EEG-Biofeedback and Epilepsy: Concept, Methodology and Tools for (Neuro)therapy Planning and Objective Evaluation

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Acknowledgment

„*You're sure you want walk through this wall with me...? You know, for me it's easy. Whatever happens, I am coming home. But you are leaving home.* ' ***True journey is return***...' "[1], Shevek (Dr.)[2]

It was a hard decision for a long journey at the beginning: Choice between paths... Uncertainties... Insecurities... Finally, the decision was made; and probably, the more challenging path was taken. The journey itself was not easier than the decision: Problems with a new language, a new culture, a new climate and, certainly not the least, with all the repetitive bureaucratic procedures, which I had to face, often alone, far away from home. The main motivation that helped be overcome all these difficulties was my fascination with brain research. And now, the only thing I feel is the satisfaction of being able to present the results of my work.

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[1] Ursula Le Guin, The Dispossessed: An Ambiguous Utopia, p. 319, HaperCollinsPublishers, London, 1996.

[2] The main character in the a.m. book who is a scientist and leaves his homeplanet (Anarres) to go to another one (Urras) for his research.

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The journey is now coming to an end, opening new paths and new challenges not only scientifically but also personally. New decisions are waiting to be made. Surely, they will not be easier than the ones at the beginning. Maybe further journeys are ahead, who knows, maybe, the true journey is, indeed, return...

Ilmenau, June 2004 Mehmet Eylem Kirlangic

[3] "Where the sky is blue", a common description in German used for Ilmenau.

[4] The color gray in German.

Abstract

Objective diagnosis and therapy evaluation are still challenging tasks for many neurological disorders. This is highly related to the diversity of cases and the variety of treatment modalities available. Especially in the case of epilepsy, which is a complex disorder not well-explained at the biochemical and physiological levels, there is the need for investigations for novel features, which can be extracted and quantified from electrophysiological signals in clinical practice. Neurotherapy is a complementary treatment applied in various disorders of the central nervous system, including epilepsy. The method is subsumed under behavioral medicine and is considered an operant conditioning in psychological terms. Although the application areas of this promising unconventional approach are rapidly increasing, the method is strongly debated, since the neurophysiological underpinnings of the process are not yet well understood. Therefore, verification of the efficacy of the treatment is one of the core issues in this field of research.

Considering the diversity in epilepsy and its various treatment modalities, a concept and a methodology were developed in this work for increasing objectivity in diagnosis and therapy evaluation. The approach can also fulfill the requirement of patient-specific neurotherapy planning. *Neuroprofile* is introduced as a tool for defining a structured set of quantifiable measures which can be extracted from electrophysiological signals. A set of novel quantitative features (i.e., *percentage epileptic pattern occurrence*, *contingent negative variation level difference measure*, *direct current recovery index*, *heart rate recovery ratio*, and *hyperventilation heart rate index*) were defined, and the methods were introduced for extracting them. A software concept and the corresponding tools (i.e., *the neuroprofile extraction module* and a *database*) were developed as a basis for automation to support the methodology.

The features introduced were investigated through real data, which were acquired both in laboratory studies with voluntary control subjects and in clinical applications with epilepsy patients. The results indicate the usefulness of the introduced measures and possible benefits of integrating the indices obtained from electroencephalogram (EEG) and electrocardiogram for diagnosis and therapy evaluation. The applicability of the methodology was demonstrated on sample cases for therapy evaluation. Based on the insights gained through the work, *synergetics* was proposed as a theoretical framework for comprehending neurotherapy as a complex process of learning. Furthermore, direct current (DC)-level in EEG was hypothesized to be an order parameter of the brain complex open system. For future research in this field, investigation of the interactions between higher cognitive functions and the autonomous nervous system was proposed.

Keywords: EEG-biofeedback, epilepsy, neurotherapy, slow cortical potentials, objective diagnosis, therapy evaluation, epileptic pattern quantification, fractal dimension, contingent negative variation, hyperventilation, DC-shifts, instantaneous heart rate, neuroprofile, database system, synergetics.

Zusammenfassung (Abstract in German)

Die Epilepsie ist eine komplexe neurologische Erkrankung, die auf biochemischer und physiologischer Ebene nicht ausreichend geklärt ist. Die Vielfalt der epileptischen Krankheitsbilder und der Behandlungsmodalitäten verursacht ein Defizit an quantitativen Kenngrößen auf elektrophysiologischer Basis, die die Objektivität und die Effizienz der Diagnose und der Therapieevaluierung signifikant erhöhen können. Die Neurotherapie (bzw. EEG-Biofeedback) ist eine komplementäre Behandlung, die bei Erkrankungen, welche in Zusammenhang mit Regulationsproblemen des Zentralnervensystems stehen, angewandt wird. Obwohl sich die Applikationen dieser unkonventionellen Methode erweitern, wird sie nach wie vor stark diskutiert, da deren neuro- und psychophysiologischen Mechanismen wenig erforscht sind. Aus diesem Grund ist die Ermittlung von Kenngrößen als elektrophysiologische Korrelaten der ablaufenden Prozesse zur objektiven Einstellung und Therapievalidierung eines der Kernprobleme des Forschungsgebietes und auch der vorliegenden Arbeit.

Unter Berücksichtigung der aktuellen neurologischen Erkenntnisse und der durch Untersuchungen an Probanden, sowie an Epilepsie-Patienten gewonnenen Ergebnisse, wurden ein Konzept und eine Methodologie entwickelt, um die Objektivität in der Diagnose und Therapieevaluierung zu erhöhen. Die Methodologie basiert auf einem *Neuroprofil*, welches als ein signalanalytisches mehrdimensionales Modell eingeführt wurde. Es beschreibt einen strukturierten Satz quantifizierbarer Kenngrößen, die aus dem Elektroenzephalogramm (EEG), den ereignisbezogenen Potentialen und dem Elektrokardiogramm extrahiert werden können. Als Komponenten des Neuroprofils wurden neuartige quantitative Kenngrößen (*percentage epileptic pattern occurrence*, *contingent negative variation level difference measure*, *direct current recovery index*, *heart rate recovery ratio*, *hyperventilation heart rate index*) definiert und die Methoden zu deren Berechnung algorithmisiert. Die Anwendbarkeit der Methodologie wurde beispielhaft für die Evaluierung von Neurotherapien an Epilepsie-Patienten demonstriert. Als Basis für eine zukünftige Automatisierung wurden ein Softwarekonzept und entsprechende Tools (*neuroprofile extraction module* und die Datenbank „*NeuroBase*“) entwickelt. Der Ansatz erfüllt auch die Anforderungen der patientenspezifischen Therapieplanung und kann auf andere Krankheitsbilder übertragen werden.

Durch die neu gewonnenen Erkenntnisse wurde die *Synergetik* als ein theoretischer Rahmen für die Analyse der Neurotherapie als komplexer Lernprozess vorgeschlagen. Es wurde die Hypothese aufgestellt, dass das Gleichspannungsniveau im EEG ein Ordnungsparameter des Gehirn ist, wobei das Gehirn als ein komplexes offenes System betrachtet wird. Für zukünftige Forschungen auf dem Gebiet wird empfohlen, die Wechselwirkungen zwischen den höheren kognitiven Funktionen und dem autonomen Nervensystem in diesem Kontext zu untersuchen.

Schlüsselwörter: EEG-Biofeedback, Epilepsie, Neurotherapie, langsame kortikale Potentiale, objektive Diagnose, Therapieevaluierung, epileptische Musterquantifizierung, Fraktal Dimension, Kontingent negative Variation, Hyperventilation, DC-Verschiebung, momentane Herzschlagfrequenz, Neuroprofil, Datenbanksystem, Synergetik.

Özet (Abstract in Turkish)

Birçok nörolojik bozuklukta, vak'aların ve tedavi yöntemlerinin çeşitliliği, nesnel tanı ve tedavi değerlendirmelerini güçleştirmektedir. Özellikle epilepsi gibi, gerek biyokimyasal gerekse fizyolojik düzlemlerde yeterince açıklanamamış rahatsızlıklarda, elektrofizyolojik sinyallerden elde edilebilecek yeni nesnel parametrelere ihtiyaç duyulmaktadır. Davranışsal tedavi olarak sınıflandırılıp psikoloji terimiyle 'aletli koşullanma' olarak tanımlanan nöroterapi, epilepsi de dahil olmak üzere merkezi sinir sisteminin regülasyon bozukluklarında kullanılan bir yöntemdir. Uygulama alanları giderek yaygınlık kazanmakla birlikte, nörofizyolojik temelleri henüz açıklık kazanmadığından, bu yöntemin geçerliliği büyük ölçüde tartışılmaktadır. Dolayısıyla, nöroterapinin etkinliğinin saptanması bu araştırma alanının önemli konularındandır.

Bu çalışmada, epilepsi hastalığının ve tedavi yöntemlerinin çeşitliliği göz önünde tutularak, tanı ve tedavi değerlendirmelerinde nesnelliği artırmak amacıyla yöntem ve araçlar geliştirilmiş, yeni parametreler tanımlanmıştır. Elektorfizyolojik sinyallerden elde edilebilecek nicelikler kümesini içeren matematiksel bir araç olarak 'Nöroprofil' kavramı tanımlanmıştır. Nöroprofilin bileşenlerinin bir alt kümesi olarak yeni parametreler (*epileptik örüntü sıklığı*, *bağıl negatif değişim düzeyi ölçüsü*, *hiperventilasyonda doğru akım değişim göstergesi*, *hiperventilasyonda nabız değişim oranı* ve *nabız göstergesi*) ve bu parametrelerin hesaplanma yöntemleri ortaya konulmuştur. Geliştirilen yöntemlerin otomasyonunu sağlayabilecek yazılım araçları (*nöroprofil çıkarım modülü* ve *veri tabanı*) geliştirilmiştir.

Tanımlanan parametreler, gerek epilepsi hastalarından gerekse gönüllü katılımcılardan elde edilen sinyallerle hesaplanmış ve karşılaştırılmıştır. Sonuçlar, bu parametrelerin tanı amaçlı kullanılabilirliğini göstermektedir. Özellikle hiperventilasyon sonucu EEG ve EKG sinyallerinde meydana gelen degişimleri niceliklendirmek için tanımladığımız göstergelerin birleşik analizi yeni bir yöntem olarak önemli sonuçlar vermiştir. Geliştirilen yöntemler, tedavi değerlendirilmesi amaçlı örnek vak'alarda kullanılmıştır. Çalışmalarda elde edilen gözlem ve sonuçlar doğrultusunda, karmaşık bir öğrenme süreci olarak nöroterapinin daha iyi anlaşılabilmesi için yeni bir düşünce sistematiğininin gerekliliği tartışılmıştır. Sinerjetik yaklaşımın bu alanda teorik bir çerçeve sağladığı öne sürülmüştür. Bu açıdan, EEG'nin doğru akım bileşeninin, beyin karmaşık açık sisteminin bir 'düzen parametresi' olduğu hipotezi ortaya atılmıştır. Bu alandaki bilimsel çalışmaların, beynin bilişsel işlevleri ve otonom sinir sistemi arasındaki etkileşimlere yoğunlaştırılması önerilmiştir.

Anahtar Sözcükler: EEG-biyogeribildirim, epilepsi, nöroterapi, yavaş kortikal gerilimler, nesnel tanı, tedavi değerlendirilmesi, nöroprofil, veri tabanı, epileptik örüntü nicelendirilmesi, fraktal boyut, bağıl negatif değişim, hiperventilasyon, doğru akım kayması, anlık nabız, sinerjetik.

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List of Abbreviations

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ATHM	Respiration curve
BCI	Brain-computer-interface
BP	Bereitschaftspotential
CEN	European Standardization Committee
CNS	Central Nervous System
CNV	Contingent Negative Variation
CSE	Common Standards for Quantitative Electrocardiography
CT	Computed Tomography
DBMS	Database management system
DC	Direct current
EBS	Extensible Biosignal Format
ECG	Electrocardiogram
EDF	European Data Format
EEG	Electroencephalogram
EOG	Electrooculogram
ERD	Entity-relationship diagram
ERM	Entity-relationship modeling
ERP	Event-related Potentials
FCMI	Fuzzy c-means iterative algorithm
FD	Fractal dimension
FFT	Fast Fourier Transformation
fMRI	Functional Magnetic Resonance imaging

GABA	Gamma-amino butyric acid
GUI	Graphical user interface
HEOG	Horizontal electrooculogram
HV	Hyperventilation
IAPS	International Affective Picture System
ID	Identity code
IHR	Instantaneous heart rate
IHRC	Instantaneous heart rate curve
ILAE	International League Against Epilepsy
LTP	Long-term potentiation
MEG	Magnetoencephalogram
NCRG	NeuroCybernetics Research Group
NMDA	N-methyl-D-aspartate
ODBC	Open database connectivity
OEDIPE	Open European Data Interchange and Processing for Electrocardiography
PDS	Paroxysmal depolarization shift
PET	Positron Emission Tomography
PS	Photostimulation
qEEG	Quantitative electroencephalogram
SCP	Slow Cortical Potentials
SMR	Sensorimotor rhythm
SNOMED	Systematized Nomenclature of Medicine
SP	Slow potentials
SPECT	Single Photon Emission Computed Tomography
SQL	Structured Query Language
TC251	Technical Committee 251
VEOG	Vertical electrooculogram

VITAL	Vital Signs Information Representation
VM	Värri measures

List of Symbols

a_c	Adaptation constant
a_p, b_p, c_p	Measures of a pattern
A	Amplitude measure
$ADIF$	Amplitude difference measure
B	Block size of analysis in data points
c	Number of clusters
c_a	Amplitude difference measure coefficient
c_f	Frequency difference measure coefficient
Ca^+	Calcium ion
d_{CNV}	Contingent negative variation level difference measure
D	Euclidean distance
DCI_{rec}	Direct current recovery index
E	Maximum error
EPO	Epileptic pattern occurrence measure
f	Number of measures used for pattern characterization
F	Derivate measure
$FDIF$	Frequency difference measure
FD	Fractal dimension
G	Measure difference function
GV_k	Measure difference function of Värri measures
GD_k	Measure difference function of fractal dimension
Hz	Hertz

HR_{bsl}	Baseline heart rate
HR_{hv}	Average heart rate during hyperventilation
HR_{rec}	Average heart rate during recovery
$HR_{rec/hv}$	Heart rate recovery ratio
HRI_{hv}	Hyperventilation heart rate index
$I_f(i)$	Local fuzzy performance index
K^+	Potassium ion
L	Curve length
lt	Liters
m	Number of patterns
ml	Milliliters
min	Minutes
ms	Milliseconds
mV	Millivolts
M	Maximum number of iterations
Na^+	Sodium ion
ol	Overlap of successive windows in data points
p_m	EEG segments
P_{ij}	Degree of membership of pattern p_j
pCO_2	Partial pressure of carbon dioxide
pO_2	Partial pressure of oxygen
pH	Acidity
Q_n	Adaptive recursive threshold function
R	Estimated diameter
R_l	Left hand thumb response in SMR paradigm
R_r	Right hand thumb response in SMR paradigm
s	Seconds

s_{hv}	Rate of change of DC-level during hyperventilation
s_{rec}	Rate of change of DC-level during recovery
S_1	Stimulus 1 in S1-S2 paradigm
S_2	Stimulus 2 in S1-S2 paradigm
S_l	Stimulus for left hand reaction in SMR paradigm
S_o	Stimulus for no-reaction in SMR paradigm
S_r	Stimulus for right hand reaction in SMR paradigm
S_s	Standard tone in odd-ball paradigm
S_t	Target tone in odd-ball paradigm
t	Time
T	Over all duration of a measurement
TH	Adaptive segmentation threshold
$U = \{p_i\}$	Set of EEG segments
wl	Window length in data points
$W(t)$	Weierstrass cosine function
x_i	Signal
$Y_0 = \{y_{i0}\}$	Set of initial cluster centers
z_i	Cluster center
α	Quantile parameter
β	Tuning parameter of fuzziness
ε	Tolerance
µV	Microvolts

1 Introduction

Biofeedback is an unconventional method introduced for the treatment of diverse disorders related to regulation problems in human physiology. The method, which is defined as a process of learning (i.e., operant conditioning), and subsumed under behavioral medicine, is based on the capability of learning to bring the physiological functions under voluntary control. If the physiological function under consideration is a brain function, then terms such as operant brain regulation, cortical self-regulation or neurofeedback are utilized.

Parallel with developments in computer technology and on-line signal processing in recent decades, neurofeedback treatment, which is often referred to as neurotherapy, has enlarged its fields of application beyond the more historically established research in treatment of epilepsy and attention deficit hyperactivity disorder (ADHD).

Research in this field has many facets and needs highly interdisciplinary cooperation: On the one hand, psychologists and neurologists search for new protocols, investigate their applicability in different disorders, and try to explain the underlying neuronal mechanisms. On the other hand, engineers work on the development of new brain-computer-interface (BCI) systems which can comply with the requirements of high flexibility and adaptability. The present state of investigations shows that, in order to achieve success in neurotherapy, patient-specific clinical manifestations have to be considered for adapting the learning process according to the subject's individual characteristics

In our studies at the Technische Universität Ilmenau, the Institute of Biomedical Engineering, we (i.e., the NeuroCybernetics Research Group (NCRG) [1]) have developed a prototype of a flexible BCI system which can also be employed for neurofeedback applications for different disorders [2]-[4]. Using this system we held training sessions with healthy controls and clinical applications with refractory epilepsy patients. The training sessions were based on the self-regulation of the so

called slow cortical potentials (SCP). These are slow potentials (SP) recorded on the scalp which include direct current (DC) and near DC components.

The present work does not focus on the developed BCI system[5], but on two other issues in the research field, namely, (1) a patient-specific neurotherapy strategy, and (2) an objective, possibly automated, evaluation of the applied therapy. The problem in objective evaluation, as in other medical treatment processes, is concentrated in the determination and quantification of the changes resulting from therapy by means of pre- and post-therapy comparisons. The prerequisite for these comparisons is, however, the determination of features which distinguish a certain pathological state from normal functioning. The issue of patient-specific neurotherapy can similarly be addressed by means of quantitative features which reflect the neurophysiological differences between the individuals.

The neurometric quantitative electroencephalogram (qEEG) analysis, as defined in [5]-[8], appears to be a possible tool for solving this problem. However, in epilepsy, as in several other neurological disorders, the qEEG cannot be considered apart from additional medical information, such as the results of the clinical examination, medical history, previous and current pharmacological and other (e.g. surgical) treatments, and further disorder specific information. Especially in case of refractory epilepsy patients with a long history of the disorder, it is necessary to include all accessible information for the evaluation of the therapy. Additionally, the therapy specific information regarding its modalities must be considered. For pharmacological treatment, this can be the active substance, its daily doses and the time span of prescription. For neurotherapy, it is essential to access information such as

- the feedback parameter (i.e., frequency bands, slow cortical potentials etc.),
- the stimuli used for the task definition (i.e., visual, acoustic or tactile),
- the feedback used (i.e., visual or acoustic),
- the duration and number of trials, and
- the information related to the simultaneously acquired polygraphical signals.

[5] The BCI system has been awarded with the German Innovation Award 2004 for Biomedical Engineering given by the "Stiftung Familie Klee".

All these necessities yield an excessive amount of data which need to be structured and managed. This is one of the components of the problem solved via a software concept linked to a data warehouse in this study.

The scope of the problem, however, extends far beyond this aspect alone, because in many epilepsy cases there is no significant deviation from the normal neurometric qEEG values. The present state of investigation reflects a very high individual diversity. Due to the lack of distinguishing features, epilepsy cannot be clustered in any existing normative qEEG database. Hence, in order to evaluate and validate the success of neurotherapy in epilepsy, there is the need for a better understanding of both neurotherapy as an emerging unconventional treatment and of epilepsy as an inadequately explained disorder. From this perspective, the problem extends over the disciplines of psychology, neurology and engineering.

For this reason, an overview of the conventional medical fundamentals of epilepsy and of the two main neurotherapy protocols proposed for epilepsy treatment is provided in chapter 2. The SCP based neurotherapy is described in more detail, since it is the clinically applied protocol in the current study. In the same chapter, the DC potentials associated with diverse states of the brain are introduced in order to complete the basics necessary for problem orientation and analysis.

After a critical analysis of the interdisciplinary issue with its biomedical engineering aspects and roots in both neurology and psychology, the guidelines for a possible solution are sketched in chapter 3.

In chapter 4, associated with the developed therapy evaluation strategy, the concept of neuroprofile is coined, and the protocol for the initial and evaluation measurements, which is determined in consultation with medical partners, is presented.

A separate chapter (chapter 5) is dedicated to data acquisition, since the measurements in both healthy controls and epilepsy patients constitute a significant part of the study. In this chapter, the equipment, including the developed BCI system and the technical settings of the measurements, is introduced shortly. The laboratory studies with voluntary control subjects and the clinical applications with epilepsy patients, which involve learning and training the self-regulation of the central or frontocentral SP, are

presented along with the corresponding details of the acquired electrophysiological signals.

Chapter 6 comprises the signal analytical methodology developed or, respectively, used for extraction and quantification of the selected feature candidates. The unsupervised and supervised approaches are introduced for quantifying epileptic patterns (i.e., graphoelements) in electroencephalogram (EEG). The procedures for analyzing contingent negative variation (CNV), as well as hyperventilation induced DC-shifts in EEG and changes in simultaneously acquired electrocardiogram (ECG) are presented.

The data management component of the solution is addressed in chapter 7. The developed software concept and the corresponding database system are introduced with their implementations.

Chapter 8 presents the essential results of signal analysis, comparisons between healthy controls and epilepsy patients, as well as sample pre- and post- therapy comparisons for the patients who were available for follow-up.

After this overview of the obtained results, the thesis continues with a detailed discussion in chapter 9. Based on the essentials of the results, the discussion focuses on the necessity of a change in paradigm for understanding neurotherapy and its effects in epilepsy, in order to comprehend a complex process of operant conditioning (i.e., neurotherapy as a process of learning) which elicits alterations on a very complex system: The human brain with its more than 100 billion neurons, 10^4 connections per neuron, and 10^{22} molecules per cubic centimeter is a giant dynamical system [9]. The neurofeedback process, on the other hand, is a voluntary intervention with the central nervous system (CNS) at a macroscopic level and involves both psychological and neurological processes. At this point, the discussion reaches to the depth of the philosophical mind-body problem. Even though the problem appears to be very complicated, changing our paradigm and using new concepts such as open systems, self-organization, circular causality and synergy, which are the foundations of *synergetics* as coined by Haken [9], [10], lead us to new possible approaches, which should be a subject of further research in the field. From this perspective, not only neurotherapy and epilepsy but also the SP on the scalp gain new meaning.

In chapter 10, conclusions are derived and future research directions are proposed based on new perspectives obtained from synergetics. A new path concentrating on parameters, which shall and can reflect functional couplings between the participating subsystems in the neurofeedback process (e.g., the higher cognitive functions and the autonomic nervous system), is proposed for further investigations in both epilepsy research and objective *(neuro)therapy*[6] evaluation.

[6] The form with parentheses is used for the term *(neuro)therapy* in order to emphasize that the results and conclusions in terms of engineering, as well as in terms of psychology and neurology, achieved in this work can also be employed for other therapies in epilepsy.

2 Fundamentals: Epilepsy and EEG-Biofeedback

In order to have a point of reference for the issues of patient-specific neurotherapy strategy and objective (neuro)therapy evaluation in epilepsy, it is necessary to have an overview on the disease, its therapies and corresponding treatment modalities. These will be summarized in this chapter.

2.1 Epilepsy

"A disease of the nervous system, characterized (in its severer forms) by violent paroxysms, in which the patient falls to the ground in a state of unconsciousness, with general spasm of the muscles and foaming at the mouth."

The above description of the Oxford English Dictionary is also the common public imagination of an epileptic seizure. A "generalized seizure" is, however, only one of the categories of possible epileptic symptoms. One can even prefer to consider the term "epilepsies" representing the plurality of the forms of the disorder [11], [12]. Epilepsies are characterized by the episodic recurrence of paroxysmal neurological or behavioral manifestations caused by abnormal synchronous and excessive discharges of large groups of neurons. In this chapter, the term "epilepsy" will be used as a genus for the group of diseases and syndromes of which the common feature is the occurrence of epileptic seizures.

2.1.1 Clinical Features

The incidence of human epilepsy is estimated to range between 0.5 and 1% of the general population. After disorders of circulation, epilepsy is the most frequent chronic disorder of the nervous system [11], [13].

Epilepsy is not a unitary disease. It varies not only in etiology, but also in seizure types and accompanying somatic and/or psychic symptoms, as well as in the course of

occurring seizures. The differential diagnosis of epilepsy must consider other episodic disturbances of CNS functions such as syncope, migraine, hysteria, and other psychiatric disorders, and determine whether the seizures are caused by a structural brain lesion, a metabolic derangement, or a genetically determined brain disorder [14].

In fact, epilepsy is a multi-factorial condition reflecting acquired and genetic factors. Factors such as prenatal and postnatal cerebral trauma, infections of the CNS, brain tumors, cerebral vascular lesions, congenital malformations, and some metabolic disorders can be listed as possible exogenous factors. Such epilepsies, for which an exogenous factor is identifiable, are defined as symptomatic epilepsy. Identification of the exogenous factors involved in the causation of epilepsy is relevant for its prevention, since the incidence of disorder can be reduced by prenatal care or by prevention of brain injuries. The idiopathic epilepsies, on the other hand, are those which have genetic factors as an identifiable cause. These may include seizures caused by a single gene disorder (e.g., some inborn errors of metabolism) and other genetic factors that interact with exogenous factors. In some forms of inherited seizure disorders in animals, significant progress has recently been made in understanding their molecular biology. In many epilepsy cases, however, the etiology remains unknown. Therefore, a large group of epilepsies is classified under the term cryptogenic epilepsy [14].

2.1.2 Focal (Partial) and Generalized Epilepsy

Epileptic discharges may involve any structure of the CNS, although they usually originate in some of them (most often the cerebral cortex, including the hippocampus, or the amygdala) [14]. The most dramatic clinical manifestation is loss of consciousness with generalized tonic-clonic convulsions (i.e., a generalized seizure), which actually may be the final outcome of any epileptic seizure, but particular seizures exhibit a great variety of clinical signs and symptoms. Their distinctive features depend upon differences in the site of origin and in the extent and pattern of spread of the seizure discharge. Thus, the symptomatology of an epileptic seizure reflects the functional significance of the brain area involved in the seizure discharge. For instance, twitching of the left or right facial muscles can be associated with discharges involving the contra-lateral face area of the precentral gyrus, or phosphenes occurring in the visual

field with discharges in the contra-lateral visual cortex, or evocation of past memories can be related to discharges in temporal lobe. Such symptoms result from ictal activation of neuronal mechanisms represented in the corresponding areas, whereas other manifestations such as the inability to utter or understand speech result from disruption of the normal function of the speech cortex when this area is involved in ictal discharge [14].

Depending on whether the brain is entirely or only partially involved in a seizure discharge at its onset, which is evaluated by both clinical and EEG criteria, epileptic seizures are subdivided into two main categories: (1) partial (i.e., focal) and (2) generalized. Each category is further subdivided into subcategories according to the ictal symptoms of the seizure [12]-[14]. The International League Against Epilepsy (ILAE) classifies epileptic seizures mainly as (1) focal, (2) complex focal, (3) secondary generalized, and (4) (primary) generalized seizures [15]-[16]. Although epilepsy classification has various aspects and is much more complicated, the separation as focal and generalized will be taken as a basis in this work, since focal epilepsy patients are considered as more suitable for neurotherapy.

2.1.3 The Neurophysiology

Although the biochemical mechanisms are not yet clearly explained, certain typical electrical phenomena are observed in epilepsy. Intercellular measurements at epileptic foci show an extraordinary long lasting, high amplitude membrane depolarization accompanied with spike trains. This phenomenon is defined as paroxysmal depolarization shift (PDS). This was first described in neurons lying under experimentally induced foci. The long-lasting depolarization corresponds to epileptic discharges observed at surface electrodes. There may be various mechanisms or combinations of them promoting this phenomenon:

a. decreased inhibition (insufficient gamma-amino butyric acid –GABA),
b. increased excitation (derangement in N-methyl-D-aspartate (NMDA) receptor and glutamate),
c. alterations in Na^+, Ca^+, K^+ ion concentrations, or
d. alterations in membrane ion channels.

Mechanisms of kindling (i.e., long-term sub-threshold stimulation giving rise to persistent primary and secondary foci) and long-term potentiation (LTP) (i.e., modification of synaptic activity upon synchronously recurrent firing), which are addressed for memory and learning processes in normal brain functioning, are also considered for their involvement in epileptogenesis [17].

2.2 Therapies in Epilepsy

The objective of any epilepsy therapy is that the patient becomes seizure free, or at least a significant reduction in the frequency and/or intensity of seizures is aimed with the least possible physical and psychological disruption for the patient (i.e., side effects). The therapies offered in epilepsy today can be listed as: pharmacological, surgical, alternative and behavioral therapies.

2.2.1 Pharmacological Therapy

Traditionally, the first choice in epilepsy treatment is pharmacological therapy. Based on the possible biochemical mechanisms presumed, different anti convulsive substances are offered in pharmacological therapy. These aim at acting on the corresponding biochemical components such as the ion balance of the neuronal environment through either

a. changing the ion concentrations or the permeability of the neuronal membranes to certain ions such as K^+, Na^+, Ca^+ (i.e., Type A medication: carbamazepine, phenytoin, lamotrigine); or
b. increasing the inhibition (GABA energic) (i.e., Type B medication: valproate, benzodiazepine, vigabatrin, tiagabin); or
c. decreasing the excitation (acting on NMDA-receptor/glutamate) (i.e., Type C medication: NMDA-antagonist, losigamon, dextromethorphan, felbamat, gabapentin) [18].

The pharmacological therapy in epilepsy has two main problems: First is pharmaco-resistance (i.e., refractory epilepsy patients) of a significant percentage of the patients (i.e., 25%), and the second is the strong side-effects of the medication on both organic

(e.g., hepatic side effects) and psychophysiological (e.g., perceptive and cognitive side effects) levels [19].

2.2.2 Surgical Therapy

Surgical treatment is the second choice in mainly intractable focal epilepsy cases for which the focus can be precisely determined, so that it can be removed by a surgical operation. It is also applied to remove larger brain areas or to severe the corpus callosum so that communication between the cerebral hemispheres is interrupted (i.e., callosotomy). Due to the problems with focus localization and the high risks of surgical intervention, this treatment can be applied to a rather small group (20%) of patients with refractory epilepsy [20].

Vagus Nerve Stimulation

Another relatively new treatment, which can be classified under surgical therapy, is vagus nerve stimulation. In this treatment an electrical pacemaker is implanted into the body in order to stimulate the vagus nerve at different frequencies, which result in an increased desynchronization in EEG. It can be applied in severe intractable epilepsy cases and may be a possible alternative to callosotomy. However, it is contraindicated for patients with obstructive lung or heart diseases [21].

2.2.3 Alternative Therapies

There are other treatment approaches which can be summarized under the term alternative treatment. In this category, therapies such as diet, acupuncture or yoga can be listed [22].

2.2.4 Behavioral Approaches

The behavioral approaches for seizure control arise mainly from studies in psychology and learning rather than neurology, and are based on the concept that the seizures occur as a reaction to certain environmental stimulants or as reinforced behavior. These approaches are also considered for treatment as a second choice, if no success is achieved in pharmacological treatment.

In these approaches, both the brain electrical activity and its clinical manifestations during seizures are considered as behavior, which is influenced by both external stimuli and internal contingence, from a learning theoretical perspective [23]. The episode of a seizure is viewed in its temporal structure with its prodromi, aura, seizure and post-ictal phases. The antecedent events and initiating stimuli are defined and consequently, the seizure facilitating conditions are specified. Correspondingly, by means of classical and operant conditioning, an alteration not only in behavioral components but also in contingencies are sought. In this context, several approaches are studied. These involve modification of, (1) external and internal seizure supporting stimuli and reactions, (2) seizure facilitating contingencies, (3) the motion of the limbs participating in the behavior chain of the seizure, and (4) electro-cortical processes [23].

Desensibilization therapy in reflex epilepsies caused by certain visual, acoustic, olfactory or tactile stimuli, psychological self-control programs in which the patients learn to perceive the seizure facilitating factors via self-observation, and EEG-biofeedback belong to behavioral approaches in epilepsy treatment.

2.3 Neurotherapy in Epilepsy

Biofeedback is the method of feeding back a quantitative parameter of a physiological function of the body to the perception of a subject through artificial equipment so that the person learns to control the quantitative parameter voluntarily. Consequently, it is expected that the subject gain the skill of controlling the physiological dynamics generating the given parameter which otherwise proceed unconsciously.

If the quantitative parameter is obtained from the brain electrical activity (e.g., EEG), then it is defined as EEG-biofeedback, neurofeedback [24], learned cortical self-regulation [25]-[27], or operant brain regulation [28], [29]. The therapeutic applications of EEG-biofeedback are commonly referred to as neurotherapy [30].

Studies of the operant control of EEG components go back to the 1960s. An alpha rhythm feedback study was first published in 1969 [31]. Since then, EEG-biofeedback has enlarged its protocols as well as its application spectrum beyond the treatment of epilepsy and ADHD. Like other biofeedback approaches (i.e. self-regulation of heart

rate, blood pressure, galvanic skin response, finger tip temperature etc.), the method is subsumed under the term behavioral medicine. The different approaches, which use different EEG components, vary basically in the physiological relevance of the extracted quantitative parameter.

