Induced Brain Activity as Indicator of Cognitive Processes: Experimental-Methodical Analyses and Algorithms for Online Applications

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Abstract

Processing of electroencephalographic (EEG) signals is a key step towards understanding cognitive brain processes. Particularly, there is growing evidence that the analysis of induced brain oscillations is a powerful tool to analyze cognitive performance. Thus, the extraction of electrophysiological features characterizing not only cognitive processes but also cognitive dysfunctions by neurological diseases is fundamental. Especially in the case of epilepsy, cognitive dysfunctions such as memory or attentional problems are often present additionally to seizures. Neurofeedback (or EEG-biofeedback) is a psychological technique that, as a supplement to medication and surgical therapies, has been demonstrated to provide further improvement in many neurological diseases, including epilepsy. However, most efforts of neurofeedback have traditionally been dedicated to the reduction of seizure frequency, and little attention has been paid for improving cognitive deficits by means of specific electrophysiological changes. Furthermore, current neurofeedback approaches are not suitable for these purposes because the parameters used do not take into consideration the relationship between memory performance and event-induced brain activity. Considering all these aspects, the cognitive performance of a group of epilepsy patients and a group of healthy controls was analyzed based on the event-related de-/synchronization (ERD/ERS) method. Significant differences between both populations in the theta and upper alpha bands were observed. These findings support the possible exploitation of cognitive quantitative parameters in epilepsy based on ERD/ERS. An algorithm for the online ERD/ERS calculation was selected for future neurofeedback applications, as the result of a comparative dynamic study. Subsequently, a methodology for the online extraction and quantification of cognitive-induced brain activity was developed based on the selected algorithm. The procedure is functionally organized in blocks of algorithms in order to increase applicability. Several aspects, including the role of electrode montages and the reduction or minimization of the evoked activity, were examined based on cognitive studies as part of the optimization process. Future steps should include the design of a special training paradigm as well as a pilot study for confirming the theoretical approach proposed in this work.

Keywords: signal processing, EEG, working memory, cognitive-induced brain activity, non-phase-locked activity, theta band, alpha band, band power, event-related desynchronization, event-related synchronization, online estimation, source derivation, neurofeedback, epilepsy.

Zusammenfassung (Abstract in German)

Die Signalverarbeitung von elektroenzephalographischen (EEG) Signalen ist ein entscheidendes Werkzeug, um die kognitiven Prozessen verstehen zu können. Beispielweise wird induzierte Hirnaktivität in mehreren Untersuchungen mit kognitiver Leistung assoziiert. Deshalb ist die Gewinnung von elektrophysiologischen Parametern grundlegend für die Charakterisierung von kognitiven Prozessen sowie von kognitiven Dysfunktionen in neurologischen Erkrankungen. Besonders bei Epilepsie treten häufig Störungen wie Gedächtnis-, oder Aufmerksamkeitsprobleme auf, zusätzlich zu Anfällen. Neurofeedback (bzw. EEG-Biofeedback) ist eine Therapiemethode, die zusätzlich zu medikamentösen- und chirurgischen Therapien bei der Behandlung vieler neurologischer Krankheiten, einschließlich Epilepsie, erfolgreich praktiziert wird. Neurofeedback wird jedoch meist dafür angewendet, eine Anfallsreduzierung zu erzielen. Dagegen wird eine Verbesserung kognitiver Fähigkeiten auf der Basis elektrophysiologischer Änderungen selten vorgesehen. Darüber hinaus sind die aktuellen Neurofeedbackstrategien für diesen Zweck ungeeignet. Der Grund dafür sind unter anderem nicht adäquate Verfahren für die Gewinnung und Quantifizierung induzierter Hirnaktivität. Unter Berücksichtigung der oben genannten Punkten wurden die kognitiven Leistungen von einer Patientengruppe (Epilepsie) und einer Probandengruppe anhand der ereignisbezogenen De-/Synchronisation (ERD/ERS) Methode untersucht. Signifikante Unterschiede wurden im Theta bzw. Alpha Band festgestellt. Diese Ergebnisse unterstützen die Verwertung von auf ERD/ERS basierten kognitiven Parametern bei Epilepsie. Anhand einer methodischen Untersuchung von dynamischen Eigenschaften wurde ein onlinefähiger ERD/ERS Algorithmus für zukünftige Neurofeedback Applikationen ausgewählt. Basierend auf dem ausgewählten Parameter wurde eine Methodik für die online Gewinnung und Quantifizierung von kognitionsbezogener induzierter Hirnaktivität entwickelt. Die dazugehörigen Prozeduren sind in Module organisiert, um die Prozessapplikabilität zu erhöhen. Mehrere Bestandteile der Methodik, einschließlich der Rolle von Elektrodenmontagen sowie die Eliminierung bzw. Reduktion der evozierten Aktivität, wurden anhand kognitiver Aufgaben evaluiert und optimiert. Die Entwicklung einer geeigneten Neurofeedback Strategie sowie die Bestätigung der psychophysiologischen Hypothese anhand einer Pilotstudie sollen Gegenstand der zukünftigen Arbeitschritte sein.

Schlüsselwörter: Signalverarbeitung, EEG, Arbeitsgedächtnis, kognitionsbezogene induzierte Hirnaktivität, Non-Phase-Locked, ereignisbezogene De-/Synchronisation, Theta Band, Alpha Band, online Schätzung, Quellenableitung, Neurofeedback, Epilepsie.

