift of the brain to an attention state [31, 119]. The percept-related neuronal activity in the alpha and beta bands is also reported in the context of the information transfer in visual areas [73]. Thus, the frequency bands of interest can be predefined as  $\Delta f_{\alpha} = [8-12]$  Hz (alpha-band), and  $\Delta f_{\beta} = [20-30]$  Hz (beta-band).

For these frequency bands the corresponding wavelet energy values  $E_{\alpha}(t)$  and  $E_{\beta}(t)$  are calculated by averaging the spectral energy  $E^{n}(f, t)$  over the corresponding alpha and beta bands as

$$E^n_{\alpha,\beta}(t) = \frac{1}{E^n_*(t)} \int_{\Delta f_{\alpha,\beta}} E^n(f',t) df', \qquad (8.3)$$

where  $E_*^n(t)$  is the energy value  $E^n(f, t)$  averaged over the whole considered spectrum of the EEG signal

$$E_*^n(t) = \int_{1\text{Hz}}^{30\text{Hz}} E^n(f', t) df'$$
(8.4)

The values of the wavelet energy (8.3) calculated for whole time of experimental session are then averaged over the time segments  $\tau_i$  and  $\gamma_i$ , related to the perception of *i*th visual stimulus. and over all EEG channels used for the analysis, as follows

$$\langle E_{\alpha,\beta} \rangle_{\tau_i,\gamma_i} = \frac{1}{N} \sum_{n=1}^N \int_{\tau_i,\gamma_i} E_{\alpha,\beta}^n(t') dt'.$$
(8.5)

Finally, coefficients (8.5) are averaged over all M presentations

$$\langle E_{\alpha,\beta} \rangle_{\tau,\gamma} = \frac{1}{M} \sum_{i=1}^{M} \langle E_{\alpha,\beta} \rangle_{\tau_i,\gamma_i}.$$
(8.6)

The values  $\langle E_{\alpha,\beta} \rangle_{\tau,\gamma}$  are calculated for each experiment.

Along with the analysis of wavelet energy, the time-frequency structure can be considered using wavelet "skeletons"—lines on a time-frequency plane, following the spectral components' position with maximal wavelet energy. For every moment  $t^*$ , the set of three skeletons describes the behavior of the 1st, 2nd, and 3rd maximal components of the wavelet spectrum. The skeleton of the first kind defined the value of frequency  $f_1^*$  for which the value of wavelet energy  $E(f_1^*, t^*)$  reached maximal value for  $t = t^*$ . Similarly, 2nd and 3rd skeletons correspond to the frequency  $f_{2,3}^*$  for which the wavelet energy  $E(f_{2,3}^*, t^*)$  reached the values next to the maximal.

# 8.3.2.1 Band-Specific Neural Activity During Stimulus Processing in Occipito-Parietal Regions

Figure 8.6 illustrates the evolution of wavelet energy before and after the beginning of image presentation in the  $\alpha$  and  $\beta$  frequency bands. Box-and-whiskers diagrams in Fig. 8.6a present the median wavelet energy  $\langle E_{\alpha,\beta} \rangle_{\gamma}$ , calculated before the presentation of the image compared to the values  $\langle E_{\alpha,\beta} \rangle_{\tau}$ , calculated immediately after the presentation. One can see that the  $\alpha$ -band energy significantly decreases when the subject starts to perceive the visual stimuli. At the same time,  $\beta$ -band energy increases during visual perception. While a decrease in  $\alpha$ -band energy is observed for all participants, an increase of  $\beta$ -band energy is observed in 60% subjects. Such inter-subject differences can be caused by the individual human condition, e.g., the ability to concentrate attention on the presented stimuli. According to [68], the stimulus-related  $\beta$ -band energy grows for the highly-motivated subjects and when the complexity of the visual task increases.

Obtained characteristics  $\langle E_{\alpha,\beta} \rangle_{\tau,\gamma}$  are averaged over N = 5 EEG channels. Thus, they can reflect only the global trend but do not give information about local changes in the neural dynamics, i.e, processes of the interactions and coupling between the neural subnetworks located in different parts of the occipito-parietal area.

Figure 8.6b shows the typical EEG traces registered by these channels. With the EEG fragments, one can see the location of the maximal spectral components. Lines show the evolution of three maximal spectral components. The line's color reflects the appearance of the spectral component in the  $\alpha$  (red) and  $\beta$  (blue) frequency bands. The spectral components, which appear in neither  $\alpha$  nor  $\beta$  frequency bands, are excluded from the consideration.

First, one can see that when the stimuli appear, the maximal spectral components change their locations—they move from the  $\alpha$ -band to the  $\beta$ -band. It means that the corresponded neural ensembles start to be involved in the generation of  $\beta$ -band activity more intensive than the  $\alpha$ -band one. It can reflect the increase in the number of neurons participating in the generation or increased synchronization. Taking together, neuronal activity in the different bands start to interplay: a decrease of  $\alpha$ -band energy induces an increase of the  $\beta$ -band energy and vice-versa.

Second, similar stimulus-related behavior is observed in all considered EEG channels. It means that the oscillatory modes of the neural ensembles, located in the vicinity of the corresponded EEG electrodes in occipital and parietal areas, begin to be synchronized by the external intervention—presentation of the visual stimuli.

# 8.3.2.2 Functional Interactions Between the Neural Ensembles in the Occipito-Parietal Areas

Understanding how the occipital and parietal brain structures interact is an essential issue [109]. In particular, an increase of parieto-occipital interactions was observed during the visual stimuli processing with the help of functional magnetic resonance



**Fig. 8.6** Alpha- and beta-band activity. **a** Left: median alpha- and beta-band power on the intervals, preceded ( $\gamma$ ) and followed by ( $\tau$ ) the stimuli presentation (n = 12, \*p < 0.05 via paired-sample *t*-test). **b** Typical EEG traces, associated with the perception of a single visual stimulus, and the wavelet skeletons, reflecting the location of the spectral components with maximal power. The curve's color defines the frequency band, in which the spectral component appears: red corresponds to alpha band, blue-beta band. Vertical dashed line defines the beginning of stimulus presentation

imaging [44]. In Ref. [75], ERP analysis revealed parieto-occipital interactions associated with the processing of multisensory (auditory-visual) information.

Estimating the coupling strength between different brain areas based on the analysis of corresponding EEG or MEG signals is a fundamental issue, and many different techniques are applied. In particular, the different features of brain connectivity are revealed by means of Granger causality [73, 114], nonlinear associations [105], recurrence-based methods [80] and entropy transfer methods [115]. Here we focus on the wavelet-based approach. Continuous wavelet analysis is a well-established time series processing method that allows extracting the time-frequency structure of the nonstationary signals. In neuroscience, wavelets are successively used to detect the specific patterns of oscillatory activity [42], including estimation of the coupling strength between the brain areas [65]. The degree of interaction between the neural ensembles, whose collective dynamics is described by corresponded EEG signals, is estimated via wavelet bicoherence. This method provides insight into nonlinear interactions of different nature and often applied for the analysis of biological signals [42, 94] such as electrocardiogram [100], EEG [54], MEG [91] etc.

To calculate the degree of interaction between two dynamical systems, whose states are described by the variables  $x_1(t)$  and  $x_2(t)$ , the corresponded complex-valued wavelet coefficients  $W_1(f, t) = a_1 + ib_1$  and  $W_2(f, t) = a_2 + ib_2$  should be considered.

Wavelet bicoherence is estimated based on the mutual wavelet spectrum  $W_{1,2}(f, t)$  of the signals  $x_1(t)$  and  $x_2(t)$ . Similarly to [4] the coefficients  $\cos [\Delta \phi(f, t)]$  and  $\sin [\Delta \phi(f, t)]$  represented as real and imaginary parts of mutual wavelet spectrum can be calculated via Eqs.

$$\cos\left[\Delta\phi(f,t)\right] = \frac{a_1(f,t)a_2(f,t) + b_1(f,t)b_2(f,t)}{\sqrt{a_1^2(f,t) + b_1^2(f,t)}\sqrt{a_2^2(f,t) + b_2^2(f,t)}}$$
(8.7)

and

$$\sin \left[ \Delta \phi(f, t) \right] =$$

$$= \frac{b_1(f, t)a_2(f, t) - a_1(f, t)b_2(f, t)}{\sqrt{a_1^2(f, t) + b_1^2(f, t)}\sqrt{a_2^2(f, t) + b_2^2(f, t)}}$$
(8.8)

Here  $\Delta \phi(f, t) = \Delta \phi_2(f, t) - \Delta \phi_1(f, t)$  is the phase difference, calculated for considered signals  $x_1(t)$  and  $x_2(t)$  in time-frequency domain. For further calculations, values (8.7) and (8.8) have to be averaged over time intervals, for which the degree of coherence is considered.

Here the wavelet bicoherence is applied to analyze the degree of coherence between the different EEG signals recorded in occipital and parietal brain areas during the rest state and visual stimuli perception. For the stimulus-related brain state Eqs. (8.7) and (8.8) were averaged over time intervals  $\tau_i = 1$  s for each stimulus perception. For the rest state, averaging was performed over time intervals  $\gamma_i = 1$ .

As the result, for *i*th interval (both for percept-related and background EEG) coefficients  $(\cos [\Delta \phi(f)])_{\tau_i,\gamma_i}$  and  $(\sin [\Delta \phi(f)])_{\tau_i,\gamma_i}$  were obtained as

$$(\cos\left[\Delta\phi(f)\right])_{\tau_i,\gamma_i} = \int_{\tau_i,\gamma_i} \cos\left[\Delta\phi(f,t)\right] dt$$
(8.9)

and

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$$(\sin\left[\Delta\phi(f)\right])_{\tau_i,\gamma_i} = \int_{\tau_i,\gamma_i} \sin\left[\Delta\phi(f,t)\right] dt.$$
(8.10)

Based on coefficients (8.9) and (8.10) the degree of coherence between the EEG signals on the *i*th interval was estimated based on the value of  $\sigma(f)_{\tau_i,\gamma_i}$ , calculated as the amplitude of mutual wavelet spectrum.

$$\sigma(f)_{\tau_i,\gamma_i} = = \sqrt{(\cos\left[\Delta\phi(f)\right])^2_{\tau_i,\gamma_i} + (\sin\left[\Delta\phi(f)\right])^2_{\tau_i,\gamma_i}}.$$
(8.11)

The  $\sigma(f)_{\tau_i,\gamma_i}$  function takes the values from 0 to 1, containing the information about the degree of phase coherence of the two signals  $x_1(t)$  and  $x_2(t)$  for the particular frequency. Thereat  $\sigma(f)_{\tau_i,\gamma_i} = 0$  implies that there is no phase coherence at the current frequency, while for  $\sigma(f)_{\tau_i,\gamma_i} > 0$  coherence takes place.

Obtained values (8.11) were then averaged over M intervals and over frequency bands ( $\alpha$  and  $\beta$ ). As the result, coefficients  $\sigma_{\text{per,bcg}}^{\alpha,\beta}$ , defined the coherence between EEG signals during perception (per) and rest-state activity (bcg) in  $\alpha$  and  $\beta$  frequency bands were analyzed.

$$\sigma_{\text{per,bcg}}^{\alpha,\beta} = \frac{1}{M} \sum_{i=1}^{M} \int_{\alpha,\beta} \sigma(f)_{\tau_i,\gamma_i} df$$
(8.12)

Finally, in order to estimate the stimulus-related activity changes in the degree of coherence, the differences  $\Delta \sigma_{\alpha,\beta} = \sigma_{\text{per}}^{\alpha,\beta} - \sigma_{\text{bcg}}^{\alpha,\beta}$  were calculated for each pair of EEG recordings.

In Fig. 8.7 box-and-whiskers diagrams correspond to the median difference between  $\sigma_{per}$  and  $\sigma_{bcg}$ , calculated for the group of 12 subjects in the  $\alpha$  (a) and  $\beta$ (b) frequency bands. Symbol "\*" defines the channel pairs for which the significant change (p > 0.05) is observed. Links between such pairs are shown schematically. The line width illustrates the mean value of  $\Delta\sigma$  (degree of the change of the coupling strength between corresponded EEG traces caused by the processing of the stimuli). One can see that in both  $\alpha$  and  $\beta$  frequency bands, most channel pairs demonstrate an increase of the coupling strength during the Necker cube observation, which coincides with the results of functional magnetic resonance imaging [44]. It also coincides with [73], where the increase of interaction between areas of the visual cortex has been observed across the  $\alpha$  and  $\beta$  frequency ranges. However, in Refs. [10, 73] such stimulus-related activity has been associated with the frequency band 10–30 Hz included both  $\alpha$  and  $\beta$  frequencies. Simultaneously, presented results, similarly to [32, 33], reveal the differences in  $\alpha$  and  $\beta$  activity. Namely, the difference is observed in the structure of the links in these bands. To quantify these differences, we demonstrate the sum of  $\Delta \sigma$  values related to each EEG channel. This coefficient illustrates the change of each node's weight (in our case, the corresponded brain region) caused by the stimulus processing.



**Fig. 8.7** Group analysis of stimulus-related differences in inter-channel interactions. **a**  $\alpha$ -band, **b**  $\beta$ -band: box-and-whiskers diagrams show median of the difference between the degrees of coherence, calculated for stimulus-related and background EEG (n = 12, \*p < 0.05 via paired-sample *t*-test); histogram shows the sum change in the degree of interaction for each EEG channel; Schematic visualization demonstrates the change in the degree of coherence by the width of line and excludes the links, for which such change is judged as insignificant

The values  $\Delta\sigma$  are shown in Fig. 8.7 by the histograms. One can see that in the  $\alpha$ -band (Fig. 8.7a)  $\Delta\sigma$  is distributed homogeneously within the occipital and parietal EEG channels. In the  $\beta$ -band (histogram in Fig. 8.7b), unlikely one can observe a sharp increase of  $\Delta\sigma$  for occipital channel O2. It means that the alpha activity is produced by the network of interconnected brain regions, with the links' homogeneous structure, which is similar to the structure, associated with background neural activity (but with the increased weights of the links).  $\beta$ -band activity is produced by the network, where one can see the formation of the hub in the occipital area, which plays key functional roles in inter-regional interactions. This result is in good agreement with earlier work of Wróbel et al. [119] which describes the hypothesis about the leading role of  $\beta$ -band oscillations in perception. The revealed impact of the occipital area can be explained by the leading role of this area in the perception of stimuli with different spatial orientation [107].

Having considered the stimulus-related change in the degree of coupling strength, one can conclude: (i) processing of visual stimuli results in the increase of the degree of coupling strength between EEG channels belonging to occipital and parietal lobes both in  $\alpha$  and  $\beta$  frequency bands; (ii) In the  $\alpha$ -band interaction between all EEG channels increases equally and one cannot extract the brain area where the increase of the inter-region coupling is the most pronounced; (iii) In the  $\beta$ -band one can find



occipital channel O2 which demonstrates a sharp increase of the coupling strength with other EEG channels. Obtained results confirm the formation and coexistence of different regimes of neuronal activity in different frequency bands. These regimes are characterized by the different structure of the links between brain areas in the occipital and parietal lobes.