In epilepsy, two main protocols of neurotherapy are singled out: the sensorimotor rhythm (SMR) studies and SCP studies:

2.3.1 Sensorimotor Rhythm Studies

Conditioning of certain frequency bands of EEG and its effects on seizure frequency and intensity was initially examined by Sterman [32], [33] and Lubar [34]. The term SMR, which refers to the activity between 12-15 Hz in EEG over the sensorimotor cortex and is associated with motoric inactivity, was first coined by Sterman during his studies with cats [35]. The findings in the animal experiments and measurements on the sensorimotor cortex of the cats during different states of sleep showed that the SMR activity occurs as a consequence of increased recurrent inhibition and blockage of over-excitation in the thalamus [35], [36]. The possible seizure preventing benefit of SMR-feedback was also observed during the same studies [35]-[38].

Significant seizure reductions following the SMR feedback training were reported by Sterman [32], [33], by Lubar and Bahler [34], and by Finley et al. [39]. In [34], the feedback protocol included increasing the SMR activity and suppressing the slower (3-7 Hz) frequency activity at the same time. The protocol was applied at central brain regions. In 50% of the patients, a 35-50% seizure rate reduction was observed. Additionally, a normalization of sleep EEG, especially in the patients with abnormal sleep-EEG patterns, e.g., absence of sleep spindles, was observed. According to [37], Wyler et al. [40], who provided a reward for higher frequencies in the central cortical EEG (14-26 Hz), reported similar successful seizure reduction.

2.3.2 Slow Cortical Potentials Studies

The second protocol of neurotherapy applied in epilepsy is based on SCP. SCP, which are often referred to as DC-shifts [41]-[44] and studied in various contexts under different provocations and paradigms, are the shifts observed in the EEG-baseline

(Fig. 2.1), which can last from seconds to minutes [23], [29], [41], [44]. Although there is no consensus on the origin and generation mechanism of these potentials, they are reported to be fundamental in diverse states of the brain and are accepted to be indicators of cortical excitability [29], [43], [44].

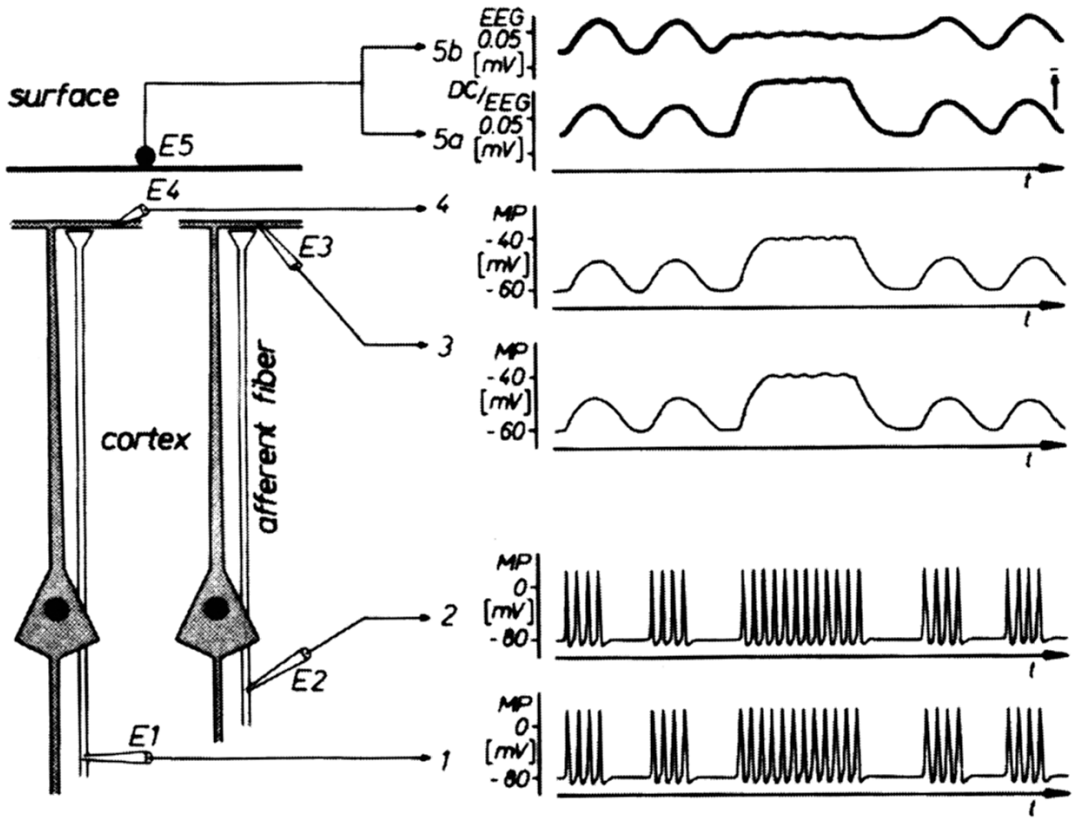


Fig. 2.1 EEG and DC/EEG. Principles of wave generation. The excitatory synapses of two afferent fibers contact the superficial dendritic arborisation of two longitudinal neuronal elements. The afferent fiber activity is recorded by means of the intracellular electrodes E1 and E2, and the membrane potentials (MP) of the dendritic elements are recorded by the electrodes E3 and E4. The field potential at the surface of the neuronal structure (cortex) is led by the electrode E5. Synchronized groups of action potentials in the afferent fibers (E1, E2) generate wavelike excitatory postsynaptic potentials (EPSPs) in the dendritic areas (E3, E4) and corresponding field potentials in the EEG and DC/EEG recording (E5). Tonic activity in the afferent fibers results in a long-lasting EPSP with small fluctuations. During this period the EEG (5b) shows only a reduction in amplitude, whereas the DC/EEG recording (5a) reflects the depolarization of the neuronal elements as well. [Erwin-Josef Speckmann and Christian E. Elger, "Introduction to the Neurophysiological Basis of the EEG and DC Potentials" in Ernst Niedermeyer and Fernando Lopes da Silva (Eds.) , Electroencephalography: Basic principles, Clinical Applications, and Related Fields, p. 20, 4th Ed., Williams & Wilkins, Baltimore 1999.]

According to Caspers [44], the cortical DC potential shift is an indicator of the cortical excitability changes with a negative shift showing an increased cortical excitability and a positive shift showing a decreased one. At the neuronal level, these potentials are proposed to reflect changes in the depolarization of apical dendrites and regulate local thresholds of excitability in cortical cell assemblies [29], [42]-[44]. The amplitude of SCP is reported to range from several µV (i.e., during a cognitive task) to more than 100 µV during seizures [29].

In [28], different negative polarizations observed in different experimental settings are considered as the members of a family having different labels: "orienting wave", "processing negativity", "Bereitschaftspotential" in preparation for voluntary movements, and CNV if it occurs between two consecutive stimuli or responses. The neuroanatomical sources of SCP are claimed to depend on the stimulus modality and the type of information processing or motor responses involved. Local synchronous depolarization of the apical dendrites reflected in negative SCP is reported to increase the firing probability, whereas positive SCP disfacilitate the respective cell assembly in those instances in which no actual processing of stimuli or responses occurs [42]. Therefore, SCP are ascribed an active role in the preparatory distribution of sensory, motor, and attentional resources into the respective cortical areas [29]. It is shown that the response organization, perceptual processing, and problem solving accuracy are increased when the tasks are presented during negative SCP [29], [42]. Both in patients and in some animal experiments, high amplitude negative SCP shifts (e.g., over 100 µV) are observed shortly before and during seizures, as well as during epileptic patterns in EEG [44].

Based on the view of an active modulatory role of the topographically specific SCP in cortical processing, it was hypothesized that patients with intractable epilepsy are characterized by an impaired ability to regulate their level of cortical activation using cortico-thalamic feedback loops. Thus, it is suggested that epilepsy patients can acquire the lacking cortical self-regulation during a process of learning based on the biofeedback of the SCP [45]. In several studies [25]-[27], [45], [46] it is reported that using this method, most patients with drug-resistant epilepsy could learn to control their SCP, resulting in a significant decrement in the seizure rate. Results of 1.5-year follow up studies have demonstrated a 50% average reduction of seizures, with some

patients being seizure free and some unchanged [23], [25]. A further study to predict the outcome of SCP based neurotherapy [47] reports that patients who have extreme negative SCP values before training respond less favorably.

2.4 DC-Potentials in the Brain

As mentioned in section 2.3.2, the DC-potentials are studied in various contexts under different provocations and paradigms. Behavioral changes associated with the sleep-wake cycle, seizure activity, and deviations of gas pressures in blood and tissue serve as experimental models for investigating the DC-potentials in the brain.

The following subsection presents an overview of different states of the brain, in which DC-shifts are observed, in order to have a more detailed insight of their role in brain functioning:

2.4.1 Cortical DC-Shifts and Seizure Activity

In experiments with cats, a negative cortical DC potential shift was found to be associated with a depolarization of the cortical neurons during tonic-clonic convulsive seizures. Although the changes of the fast DC-transients (i.e., EEG spikes) were observed to be more complex in the course of a generalized seizure activity, the shape and the polarity of the spikes have also been found to depend on the amplitude of sustained negative DC shift [48], [49].

Many investigations have confirmed that seizure activity (both in focal and generalized convulsive discharges) in the cerebral cortex is associated with distinct deviations of the DC baseline in the negative direction with respect to the reference level, which is determined in the pre-ictal phase. Caspers [44] states:

“With focal seizure activity elicited by topical application of a convulsant agent or by direct electrical stimulation, the negative DC shift exhibits maximum amplitude in the center of the focus and declines toward peripheral regions. Beyond a zone of complete extinction the evoked DC shifts often reverse in sign. Generalized convulsive discharges evoked, for example, by systemic application of convulsant agents are

usually preceded by a stage of increasing seizure susceptibility. As a rule, this phase is marked by slowly rising negative shift of the DC baseline all over the cortex."

Caspers [44] concludes that the negative DC shifts associated with seizure activity originate from a mixed generator of neurons and are functionally related to glial cells, and that the contribution of each of these elements to the compound response may vary in different brain regions depending on factors such as the relative density of the generator structures and the actual rise of the local K^+ concentration.

2.4.2 Cortical DC-Shifts and Gas Pressures in Blood and Tissue

The DC-potentials are studied in association with the alterations of partial gas pressures, both pCO_2 and pO_2, in blood and tissue [44]. DC displacements are reported to result from a rise in the inspiratory CO_2 contents as well as from a reduction of the ventilation rate (apnoea) or from a respiratory arrest following a period of breathing pure oxygen (oxygenated apnoea). The amplitude of the DC-shifts increases logarithmically with the rise of pCO_2 and linearly with the fall in pH. A number of studies have been devoted to the origin and electrogenesis of the DC-shifts elicited by changes in pCO_2 and/or pH. Besides neurons, glial cells and blood brain barrier have been taken into account as generator structures [44].

2.4.3 Cortical DC-Shifts and Cognitive Information Processing

Cognitive information processing is another field of investigation related to cortical DC-shifts. Birbaumer [28] defines the SCP (e.g., CNV, Bereitschaftspotential, negativation during memory search) observed by using different paradigms as members of a family.

Contingent negative variation (CNV)

The CNV, which is observed in a paradigm where a warning signal precedes an imperative stimulus for a motoric activity, is shown to be related to the expectation and anticipatory attention, and claimed to be observable in all situations of subjective mobilization and anticipatory attention even without any motoric activity [28].

Bereitschaftspotential (BP)

Before a planned movement, a negativation occurs in the supplementary motoric cortex, which is shortly before the execution of the movement overlapped with a negativation at the contra lateral primary motoric cortex. The amplitude of BP is reported to depend on many psychological and kinematic characteristics, of which the automation level of the movement plays a primary role. The more the movement exercised, the lower the amplitude [50], [51].

Negative DC-shift during memory search

In circumstances demanding memory search due to their complexity, a negative DC shift of 400 ms (or longer) occurs after the stimulus processing, which returns to the reference level after the solution of the task [52].

SCP associated with postural adjustment

Saitou et al. [53] have investigated the existence of a cortical potential, similar to the BP, preceding postural adjustment followed by voluntary ballistic rising on tiptoe in healthy subjects. The slopes of the slow negative potential associated with the pre-motion silent period onset were significantly more negative than those of the potential associated with rise-on-tiptoe movement, particularly over the frontal electrode positions. They conclude that the results suggest that a cortical potential precedes postural adjustment, which is followed by voluntary rising on tiptoe.

2.4.4 Cortical DC-Shifts and the Sleep-Wake Cycle

In animal experiments, the well-known changes in EEG waves during sleep-wake cycle are shown to be accompanied by distinct DC-shifts on the cerebral cortex too [44]. It is reported that at the transition from wakefulness to sleep, the baseline of the DC recordings usually shifts to the positive side of the reference level determined in the awake but relaxed animal. Furthermore, in most cortical regions, the amplitude of the DC-shift increases with the progressive slowing of the transients in the EEG frequency range [44].

2.4.5 Cortical DC-Shifts Associated with Anesthesia and Related Burst Suppression

Yli-Hnakala et al. [54] demonstrated that the instantaneous heart rate (IHR) decreases during EEG suppression in deep enflurane anesthesia. Combining their results with two other observations, (1) burst suppression pattern in EEG occurs after ischemic brain damage [55] and during enflurane, isoflurane or barbiturate anesthesia [56], and (2) under enflurane anesthesia, hyperventilation provokes epileptic discharges during burst suppression pattern [57], Jäntti and Yli-Hankala [58] hypothesized that a non-linear inhibiting mechanism exists in the CNS which inhibits the burst activity in both EEG and heart rate. They concluded that there is a control system in the CNS which synchronously inhibits EEG burst activity and heart rate. They presented the hypothesis that this inhibitory mechanism is related to the mechanisms that inhibit or limit epileptiform discharges. In their study in 1993, they combined their observations on burst suppression and IHR with the cortical DC potential shifts. They expanded their hypothesis and proposed that a non-linear (on-off) control system exists, which controls both the bursting and DC-shifts, as well as IHR [59].

3 Problem Analysis: Objective (Neuro)therapy Planning and Evaluation in Epilepsy

Neurotherapy is introduced as a complementary treatment in various disorders of the CNS such as epilepsy, attention deficit hyperactivity disorder, depression, and chronic fatigue syndrome. The method is subsumed under behavioral medicine, and is considered an operant conditioning in terms of psychology. Although the application areas of this promising unconventional approach are rapidly increasing, the physiological underpinnings of the process are not yet well understood. Due to the lack of controlled studies for its evaluation, the approach is strongly debated: There is consensus neither on the applicability of double blind studies in this behavioral approach nor on its possible placebo effects. Especially in the case of epilepsy, which is also, as a complex disorder, not well-explained at the biochemical and physiological levels, the success of the treatment is even more debated. Therefore, verification of the efficacy of the treatment is one of the core issues in this field of research.

Another issue of discussion is the individual diversity which has to be considered in neurotherapy: current investigations indicate that if the treatment is not individually adapted according to patient specific characteristics, the expected efficacy is not achieved [8], [24]. Neurotherapy needs to be planned and monitored subject specifically.

Both of these issues, individualization of neurotherapy and verification/validation of the treatment, can be addressed under the heading of objectivity in diagnostics and therapy evaluation. The very basic questions underlying the problem are:

a. What is the specific pathology in a certain case, so that the therapy can be planned accordingly?
b. What is altered in the brain through (neuro)therapy ?

These questions, of their very nature, pertain to both neurology and psychology, and are related to the rationale of neurotherapy at both levels. Both of them can be handled via

determination and comparison of quantitative parameters reflecting the basic neurological functions, so that the therapy can be accordingly planned and evaluated. Thus, two further questions arise:

c. How can we determine the pathology, or respectively, the changes in a certain case?
d. How can we quantify them for an objective diagnostics, therapy planning, and evaluation?

These latter two questions add the first engineering component to the problem as they are mainly related to data acquisition and signal processing.

Another very important aspect of the problem orientation is the clinical practice. The practical aspects of clinical use and applicability must be considered in the solution. The iterative process of therapy evaluation which accompanies any treatment in medical practice can be summarized in a flow diagram Fig. 3.1.

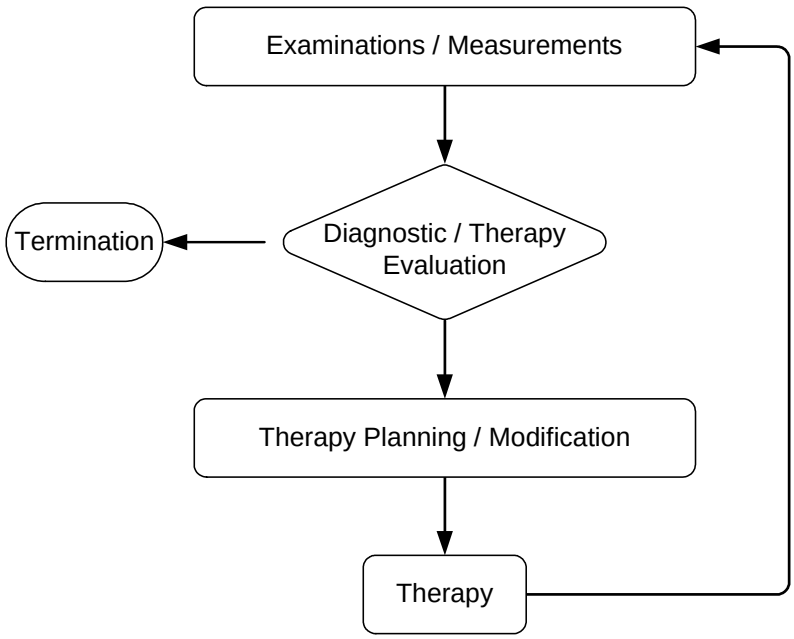


Fig. 3.1 General therapy evaluation flow diagram

At the first step, diagnostic measurements and examinations are carried out. Based on the evaluation of the diagnostic results, the medical expert plans and then applies the therapy. After a certain period of treatment, the examinations (i.e., evaluation measurements) are repeated. Upon a therapy evaluation process, the therapy is either

continued, respectively modified, by the medical expertise, or terminated if success is achieved (i.e, certain measures are normalized and clinical symptoms are overcome).

As implicitly expressed in the above description, the therapy planning and evaluation procedures in medical practice is a more subjective process which highly depends on the expertise of clinical personnel. Despite the necessity, objectivity is achieved neither in neurotherapy nor in other therapies (e.g., pharmacological, surgical, etc.) applied in many neurological diseases. This is highly related to the lack of quantitative measures which can bring more objectivity to both procedures. The determination of generally applicable quantitative measures, however, has not been achieved, due to the diversity of cases and variety of the treatment modalities in epilepsy as in many other neurological disorders. Additionally, the diversity yields an excessive amount of information to be managed and processed in both diagnostics and therapy evaluation. The desired solution to the problem of objectivity shall be applicable (with some modifications or supplements) to neurological disorders in the realm of the neurotherapy, though our focus shall be on epilepsy as a specific disorder. This aspect adds the second engineering component to the problem: development of a strategy which can be implemented in terms of information technology for a possible automation of the process. Hence the problem considered is an interdisciplinary one, having neurology, psychology and biomedical engineering (in terms of data acquisition, signal processing and data management) as its components (Fig. 3.2).

Having elucidated the fundamental problem orientation, for a possible solution, we need to advance to a more detailed analysis of procedures followed in therapy evaluation in epilepsy.

Traditionally, pharmacotherapy is the first treatment addressed in epilepsy. It begins with monotherapy in which the patient is prescribed a single substance. According to the outcome of the therapy, the substance is either replaced by another one or supplemented with further substances (i.e., co-medication). The sort and doses of the substance is decided according to the seizure frequency and intensity as well as the side-effects [11], [61]. Despite the further development of highly effective antiepileptic substances, a significant percentage (i.e., 25%) of epilepsy patients is still pharmaco-resistant [60].

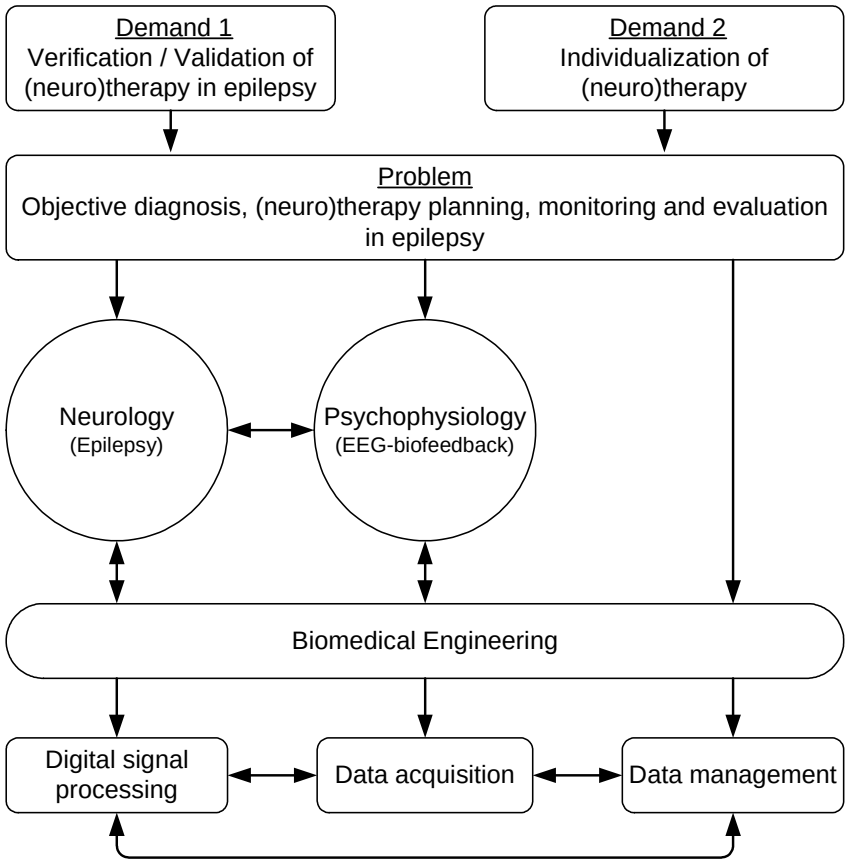


Fig. 3.2 Components of the problem analysis and orientation.

As explained in section 2.2, the main target of epilepsy treatment is preventing, or at least, reducing the seizures. Therefore, the main criteria in the clinical evaluation of epilepsy are the frequency and intensity of the seizures which are registered on a seizure calendar kept by the patients.

The conventional clinical follow-up of pharmacological epilepsy therapy is based on three main tools [61]:

a. the seizure calendar which documents the type, the number and the intensity of the seizures,
b. the data on the pharmacotherapy (sort of medicine prescribed, the time span of prescription), and
c. the blood serum level of the active substance acquired in time intervals.

Based on this information, the course of the treatment can be graphically represented [61]. The change in frequency and/or intensity of seizures is an important

quantitative clinical parameter for therapy evaluation. Nevertheless, the evolution of epilepsy, with or without treatment, can be vicissitudinous in most cases. A spontaneous improvement can be misinterpreted, especially if a sufficiently long time-span is not considered [61].

The seizure calendar is an invaluable tool for clinical evaluation. There are additional clinical examination results which are considered in diagnostics and therapy evaluation by the medical expert. These include the verbally expressed information such as the anamnesis, family history for genetic relevance, the impressions of the doctor, and clinical reaction tests on the general neurological and psychological state of the patient. The difficulty of using this information is the quantification, since they are purely verbal. This issue can be addressed by a knowledge-based system approach in terms of information systems. Nevertheless, none of these information components reflect any objective psycho- or neuro-physiological correlates of the efficacy of any treatment and cannot answer the question of placebo effects.

Therefore, other tools which can yield objective parameters are needed. The possible parameters of biochemical level (i.e., alterations in neurotrasmitters or in membrane mechanisms) have to be excluded, since the corresponding in vivo data acquisition (i.e., measurements at the neuronal level) is not possible for clinical use. The in vitro tools can be methods such as electroencephalogram (EEG), magnetoencephalogram (MEG); and imaging techniques such as computed tomography (CT), single photon emission computed tomography (SPECT) and positron emission tomography (PET), and functional magnetic resonance imaging (fMRI).

Among these methods, the EEG is the one which is more established in clinical use, not only in epilepsy but also in other neurological and/or psychological disorders because of its relative simplicity and lower costs compared to other methods of neurological diagnostics. Although the spatial resolution of the clinically practiced 10/20 system EEG measurements cannot compete with of the other methods, the time resolution is superior, and thus can yield essential information on the cerebral functions or respectively, dysfunctions.

3.1 EEG in Epilepsy

The EEG examinations in epilepsy are employed, basically in order to observe the so called epileptic graphoelements which *may* occur in interictal (i.e., the intervals between seizures) periods. The epileptic graphoelements are characterized by short lasting EEG abnormalities such as high amplitude spikes or sharp-waves, spike wave complexes, slow spike wave complexes, and polyspikes [62]. The time characteristics as well as the topography of such graphoelements are considered in epilepsy for diagnosis. The ictal charges (i.e., recorded during a seizure) which vary more, but usually consist of abnormally rhythmic EEG patterns are also important for epilepsy diagnosis. In some rare cases, there might also be alterations (e.g., slowing), which are often unspecific, in EEG background activity. Such alterations in background EEG activity can also be due to medication [62].

The standard EEG measurement in clinical practice lasts commonly between 20-30 minutes. This duration is often insufficient for detecting epileptic graphoelements or a seizure. Additionally, the existence of epileptiform discharges does not always mean existence of a seizure in clinical terms. Therefore, long-term EEG monitoring (over 24 hours), either ambulatory or combined with video monitoring if the patients are in-patient, is emphasized as an important tool in diagnosis and differential diagnosis of epilepsy [63].

Activation Methods

Several activation methods, such as hyperventilation, photostimulation, and sleep deprivation are also commonly used in clinical routine in order to provoke epileptic discharges and other diagnostically relevant alterations in EEG [64].

Although all these methods are important tools, the resulting EEG data are in general visually analyzed and evaluated. Therefore, the evaluation depends strongly on the clinical expertise, hence it is subjective.

3.2 Quantitative EEG in Epilepsy

In order to overcome the problem of subjectivity, relevant EEG measures need to be quantified. With the developments in computer technology and digital time-series analysis, numerous mathematical and statistical methods are also applied in EEG analysis. These include a wide spectrum of methods from the established spectral analysis to more recent methods of non-linear analysis such as fractal dimension, Lyapunov exponents, and wavelets. The relevance of these parameters to certain pathologies, as in epilepsy, however, is incomplete in the literature.

Although all the methods mentioned above are means of EEG quantification, the qEEG, as a term in the realm of objective and automatic neurological and psychiatric diagnostics and therapy evaluation (i.e., neurometrics [5]), defines a certain set of measures, which are extracted from EEG data at a standardized state (i.e., 2 minutes of artefact free eyes closed alert resting state EEG) [6]-[8]. These measures include [6]:

a. absolute and relative spectral power in the traditionally accepted EEG frequency bands (delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz, beta (12.5-20.5 Hz)),
b. mean frequency in these bands,
c. mean coherence between homologous electrode pairs of hemispheres,
d. inter- and intrahemispheric symmetry (or asymmetry) of the absolute power of the frequency bands between homologous electrodes.

On the other hand, the neurometrics [5], as the methodology of analysing these measures defines the whole procedure of:

a. fast Fourier transformation (FFT),
b. calculation of the quantitative parameters,
c. logarithmic transformation of these measures to obtain Gaussianity,
d. age-regression,
e. Z-transformation relative to population norms,
f. topological presentation of the results via mapping, and
g. multiple stepwise discriminant analysis for clustering according to disorders.

In spite of the fact that qEEG and neurometrics offer a possible solution in many neurological and/or psychiatric disorders (e.g, schizophrenia, major affective disorder,

alcoholism, dementia and learning disabilities [5], [8]), distinguishing them from healthy controls as well as from each other, this is not the case in epilepsy. This is not only because these measures often do not deviate from the norms in epilepsy, but also because the deviations cannot be clustered due to the high diversity.

There have been some approaches for possible objective therapy evaluation in SMR-based neurotherapy studies in epilepsy. The earlier study focuses on the normalization of sleep EEG (i.e, reoccurrence of sleep spindles, which were absent before EEG-biofeedback in some patients) after neurotherapy [65]. The recent studies take the so called comodulation (as coined by Sterman and Kaiser [66]) as the metric of quantification. The parameter is described to examine the temporal correspondence of magnitude modulation between cortical recording sites, and is applied as a cross-correlation analysis either within the subject, or statistically between subject and a control database. The mathematical formulation of the metric, however, is not explicitly defined in the literature.

3.3 Objectives

Based on the analysis in the previous sections of the current chapter and the basics introduced in chapter 2, we can now continue with our strategy for a possible solution:

Primarily, it is necessary to search further quantifiable information from the EEG and possibly from evoked potentials and/or event related potentials which might also reflect dysfunctions related to epilepsy. These measures should correspond to the following aspects:

a. Because of their relevance to clinical practice, they should correspond to
    i. the possible graphoelements in standard or long-term EEG, and
    ii. the reaction to activation methods used in epilepsy diagnostics,
b. Because of their relevance to neurotherapy protocols proposed in epilepsy, they should correspond to
    i. possible alterations in the evoked and/or event related potentials, and
    ii. possible alterations in the slow cortical potentials.

Although automatic detection, quantification and statistical analysis of graphoelements for diagnostics and therapy evaluation has been studied to some extent, the other parameters have not been considered for the purposes of objective diagnostics, (neuro)therapy planning and evaluation. This is highly related to the gap between basic research and the clinical practice in neurology and psychology, as well as the fact that epilepsy is a complex disorder which is not well explained at either the biochemical or the physiological level. Thus, at this point, we come back to the fact that our problem has roots in basic research in neurology and psychology (Fig. 3.2).

For the solution of the problem, a therapy evaluation strategy with a data acquisition protocol including the necessary measurements for these further parameters needs to be developed. The protocol should also be clinically applicable. The measurements included in the protocol shall be taken from patients and healthy controls. Corresponding signal processing algorithms are to be chosen and applied to the acquired data. Since the analysis of all the parameters is far beyond the scope of the current study, selected parameters shall be compared between patients and controls according to their relevance to the rationale of neurotherapy. For a possible automation of the process, the procedures should be integrated in a software concept, which also considers structuring and management issues of the excessive amount of data and clinical information gathered.

In terms of biomedical engineering, the solution can be subdivided into the following major parts:

a. Development of a strategy for objective diagnosis, (neuro)therapy planning, and evaluation
b. Data acquisition corresponding to the strategy
    i. A protocol for the pre- and post- therapy measurements necessary for further measures
    ii. Measurements from healthy controls and patients
    iii. Realization of neurotherapy on patients
    iv. Repetition of the protocol after the therapy
c. Signal processing
    i. Analysis of selected parameters

ii. Extraction of possible quantitative features

iii. Comparisons between healthy controls and patients

iv. Pre- and post-therapy comparisons

d. Data management

i. A software concept which can cover the components for signal processing and management of the extracted parameters, so that an automation of the procedures can be achieved

4 Therapy Evaluation and the Neuroprofile

In this chapter, the developed therapy evaluation strategy with the concept of neuroprofile will be introduced. Associated with this strategy, the protocol for initial and evaluation measurements will be presented.

4.1 The Therapy Evaluation Strategy

As discussed in chapter 3, one of the main components of the solution to the problem of an objective diagnosis and (neuro)therapy evaluation, is a strategy which can standardize the process. Hence, in this section, a therapy evaluation strategy based on a new concept and tool, the neuroprofile, will be introduced.

The information processed in therapy evaluation in epilepsy can be roughly divided into two categories:

a. the signal analytically quantifiable, purely numeric measures which can be extracted from EEG and possibly from other bioelectrical signals, and
b. the verbal medical information which includes the clinical examination results as expressed by the expertise.

More objectivity can be attained via a strategy based on the first category of information. The second category of information, however, should also be accessible.

4.1.1 The Neuroprofile

The term *neuroprofile* is coined in order to define a structured set of possible quantifiable measures which can be extracted from electrophysiological signals and characterize the neurological functions of a subject. The neuroprofile, as a clinical tool, is conceptualized as a three dimensional vector having the dimensions:

a. Quantitative measure,
b. Localisation (e.g., electrode position), and

c. Time.

The dimension time involves the smaller intervals within the measurements having different provocations, as well as the successive measurements. The dimension localisation projects the electrode positions of EEG recordings according to the international 10/20 system, or of other electrophysiological signals (e.g., ECG, electrooculogram (EOG)) according to the type of derivation. And finally, the quantitative measures dimension represents the parameters extracted from the signals after processing. Fig. 4.1 illustrates the model for the neuroprofile.

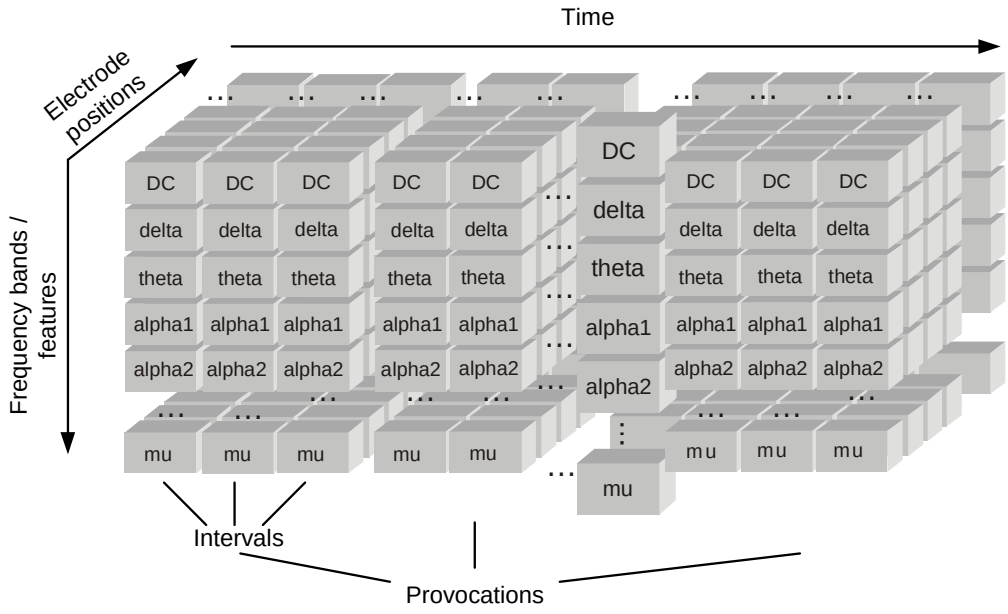


Fig. 4.1 Sample section from the qEEG part of the neuroprofile model. The highlighted column shows the parameters extracted from EEG (e.g., DC-level; delta, theta, alpha1, alpha2-frequency band powers; amplitude of mu rhythm) from a single time-interval of a single provocation for a given channel. © IEEE Transactions on Information Technology in Biomedicine.