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List of Abbreviations

AAR	Adaptive autoregressive
ADFT	Adaptive discrete Fourier transform
ARE	Adaptive recursive estimation
ARMA	Autoregressive moving average
BCI	Brain-computer interface
BMTI	Institute of Biomedical Engineering and Informatics
BP	Band power
cf.	Confer
EEG	Electroencephalogram
EOG	Electrooculogram
EP	Evoked potential
ERBP	Event-related band power
ERD	Event-related desynchronization
ERP	Event-related potential
ERS	Event-related synchronization
ERSP	Event-related spectral perturbation
FT	Fourier transform
FFT	Fast Fourier transform
FIR	Finite impulse response
fMRI	Functional magnetic resonance image
HEOG	Horizontal electrooculogram
IBP	Induced band power
ICA	Independent component analysis
IIR	Infinite impulse response
IQ	Intelligence quotient
IV	Intertrial variance
LTM	Long-term memory
NPLA	Non-phase-locked activity
PC	Personal computer
PET	Positron-emissions-tomography
PLA	Phase-locked activity
R	Reference interval

RE	Thalamic reticular nucleus
RT	Response time
SCP	Slow cortical potentials
SF	Squaring and filtering
SMR	Sensorimotor rhythm
SNR	Signal-to-noise ratio
STD	Standard deviation
STDn	Normalized standard deviation
STFT	Short-time Fourier transform
STM	Short-term memory
TCR	Thalamic relay cells
TRPow	Task-related power
VEOG	Vertical electrooculogram
WM	Working memory

List of Symbols

$a(k)$, $b(k)$	Coefficient vectors
c, c_1, c_2	Adaptation constants
d_{ij}	Distance from the i^{th} to the j^{th} electrode
dB	Decibel
$E(t)$	Second statistical moment
EEG	EEG channel
EEG_{ind}	Induced EEG activity
EEG_p	Preprocessed EEG signal
EEG_p^{init}	Preprocessed EEG sweeps (initialization stage)
$E\hat{R}P$	Estimated ERP
F	Fourier-operator
G	Number of surrounding electrodes
$h(t)$	Hilbert transform
$H(z)$	Discrete transfer function of filter
Hz	Hertz
i	Imagery root
IV	Intertrial variance
J	Number of sweeps
KHz	Kilohertz
K	Number of samples
KΩ	Kilo ohm
m	Meter
mm	Millimeter
ms	Millisecond
M	Order of denominator
$M(t)$	Adaptive recursive mean
N	Number of points in a sweep
nfft	Length of the analysis window
P	Band power
P_{ref}	Band power in the reference interval
Q	Order of numerator

ρ	Correlation factor
s	Second
std	Standard Deviation
t	Time
tr	Response time
ts	Stimulus time
µs	Microsecond
µV	Microvolt
V_i	Potential at the i^{th} electrode
V_i^T	Transformed potential at the i^{th} electrode
W	Unit root
x	Input signal
X(z)	Discrete transfer function of input signal
x^{cor}	Corrected signal
$\bar{x}$	Mean value of x
Y(t)	Signal envelope
Y	Output signal
Y(z)	Discrete transfer function of output signal

Chapter 1

Introduction and Motivation

Processing of biomedical signals is fundamental for understanding the functionality of biological systems and brain processes in particular. Especially in the neurophysiology and cognitive psychology fields, the extraction and quantification of specific parameters from the brain activity require certain accuracy in order to assure reliable results. Several studies link oscillatory brain activity to specific cognitive processes and support that neuronal information processing is reflected in brain oscillations (Klimesch, 1999; Yordanova et al, 2001). It is well-known that brain activity in distinct frequency bands responds differently to an increase in specific task demands. For example, the amplitude in alpha band decreases with an increase in task demand during semantic processing (Röhm et al., 2001); the opposite occurs for theta activity, which increases as response to working memory (WM) related tasks (Burgess and Gruzelier, 2000).

Thus, there is growing evidence that the analysis of brain oscillations is a powerful tool to analyze cortical processes in general and cognitive performance in particular (Başar, 1998). The extraction of electrophysiological features characterizing cognitive processes (and cognitive dysfunctions) is a key step towards understanding the relationship between brain and cognition. However, the role of brain oscillations in the neurological system and their relation to cognitive features such as memory and integrative functions remain open questions and further research in this field is indispensable.

Additionally to the respective symptoms, individuals affected by neurological diseases usually have cognitive impairments, e.g. memory, attentional, or language problems. In general, there is an increasing interest on the improvement of the cognitive functions.

Nevertheless, the responses of the brain to specific cognitive tasks are hardly considered for their possible value in therapy evaluation.

The emergence of supplementary psychological techniques, such as neurofeedback, has meant an important advance for the treatment of neurological diseases. Neurofeedback is a successful supplement to medication and surgical therapies, leading to further improvement in the treatment of many diseases, such as epilepsy or attention deficit disorders (cf. review in Evans and Abarbanel, 1999). The term neurofeedback indicates the operant conditioning of electroencephalographic (EEG) rhythms and is based on the self-regulation of brain responses. However, traditionally most efforts have been made in the reduction of seizure frequency and little attention has been paid to improve cognitive deficits directly, particularly memory-related problems.