Considering the ratio between the  $\alpha$ - and  $\beta$ -band energy in these brain areas during the rest-state, one can see that  $\alpha$ -band energy is higher in the parietal area. In contrast, the  $\beta$ -band energy prevails in the occipital part. In Fig. 8.8b box-andwhiskers plot shows the median wavelet energy in the  $\alpha$  and  $\beta$  frequency bands in occipital (O) and parietal (P) areas (\*p < 0.05). In Fig. 8.8c the values of wavelet energy, characterizing generation of  $\alpha$ - and  $\beta$ -rhythms during the rest state are shown for each EEG channel (presented data are averaged over 12 subjects). In the reststate, despite the difference in the  $\alpha$ - and  $\beta$ -band energy in different channels, the difference between these rhythms' energy is more pronounced. During the stimulus processing situation is changed. The  $\beta$ -band energy in the occipital area (channels O1 and O2) increases. In the parietal area (channels P3, P4, Pz),  $\alpha$ -band activity remains more pronounced, but its power becomes much less than during the rest state (see Fig. 8.8d). According to earlier EEG and functional magnetic resonance imaging (fMRI) study, such differences in the neural dynamics of in parietal and occipital area can be associated with the existence of "visual" areas in the occipital lobe and "attentional" areas in the parietal region [53]. Taking into account Ref. [95], where the stimulus-related generation of  $\beta$ -waves in the visual cortex has been observed, one can conclude that the occipital area first exhibits the excitation in the  $\beta$ -band and then causes the increase of  $\beta$ -wave activity in the parietal region. Simultaneously, for each channel (occipital and parietal), the increase of the  $\beta$ -band power is accompanied by a decrease in the  $\alpha$ -band power.

One can propose that in the neural ensembles, located in the vicinity of the corresponding electrodes, during the rest state, most of the neurons are involved in the generation of  $\alpha$ -band activity, while a much smaller amount of neurons are acting in the  $\beta$  frequency range. In the occipital area, the neural ensemble generating  $\beta$ -band activity is larger than in the parietal region, which can be caused by excitation of the "visual" center by the visual information. During the perception of ambiguous stimuli, the amount of visual information may grow. In this case, a large proportion of the occipital neurons starts acting in the  $\beta$ -band. The  $\alpha$ -band power in this region starts decreasing (see Fig. 8.8d). According to the connectivity analysis, the occipital ensembles play a leading role in the occipital-parietal network dynamics, leading to increased  $\beta$ -band activity in the parietal area. An increase of  $\beta$ -band power in occipital and parietal areas accompanies decreased  $\alpha$ -band power in these regions. Such changes in the  $\alpha$ -band power is thereby observed in all EEG channels belonging to occipital and parietal brain areas. This also causes increased coupling strengths between the channels in these areas in the  $\alpha$ -band.

# 8.3.2.3 Effect of the Stimulus Ambiguity of the Occipito-Parietal Functional Interactions

The features of stimulus-related brain activity are known to depend on the parameters of the stimuli. For Necker Cube, the difference in the time-frequency structure is observed for different values of ambiguity a. For instance, in [68] perception of the cubes with high ambiguity ( $a \sim 0.5$ ) induced a more pronounced increase of the spectral energy above 30 Hz. Thus, the coupling strength between the regions of the parieto-occipital brain network may also depend on the ambiguity. To verify this hypothesis, the degree of interaction between the pairs of EEG channels was compared during the perception of the Necker cubes with high ambiguity (HA) (0.6 > I > 0.4) and low ambiguity (LA) (I > 0.8 or I < 0.2). Figure 8.9 illustrates differences  $\Delta \sigma^{\text{HA}-\text{LA}}$  in beta (a) and alpha (b) frequency bands. One can see that in the alpha band mean value of  $\Delta \sigma^{HA-LA}$  is mostly negative. This evidences that in this band increase of image ambiguity results in a decrease of inter-channel interaction. In the beta frequency band, some channel pairs are characterized by the negative value of  $\Delta \sigma^{\text{HA}-\text{LA}}$ , while for others  $\Delta \sigma^{\text{HA}-\text{LA}}$  is positive. One can see that significant difference  $\Delta \sigma^{\text{HA}-\text{LA}} > 0$  is observed for P3–P4, P2–P4, P3–O2 channel pairs as shown in the inserts in Fig. 8.9. This means that processing of the images with high ambiguity increases human attention and, therefore, causes the increase of the neural interactions in the parietal lobe, where "attentional" center is located [53].



**Fig. 8.9** Effect of image ambiguity: difference between the degree of inter-channel interaction (mean $\pm$ SD) calculated during the processing of the images with high ambiguity (0.6 > I > 0.4) and low ambiguity (I > 0.8 or I < 0.2) in beta (**a**) and alpha (**b**) frequency bands (n = 12, \*p < 0.05 via paired-sample *t*-test)

# 8.4 Visual Sensory Processing and the Human Factors

Cognitive brain function is usually affected by individual human physiological features, i.e., the same type of human activity can be associated with different scenarios of cognitive brain processes, depending on the motivation, alertness, health status, weariness, etc. of the person [12, 18, 45, 117]. Therefore, along with the knowledge of basic features of the brain activity in solving particular tasks, it is of great practical importance to study the influence of the human factors.

It is known that visual information processing activates the occipital and parietal cortex. Simultaneously, the visual perception is affected by the human factor, such as motivation, alertness, attention, responsibility, health conditions, etc. [7]. The influence of attention on perception was studied using event-related potential (ERP) recordings [62] in electroencephalographic (EEG) or magnetoencephalographic (MEG) data by averaging over many EEG (or MEG) traces associated with the perception of stimuli. Scientists often analyze visual attention using the ERP. According to the Ref. [23], the specific brain response to a particular stimulus is too small to be distinguished in a single EEG. Even though the findings based on the ERP are useful for identifying characteristic features of the brain activity during a long experimental session, they are useless for the analysis of its variation in time. To study how motivation and attention affect alpha activity, Vázquez et al. [70] applied temporal spectral evolution technique. They discovered that increasing attention resulted in a decrease in alpha-band power. Later, it was found that alpha-band activity was related to anticipatory and temporal attention [14]. The suppression of alpha activity was connected to sensory attention [50]. It was also shown that changes in attention induced by special auditory stimuli could modulate alpha-band power [38].

In this section, we consider the influence of motivation and alertness on the visual processing of the Necker cube stimuli, similarly with the Ref. [69]. Reference [69] suggests that the brain may process visual stimuli in different ways (scenarios) depending on attention, which, in turn, could be affected by the motivation of the subject and the complexity of the task.

In line with the previous sections, we focus on the EEG analysis in the  $\alpha$ -band (8–12 Hz) and  $\beta$ -band (20–30 Hz) before and during the presentation of each stimulus to find appropriate criteria for the classification of each perception into one or another scenario. If the perception of individual stimuli could be effectively classified in different scenarios according to the attention, one would be able to identify the ratio between the the occurrence of one or another scenario in real-time based on the spectral properties of multichannel EEGs. The relationship between different scenarios would allow one to estimate the degree of alertness during visual perception and analyze the effect of motivation and task complexity.

# 8.4.1 Different Scenarios of Visual Perception

Ten subjects participated in the experiment. During the experiment, the Necker cubes with different contrasts were presented 400 times to each subject. EEG signals were recorded by five electrodes (O<sub>1</sub>, O<sub>2</sub>, P<sub>3</sub>, P<sub>4</sub>, P<sub>z</sub>), and subjected to the wavelet analysis. The wavelet energy spectrum  $E^n(f, t) = \sqrt{W_n(f, t)^2}$  was calculated for each EEG channel  $X_n(t)$  in the frequency range  $f \in [1, 30]$  Hz. Here,  $W_n(f, t)$  is the complex-valued wavelet coefficients calculated as

$$W_n(f,t) = \sqrt{f} \int_{t-4/f}^{t+4/f} X_n(t) \psi^*(f,t) dt, \qquad (8.13)$$

where n = 1, ..., N is the EEG channel number and \* defines the complex conjugation. The mother wavelet function  $\psi(f, t)$  is the Morlet wavelet,

In Ref. [69], authors estimated the value of frequency  $f_{max}(t)$  corresponding to the maximal energy in the wavelet spectrum for every moment of time. The whole experimental series were split into  $N_{tr}$  3-s trials associated with perception of each stimulus. Each trial consisted of three subsequent segments: (I) before image

![](_page_338_Figure_1.jpeg)

**Fig. 8.10** a The typical set of registered EEG traces. Different segments of the EEG recording are named I, II, III, which correspond, respectively, to the 1-s time interval preceding the cube presentation (*before perception*), ~1-s interval of the cube observation (*perception*), and 1-s interval after the cube observation (*after perception*) and **b** The values of  $L_{\alpha}^{I}/L_{\alpha}^{II}$  (triangles) and  $L_{\beta}^{I}/L_{\beta}^{II}$  (circles) illustrating the relation between the power of alpha and beta waves in intervals I and II obtained by the statistical analysis of the 40-min experimental session of each of the ten subjects. The horizontal dashed lines indicate threshold values defining a >40% decrease of alpha-activity (line 1) and a >20% increase of beta-activity (line 2) used to identify different perception scenarios. The solid red boxes highlight the subjects (2, 3, 9) following the first scenario. Other subjects are associated with the second scenario

presentation, (II) during presentation, and (III) after presentation, as illustrated in Fig. 8.10a. Then, every trial was split into  $N_{\delta_t} = 15$  time intervals of  $\delta_t = 0.2$  s long, and its power spectrum was split into  $N_{\delta_f} = 15$  bands of  $\delta_f = 0.2$  Hz width. For the considered time-frequency plane ( $t \in [0, 3]$  s,  $f \in [1, 30]$  Hz) the distribution of frequency  $f_{max}$  corresponding to the maximum energy was calculated as follows

$$L(f,t) = \sum_{N_{tr}} \sum_{N_{\Delta t}} \sum_{N_{\Delta f}} \gamma, \gamma = \begin{cases} 1, \ f_{max}(t) \in \delta f & \wedge \quad t \in \delta t \\ 0, \ \text{otherwise.} \end{cases}$$
(8.14)

In order to quantitatively characterize the distribution L(f, t), for each participant the ratios  $L^{I}_{\alpha}/L^{II}_{\alpha}$  and  $L^{I}_{\beta}/L^{II}_{\beta}$  were calculated as

$$L^{I,II}_{\alpha,\beta} = \int_{\Delta t_{I,II}} \int_{\Delta f_{\alpha,\beta}} L(f',t') df' dt', \qquad (8.15)$$

where  $\Delta f_{\alpha,\beta}$  is the range of alpha and beta activities and  $\Delta t_{I,II}$  is the duration of segments I and II.

Figure 8.10 illustrates  $L_{\alpha}^{I}/L_{\alpha}^{II}$  and  $L_{\beta}^{I}/L_{\beta}^{II}$  in the group of 10 subjects, by circles and triangles, respectively. One can see that the subjects can be divided into two groups, according to two different scenarios of the perception process. Each subject

![](_page_339_Figure_1.jpeg)

Fig. 8.11 The distribution of the statistical measure L(f, t) calculated by Eq. (8.14) which indicates the location of the maximal spectral component during the 40-min session for two subjects demonstrating the **a** first and **b** second perception scenarios

was classified into one or another group based on a set of threshold values (dashed lines in Fig. 8.11) defined by a >40% decrease in alpha activity (line 1) and a >20% increase in beta activity (line 2). For the subjects 2, 3, and 9  $L_{\alpha}^{I}/L_{\alpha}^{II}$  and  $L_{\beta}^{I}/L_{\beta}^{II}$  satisfy the threshold values. These subjects were associated with the first scenario, while other subjects belonged to the second scenario.

Figure 8.11a and b show the typical distributions L(f, t) for the first (subject #9) and the second (subject #7) perception scenarios, respectively. The first scenario illustrated in Fig. 8.11a) is characterized by significantly low power of the 8–12 Hz oscillations ( $\alpha$ -wave) during the cube observation (segment II) and relatively high power of the 20–30 Hz oscillations ( $\beta$ -wave). The second scenario (Fig. 8.11b) implies a strong contribution of the  $\alpha$ -rhythm and much lower pronounced generation of the  $\beta$ -rhythm during all segments, while the low-frequency  $\delta$ -rhythm (1–4 Hz) has low activity in segment II during the cube presentation.

# 8.4.2 Spectral Properties of the Different Scenarios

For the observed scenarios, the EEG signals were analyzed in three frequency bands:  $\Delta f_{\delta} = [1-4]$  Hz ( $\delta$ -rhythm),  $\Delta f_{\alpha} = [8-12]$  Hz ( $\alpha$ -rhythm), and  $\Delta f_{\beta} = [20-30]$ Hz ( $\beta$ -rhythm). The EEG power spectrum was characterized by the location of the dominant (most pronounced) spectral components. In particular, the first (maximal) spectral component in the *n*th EEG channel occurred at frequency  $f_1^n(t)$  at which the global maximum  $E^n(f_1^n(t), t)$  took place. Respectively, the second, third, ..., *M*th spectral components appeared at frequencies  $f_{2,...,M}^n(t)$ , where  $E^n(f_{2,...,M}^n(t), t)$ exhibited subsequent local maxima.

Using the values  $f_{2,\dots,M}^{n}(t)$  the EEG spectral properties were characterized by spectral coefficients  $F_{\alpha,\beta,\delta}^{n}(t)$  calculated for each channel at every moment of time

![](_page_340_Figure_1.jpeg)

Fig. 8.12 Coefficients  $\langle F_{\alpha,\beta,\delta} \rangle$  characterizing the location of the maximal spectral components averaged over all channels and time intervals  $\Delta \tau_{I,II,III}$  corresponding to different segments during perception for subjects belonging to **a** group 1 and **b** group 2. The error bars indicate standard deviations for each group. The horizontal bars with stars show significant differences in contributions of the  $\alpha$  and  $\beta$  components according to the statistical analysis using paired t-test

$$F_{\alpha,\beta,\delta}^{n}(t) = \sum_{j=1}^{M} \Theta_{\alpha,\beta,\delta}^{n}(j,t), \quad \Theta_{\alpha,\beta,\delta}^{n}(j,t) = \begin{cases} 1/j, \text{ if } f_{j}^{n} \in \Delta f_{\alpha,\beta,\delta}, \\ 0, \text{ if } f_{j}^{n} \notin \Delta f_{\alpha,\beta,\delta}. \end{cases}$$
(8.16)

The obtained spectral coefficients  $F_{\alpha,\beta,\delta}^n(t)$  were averaged over all channels and time intervals for each segment (I, II, III) as follows

$$\langle F_{\alpha,\beta,\delta} \rangle_{\Delta t_{\mathrm{I},\mathrm{II},\mathrm{III}}} = \frac{1}{N} \sum_{n=1}^{N} \int_{\Delta t_{\mathrm{I},\mathrm{II},\mathrm{III}}} F_{\alpha,\beta,\delta}^{n}(t') dt'.$$
(8.17)

Then, for every subject the values of  $\langle F_{\alpha,\beta,\delta} \rangle_{\Delta t_{I,II,III}}$  were averaged over K = 400 trials associated with individual perceptions:

$$\langle \overline{F}_{\alpha,\beta,\delta} \rangle_{\Delta t_{\mathrm{I,II,III}}} = \frac{1}{K} \sum_{i=1}^{K} \langle F_{\alpha,\beta,\delta} \rangle_{\Delta t_{\mathrm{I,II,III}}^{i}}, \qquad (8.18)$$

where  $\Delta t_{I}^{i}$ ,  $\Delta t_{II}^{i}$ ,  $\Delta t_{III}^{i}$  are the time intervals of segments I, II, III, associated with the *i*th perception event, and  $\overline{F}$  defines the averaging over all presentations.