The neuroprofile is central in the developed strategy. The quantitative results of pre-therapy, as well as follow-up measurements are registered in the neuroprofile for further statistical comparisons. The developed strategy can be illustrated in a flow diagram (Fig. 4.2).

The process begins with initial measurements and consideration of already existing information (i.e., previous measurements and examination results) for a given case. In order to have a standard for later statistical comparisons, an extended protocol of

clinical EEG measurements including different provocations, and event related potentials (ERP) measurements relevant to epilepsy (i.e., initial and evaluation measurements) are carried out.

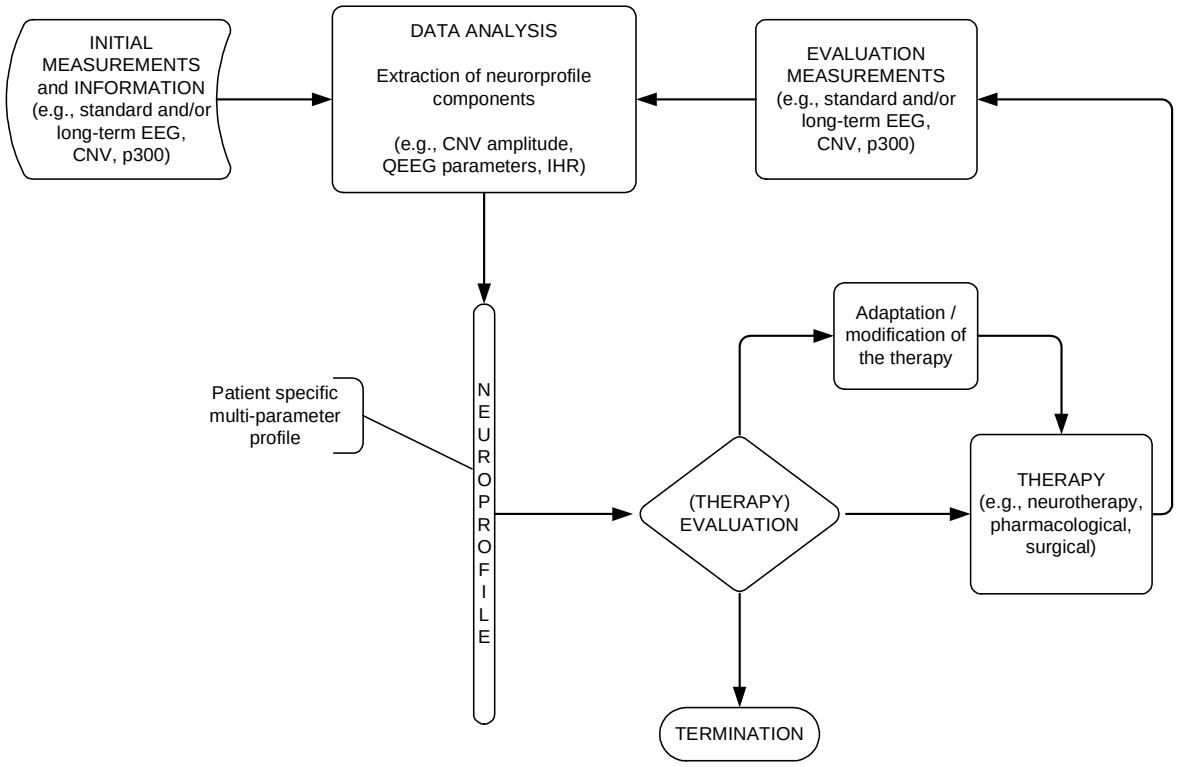


Fig. 4.2 Therapy evaluation flow diagram. Initial measurements, as well as evaluation measurements are analyzed by the data analysis module, which extracts the neuroprofile. Based on the neuroprofiles, therapy is evaluated and accordingly, is either continued unchanged or modified, or terminated.

The protocol will be explained in detail in this chapter. The measurements are analyzed in order to extract different quantitative measures which compose the user specific information (i.e., data analysis). The quantitative results are then integrated into the neuroprofile. Based on the initial neuroprofile, a neurotherapy modality (i.e., the feedback parameter, the electrode position to be trained, the modalities of feedback and task definitions –visual, acoustic or combined) is proposed, and an initial supervised training is realized. The therapy is conducted if the supervising medical doctor approves the proposed modality. In the course of the therapy, the evaluation measurements protocol is repeated and the neuroprofile is updated. The neuroprofiles referring to a particular case are statistically compared (i.e., evaluation). Accordingly,

the therapy is continued or modified. The iterative process is repeated until clinical success is achieved.

4.2 Protocol for Evaluation Measurements

An extended protocol of clinical EEG measurements is proposed in this study in order to obtain standardization for the comparison of neuroprofiles. Clinical factors considered for the proposal include applicability, duration, priority of relevance to epilepsy and neurotherapy, and recent findings in basic research in neurology and psychology, which do not have clinical applications yet. The measurements included were determined through consultation with the medical partners. After some modifications, the final protocol is as follows (Table 4-1):

The first part (standard I) of the protocol includes background EEG/DC acquisition in an open-eyes alert state as well as during essential clinical activations such as the Berger effect, hyperventilation and apnoea.

The ERP measurements include three paradigms: Odd-ball paradigm for P300, S1-S2 for CNV and a motoric reaction paradigm for SMR measurements. Photo-stimulation is used for the final measurement (standard II). This activation method is separated from the first part because of the influences of light adaptation processes on the measured DC component [67].

In order to gain a better insight for the protocol, the activation methods and the paradigms used will be explained below:

Activation Methods

a. Berger Effect

This method refers to the alpha activity predominant in occipital region in an eyes-closed alert state, which is suppressed when the eyes are open, as described by Hans Berger. This activation method is normally applied for 3-5 sec in order to examine the reactivity, which may be absent in some epilepsy cases, especially due to long term medication [62]. The eyes-closed and eyes open alert states are also essential for comparison of the two states. Additionally, for further signal analysis,

the eyes-closed alert state is more suitable, since the EEG is less contaminated with ocular artefacts. The duration of an eyes-closed alert state in the protocol is, therefore, longer (i.e., 5 min).

b. Hyperventilation (HV)

It is well-known that hyperventilation precipitates seizure activity in epilepsy patients. Therefore, it is commonly used as an EEG activation method in clinical routine examinations. The epileptic discharges induced by hyperventilation have a crucial diagnostic value. This method consists of deep and regular respiration at a rate of about 20cycles/min for a period of 2-4 minutes. In adults, such HV causes an air exchange of 20-50lt/min and a drop in pCO2 in the range of 4-7ml%. The characteristic EEG response to HV, most prominent in children, consists of fluctuating increase of bilaterally synchronous slow activity and the slowing of alpha and beta rhythms. In normal adults, although the slowing is generally not marked, there are wide differences among individuals. For the purpose of routine examination with HV, however, it is suggested that the rate of breathing be as close as possible to that of the resting rhythm (15-20 breaths/min) [68].

Another effect of hyperventilation on the EEG is observed in the DC-shifts, especially at the vertex. These potentials, however, are not commonly studied, since the measurement requires more sophisticated equipment and is highly open to low frequency artefacts. They are addressed, though, for their relevance in the context of the SCP based neurotherapy in epilepsy [43], [60], but not studied for their possible diagnostic value. Therefore, this activation constitutes an essential part of the protocol.

c. Apnoea

An apnoeic episode is defined as a cessation of breathing of longer than a 10 sec duration. Although such episodes are mostly considered in sleep EEG studies (e.g., sleep disorders) and it is not a standard activation in epilepsy diagnosis, it is an important activation which needs to be investigated more in detail in the realm of basic neurology research within the realm of DC studies, as a counter reaction of hyperventilation.

Table 4-1 The protocol for evaluation meaurements.

Measurement	State	Activation/Paradigm	Activity	Duration
Standard I	Eyes-open alert	---	Background EEG/DC	2 min
	Eyes-closed alert	Berger effect (reactivity)	Background EEG/DC	5 min
	Eyes-open alert	---	Background EEG/DC	2 min
	Eyes-open alert	Hyperventilation (HV)	EEG/DC	3 min
	Eyes-open alert	Recovery from HV	EEG/DC	3 min
	Eyes-open alert	Apnoea	EEG/DC	20 sec
	Eyes-open alert	Recovery from apnoea	EEG/DC	3 min
	Eyes-closed alert	Berger effect (reactivity)	EEG/DC	2 min
	Eyes-open alert	---	EEG/DC	2 min
ERP 1	Eyes-open alert	Odd-ball	P300	200 trials
	Eyes-closed alert	Odd-ball	P300	200 trials
ERP 2	Eyes-open alert	S1-S2	CNV	44 trials
ERP 3	Eyes-open alert	Motoric reaction	SMR	100 trials
Standard II	Eyes-closed alert	Photo-stimulation Ramp (1-30 Hz): 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30 Hz and backwards.	Photosensibility	8 sec stimulation, 8 sec pause at the listed frequencies.

d. Photo-stimulation (PS)

Photo-stimulation is especially important for the evaluation of photosensitivity, which is encountered in certain seizure types. The paroxysmal discharges related to PS are crucial for diagnosis. Details of PS use in routine examination vary highly between EEG labs. According to [69], the following protocol is suggested by Bickford [70]: flashes at frequencies of 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, and 30 Hz each are given for a duration of 5 seconds with eyes open and closed in a room with

reduced illumination. The PS is integrated into the protocol with the above listed frequencies only when the eyes are closed, with 8 seconds stimulation, 8 seconds pause intervals. The intervals are assigned longer, so as to facilitate the signal analysis afterwards.

Paradigms

a. Odd-ball

Selective and sustained attention and short term memory deficits have been reported in epilepsy. P300 as a measure of attentional resource and as a measure of cognitive functions is discussed in the context of epilepsy diagnosis, and differences are reported in the latency and amplitude of P300 in epilepsy [71]-[73]. These findings, however, are not integrated to the clinical practice yet. Therefore, an auditory odd-ball paradigm is included in the protocol. Standard tones of 1000 Hz (100 ms duration) are presented once every 2 sec with a 2000 Hz target tone occurring randomly in 20% of the trials. Subjects are requested to press a button with the thumb of their right hand as quickly and accurately as possible when the target tone is perceived. The eyes closed and eyes open options are necessary for a possible comparison of the two states.

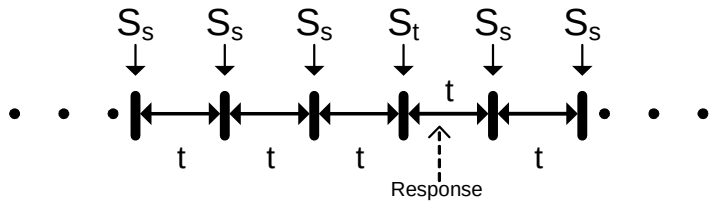


Fig. 4.3 Odd-ball paradigm. S_s = standard tone of 1000 Hz (duration 100 ms); S_t = target tone of 2000 Hz (duration 100 ms, occurrence 20%); t = 2 sec.

b. S1-S2

The CNV is a long-latency event-related potential elicited by paired or associated stimuli. The slow negativity in the EEG appears during the anticipation period between a warning stimulus (S1) and a target response "imperative" stimulus. Its neural generators are hypothesized to be at the prefrontal cortex. This activity is

considered one of the possible negative polarizations, an example of which is Bereitschaftspotential. CNV is addressed in the context of SCP based neurotherapy. According to [28], CNV is observable in all situations of subjective mobilization and anticipatory attention regardless of motoric activity.

Hence, a modified S1-S2 paradigm without motoric activity is integrated into the protocol: An acoustic stimulus (S1) preceding a visual aversive or non-aversive one (S2) is presented. The S1 (i.e., two distinguished tones) warns whether the S2 is aversive or non-aversive. And accordingly, the S2 is a randomly assigned aversive or non-aversive picture from the International Affective Picture System (IAPS)[7]. For the standardization of the measurements, the inter stimulus intervals are assigned as t1=6 sec, t2=6 sec, and t3=4 sec (Fig. 4.4).

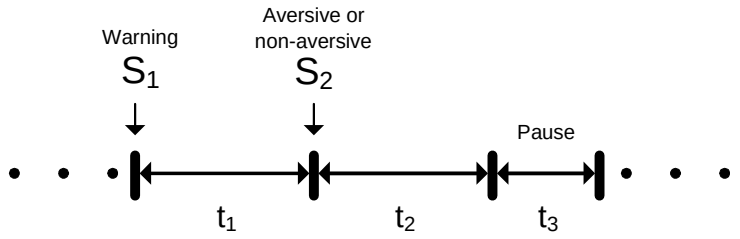


Fig. 4.4 Modified S1-S2 paradigm. S1 = acoustic warning stimulus, S2 = visual aversive or non–aversive stimulus. t_1 = 6 sec, t_2 = 6 sec, and t_3 = 4 sec.

c. Motoric reaction (SMR)

The SMR activity, which forms the basis of one of the main neurotherapy protocols in epilepsy, is included because of its relevance to neurotherapy (see. chapter 2 section 2.3.1).

An SMR paradigm is constructed for the protocol where the subject is requested to respond according to the presented imperative visual stimulus by pressing two different buttons either with the left hand thumb or the right hand thumb, or by show no reaction (Fig. 4.5).

[7] International Affective Picture System (IAPS) is a development of the Center for the Study of Emotion and Attention (CSEA) directed by P. J. Lang at the University of Florida.

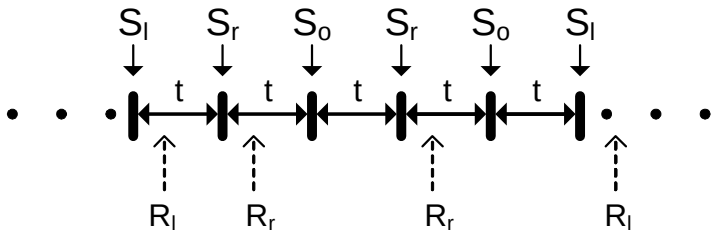


Fig. 4.5 Paradigm for SMR measurements. S_l = visual stimulus for left hand thumb response R_l, S_r = visual stimulus for right hand thumb response R_r, S_o = visual stimulus for no-reaction. t = 3 sec.

There are certainly other possible measurements which can be included in the protocol. Nevertheless, the solution considers to optimize the over-all measurement duration and the priority of the relevance to epilepsy and neurotherapy. The durations of single measurements are assigned according to the necessities of further signal processing.

Although not all the measurements included in the protocol can be analyzed within the scope of this work, the protocol is extensively structured so as to provide vital information embedded in the initial measurements, which cannot be replicated after the therapy. The signal analysis (quantification) will only consider selected measurements.

5 Data Acquisition

The current chapter is devoted to the measurements and the acquired data. After a brief introduction of the EEG-biofeedback system, the technical settings of different measurement types, as well as the details of the acquired electrophysiological signals are presented. The focus shall then be on the laboratory studies with voluntary control subjects and clinical applications with epilepsy patients.

5.1 The EEG-Biofeedback System

The original system used for data acquisition in this study was a 32- channel AC/DC polygraphic amplifier system [74]. Using certain modalities of the original one, a laboratory prototype for an adaptive BCI system, which can be also utilized for EEG-biofeedback and neurotherapy applications, was developed by the NeuroCybernetics Research Group [1], at the Technische Universität Ilmenau, Institute of Biomedical Engineering and Informatics.

The system is conceptualized in the form of two units; one central and one portable. It can be configured for different disorders and adapted according to the individual needs and characteristics of the subject for flexible EEG-biofeedback [2]. The central unit involves modules for selecting an individual specific training protocol and configuring the corresponding necessary software components [4]. After determining the configuration for a certain subject, the initial familiarization stage of EEG-biofeedback can be realized with the central unit under the supervision of a medical professional. Upon completion of the first stage, the training process can be continued either at the central unit or, after the transfer of the subject-specific configuration to the portable unit, on the portable one (i.e., home-training) [3]. A simplified block diagram of the central unit is illustrated in Fig. 5.1.

The AC/DC amplifier system acquires EEG signals, which are monitored by a software component. The control/monitoring software also assigns the feedback parameter(s)

and the sequences of stimulation/task-definitions. Based on the assigned feedback parameter, a control time-series is extracted by a separate on-line signal processing software module. The multimedia animation is then controlled by the extracted time-series. During the session, an additional software component continuously updates the results. After the sessions, it presents over-all averages.

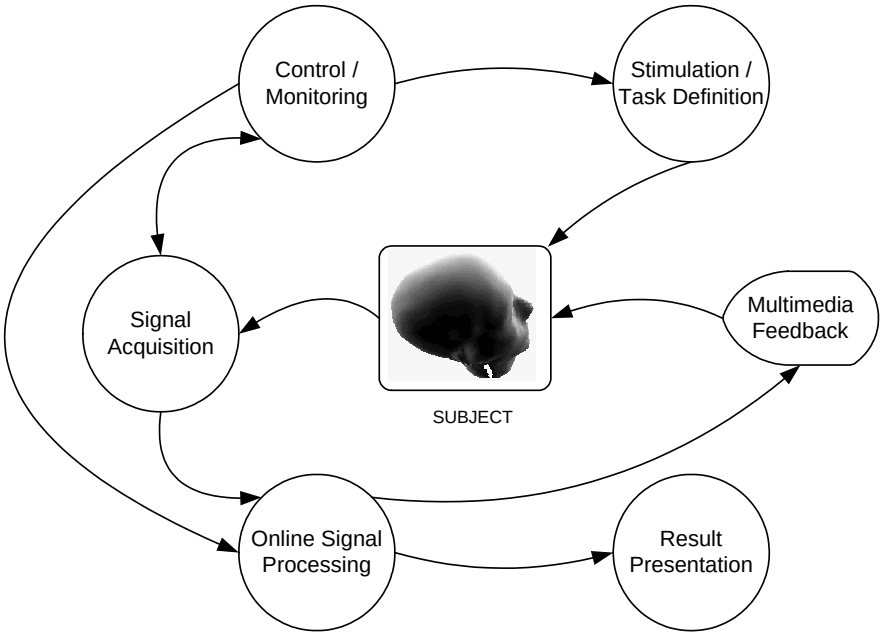


Fig. 5.1 Simplified block diagram of the developed EEG-biofeedback system. EEG/DC signals are acquired by the signal acquisition module, which is controlled and monitored by a separate software module. The signals are processed on-line, and the multimedia feedback is controlled by the extracted feedback parameter.

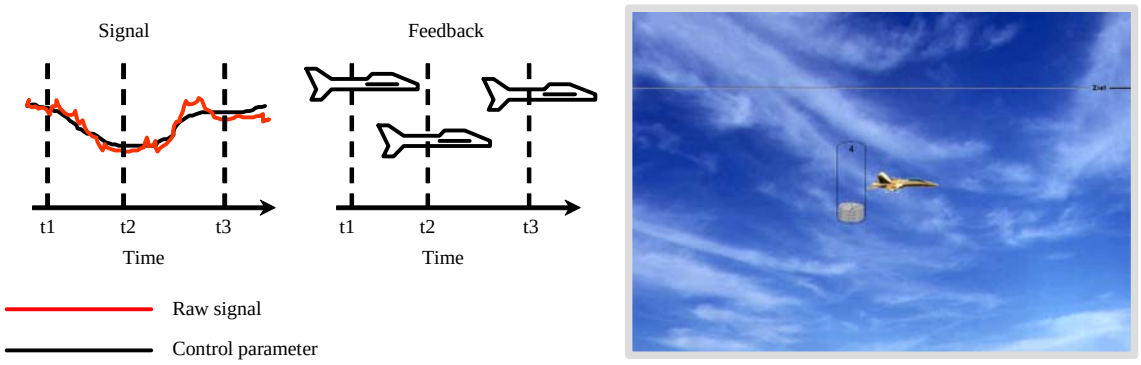
Three distinguishing features of the system can be listed as follows:

a. Not only higher frequency components, but also very slow components (including 0 Hz) can be acquired.
b. Besides EEG, other polygraphic signals such as electrocardiogram (ECG), vertical and horizontal electrooculograms (VEOG and HEOG), and respiration curves (ATHM) can be simultaneously acquired.
c. Multimedia feedback components can be configured according to the needs of the subject.

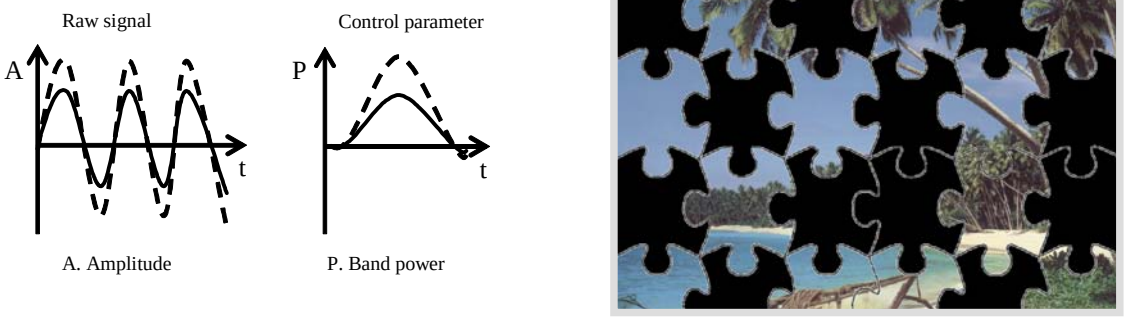
Some modalities of the system are illustrated in Fig. 5.2 and Fig. 5.3. More details about the developed system can be found elsewhere [2]-[4].

(a) (b)

Fig. 5.2 Modalities of the system. (a) Evaluation measurement using LCD glasses (28 channels EEG), (b) Biofeedback session (single channel EEG). © The NeuroCybernetics Research Group.



(a)



(b)

Fig. 5.3 Samples of the multimedia feedback components. (a) Airplane: amplitude controlled feedback, (b) Puzzle: band power controlled feedback. © The NeuroCybernetics Research Group.

The measurements obtained through the study can be roughly grouped into two types:

a. evaluation measurements, and
b. EEG-biofeedback sessions.

These will be addressed in the following sections:

5.2 Evaluation Measurements

Both the initial diagnostic measurements and the therapy evaluation measurements are grouped under this category. These measurements mainly involve the application of the protocol proposed in section 4.2. The acquired polygraphic data consist of:

a. 28 unipolar EEG channels according to the International 10/20 System (reference: linked mastoids) (see Fig. 5.4 for electrode positions),
b. an ECG channel according to Einthoven I derivation (right and left arm),
c. a bipolar VEOG channel,
d. a bipolar HEOG channel, and
e. a bipolar respiration channel (via respiration belt).

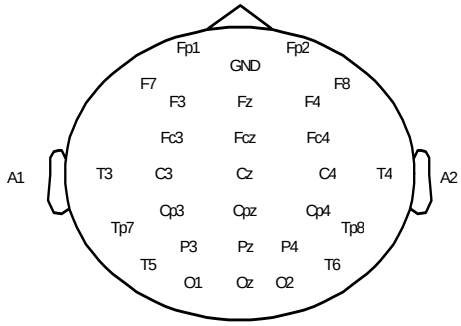


Fig. 5.4 The 28 channels of EEG acquired in an evaluation measurement (10/20 System).

A sampling rate of 500 Hz is assigned to all channels for a higher frequency resolution. The DC modus is used (no high pass filtering) for the EEG channels, where the low pass filter (i.e., high cut-off) is set to 70 Hz. For all measurements, the electrode impedances are guaranteed to be less than 2 kΩ. A sample interval of the signals acquired during an evaluation measurement is shown in Fig. 5.5. The room conditions (i.e., light and temperature) are kept constant during a measurement. In order to avoid the influences of the highly discussed "time of the day" factor in EEG measurements,

the evaluation measurements referring to a particular subject are started at the same hour of the day each time the measurements are taken.

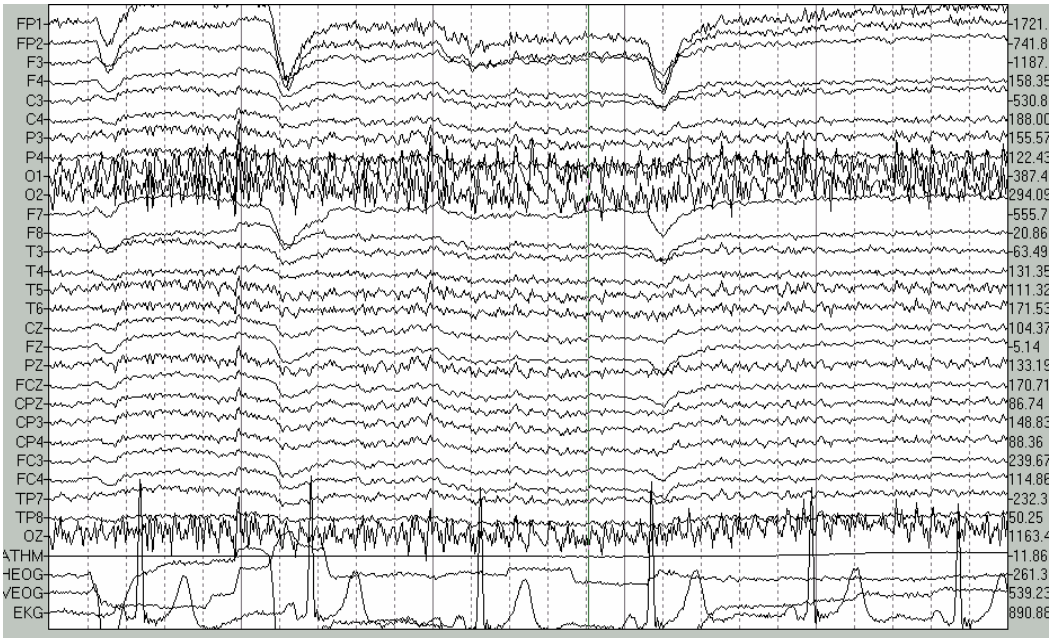


Fig. 5.5 An interval from the polygraphic signals acquired during an evaluation measurement.

5.3 EEG-Biofeedback Sessions

According to our experience, the long-term process of EEG-biofeedback can be divided into the following stages:

a. familiarization: getting familiar with the procedure,
b. training: gaining the skill, and improving it (i.e., achieving a higher success rate in trials),
c. transfer: training without feedback for transferring the skills to daily conditions, and
d. refreshment: maintenance of the skills gained after longer breaks.

The first two stages, (a) and (b), together can be considered as "the process of learning". The third stage (c) is essential for the patients to apply the learned skills in day to day situations, in which no feedback can be supplied. The last stage is important for the long-term follow-up in order to sustain the skills gained. The term "EEG-biofeedback sessions" refers to the sessions at all four stages, otherwise explicitly stated in the text.

In our studies, the sessions were based on self-regulation of the central or frontocentral SP. Sessions were configured subject specifically: The feedback electrode was assigned according to the topology of the CNV, and the range of the feedback component according to the amplitude of the CNV, which were determined after the evaluation of the initial measurements. Different modalities (e.g., acoustic, visual or combined) of the multi-media feedback module of the BCI system were configured according to the needs and preferences of the subjects. The task was defined as controlling the selected multimedia feedback component in two opposite directions corresponding to positive and negative DC shifts according to the delivered random sequence of instructing stimuli. Subjects were given no further instructions.

We define a session as an approximately 15 minutes of continuous feedback containing 40±1 trials. Two successive trials in a session are separated with a break interval which randomly varies between 6 and 12 seconds in order to prevent habituation. All the parameters related to the task declaration can be configured subject-specifically too. A subject is expected to complete 4 to 6 sessions during an EEG-biofeedback measurement.

In a session, the subject is expected to distinguish between two different states of activation at the selected electrode position. In SCP based EEG-biofeedback, these two states are defined as “negativation” and “positivation”. As the terms suggest, they refer to the shifts in the baseline (i.e., DC) either in the negative or positive direction with respect to a reference level. In our realization, the reference level is automatically initialized before each trial.

A standard EEG-biofeedback session data-set is composed of:

a. a single EEG channel (i.e., the feedback electrode),
b. a bipolar VEOG,
c. a bipolar HEOG, and
d. an ECG channel.

For standard sessions a sampling rate of 100 Hz is assigned to channels. The DC modus is used (no high pass filtering) for the EEG channel, where the low pass filter (i.e., high cut-off) is set to 30 Hz. In certain training sessions, the respiration channel is added to

the set-up. The feedback electrode impedances are assured to be less than 1 kΩ. In order to avoid the influence of light adaptation on the recorded DC shifts, which was observed in the course of the study, the illumination of the room is kept constant through a session.

Besides standard sessions, several training sessions were carried out in addition to the evaluation measurements, where the acquisition set-up was kept the same as the evaluation measurements (section 5.1). The feedback electrode was assigned to the same position as the standard sessions, and signals of all 28 EEG channels were recorded. The acquired signals can be summarized in the diagram below (Fig. 5.6).

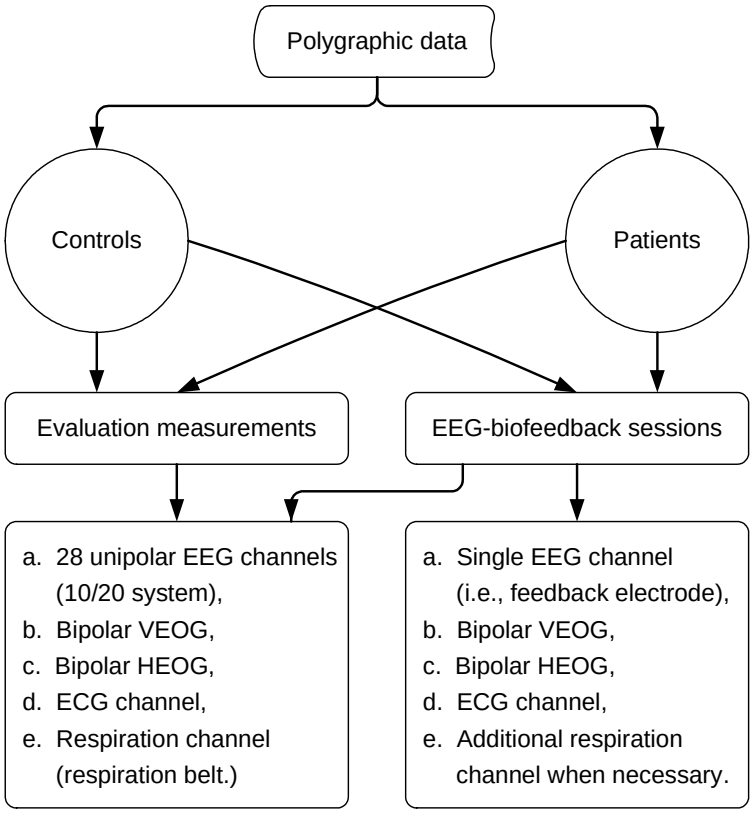


Fig. 5.6 Acquired signals in different measurements from controls and patients.

5.4 Studies with Control Subjects

A control group is studied within the realm of the current thesis. The primary purpose was to acquire data for comparison with the patients. The secondary purpose was to conduct EEG-biofeedback sessions in order to test the functions of the developed

system, as well as to observe possible influences of neurofeedback on healthy controls. The study was necessary to establish a basis for clinical applications.

Six voluntary subjects (4 males, 2 females) participated in the studies at the Electrophysiological Laboratory of the Institute of Biomedical Engineering and Informatics, Technische Universität Ilmenau. The subjects were expected to take part in 6 EEG-biofeedback sessions per week until having completed at least 40 sessions in total, as well as the evaluation measurements. The schedules were determined according to the availability of the candidates.

The proposed protocol of evaluation measurements was employed at the beginning for the initial evaluation. The feedback electrode is individually determined after the initial evaluations. The protocol is repeated after completing 21±3 sessions (i.e., evaluation measurement 2) and at the end of the study (i.e., evaluation measurement 3). The resulting measurements are listed below in Table 5-1.

Table 5-1 Measurements carried out with control subjects.

Subject Code	Sex (m=male, f=female)	Age	Evaluation Measurements			Standard sessions	Sessions with 28 channels EEG	Feedback Electrode	Feedback Type	Task Declaration
			1	2	3	(#)	(#)			
S1JN	f	21	+	+	+	42	5	Fcz	Visual	Audio
S2MN	f	21	+	+	+	30	7	Fcz	Visual	Audio
S3AD	m	21	+	+	+	39	6	C3	Visual	Audio
S4OL	m	26	+	+	+	36	6	Fcz, Cz	Visual	Audio
S5PT	m	21	+	+	+	45	7	Fz, Fcz	Visual	Audio
S6CR	m	24	+	-	-	18	-	Fz	Visual	Audio

Four subjects (2 males and 1 female) completed the required minimum number of sessions, as well as the evaluation measurements. A female subject (S2MN) missed 3 sessions, whereas a male subject (S6CR) dropped out after 18 sessions because of private problems.

5.5 Studies with Epilepsy Patients

The clinical applications were conducted under the supervision of medical partners, either at the Neurology Clinic of the Zentral Klinik Bad-Berka (supervision by Chefarzt Doz. Dr. med. habil. R. Both) or at the Electrophysiological Laboratory of the Institute of Biomedical Engineering and Informatics (supervision by Prof. Dr. med. D. Müller, Neurological Praxis Ilmenau). The patients are selected and assigned for neurotherapy by the medical partners. Therefore, various patients were evaluated and treated at different times throughout the study. The patients (n=6, 4 females, 2 males) were diagnosed with focal or multi-focal epilepsy with at least 15 years of intractable epilepsy history.