Considering all the exposed above, the need for extending the scope of neurofeedback based on cognitive components derives. The aim of the present work is to find appropriate electrophysiological parameters reflecting cognitive processes and to study their possible use for neurofeedback purposes. From the biomedical engineering point of view, this thesis has a twofold goal: the selection of an appropriate electrophysiological indicator of cognitive processes, and the subsequent signal processing for its online extraction and quantification.

In order to facilitate reading comprehension, the chapters of this work are organized as follows:

In chapter 2, a selection of basic neurophysio- and neuropsychological concepts as well as their relation to the goal of this work are explained for the better understanding of the further chapters. First, the fundamentals of the EEG and its principal characteristics are briefly described. The distinction between spontaneous EEG, event-related (evoked) potentials and event-related (induced) desynchronization/synchronization is elucidated. Definitions of psychological terms such as cognition and memory are also given. Afterwards, the relationships between brain and cognition are highlighted, focusing on the functionality of cognitive-related frequency bands and cortical areas, especially on the relationship between memory and induced brain activity. The question whether the event-induced brain activity can be a valid parameter for detecting abnormal cognitive dysfunction in human subjects is addressed. The term neurofeedback, as a technique for operant conditioning of the EEG, is introduced in section 2.4. Both of the psychological and technical characteristics are exposed.

Finally, a brief introduction in the epilepsy field and the most frequent cognitive impairments associated with this disease are reported.

In chapter 3, a review of the most established neurofeedback approaches, since its discovery in the 60s, and their application fields as supplementary psychological technique, are introduced. Afterwards, a selection of methods for the (online) extraction and quantification of cognitive-induced brain activity is critically reviewed. Since cognitive functions are characterized by rapid changes over time, only time-variant methods are included in this review. The methods are grouped in two main categories, depending on whether or not they are based on calculations in the frequency domain.

The first part of chapter 4, *Problem Analysis*, deals with the reasons of why the existing neurofeedback techniques are insufficient for the treatment of cognitive and memory deficits in particular. Consequently, the need for extending the current neurofeedback approaches beyond the existing ones is discussed. Afterwards, and based on the existing methods for quantification and extraction of induced brain activity reviewed in chapter 3, the need for developing an appropriate methodology that corresponds with the requirements of a new neurofeedback technique is discussed. At the end of the chapter, and considering all the exposed in the previous sections, the questions to be addressed in this work are listed and explained in the subsection *Objectives*.

The recording system used in the measurements and the cognitive tasks used for the acquisition of experimental data are described in chapter 5. The recorded material is used for the experimental studies as well as for testing the methodology proposed. Data from a group of epilepsy patients and a group of healthy controls, participating in a series of cognitive measurements, are considered for the analyses.

Chapter 6 is divided into three main parts. Subsection 6.1 contains the experimental analyses carried out in order to find an appropriate method for quantifying differences in cognitive performance between healthy controls and patients. Subsection 6.2 includes a comparative analysis of the topographical distribution of the band power (BP) at resting state in cognitive-related frequency ranges. The third part of the chapter is devoted to the investigation of a suitable algorithm for online purposes based on the selected method. The results are discussed in detail at the end of each subsection.

A methodology for the online signal processing of cognitive-induced brain activity is presented in chapter 7. Several aspects are evaluated based on real data acquired during the performance of cognitive tasks as part of the optimization process. The question how the proposed methodology should be integrated in a neurofeedback application is assessed.

The thesis continues with a general discussion in chapter 8. The advantages as well as possible future improvements of the methodology are exposed and discussed in detail. The integration of further parameters and algorithms for a potential extension of the process is considered. Steps for further research in this field are also proposed.

Finally, an overview of the results obtained and a summary of the most important conclusions is given.

Chapter 2

Fundamentals of Neurophysiology and Cognitive Psychology

Biomedical engineering is an interdisciplinary field that requires not only technical but also biological knowledge. In order to give the reader the biological background of the topics discussed in this work, some basic neuropsycho- and neurophysiological concepts are introduced in this chapter.

2.1 Electroencephalography: Basic Concepts

Since its discovery in 1924 (Berger, 1929), the EEG technique has provided not only an important source for studying certain normal behavioral states, such as sleep, dreaming, or wakefulness, but also a tool for clinical applications, e.g. for diagnosis of cognitive physiological processes. Andrew (1997) describes the physiological generation of the EEG as a process of neural synchronization. He states that the EEG is mainly caused by "*current sources arranged in dipole layers of varying size within the neocortex… The ability for neural sources to operate in synchrony depends on the connectivity between these sources, as this connectivity determines the interactions which take place between them*". Due to the higher density of nerve cells on the cerebral cortex, the EEG is particularly well-suited to be used here. A disadvantage is that, because of the separation between the scalp and the current sources, and the effects of the poorly conducting skull, the signal is weakened and distorted.

The brain potentials recorded from the human scalp represent a complex signal containing frequencies within the range 0-100 Hz and amplitudes up to 100 μV. The frequency spectrum of the EEG is typically divided into 5 frequency domains or bands: delta (0.1-3.5 Hz), theta (4-7.5 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (above 30 Hz but unlimited in the upper range), each having a different clinical significance (Niedermeyer, 1999).

Activity in the delta band, often referred to as "slow wave", is mainly associated with deep sleep and predominates in children up to age of 4. If it predominates in the waking state in adults, it is a particularly strongly pathological finding. In this way, excessive delta activity on the vertex is related to serious disorders including head injury, coma, severe anxiety, and major vegetative depression (see Laibow, 1999).