The obtained results are shown in Fig.8.12a and b for group 1 and group 2, respectively. The error bars define the standard deviation of the considered values within all subjects in the group. One can see from Fig.8.12a that the subjects of group 1 exhibit a decrease in alpha activity from  $0.81 \pm 0.23$ SD in segment I to  $0.36 \pm 0.16$ SD in segment II and an increase in beta activity from  $0.44 \pm 0.22$ SD in

segment I to  $0.78 \pm 0.21$ SD in segment II. According to the statistical analysis based on paired t-test such changes are judged as significant ( $p_{\alpha,\beta} < 0.05$ ) and marked by stars in Fig. 8.12a. For the subjects in group 2 (Fig. 8.12b), no significant changes were found in alpha and beta activity ( $p_{\alpha} = 0.23$ ,  $p_{\beta} = 0.36$ ). Instead, the statistical analysis of  $\langle F_{\alpha} \rangle_{\Delta t_{I,II}}$  and  $\langle F_{\beta,} \rangle_{\Delta t_{I,II}}$  for each subject, based on a large number of image perceptions, showed the existence of significant changes between the subjects in group I. So, each subject in group I demonstrated  $p_{\alpha,\beta}$ -value less than 0.05, whereas for the subjects in group II the  $p_{\alpha}$  value varied from 0.085 to 0.43 and  $p_{\beta}$  from 0.175 to 0.492.

### 8.4.3 Single-Trial Analysis

To analyze the effect of human factor on the type-1 or type-2 events, the additional experiments were carried out. All subjects were divided into two groups (10 subjects in each group) according to the degree of their motivation. The members of the first group (GROUP I) were financially motivated and instructed to focus their attention on every cube as much as possible until the experiment ended. For the participants from this group, the experiments were arranged at the most convenient time for each subject. In contrast, the second group members (GROUP II) were unpaid volunteering students and staff, subjected to experimental sessions at random times. They got the task to press a button based only on their first impression. It was supposed that due to the long duration of the session and high similarity of the cubes, the unmotivated subjects would lose their attention since it was not a special requirement.

Similarly to the first stage of the experiment, all participants were subjected to 40-min sessions during which the Necker cube was presented about 800 times. The number of type-1 and type-2 events was calculated according to the spectral properties described above. The results are shown in Fig. 8.13a where the colors mark the areas containing dependencies of the percentage of type-1 events on the number of cube presentations for subjects belonging to GROUP I (upper region) and GROUP II (lower region). The first 500 presentations can be considered as transients characterized by considerable fluctuations. After the transient process was accomplished, the percentage of the events in each group remained constant. The histogram in Fig. 8.13b show the percentage of type-1 events averaged over time, and the error bars indicate the deviation of this value within each group. One can see that the percentage of type-1 events varied from 73% to 87% in GROUP I and from 47% to 77% in GROUP II, and the averaged percentages were  $\sim 81\%$  and  $\sim 62\%$ , respectively. These results demonstrated the experimental evidence that GROUP I, affected by the financial motivation and the opportunity to choose the most convenient time for the experiment, processed the visual object much more carefully than GROUP II.

To study how ambiguity affects perception, the additional experiment with ten extra volunteers was carried out. Subjects participated in two 20-min sessions for which the cubes with low and high ambiguity were presented. It was expected that

![](_page_342_Figure_1.jpeg)

**Fig. 8.13 Effect of motivation. a** Colored areas show the percentage of type-1 events depending on the number of the cube presentations for participants from GROUP I (motivated subjects) and GROUP II (unpaid volunteers). **b** Percentage of type-1 events averaged over all stimuli. The error bars show the standard deviation for each group

![](_page_342_Figure_3.jpeg)

Fig. 8.14 a Percentage of type-1 events depending on the number of presentations for the stimuli with low and high ambiguity. b Averaged percentage of type-1 events observed in sessions with low and high ambiguity for all subjects

high ambiguity would increase the alertness so that the subject would make a decision more carefully.

The results of the analysis are presented in Fig. 8.14. Figure 8.14a shows the percentage of type-1 events depending on the number of presentations. After some transients, these dependences approach 30% and 50% for low and high ambiguity, respectively. Figure 8.14b shows the percentage of type-1 events generated by the cubes with low and high ambiguity for all participants. The error bars indicate the deviation of these values among all participants. The obtained results confirm the hypothesis that an increase in cube ambiguity improves attention leading to an increasing number of type-1 events.

# 8.5 BCIs for the Control of Human Condition During Sensory Processing Tasks

Summarizing the results of the experiments described above, one can see that human alertness can vary during perception of bistable images depending on the motivation level and the task complexity. The results also suggest that alertness can be estimated by the ratio between the number of perception trials classified into type-1 and type-2 events, according to the EEG spectral properties. Thus, classifying perceptions into one of the two types makes it possible to estimate how the alertness changes in time.

Latter underlies the brain-computer interface (BCI) for estimation and control of human alertness. The experimental setup of such BCI is shown in Fig. 8.15.

BCI's general aim is to repair or enhance human performance in solving different tasks, including visual processing. They require the information exchange between the brain and computer. The information coming from the brain to the computer allows continuous monitoring of the brain state and generation of control commands. The information coming back to the operator is used either by the operators for their brain activity self-control or by computer to affect the brain directly. Such an exchange of information between brain and computer is known as *biological feedback*.

Biological feedback is a key component for different BCI. For instance, in neuroprosthetics, sensory feedback allows the user to "feel" rigidity and elasticity of the object and effectively modulate a prosthesis's grasping force. Along with motor-related brain activity, feedback enables controlling psycho-physiological states, especially those associated with high mental functions.

In this section, we consider how feedback affects human visual attention during the perception of ambiguous stimuli. We will follow the experimental paradigm described in Ref. [66]. Reference [66] suggested that during a long experiment, the subject's attention weakened, and the audio signal might let them know that attention decreased. One could expect that such feedback increased the mean level

![](_page_343_Figure_7.jpeg)

of attention during the experimental session. However, the result showed a rather unexpected outcome. The feedback led to an enlargement of the time intervals with a relatively high level of attention; however, the level of attention on these intervals decreased.

# 8.5.1 Wavelet-Based Approach to Estimate Attention in BCI

The algorithm flowchart is schematically illustrated in Fig. 8.16. It includes six steps:

![](_page_344_Figure_4.jpeg)

**Fig. 8.16** Algorithm flowchart. **a** a typical set of EEG recordings from five channels ( $t_i$  is the starting time of *i*th presentation). **b** Wavelet energy spectrum calculation and typical fragment of wavelet energy distribution during perception of *i*th stimulus. **c** Extracting spectral components and typical dependence of main spectral components on time during the transition from background EEG ( $\Delta t_I$ ) to the perception of the visual stimulus ( $\Delta t_{II}$ ). Red and blue colors indicate  $\alpha$  (red) and  $\beta$  (blue) frequency bands, respectively. **d** Histogram showing the values of *A* and *B* calculated by Eqs. (8.19) and (8.20) in time intervals  $\Delta t_I$  and  $\Delta t_{II}$ . **e** Temporal evolution of the value *I* which quantifies the degree of visual attention during an experimental session. The threshold value  $I_{th} = 0$  is shown by the horizontal dashed line. **f** Logical condition for feedback control activation

- 1. **EEG acquisition.** As mentioned above, the EEG signals were recorded by five electrodes  $(O_1, O_2, P_3, P_4, P_z)$  with a 250-Hz sampling rate. The typical recording set is shown in Fig. 8.16a. A vertical dashed line shows the starting time of the *i*th image presentation in the right panel.
- 2. **Time-frequency EEG analysis.** We used the continuous wavelet transform [84]. The wavelet energy spectrum  $E^n(f,t) = \sqrt{W_n(f,t)^2}$  was calculated for each EEG channel  $X_n(t)$  in the  $f \in [1, 30]$ -Hz frequency range. Here,  $W_n(f, t)$  is the complex-valued wavelet coefficients, n = 1, ..., N is the EEG channel number. The mother wavelet function was the complex Morlet wavelet. Figure 8.16c shows a typical wavelet spectrum during visual stimulus representation.
- 3. Extracting spectral components. To follow the dynamics of the main spectral components, one can extract the frequencies (f<sub>1</sub>,..., f<sub>5</sub>) characterized by maximal values of wavelet energy E(f<sub>1</sub>),..., E(f<sub>5</sub>). According to recent works, visual attention induces changes of the wavelet energy in the α (8–12 Hz) and β (15–30 Hz) frequency bands in occipital and parietal areas. Therefore, one can check whether f<sub>1</sub>,..., f<sub>5</sub> belong to these bands. Figure 8.16c shows the typical time dependency of frequencies f<sub>1</sub>,..., f<sub>5</sub> in the α and β frequency bands, during the transition from background EEG (Δt<sub>I</sub>) to the stimulus perception (Δt<sub>II</sub>). Different colors indicate α (red) or β (blue) frequency bands.
- 4. Quantification of perceptual process. To quantify visual attention the EEG spectral features we compared on 1-s intervals before and after the stimulus presentation. For this purpose, we calculated the values  $A_i^1$ ,  $A_i^2$ ,  $B_i^1$ ,  $B_i^2$  during the presentation of *i*th stimulus, which statistically described the location of the maximal spectral components using EEG data taken from all occipital and parietal channels before and after the onset of image presentation, as follows:

$$A_{i}^{1,2} = \sum_{n=1}^{N} \int_{t \in \Delta t_{1,2}^{i}} \left[ \sum_{k=1}^{K} \xi_{k}^{n}(t') dt' \right], \quad \xi^{n}(t) = \begin{cases} 1/k, \text{ if } f_{k}^{n} \in \Delta f_{\alpha}, \\ 0, \text{ if } f_{k}^{n} \notin \Delta f_{\alpha}. \end{cases}$$
(8.19)

$$B_{i}^{1,2} = \sum_{n=1}^{N} \int_{t \in \Delta t_{1,2}^{i}} \left[ \sum_{k=1}^{K} \xi_{k}^{n}(t') dt' \right], \quad \xi^{n}(t) = \begin{cases} 1/k, \text{ if } f_{k}^{n} \in \Delta f_{\beta}, \\ 0, \text{ if } f_{k}^{n} \notin \Delta f_{\beta}. \end{cases}$$
(8.20)

Here, N = 5 is the number of EEG channels,  $f_k^n$  is the location of *k*th maximal spectral component, belonging to *n*th channel, K = 5 is the number of analyzed spectral components, and  $\Delta t_{1,2}^i$  indicate the 1-s time intervals preceding and following the *i*th image presentation (see Fig. 8.16c). The histogram in Fig. 8.16d shows typical A and B values calculated for each image presentation.

5. Assessment of subject's attention. As described above, visual attention is associated with the activation of an "attentional center" in the parietal cortex, which operates at 15–30 Hz frequencies, i.e., increased visual attention activates the  $\beta$ -waves in the parietal area. Also, visual stimuli processing strengthens connectivity between occipital and parietal regions in  $\alpha$  and  $\beta$  frequency bands, causing

the growth of  $\beta$ -activity in the occipital cortex. Finally, visual attention causes a percept-related increase in  $\beta$ -activity with an accompanying decrease in  $\alpha$ activity. Thus, the attention during visual stimulus processing can be quantified as

$$I(t_i) = \frac{(\overline{A}_i^1 - \overline{A}_i^2) + (\overline{B}_i^2 - \overline{B}_i^1)}{2},$$
(8.21)

where  $\overline{A}_i^{1,2}$  and  $\overline{B}_i^{1,2}$  define the values of  $A_i^{1,2}$  and  $B_i^{1,2}$  averaged over six preceding events (i - 6, ..., i). Such averaging is performed since the subject sometimes exhibits low attention *I* during a single event, even while demonstrating overall high attention during the whole session. One can see that  $I(t_i)$  reaches a maximal positive value, if the values in both brackets in Eq. (8.21) are high and positive. It corresponds to a state of high attention when  $\overline{A}_i^1 > \overline{A}_i^2$  and  $\overline{B}_i^2 > \overline{B}_i^1$ , ii.e.,  $\alpha$ -activity decreases and  $\beta$ -activity increases. On the contrary, I(i) reaches a minimal negative value when  $\overline{A}_i^1 < \overline{A}_i^2$  and  $\overline{B}_i^2 < \overline{B}_i^1$ . Finally, I(i) is zero when changes in  $\alpha$ - and  $\beta$ -activity are insignificant. Figure 8.16e shows a typical distribution of attention *I* during the experiment.

6. Feedback activation. The value of attention I was calculated after each visual stimulus was processed by the subject and compared to the threshold value  $I_{\text{th}}$  (see Fig. 8.16f).  $I_{\text{th}}$  was set to zero, and the feedback was organized as a short audio tone after the stimulus was processed, each time when  $I \leq I_{\text{th}}$ . The subject was previously instructed to associate this sound message with a low attention state.

# 8.5.2 Testing the Feedback Effect

To test feedback effect, ten subjects were divided into two groups, five in each group. The first group served as the *control group*, while the second group as the *experimental group*. For each subject, the experimental procedure consisted of two sessions. The subjects from the control group took part in the first and second sessions without feedback control, whereas the subjects from the experimental group participated in the first session without feedback control and in the second session with feedback control. The design of the experiment was similar to the one described in the previous section.

Figure 8.17a shows the change in the attention value I for one subject from the control group during the first (red line) and second (blue line) experimental sessions.

At the first stage, the mean degree of attention during first  $(\overline{I}_I)$  and second  $(\overline{I}_{II})$ experimental sessions for every subject from the control (GROUP1) and experimental (GROUP2) groups to find the difference  $\Delta I = \overline{I}_{II} - \overline{I}_I$ . Figure 8.17b shows that the mean difference between  $\overline{I}_I$  and  $\overline{I}_{II}$  in the experimental group is positive ( $\overline{\Delta I} > 0$ ), while in the control group it is negative ( $\overline{\Delta I} < 0$ ). To define whether the change between  $\overline{I}_I$  and  $\overline{I}_{II}$  is significant for these groups, we applied the Wilcoxon signed-

![](_page_347_Figure_1.jpeg)

**Fig. 8.17** a Typical time evolution of the degree of visual attention *I* during first (red) and second (blue) experimental sessions for one subject from the control group. **b** Changes in the mean value of attention *I* during first and second sessions for subjects from experimental (black box) and control (white box) groups. The data are shown as mean $\pm$ SD (\*p < 0.05). **c** Definition of coefficients  $\delta$  and  $\gamma(\delta)$ .  $\delta$  is the length of the time interval where I > 0 and  $\gamma(\delta)$  is the mean value of *I* on this interval. Distribution of mean attention  $\gamma(\delta)$  on time intervals  $\delta$  extracted from first (red) and second (blue) sessions for subjects from bf d control and **e** experimental groups. **f** Ratio between values  $\delta_{II}^{max}$  and  $\gamma_{II}^{max}$  and  $\gamma_{II}^{max}$  obtained for the first and second sessions for subjects from control (white box) and experimental (black box) groups. Data are shown as mean $\pm$ SD (\*p < 0.05)

rank test, usually used to compare two related short samples. As a result, we obtained p = 0.345 and p = 0.51 for the experimental and control groups, respectively. This evidences that the changes in the mean level of visual attention between the first and second sessions in both groups are insignificant. This result was expected for the control group because the subjects demonstrated more or less the same mean value of *I* in two different sessions. The experimental group is rather surprising for the experimental group. The reason for this kind of behavior can be understood if we

suppose that the cognitive resource to maintain sustained attention for a long time is limited so that the subject needs to rest to recover his/her resource.

Then time evolution of *I* was considered in detail. For each experimental session, we extracted time intervals where I > 0. Such intervals are shown in Fig. 8.17c. One can see that attention *I* oscillates with an average period of  $T \approx 150$  s. During this time interval, the subject processes about 20 visual stimuli. For every such interval, we calculated its length  $\delta$  and the mean value of *I* as

$$\gamma(\delta) = \int_{t'\in\delta} I(t')dt'.$$
(8.22)

The pair of values  $(\delta, \gamma(\delta))$  characterize each extracted interval, as shown in Fig. 8.17d and e, where we plot the two-parameter diagrams for subjects from the control and experimental groups, respectively. The red and blue colors indicate the values obtained during the first and second experimental sessions, respectively. We remind the feedback was only applied in the second session for the experimental group (blue dots in Fig. 8.17e). One can see that in the control group, there is no difference between the distributions obtained in different sessions. Instead, in the experimental group, there is a notable difference. While in the first session (without feedback) in the experimental group, all points are distributed in the range of  $\delta < 100$  s (red dots), in the second session (feedback is applied), some points lie in the time intervals of  $\delta > 100$  s. This means that the feedback control forces the subject to focus his/her attention on the visual stimuli for a longer time than the first session (without feedback).