The neurotherapy sessions had to be organized according to the availability of the patients. A different schedule had to be followed for the patients, due to the health insurance regulations: In the first two weeks of the therapy, which was in-patient and covered by the insurance, the patients were trained intensively (i.e., daily except Sundays with an average of 8 sessions per day). The training continued once a week (i.e., 6 to 8 sessions), until the learning was achieved. Learning was accepted to be achieved, if at least 70% of the trials in successive sessions were successful. After the learning stage was completed, transfer sessions were conducted. The follow-up continued with refreshment sessions once every three months for those patients who accepted to continue with the treatment ambulatory after the first two weeks.

The evaluation measurements are obtained at the beginning of the therapy, after the completion of the first two weeks, and in the course of further training. The resulting measurements are listed in Table 5-2.

For certain comparisons between the controls and patients, for which no neurotherapy is required (e.g., CNV amplitude and topology), additional data from previous studies have been integrated into the analysis. The additional data includes measurements from other controls (n=5) and epilepsy patients (n=6) with focal or multi-focal epilepsy.

Table 5-2 Measurements carried out with epilepsy patients.

Patient Code	Sex (m=male, f=female)	Age	Diagnosis	History	Evaluation Measurements			Standard Training sessions	Sessions with 28 channels EEG	Transfer sessions	Feedback Electrode	Feedback Type V=visual A=audio C=combined	Task Declaration V=visual A=audio
				(years)	1	2	3	(#)	(#)	(#)			
P1MH	f	51	Focal epilepsy (focal seizures)	45	+	+	-	78	5	3	Cz	V	A
P2WM	m	47	Focal epilepsy (complex focal and secondary generalized seizures)	44	+	+	+	264	13	11	Cz	V, A, C	V, A
P3GM	f	31	Focal epilepsy (complex focal and secondary generalized seizures)	30	+	+	+	112	3	-	Cz	V, A, C	V, A
P4ES	f	52	Focal epilepsy (focal and complex focal seizures)	49	+	+	-	76	4	-	C4	V	A
P5RB	f	33	Focal epilepsy(focal and generalized seizures)	21	+	+	+	276	3	-	Fz	V, A, C	V, A
P6MU	m	41	Focal epilepsy (focal and generalized seizures)	27	+	-	-	27	-	-	Cz	V	A

6 Signal Processing for Feature Extraction and Quantification

The electrophysiological signals acquired according to the evaluation measurement protocol introduced in chapter 4 (Table 4-1) need to be processed for a quantification of the relevant measures (i.e., the features). The procedure can be illustrated in a block diagram (Fig. 6.1):

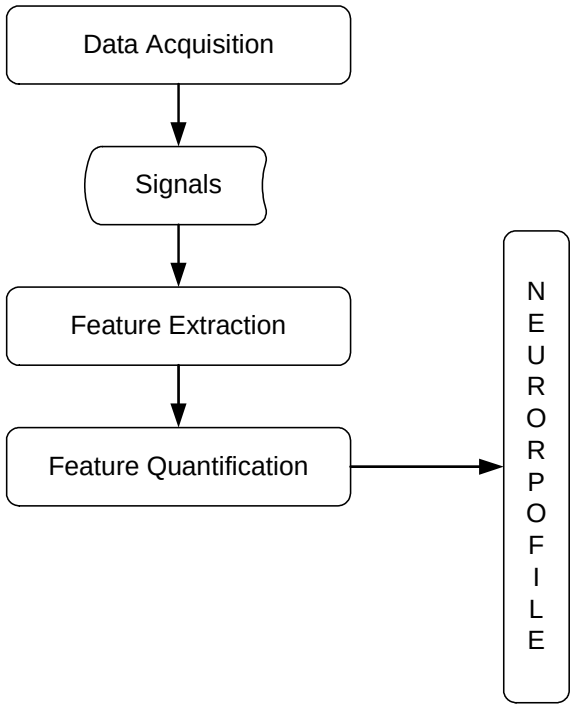


Fig. 6.1 Block diagram of the analysis process.

In this chapter, two stages of the analysis process, which comprise the signal processing tasks, will be elucidated: Feature extraction and feature quantification.

The possible measures which can be extracted from the acquired data from different measurements are numerous. Based on the discussions in chapter 3, two groups of features will be focused upon for quantification because of their priority in epilepsy diagnostics and relevance to SCP based neurotherapy:

a. Epileptic graphoelements, which can possibly occur in any EEG measurement, will be studied for their clinical priority in epilepsy diagnosis. Depending on the occurrence frequency of such epileptic patterns, long-term EEG monitoring may be required. Via activation methods such as hyperventilation, the occurrence probability of such patterns in EEG is increased. Therefore, the measurement Standard I (Table 4-1) will be considered for the graphoelements analysis.

b. DC-shifts and other related neurophysiological features will be studied for their relevance to SCP based neurotherapy. Considering CNV under the category "DC-shifts", we will focus on the S1-S2 paradigm measurements, as well as the hyperventilation activation method for analyzing the associated DC-shifts. Changes in IHR resulting from hyperventilation will be analyzed as an additional measure based on the hypothesis by Jäntti and Yli-Hankala [58], [59] discussed in section 2.4.5.

Next, the methodology necessary for signal processing will be introduced for the extraction (or detection) and quantification of the selected features.

6.1 Epileptic Pattern (Graphoelement) Analysis

Epileptic patterns in EEG are characterized by distinctive transient waveforms such as spikes, sharp-waves, spike wave complexes, slow spike wave complexes and polyspikes. A spike is a transient with a pointed peak at conventional paper EEG speeds with a duration of 20-70 ms, and a sharp wave is defined similarly but with a duration of 70-200 ms. The slower transients may occur individually or accompanying the spikes. A spike wave-complex defines a slow wave (250-350 ms) following a spike [75].

The percentage occurrence of any epileptic activity in an EEG measurement can be regarded as a feature for objective therapy evaluation. In order to achieve a quantification of similar patterns or certain selected patterns in a given data set, we suggest two approaches (Fig. 6.2):

a. Supervised, and
b. Unsupervised pattern analysis.

Supervised detection is based on the assignment of a representative epileptic pattern by an expert (i.e., supervisor) on the real data. Similar patterns are then searched for in the EEG recordings. On the other hand, in the unsupervised approach, the EEG is segmented adaptively and the segments obtained are classified by a clustering algorithm. Both approaches require measures to characterize the patterns in EEG.

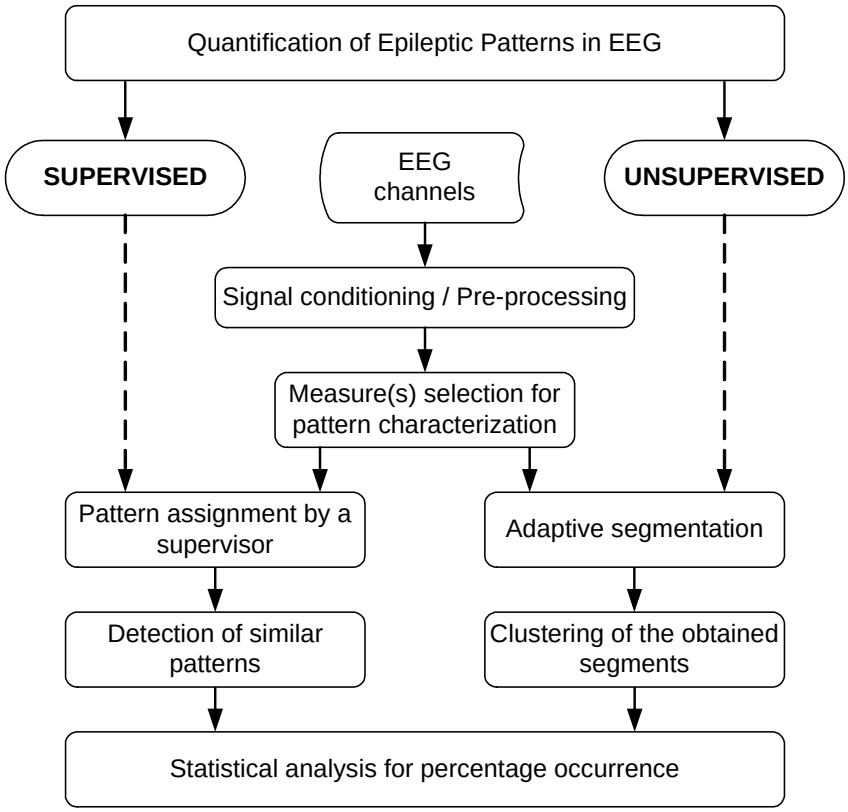


Fig. 6.2 Supervised and non-supervised strategies for quantification of epileptic patterns. After pre-processing, measures need to be assigned for pattern characterization in both approaches. In the supervised path, the supervisor selects the pattern of interest from the real data, and subsequently similar patterns are searched for in the data. In the unsupervised path, EEG is segmented adaptively and the segments obtained are clustered by a classification algorithm.

6.1.1 Measures of Pattern Characterization in EEG

The performance of both supervised and unsupervised approaches depends highly on the measure(s) used, because these measures determine either the segments obtained in adaptive segmentation in the unsupervised approach or, respectively, the pattern to be recognized in the supervised approach. Measure(s) should be able to characterize patterns in EEG distinctively.

6.1.1.1 Värri Measures

Different measures can be used for this purpose. In an earlier study [76], a measure of spectral density calculated via FFT was used in the context of adaptive EEG segmentation. Because of the computational inefficiency in huge data sets, Värri [77] introduced an amplitude measure *A* (eq. 6.1) and a derivate measure *F* (which can be regarded as a measure of frequency) (eq. 6.2) for pattern characterization in EEG.

$$A_j = \sum_{i=j}^{j+wl-1} |x_i| \tag{6.1}$$

$$F_j = \sum_{i=j}^{j+wl-1} |x_{i+1} - x_i| \tag{6.2}$$

where x_i is the i^{th} data point, j is the first data point in the analysis window of the length wl (in data points). These two measures will be referred to as Värri measures (VM).

6.1.1.2 Fractal Dimension

In the current work, fractal dimension (FD) is investigated as a new measure for detecting epileptic patterns, and its performance is compared with VM.

FD is commonly applied in both system and signal analysis. In non-linear system analysis, it is used for representing attractors which have fractional dimensions. The algorithm most commonly used for this purpose is the Grassberger and Proccacia method [78]. In signal processing, FD was investigated for its ability to detect non-stationarities in time series. It has been shown to be a useful tool for detecting transients in biomedical signals including EEG, as well [79], [80]. The changes in FD were shown to characterize changes in EEG due to alterations in the physiological state of the brain, not only in normal, but also in pathological functioning like epilepsy. Thus, in this study, the FD is also tested for its performance in pattern characterization.

In the study by Esteller [81], the most prominent methods are compared for FD computing in EEG analysis. It is concluded, that the Katz algorithm is the most consistent method for the discriminating epileptic states from intracranial EEG. Therefore, we selected the Katz algorithm for fractal dimension calculation in our application. According to Katz, the FD of a curve is defined as:

$$FD = \frac{\log_{10}(L)}{\log_{10}(r)} \tag{6.3}$$

where L is the total length of the curve, and r is the diameter estimated as the distance between the first data point and the data point that gives the largest distance. Normalizing the distances by the average distance between successive data points y, the eq. (6.4) is obtained.

$$FD = \frac{\log_{10}(L/y)}{\log_{10}(r/y)} \tag{6.4}$$

Defining $n=L/y$, the number of steps in the curve, we get eq. (6.5),

$$FD = \frac{\log_{10}(n)}{\log_{10}(r/L) + \log_{10}(n)} \tag{6.5}$$

For FD calculation Katz algorithm is implemented and tested on simulated data which is produced using the deterministic Weierstrass cosine function [82]:

$$W(t) = \sum_{n=0}^{\infty} \omega^{-nH} \cos(\omega^n t) \tag{6.6}$$

where $\omega > 1$ and H, $0 < H < 1$, is the constant determining the FD. Accordingly, the FD of the generated signal is given by $FD=2-H$.

6.1.2 Supervised Quantification of Epileptic Patterns in EEG

The supervised approach (Fig. 6.1), which is, to our knowledge, not addressed in this form in the literature, aims at automatic detection of *a priori* assigned patterns in EEG. The assignment has to be done by a supervisor on the real data. Then, the patterns, which are within a given tolerance similar to the original ones, are detected for further statistical analysis.

The method used for pattern recognition is a template matching algorithm based on a data window containing the template (i.e., the assigned measure(s) calculated for the selected pattern) that moves along the signal. The window length of detection is the

same as the window length of the selected pattern. The measure(s) in the current window of analysis is (are) compared with those in the original one. When the difference between the current window and the reference pattern is smaller than an assigned tolerance, then a pattern is assumed to be recognized. After selection of the set of patterns to be recognized, two parameters need to be assigned in the developed approach: a. window overlapping, b. the maximum allowed error (*E*).

The measure used for comparison of the patterns is the Euclidean distance,

$$D_j = \sqrt{(a_p - a_j)^2 + (b_p - b_j)^2 + (c_p - c_j)^2 \ldots} \tag{6.7}$$

where a_p, b_p, c_p are the measures of the selected original pattern, a_j, b_j, c_j are the measures of the pattern in the j^{th} window analyzed, and *D* is the Euclidean distance. If $D_j \leq E$, then the pattern in the current window *j* is recognized as a similar pattern. E is assigned according to empirical results.

The percentage epileptic pattern occurrence (%EPO) is not assigned via the number of patterns detected, rather via the ratio of the sum of the duration of similar patterns to the total duration of the measurement:

$$\%EPO_i = \frac{\sum_{j=1}^{n} t_{ij}}{T} \times 100 \quad , i = 1, \ldots, m \tag{6.8}$$

where $\%EPO_i$ is the percentage occurrence of the i^{th} pattern, *T* is the over-all duration of the measurement, t_{ij} is the duration of the j^{th} similar pattern, *n* is the total number detected similar patterns, and *m* is the number of distinctive patterns.

6.1.3 Unsupervised Quantification of Epileptic Patterns in EEG

Though not identified as "unsupervised quantification", adaptive segmentation and clustering of obtained EEG segments have been found to be a convenient solution to the problem of visual inspection of huge EEG data sets [76], [83], [84]. The term "unsupervised quantification" is coined in this study, since the segments to be classified

are not defined *a priori* by a supervisor, but rather are obtained through an adaptive process.

6.1.3.1 Adaptive EEG Segmentation Algorithm

The adaptive segmentation approach, which is selected for its proved efficiency in other studies [77], [84], has been proposed by Silin and Skrylev [76]. The procedure uses two successive windows moving on the time series in which the selected feature(s) is/are calculated. A measure difference function *G* is obtained through the difference of measure(s) in the two successive windows. The adaptive segment boundaries are then assigned to be the local maxima of *G*.

As proposed in [77], [84], the difference measures, *ADIF* and *FDIF* in eq. (6.9), computed from the successive windows, are derived from the VM in eq. (6.1) and eq. (6.2),

$$\begin{aligned} ADIF_k &= \left| A_j - A_k \right| \\ FDIF_k &= \left| F_j - F_k \right| \quad , k = j + wl - ol \end{aligned} \tag{6.9}$$

where *j* and *k* are the data points, *wl* is the window length and *ol* is the overlapping of the successive windows (both in sample points).

Accordingly, the corresponding difference function *GV* is obtained as

$$GV_k = c_a \cdot ADIF_k + c_f \cdot FDIF_k \tag{6.10}$$

where c_a and c_f are coefficients for amplitude and frequency measures respectively. The suggested values for the coefficients are $c_a = 1$ and $c_f = 7$ in the literature [84], [85].

In the adaptive segmentation application, the FD was assigned as a single measure for the function *G*. Thus, the corresponding difference function *GD* is obtained as

$$GD_k = \left| FD_j - FD_k \right| \quad , k = j + wl - ol \tag{6.11}$$

where, similar to eq. (6.9), *j* and *k* are the data points, *wl* is the window length and *ol* is the overlapping of the successive windows (both in sample points).

The Threshold in the Algorithm

In order to avoid excessive segmentation due to redundant small segments, Krajca [84] introduced a threshold for the measure difference to the algorithm. The local maxima of the function *G*, which are over an assigned threshold, are assumed to position the segment boundaries. The threshold *TH* proposed in [84] is computed within the incoming block *B* of analysis as:

$$TH = \frac{1}{B}(c_a \cdot A_B + c_f \cdot F_B) \tag{6.12}$$

where A_B and F_B are the measures calculated for the whole block of analysis; c_a and c_f are the corresponding coefficients as in eq. (6.10).

For achieving a higher adaptability of the threshold to the signals, an adaptive recursive approach was used in the current work. The threshold function Q_n is obtained according to eq. (6.13)

$$\begin{aligned} Q_1 &= G_1 \\ Q_n &= \begin{cases} Q_{n-1} + a_c \cdot \alpha & ,if \quad G_n \geq Q_{n-1} \\ Q_{n-1} - a_c \cdot (1-\alpha) & ,otherwise \end{cases} \end{aligned} \quad ,n = 2,\ldots,N \tag{6.13}$$

where *n* is the number of steps in the function *G* with *N* number of points; a_c, $0 \leq a_c \leq 1$, is an adaptation constant and α, $0 \leq \alpha \leq 1$, is the quantile parameter. The details on the adaptive recursive threshold can be found in [87].

6.1.3.2 Clustering the Obtained Segments

The next step of the unsupervised approach is clustering the obtained segments. Due to the fact that the conventional clustering methods have the drawback of disjunctive classification, which does not apply to EEG, we follow the suggestions in [84] and use a fuzzy clustering algorithm. In a fuzzy classification, the patterns can have different degrees of membership in different classes at the same time.

Below, the FCMI algorithm used according to [86] and its application to EEG segments will be explained: Given a group of segments $U=\{p_1, p_2,...,p_m\}$, it is assumed that a specific number *c* of clusters exist. The centers of the clusters are unknown and the initial values $y_{10}, y_{20},...,y_{c0}$ are given. In our application, these initial points are set according to the measures of the first *c* segments of the first channel analyzed. Segments of each EEG channel are clustered separately.

After each iteration, the membership values of a pattern to the corresponding clusters are obtained. The cluster centers are then updated by minimizing the local fuzzy performance indices $I_f(i)$ of eq. (6.14). The process is terminated when the difference between two consecutive iterations does not exceed a given tolerance or when the current iteration is equal to the maximum number of iterations allowed (i.e., an upper boundary for avoiding infinite loops).

$$I_f(i) = \sum_{j=1}^{m} P_{ij} \left\| z_i - p_j \right\|^2 \quad , 1 \le i \le c \tag{6.14}$$

where $I_f(i)$ is the i^{th} local fuzzy performance index and P_{ij} denotes the grade of membership of pattern p_j to the iteratively updated *c* number of clusters with the centers z_i. *m* is the number of patterns (i.e., obtained EEG segments).

The details of the used fuzzy clustering algorithm according to [86] are as follows:

Input:
- *f*, the segments dimension (number of measures).
- *m*, the number of segments.
- *c*, the number of clusters.
- $U = \{p_i\}, 1 \le i \le m$, the given segments in R^n.
- $Y_0 = \{y_{i0}\}, 1 \le i \le c$, the initial *c* cluster centers.
- M, maximum number of iterations allowed.
- ε, a given tolerance.
- β, a tuning parameter which controls the degree of fuzziness in the process.

Output: $Y = \{y_i\}, 1 \le i \le c$, the final c cluster centers.

(P_{ij}), $1 \le i \le c$, $1 \le j \le m$, the final matrix of membership values.

it, the number of iterations performed.

Step 1. Initialization: set $k = 0$ and $y_i^{(0)} = y_{i0}$, $1 \le i \le c$.

Step 2. For $1 \le i \le c$ and $1 \le j \le m$ calculate

$$e_{ij}^{(k)} = \left\| p_j - y_i^{(k)} \right\| \tag{6.15}$$

Step 3. For $1 \le i \le c$ and $1 \le j \le m$ calculate

$$P_{ij}^{(k)} = \left[\sum_{l=1}^{c} \left(\frac{e_{ij}^{(k)}}{e_{lj}^{(k)}} \right)^{2/(\beta-1)} \right]^{-1} \tag{6.16}$$

Step 4. If $e_{ij}^{(k)} = 0$ for some $l = l_0$, set $P_{l0j}^{(k)} = 1$ and $P_{ij}^{(k)} = 0$ for all $i \neq l_0$. For $1 \le i \le c$ update the cluster centers, using eq. (6.17)

$$y_i^{(k+1)} = \frac{\sum_{j=1}^{m} P_{ij}^{(k)} p_j}{\sum_{j=1}^{m} P_{ij}^{(k)}} \tag{6.17}$$

Step 5. If

$$\left[\sum_{i=1}^{c} \left\| y_i^{(k+1)} - y_i^{(k)} \right\|^2 \right]^{1/2} < \varepsilon \tag{6.18}$$

set $y_i = y_i^{(k+1)}$, $1 \le i \le c$; $P_{ij} = P_{ij}^{(k)}$, $1 \le I \le c$, $1 \le j \le m$; $it = k+1$; output y_i, P_{ij} for $1 \le i \le c$, $1 \le j \le m$ and stop. Otherwise continue.

Step 6. If $k = N$ output 'no convergence' and stop. Otherwise, set $k \leftarrow k+1$ and go to Step 2.

6.2 Contingent Negative Variation Analysis

The data acquired upon the employment of the modified S1-S2 paradigm (section 4.2) are segmented according to the type of S2 (i.e., aversive or non-aversive) for extracting the sweeps of trials. The contaminated trials are excluded from the analysis. The artifact free sweeps are then averaged in time. Excluding the auditory evoked response (i.e., the first 200 ms after the presentation of S1), the mean value of amplitude of CNV is calculated within the time interval 0.2-6 sec after S1 for the interval, t1, and after S2

for the interval, t2 (see Fig. 4.4). The steps followed in the sweep based analysis of the employed S1-S2 paradigm, in order to extract CNV quantitatively, are given in Fig. 6.3.

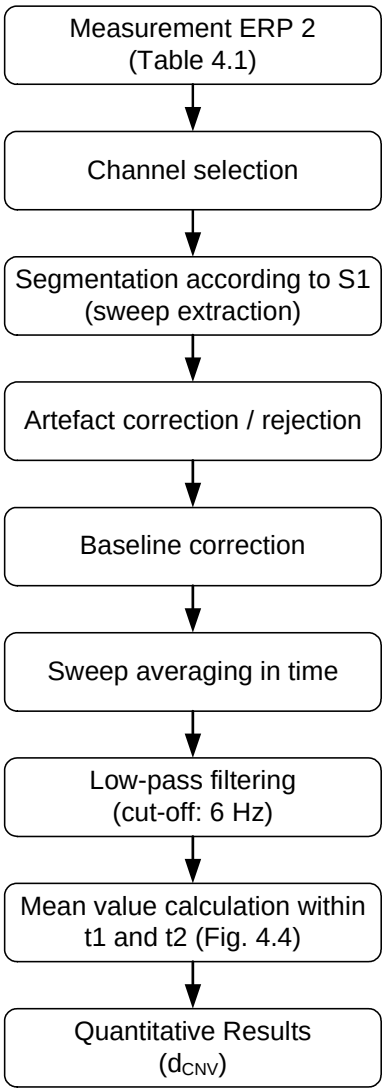


Fig. 6.3 Signal processing steps for quantification of CNV.

As the quantitative measure d_{CNV}, the difference between the mean value of CNV and the mean value of the post S2 interval (i.e., t_2) response, is assigned

$$d_{CNV} = mean(\text{CNV}) - mean(\text{Post\_S2}) \tag{6.19}$$

The quantitative results obtained corresponding to aversive and non-aversive S2 are statistically compared between healthy controls and epilepsy patients.

6.3 Analysis of Hyperventilation Induced DC-Shifts

In order to investigate the DC shifts during the hyperventilation measurements, the 28 channel EEG signals are averaged in time within a window length of 4 sec without overlapping through the measurements. The rate of change of the DC level is calculated via linear regression within the hyperventilation (s_{hv}) and recovery (s_{rec}) intervals. The slopes of the DC shifts, corresponding to the fitted lines, are assigned as quantitative measures. The flow diagram of the DC-level analysis during and after hyperventilation is given in Fig. 6.4.

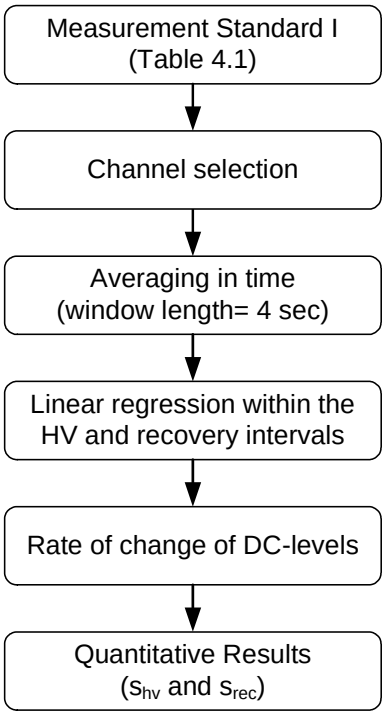


Fig. 6.4 Signal processing steps for quantification of hyperventilation induced DC-shifts.

A percentage DC recovery index (DCI_{rec}) is calculated from the parameters s_{hv} and s_{rec} as in eq. (6.20).

$$\%DCI_{rec} = -\left(\frac{s_{rec}}{s_{hv}}\right)\times 100 \qquad (6.20)$$

6.4 Analysis of Hyperventilation Induced Changes in Instantaneous Heart Rate

For extracting parameters reflecting the changes in IHR resulting from hyperventilation, R-peaks of the simultaneously acquired ECG channel are detected automatically by a QRS detector which is optimized for different sampling rates. The QRS detector is based on the basic principle of a peak detector, whereby it has a distinguishing approach of exploiting both the rising and falling edges of the R-peak [88]. IHR is calculated at each R-peak from the succeeding R-R interval. The R-R intervals are then linearly interpolated. Fig. 6.5 shows the analysis steps for obtaining IHR curves (IHRC) and for parameter quantification.

The average HR values are extracted from IHR curves (IHRC) within three intervals, (1) before hyperventilation, the baseline reference value, (2) during hyperventilation, and (3) during recovery intervals as in eq. (6.21).

$$\begin{aligned} HR_{bsl} &= mean(IHRC_{bsl}) \\ HR_{hv} &= mean(IHRC_{hv}) \\ HR_{rec} &= mean(IHRC_{rec}) \end{aligned} \tag{6.21}$$

where notation *bsl* (baseline) denotes the 3 minute interval before hyperventilation, *hv* denotes the 3 minute hyperventilation interval, and *rec* denotes the 3 minute interval after hyperventilation (i.e., recovery).

From the average IHR values obtained (i.e., HR_{bsl}, HR_{hv}, HR_{rec}), two indices are calculated for quantifying changes in the heart rate: The heart rate recovery ratio ($HR_{rec/hv}$) and the hyperventilation heart rate index (HRI_{hv}), which are given in percentage in eq. (6.22) and in eq, (6.23), respectively.

$$\%HR_{rec/hv} = \left(1 - \frac{HR_{rec}}{HR_{hv}}\right) \times 100 \tag{6.22}$$

$$\%HRI_{hv} = \frac{HR_{hv} - HR_{rec}}{HR_{hv} - HR_{bsl}} \times 100 \tag{6.23}$$

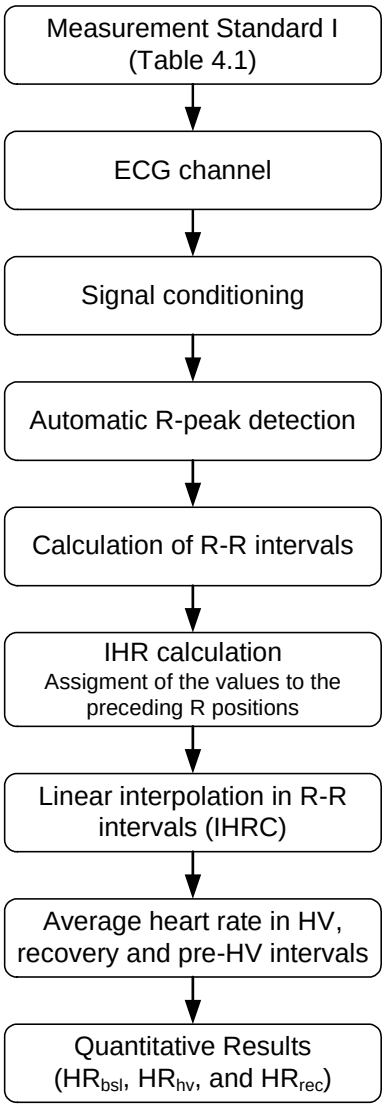


Fig. 6.5 Signal processing steps for IHR calculation during hyperventilation.

The obtained results of IHR analysis are combined with the results of DC analysis for comparisons between patients and controls.

7 Software-Technical Aspects as a Basis for Automation

A software technical approach is necessary, not only for processing the acquired signals for feature extraction and quantification, and subsequent analysis, but also for recording the supplementary medical information such as the seizure calendar and verbal results of clinical examinations, there is the need of an information technological approach. For a possible automation of the signal processing options, a software concept has been developed within the scope of current study. If the dimensions of the neuroprofile and the additional clinical data are considered, the information to be processed in therapy evaluation is immense. In order to solve the problem of managing the excessive amount of data, a database system, which is linked to the signal processing software, has been planned, designed and implemented.

Even though the current study concentrates on epilepsy, the system introduced in chapter 5 is also applicable to other neurological disorders, such as attention deficit disorder (ADD), ADHD, depression and sleep disorders. Therefore, in the conceptualization of the software and the database, applicability and extension to other neurological diseases in the realm of neurotherapy, is taken into account. The database system developed is presented in [89].

7.1 The Neuroprofile Extraction Module

In order to extract the selected parameters of the neuroprofile, the components of signal processing procedures introduced in chapter 6 (i.e., for supervised and unsupervised epileptic pattern analysis and fuzzy clustering; for DC-level analysis during hyperventilation and thereafter, as well as CNV; and for IHR analysis) are integrated in a software concept. The software concept of the neuroprofile extraction module is illustrated in Fig. 7.1. Different procedures of signal processing, implemented as sub-modules in Matlab, are integrated in the structure.

The module reads polygrahic data (i.e., EEG, ECG, VEOG; HEOG, respiration curve) of different formats from different systems (e.g., BrainQuick and NeuroScan). A graphical user interface (GUI) (Fig. 7.2) enables interactive presentation of data and results of analyses. There is a separate sub-module is developed for signal conditioning (i.e., pre-processing, e.g., downsampling, artefact rejection and/or correction). The analysis module, which contains the feature extraction and quantification components, is the central element in the concept. The current version of the neuroprofile extraction module can extract

a. graphoelements and their corresponding statistics from clinical EEG,
b. DC-shifts in EEG accompanying provocations such as hyperventilation and apnea,
c. parameters corresponding to event-related potentials (e.g., amplitude of CNV), and
d. parameters of simultaneously acquired polygraphic signals (e.g., IHR and respiration rate).

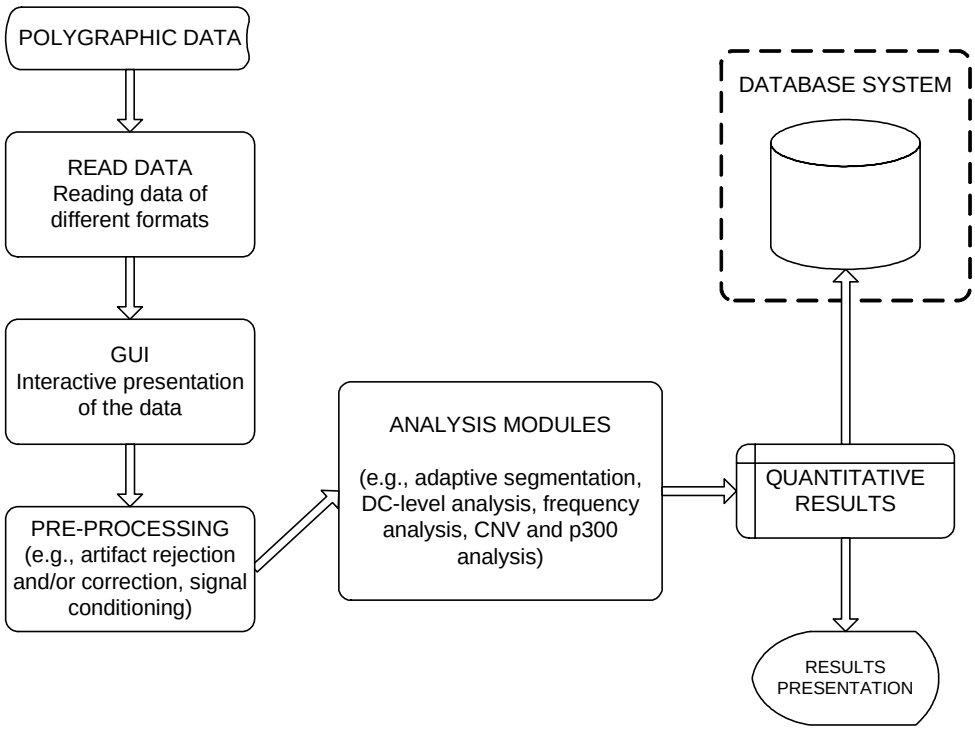


Fig. 7.1 Software components and flow diagram of the neuroprofile extraction module. Polygraphic data of different formats are read, interactively presented, and pre-processed for the main analysis, which contains software components for extraction of the relevant parameters. The quantitative results are stored in proprietary files. © IEEE Transactions on Information Technology in Biomedicine.