Theta waves are particularly seen in infancy and childhood, as well as in states of drowsiness and sleep. Excessive theta activity in the waking adult is abnormal and is caused by various forms of pathology (Niedermeyer, 1999). During healthy function, synchronization in the theta band is associated with deep creativity (Laibow, 1999) and memory-related processes (cf. review in Klimesch, 1999).

In the alpha range, several rhythms, reflecting different phenomena and having probably different generators, have been reported in the literature. Berger (1929) found alpha rhythm over the posterior regions of the head with eyes closed. It turned suppressed or blocked with eyes opening. This was called the "alpha rhythm". The Rolandic (central) "mu" rhythm coincides partially with the "alpha rhythm" in frequency and amplitude but its topography and physiological significance are quite different. This rhythm is mostly related to functions of the motor cortex (Niedermeyer, 1999).

The lower subdomain (12-15 Hz) in the beta band is usually called the sensorimotor rhythm (SMR) and is related to periods of inactivity or motor inhibitory processes (Sterman, 1981). Reduced amount of SMR activity has been found in a variety of different seizure types (see Lubar, 1989). Beta waves in the range 16-24 Hz are associated with states of physiological arousal and response to threat. Pathological elevated beta levels have been observed in stress-related disorders and substance abuse, among other disorders (see Laibow, 1999).

Synchronization in the gamma band (about 40 Hz) over the sensorimotor area has been interpreted as a mechanism for integration of sensory and motor processes during programming of movement (Pfurtscheller et al., 1993). Activity in this band has been also related to sleep and binding processes. Pathological high activity in the gamma band (about 40 Hz) has been found at seizure onset in partial epilepsy and may be related to motor dysfunctions in Parkinson patients (cf. review in Alegre and Artieda, 2000).

When compared with other measuring techniques, like brain imaging methods (positron-emissions-tomography (PET), or functional magnetic resonance imaging (fMRI), among others), EEG has a better temporal resolution (in the millisecond range). This feature makes it appropriate for the study of rapid and temporal cognitive processes. Another advantage is its non-invasive condition and easy realization when compared with invasive EEG recordings, which are made with electrodes that have been surgically implanted on the surface or within the depth of the brain. During the past 20 years, some researchers have utilized a combination of two or more methods in order to increase both temporal and spatial resolution (Altenmüller and Gerloff, 1999).

2.1.1 Event-Related Potentials

Event-related potentials (ERP) appear usually after an external stimulus (visual, olfactory, auditory or sensorial) is presented and produce changes in the EEG time course that are both time- and phase-locked to the event. ERP have smaller amplitudes compared with the background EEG and are usually only visible with high intensity stimuli.

From a psychological point of view, it is convenient to distinguish between different types of ERP. First, we can identity those ERP whose characteristics are mostly controlled by the properties of the external eliciting event, e.g., intensity, frequency, and probability. Such evoked potentials are considered to be obligatory and are referred to as “sensory” or “exogenous” (also called “evoked potentials”, EP). An example of EP is the visual evoked potential: if a stimulus is given in the form of a flashing light, the EEG over the visual cortex will have the same frequency as the flashing light. Second, we can identify ERP that are determined more by the nature of the interaction between the subject and the event, providing electrophysiological insight into brain functions during cognition. These potentials are referred to as “endogenous” (Fabiani et al., 2000; Yordanova et al., 2001). For example, the N100 component is associated with orienting response, the N200 can be observed during stimulus evaluation, and the P300 is elicited after presentation of unexpected and infrequent stimuli. Another example are the slow cortical potentials (SCP), which appear as a large increase of cortical DC potential, caused by cognitive processing in the brain lasting up to several seconds (cf. review in Altenmüller and Gerloff, 1999; Coles and Rugg, 1995). Properties like amplitude, latency and topography of the responses to different sensory modalities of paradigms differ with each modality and are sensitive to stimulus probability too (Hruby and Marsalek, 2003).

There are mainly two approaches regarding the origin of the ERP: the classical amplitude modulation approach, based on fixed-latency, fixed-polarity brain events; and the phase modulation approach, based on a partial stimulus-induced phase resetting of the ongoing EEG rhythms (Penny et al., 2002; Makeig et al., 2002; Rizzuto et al., 2003).

2.1.2 The Phenomenon of Event-Related De-/Synchronization

External or internal stimuli can also result in a second type of potential changes in the ongoing EEG. In contrast to ERP that are phase-locked to an event, dynamic changes in the ongoing EEG are also related, although in a non-phase-locked manner, to a given event. These phenomena can be seen as event-related brain responses or induced oscillations. In other words, induced brain activity can also be considered as a reactivity of the brain in form of an event-related desynchronization (ERD) or synchronization (ERS), reflecting a decrease or increase in amount of synchrony, respectively. This kind of synchronization refers to processes occurring in the same location. Since ERD and ERS may take place at the same time in other bands and/or areas, they must always be related to a well-defined frequency band and to a specific brain area (Pfurtscheller and Lopes da Silva, 1999b; Lopes da Silva and Pfurtscheller, 1999).