Since the cognitive brain resource is limited, the occurrence of prolonged intervals of sustained attention led to a decrease in the mean value of attention *I* calculated for these intervals, as clearly seen from Fig. 8.17d, e. While in the control group, the subjects sometimes exhibited high mean values of attention ( $\gamma(\delta) > 100$ ) in both sessions (Fig. 8.17d), in the experimental group, the subjects had high mean values of attention ( $\gamma(\delta) > 100$ ) in the first session only (without feedback), but not in the second session with feedback (Fig. 8.17e). Nevertheless, the relative number of time intervals (the ratio between red and blue dots), where the mean attention took positive value ( $\gamma(\delta) > 0$ ), was higher in the experimental group than in the control group. This means that the feedback control increased not only the duration of time intervals of sustained attention but also the number of these intervals.

Finally, to statistically analyze changes in the values  $\delta$  and  $\gamma(\delta)$  calculated for the first and second sessions in both groups, we extracted their maximal values  $\delta_{I,II}^{max}$ and  $\gamma_{I,II}^{max}$  obtained in the first and second sessions. Then, we calculated the ratios between these maximal values in the first and in the second session, i.e.  $\gamma_{II}^{max}/\gamma_{I}^{max}$ and  $\delta_{II}^{max}/\delta_{I}^{max}$ . The obtained results are presented in Fig. 8.17f as mean±SD for subjects from the control (white box) and experimental (black box) groups. One can see that the ratio  $\delta_{II}^{max}/\delta_{I}^{max}$  for the subjects from the experimental group is higher than that for the subjects from the control group (1.6 ± 0.52 versus 1.1 ± 0.51). This evidences that feedback control increased the maximum duration of the state of high attention for the subjects from the experimental group. The statistical analysis of the values  $\delta_{I,II}^{\text{max}}$  obtained in the first and second sessions, performed via Wilcoxon signed-rank test yielded p < 0.05 for the experimental and p = 0.893 for the control group.

While the maximal duration of the time interval for which I > 0 increased in the presence of feedback, the maximum mean value of I, which was achieved on this interval, decreased. This decrease of attention is demonstrated via the ratio  $\gamma_{II}^{\text{max}}/\gamma_{I}^{\text{max}}$  in Fig. 8.17f. One can see that the ratio  $\gamma_{II}^{\text{max}}/\gamma_{I}^{\text{max}}$  is equal to  $0.71 \pm 0.08$  and  $1.13 \pm 0.44$  for the experimental and control groups, respectively. The Wilcoxon signed-rank test provided p < 0.05 for the experimental and p = 0.686 for the control group.

Thus, feedback led to an increase in time intervals. The subject maintained a high level of sustained attention (length of the maximal interval was about  $100 \pm 20$  s without feedback versus  $150 \pm 40$  s with feedback). Simultaneously, the degree of attention during these time intervals was 27% lower than in the group without feedback. The obtained results evidence that the brain's cognitive resource is limited, and therefore when the subject is asked to provide high performance for a long time, it switches to a "safe-mode" regime.

# 8.5.3 Cognitive Load Distribution via BCI

As mentioned above, BCIs may increase human performance in solving different tasks. In this particular case, the "computer" controlled by human's brain activity, assumes the part of the cognitive or physical human load. The feedback information acquired from sensors allows controlling the machine power following the load subjected by the human.

Similarly to this "human-machine" interaction, a human-human interaction may also enhance human performance. In this situation, the machine component of traditional BCI can be replaced by another human linked to the first one by an interface. As a result, assistance would enhance the subject's performance in managing a particular task. This would help a group of people subjected to a joint job task that requires sustained attention and alertness. In everyday practice, this is a common occurrence, for example, among pilots of a military [26], or a civil aircraft [92], or a power plant operators, whose routine work includes continuous monitoring of instrument readings that requires sustained alertness, and concentration [3, 46, 111]. A human-human interface could help them have effective interactions by estimating and monitoring each person's physical conditions, particularly degree of alertness, to distribute workloads among all participants according to their current physiological status.

This section describes a BCI to heighten human-human interaction while performing collective tasks requiring visual attention. BCI's efficiency is estimated in experimental sessions, where subjects participate in the prolonged task of classification of ambiguous visual stimuli (Necker cubes) with different degrees of ambiguity. Finally, we discussed the perspectives and limitations of the human-human interaction via BCIs.

#### 8.5.3.1 Experimental Paradigm

Figure 8.18 illustrates The scheme of BCI, which allows human-human cognitive interaction.

Ambiguous visual stimuli with different degrees of ambiguity were consistently presented to participants who had to classify them. The complexity of the task was determined by the degree of ambiguity. As shown above, the higher the ambiguity, the higher the observer's attention. First, each stimulus was simultaneously presented to a pair of subjects (subject 1 and subject 2) using a special software running on the corresponding client personal computers (PC1 for subject 1 and PC2 for subject 2). Then, the subjects' EEGs were simultaneously recorded and transmitted to the PCs. The performance was estimated using stimulus-related brain response I(i) to every presented *i*th stimulus (see the algorithm described in the previous section)

The brain responses  $I_1(i)$  and  $I_2(i)$  of subject 1 and subject 2 were transmitted to the computational server for the comparative analysis. Depending on the result of their comparison, the corresponding control command is sent to each PC to adjust the stimuli ambiguity for each subject. For example, if  $I_1(i) > I_2(i)$ , then subject 1 receives a stimulus with high ambiguity, while subject 2 perceives a stimulus with low ambiguity. Thus, the feedback signal from server manages the task handout depending on the stimuli complexity and the human performance.

The proposed BCI was tested in two experiments. During the first experiment (EXP1), a pair of participants interact through a non-delayed coupling, i.e., task complexity is distributed based on the instantaneous alertness level of participants; the partner with higher alertness receives stimuli with high ambiguity (HA), while another partner is tasked with low ambiguity stimuli (LA). Unlike EXP1, during the second experiment (EXP2), there was a delay in the coupling between the participants. Thus, if the difference in degrees of alertness between them exceeded 10%, the partner with higher alertness received HA stimuli. Both EXP1 and EXP2 were

![](_page_350_Figure_6.jpeg)

Fig. 8.18 Schematic illustration of human-human interaction

preceded by the non-coupled session where both subjects perceived a whole set of stimuli, i.e., ambiguity was randomly chosen from the range [0, 1], and the feedback signal from the computational server was absent. This preliminary experimental session measured the individual brain response level before the coupling was applied.

For each session, average performance  $\langle I \rangle$  was calculated for each subject by averaging his brain response *I* over 200 image presentations. According to  $\langle I \rangle$  estimated during the preliminary non-coupled session, subjects in each pair were classified as a leader (L) (subject with higher  $\langle I \rangle$ ) and an assistant (A) (subject with lower  $\langle I \rangle$ ). Then,  $\langle I \rangle$  of L and A obtained during non-coupled and coupled sessions are calculated and compared.

#### 8.5.3.2 Results of the Cognitive Load Distribution

The results of this comparison for the first experiment (EXP1) are presented in Fig. 8.19a in the form of box-and-whiskers diagrams, which show average performance  $\langle I \rangle$  for leaders and assistants in all pairs. According to the group analysis, the interaction between subjects in EXP1 does not bring a significant effect on the

![](_page_351_Figure_5.jpeg)

**Fig. 8.19 a** Schematic illustration of human-human interaction; **b** Left, average leader's brain response  $\langle I \rangle$  during first experiment (EXP1): session 1 (S1) (no link between subjects, p = 0.938) and session 2 (S2) (no delay in coupling between subjects, p = 0.965) (p = 0.67); right, average assistant's brain response  $\langle I \rangle$  during EXP1: S1 (no link between subjects, p = 0.402) and S2 (no delay in coupling between subjects, p = 0.485) (p = 0.37). **c** Left, average leader's brain response  $\langle I \rangle$  during second experiment (EXP2): S1 (no link between subjects, p = 0.131) and S2 (delayed coupling between subjects, p = 0.889) (\*p < 0.05); right, average assistant's brain response  $\langle I \rangle$  during EXP2: S1 (no link between subjects, p = 0.169) (p = 0.06). **d** Left, mean brain response  $\langle I \rangle$  for pairs during EXP1: S1 (no link between subjects, p = 0.485) (no significant, n = 10, p = 0.48 by paired sample *t*-test); right, mean brain response  $\langle I \rangle$  for pairs during EXP1: S1 (no link between subjects, p = 0.622) (\*p < 0.05 by paired sample *t*-test). Medians (yellow bars), 25 ÷ 75 percentiles (box) and outlines (whiskers) are shown

![](_page_352_Figure_1.jpeg)

**Fig. 8.20** a Typical oscillations of the brain response value (*I*) depending on the number of presented visual stimuli during the experimental session. **b** Detailed illustration of a single period of (*I*) oscillations (~20 presented stimuli), where "hump" and "hollow" demonstrate the state of high brain response (high performance) and low response (state of restoration), respectively. **c** Average brain response  $\langle I \rangle$  of the subject during experimental session, where the images with low ambiguity (LA) and high ambiguity (HA) are presented (\*p < 0.05). Medians (yellow bars), 25 ÷ 75 percentiles (box) and outlines (whiskers) are shown. **d** Typical oscillations of the brain response value (*I*) depending on the number of presented visual stimuli during the perception of the images of high degree of ambiguity (solid curve) and low degree of ambiguity (dashed curve)

performance of leaders and assistants. On the contrary, a considerable increase in the leader's alertness was observed in EXP2, where the task complexity is changed with a delay (Fig. 8.19b). Simultaneously, the observed changes in the assistants' alertness are insignificant. Such an increase in the leader's performance causes an enhancement of the overall pair's performance (Fig. 8.19c).

To explain the obtained result, let us consider the evolution of the brain response during an experimental session. The typical dependence I(i) reflects a change in the amplitude of the brain response as the number of presented Necker cubes *i* is increased. The result shows oscillations whose period varies from 15 to 40 presented stimuli (see Fig. 8.20a). The brain response evolution can be associated with the existence of the brain restoration state caused by the relaxation of the neural ensemble (Fig. 8.20b). The degree of image ambiguity (complexity of the visual task) strongly affects the brain response's amplitude. Figure 8.20c shows the average values of the brain response calculated for the preliminary experimental session conducted individually for each participant, where visual stimuli with a low degree of ambiguity have been presented. The base value is chosen when the observer is subjected to ambiguous stimuli. One can see that increase in the degree of image ambiguity (an increase in the task complexity) leads to a corresponding increase in the average amplitude of the brain response  $\langle I \rangle$ . According to our recent study [69], such a change in the brain response is caused by an increase in alertness. In this case, the EEG signals' time-frequency structure exhibits significant changes for each subsequent *i*th stimulus. The origin of these changes lies in the contribution of  $\alpha$  and  $\beta$  brain rhythms. From the viewpoint of neural dynamics, this means that large neural populations take part in image classification [65]. As the image ambiguity grows, the average response I(i) increases. Figure 8.20d illustrates I(i) oscillations for the participant subjected to HA and LA stimuli. In the case of high ambiguity, the oscillation amplitude significantly increased (solid curve). The value of I(i) reached much higher values and lower values than the values obtained in the case of low ambiguity. For low ambiguity, I(i) oscillates near some average value with a smaller amplitude (dashed curve). We suppose that for HA stimuli, neural ensemble in the brain are effectively involved in perception and requires much more time to be restored. For LA stimuli, visual perception requires less intensive neural participation. This reflects in the lower amplitude of the response and less time of the restoration.

According to the above result, the performance increases if the image ambiguity is adjusted according to the brain response. This can be implemented with the help of biological feedback and the following algorithm: (i) in case of high operator performance defined by a high value of the brain response baseline, the operator is subjected to the stimuli with a high degree of ambiguity, i.e., the task complexity is being increased with the corresponding cognitive load increment, (ii) as the cognitive load increases, it leads to an augmentation in neuronal tiredness which immediately causes a decrease in the brain response, (iii) in contrast, with a low brain response, the operator is subjected to stimuli with a low degree of ambiguity, i.e., the level of cognitive load decreases, and (iv) a decrease in cognitive load causes a faster restoration. Thus, high performance has to be correlated with increased complexity and restoration phase with low complexity defined by the I(i) oscillations frequency.

To check how this criterion is satisfied in two conducted experiments, EXP1 and EXP2, the corresponding experimental sessions are analyzed in detail. When comparing the sub-plots in Fig. 8.21a, one can see that during EXP2, where the task complexity is switched immediately as the amplitude of the brain response of one subject  $(I_1(i))$  starts to exceed the brain response of the other subject  $(I_2(i))$ , there are a lot of short switchings for which the value of  $\Delta < 5$  presents stimuli smaller than the period of I(i) oscillations. In this case, the dependencies  $I_1(i)$  and  $I_2(i)$  obtained for both subjects do not demonstrate an antiphase mode. On the contrary, the values of I(i) obtained for subjects in experiment EXP2 behave mostly in antiphase, and switchings appear less. In Fig. 8.21b the box-and-whiskers diagram compares the mean number of switchings  $\langle N_{TC} \rangle$  averaged over the subjects during the experiments EXP1 and EXP2. One can see that in experiment EXP2, the number of switchings significantly decreases (significance is judged from p < 0.05 estimated via paired t-test).

![](_page_354_Figure_1.jpeg)

**Fig. 8.21 a** The detailed illustration of the structure of experiments (EXP1) and (EXP2): solid curves represent the brain response for both subjects (*I*), dashed lines, marked as (HA) and (LA) indicate the two types of visual tasks, associated with high and low complexity, solid lines appeared between these dashed lines represent the switching between the tasks (TC), the arrow shows the moment of single switching, the length of the interval ( $\Delta$ ) between two successive switchings is measured in the number of presented stimuli; **b** Comparison between the number of switches  $< N_{TC} >$ , averaged over the subjects during the experiments (EXP1) and (EXP2). The statistical significance is estimated via paired t-test. Medians (yellow bars), 25 ÷ 75 percentiles (box) and outlines (whiskers) are shown. **c** Distribution of time intervals between switches (5–10 units); optimal switches (11–20 units); long switches (>20 units)

One can surmise that in EXP1, the multiple unnecessary spontaneous switchings, caused by low-frequency fluctuations of I(i), interfere with an antiphase mode between oscillations of the values  $I_1$  and  $I_2$  of the leader and assistant in the pair. Unlike experiment EXP1, during experiment EXP2, such switchings appear more scarcely. The interval  $\Delta$  between two successive switchings matches the period of the I(i) oscillations, which is estimated to vary from 15 to 40 stimuli presentations. For both experiments, the intervals distribution is calculated for  $\Delta \in [0, 40]$ and compared (see Fig. 8.21c). This distribution shows a significant number of rapid switches (<5 presented cubes) observed during EXP1, whereas medium (5–10 presented cubes) and optimal (11–20 presented cubes) intervals between the switches dominate in EXP2. Considering that the period of I(i) oscillations appears in the same range, we can conclude that the switching regime in experiment EXP2 mostly satisfies the criteria described above, leading to an increase in performance.