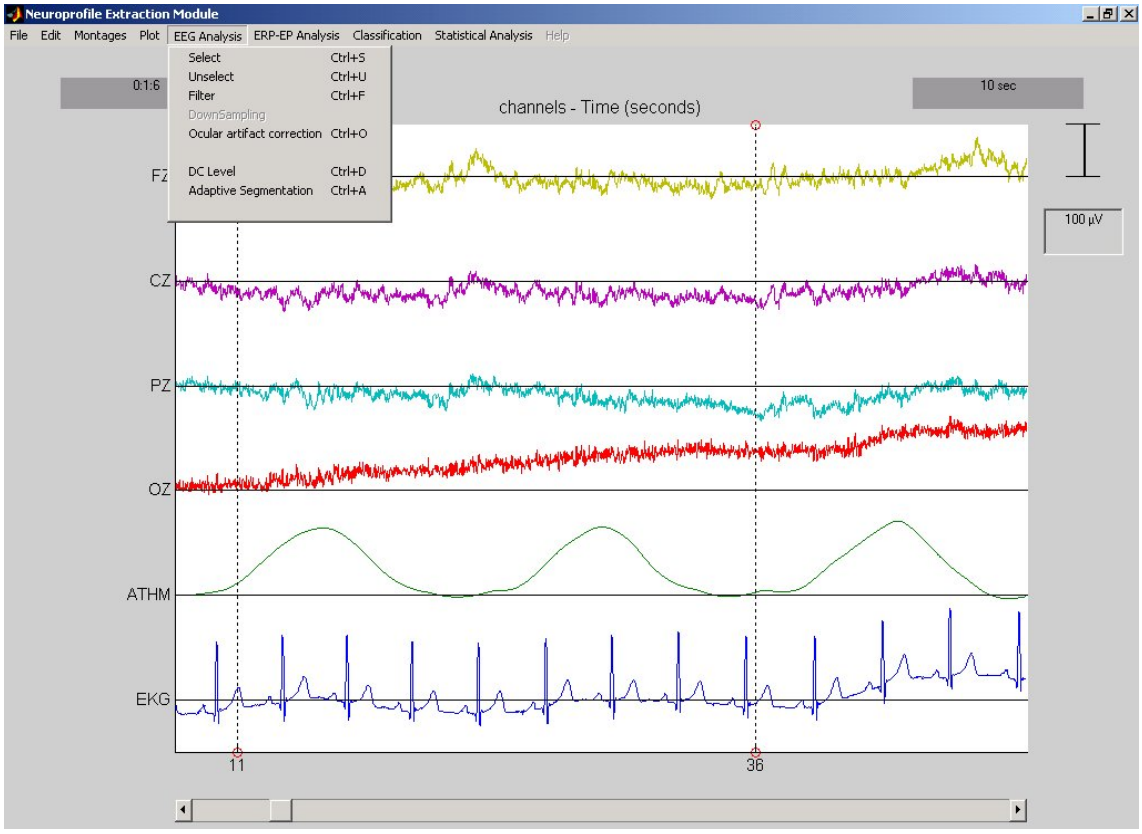


Fig. 7.2 Graphic User Interface of the Neuroprofile Extraction Module.

The quantitative results obtained from the analysis module are saved in a pre-defined format in a file system. These results can be recalled and presented either as curves or statistics or, for EEG, as topographic mappings. The details on the realization of the software components for epileptic pattern analysis can be found in [90]. At a further stage of development, a database system was developed in order to manage the obtained quantitative results.

7.2 Database Development

For systematically managing the extracted quantitative features resulting from the developed software components, as well as the supplementary medical information, a database system was planned, designed and implemented:

7.2.1 Methodological Concerns

According to the ANSI-SPARC[8] model, three levels of abstraction can be distinguished during the database design process [91]. At an external level the real world's cutout to be modeled is structured, and the database is described from each user's point of view. The resulting external user views are merged at the conceptual level into an integrative conceptual database scheme that describes the database structure for all types of users. It contains information about the objects modeled by the database, their properties, the relations between objects and constraints derived at the external level. Finally, the internal level describes the parameters of the database management system used to implement the database model. As a result, the physical structures of the database are determined by the internal scheme.

Fig. 7.3 shows the database design process and the corresponding generated documents [92], [93]. The requirements specification obtained after the requirements analysis documents the needs of the user(s). This specification is formalized by a conceptual database scheme, which is the outcome of the conceptual design. The logical design process transforms the conceptual scheme into the data model of the target database management system, the parameters of which are determined by the physical design process. The whole design process and its results are finally documented by the data dictionary.

7.2.2 Database Planning

7.2.2.1 Requirements Analysis

The requirements analysis can be divided into two components: the information requirements and the functional requirements. Functional requirements include the dynamic processes which are expected to be carried out by the database: The transactions (the requests, evaluations, and report generations) which are to be realized through the system, and the corresponding access regulations for different types of users belong to functional requirements. The information requirements, on the other hand, include the static information, which the database system will contain. The

[8] American National Standards Institute, Standards Planning and Requirements Committee.

objects of the real world with their properties, types and ranges, their relationships and integrity conditions refer to information requirements.

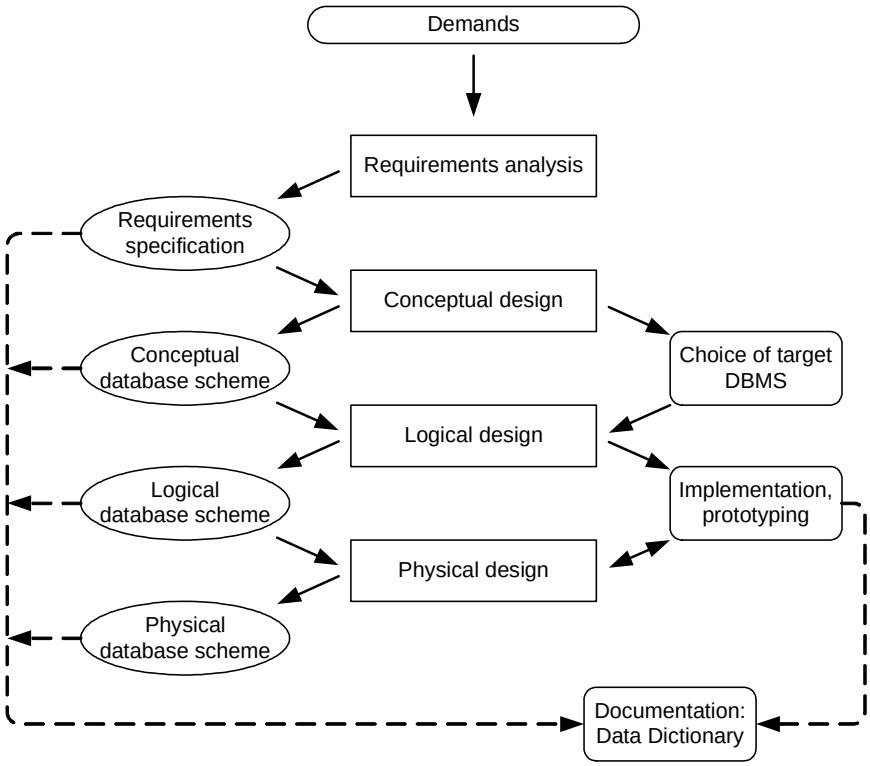


Fig. 7.3 The database design process according to [92]. © IEEE Transactions on Information Technology in Biomedicine.

The information requirements will be discussed in detail, since the current study is concerned with the extraction of essential features; both quantitative (results of the signal processing procedures) and verbal data (the verbal clinical information and seizure calendar, which can be quantified in a knowledge-based approach in further studies). The clinical relevance and priority are considered for the data concept.

The database is expected to combine two types of information which are inherently different: The quantitative data is well structured, purely numeric and extensive. In contrast, the medical information is rather unstructured, verbal and concise. The combination of these two types of information makes the design process demanding. Therefore, from the information technology point of view, the database to be conceptualized is not an operational system but a data warehouse [94], [95]. It regularly collects data from different sources (residing in different places using

different formats) and concentrates them in the database warehouse. The data are integrated in advance, meaning the necessary information are fetched, filtered, processed, consolidated and stored in the warehouse prior to the analyses being done. In order to provide the data necessary for a specific analysis none of the original data sources have to be accessed again.

Due to the consideration that the database can be extended to further disorders, it needs to be structured in two parts: a disorder-independent and a disorder-specific division (Fig. 7.4). The first version of the database contains the epilepsy-specific component, which is related to the content of the current study. Further versions can be supplemented with other disorder-specific components.

The database has to contain information regarding not only the patients but also healthy controls, so that comparisons with the norms will be possible. The control subjects (i.e., probands) are assured not to have any registered neurological disorder. This is tested via an inventory of yes/no questions. Thus, inter-group comparisons of the neuroprofiles (considering factors such as age, sex and handedness) shall also be done when a statistically significant number of control subjects and patients are obtained. The data warehouse, which will be introduced next, is conceptualized according to these requirements.

7.2.2.2 Data Warehouse Outline

Fig. 7.4 shows the outline of the data warehouse. Apart from the distinction between disorder independent/specific components, the database can be divided into five parts, each of which contains information essential for therapy evaluation purposes.

General information

This part contains information that is collected for both patients and control subjects. It incorporates personal data (identity code (ID), birth date, sex etc.), the neurofeedback sessions done along with their parameters and a list of EEG measurements performed. The polygraphic raw data are not included in the database; rather they are linked to the system over a file-system due to their large size and quantity.

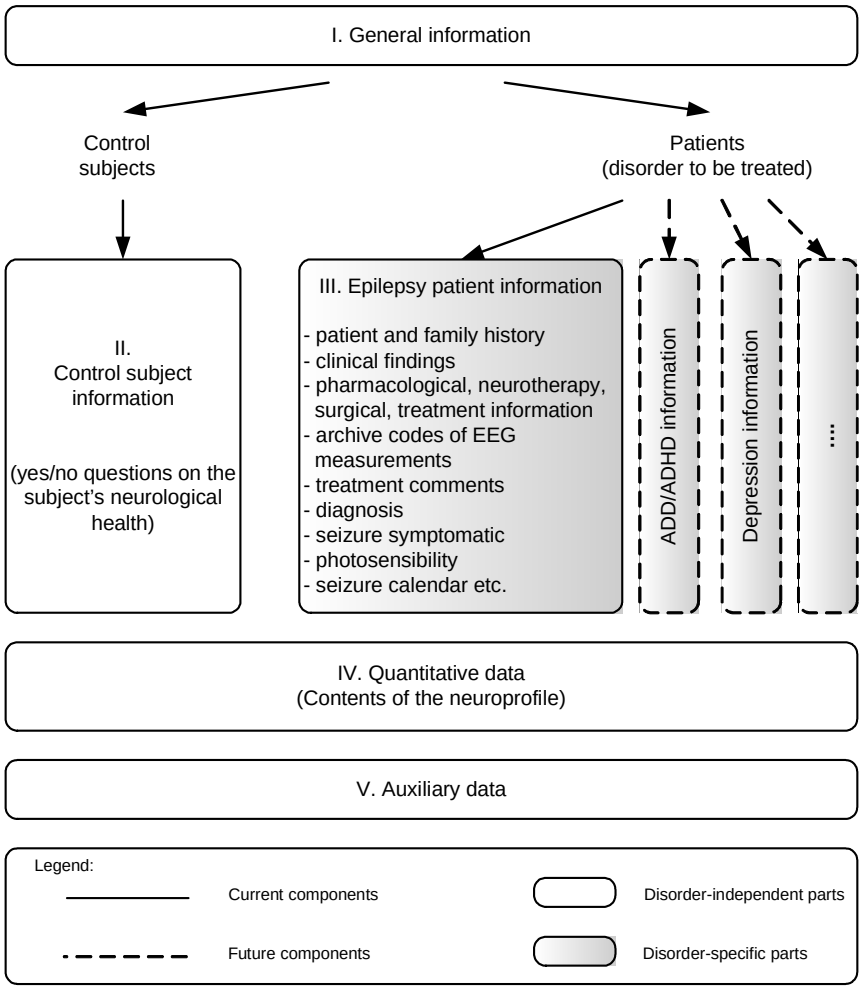


Fig. 7.4 Datawarehouse outline. © IEEE Transactions on Information Technology in Biomedicine.

Control subject information

This information is vital to ensuring that the control subjects have no neurological disorders that would disqualify them from being considered healthy for our investigations. It includes yes/no questions about any history of head injury, alcohol addiction, drug abuse, or neurological disorders (see Appendix A).

Patient (epilepsy) information

This division documents a detailed history of the patients's disorder and the treatment(s) applied. In the case of epilepsy, it includes the type of epilepsy, its classification and symptomatic, the seizure types, a list of occurred seizures (seizure calendar), all treatment modalities apart from neurotherapy (pharmacotherapy, surgery

etc.), clinical examination results, and measurements performed along with their results and findings. Summarized inventories can be found in Appendix B. Future extensions in this division will include supplements with specific information related to other neurological disorders.

Quantitative data

This part constitutes the largest part of the database. It contains the components of the neuroprofile (i.e., the measures addressed in chapter 6, qEEG and other quantitative parameters extracted from polygraphic signals).

Auxiliary data

This section contains data used by the other parts of the database, such as a list of antiepileptic medication that can be prescribed, possible electrode positions, and provocations.

7.2.2.3 Software Concept

Fig. 7.5 illustrates the integration of the database into the applications and the data that remain outside the database. The parts of the concept that will be completed in the future are marked with dashed lines (see Fig. 7.5).

Due to their size, acquisition and storage modalities, it is preferable not to store the polygraphic raw data in the database, but rather to maintain them in an encrypted directory structure on a file server. Based on the type of EEG session (diagnostic/therapy), the date of the recording and the patient's or control subject's ID, the file name and the directory in which the data are stored, are coded. The database only contains a list of the recordings done for a particular person. At the first stage of implementation (Fig. 7.5), calculation of the quantitative parameters and extraction of relevant features are done both by the implemented sub-modules of the neuroprofile extraction module (Version I) and by different commercial software packages. The obtained results are stored in proprietary files. The wrapper, a converter program accessing the database via ODBC or embedded SQL, stores the content of the proprietary files in the database.

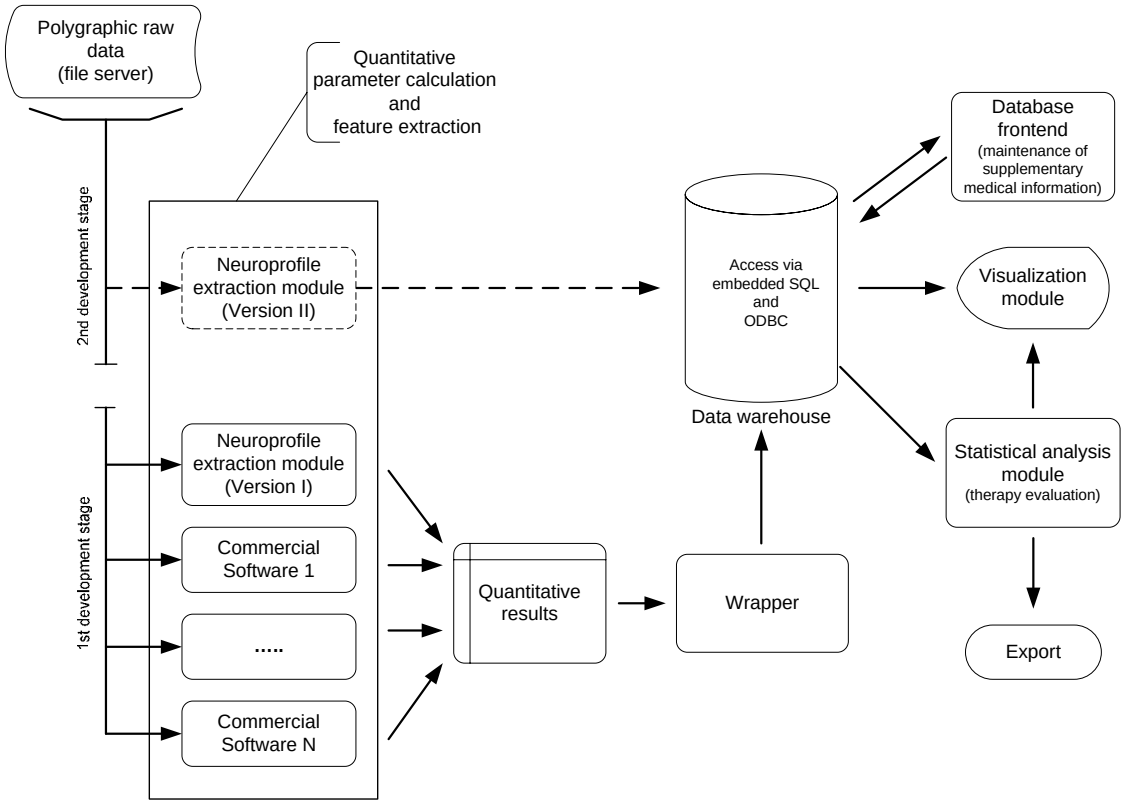


Fig. 7.5 Software concept using the database. 1st development stage (current): Quantitative results are extracted both by the implemented sub-modules of the neuroprofile extraction module (version I) and the commercial software packages. They are entered into the data warehouse via a wrapper. Database frontend is used for maintenance of supplementary medical information. Results stored in the data warehouse can be visualized or statistically analyzed by the corresponding modules which have access via embedded SQL or ODBC. 2nd development stage (future): Neuroprofile extraction module (Version II) shall overtake the quantitative analysis completely and store the results directly into the data warehouse.

At a later stage of development, the commercial software packages will be completely substituted with the neuroprofile extraction module (Version II), which is still under development. Version II will have direct access to the database, thus the temporary storage of the results in proprietary files will become obsolete. This will not only enable the usability in different clinics, but also hasten the automation. The maintenance of non-quantitative data is accomplished by means of a database frontend. It shall be done by the medical-technical personnel who apply the therapy.

7.2.3 Design and Implementation

Having analyzed the requirements, the database development process is continued with the design and implementation. Corresponding steps of conceptual, logical and physical design (Fig. 7.3) will be addressed next:

7.2.3.1 Conceptual Design

The objective of the conceptual design process is to describe the cutout of the real world that is to be modeled by the database in a formal way, independent from the characteristics of the target database management system. In most cases it is done using Entity-Relationship Modeling (ERM) [96].

In ERM, physical or virtual objects and concepts of the real world are termed as entities. Similar entities are abstracted by entity types and clustered in entity sets. Likewise, similar relationships between entities are abstracted by relationship types and clustered in relationship sets. The entity sets are universally characterized by attributes which describe the owner's properties, whereas the relationship sets may or may not have attributes. Functionality and cardinality are two other elements which belong to the description of the real world. They quantitatively define the links between the entity sets which are connected via relationships. By means of these elements, a real world system can be modeled in an entity-relationship diagram (ERD) [93], [96].

Thus, the data warehouse outline described above is given full particulars in a global ERD. The five parts of the database are modeled with all of their details and linked together adequately. Fig. 7.6 shows a small part of the final diagram. The overall ERD contains many more entity types which relate to person, proband, epilepsy patient or diagnostic raw data.

7.2.3.2 Logical Design

The aim of this step of the design process is to map the conceptual database scheme into the data model utilized by the target database management system (DBMS) [97]. The data model is the paradigm used by the database to store information. Currently there are three types of data models used by databases. The relational data model is the prevalent model used by most databases. The object-oriented model integrates aspects

of software development into the database world and is more flexible. The object-relational model [98] is a hybrid of both which combines the sophisticated mechanisms of relational databases with the advanced features of object-oriented databases.

Because of the fact that most of the warehouse contents have a simple structure that can be modeled easily with relations, the object-relational data model was chosen for the warehouse. The three-dimensional structure of the neuroprofile (Fig. 4.1) can be adequately mapped into multi-dimensional arrays.

As a result of logical database design, a list of relations was produced from the conceptual scheme. The entity and relationship types of the ERD became relations (see Fig. 7.6). As an example, the "epilepsy patient" entity type was mapped to the relation "epilepsy patient" (i.e., ID, employed, patient history, family history, epilepsy type, epilepsy classification, focus, position, photosensibility exists, photosensibility description).

7.2.3.3 Physical Design

This last step addresses the internals of the database system. It comprises the choice of the target database management system, the definition of the structures used to store the information, the mechanisms used to speed up searches, the implementation of constraints that ensure a consistent data stock, and the management of access rights [99].

As the target system several candidates (Borland [100], Frontbase [101], mySQL AB [102], and Postgres [103]) were compared in facilities such as administration, interface options, network capability, multi-user option, and costs. Finally, the PostgreSQL[9] was chosen: It is an open-source object-relational database system which offers a variety of object-relational features. Apart from its sophisticated mechanisms to enforce data consistency and its ability to handle large amounts of data, it has the advantage of being free, compared to the expensive commercial database servers. For the enforcement of data consistency domain constraints, functions and rules were used.

[9] PostgreSQL was developed at the University of California at Berkeley.

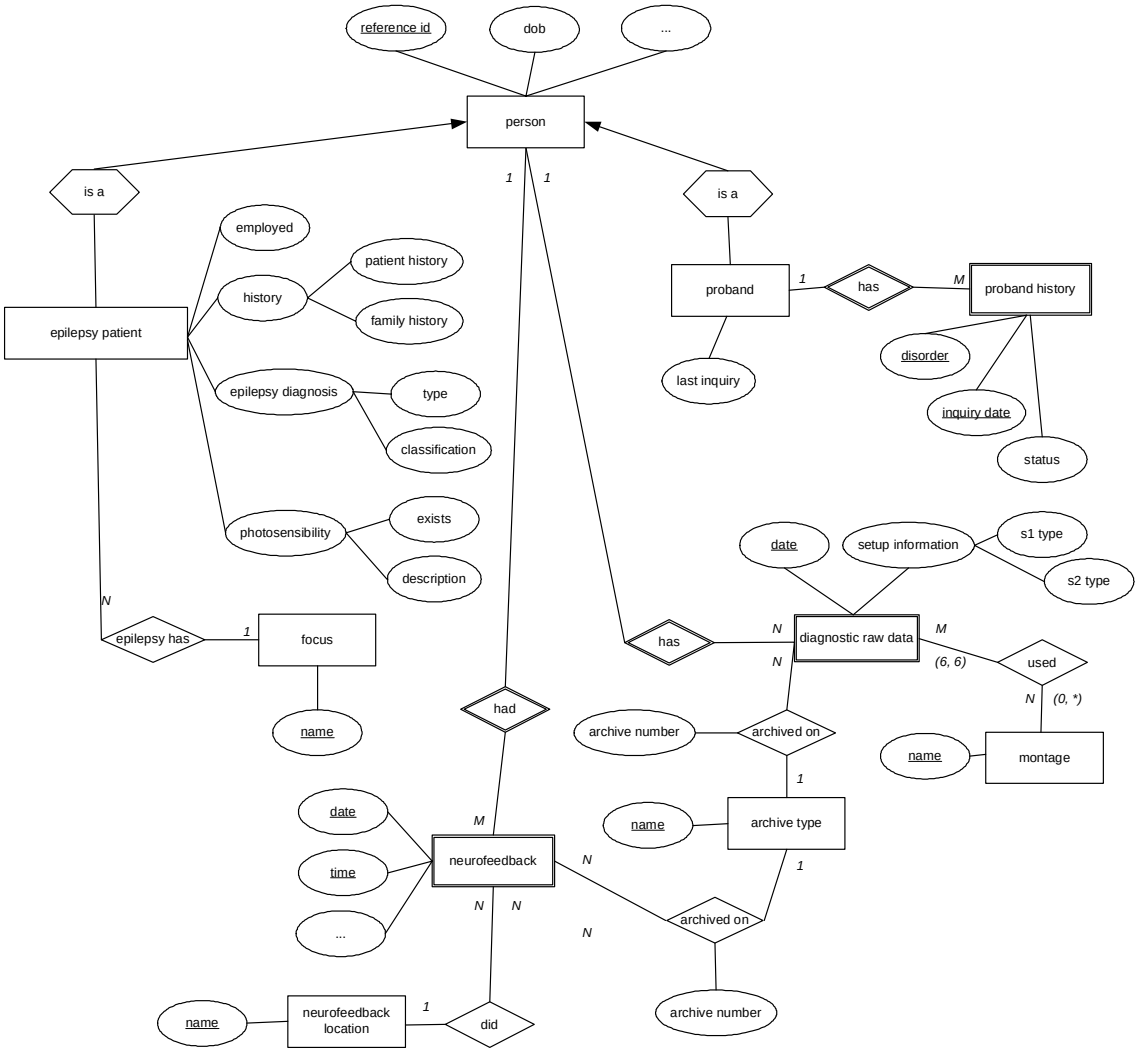


Fig. 7.6 A sample part from the entity-relationship diagram. Person, proband and epilepsy patient are central entity types of the model. Neurofeedback represents a session of neurofeedback training performed with a person, diagnostic raw data is a set of EEG data recorded for a particular person. © IEEE Transactions on Information Technology in Biomedicine.

7.2.3.4 Realization

The PostgreSQL 7.1.2 database server was set up on a Windows 2000 Workstation. Since PostgreSQL supports only Unix-like operating systems, the emulation *Cygwin* had to be used to provide PostgreSQL with a Unix platform [103]. The emulation is only required by the machine that runs the server; the client machines may run any Windows operating system.

Although using the PostgreSQL server on a Linux machine can be more efficient, a Windows based solution is preferred because of the fact that our medical partners

mainly use Windows operating systems, and the software components of the developed EEG-biofeedback system are also Windows based.

As shown in Fig. 7.5, at this first stage of the development several applications are used to enter data into the warehouse: The quantitative data are inserted by the wrapper which gets access via ODBC, whereas the non-quantitative information needs to be entered manually by means of the database frontend, the *Neurobase* (Fig. 7.7), which is implemented in Microsoft Access. The statistical analyses are carried out by the corresponding application (Fig. 7.5) which also has access to the database via ODBC. More details on the data warehouse realization can be found in [104].

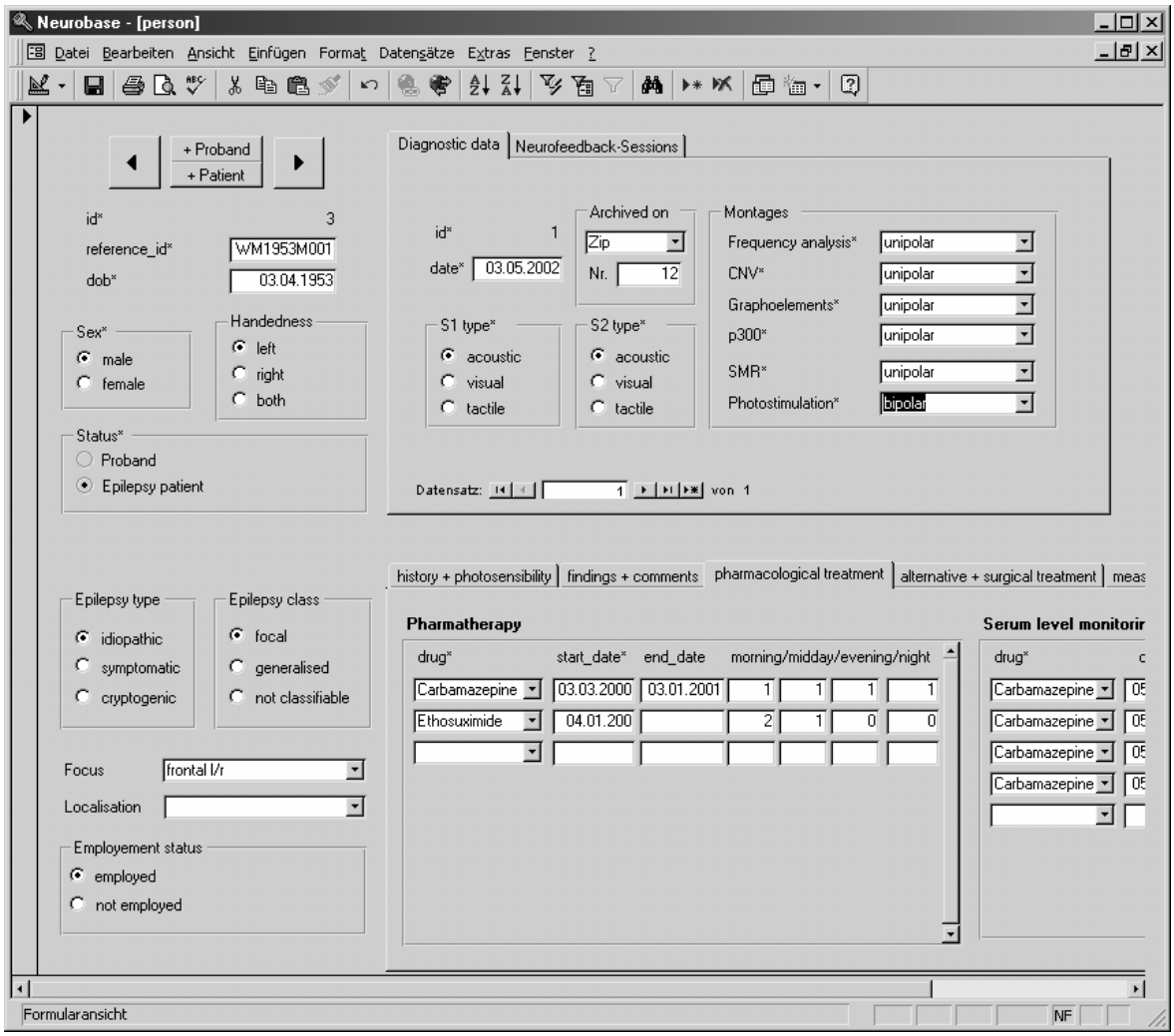


Fig. 7.7 NeuroBase for entering clinical information. © IEEE Transactions on Information Technology in Biomedicine.

8 Results

Having introduced our approach, measurements, methodology, and software realizations, the results[10] obtained by application of the methods on real data will be presented next.

8.1 Epileptic Patterns Analysis

The performance of both supervised and unsupervised approaches to epileptic pattern detection depends primarily on the measure(s) used. The better the measures characterize epileptic activities, the higher the performance is. Hence, the performance of the measures for pattern recognition (i.e., VM as the previously used measures, and FD as a new feature introduced in this study) is tested and compared [105] in a set of randomly chosen epileptic patterns (n=30) from data acquired in previous studies. Representative results are illustrated on 3 sample patterns (Fig. 8.1-Fig. 8.3). For facilitation of comparison, the threshold for preventing redundant segmentation is assigned differently for each case as the value for which the highest number of redundant segments is eliminated, without missing the desired segment boundaries.

8.1.1 Värri Measures versus Fractal Dimension

When the performance of the features was compared in the 30 randomly selected epileptic patterns, 14 patterns (47 %) showed FD to be more sensitive to the end points of the patterns, whereas VM detected some redundant boundaries within the patterns before the end points were detected, as shown in Fig. 8.1 a, b. In 3 patterns (10%), VM failed to detect the segment boundaries correctly (Fig. 8.2 a), whereas FD was successful (Fig. 8.2 b). The results in the remaining 13 patterns were similar for both VM and FD. The detection results as shown in Fig. 8.3 a, b, are accepted to be equally successful. Based on these results, it was concluded that FD performs superiorly to VM in extracting epileptic patterns in EEG [105].

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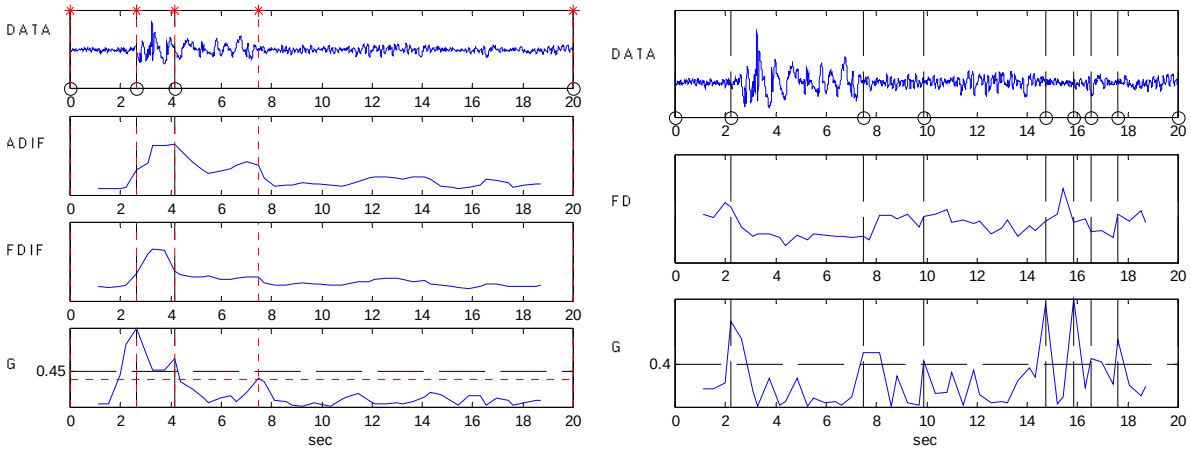
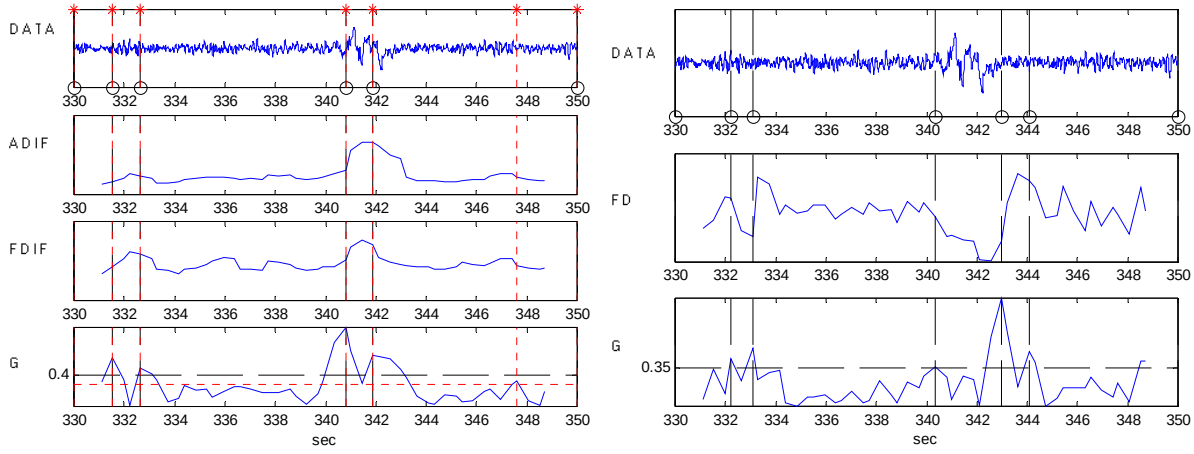
[10] Some partial results have been presented in different publications [89], [105]-[107].