Regarding the origin of induced oscillations, different neural generators for activity of different frequency bands have been suggested. Although several hypotheses have been proposed up to date, no theory has yet found general acceptance. In relation to the theta band, some authors have pointed out that oscillations in this frequency band reflect hippocampal neural activity (Klimesch et al., 1996; Burgess and Gruzelier, 1997). Concerning alpha activity, there is some agreement that EEG alpha desynchronization is generated by thalamo- and cortico-cortical feedback loops (Klimesch, 1999; Steriade et al., 1990). For a much broader definition of induced rhythms, the reader is referred to (Başar and Bullock, 1992).

Besides synchronization phenomena of neural networks in a determined brain area and frequency band, synchronization between distinct cortical areas and/or frequency ranges may also occur. However, the physio- and psychological significance of these phenomena are beyond of the scope of the current thesis and, thus, not included in this work.

2.1.3 Phase-Locked versus Non-Phase-Locked Activity

Phase-locked brain activity (PLA) is well-known to be time-locked to events. PLA represents the responses generated by transient post-synaptic potentials triggered by the event (Lopes da Silva and Pfurtscheller, 1999). According to Kolev et al. (1998), PLA is suggested to include all types of ERP. This activity can be distinguished from non-phase-locked activity (NPLA), having particular characteristics and reflecting different cognitive processes. NPLA is considered as oscillations modulated by stimuli or state changes and includes the background EEG. The NPLA reflects changes in parameters controlling dynamic interactions within and between brain structures (Bastiaansen and Hagoort, 2003; Pfurtscheller and Lopes da Silva, 1999b). Hence, the NPLA is a class of endogenous rhythms distinguished from the PLA.

Although PLA and NPLA may be linked, many studies have demonstrated that they reflect different cognitive processes (Klimesch et al., 1998a; Yordanova et al., 2001). For example, although it has been argued that there is a close relationship between enhancement of the theta rhythm and P300, differences between induced theta responses and the P300 suggest that they are distinct phenomena (Yordanova and Kolev, 1998a).

Regarding the generation of PLA and NPLA, different mechanisms have been suggested to underlie them (Lopes da Silva and Pfurtscheller, 1999): the PLA "*can easily be understood in terms of the response of a stationary system to the external stimulus, the result of the existing neuronal networks of the cortex (Fig. 2.1, right side). The induced changes cannot be taken into account in such terms. The latter can be understood as a change in the ongoing activity, resulting from changes in the functional connectivity within the cortex (Fig. 2.1, left side)*".

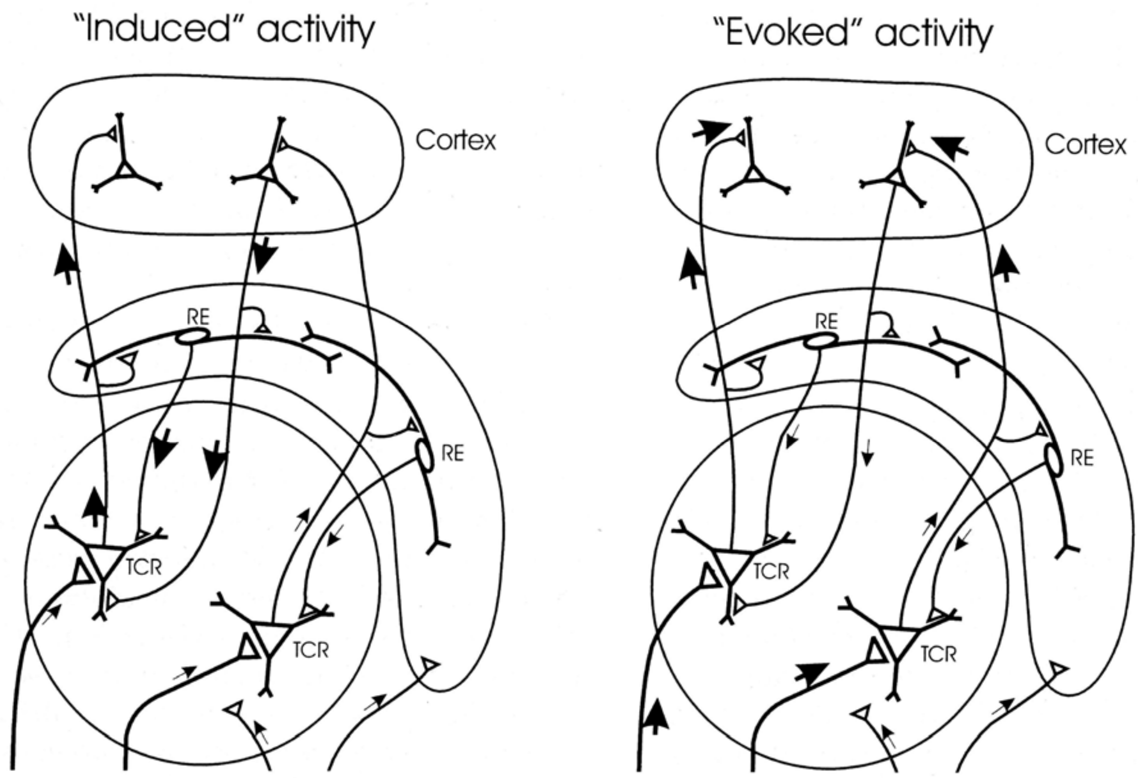


Fig. 2.1 Schema of generation of time-locked but not phase-locked changes in rhythmic activity (ERD/ERS) (left side) and synchronous summation of event-related potentials (right side). TCR: thalamic relay cells; RE: thalamic reticular nucleus (Lopes da Silva and Pfurtscheller, 1999).