#### 8.5.3.3 Role of the Human Condition in BCI

The possibility of estimating and controlling the human psychophysiological condition via a brain-computer interface is of significant fundamental and practical interest [8]. In this context, the estimation and control of such human factor as alertness is essential [51, 57, 61]. Alertness is an active attention state marked by high sensory awareness, such as being watchful and ready for any potential danger or emergency or responding to it fast. The neurophysiological studies showpeople who have to be alerted during their jobs, such as air traffic controllers or pilots, often have trouble maintaining their alertness. In some situations, people use drugs to increase their attention, but a safer and more effective way is to use BCI to improve the ability to maintain alertness. Such BCI can give rise to the development of training systems, in particular, for children with attention deficit hyperactivity disorder [40, 57], as well as assistant systems, which allow controlling the attention during long-lasting job tasks. Moreover, they can be used for the development of BCI for completely paralyzed people [39, 47].

A core feature of such type of BCI is the possibility to objectively monitor the degree of human attention at any time point based on the analysis of neurophysiological data, e.g., multichannel EEG using different approaches, such as artificial neural networks [58], vector machines [110] and time-frequency analysis [69]. These techniques allow estimating changes in the degree of alertness in real-time during one experimental session.

In this regard, we have previously shown that the degree of alertness can be estimated in real-time based on changes in the time-frequency structure of human EEG [69]. We have also demonstrated that the degree of alertness can be controlled by biological feedback. Based on the obtained results, here we study the possibility to improve human-human interaction by sharing cognitive load based on detecting and comparing alertness of interacting people in real-time.

It should be noted that human-human interaction has recently become a very hot topic in neuroscience, physics, and IT-technologies. Recently, the possibility of human-human interaction via a brain-to-brain interface was performed in a way where motor information registered in the cortical region was transmitted to the motor cortex region of another subject with the help of brain stimulation. Such possibility was first demonstrated by Pais-viera et al. [81] in rats. One year later, human-human interactions have been considered by Rao et al. [88], who proposed a noninvasive interface that combined EEG with transcranial magnetic stimulation (TMS) for delivering information to the brain. Their brain-to-brain interface detected motor imagery in EEG signals recorded from one subject (the "sender") and transmitted this information over the Internet to the motor cortex region of the other subject (the "receiver"). The brain-to-brain interaction was also implemented in the form of human-animal interaction [123], where the human volunteer's intention was translated to stimulate a rat's brain motor area responsible for the tail movement. Another type of the brain-to-brain interface was demonstrated by Mashat et al. [71] in a closed-loop form, where the intention signal from one subject ("sender") was recognized using EEG and sent out to trigger transcranial magnetic stimulation of the other subject ("receiver") to induce hand motion; meanwhile, transcranial magnetic stimulation resulted in a significant change in the motor evoked potentials recorded by electromyography of the receiver's arm, which triggered functional electrical stimulation applied to the sender's arm and generated hand motion.

Although these studies provided experimental evidence of the information transmission between brains, they did not demonstrate the possibility of improving the performance of a "sender" and a "receiver". The control command was translated to the receiver's brain in any case, not considering its willingness to perform an action. In other words, previously proposed systems did not take into account the brain states of interacting people. Instead, in our study, we analyze and compare human brain states as a core feature of the human-human interaction. We demonstrate that such type of human-human interaction improves human performance in tasks that require sustained attention, in particular, image classification, which perceiving consecutively presented ambiguous stimuli. At the same time, possible applications of the proposed BCI are widespread. In any type of human-human interaction aimed to increase performance, the cognitive or physical load is distributed unequally over participants depending on their current psychophysiological conditions.

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# Chapter 9 Analysis and Real-Time Classification of Motor-Related EEG and MEG Patterns



Abstract This chapter describes wavelet analysis of the motor-related cortical activity. First, it introduced real and mental motor activity in the young and the middleaged healthy subjects. The real motor acts, or motor execution (ME), enables interaction with the environment and induces the motor-related changes in 8-12 Hz and 15–30 Hz wavelet power in the motor cortex. The mental motor acts, or motor imagery (MI), did not include muscle control but may have a motor-planning stage, similar to ME. Detecting the ME and MI brain states underlies the brain-computer interfaces (BCI) for motor control. The ME-BCIs can be used to control exoskeletons and robots. The MI-based BCIs may detect the motor intentions in the paralyzed patients to recover their motor abilities. Second, we described two types of motor imagery: kinesthetic and visual. Visual imagery (VI) corresponds to the self-visualization of the subject moving a limb that does not require special training. Kinesthetic imagery (KI) is the feeling of muscle movement that can only be realized by athletes or specially trained persons. Finally, we considered how the ME brain states change with age representing criteria for an objective assessment of the motor abilities in elderly adults.

## 9.1 Real and Imagery Movements

Recent work analyzes spatio-temporal and time-frequency characteristics of electrical brain activity associated with real and imagery motor actions in the group of untrained subjects, using the wavelet-based approach. As a result, the authors revealed characteristic oscillatory patterns, which occurred in different brain areas and interacted with each other when the motor action (or imagery) took place. Obtained results allowed detecting real and imagery motor actions in the real time.

Twelve untrained healthy volunteers participated in the experiments. Their brain activity signals (EEG) were recorded at a 250 Hz sampling rate from 31 electrodes with two reference electrodes placed at the standard positions of the 10–10 international system. Each participant was subjected to one experiment, lasting approximately 30 min. Participants were instructed to perform two types of tasks: to lift slowly the right hand (in the shoulder joint) (RAM) and imagine such a movement

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**Fig. 9.1** Experimental design. **a** Two types of tasks: (left) real movement of the right arm (RAM) and (right) imaginary movement of the right arm (IAM). **b** The structure of experimental sessions: RAM<sub>i</sub> and IAM<sub>i</sub> ( $i = \overline{1, M}$  being the number of an individual event in the session) define a single real and imaginary movement, respectively. M = 20 is the total number of events in the session,  $\Delta t = 4$  s is the time interval reserved for the task. Each session is preceded by a video message with instructions, and each event in the session is preceded by an audio message. RE<sub>j</sub> and IM<sub>j</sub> ( $j = \overline{1, N}$  being the session number) correspond to the sessions in which the real and imaginary movements take place, respectively, N = 5 is the total number of sessions, associated with each type of movement. The experiment starts with a 5-min background EEG recording (BCG<sub>1</sub>) and ends with a 5-min background recording (BCG<sub>2</sub>)

during a given time interval (IAM) (see Fig. 9.1a). The whole experiment comprised ten sessions, five sessions (RE<sub>j</sub>) of real movements and five imagery movements (IM<sub>j</sub>). Each RE session followed by a IM session. The experiment started with a 5-min background EEG recording (BCG<sub>1</sub>) and ended with a 5-min background recording (BCG<sub>2</sub>) (see Fig. 9.1b). Each session started with a short visual message with instructions and contained M = 20 similar events. Each event in the session began with a short sound message and should be performed within a reserved time interval  $\Delta t = 4$  s.

#### 9.1.1 Wavelet-Transform Modulus Maxima (WTMM)

The obtained EEG signals were analyzed with wavelet-based approaches. First, the Wavelet-transform modulus maxima (WTMM) was applied to estimate the complexity of the EEG signals. This method describes scaling phenomena in nonstationary time series [65]. It gives the singularity spectrum of a signal x(t) based on the continuous wavelet transform

$$W(a,\tau) = \frac{1}{a} \int_{-\infty}^{\infty} x(t)\psi\left(\frac{t-\tau}{a}\right) dt$$
(9.1)

with parameters a and  $\tau$  characterizing the scale and translation of wavelet function  $\psi$ . In the multifractal analysis, real-valued wavelets are mainly used, such as the MHAT-function

$$\psi(t) = (1 - t^2) \exp\left(-\frac{t^2}{2}\right).$$
 (9.2)

Near the singularity point  $t^*$ , the power-law dependence of the wavelet-coefficients

$$W(a, t^*) \sim a^{h(t^*)}$$
 (9.3)

takes place with the Hölder exponent *h*. The value of *h* characterizes the singularity strength and varies with the signal x(t). To provide a statistical analysis of singularities, the an approach based on the partition functions is mainly applied. It assumes the extraction of all skeleton lines (the lines of local maxima of |W(a, t)|) and the construction of the functions

$$Z(q, a) = \sum_{l \in L(a)} \left( \sup_{a' \le a} |W(a', t_l(a'))| \right)^q \sim a^{\tau(q)}$$
(9.4)

with L(a) being a full set of skeleton lines at the scale a,  $t_l(a)$  being the position of the maximum related to the line l and  $\tau(q)$  being the scaling exponents.

The values  $\tau(q)$  can be found by the analysis of the dependence (9.4) in the double-logarithmic plot. After their estimation, the Hölder exponents h(q) and the singularity spectrum D(h) are obtained as

$$h(q) = \frac{d\tau(q)}{dq},\tag{9.5}$$

$$D(h) = qh - \tau(q). \tag{9.6}$$

The function D(h) is the Hausdorff dimension D of singularity points characterized by the exponent h(t) = h. The position of the singularity spectrum is determined by the mean Hölder exponent H = h(0), while the width of the singularity spectrum





quantifies the degree of inhomogeneity of the analyzed data. It is often used as a complexity measure of nonstationary processes.

WTMM combines complexity and correlation analysis representing a powerful tool for studying nonstationary and inhomogeneous processes. Application of wavelet-transform at the first stage of the method allows ignoring polynomial trends presented in the analyzed data. As a result, there is no need to pre-process experimental EEG data before applying the WTMM-method. Computing the singularity spectrum D(h) provides two main measures: the spectrum width characterizing the degree of inhomogeneity (complexity) of data, and the mean Hölder exponent Hreflecting correlation properties. The performed analysis has revealed the main distinctions in the second quantity. WTMM provides a faster convergence of estimated quantities than the standard correlation analysis and, therefore, a better characterization of complex processes based on short data sets. The latter improves the quality of separation between different physiological states for limited amounts of physiological data [40].

Mean Hölder exponents were calculated for each 4-s EEG trial, associated with motor execution  $H_{\text{RE}}$  and motor imagery  $H_{\text{IM}}$ . The obtained values were then averaged over 100 EEG trials and mean values  $\overline{H}_{\text{RE}}$  and  $\overline{H}_{\text{IM}}$  were used to characterized real and imagery movements. The background activity was analyzed by averaging the mean Hölder exponent  $\overline{H}_{\text{BCG}}$  over the 5-min background EEG (BCG<sub>1</sub>), preceding the motor-related experimental sessions. Analysis of the singularity spectra revealed significant distinctions between real and imagery movements reflected in the position of D(h), i.e., in the mean Hölder exponent H illustrated in Fig. 9.2.

Figure 9.2a shows the mean Hölder exponents for the real (RE) and imagery (IM) movements of the right arm, estimated from the EEG channel Cz for all subjects and averaged over a large number (N = 100) of events. The error bars indicate the stan-

dard error, which quantifies the deviation of the mean Hölder exponent within individual events. According to the presented results, the multifractal analysis allowed us to distinguish between real and imaginary arm movements using Cz EEG channel.

Along with the distinctions between motor execution and motor imaginary, the possibility to extract the brain state associated with both ME and MI from the background EEG is also of great interest. For this purpose the mean Hölder exponents corresponding to motor execution  $\overline{H}_{RE}$ , motor imaginary  $\overline{H}_{IM}$ , and background EEG  $\overline{H}_{BCG}$  were considered. The difference between ME and BCG was well-pronounced in all channels, while the distinction between BCG and MI depended on the electrode position. As an example, Fig. 9.2b shows the values of the mean Hölder exponents related to real and imaginary movements and background calculated from EEG channels Cz and C3 (the data are averaged over all subjects and the bars define the standard error). One can see that for the Cz-channel, the mean Hölder exponent increased for motor execution and decreased for motor imagery. The statistical analysis based on paired t-test showed that both these changes were judged as significant (p < 0.05). At the same time, the mean Hölder exponent calculated from the C3-channel demonstrated significant (p < 0.05) changes for motor execution, but changes in H-values between background EEG and motor imaginary were found to be insignificant (p = 0.12). Thus, according to Fig. 9.2b, imagery movements of all subjects can be effectively classified from background EEG based on the Hölder exponents calculated from the Cz-channel, while the difference between imaginary movements and background EEG extracted the C3-channel was insignificant.

Figure 9.2c illustrates the differences between the mean Hölder exponents corresponding to real/imaginary movement and background EEG averaged over all subjects. The results show that the largest differences between ME and background EEG and between MI and background EEG in untrained subjects occur in the frontal brain area. Motor execution resulted in a significant increase in the mean Hölder exponents calculated from EEG channels located in the frontal area, whereas motor imaginary led to a decrease in  $\overline{H}$  -values.

The obtained results revealed a significant influence of the frontal brain areas on the mean Hölder exponents calculated for the EEG segment associated with motor execution and motor imaginary. Simultaneously, the analysis of the EEG data from other brain areas, e.g., temporal and central, did not reveal any changes in the Hölder exponents. The observed behavior of the Hölder exponents may suggest the complex interaction between different oscillatory patterns in these brain areas in the time\_frequency domain.

Time-frequency analysis used the continuous wavelet transformation where complex-valued Morlet-wavelet was chosen as the mother function (2.36) with  $\omega_0 = 2\pi$  being the central frequency of the Morlet and  $i = \sqrt{-1}$ .

The wavelet energy spectrum  $E(t, f) = W^2(t, f)$  was calculated in the frequency band  $f \in [1, 30]$  Hz (f = 1/a). For each EEG channel the values of whole wavelet energy  $E_{\text{RE}}$ ,  $E_{\text{IM}}$ ,  $E_{\text{BCG}}$  associated with motor execution, motor imaginary and background EEG, respectively, were calculated by averaging E(t, f) indicated frequency band and over the experimental sessions (RE), (IM) and (BCG)



**Fig. 9.3** a Differences between the values of wavelet energy calculated for real movement  $E_{\text{RE}}$  and background EEG  $E_{\text{BCG}}$ . **b** Imaginary movement  $E_{\text{IM}}$  and background EEG  $E_{\text{BCG}}$ . **c** Real  $E_{\text{RE}}$  and imaginary  $E_{\text{IM}}$  movements. The values of energy (E) were calculated by averaging W(f, t) over the frequency band from 1 Hz to 30 Hz, time interval t = 4 s, and 100 trials.  $\langle \dots \rangle$  denotes group averaging over all subjects

$$E_{\text{RE}} = \int_{\substack{IM \\ BCG}} \int_{t \in \text{IM}} \int_{t \in \text{BCG}}^{30\text{Hz}} E(t', f')df' dt'. \quad (9.7)$$

In the frequency ranges of  $\delta$ -band (1–5 Hz),  $\mu/\alpha$ -band (8–13 Hz), and  $\beta$ -band (10– 30 Hz), the energy values  $E_{\delta}(t)$ ,  $E_{\mu}(t)$  and  $E_{\beta}(t)$  were calculated for each EEG channel by averaging the value E(t, f) over the corresponding frequency band

$$E_{\mu,\beta,\delta}(t) = \int E(t, f')df'.$$

$$f \in \mu - \text{band}$$

$$f \in \beta - \text{band}$$

$$f \in \delta - \text{band}$$
(9.8)

In the first stage, the differences between motor execution/imagery and background EEG were judged based on the calculation of the coefficients  $\langle E_{\rm RE} - E_{\rm BCG} \rangle$ ,  $\langle E_{\rm IM} - E_{\rm BCG} \rangle$ ,  $\langle E_{\rm RE} - E_{\rm IM} \rangle$  describing the change of the whole spectral energy associated with the considered states. These values were calculated for each EEG channel and averaged over the group of participants.

Figure 9.3 displays the revealed differences distributed over the brain surface. One can see that compared to background EEG, real movements were characterized by an increase in the energy over most of the EEG channels (Fig. 9.3a). Imaginary movements, on the contrary, resulted in a decrease in the energy in the corresponding brain areas (Fig. 9.3b). In particular, real movements were associated with a

significant increase in the energy in frontal and temporal areas, whereas imaginary movements decreased the energy in the same areas. As a result, real and imaginary movements in untrained subjects can be effectively distinguished by analyzing frontal and temporal EEG signals these results of energy analysis correlated with the behavior of the Hölder exponents.