(a) (b)

Fig. 8.1 Segmentation results for sample pattern 1, (a) Värri measures (threshold = 0.4 (*) and 0.45 (o)), (b) FD (threshold = 0.4). Window width = 1.1 sec, window overlapping = 60%. © IEEE Engineering in Medicine and Biology



(a) (b)

Fig. 8.2 Segmentation results for sample pattern 2, (a) Värri measures (threshold = 0.3 (*) and 0.4 (o)), (b) FD (threshold = 0.35). Window width = 1.1 sec, window overlapping = 60%. © IEEE Engineering in Medicine and Biology.

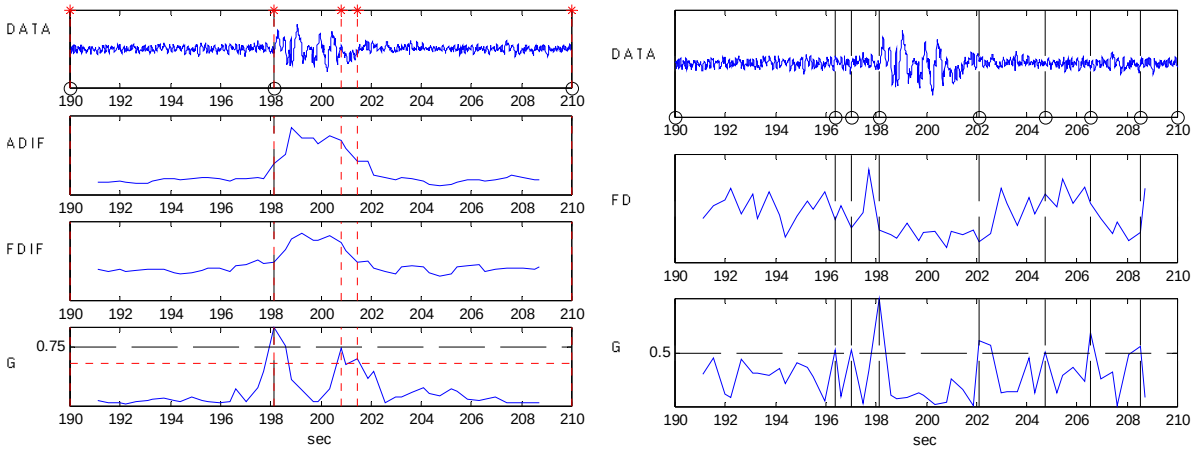


Fig. 8.3 Segmentation results for sample pattern 3, (a) Värri measures (threshold = 0.6 (*) and 0.75 (o)), (b) FD (threshold = 0.5). Window width = 1.1 sec, window overlapping = 60%. © IEEE Engineering in Medicine and Biology.

There are further observations which need to be emphasized concerning the FD as a feature for adaptive EEG segmentation and epileptic pattern extraction [105]: The first observation is that FD decreases in epileptic pattern intervals (Fig. 8.1 b, Fig. 8.2 b, Fig. 8.3 b). Secondly, FD is more sensitive to the end points of the epileptic patterns, and it is more stable within the pattern interval. If we assume that the brain switches from a higher dimensional "normal" state to a lower dimensional "pathological" stationary state in the epileptic pattern intervals, it can be stated that the FD, as a feature, better reflects these changes in physiological state. Another advantage of FD is that it can be used as a single measure without any weight coefficients in the adaptive segmentation algorithm eq. (6.12). On the other hand, FD was observed to detect more segment boundaries *outside* the pattern intervals than the VM. This was regularly observed in the sample patterns (Fig. 8.1-Fig. 8.3). Further discussion and investigations are required in order to determine whether these are redundant segment boundaries or really significant state changes.

8.1.2 Supervised and Unsupervised Detections

For supervised detection, the performance of the measures also reflects the performance of detection, since the patterns are assigned as "recognized" if the measures are within a

range of tolerance. The decisive parameter of the method is the tolerance E, which determines the recognition sensitivity.

In addition to the measures, the efficiency of clustering is important to the overall performance in unsupervised quantification. Having concluded that FD is superior to VM as a feature for extracting epileptic patterns, it was applied to unsupervised quantification via fuzzy clustering. A sample analysis result is given for a channel of an EEG recording, in which epileptic patterns were observed. The number of clusters is *a priori* assigned as 6, according to experimental results on different data.

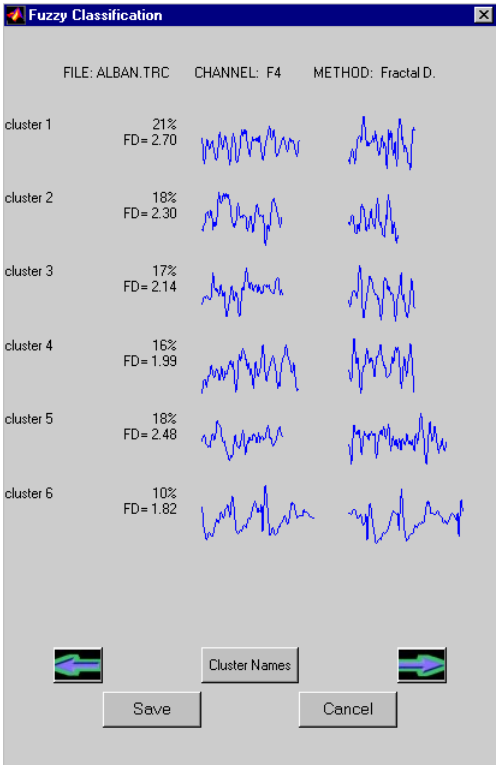


Fig. 8.4 Sample results of fuzzy clustering after adaptive segmentation based on FD on an EEG channel. Statistics (percentage occurrence) of the clusters which have the corresponding FD value as the center.

Based on the observation that FD decreases in epileptic pattern intervals, the clusters, which have lower FD values as their centers, should be considered epileptic pattern clusters: As seen in Fig. 8.4, cluster 6 (FD=1.82), cluster 4 (FD=1.99) and cluster 3 (FD=2.14) should be considered possible epileptic pattern clusters. The medical expert must decide which clusters are to be accepted as such. Epileptic spike wave complexes are clearly seen in cluster 6.

The adaptive segmentation algorithm has three important parameters which need to be discussed: the window width, the percentage overlapping of the successive windows, and the threshold.

a. The window width should not be selected larger than 1.5 sec in order to more accurately detect non-stationarities. It should also conform to the number of data points required to sufficiently calculate the selected feature. On the other hand, the smaller the window width, the higher the computational load.

b. The overlapping has a similar effect to the algorithm: The longer the overlapping is (smaller step length), the greater the number of segments found. This means a longer computation time and an increase in the number of redundant segments. However, if the overlap is too small, the necessary segment boundaries to be detected can be missed.

c. The threshold is the parameter which determines the sensitivity of the algorithm. The higher the threshold is, the less sensitive the algorithm is to the non-stationarities. If the threshold is too low, then the problem of redundant segmentation appears.

The setting of all three parameters is a trade-off between topical sufficiency (respectively redundancy) and computational complexity. In our software development, these parameters can be input as desired so that their influence on the performance of the algorithm can be observed. Based on our empirical results, we recommend a window length of 1.1 sec at a sampling rate of 128 Hz, and a window overlapping of 60%. The software also allows the automation of the analysis where we assign the window width and the overlapping a priori according to experimental results. For automated analysis, the threshold for the segment boundary detection (i.e., for function G see section 6.1.3.1) is determined adaptive recursively according to the distribution of the normalized values of G through the data interval analyzed [87].

8.2 Differences in the Contingent Negative Variation between Patients and Controls

The CNV measurements are analyzed according to the procedures presented in section 6.2. In order to enlarge the statistical pool, additional measurements from previous studies are integrated into the analysis. The data are analyzed for both the patient group (n=12) and healthy controls (n=11). Sample results from a control subject are illustrated in Fig. 8.5 for 28 EEG channels.

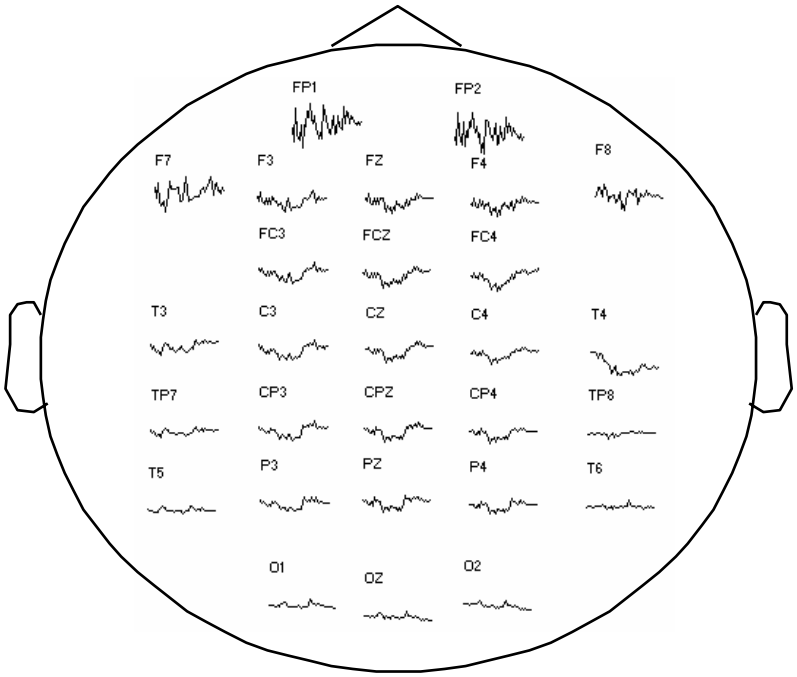


Fig. 8.5 Sample CNV results for 28 EEG channels. Initial measurement of subject S1JN. Time average of 20 sweeps.

According to our results, CNV occurs after presentation of the warning stimulus S1, whereas positive DC shifts occur after the presentation of the stimulus S2 (Fig. 8.6). The topology of d_{cnv} is demonstrated for a control subject (Fig. 8.7 a) and a patient (Fig. 8.7 b). Comparisons of the central line electrodes Fcz, Cz, Cpz, and Pz between the patient group and the controls indicate significant differences (Table 8-1) [89], [106]. In the control group, the mean values of the CNV and the post-S2 level are significantly different at all electrode positions with exception of Pz in the non-aversive case, whereas in the patient group, these levels are significantly different only at the electrode position Cz in the aversive case (Wilcoxon-Signed-Rank-Test, $p<0.05$). The

d_{cnv} for aversive stimuli is higher than for non-aversive stimuli in all subjects and patients in all channels at which CNV is clearly observed.

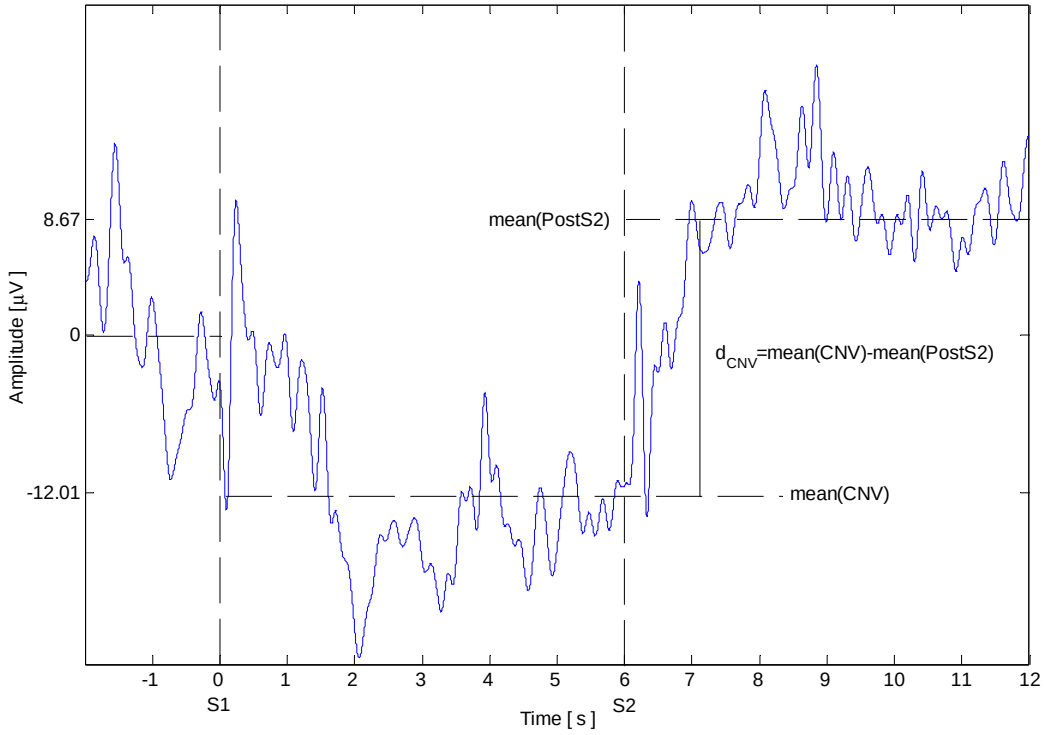


Fig. 8.6 Quantification of CNV results, d_{cnv}. Subject S5PT, initial measurement, channel Cz.

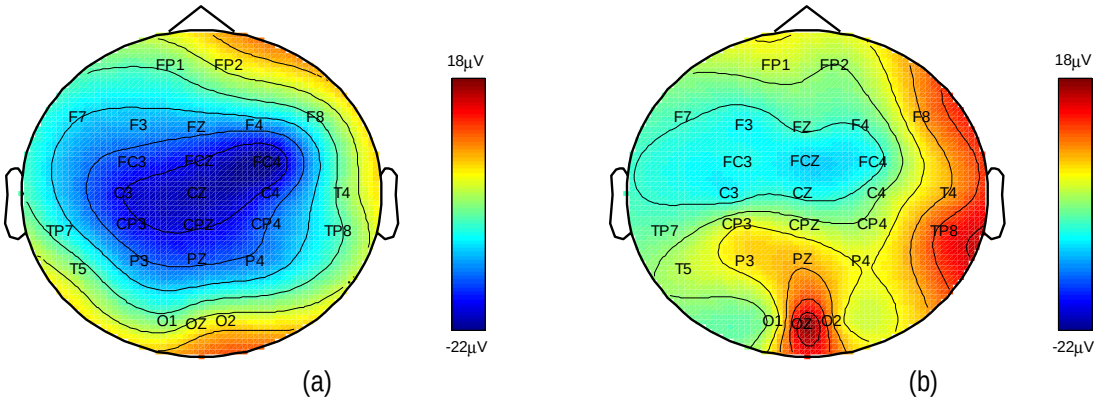


Fig. 8.7 Topological mapping of the measure d_{CNV} from, a) control subject S2MN, initial measurement; b) epilepsy patient P4ES, pre-therapy measurement.

Table 8-1 CNV Comparison between patients and control subjects. © IEEE Transactions on Information Technology in Biomedicine.

	Results (p) Wilcoxon Signed-Rank-Test, p<0.05			
Channel	Patients Aversive case	Patients Non-aversive case	Controls Aversive case	Controls Non-aversive case
Fcz	0.077	0.204	0.001	0.005
Cz	0.042	0.569	0.003	0.024
Cpz	0.063	0.424	0.003	0.019
Pz	0.110	0.569	0.010	0.413

8.3 Differences in the Hyperventilation Induced DC-Shifts

Hyperventilation induced shifts in DC-potentials are analyzed via the method introduced in section 6.3. In Fig. 8.8, a sample result of the DC analysis is given for a standard measurement from a control subject:

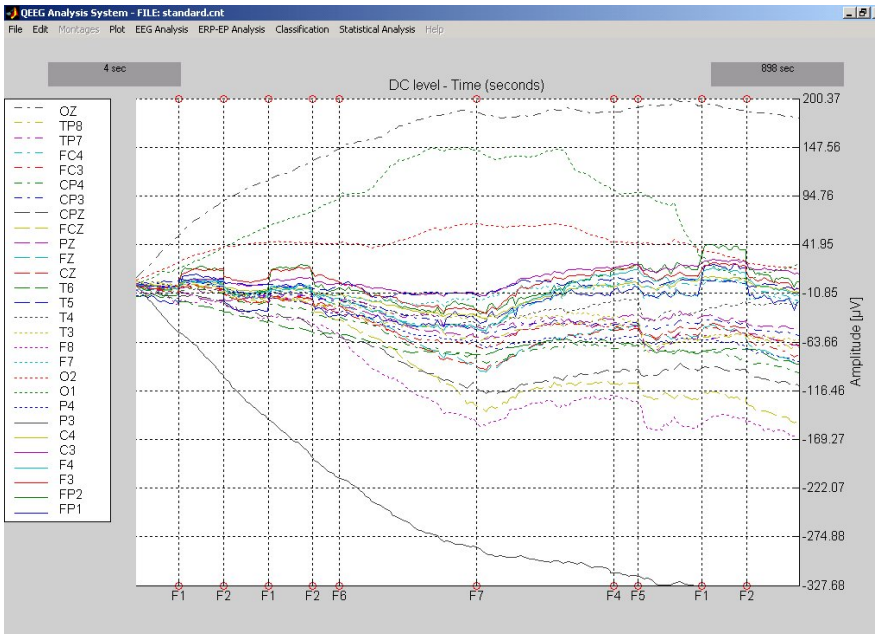


Fig. 8.8 DC-level during a standard measurement for all EEG electrodes. Subject S5PT, initial measurement. Triggers: F6=HV-start, F7=HV-end, F4=recovery-end.

As seen in Fig. 8.8, not all electrodes are stable (i.e., artifact free) along the measurement (e.g., P3). Nevertheless, a pattern appears, which can be extracted from the results within the hyperventilation interval and thereafter: The trigger F6 is the beginning and F7 is the end of hyperventilation, which continues for three minutes. The

trigger F4 points to three minutes after the end of hyperventilation. We define this interval as recovery. If we select the central electrode positions (Fz, Cz, Pz, and Oz) and also include other frontal (Fp1, Fp2) and occipital (O1, O2) electrodes, we obtain the following pattern in Fig. 8.9 for a control subject and Fig. 8.10 for a patient.

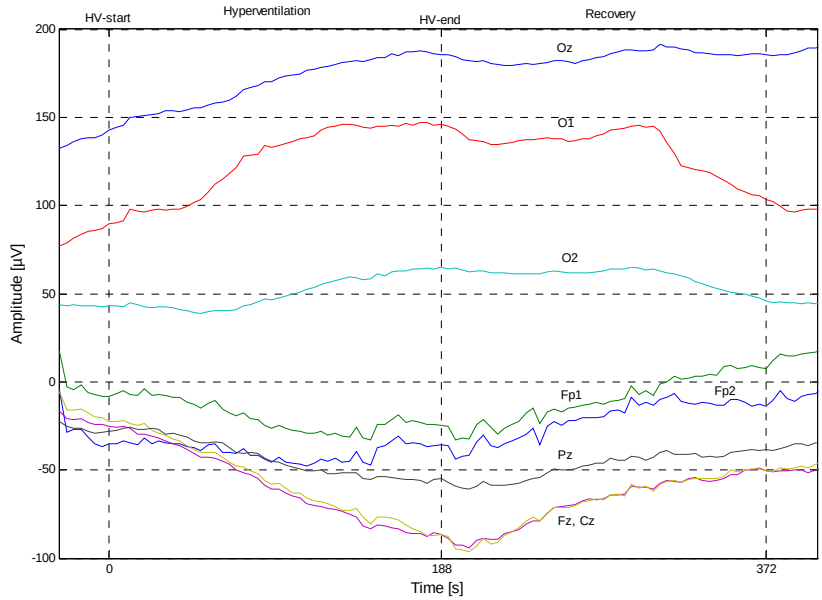


Fig. 8.9 DC-shifts during and after hyperventilation at electrode positions Fp1, Fp2, Fz, Cz, Pz, Oz, O1, and O2. t = 0, hyperventilation starts; t = 185 s, hyperventilation ends. Subject S5PT, 1st evaluation measurement.

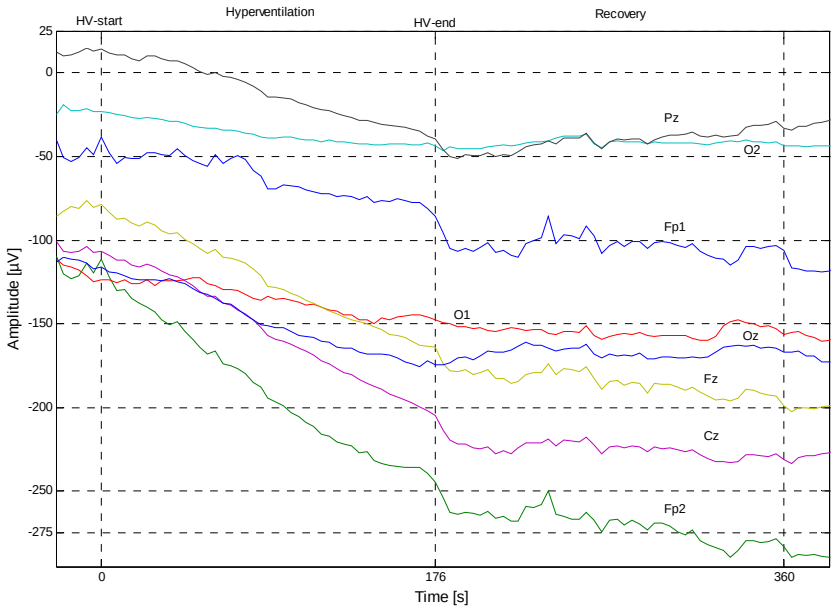


Fig. 8.10 DC-shifts during and after hyperventilation at electrode positions Fp1, Fp2, Fz, Cz, Pz, Oz, O1, O2. t = 0, hyperventilation starts; t = 176 s, hyperventilation ends. Patient P2WM, pre-therapy measurement.

After the linear regression (Fig. 8.11), the quantitative parameters s_{hv} and s_{rec} are extracted.

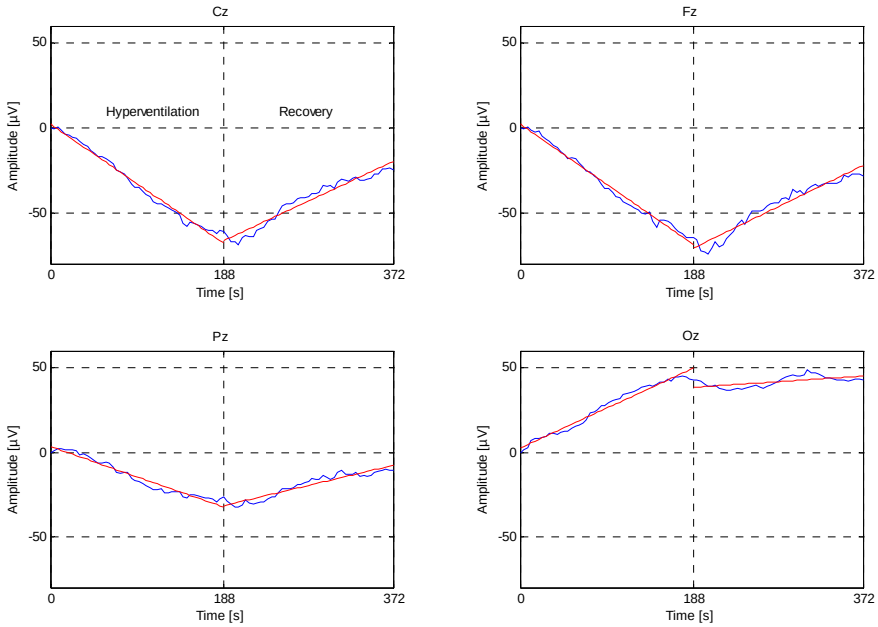


Fig. 8.11 Linear regression for determining the rate of change of DC-level within HV and recovery intervals.

The topographic distribution of the rate of change of DC-level at different electrode positions can be mapped as in Fig. 8.12 and Fig. 8.13.

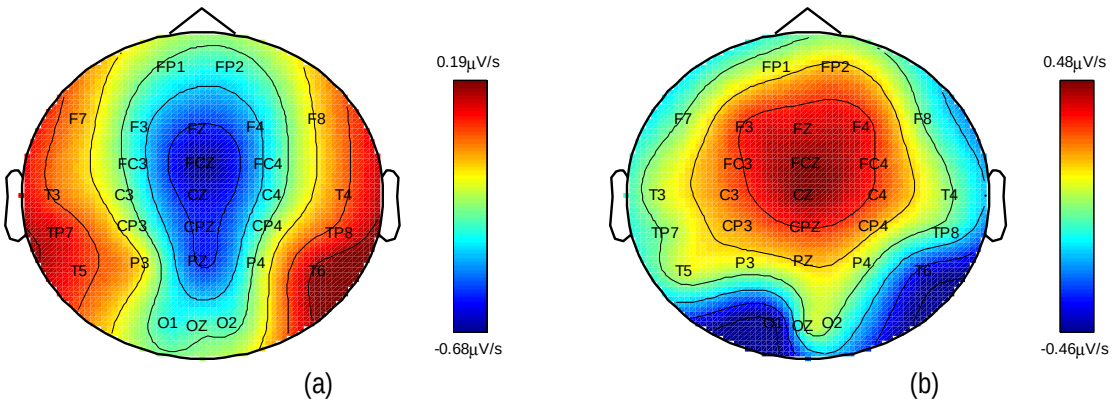


Fig. 8.12. Topological mapping of the rate of change of DC-level for a control subject (S1JN, initial measurement), a) hyperventilation (s_{hv}), and b) recovery (s_{rec}).

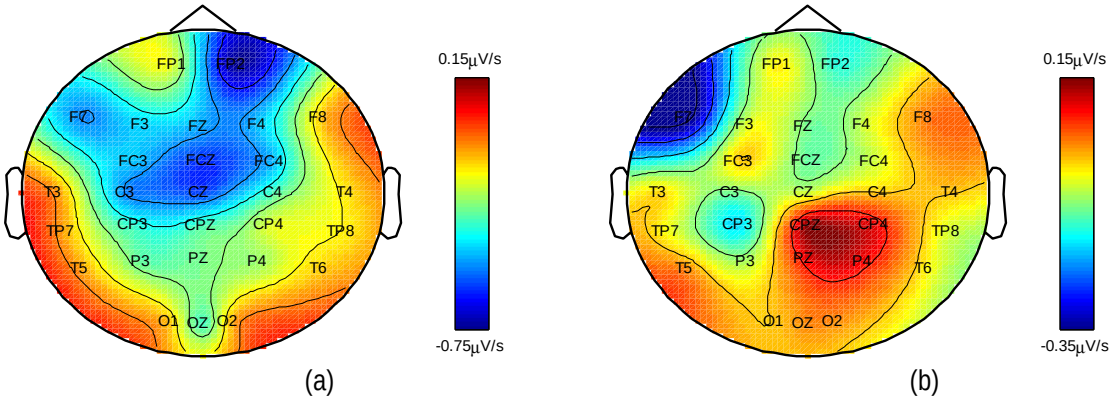


Fig. 8.13 Topological mapping of the rate of change of DC-level for an epilepsy patient (P2WM, pre-therapy measurement), a) hyperventilation (s_{hv}), and b) recovery (s_{rec}).

As seen in Fig. 8.12 and Fig. 8.13, the highest DC-shifts, both in hyperventilation and recovery, are observed either at Cz and/or Fz. Therefore, the rate of change of DC-levels in HV and recovery intervals at the vertex (Cz) are compared between control subjects and epilepsy patients for those measurements in which the stability of the electrodes was satisfactory. The results at the central electrode positions (Fz, Cz, Pz and Oz) for the control subjects (Table 8-2) and for the pre-therapy measurements of the patients (Table 8-3) are given below:

Table 8-2 Rate of change of DC-level within HV and recovery intervals for control subjects.

Subject Code	Rate of Change of DC-level							
	Hyperventilation s_{hv} (µV/s) Electrode				Recovery s_{rec} (µV/s) Electrode			
	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz
S1JN	-0.56	-0.60	-0.56	-0.29	0.40	0.48	0.18	0.05
S2MN	-0.18	-0.25	-0.16	0.01	0.21	0.31	0.20	0.04
S3AD	-0.34	-0.73	-0.05	0.60	0.47	0.58	0.22	-0.83
S4OL	-0.28	-0.43	-0.22	0.35	0.23	0.21	0.04	-0.35
S5PT	-0.51	-0.47	-0.34	-0.08	0.30	0.41	0.08	-0.01
S6CR	-0.57	-0.53	-0.53	-0.33	0.20	0.26	-0.00	0.03

Table 8-3 Rate of change of DC-level within HV and recovery intervals for patients.

Patient Code	Rate of Change of DC-level							
	Hyperventilation s_{hv} (μV/s) Electrode				Recovery s_{rec} (μV/s) Electrode			
	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz
P1MH	-0.05	-0.17	-0.14	-0.09	0.10	0.27	0.29	0.09
P2WM	-0.50	-0.59	-0.31	-0.37	-0.11	-0.07	0.09	0.02
P3GM	0.01	-0.50	-0.21	-0.12	0.22	-0.00	0.40	0.15
P4ES	-0.10	-0.17	-0.19	0.35	0.32	0.26	-0.00	-0.73
P5RB	-0.37	-0.40	-0.05	0.46	0.55	0.59	0.19	-0.90
P6MU	-0.76	-0.80	-0.37	-0.08	0.09	-0.14	0.06	-0.11

Table 8-4 Percentage DC-recovery after hyperventilation in patients and controls.

Patient Code	% DCI_{rec} at the vertex (Cz)	Subject Code	% DCI_{rec} at the vertex (Cz)
P1MH	159%	S1JN	80%
P2WM	-12%, negative shift, no recovery	S2MN	124%
P3GM	-0.8%, negative shift, no recovery	S3AD	80%
P4ES	153%	S4OL	49%
P5RB	148%	S5PT	87%
P6MU	-11%, negative shift, no recovery	S6CR	49%

The results of the DC-level analysis during and after hyperventilation (Table 8-2, Table 8-3) indicate that [107]:

a. the observed negative DC shifts upon hyperventilation are highest at either Cz or Fz electrode position in both groups;
b. positive DC shifts are observed at occipital electrodes in 3 control subjects (50%), and 2 patients (33%);
c. the DC shifts tend to recover after the hyperventilation in the control group;
d. in three patients (P2WM, P3GM, P6MU) (50%), the shifts tend to continue in negative direction (i.e., recovery is not observed) at the vertex (Cz). (Table 8-4);
e. in the other three patients (50%), the percentage recovery at the vertex is much higher (Table 8-4, P1MH=159%, P4ES=153%, P5RB=148%) than the average of control group (78%).

8.4 Instantaneous Heart Rate and Hyperventilation

Changes in the IHR resulting from hyperventilation are analyzed according to the procedure defined in section 6.4 in both groups. Sample results from a control subject and a patient are illustrated in Fig. 8.14 and Fig. 8.15, respectively. The first observation is that the increases in IHR resulting from hyperventilation have a non-linear character. Similarly, the decreases in IHR within the recovery interval show a non-linear character. Standard deviation of IHR within these intervals indicates subject specific variety. The results of HR_{bsl}, HR_{hv}, and HR_{rcc}, as well as $\%HR_{rcc/hv}$ and $\%HRI_{hv}$, are listed for control subjects in Table 8-5 and for patients in Table 8-6.

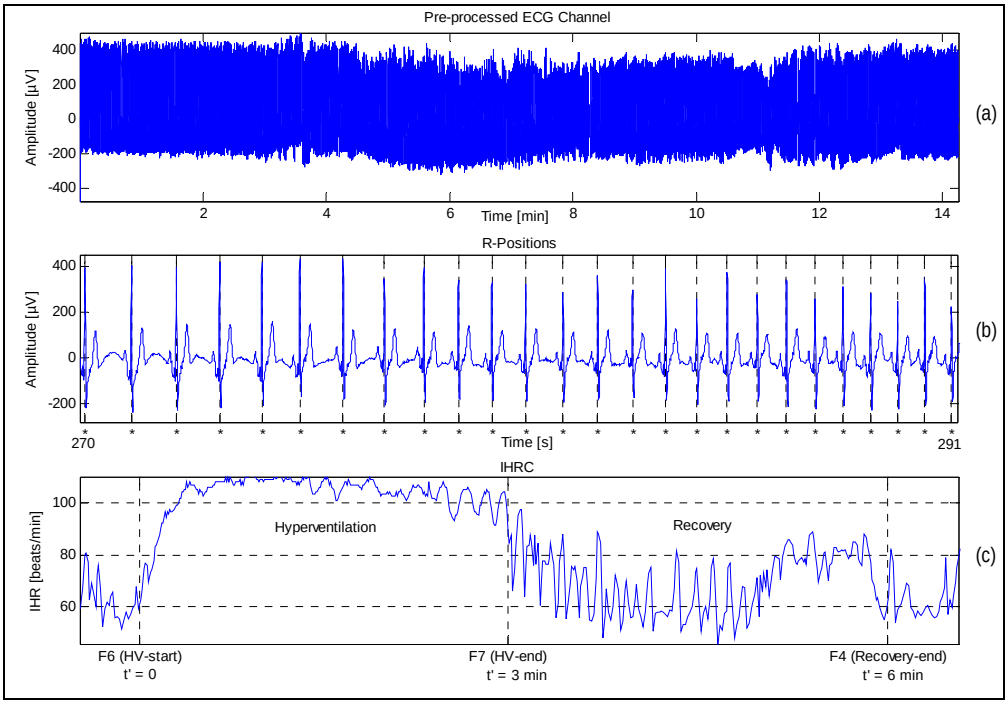


Fig. 8.14 IHR analysis result during HV and recovery for a control subject (S4OL). (a) the ECG channel after pre-processing from the standard I measurement, (b) the detected R peaks (an interval zoomed from (a)), (c) the corresponding IHRC.