2.2 Cognition and Memory: Basic Concepts

Numerous brain studies in the literature focus on the link between brain and cognitive functions. According to Schaub and Zenke (1995), cognition is described as the process and the result of information processing and decision making including knowledge, perception and judgment. The Encyclopedia Britannica (2006) extends this definition and includes within the term cognition "*every mental process that can be described as an experience of knowing as distinguished from an experience of feeling or of willing. It includes, in short, all processes of consciousness by which knowledge is built up*". This includes imagery, reasoning, learning, remembering, supposition, awareness, and memory among others.

Especially, many efforts have been paid in understanding how memory functions. Memory is defined as the ability of the brain to store information and to remember it again when needed (Brauer et al., 1995). Regarding the question how memory functions, the theory suggested by Atkinson and Shiffrin (1968) is the most accepted by the scientific community. In this theory, the memory is divided into two main areas, long-term memory (LTM) and short-term memory (STM), and the sensory registers. The sensory memory is the memory that results from our perceptions automatically and generally disappears in less than a second. It includes two subsystems: iconic memory of visual perceptions and echoic memory of auditory perceptions. The LTM is defined as the memory of long duration. Because the LTM itself is a very complex system, some criteria are used for dividing the LTM into separate components. The LTM can be divided into declarative and non-declarative memory, attending the question whether or not it can be verbalized. The non-declarative memory refers to those skills that can be demonstrated but cannot express in words. Into this category fall those learned habits and automatic sensorimotor behaviors that do not need language to be expressed, such as driving a car or riding a bike. These actions do not need our complete attention to be performed. Although such procedural memories generally take a long time to acquire, they remain for a long time too.

Conversely, the declarative memory reflects the memory of things and facts that can be described verbally. It can be further divided into implicit and explicit memory. In the implicit memory one does not remember the experience that gave rise to it, being mostly the origin for our emotional conditioning and automatic thinking. On the other hand, the explicit memory lets us consciously remember things and facts. Traditional studies have concentrated on this form of memory.

Two memory subtypes are distinguished within the explicit memory: the episodic and the semantic memory. The episodic memory, also called autobiographical, allows events experienced at a specific time and place to be remembered, e.g. the date of some important public event. In the semantic memory, the personal knowledge of the world is stored. The semantic memory includes the memory of the rules and concepts for a mental representation of the world without any immediate perceptions. Thus, its content is abstract and is associated with the meaning of verbal symbols (The Brain from Top to Bottom, 2006). Graphically, the classification of the different types of LTM can be summarized as shown in Fig. 2.2.

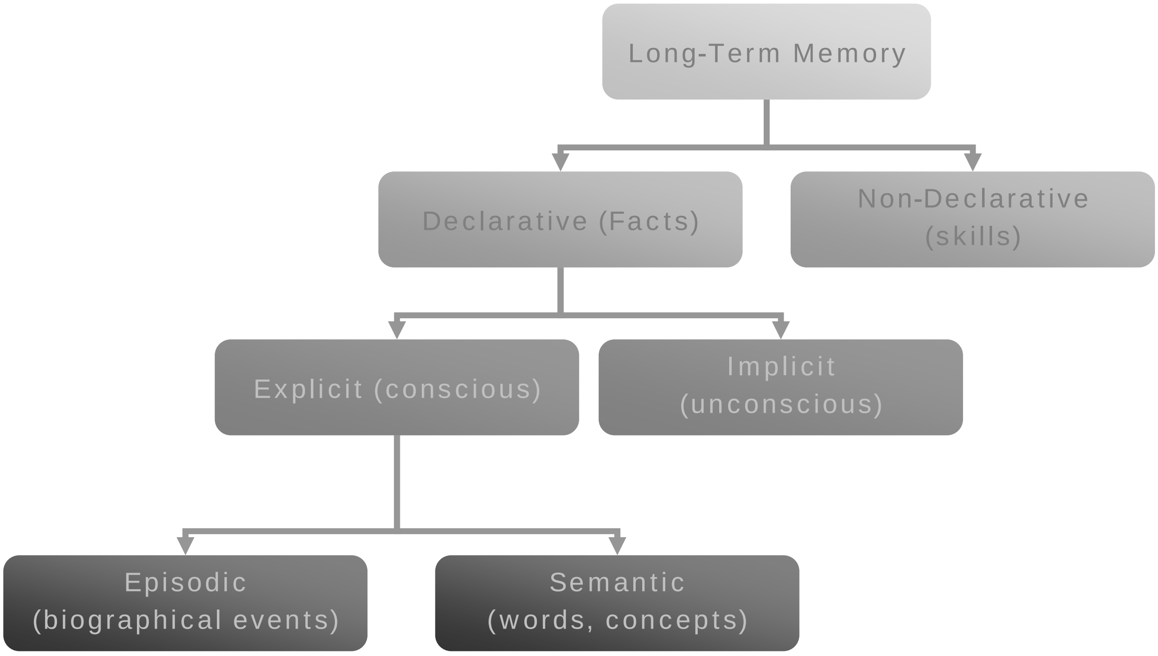


Fig. 2.2 Classification of memory subtypes within the LTM system.