## 9.1.2 Time–Frequency Analysis

Then, the time-frequency structure of EEG signals was analyzed in detail.

Figure 9.4 we present the time-frequency dependencies which illustrate the changes in the value of wavelet energy E(f, t),  $f \in (1, 30)$  Hz,  $t \in (0, 4)$  s associated with (a) real and (b) imaginary movements with respect to the background EEG. Presented data were averaged over 100 EEG trials recorded from all 21 EEG channels of one subject. The time-frequency plots are labeled and located on the head-like layout, according to the position of the recording electrodes. Red and blue colors indicate time-frequency plane for which the energy value, respectively, increased and decreased during real or imaginary movement. Color saturation shows the degree of changes.



**Fig. 9.4** Time–frequency plots of changes in wavelet energy E(f, t),  $f \in (1, 30)$  Hz,  $t \in (0, 4)$  s associated with (a) real and (b) imaginary movements with respect to the background EEG. Presented data were averaged over 100 trials and shown for each of 21 EEG channels. Red and blue colors indicate the time–frequency plane for which the energy value, respectively, increased and decreased during real or imaginary movements. Color saturation shows the degree of changes

One can see that a significant increase for real movement and a significant decrease for imaginary movements of wavelet energy in frontal and temporal lobes were mainly determined by the low-frequency  $(1-5 \text{ Hz}) \delta$ -waves. The energy of  $\delta$ -waves exhibited a significant change in the frontal area, which decreased rapidly while moving from the frontal to the parietal area. This resulted in a significant change in wavelet energy. At the same time, the time-frequency structure of the EEG signal was much more complicated. The features of real and imaginary movements were characterized by the transition and distribution of the energy between different frequency bands. Considering real movement (Fig. 9.4a) one can see that electrical activity in the temporal area together with an increase in  $\delta$ -waves' amplitude was characterized by a decrease of the wavelet energy for  $f \in [8, 12]$  Hz ( $\mu$ -rhythm) and decreasing energy in  $f \in [15, 30]$  Hz ( $\beta$ -activity). This effect is known in scientific literature as event-related desynchronization (ERD) [17]. The ERD associated with motor activity was previously observed in the frequency bands of 8-10, 10-12, 12–20, and 20–30 Hz [99]. It is known that motor execution is characterized by both event-related desynchronization and event-related synchronization (ERS). The ERD was usually observed in  $\alpha$  (or  $\mu$ ) and  $\beta$ -bands [11], while such effect in  $\delta$ -band was much less studied [32]. At the same time, according to Fig. 9.4a, eventrelated synchronization of  $\delta$ -activity took place during motor execution together with event-related desynchronization of  $\mu/\alpha$ )- and  $\beta$ -rhythms.

In Fig. 9.4a the colored areas **A**, **B** indicate the brain segments where the considered event-related behavior was the most pronounced. One can see that the observed ERD in  $\mu$ -rhythm prevailed in temporal, central, and parietal lobes (colored area **A**), where the motor area took place [10]. It should be noted that this area is shifted from the center to the left side, which is connected with hemispheric asymmetry, associated with arm movements [98]. An accompanying event-related increase in the amplitude of the low-frequency  $\delta$ -activity was more pronounced in frontal region (shaded area **B**).

Motor imaginary, in turn, induced changes in  $\delta$ -activity, in the frontal region (colored area **B** in Fig. 9.4b. However, the energy of  $\delta$ -waves decreased due to event-related desynchronization. While ERD took place in  $\delta$ -band,  $\mu$ -rhythm exhibited event-related synchronization in most areas of the brain with the maximal value in the central and parietal areas and decreased in temporal regions (colored area **A** in Fig. 9.4b).

As we already mentioned above, the brain activity associated with motor functions is characterized by the interaction between different brain rhythms. Figure 9.5 illustrates this process for the motor execution. In Fig. 9.5a shows the typical EEG traces recorded in parietal and occipital lobes during a single experimental session (RE) associated with alternating motor executions. In Fig. 9.5b the location of the spectral components characterized by the maximal energy is shown for the considered EEG recordings. In Fig. 9.5c the mean values of the spectral energy averaged over  $\alpha$ -band  $\langle E \rangle_{\alpha}$ ,  $\delta$ -band  $\langle E \rangle_{\delta}$  and the set of EEG signals, are shown. It is seen that the motor execution was accompanied by the transition of the spectral energy between  $\alpha$ - and  $\delta$ -bands. It was demonstrated by both the location of the most pronounced spectral components and changes in mean (band-related) spectral energy. In Fig. 9.5b demon-



**Fig. 9.5** a Set of EEG signals recorded from occipital and parietal lobes during experimental session RE when alternating real movements were performed. The vertical dashed lines indicate the moments when the actions start. The considered brain area is shown by the shadow. **b** Location of most pronounced spectral components and changes in mean (band-related) spectral energy

strated that the spectral components with the high energy appeared in  $\delta$ -band during motor execution and disappeared in  $\alpha$ -band. Vise-versa, such components occurred again in  $\alpha$ -band after the motor execution finished. At the same time, the values of spectral energy  $\langle E \rangle_{\alpha}$ ,  $\langle E \rangle_{\delta}$  calculated for these bands, evolved in anti-phase, i.e., the value of  $\langle E \rangle_{\alpha}$  decreased during motor execution and  $\langle E \rangle_{\delta}$  increased (see Fig.9.5c).

It is important to note that, according to Fig. 9.5, the characteristic features associated with motor executions in  $\alpha$ - and  $\delta$ -bands can be identified for every single event. This was exciting since most studies on motor execution and imaginary judged ERS and ERD from the data obtained by averaging over a large number of events. Presented results show that for a single event, changes in the motor-related energy in  $\alpha$ - and  $\delta$ -bands can be extracted from EEG trials by averaging them over particular brain areas. One can expect that taken into account the identified brain areas, where the effects of ERD and ERS are the most pronounced (see Fig. 9.4) it is possible to detect a single motor execution or imagination in real-time.

### 9.2 Visual and Kinestetic Motor Imagery

Revealing brain activity features during motor imagery is very important for the brain-computer interfaces (BCIs) which can help in rehabilitation of patients after trauma or stroke and noninvasive brain-controlled exoskeletons and bioprostheses [20, 64, 73]. Motor imagery [43] results from the rehearsal of a given motor act in the working memory without any overt movement of the corresponding muscle. Generally, MI follows two categories: visual imagery (VI) and kinesthetic imagery (KI). VI corresponds to the self-visualization of the subject moving a limb, that does not require a special training. In contrast, KI is the feeling of muscle movement, that can only be realized by athletes or specially trained persons [63].

MI was studied by many researchers who used different experimental techniques (for comprehensive review see [23]). The most popular are the functional magnetic resonance imaging (fMRI) [30, 91], positron emission tomography (PET) [6, 61, 94], electroencephalography (EEG) [13, 33, 69, 75, 76, 100], transcranial magnetic stimulation (TMS) [41, 46, 53, 63, 95], and magnetoencephalography (MEG) [27, 28, 48, 83, 84]. Previous fMRI studies [30, 91] indicated that brain activity during KI is similar to real movement because it includes control of muscle contractions which are then blocked at some level of the motor system by inhibitory mechanisms. Thus, MI shares a part of the neuronal network involved in the movement execution, but without any corresponding muscle movement. TMS studies [41, 46, 53, 63, 95] also confirmed the overlapping activity in the brain areas during KI and real movement.

To understand MI, many methods of time–frequency and spatio-temporal analyses are used. Among them, the most common techniques are event-related synchronization (ERS) and event-related desynchronization (ERD) [45, 83, 97, 103], power spectral density, wavelet transform, empirical mode decomposition, common spatial patterns, spatio-decomposition, as well as their combinations [19, 72, 89]. Also, to classify the brain states, the methods of machine learning and artificial intelligence are applied to EEG and MEG data [35, 36, 59].

MI is actively studied to classify the brain states corresponded to the different MI limbs [27, 28, 48, 83, 84]. A relatively good accuracy has been achieved in classification between left-hand and right-hand MI and between MI and rest-state using the combination of spatio-spectral decomposition and common spatial patterns analyses by Halme and Parkkonen [27]. Recently, they used both MEG and EEG in brain-computer interfaces for training MI classifiers [28]. In their study, authors demonstrated rather efficient classification of MI even without separation of participants into KI and VI categories. At the same time, KI and VI scenarios affect the classification accuracy, e.g., the accuracy rate obtained for KI is usually better than the results for VI [69]. Finally, untrained subjects often demonstrate VI imagery mode. The possibility to increase the accuracy rate for VI is in demand for BCI applications. This chapter considers brain activity associated with MI in untrained subjects and describes the distinctive features of VI and KI imagery.

To analyze brain activity, 306 MEG signals (102 magnetometers and 204 planar gradiometers) were recorded with a sampling frequency of 1000 Hz and a bandpass



**Fig. 9.6** a Sketch of the participant during MEG experiment on MI and b schematic representation of experimental paradigm.  $RMI_i$  and  $LMI_i$  denote right motor imagery and left motor imagery respectively, *i* indicates the number of repetition and  $\Delta t$  denotes the duration of each repetition

filter between 0.1 and 330 Hz. During the experimental session, participants were sat in a comfortable chair inside the Vectorview MEG system as shown in Fig. 9.6a and performed motor imagery following the experimental paradigm illustrated in Fig. 9.6b.

To distinguish the participants into VI and KI categories, we applied time– frequency and hierarchical cluster analysis (HCA) to MEG recordings obtained during the experimental procedure. It is known, that motor imagery affects the neural activity in  $\mu$  (8–12Hz) and  $\beta$  (15–30Hz) frequency bands [76, 78].

#### 9.2.1 Wavelet Analysis

The time-frequency structure of MEG signals was analyzed with the help of a wavelet-based approach. For each limb, the Morlet wavelet with  $f_0 = 1$  Hz central frequency and 3-s full width at half maximum (FWHM) was used to evaluate the time-frequency spectrogram (TFS) for all extracted epochs of that limb. Then, the TFS was also averaged over the desired motor-related frequency ranges of  $\mu$  (8–13 Hz) and  $\beta$  bands (15–30 Hz). The same process was repeated over the background resting state using the same parameters. To evaluate ERS/ERD, we took a difference between the spectrogram for the trials and the averaged-over-time spectrogram of the background and then normalized it to the background. This normalized difference was positive for ERS and negative for ERD. The values of wavelet energy  $E_{\mu}^{n}(t)$  and  $E_{\beta}^{n}(t)$  were calculated, respectively, in frequency bands 8–13 Hz, and 15–30 Hz for each *n*th MEG channel as

$$E^{n}_{\mu,\beta}(t) = \frac{1}{\Delta f} \int_{f \in \mu,\beta} E^{n}(f,t) df.$$
(9.9)

The event-related potentials (ERPs)  $LA^n_{\mu}(t)$  and  $LA^n_{\beta}(t)$ ,  $RA^n_{\mu}(t)$  and  $RA^n_{\beta}(t)$ ,  $BC^n_{\mu}(t)$  and  $BC^n_{\beta}(t)$  were extracted for each limb by averaging the values  $E^n_{\mu}(t)$  and  $E^n_{\beta}(t)$  over the trials corresponding to left arm (LA) and right-arm (RA) motor imagery, and background activity (BC), respectively.

Finally, in order to estimate ERD (or ERS) associated with left- and right-arm imagery, we calculated integral differences  $dLA^n_{\mu}$ ,  $dLA^n_{\beta}$  and  $dRA^n_{\mu}$ ,  $dRA^n_{\beta}$  between MI and background activity as

$$dLA^n_{\mu,\beta} = \int_{t\in T} \left( LA^n_{\mu,\beta}(t) - BC^n_{\mu,\beta}(t) \right) dt, \qquad (9.10)$$

$$dRA^n_{\mu,\beta} = \int_{t\in T} \left( RA^n_{\mu,\beta}(t) - BC^n_{\mu,\beta}(t) \right) dt, \qquad (9.11)$$

where T = 3 s is the trial length.

#### 9.2.2 Cluster Analysis

To distinguish KI and VI, we applied the hierarchical cluster analysis (HCA) [102]. Suppose that each participant is characterized by a point in the M-dimensional feature space, where M is a number of features necessary to describe MI of the subject. To perform HCA, we used a complete-linkage clustering, which belongs to the agglomerative ("bottom-up") group of clustering methods [102]. At the beginning of the

algorithm, each participant represents its cluster and during further iterations existing clusters are joined into larger clusters until all points are combined in one cluster. The link between two clusters is a farthest distance in a feature space between two elements, each in its own cluster. In the mathematical form, the complete-linkage function D(X, Y) is

$$D(X, Y) = \max_{x \in X, y \in Y} d(x, y),$$
(9.12)

where X and Y are considered clusters, x and y are objects in X and Y, respectively, and d(x, y) is a distance between two objects in a feature space. We calculated this distance using Euclidean metric as

$$d(x, y) = \frac{1}{M} \sqrt{\sum_{i=1}^{M} (x_i - y_i)^2},$$
(9.13)

where  $x_i$  and  $y_i$  are an *i*th feature of the x and y objects, respectively.

Concerning the stated problem of the MI-type clustering, we considered the differences  $dLA^n_{\mu,\beta}$  and  $dRA^n_{\mu,\beta}$  (i = 1, ..., N) as a feature set of the MI process for left and right arms, respectively. In addition, for HCA we averaged the wavelet energy differences over the limb types as follows:

$$dE_{\mu}^{n} = \frac{dLA_{\mu}^{n} + dRA_{\mu}^{n}}{2},$$
(9.14)

$$dE^n_\beta = \frac{dLA^n_\beta + dRA^n_\beta}{2}.$$
(9.15)

The dimensionality of the feature space in the case of MEG measurements is equal to 2N = 204 for each limb. It is clear that the number of dimensions is quite large. To reduce the dimensionality of the feature space, we averaged  $dE_{\mu,\beta}^n$  over the channels, so that overall wavelet energy difference  $dE_{\mu,\beta} = 1/N \sum_{n=1}^{N} dE_{\mu,\beta}^n$ .

Hence, each subject is described by a point in the two-dimensional MI feature space  $(dE_{\mu}, dE_{\beta})$ . We will show below that solving the MI clustering problem in a given two-dimensional feature space is more demonstrative and easy for interpretation.

Figure 9.7a shows the coefficients  $dE_{\mu}^{n}$ ,  $dE_{\beta}^{n}$  which characterize changes in the ERP amplitudes in  $\mu$  and  $\beta$  frequency bands of *n*th MEG channel, associated with MI. The colored clouds of small dots correspond to the values  $(dE_{\mu}^{n}, dE_{\beta}^{n})$  obtained for each of 102 MEG channels. The dot color defines the subject. The horizontal dashed line indicates  $dE_{\beta}^{n} = 0$  when the energy does not change. All dots located above this line correspond to the MEG channels where an increase in the ERP (or ERS) amplitude in the  $\beta$ -frequency band is observed, while the dots located below this curve correspond to the channels where the ERP (or ERD) amplitude decreases. In turn, the vertical dashed line separates ERD and ERS in the  $\mu$ -band; ERS corresponds



**Fig. 9.7** Results of HCA illustrating the clustering of subjects belonging to KI and VI types. **a** Wavelet energy differences during MI in the feature space  $(dE_{\mu}, dE_{\beta})$ . Here, different colors indicate different subjects, clouds of small dots represent wavelet energy differences for *i*th channel (i = 1, ..., N) and big dots show individual wavelet energy differences averaged over the channels (big red and black dot highlight the belonging to KI and VI types, respectively). **b** Dendrogram showing formation of two subgroups (KI and VI) in the group of participants in terms of Euclidean distances between clusters in the feature space  $(dE_{\mu}, dE_{\beta})$ . **c** Wavelet energy differences during MI plotted in the feature space  $(dE_{\mu}, dE_{\beta})$  colored with respect to the belonging of each subject to either KI (big red dots) or VI (big black dots) type. **d** Stars show centroids of KI and VI clusters obtained by *k*-means clustering

to the positive values of  $dE_{\mu}$ , while ERD to the negative values. The closed circles in Fig. 9.7a show the overall difference between wavelet energies in  $\mu$ , and  $\beta$  ranges averaged over MEG channels individually for each subject. Therefore, each circle is an individual MI characteristic of each participant.