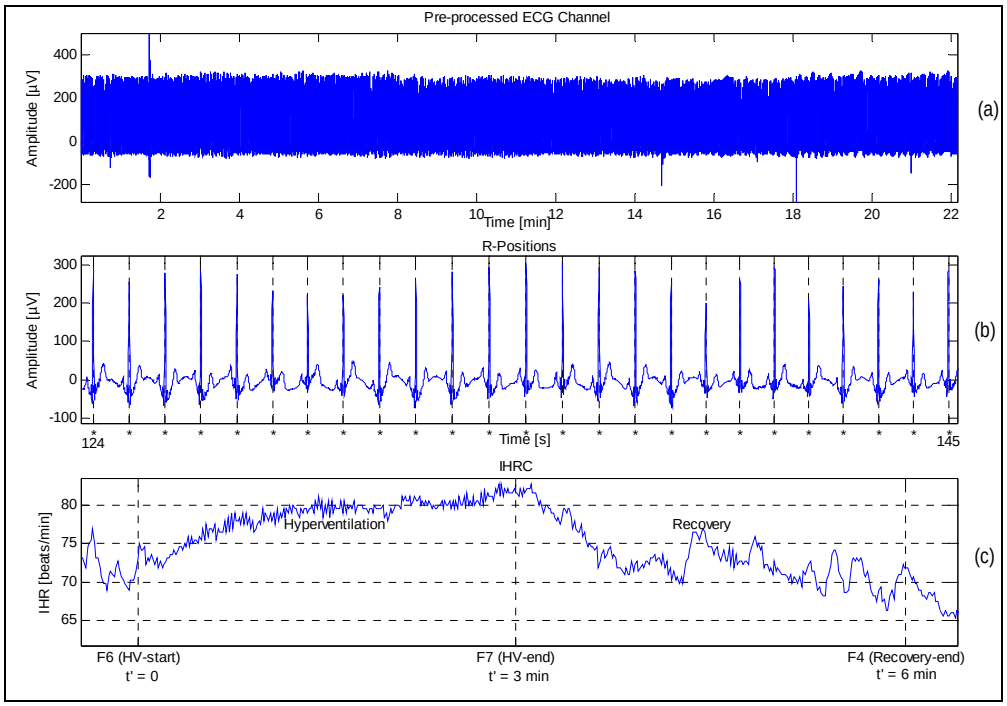


Fig. 8.15 IHR analysis result during HV and recovery for a patient (P2WM). (a) the ECG channel after pre-processing from the standard I measurement, (b) the detected R peaks (an interval zoomed from (a)), (c) the corresponding IHRC.

Table 8-5 Measures HR_{bsl}, HR_{hv}, HR_{rec} and the indices $\%HR_{rec/hv}$ and $\%HRI_{hv}$ for control subjects in initial measurements.

Subject Code	HR_{bsl} (beats/min)	HR_{hv} (beats/min)	HR_{rec} (beats/min)	$\%HR_{rec/hv}$	$\%HRI_{hv}$
S1JN	93	107	93	13%	100%
S2MN	78	89	75	16%	127%
S3AD	84	129	95	36%	76%
S4OL	65	104	71	32%	85%
S5PT	71	109	90	17%	50%
S6CR	61	78	62	21%	94%

Table 8-6 Measures HR_{bsl}, HR_{hv}, HR_{rec} and the indices $\%HR_{rec/hv}$ and $\%HRI_{hv}$ for patients in pre-therapy measurements.

Patient Code	HR_{bsl} (beats/min)	HR_{hv} (beats/min)	HR_{rec} (beats/min)	$\%HR_{rec/hv}$	$\%HR_{rec}$
P1MH	68	71	69	3%	67%
P2WM	72	79	74	6%	71%
P3GM	67	76	71	7%	56%
P4ES	58	62	57	8%	125%
P5RB	68	85	73	14%	71%
P6MU	83	105	98	7%	32%

8.5 DC-Shifts and Instantaneous Heart Rate in Patients and Controls

Combining the quantitative measures of EEG/DC-shifts and of the changes in IHR induced by hyperventilation, we obtain the following results illustrated in Fig. 8.16 and Fig. 8.17 for patients and controls:

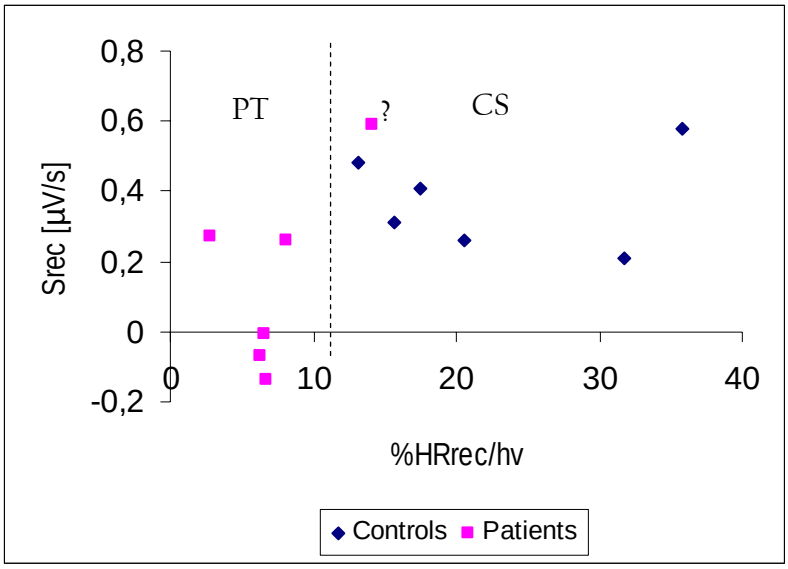


Fig. 8.16 s_{rec} at the vertex (Cz) versus $\%HR_{rec/hv}$ in patients (PT) and controls (CS).

As seen in Fig. 8.16, where the measure s_{rec} is plotted versus the index $\%HR_{rec/hv}$, the patients can be distinguished from the controls with a single exception.

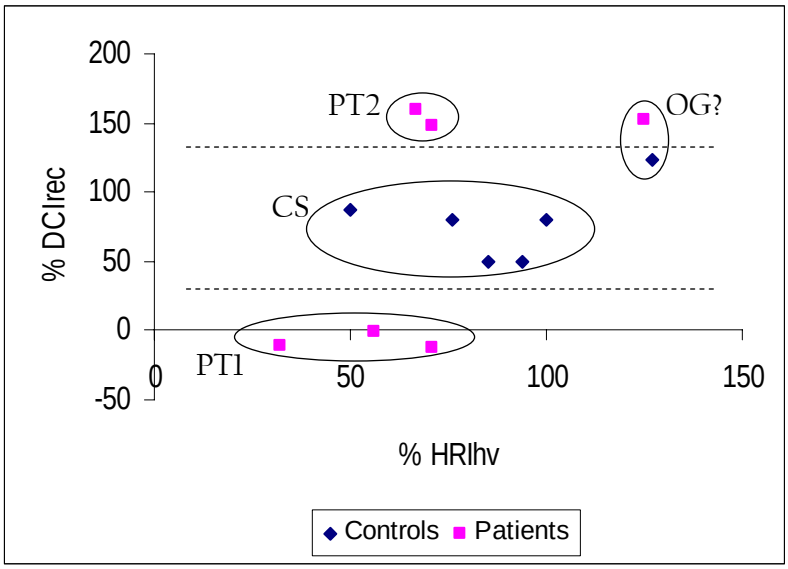


Fig. 8.17 DCI_{rec} at the vertex versus HRI_{hv} in patients and controls.

Using the indices $\%DCI_{rec}$ and $\%HRI_{hv}$, we obtain another view (Fig. 8.17). Two clusters of patients (i.e., PT1 and PT2) can be distinguished from the controls (CS). There is a fourth cluster (OG) which includes a patient and a control subject. If we set a range for $\%DCIrec$, for instance 30-130%, the controls can be placed in a zone between the patient groups.

8.6 EEG-Biofeedback Adjustment and Learning

Depending on the results of the initial measurements, namely, according to the amplitude and topology of the CNV, EEG-biofeedback sessions are configured subject specifically: The training electrode position and the scaling of the feedback are assigned accordingly. As defined in chapter 5, learning was accepted to be achieved, if at least 70% of the trials in successive sessions were successful. Hence, all the control subjects (100%) learned to control the SCP at the assigned feedback electrode position. In the patient group, learning was achieved in five patients (83%) in one case (i.e, P3GM) not. The patient P3GM had strong visual and acoustic cognitive deficits which could not be compensated by various configurations of the EEG-biofeedback system.

8.7 Application of the Methodology on Sample Cases for Pre- and Post-Therapy Comparisons

Two patients (P2WM and P5RB) were available for the longer follow-up of the applied therapy. The developed methodology for therapy evaluation will be demonstrated next with these two cases.

8.7.1 Case I – P2WM

P2WM is a 47 years old male focal epilepsy patient with complex focal and secondary generalized tonic-clonic seizures. He has an intractable epilepsy history of 44 years. Focus is diagnosed to be right temporal with interference to the contralateral region. The feedback electrode was at the vertex (Cz electrode position) and the training was carried out with different feedback types (i.e., visual, acoustic and combined). See Table 5-2 for further details. The medication type and doses were kept constant through the neurotherapy. Clinical success was achieved in two aspects in this case: a. seizure frequency was reduced, b. the patient gained control over the seizures which were accompanied by an aura. The results of feature quantification at the central line EEG electrodes and the ECG channel are listed in Table 8-7 for all three evaluation measurements (evaluation measurement 1 is the pre-therapy measurement) for the case.

Table 8-7 Results of follow-up for patient P2WM.

Patient P2WM	Evaluation Measurement 1				Evaluation Measurement 2				Evaluation Measurement 3			
Parameter	Electrode				Electrode				Electrode			
	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz
DC-hypervetilation s_{hv} (µV/s)	-0.50	-0.59	-0.31	-0.37	-0.24	-0.24	-0.13	-0.02	-0.30	-0.45	-0.33	-0.05
DC-recovery s_{rec} (µV/s)	-0.11	-0.07	0.09	0.02	0.41	0.27	0.31	0.14	0.22	0.23	0.21	0.27
CNV d_{CNV} (µV)	6.67	-1.80	-0.66	11.83	0.56	-14.71	-6.75	4.54	-4.99	-6.09	-1.43	-18.30
Epileptic patterns %Op_i	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IHR %HR2rec	71%				60%				Strong artifact in ECG channel			

In this patient, we observed changes in the quantitative parameters of the DC-shifts associated with hyperventilation. The measure s_{rec}, which had negative values before the therapy, has positive values in evaluation measurements in the follow up (compare Fig. 8.10 and Fig. 8.18). These results indicate that the recovery, which was not observed at the electrode positions Fz and Cz before the therapy, occurs after the therapy.

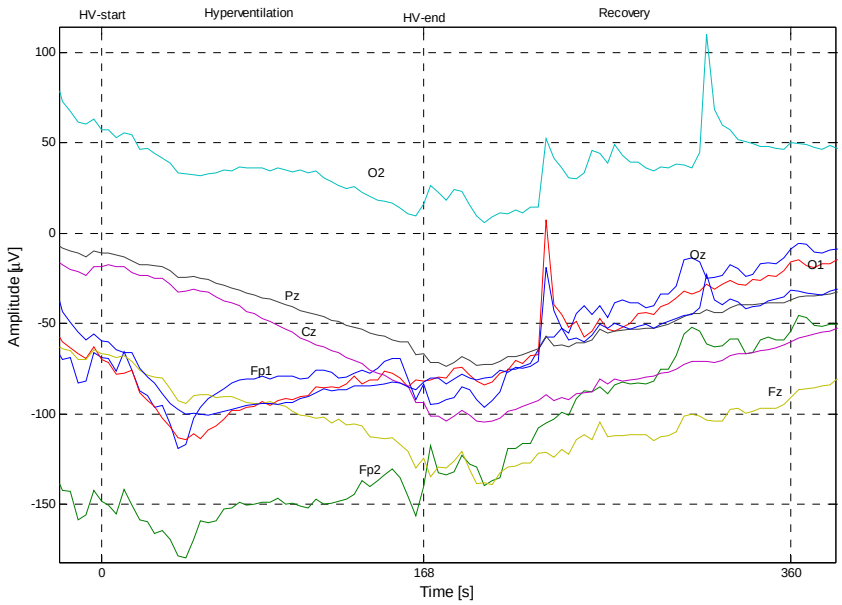


Fig. 8.18 DC-shifts during and after hyperventilation at electrode positions Fp1, Fp2, Fz, Cz, Pz, Oz, O1, and O2. t = 0, hyperventilation starts; t = 176 s, hyperventilation ends. Patient P2WM, evaluation measurement 3.

As seen in Table 8-7, the parameter $\%EPO_i$ is 0.0 for all electrode positions, namely, no epileptic patterns were observed in any measurements in this patient. The $\%HRI_{hv}$ decreases in the second measurement and cannot be computed due to strong artifacts in the ECG channel in the third measurement.

Changes in terms of "normalization" were observed in the parameter of CNV. The topological distribution of the measure d_{CNV} is mapped using the same scale for all three measurements in Fig. 8.19. When Fig. 8.19 (a), (b) and (c) are compared, the measure d_{CNV}, which was hardly observable in the pre-therapy measurement (at Cz=-1,80), is seen to enlarge topologically and becomes more dominant at the fronto-central electrode positions in the second (at Cz=-14,71) evaluation measurement. Although it becomes less in the third evaluation (at Cz=-6,09) measurement, it is still much higher than in the first measurement.

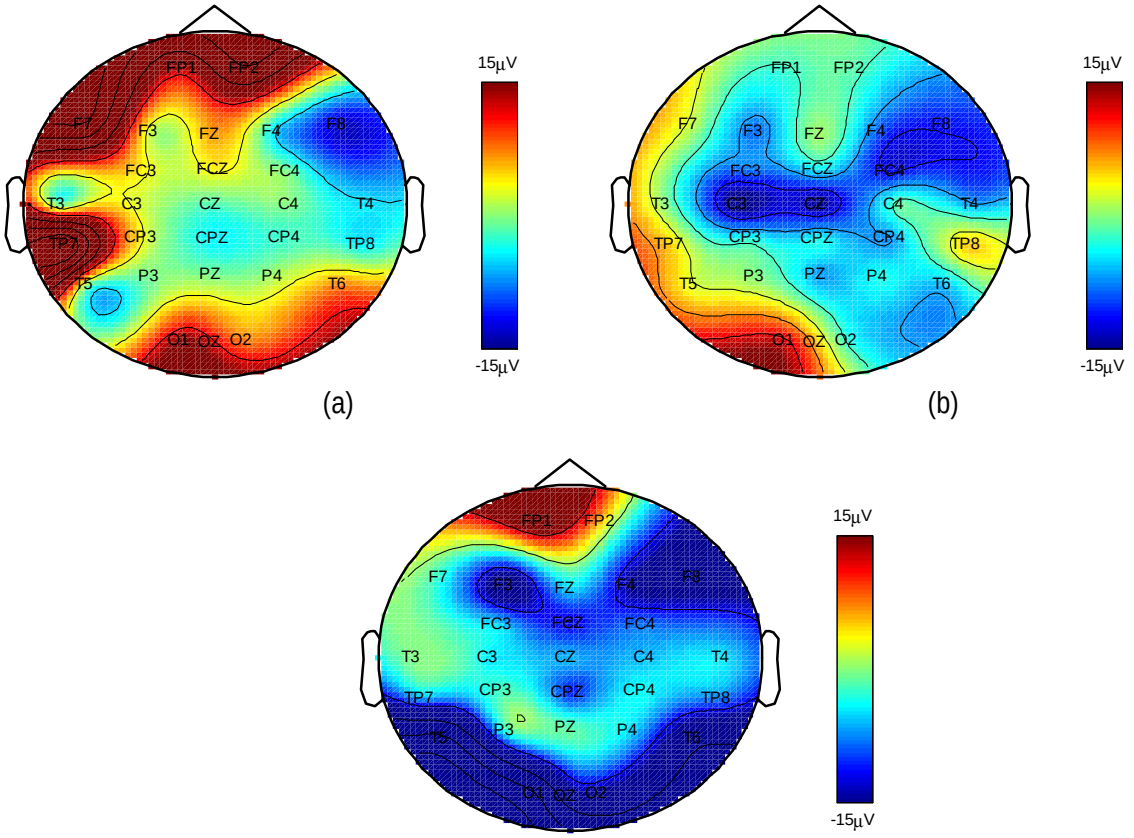


Fig. 8.19 CNV results of evaluation measurements in patient P2WM, (a) evaluation measurement 1 (pre-therapy), (b) evaluation measurement 2, (c) evaluation measurement 3.

8.7.2 Case II – P6RB

P6RB is a 33 years old female focal epilepsy patient with focal and generalized seizures. The focus is diagnosed to alternate in different measurements (i.e, left and right temporal regions). She has 21 years of intractable epilepsy history accompanied with organic psychosyndrome and depression. In neurotherapy, the feedback electrode position was Fz and the patient was trained with different feedback types (i.e., visual, acoustic and combined). See Table 5-2 for further details. In this patient medication reduction was achieved. Although fewer seizures were registered, the decrease in seizures was not significant.

In Table 8-8, results of feature quantification at the central line EEG electrodes and the ECG channel are presented for the evaluation measurements. The topological distributions of the measure d_{CNV} in different measurements are seen in Fig. 8.20.

Table 8-8 Results of follow-up for patient P5RB.

Patient P5RB	Evaluation Measurement 1				Evaluation Measurement 2				Evaluation Measurement 3			
Parameter	Electrode				Electrode				Electrode			
	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz
DC-hypervetilation s_{hv} (µV/s)	-0.37	-0.40	-0.05	0.46	-0.61	-0.38	-0.04	0.91	-0.45	-0.61	-0.70	-0.81
DC-recovery s_{rec} (µV/s)	0.55	0.59	0.19	-0.90	-0.00	0.14	0.11	-0.34	0.07	-0.13	-0.00	-1.65
CNV d_{CNV} (µV)	-16.97	-14.16	-1.79	-2.56	-5.50	-17.15	-6.07	17.05	-15.30	-9.42	15.96	4.69
Epileptic patterns $\%Op_i$	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IHR %HR2rec	71%				58%				82%			

Comparing the maps of the measure d_{CNV}, we see that the topology changes in the course of the therapy. The frontal dominance at the Fz electrode in the pre-therapy measurement moves to te central electrode Cz in the second evaluation measurement. In the third evaluation measurement, d_{CNV} is clearly more negative (i.e, higher absolute value) again at Fz. The distribution is more circumscribed, with the central and fronto-central electrode positions in the second and third evaluation measurements, than in the pre-therapy measurement.

Changes in the s_{rec} do not conform to our expectations (Table 8-8): the DC-recovery becomes slower in all mid-line electrodes in the second measurement. In the last measurement, the percentage recovery even becomes significantly negative at the vertex. As seen in Table 8-7 (parameter $\%EPO_i$), no epileptic patterns were observed in the measurements from this patient. The $\%HRI_{hv}$ measure, which is 71% in the first measurement, decreases to 58% in the second one. In the third measurement, on the

other hand, it is higher (i.e., 82%) than the first measurement, which indicates a faster HR recovery.

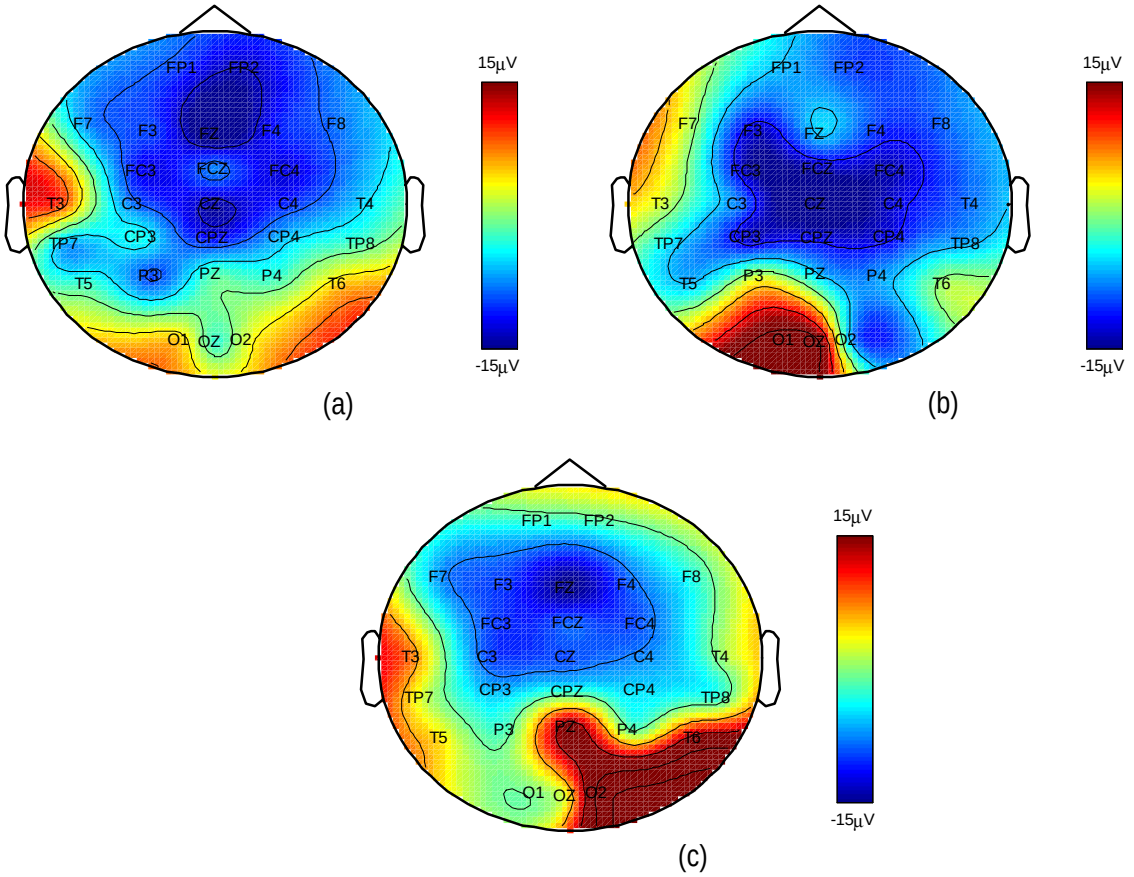


Fig. 8.20 CNV results of evaluation measurements in patient P5RB, (a) evaluation measurement 1 (pre-therapy), (b) evaluation measurement 2, (c) evaluation measurement 3.

9 Discussion

In the present chapter we will inspect the results of our work, which had several facets. It will be helpful to remember that the main objective was to develop a concept and a methodology for objective diagnosis, (neuro)therapy planning and evaluation in epilepsy. In chapter 3 (section 3.4), we had defined the major components of our solution to the problem in terms of biomedical engineering as:

a. Development of a strategy for objective diagnosis and therapy evaluation,
b. Data acquisition corresponding to the strategy,
c. Signal processing for feature extraction and quantification,
d. Data management.

It will be our goal to appraise the findings and achievements in these major components in a self-critical manner.

9.1 Clinical Tools for Decision Supporting in (Neuro)therapy Evaluation

The software concept, which has signal analysis (i.e, the neuroprofile extraction module) and data management (i.e., the database) parts as main elements, is the first step for an automation of the therapy planning and evaluation procedures. The aim is increased objectivity in these procedures through quantitative parameters, which are structured by the neuroprofile and managed by the database. It must be emphasized that the system is not conceptualized as a biomedical signals database, which would facilitate the storage of polygraphic signals, or an electronic patient record, but rather as a clinical data warehouse that documents the elements of therapies, clinical findings and the quantitative results of the analyses applied to the acquired signals of different formats (e.g., formats of BrainQuick and NeuroScan systems).

Although there are nomenclatures and data dictionaries of certain biomedical measurements and related data, for instance Vital Signs Information Representation (VITAL) by the Technical Committee 251 of European Standardization Committee

(CEN/TC251) or the Systematized Nomenclature of Medicine (SNOMED), and standard formats for the acquired raw data such as European Data Format (EDF) or Extensible Biosignal Format (EBS) for EEG; the efforts for standardization of the quantitative parameters extracted from polygraphic signals are restricted to ECG[11]. To our knowledge, there are no such efforts for the quantitative parameters of EEG signals and event-related potentials (e.g., CNV), or for neurotherapy which is an emerging unconventional treatment. Therefore, the majority of the objects and attribute structures had to be designed specifically in this study.

As a result of the database development, several aspects arose that need to be considered for improvement in the future:

9.1.1 Refinement of the Data Model

During the design process, the non-quantitative medical information proved to be more complex than expected, and its structuring was not trivial. Some of the medical information is stored in verbal phrases. This may suffice for the evaluation purposes of one particular person, but it is insufficient for analyses affecting all persons included in the database. Fruitful analysis requires the information to be stored in a structured way and broken down into manageable quantities, rather than in verbal phrases. This is only possible with extensive medical expertise. The refinement of the data model should be considered in future versions of the data warehouse.

9.1.2 Integration of Existing Clinical Databases

At the current stage, the non-quantitative data have to be entered into the database manually, even though they are, at least partially, included in other databases. A medical-technical assistant is currently responsible for the task. This fact surely complicates the sustainability of the system in the long run, since the physicians in clinical practice are not willing to invest much time for data entry. Means of integrating the already available information or importing it using standards for health informatics

[11] Common Standards for Quantitative Electrocardiography (CSE), which is a part of the Open European Data Interchange and Processing for Electrocardiography (OEDIPE) project.

should be also considered for the future improvement of the system. Integration of existing clinical databases will significantly enhance the long-term sustainability.

9.1.3 Forming a Normative Database, Data Mining and Decision Supporting

To gain knowledge not only on a particular person, but of a general nature, a representative data stock is necessary. This requires the persons comprising to the group to match certain criteria concerning factors such as age, sex, and handedness. Such a normative data stock will enable the use of data mining techniques[12] for an automated discovery of correlations and patterns in vast amounts of existing data, and thus, encourage the extraction of hidden knowledge in the stored data. The group of control subjects involved in the study is too small to achieve necessary statistical prerequisites. Further studies should be conducted to form a normative database. Another future vision is the progression of the database to a decision support system for an automated therapy evaluation. Via methods of Artificial Intelligence, suggestions for therapy adaptation and/or modification can be produced from a set of existing facts and insights, and presented to clinical experts.

9.2 Selected Quantitative Measures

The prerequisite for any quantitative measure to be accepted as a feature for therapy evaluation is that it distinguishes between a certain pathological state and normal functioning. The quantitative measures investigated in our work were selected either because of their relevance to epilepsy (i.e, percentage occurrence of epileptic patterns) or to SCP based neurotherapy (i.e, measures of CNV and hyperventilation induced DC-shifts). Epileptic patterns are clinically established features, whereas other measures had not been previously investigated in this context. Therefore, we had to test the novel measures for their applicability, namely, compare them between patients and control subjects. Our comparisons indicated statistically significant differences in measure d_{CNV} (Table 8-1) as well as measures s_{rec} and $\%DCI_{rec}$ of hyperventilation induced DC-shifts (Table 8-4). Although the measures of changes in the IHR during hyperventilation also

[12] A comprehensive overview on current data mining techniques can be found in http://damit.dfki.de/.

indicate differences between patients (Table 8-5) and controls (Table 8-6), conclusions cannot be drawn from the results for these measures. Nevertheless, the method, in which s_{rec} is plotted versus $\%HR_{rec/hv}$ (Fig. 8.16), and $\%DC_{rec}$ verus $\%HRI_{hv}$ (Fig. 8.17) demonstrate the usefulness of integrating the quantitative IHR measures in the analysis for comparisons between patients and controls.

The findings of comparisons between patients and controls are primarily useful for diagnostics. Going a step further, we tested and demonstrated the application of our methodology and measures for pre- and post-therapy comparisons in those patients, who were available for longer follow-up (section 8-7).

Changes in the measures d_{CNV} and $\%DCI_{rec}$, which can be considered as "normalization", are observed in a single case (Case I, section 8.7.1). In the second sample case (Case II, section 8.7.2), however, the results did not conform to those of Case I or to our expectations. The measure $\%DCI_{rec}$, which was positive in the pre-therapy measurement (i.e., recovery occurs), became less in the second evaluation measurement and was even negative (i.e., no recovery) in the third measurement. These two sample cases are insufficient to derive conclusions. Measurements and follow-up studies on new epilepsy patients with a successful neurotherapy history are required for conclusions based on statistical significance. The recruitment of a statistically significant number of patients exceeds the scope of the current work, since, neurotherapy, as an unconventional treatment does not yet have priority in the list of treatments, and health insurance regulations prevent the compensation of the costs of the novel treatment if a person is an outpatient. Therefore, the patients had to agree to cover their own expenses for the training and evaluation measurements in the follow-up period, in which they were outpatients.

Nevertheless, future data related to such measurements from new patients and/or healthy controls can be analyzed using the methods developed in the current work, and the quantitative results can be integrated into the data warehouse without any exertion for further statistical comparisons. Yet, it is not until all the substantial components of the neuroprofiles (e.g., additional measures related to odd-ball or photostimulation measurements – see chapter 4, section 4.2) are entered into the database that the information can be extensively exploited for diagnostics and therapy evaluation. The

extension is a long-term process involving several clinical studies. This process will be hastened by automation through the mathematical and software tools developed (i.e., neuroprofile, neuroprofile extraction module, and the database system).

Next, the selected measures will be discussed more in detail.

9.2.1 Graphoelements

The performance of the features for epileptic pattern extraction is tested on a set of randomly chosen epileptic patterns from data acquired in previous studies. In these comparisons, the new feature, FD, proved to perform superiorly to the previously used VM. Although epileptic patterns in EEG are considered clinically more established features in epilepsy, we did not commonly observe such activities in our measurements. This is probably due to the fact that such patterns are infrequent in focal epilepsy patients, who are considered to be more suitable for neurotherapy. The measure $\%EPO_i$ should be reserved as a quantitative parameter for those cases, in which such patterns are observed.

9.2.2 Contingent Negative Variation

The quantitative parameter d_{CNV} shows significant differences in amplitude and topology between the patients and controls (Table 8-1). This information can be used for diagnostics as well as therapy evaluation. In case P2WM, changes in this parameter were observed in the follow up (Table 8-7 and Fig. 8.19). in order to be statistically significant, data from further patients with a successful history of neurotherapy are necessary.

9.2.3 Hyperventilation Induced DC-Shifts in EEG and Changes in IHR

Although hyperventilation is used as a provocation to induce epileptic discharges in clinical examinations, the accompanying DC-shifts had not been considered for their potential diagnostic relevance. The results presented in this study indicate differences in the hyperventilation induced DC-shifts between patients and controls especially in the recovery process (i.e., percentage recovery) (Table 8-4). In 3 patients (50%), the recovery is not observed at the vertex, whereas in the remaining three patients the

percentage increase in the DC-level is much higher than the average of the control group. These differences can be exploited for diagnostics and therapy evaluation. In terms of therapy evaluation, the results obtained are restricted to the single case P2WM. The lack of recovery in P2WM in the pre-therapy measurement was observed in the follow up (Table 8-7).

The observation, that in 3 controls (50%) and 2 patients (33%) the hyperventilation induced DC-shifts are in positive direction in occipital electrodes, provokes the question of whether hyperventilation builds a dipole (or amplifies an already existing one, frontal being negative and occipital being positive) in the brain. This observation also needs further investigations.

In the clinical practice, there is no quantitative monitoring of the rate of hyperventilation. The instruction given to the patients is that they have to breathe deeper with approximately the same number of cycles per minute. The subject is motivated to continue three minutes of hyperventilation with further instructions during the process. In order to have a reference for the changes in the vegetative functions, the percentage changes in the average IHR is assigned in this study. The parameters of IHR are commonly accepted parameters for autonomous physiological functions.

The approach, in which the changes in IHR are additionally considered parallel with the changes in the DC potentials during hyperventilation and recovery, is unique in its form. The main aspect of the IHR analysis in a provocation such as hyperventilation is quantification of the changes in the autonomous functions. Accordingly, changes in brain activity and changes in the autonomous functions can be monitored simultaneously. Our results (Fig. 8.16, Fig. 8.17) demonstrate the benefits of the approach in a neurological disorder such as epilepsy. Integration of different quantitative parameters for the changes in the IHR (i.e., $\%HR_{rec/hv}$ and $\%HRI_{hv}$) adds a new dimension to the analysis. In Fig. 8.16, the patients can be distinguished from the controls by the parameter $\%HR_{rec/hv}$. In Fig. 8.17, two groups of patients, one with no DC recovery at the vertex (i.e., PT1), and the other with a very high percentage DC recovery (i.e., PT2), can be recognized. The control subjects, on the other hand, form another cluster between the two patient clusters (i.e., CS). There is a fourth cluster

(i.e., OG) with two members (a patient and a control subject). However, defining a zone between $\%DCI_{rec}$ values of, for instance, 30%-130% we can distinguish the controls clearly from the two patient groups. These results suggest a "normal zone" in the corresponding plot. This issue also needs further investigations in larger groups of controls and patients.