Regarding the STM, Baddeley and Hitch proposed in 1974 a three component model of WM in place of the unitary system of Atkinson and Shiffrin. The three component model comprises a control system of limited attentional capacity and responsible for binding, retrieving and modifying information, termed the central executive, which is assisted by two subsidiary storage systems: the phonological loop, which is based on sound and language; and the visuospatial sketchpad, which codes visual and iconographic information. A fourth component has been recently added to the model in order to come to terms with phenomena that were not readily captured by the original model: the episodic buffer. The episodic buffer provides an interface between the subsystems of the WM and LTM and binds information into a unitary episodic representation (Baddeley, 2000, 2003). Fig. 2.3 shows schematically the connections among the elements of the WM system.

A fundamental characteristic of WM is the ability to maintain several item representations simultaneously. This capacity is essential for many of the functions ascribed to WM. The amount of information that must be held in mind at any given time is referred to as memory load.

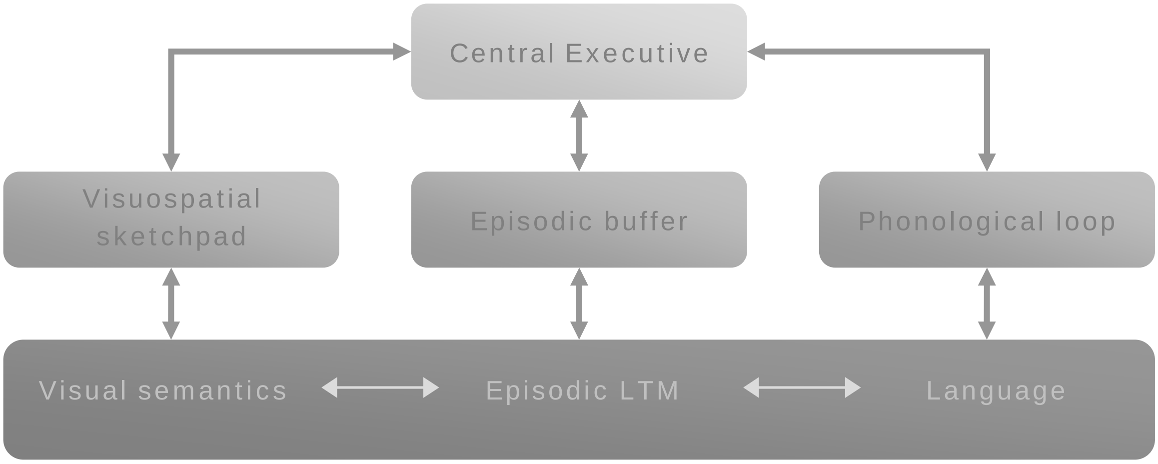


Fig. 2.3 Schema of the WM system and interconnections among components (modified from Baddeley, 2003).

2.3 Induced Brain Activity and Cognition

There is much evidence of induced brain activity reflecting cognitive performance. Many studies of recordings of spontaneous EEG activity and/or event-related brain responses, made while a subject performs some kind of perceptual or cognitive task, have reported reproducible changes in brain dynamics that are task dependent. Such studies are important for understanding normal and pathological brain processes for cognitive function. Since this work focuses on the study of cognitive functions, several findings linking oscillatory brain activity to specific cognitive processes are elucidated next.

The study of cognitive functions in humans is mostly focused on narrow frequency bands. In a particular way, frontal theta oscillations are strongly associated with memory function. Oscillations within the theta range have been observed during verbal (Tesche and Karhu, 2000; Raghavachari et al., 2001) and visual (Krause et al., 2000) WM, and haptic perception (Grunwald et al., 2001). Furthermore, frontal theta activity in humans has been found to increase with memory load during performance of the Sternberg task, reflecting active maintenance of memory representations (Jensen and Tesche, 2002; Tesche and Karhu, 2000). ERS in the theta band at frontal recording sites has also been associated with episodic memory processes: the successful encoding of new information and retrieval of remembered items are correlated with an increase in induced brain activity within theta band (Klimesch et al., 1994, 1996, 2001c; Burgess and Gruzelier, 2000).

Event-related brain oscillations in the alpha band have been typically divided into two narrower bands, called lower and higher (or upper) alpha. Klimesch and colleagues have argued that ERD in the lower alpha range reflects attentional demands such as alertness and expectancy, whereas desynchronization in the upper alpha range reflects semantic processes that are related to task performance (Klimesch et al., 1997, 1998a; Röhm et al., 2001; cf. review in Klimesch, 1999).

ERD in the alpha band has been recently related to WM too. However, different research groups have reported apparent contradictory results. Several authors have found a decrease of upper alpha activity as a function of increasing WM load (Gevins et al., 1997; Krause et al., 2000; Stipacek et al., 2003). Conversely, there are also evidences of an increase of upper alpha activity with memory demands, probably reflecting cognitive overload (Jensen et al., 2002; Klimesch et al., 1999). Moreover, Fingelkurts et al. (2003) have suggested that WM processes are complex and that different brain regions are involved in different stages of memory processing and, at the same time, different stages share common cortical regions of the brain. This fact, together with the use of different recording techniques, experimental paradigms and quantification methods, could explain these discrepancies.

Brain activity in higher frequency bands has been also related to cognitive functions. Particularly, gamma synchronization has been observed in different WM tasks. For example, gamma synchronization at widespread cortical locations has been reported during the performance of the Sternberg task (Howard et al., 2003), and induced gamma activity has been observed at frontal and occipital-temporal sites during the retention interval of a visual WM task (Tallon-Baudry et al., 1998). In both cases, these increases in gamma activity are interpreted as related to rehearsal processes in WM.