The dendrogram in Fig. 9.7b shows the arrangement of clusters obtained by HCA applied to the colored bold circles in Fig. 9.7a. Considering the first row of the dendrogram, all participants of the MEG study can be well divided into two large clusters; subjects 2, 3, and 6 are arranged in the KI group (big red dots), while the rest are arranged in the VI group (big black dots). It should be noted that the links between the subjects inside each group are much smaller than the links between the clusters. Thus, we suppose that HCA provides a good enough precision of the clustering. Comparing the dendrogram with subjects' positions in the feature space  $(dE_{\mu}, dE_{\beta})$  (see Fig. 9.7c), one can see that the brain activity during MI of the subjects belonging to the red dot group is characterized by well-pronounced ERD in both  $\mu$ - and  $\beta$ -frequency bands. This indicates that in this group, the motor-related activity dominates during MI. On the contrary, for the subjects belonging to the black dot group, the MI process is accompanied by ERS (or close to ERS) in the  $\mu$  and  $\beta$  bands that determine a key role of imagination and self-visualization of the limb movement. Moreover, the subjects arranged by HCA in the red dot group are more prone to regular physical training. In contrast, the subjects from the black dot group are more likely to experience a high cognitive load and intellectual work. Finally, using *k*-means clustering, we obtained the centroids of the red and black dot groups (Fig. 9.7d). This proximity determines the belonging of the subject to a particular cluster and consequently the type of MI.

According to the cluster analysis, the untrained subjects demonstrate different brain activity scenarios while trying to imagine motor activity. Depending on the behavior of the ERP amplitude in the motor-related  $\mu$ - and  $\beta$ -frequency bands, these scenarios can be classified as KI or VI.

## 9.2.3 Neurophysiological Aspects of Motor Imagery

The literature reports on different brain regions involved in MI, including primary motor cortex (M1), posterior parietal cortex (PPC), supplementary motor area (SMA), prefrontal cortex, and subcortical areas.

A bulk of literature associated MI with the primary motor cortex. Many researchers previously followed Talairach and Tournoux's atlas, referred to the M1 cortex as the posterior region of the precentral gyrus. Other scientists used the term "precentral knob which is only a subset of M1 representing hand movements [29]. Also, the presence of methodological differences in the experiments and the difficulty of monitoring compliance with the MI instructions [86] only made things worse. It is not surprising that there exists a controversy in the involvement of M1 during MI with studies both in favor [8, 21, 56, 80, 91] and against [18, 30] its involvement. Keeping the controversy aside, the studies still seem to suggest that M1 is indeed activated during MI, but much weaker as compared to real movement [23]. The role of M1 in timing the neuronal network activity is also highlighted [12, 50].

Numerous neuroimaging studies [14, 18, 30, 31, 39, 66] indicate that PPC actively involves in MI. When patients with lesions in PPC were asked to predict beforehand the time needed to perform movement tasks, they typically underestimated/overestimated [88]. This strongly contrasts with patients with precentral motor cortical dysfunction, who exhibit impaired movement, but retain the ability to estimate motor performance times [87]. This result suggests that there is a separate mechanism for choreographing the movement and to mentally simulate the movement for estimating the movement time and that this time analysis mechanism is localized near the parietal cortex. It is intriguing to note that bilateral parietal lesions can cause a person to accidentally execute movements when asked to imagine them and be completely unaware about it [85]. This result hints towards the possibility that the mental MI simulation is inhibited by a mechanism also localized near the parietal lobe (in one of two hemispheres or both) that fails to give way to actual movement execution during MI. Sensory modalities related to the movement can also stimulate the brain activity, such as vibratory stimuli, to induce illusion of kinesthetic activity in the primary somatosensory areas and in the M1 region [67, 68]. The temporoparietal junction has been linked with own-body imagery and self-location [5, 38]. It is not surprising that KI activates motor associated areas and the inferior parietal lobe, whereas VI activates visual-related areas (Occipital lobe) and the superior parietal lobe (Precuneus) [22]. It should be noted, that a TMS study also reveals that the inferior parietal lobe exerts inhibitory control in the M1 region during MI [52].

Recent fMRI experiments [71] identified SMA to be the best predictive region to distinguish between hand rotation and grasping movements which seems to suggest that the role of SMA is to augment the content of signals rather than mediating the signal. It was reported that electromyographic (EMG) activity during MI experiments, associated with failures of inhibitory control, was observed in both agnostic and antagonistic muscles as a function of weight to be lifted in the imagination [3] and a type of muscle contraction [24]. This seems to suggest that the imagination content affects the inhibitory mechanism. Furthermore, Kasess et al. [47] highlighted the contribution of supplementary motor area (SMA) in the inhibition of M1 during MI. Therefore, inhibitory mechanisms should be taken into account to explain the rest of the results. The underlying structure seems to be dissociable and hierarchical for neural representations of observed, imagined and imitated actions [57]. Thus, the differential analysis of each of the brain regions mentioned above must be used to understand their contribution to the brain functioning during MI.

Prefrontal areas, such as ventrolateral prefrontal cortex and anterior cingulate cortex, were also found to be involved in movement suppression, as well as in decision making on the movement [12, 49].

The results of Hanakawa [29] indicate that cerebellum and basal ganglia also participate in movement suppression. In particular, Parkinson disease affects basal ganglia causing the patients to slow down MI [9]. This indicates that basal ganglia only mediates the signal and not affect the MI content [29].

In their famous work, Pfurtscheller and Neuper [76] found that mental imagery of motor actions can produce replicable EEG patterns over primary sensory and motor areas. These patterns are associated with ERD in motor-related  $\mu$ - and  $\beta$ -frequency bands, similar to those associated with motor executions [78]. At the same time, some papers report that many participants do not exhibit the expected motor-imagery related changes in their EEG [60, 77, 100]. According to Annett [2], this is caused by the existence of different types of mental imagery of motor actions, namely, visual and kinesthetics imagery modes. The knowledge of key principles of MI is needed for effective classification of EEG/MEG trials corresponding to different types of imagination and its implementation in BCI systems. It was shown [69] that KI and VI scenarios affect the classification accuracy, e.g., the rates obtained for KI (67%) were shown to be better than the results for MI (56%).

## 9.3 Age-Related Distinctions in EEG Signals During Execution of Motor Tasks Characterized in Terms of Wavelet Spectra

One of the important problems associated with the analysis of neural activity during the executions of certain motor acts is the problem of age-related changes. It is obviously that aging causes great changes in the human life, which often include physical and mental impairments, psychological, and social changes. Research on aging is commonly associated with abnormal brain dynamics and the related diseases, such as Alzheimer's disease and dementia. The physiological mechanisms accompanying the development of these disorders of brain activity have been clearly established [1, 55, 93, 105, 106], but some features of pathological dynamics are revealed even in healthy aging [54], and their analysis can provide markers of hidden stages of disorders. Healthy aging alters the neurochemical and structural properties of the brain, that leads to decreased cognitive and motor functions during daily activities in older adults. Age-related neural impairments are quantitatively assessed by a longer reaction time, reduced coordination, and motor control [58, 92], which limit the performance of complex motor tasks [44, 90, 104]. Several studies [4, 15, 34, 51] have established additional brain areas involved during the motor activity with aging to overcome structural changes in brain dynamics. This involvement serves as a compensatory mechanism [82, 101]. Due to this, execution of motor tasks is expected to differ between younger and elderly subjects.

In this Section we consider the differences in cortical activity during the controlled execution of fine motor tasks between elderly adults and young adults using wavelet method applied to EEG [16]. First, consistent with the dedifferentiation theory [58, 62], we discuss that the motor cortex of younger adults (YA) activated much faster during the dominant hand task, while in elderly adults (EA), the time required for motor activation was equal for both hands and approached the level of the non-dominant hand of younger adults. Second, the significant differences in cortical activation are observed during the time interval preceding the motor action. In elderly adults, as well as in young adults performing the non-dominant hand task, theta-band power is increased in the frontal, central, and central-parietal EEG sensor rows, whereas theta-activation is insignificant in young adults during the dominant hand task.

## 9.3.1 Experimental Study and Motor Brain Response Time Analysis

The experimental design included the sequence of simplest motor tasks. Each task required squeezing one of the hands into a wrist after the audio signal and holding it until the second signal (30 tasks per hand). The duration of the signal determined the type of movement: short beep (0.3 s) was given to perform a non-dominant hand (left hand, LH) movement and long beep (0.75 s) was given to perform a dominant hand (right hand, RH) movement. The timeline of a single task movement included time interval between the signals during the task and the pause between the tasks were chosen randomly in the range 4-5 s and 6-8 s, respectively. The types of tasks were mixed in the course of the session and given randomly to exclude possible training or motor-preparation effects caused by the sequential execution of the same tasks.

To acquire EEG signals the the monopolar registration method (a 10–10 system proposed by the American Electroencephalographic Society [70]) was used. According to this, the EEG signals with 31 sensors (O2, O1, P4, P3, C4, C3, F4, F3, Fp2, Fp1, P8, P7, T8, T7, F8, F7, Oz, Pz, Cz, Fz, Fpz, FT7, FC3, FCz, FC4, FT8, TP7, CP3, CPz, CP4, TP8) and two reference electrodes A1 and A2 on the earlobes were recorded. The obtained raw EEG signals were sampled at 250 Hz and filtered by a 50-Hz notch filter by embedded hardware-software data acquisition complex. Additionally, eyes blinking and heartbeat artifact removal was performed by the ICA [37].

Two groups of healthy volunteers, including 10 elderly adult subjects (EA group; age:  $65\pm5.69$  (MEAN $\pm$ SD)) and 10 young adult subjects (YA group; age:  $26.1\pm5.15$ ), participated in the study. All subjects were right-handed and had no history of brain tumors, trauma or stroke-related medical conditions. Thus, we can concluded the data of a mixed-design experimental study with the movement type (LH and RH conditions) as within-subject factor and the age (EA and YA groups) as between-subject factor. As consequence, the recorded EEG signals were segmented into four sets of epochs according to the (group [YA, EA], condition [LH, RH]) combinations: (YA, LH), (YA, RH), (EA, LH), and (EA, RH). Each epoch was 10 s long, including 2 s baseline activity and 8 s motor-related activity.

On the first stage of the experimental data processing, the motor brain response time (MBRT) was esimated. A priory knowledge about the cortical activation during movements execution implies that motor brain response is determined as a pronounced event-related desynchronization (ERD) of alpha/mu-oscillations in the contralateral area of the motor cortex. Notably, a wide body of EEG studies reports that symmetrical C4 and C3 sensors evidence brain motor response in case of the LH and RH movements, respectively [17, 74, 79]. Here, we used alpha/mu-band eventrelated wavelet power (ERWP<sub>µ</sub>) at C4 and C3 sensors to estimate MBRT associated with LH and RH conditions for each subject of both groups. MBRT were defined as the first minimum of the mu-band spectral power below the 2.5th baseline level as shown in Fig. 9.8a which illustrates this procedure. Thus, four sets of MBRT corresponding to each (group, condition)—set were collected.

Let us consider the effect of aging on the MBRT, i.e., the duration of the time interval required for the brain to activate a corresponding motor area for both EA and YA groups. We estimated MBRT for each subject in both experimental conditions (Fig. 9.8d) and compared the results taking into account age and movement type factors together. The mixed-design ANOVA test revealed the significant effect of the movement type on the MBRT (F(1, 18) = 26.748, p < 0.001) while the factor of age was insignificant (F(1, 18) = 2.626, p = 0.123). Post hoc comparison via paired t-test indicated that the mean MBRT for the LH condition (M = 1.173, SD = 0.341) was significantly higher than the RH condition (M = 0.691, SD = 0.248). Thus, in the case of the dominant hand movement (RH condition), the motor cortex activated faster in 19 of 20 subjects excluding 1 EA subject (Fig. 9.8c and d). Also, two EA subjects demonstrated almost close motor response times in both experimental conditions.

Moreover, there was a significant interaction between the Movement Type and the Age of the participants (F(1, 18) = 4.967, p = 0.039). We could interpret this



**Fig. 9.8** a An illustration of the MBRT estimation. The blue curve shows single-subject ERWP<sub> $\mu$ </sub> at the C4 sensor averaged over 15 LH epochs. Black solid and red dashed horizontal lines indicate mean and 2.5th percentile level of the baseline ERWP<sub> $\mu$ </sub>, respectively. Black solid and black dashed vertical lines show the beginning of the audio command and estimated motor brain response, respectively. **b** Distribution of MBRT across subjects in each (group,condition)-set. Here, '\*' indicates p < 0.05, '\*\*\*' indicates p < 0.001 and 'n.s.' stands for insignificant difference. **c** Stripcharts of linked observations MBRT(LH) and MBRT(RH) within each group. **d** Scatterplot of paired observations MBRT(LH) versus MBRT(RH) for each subject. Here, the diagonal line is MBRT(LH)=MBRT(RH), pink diamonds indicate subjects from YA group, and blue squares—subjects from EA group. Based on data from [16]

interaction as meaning that the Movement Type influenced MBRT differently in EA and YA groups. Particularly, MBRTs were similar in the LH condition (EA: M = 1.139, SD = 0.219; YA: M = 1.206, SD = 0.427), while YA group reacted significantly faster in RH condition (EA: M = 0.865, SD = 0.230; YA: M = 0.516, SD = 0.098).

## 9.3.2 Time–Frequency Analysis of Brain Response on Motor Activity

The time-frequency analysis of the generated array of epochs was carried out using the CWT with the Morlet basis function in the range [4, 40] Hz. The obtained values of the signal spectral power E(t, f) were normalized to the mean level of the pre-

stimulus spectral power  $E_{pre}(f)$  as follows:

$$E'(t, f) = [E(t, f) - E_{pre}(f)]/E_{pre}(f).$$
(9.16)

The obtained values of the normalized spectral power show an increase or decrease in the spectral power in the post-stimulus period relative to the pre-stimulus level. The greatest interest from the point of view of neuronal activity associated with the performance of movements is the desynchronization of the alpha/mu-rhythm ([8, 14] Hz frequency band) of the electrical activity of the brain [74, 79]. Simultaneously, we analyzed activity in the theta-range ([5, 8] Hz), which underlying the majority of the processes exhibits significant age-related changes—abnormally increased theta activity in elderly people indicates subjective cognitive dysfunction and suspected dementia [81, 96].

With this aim, we performed within-subject spatio-temporal clustering analysis of the spectral power in the theta and alpha/mu frequency bands for each (group, condition)—set in the premotor period  $(0 \div 1.2 \text{ s})$ . Figure 9.9 shows the results of within-subject clustering analysis in the LH condition for both groups of subjects. It is seen that in the LH condition (non-dominant hand movement), brain activation in both YA and EA groups proceeds similarly. Specifically, the suppression of murhythm in the motor cortex at  $0.8 \div 1.2 \text{ s}$  related to the motor execution control was preceded by the theta-band activation during the period  $0.2 \div 0.8 \text{ s}$ . In the YA group, pre-motor theta-band activation involved sensors in the motor, frontal, and bilateral temporal areas. In the EA group, strong theta-band synchronization spanned widely across the frontal and motor areas. Thus, in LH condition, both groups shared the same activation mechanism and timing of the motor initiation process.