In our method of quantifying the changes in IHR, we used first-order statistical parameters; higher order analysis should be considered for describing the dynamics of the changes in future investigations. Similarly, the presented results of parallel analysis of the DC-shifts and the IHR are for a single EEG channel (i.e., Cz, the vertex), at which the highest DC-shifts are commonly observed. Nevertheless, changes at the other EEG channels can be integrated into the analysis via multivariate statistics. Such a statistical analysis task is beyond the scope of the current study and should be addressed in a study concentrating mainly on this issue.

Electrode stability is another critical issue in DC measurements that needs discussion. There is a strong debate on whether or not such DC potentials are measurable by the surface electrodes. It must be underlined that DC measurements are, indeed, very open to movement artefacts. On the other hand, the very specific patterns we observe in our measurements (i.e., triggered by stimuli S1 and S2 in CNV measurements, and by hyperventilation) cannot be considered and explained via artefacts. A more detailed discussion on sources of error in such measurements can be found in [67].

Another proposal for further research is the utilization of a quantifiable provocation method such as oxygen stimulation instead of hyperventilation. The method, in which the partial pressure of the applied oxygen can be assigned as a quantitative parameter, will be more efficient, since the comparability of the results will be increased. Subsequently, effects of oxygen stimulation on both IHR and the DC-shifts could be examined with the methods of the current work in different patient and control groups. Such a method would also reduce the possible movement artifacts encountered during hyperventilation.

9.3 Quantification of Learning

In this study, the subjects, or respectively the patients, are defined to have learned the self-regulation of SCP, if a success rate of 70% was achieved in distinguishing between the two tasks (i.e., negativation and positivation) in the training sessions. This is a sufficient definition for the current state of research in EEG-biofeedback. Nevertheless, a more detailed analysis of learning and its quantification should be addressed additionally as a separate study in the future. Consequently, correlates between the measures introduced in this study and the quantitative parameters of learning at different stages (see section 5.3) could be investigated.

9.4 Understanding Neurotherapy

In the course of clinical applications with epilepsy patients as well as laboratory studies with the controls, we encountered several phenomena which need discussion:

a. During the neurofeedback training process, the "intuitively" evolved varying respiration patterns correlated to the DC-shifts recorded on the scalp. The control of the DC-shifts, however, is not sustained via respiration feedback. An interaction between the SCP generated upon neurofeedback process and the respiration patterns was observed. The spectral power of the respiration curves was higher during the task of negativation than during the task of positivation (Fig. 9.1) [67], [109].

b. The SCP can be distorted by the spreading of the changes in the eye-potentials caused not only by slow eye and head movements, but also by the lack of light adaptation. These sources of error must be monitored during a neurofeedback process [67]. On the other hand, a similar pattern (excluding the artifacts due to ocular movements) is observed in the VEOG during the generation of CNV in the modified S1-S2 paradigm.

c. Application of acoustical or visual stimuli for the S1-S2 paradigm results in differences in the topological distribution of the resulting variations in the SCPs [110]. Visual and acoustic components do not influence the process in the same manner.

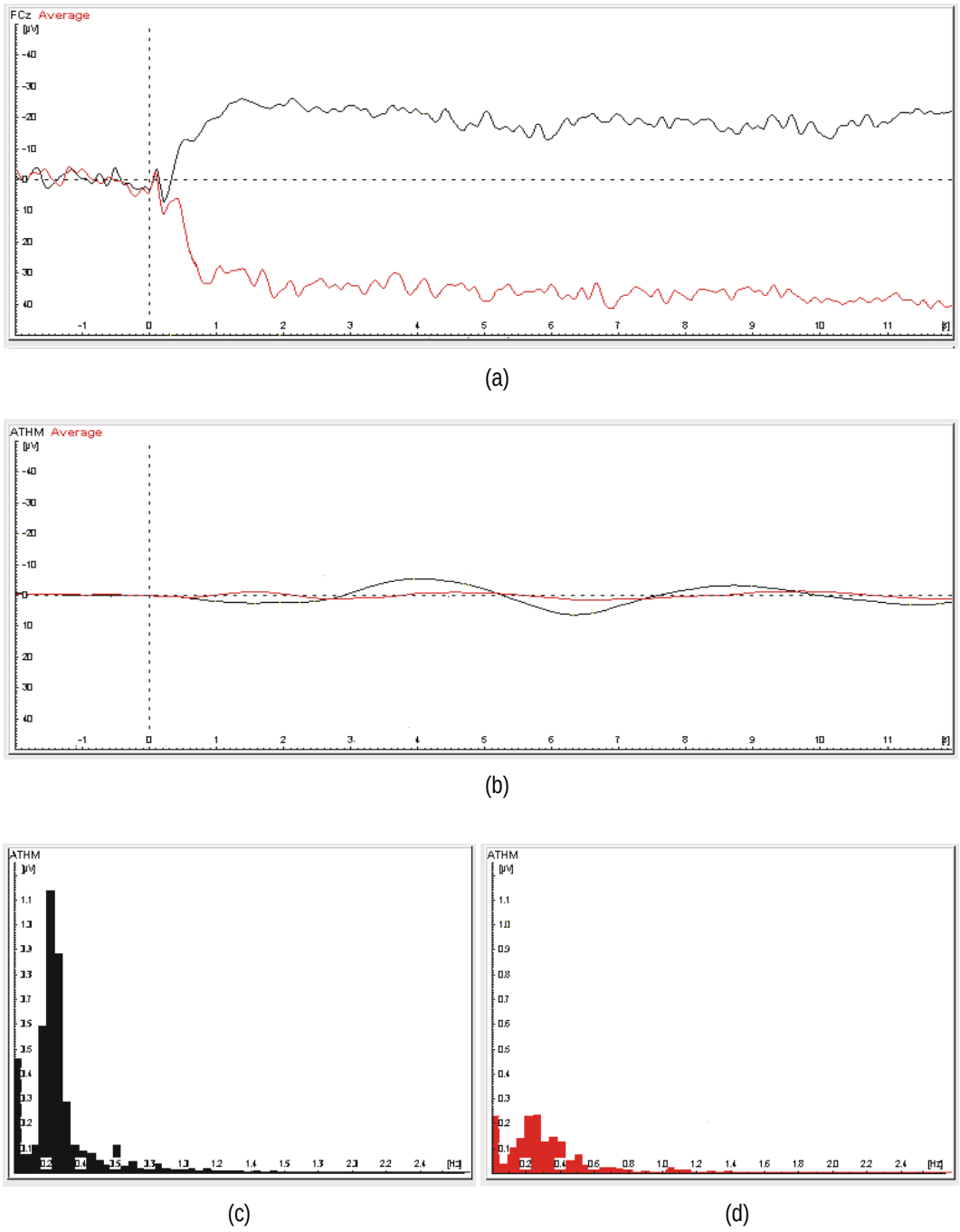


Fig. 9.1 Results of an EEG-biofeedback session based on SCP (black: negativation task, red: positivation task), (a) feedback channel Fcz, (b) respiration channel ATHM, and corresponding spectral power of the respiration channel (c) negativation task, (b) positivation task. © RGESIM/ASIM Verlag-Proceedings of World Congress on Neuroinformatics.

These observations indicate that the complex interactions between the higher CNS functions, such as perception and information processing, and vegetative physiological functions of the body, such as respiration and heart beat, are crucial in the

neurofeedback process. These functions are inseparable in the context of training self-regulation.

The CNS not only has a higher regulatory task to coordinate the functional subsystems of the body as a whole system, but is itself a functional part of it, and depends on these subsystems. Therefore, the process of neurotherapy cannot be considered as simply an extra feedback loop to the brain. Furthermore, analyzing a complex process (i.e. the neurofeedback) which causes changes on a very complex system (i.e., the nervous system) exceeds the borders of conventional system analysis approaches.

9.4.1 Changing the Paradigm

The traditional control engineering approaches to the systems are mainly based on the assumption of a "closed system". In the recent decades, this approach has been seriously debated, especially when the system considered has a biological nature. The "openness" of biological systems was first stated by the biologist von Bertalanffy [111]. In terms of thermodynamics, open systems are those which exchange energy, matter, and information with their environment. Energy and matter can enter or leave the system or be stored in a storage element (i.e., memory). Inside the system, they can interact with each other. Living systems are open systems exchanging energy, matter and information with their environment, *thus* maintaining their structures and functions.

Following these notions, we consider the human physiology, as well as the nervous system, as a complex adaptive open system. Mainzer [112] states that the complex system approach offers the possibility for modeling the neural interactions of the brain processes on the microscopic scale and the emergence of the cognitive structures on the macroscopic scale. Thus, it seems to be possible to bridge the gap between the neurobiology and the cognitive sciences of the mind, which traditionally has been considered an unsolvable problem.

Neurotherapy intervenes in the CNS at a macroscopic level: We do not go down into the system to the level of neuronal interactions, but we use a macroscopic level parameter; a parameter extracted from EEG (e.g., the DC-level).

Our observations suggest that the neurofeedback process intervenes in this "gap", at a "mesoscopic" level. The neurofeedback process involves the interactions between the psychological and neurobiological processes. We consider the extracted EEG parameter used for the feedback as a parameter of the "mesoscopic" level (i.e., an interface level) between the psychological (the macroscopic level) and neurobiological levels (the microscopic level):

Psychological processes	›	MACROSCOPIC LEVEL
Extracted EEG parameter	›	MESOSCOPIC LEVEL
Neurobiological processes	›	MICROSCOPIC LEVEL

The definition of a certain level as being microscopic, mesoscopic or macroscopic is relative. The defined mesoscopic level is a microscopic level with respect to the psychological level, and at the same time a macroscopic level with respect to the level of neurobiological processes. These levels can be regarded as representing the instability hierarchies [10].

Another property of natural systems is that they are self-organizing. Self-organization at the microscopic level is considered to be the fundamental mechanism of spontaneous pattern formations at the macroscopic level in open systems, which are far from equilibrium.

9.4.2 Self-Regulation and Self-Organization

According to Schwartz [113], the concept of self-regulation is fundamental to behavior therapy, and the main adaptation mechanisms in living systems. It is, in this sense, not a coincidence that EEG-biofeedback is also referred to as cortical self-regulation (though it is not clear whether only cortical structures or many others are involved in the process). A self-regulating system is able to maintain its essential variables within limits acceptable to its own structure in case of unexpected disturbances. This can only be achieved through feedback mechanisms which detect disturbances, and accordingly activate (positive feedback loops) or inhibit (negative feedback loops) the related subsystems. To our understanding, self-regulation and self-organization are two highly interrelated phenomena, which are both determined by the nonlinear interactions at the microscopic level.

9.4.3 EEG-Biofeedback and Non-Linear Phase Transitions

Many processes of coordination and regulation in human physiology involve phase transitions with nonlinear and non stationary properties, so does SCP based neurofeedback. The results of a training session, in which the tasks of negativation and postivation are successful (Fig. 9.1), indicate non-linear phase transitions to these two states. Such spontaneous phase transitions are commonly observed where a system changes its macroscopic state qualitatively [114]. For phase transitions of systems in thermal equilibrium the adequate treatment of fluctuations could be solved by renormalization group techniques. However, for systems far from thermal equilibrium (i.e., non-equilibrium phase transitions), the phenomena and the problem get more complex, and need novel approaches.

9.4.4 Concepts of Synergetics

Synergetics, as pioneered by Haken [9], [10], offers a theoretical framework for the self-organization phenomenon giving rise to emergent new qualities at the macroscopic level, and analyzing non-equilibrium phase transitions via the concepts of control parameters, order parameters, slaving principle and circular causality. In synergetics, the circular causal relations between different levels are explained via order parameters and the slaving principle.

A *control parameter* is a parameter which is defined to be controlling the macroscopic behavior of a system. The critical value of a control parameter leads to a bifurcation in system behavior [115].

An *order parameter* is defined as a descriptor of the system at the macroscopic level. Referring to [116]:"*When one, or maybe several control parameters are changed, the system enters instability. In other words, it leaves its former state and starts to form a qualitatively new macroscopic state. Close to the instability point, different kinds of collective configurations occur; some of them grow whereas others decay after generation by fluctuations. By a study of growing and decaying states, we may distinguish between the unstable and stable configurations and are thus led to configurations which are governed by the order parameters. The order parameters determine the behavior of the individual parts via the slaving principle. Thus the behavior of complex systems can be described and understood in*

terms of order parameters. At the same time, we need no longer to consider the action or behavior of the individual parts, but may instead describe the total system by means of the order parameters."

The *slaving principle* states that not only the behavior of the growing configurations, but also that of decaying configurations is uniquely determined by the order parameters which give rise to compression of information needed to describe the behavior of the system. The principle of circular causality defines the causality between the order parameters and the behavior of the components (i.e, sub-systems) of a system. The individual parts of the system cooperatively determine or generate the order parameters, which in turn enslave the individual parts. Enslavement and consensus finding can be regarded as similar principles [117].

9.4.5 Neurotherapy as a Process of Learning: Operant Conditioning and Coordination

EEG-biofeedback is a process of *learning*. In terms of psychology, it is defined as an operant conditioning. At the microscopic level, according to the widely accepted hypotheses of Hebb [118], learning is explained through strengthening synapses between the neurons, which are repetitively activated simultaneously. Hebb also suggests that learning should be understood as a kind of self-organization in a complex brain model. At the macroscopic level, we encounter the studies in behavioral psychology regarding different forms of conditioning. From the systems analysis point of view, synergetics offers a theoretical framework and tools for analyzing a process of learning via the effects of the learning process on the order parameters of a system.

According to [119], there may be several mechanisms by which the motion patterns described by the order parameters can change upon learning:

a. The dynamics of the order parameters may change in that the potential landscape undergoes a transition.
b. New order parameters may emerge by means of the cooperation of old order parameters.
c. New order parameters may emerge from the microscopic parts as a consequence of changes in the control parameters at the microscopic level.

An important example of analyzing an operant conditioning process with the methods of synergetics is the pedalo experiment [120], in which the movement patterns of the subjects are analyzed during the process of learning to drive a pedalo. In this example, it is demonstrated that as learning proceeds, fewer and fewer degrees of freedom dominate the movement pattern , and that, eventually the movement is governed by a single complex order parameter.

Although the EEG-biofeedback process is not concerned with motor movements, there are analogies to the pedalo experiment in terms of learning a specific "coordination" of the involved subsystems. In the pedalo experiment, the subsystems are motor units such as parts of the arms and legs which are under our voluntary control, whereas in the EEG-biofeedback process, these subsystems are units of the higher CNS functions involving the cognitive functions, and the autonomous nervous system such as respiration and heart beat. The analogies are that:

a. As a result of the learning process, a new specific coordination is achieved among the subsystems in both cases.
b. This new coordination can be recalled and activated by the subject when the corresponding situation is encountered (e.g., control of seizures in case of aura).

9.4.6 Is the DC-level an Order Parameter of the Brain Complex Open System?

Several characteristics of the DC-level or shifts in the DC-level suggest that it can be an order parameter of the brain as a complex open system [121]:

Switching role of orders parameters and the DC-level

According to the synergetical approach, the critical value of a control parameter may lead to a bifurcation where order parameter may play a switching function between two (or more) possible states [122]. The results of SCP-based neurofeedback (Fig. 9.1) can be considered as switching from a less excitable state to a more excitable one or vice versa. Also in the S1-S2 paradigm, the changes (Fig. 8.6) can be similarly interpreted.

Order parameters are long lasting

The DC-level is preserved until the introduction of the succeeding stimulus in CNV (Fig. 8.6) and in the neurofeedback session (Fig. 9.1). This observation suits the property of order parameters being long-lasting.

Governing role order parameters

The observation that the respiration patterns may differ during the tasks of negativation and positivation (Fig. 9.1) and that the voluntary DC-regulation is not achieved by respiration feedback suggests the governing role of DC-level over other sub-systems (i.e., in this case, functions of the autonomous nervous system).

An order parameter is a descriptor of the system at the macroscopic level

Referring to the definition of Caspers [44] that a DC-shift is an indicator of the cortical excitability changes, with a negative shift showing an increased cortical excitability, and a positive shift a decreased one, and to the different states (i.e., sleep-wake cycle, seizure activity, information processing, hyperventilation –see chapter 2, section 2.3.3 for details) in which DC shifts are observed, the DC-potential shift can be defined as a descriptor of the brain at macroscopic level.

One cannot claim that the DC-shifts observed at various states share the common origin and generation mechanism without investigating their correlates (i.e., control parameters) at the microscopic level. As explained in chapter 2, there is no consensus on the origin(s)/generator(s) (i.e., neurons, glial cells, blood brain barrier and cerebral blood flow) and generation mechanism(s) of the DC potentials. However, at the macroscopic level, the concept of order parameter gives us a tool to consider these DC-shifts observed at different states together, since there is a circular causal relationship between the DC-level and the microscopic level: The microscopic level generates the DC-level, which in turn determines the excitability of the microscopic level, and excitability is a measure of firing rate at the neuronal level.

9.4.7 Neurotherapy: An Interface of Psychology and Neurology via Synergetics?

Considering the brain as an open system interacting with other subsystems of the human physiology and analyzing these interactions allows for new insights. Following this paradigm, we can analyze simultaneous changes in the observables of processes participating in neurofeedback, which appear not to be limited to the observables of the brain functions. Excluding the higher macroscopic level psychology, Fig. 9.2 illustrates a synergetic representation of microscopic and macroscopic levels and the corresponding parameters.

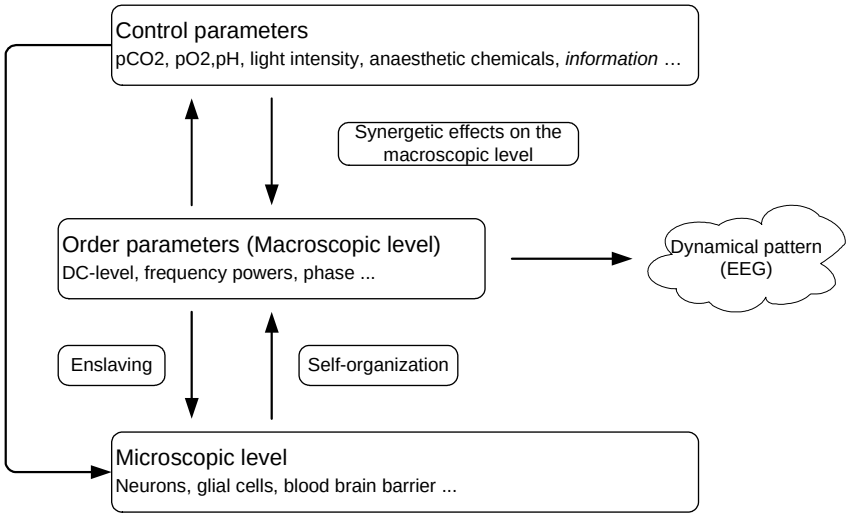


Fig. 9.2 Synergetical representation of microscopic and macroscopic interactions, and corresponding parameters. Psychology as a higher macroscopic level is excluded for simplification.

The control parameters can be external as well as internal parameters. They define the nature of interactions at the microscopic level. Examples of external control parameters can be the intensity or frequency of an acoustic or visual stimulation, whereas hormones or ional concentrations can be regarded as internal control parameters. A control parameter can also be an abstract quantity such as information, as in the case of CNV, where S1 in the paradigm carries the information of a "warning" for the succeeding aversive or non-aversive stimulus S2.

The above discussions and considerations provide us with a theoretical framework at the system level, which enables a deeper understanding of the neurotherapy process,

and accordingly its diverse influences on human physiology, which shall be investigated further in future studies.

10 Summary and Conclusion

...
Wär nicht das Auge sonnenhaft,
Die Sonne könnt es nie erblicken;
[13]
...

Johann Wolfgang von Goethe
1749, Frankfurt (Main) – 1832, Weimar

The verb "to see" has a second meaning in many languages like it has in English, namely, "to understand." As Goethe describes using the eye, probably as a metaphor, there is the need of a property of "seeing" that matches to its object of interest. Similarly, there is the need of a matching paradigm to phenomena analyzed in the scientific context.

The present work includes several aspects spanning from engineering over neurology to psychology. The main contributions and insights of this interdisciplinary work towards an automated objective (neuro)therapy planning and evaluation in epilepsy can be summarized as follows:

After a systematic overview of conventional methods and procedures of diagnosis and therapy evaluation, EEG-biofeedback protocols proposed for epilepsy were elucidated with an emphasis on slow cortical potentials based neurotherapy. The problem analysis pointed out that the diversity of cases, the variety of treatment modalities, and the lack of quantitative features complicate the objectivity in therapy planning and evaluation. In order to increase the objectivity, a concept and a methodology were developed by introducing:

a. An *evaluation measurement protocol* which brings a standardization to the diagnosis and evaluation procedures;

---

[13] Farbenlehre, The Divine is Spread Everywhere. .../ If the eye were not sun-like/ how could it ever spy the sun?/...

b. The *neuroprofile* as a concept and a tool for defining a structured set of quantifiable measures which can be extracted from electrophysiological signals;
c. A *set of novel quantitative features* (i.e., sub-set of the components of the neuroprofile) extracted from EEG (or, respectively, ERP) and ECG:
    i. Percentage epileptic pattern occurrence (*EPO*),
    ii. CNV level difference measure (d_{CNV}),
    iii. Direct current recovery index (DCI_{rec}),
    iv. Heart rate recovery ratio ($HR_{rec/hv}$),
    v. Hyperventilation heart rate index (HRI_{hv}); and
d. A software concept and the corresponding tools (i.e., *the neuroprofile extraction module* and the *database*) to support the methodology as a basis for automation.

The measurement protocol was applied to voluntary control subjects, and to epilepsy patients, who received neurotherapy as a complementary treatment to pharmacological therapy. The features introduced were investigated on these real data.

The EPO was extracted via methods of *supervised* and *unsupervised epileptic pattern quantification*. The corresponding adaptive segmentation algorithm was modified by introducing *fractal dimension* (FD) as a new feature for pattern characterization. According to our results, FD was observed to be superior to the previously used Värri measures in extracting epileptic patterns.

Analyzing the CNV acquired via a modified S1-S2 paradigm, and assigning d_{CNV} as the quantitative parameter, statistically significant differences were determined between the epilepsy patients and the healthy controls.

Changes in the EEG/DC-level were analyzed during and after hyperventilation, which is a commonly used clinical activation method to provoke epileptic patterns. Differences between patients and controls were determined, especially in the recovery process (i.e., in the quantitative measure s_{rec} defined in this study). Using the new measures s_{hv} and s_{rec}, the DCI_{rec} was defined.

The simultaneously acquired ECG signals were additionally analyzed during and after hyperventilation for extracting IHR curves. Three quantitative parameters HR_{bsl}, HR_{hv}, and HR_{rec} were calculated. Using these parameters, two indices were assigned for quantifying the hyperventilation induced changes in ECG: the $HR_{rec/hv}$ and the HRI_{hv}.

The method, in which the measures of hyperventilation induced changes in IHR were integrated to hyperventilation induced DC-shifts in EEG, is unique in its form. Our results indicate the utility of the method in distinguishing the epilepsy patients from the healthy controls. These findings are important, primarily in terms of diagnostics.

Going a step further, we demonstrated our methodology for therapy evaluation on two sample cases, which were available for longer follow-up. Changes were observed in the assigned new measures in sample cases. This is not sufficient to base conclusions on whether or not the observed changes resulted from neurotherapy. Further clinical studies on new epilepsy patients with a successful neurotherapy history are required for such conclusions.

Nevertheless, the data to be acquired in future studies can be integrated into the analysis without much exertion via the developed tools in this study: The defined measures can be extracted by the *neuroprofile extraction module* and stored in the developed *database* for further statistical investigations.

Based on the observations we gained in the course of EEG-biofeedback sessions, we discussed the necessity of a change in paradigm for understanding neurotherapy. Neurotherapy (i.e. EEG-biofeedback) is a complex process in which not only cognitive functions, such as perception and information processing, but also vegetative functions, such as respiration and heart beat, are involved. This process elicits alterations to the human nervous system and physiology as a whole system. Therefore, it cannot be regarded as a simplified control feedback loop as in the analysis of closed systems. Hence, referring to Goethe once again, changing the paradigm is inevitable in order to comprehend neurotherapy. The novel paradigm should comply with the intrinsic complexity of the human physiology as well as that of the neurotherapy process.

As a process of learning, neurotherapy has analogies to the operant conditioning experiments analyzed in the realm of *synergetics*. A synergetical approach can provide further tools for understanding the dynamics of the neurofeedback process at a macroscopic level. Accordingly, the process of neurotherapy can be regarded as *learning* a specific *coordination* of cognitive and autonomous physiological functions. Such an analogy results in further tasks such as determining the accurate *control* and *order parameters* of the neurofeedback process and quantifying them. The DC-level and its behavior show the properties of an order parameter at the macroscopic level.

The theoretical framework of synergetics leads us to investigating parameters of interactions between different sub-systems of human physiology, which are not necessarily considered to be interrelated in the context of neurotherapy or epilepsy, such as the interactions between higher cognitive functions and the autonomous nervous system. Future research in the field should be concentrated on these interactions. Knowing that such an approach might not be comprehensible to conventional thinking, it will be appropriate to end with a citation from the English poet Francis Thompson describing the interconnectedness of the macroscopic and microscopic levels:

All things by immortal power
Near or far
Hiddenly
To each other linked are,
That thou canst not stir a flower
Without troubling a star.

Francis Thompson
1859, Preston Lancashire – 1907, London

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Appendix A

- Questionnaire for the Control Subjects

FRAGEBOGEN

NCRG

Name, Vorname :		
Geburtsdatum :		
Geschlecht : ☐ weibl.	☐ männl.	
Sonstiges : Größe _____ m	Gewicht _____kg	
Adresse Info (Email) :		
Telefonnummer :		
Beruf / Studium (Richtung):		
Tag der GrM1:	Tag der GrM2:	Tag der GrM3:

Händigkeitstest:

Zähne putzen	☐ links	☐ rechts	Tennisschläger halten	☐ links	☐ rechts
Würfeln	☐ links	☐ rechts	Messer u. Gabel halten	☐ links	☐ rechts
Blumen gießen (kl.Kanne)	☐ links	☐ rechts	Essen	☐ links	☐ rechts
Schreiben	☐ links	☐ rechts	Korkenzieher halten	☐ links	☐ rechts

Haben Sie schon einmal unter einer der folgenden Krankheiten/Funktionsstörungen gelitten?

Herzerkrankungen	☐ ja, wann? _____	☐ nein
Anfälle (allgemein)	☐ ja, wann? _____	☐ nein
Kopfverletzung in der Vergangenheit	☐ ja, wann? _____	☐ nein
Gedächtnisschwierigkeiten	☐ ja, wann? _____	☐ nein
Attention Deficit Hyperactivity Disorder (ADHD)	☐ ja, wann? _____	☐ nein
Attention Deficit Disorder (ADD)	☐ ja, wann? _____	☐ nein
Depression	☐ ja, wann? _____	☐ nein
Lernbehinderung	☐ ja, wann? _____	☐ nein
Schlaganfall	☐ ja, wann? _____	☐ nein
Hirnhautentzündung	☐ ja, wann? _____	☐ nein
Durcheinander, Halluzinationen	☐ ja, wann? _____	☐ nein
visuelle Erkrankungen (Brillenträger?)	☐ ja, was? _____	☐ nein
Sonstige	was/wann? _____	
Nehmen Sie zur Zeit Medikamente?	☐ ja, was/wie viel? _____	☐ nein
Haben Sie gestern geschlafen?	☐ ja, wie lange? _____	☐ nein

Welche Genußmittel gebrauchen Sie? (freiwillig antworten)

Alkohol	☐ ja, was/wie viel? _____	☐ nein	☐ keine Antwort
Nikotin	☐ ja, was/wie viel? _____	☐ nein	☐ keine Antwort

Appendix B

- Inventories for Patient Information

Technische Universität Ilmenau
Institut für Biomedizinische Technik und Informatik

NCRG

Name, Vorname			
Referenz-ID			
Geburtsdatum			
Geschlecht	weibl.	männl.	
Status	Patient	Proband	
Händigkeit	rechts	links	beidseits
Anamnese			
Familienanamnese (für relevante Erkrankungen)			
Diagnosen			
- Epilepsietyp	idiopathisch	symptomatisch	kryptogen
- Epilepsieklassifikation	fokal	generalisiert	nicht klassif.
- Epilepsieherd (wenn focal, wo?)	Region: Elektrodenposition:		
- Andere (welche?bitte spezifizieren)			
Anfallstyp			
	visuell	akustisch	motorisch
	keine	andere (welche?)	
keine Aura vor Anfall			
Aura vor Anfall?	Aurabeschreibung:		

Symptombeschreibung eines Anfalls	
Photosensibilität	ja nein Beschreibung:
Therapie – neurochirurgisch (Datum) – andere (welche?/ von-bis)	
Messungen – EEG (Datum / Befund)	
Messungen – Andere (CT, EKG...) (Datum / Befund)	
Besonderheiten / Auffälligkeiten	Neurologisch ja nein Psychologisch ja nein
Psychol.Beurteilung des Pat. (bezügl.Wahrnehmung u.Gedächtnis)	

Datum: _____ Unterschrift:_____

Technische Universität Ilmenau
Institut für Biomedizinische Technik und Informatik

NCRG

Medikation Patient: geb.:

Medikament	Einnahme		Dosierung				Blutspiegelkonzentration		Nebenwirkungen
	von	bis	früh	mittag	abend	nachts	Datum	Befund	

Datum: _____ Unterschrift: _____

Thesen (Statements in German)

1. Neurotherapie (bzw. EEG-Biofeedback) ist eine komplementäre unkonventionelle Behandlung, die bei Erkrankungen, welche im Zusammenhang mit Regulationsproblemen des Zentralnervensystems stehen, angewandt wird.

2. Epilepsie ist eine komplexe neurologische Erkrankung, die auf biochemischer und physiologischer Ebene nicht ausreichend geklärt ist.

3. Die objektive Validierung der neurotherapeutischen Wirksamkeit ist eine der wichtigsten Aufgaben des Forschungsgebietes.

4. Die Vielfalt der epileptischen Krankheitsbilder und der Behandlungsmodalitäten verursacht ein Defizit von quantitativen Validierungskenngrößen, die die Objektivität und die Effizienz der Diagnose und der Therapieevaluierung signifikant erhöhen können. Dies trifft sowohl auf die Neurotherapie, als auch auf konventionelle Behandlungen zu.

5. Eine höhere Objektivität kann durch folgende vorgeschlagenen komplementären Komponenten erreicht werden:

    a. Ein für die klinische Routine anwendbares *Messprotokoll*, welches einen standardisierten Ablauf und Vergleich ermöglicht;

    b. Das *Neuroprofil* als ein signalanalytisches mehrdimensionales Modell, welches einen strukturierten Satz quantifizierbarer Kenngrößen definiert, die von elektrophysiologischen Signalen extrahiert werden können;

    c. Ein Satz von neuartigen quantitativen Kenngrößen, die aus dem Elektroenzephalogramm, den ereignisbezogenen Potentialen und dem Elektrokardiogramm berechnet werden. Folgende Kenngrößen werden vorgeschlagen:

i. Prozentuale epileptische Musterhäufigkeit: *Percentage epileptic pattern occurence (EPO)*;

ii. Maß des Niveauunterschiedes der kontingent negativen Variation: *Contingent Negative Variaton level difference measure (d_{CNV})*;

iii. Index der Gleichspannungsänderung während und nach Hyperventilation: *Direct current recovery index (DCI_{rec})*;

iv. Quotient der Herzschlagfrequenzänderung während und nach Hyperventilation: *Heart rate recovery ratio ($HR_{rec/hv}$)*;

v. Index der Herzschlagfrequenz bei Hyperventilation: *Hyperventilation heart rate index (HRI_{hv})*.

6. Es wurden deutliche Unterschiede in den Datenparametern d_{CNV}, DCI_{rec}, $HR_{rec/hv}$ von Epilepsie-Patienten und Probanden festgestellt.

7. Die Kombinierung von Kenngrößen des Elektroenzephalogramms (DCI_{rec}) und Elektrokardiogramms ($HRI_{hv,}$ $HR_{rec/hv}$) unterstützt die Diskriminierung der Patienten und der Probandengruppe.

8. Die prozentuale epileptische Musterhäufigkeit (EPO) wurde mit Hilfe der Methoden der überwachten und nicht überwachten Mustererkennung ermittelt. Der dazu gehörige adaptive Segmentierungsalgorithmus wurde modifiziert, indem die bislang verwendeten Värri-Parameter durch den nichtlinearen Parameter Fraktaldimension ersetzt wurden. Es wurde festgestellt, dass die Fraktaldimension die epilepsiespezifischen Änderungen des Elektroenzephalogramms, wie z.B. die epileptischen Graphoelemente, effektiver beschreibt und damit die Segmentgrenzen präziser ermittelt werden können.

9. Die entwickelten Software-Tools, das Neuroprofilextrahierungsmodul und die Datenbank „Neurobase“, bilden eine Basis zur Automatisierung der Prozeduren für die Diagnose und Therapieevaluierung.

10. Die Neurotherapie ist ein komplexer Lernprozess, bei dem höhere kognitive Funktionen sowie das autonome Nervensystem beteiligt sind. Die Synergetik bietet einen geeigneten theoretischen Rahmen für die Analyse der an einem solchen Lernprozess beteiligten physiologischen bzw. psychophysiologischen Subsystemen auf einer makroskopischen Ebene.

11. Basierend auf den gewonnenen Erkenntnissen wurde die Hypothese aufgestellt, dass das Gleichspannungsniveau im Elektroenzephalogramm ein Ordnungsparameter des Gehirns ist, wobei das Gehirn als ein komplexes offenes System betrachtet wird.

12. Diese Hypothese sowie die Wechselwirkungen zwischen der höheren kognitiven Tätigkeit und dem autonomen Nervensystem sollten Gegenstand der zukünftigen interdisziplinären Forschung auf den Gebieten Signalanalyse, Systemtheorie, Epilepsiediagnostik und Neurotherapie sein.