On the contrary, the way of cortical activation during the pre-motor period in the RH condition (dominant hand movement) was different in considered age groups (Fig. 9.10). In the YA group, the theta-band spectral power did not change significantly during the pre-motor period and the mu-band suppression in the motor cortex began earlier compared to the LH condition  $(0.6 \div 0.8 \text{ s})$  instead of  $0.8 \div 1.0 \text{ s})$ . At the same time, in the EA group, the pre-motor brain dynamics in the RH condition completely reproduces the LH condition scenario in terms of spatio-temporal localization of synchronization and desynchronization in the theta and alpha/mu bands, respectively.

Based on the above MBRT analysis, we assumed that age-related changes affecting the speed of brain motor activation should be found in the pre-motor period. With this aim, we performed within-subject spatio-temporal clustering analysis of the spectral power in the theta and alpha/mu frequency bands for each (group, condition)-set in the premotor period  $(0 \div 1.2 \text{ s})$ . Figure 9.9 shows the results of within-subject clustering analysis in the LH condition for both groups of subjects. It is seen that in the LH condition (non-dominant hand movement), brain activation in both YA and EA groups proceeds similarly. Specifically, the suppression of mu-rhythm in the motor cortex at  $0.8 \div 1.2 \text{ s}$  related to the motor execution control was preceded by the theta-band activation during the period from 0.2 s to 0.8 s. In the YA group, pre-motor theta-band activation involved sensors in the motor, frontal, and bilateral



#### A. LH condition, YA group

**Fig. 9.9** Sensor-level within-subject analyses of the pre-motor activity for LH condition. Baselinecorrected topomaps of the theta-band (upper row) and alpha/mu-band (lower row) spectral power for the YA (**a**) and EA (**b**) groups. Red and blue dots indicate clusters of significant spectral power increase and decrease respectively. Pairwise comparison is performed via t-test for related samples with  $p_{pairwise} = 0.01$  (dF = 9,  $t_{critical} = \pm 2.821$ ) and cluster-based analysis is performed via non-parametric permutation test with  $p_{cluster} = 0.01$ 

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#### A. RH condition, YA group

Fig. 9.10 Sensor-level within-subject analyses of the pre-motor activity (RH condition). Baseline-corrected topomaps of the theta-band (upper row) and alpha/mu-band (lower row) spectral power for the YA (a) and EA (b) groups. Red and blue dots indicate clusters of significant spectral power increase and decrease respectively. Pairwise comparison is performed via t-test for related samples with  $p_{pairwise} = 0.01$  (dF = 9,  $t_{critical} = \pm 2.821$ ) and cluster-based analysis is performed via non-parametric permutation test with  $p_{cluster} = 0.01$ 

ization of synchronization and desynchronization in the theta and alpha/mu bands, respectively.

To address the age-related changes of the pre-motor theta-band activation in detail, we provided a between-subject analysis of spectral power topo-maps. Figure 9.11a shows the results of between-subject spatio-temporal clustering analysis performed separately in each experimental condition. In LH condition, the significant between-subject difference in the theta-band activation was not observed. On the contrary, the between-subject differences were found in the spatial cluster, which included Cp3, Cpz, and Cp4 sensors (dorsal stream region of the sensorimotor area) in  $0.4 \div 0.6$  s window before the RH movement execution. Thus, we localized the effect in the spatio-temporal domain.



**Fig. 9.11** a Between-subject analysis of the event-related theta-band spectral power preceding the LH (left column) and RH (right column) movements execution. Red circles indicate cluster of sensors with significant differences via non-parametric clustering test. Pairwise comparison is performed via two-tailed F-test for independent samples with  $p_{pairwise} = 0.05$  (dF1 = 1 and dF2 = 18,  $F_{critical} = 5.978$ ) and cluster-based analysis is performed via non-parametric permutation test with  $p_{cluster} = 0.05$ . **b** Distribution of the event-related theta-band spectral power averaged over the sensors Cp3, Cpz, and Cp4 forming a positive cluster in **a** across subjects in each (group, condition)—set. Here, \* indicates p < 0.05 and n.s. stands for insignificant difference. **c** Strip-charts (left) and scatterplot (right) of paired observations within each group. Here, diamonds indicate subjects from YA group and squares indicate subjects from EA group

To estimate age-related differences of theta-band activation taking into account both Age and Movement Type factors, we compared mean theta-band spectral power over the evaluated spatio-temporal cluster via mixed-designed ANOVA (see Fig. 9.11b). The mixed-design ANOVA test revealed the significant effect of the Age on the pre-motor theta-band power (F(1, 18) = 4.636, p = 0.045), while the factor of Movement type was insignificant (F(1, 18) = 4.158, p = 0.056). Post hoc comparison via unpaired t-test indicated that the mean pre-motor theta-band spectral power for the EA group (M = 0.636, SD = 0.429) was significantly higher than the YA group (M = 0.294, SD = 0.336). Also, similarly to the MBRT analysis, there was a significant interaction between the Movement Type and the Age of the participants (F(1, 18) = 4.770, p = 0.042). We interpret this interaction as follows: pre-motor theta-band power was similar for LH condition the EA and YA groups (EA LH: M = 0.631, SD = 0.524; YA LH: M = 0.446, SD = 0.376), while the YA group demonstrated higher pre-motor theta-band power in RH condition (EA RH: M = 0.641, SD = 0.365; YA RH: M = 0.142, SD = 0.242).

## 9.3.3 Classification of Wavelet Spectra by Machine Learning Techniques

To localize the statistically significant effect of alpha/mu-rhythm desynchronization obtained with the help of CWT (9.16), a nonparametric cluster test in the spacetime domain was performed in all subjects with the significance level of pairwise comparisons p < 0.001 (df = 30,  $t_{critical} = -2.745$ ). The statistical test showed the presence of two clusters: the first cluster, covering all EEG sensors and localized at the interval 0.45–3.42 s, and the second cluster, including all EEG sensors except for the occipital and parietal lines and localized at the interval 3.468–7.448 s. It should be noted that the most pronounced ERD effect is observed in the left hemisphere of the motor cortex (FC3, C3, Cp3 sensors), but also there is a less pronounced effect in the right hemisphere on symmetric sensors FC4, C4, Cp4. Such bilateral activation of the motor cortex may be associated with the presence in the sample of elderly subjects, characterized by the attraction of additional neuronal populations of the ipsilateral hemisphere during motor control [34].

According to the results of the statistical analysis of the spatiotemporal evolution of the alpha/mu-rhythm, it was proposed to divide the subjects into groups using cluster analysis based on the property of lateralization of the suppression of the alpha/mu-rhythm in the interval  $0.45 \div 7.45$  s. Thus, each subject was characterized by two features: (i) the average ERD of the alpha/mu-rhythm in the left hemisphere of the motor cortex (FC3, C3, Cp3 sensors, and the certain time interval), and (ii) the average value of ERD of the alpha/mu-rhythm in the right hemisphere of the motor cortex (FC4, C4, Cp4 sensors, and the certain time interval). For the cluster analysis, the k-means algorithm was used [42]. The division of subjects into groups for different values of the number of identified clusters n shown the satisfying results for n = 5. In this case, 3 rather large groups of subjects were identified (Cluster0: 7 subjects; Cluster1: 11 subjects; Cluster2: 7 subjects), in which the age differences are statistically significant (p = 0.017, F(2.22) = 4.904) (see Fig. 9.12). The Cluster0 group includes only young subjects, the Cluster2 group includes 6 elderly subjects and 1 young subject. At the same time, the Cluster1 group includes 5 young and 6 elderly subjects.

A statistically significant effect of the alpha/mu-rhythm desynchronization between the groups of subjects was localized using a nonparametric cluster test in the space-time domain with a significance level of group comparisons p < 0.005 (df 1 = 2, df 2 = 22,  $F_{critical} = 6.8064$ ). The statistical test showed the presence of two clusters: the first cluster, covering all EEG sensors {Fz, FC3, FCz, C3, Cz, C4, Cp3, Cpz} at the interval ( $1.78 \div 2.53$  s, corresponding to wrist flexion (Fig. 9.13a, c), and the second cluster including practically all the EEG sensors of the occipital,



Fig. 9.12 a Optimal distribution of subjects across clusters using the k-means algorithm for n = 5, and **b** distribution of the age of subjects in the largest Clusters 0, 1 and 2

parietal, central, temporal and frontal areas and localized at the interval  $4.53 \div 7.27$  s, corresponding to wrist extension (Fig. 9.13b, d). The topograms shown in Fig. 9.13a, b, show that the most significant effect in both clusters is demonstrated by channel C3, which belongs to the left hemisphere of the motor cortex and is associated with normal neuronal activation during movements of the right limb. From the dynamics of the normalized wavelet power in the detected clusters (Fig. 9.13c, d) it can be seen that, while the Cluster0 (YA subjects) and Cluster2 (EA subjects) groups demonstrate pronounced alpha/mu-rhythm desynchronization, the Cluster1 group, which includes subjects of both age groups, does not demonstrate changes in the level of the wavelet power of the alpha/mu-rhythm in relation to the prestimulus state.

Let us consider the averaged patterns of the spatial distribution of the normalized wavelet power of the alpha/mu-rhythm at time intervals corresponding to statistically significant differences between the groups of subjects during movements of the right hand (see Fig. 9.14). YA subjects in the Cluster0 group (18–33 years old) demonstrate the most pronounced alpha/mu-rhythm desynchronization localized in the motor cortex (Fig. 9.14, left column). At the same time, while flexion of the hand activates both hemispheres of the motor cortex (sensor C3 in the left hemisphere, and sensors C4 and Cp4 in the right one), the subsequent extension of the hand activates the suppression of the alpha/mu-rhythm strictly in the left hemisphere (sensor C3). The described neural activity is normal for healthy people without neurological pathologies. As consequence, we can considered the Cluster0 group as a control group.



**Fig. 9.13** Topograms **a**, **b** illustrate the distribution of F-statistics values in spatio-temporal clusters obtained in the course of a nonparametric test aimed at identifying areas of statistically significant differences in alpha/mu-rhythm desynchronization between groups of subjects determined on the basis of cluster analysis. Panels **c**, **d** show the time series of the wavelet power of the alpha/mu-rhythm averaged over the identified clusters. Orange areas indicate time intervals corresponding to statistically significant differences, and the horizontal line—the background level of wavelet energy



**Fig. 9.14** Topograms illustrate the spatial distribution of the wavelet power of the alpha/mu-rhythm at time intervals corresponding to statistically significant differences between the groups of subjects during squeezing (top line) and unclenching (bottom line) of the right hand. The columns correspond to different groups of subjects identified using cluster analysis

In turn, the Cluster2 group, consisting mainly of EA people (53–67 years old), demonstrates significantly less pronounced suppression of oscillations in the 8–14 Hz band, however, it covers a much wider range of EEG channels, including the occipital and parietal sensors during flexion as well as parietal and frontal sensors when extending the right hand (Fig. 9.14, middle column). The Cluster2 group is also characterized by less pronounced lateralization of neuronal activity, which is also an important feature on the basis of which these subjects were combined into one group at the stage of cluster analysis. Such the changing of normal activation can be associated with age-related neurodegenerative processes progressing under the influence of healthy aging [101]. There are two competing hypotheses explaining the described extensive activation from the standpoint of (i) compensatory mechanisms that use more distributed neural ensembles of neighboring regions of the brain to maintain the proper level of motor control [82], or (ii) dedifferentiation of brain functions in the elderly, associated with a gradual loss of the expressed functional role of local neural networks [7].

Finally, Cluster1, which includes subjects of both YA and EA groups, shows weak activation in the motor cortex during hand flexion and does not show alpha/murhythm suppression during hand extension (Fig. 9.14, right column). It should be noted that this group includes the oldest participants in the experiments (68–72 years old), which may explain the statistically insignificant level of desynchronization of the mu rhythm in comparison with the prestimulus activity. Perhaps this may be due to a shift in the activation of the motor cortex to a higher frequency range of beta waves (15–30 Hz) under the influence of GABA inhibitors, which appear under the influence of neurochemical changes in the brain during healthy aging [25, 26]. However, this group also includes subjects of the younger age group (25–27 years old), which can potentially be a wavelet-based biomarker for them of violations of the normal functioning of the brain, namely, structural, neurochemical or functional changes.

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# Chapter 10 Conclusion



Wavelet analysis remains a somewhat exotic method in contemporary neuroscience and neurophysiology. It seems that new mathematical or experimental methods, despite all their benefits and technological advantages, need time to become accepted as a convenient tool for routine applications. It is particularly noticeable in the clinical and biological sciences, where novel mathematical tools must undergo a thorough examination, adaptation, and verification, and only then can they be accepted for practical use. In this context, it should be emphasized that wavelet analysis is suitable for time–frequency analysis of neurophysiological signals, and can also be incorporated into more complex algorithms for experimental data processing that increase the efficacy of data analysis in neurophysiological studies. We believe that the wavelet-based analysis will naturally evolve into a family of standard methods for signal processing in biology and medicine. This does not mean replacement of the conventional by new techniques, but improvement of existing approaches to make wavelet analysis more widely applicable in experimental neuroscience.

The present monograph addresses just a few problems that are frequently encountered in neuroscience and neurophysiology. Even this brief review demonstrates several beneficial ways and promising perspectives for using wavelet analysis in neurophysiological research. Applications of the powerful mathematical analysis of nonlinear dynamics to neuronal systems, both at the micro- and macrolevels of the central nervous system, opens new perspectives for the study of the extremely complex mechanisms of brain functions. At the same time, interpretation of results obtained by this interdisciplinary approach is difficult in the context of neurophysiology due partly to the extreme complexity of the explored object (the nervous system of living organisms), and partly to the difficulty in identifying the appropriate physiological meaning of results obtained by such sophisticated mathematical methods. Here we would like to quote A. M. Ivanitskii and A. I. Lebedev, who commented that "[...] the integration of mathematics and physiology gives the best result when

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the application of a specified mathematical transform is underlain by a fruitful physiological idea" [1]. Indeed, success in developing new data-processing technologies in any interdisciplinary field including contemporary neuroscience depends on the introduction of new neurophysiological ideas and clearly defined goals, along with appropriate ways to achieve them.

There can be little doubt that the number of neurophysiological studies using wavelet-based methods will continue to grow, because it provides a solution for many challenging problems, such as the principles of information coding and presentation. Further progress in understanding the functions of the central nervous system requires not only the development of experimental research facilities (where considerable progress has been made in the last few decades), but also the introduction of new mathematical methods for decoding neural signals. The extraordinary complexity and intricacy of brain processes make it impossible to decipher neural signals using only the methods of statistical analysis. From the viewpoint of nonlinear dynamics, the adaptation of living systems (organisms and their neural systems) to the environment is accompanied by changes in their dynamics, whereupon neurophysiological signals recorded at this time should be considered as time series of nonstationary processes produced by dynamical systems with an unlimited number of degrees of freedom. If we ignore this fact, we may miss important information about the neural system, whereas understanding adaptive processes facilitates the study of the basic principles of neural activity.

Wavelet analysis can be expressed by the metaphor of a "mathematical microscope", highlighting the fact that we need to use appropriate magnification in order to disclose certain hidden features that cannot be detected by the naked (or inadequately armed) eye. There is still great (yet hidden) potential for this research tool. The present monograph describes some modifications to the mathematical processing of experimental data and addresses some problems of neural system dynamics, but also tries to inspire the reader by describing the promising new prospects for wavelets in neurophysiological applications. In the coming years, wavelet analysis should become an effective research tool that will help to improve the quality of research in the field of neuroscience. Moreover, the wavelets become an effective tool for the development of the different neurotechnologies, including systems for automatic processing of neurophysiological data and brain-computer interfaces.

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