Regarding the performance of cognitive tasks, Klimesch has suggested that large alpha power during the resting state, which is correlated with a pronounced decrease in event-related BP, and small theta power, which is correlated with a pronounced increase in BP, indicate good performance (Klimesch et al., 2001a, 2001b). In this way, the reactivity in BP ('phasic' activity) can be predicted from the level of absolute power ('tonic' activity) during the resting state. In the case of theta, if there is a large activity during the resting interval, there would be no possibility of a further power enhancement during task performance (Fig. 2.4), reducing or blocking the ability to encode new information. The contrary holds true for the alpha band. These relationships can be seen as a double dissociation (cf. review in Klimesch, 1999).

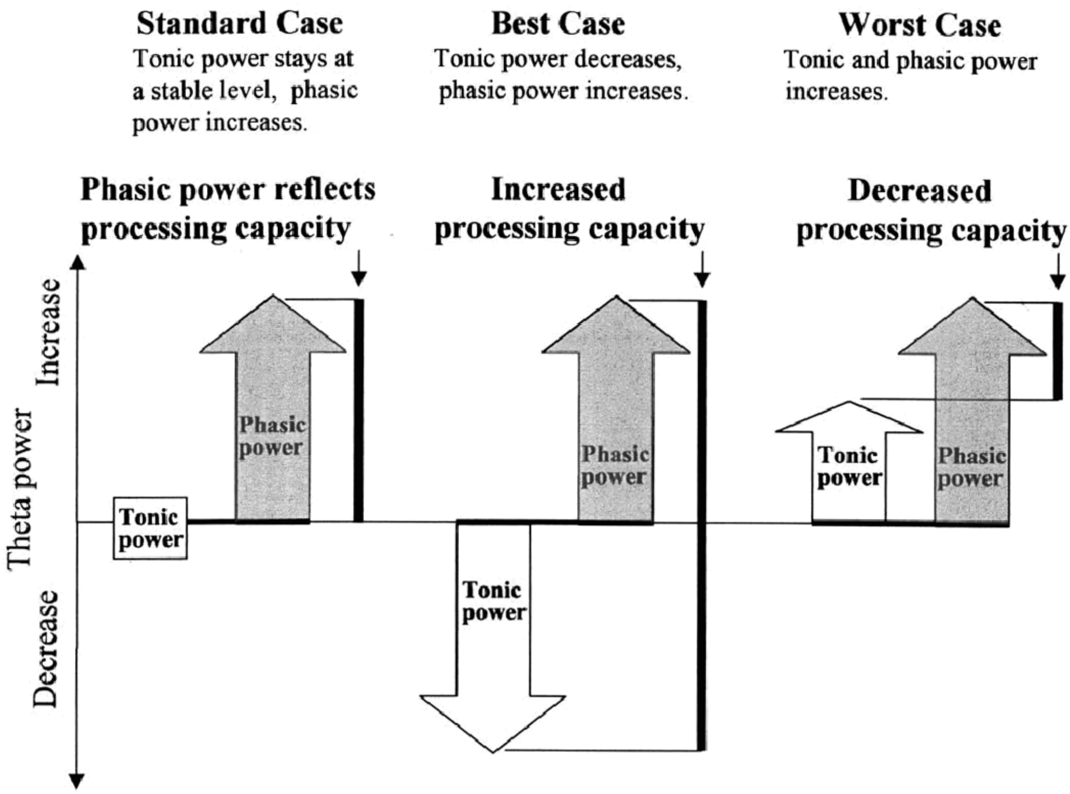


Fig. 2.4 The functional meaning of the relationship between 'tonic' and 'phasic' theta BP (Klimesch et al., 2001a).

2.3.1 Induced Brain Activity as Index for Cognitive Impairment

Evidences, showing that cognitive impairments in different diseases can be indexed by induced-related brain activity, have been reported. In two parallel studies with dyslexic children during a visual WM task, it has been shown that NPLA in different frequency bands may distinguish between dyslexics and healthy controls. When compared with controls, dyslexics showed different results in the theta, lower and upper alpha, and beta bands, reflecting a lack at attentional control during the encoding of certain items (Klimesch et al., 2001a, 2001b).

In a recently study, differences in the information processing during performance of different WM and learning tasks were reported between individuals with high and low intelligence quotient (IQ). High-IQ subjects used more focused brain areas and low-IQ more irrelevant brain areas. The results of this study showed that high-IQ subjects present a greater induced alpha desynchronization at parietal-occipital areas (because of the automation of (retrieval) processes, and more adequate learning strategy) whereas it concentrates in frontal areas for low-IQ subjects. In opposition to high-IQ individuals, who showed extremely high induced theta synchronization from stimulus onset till 500 ms, the low-IQ group showed a time-related increase in theta synchronization, suggesting a slower speed of information processing during the learning tasks (Jausovec and Jausovec, 2004).

These findings in the theta band point out possible additional dysfunctions that may be related to the attentional control of behavior or WM processes. These studies indicate that patients not only suffer the symptoms of the disease, but also have cognitive impairments.

2.4 Epilepsy: A Brief Introduction

For the experimental studies in this work, not only healthy subjects participated in the measurements but also patients with refractory epilepsy. Therefore, a brief introduction to epilepsy and its relationship with cognitive impairments and memory problems in particular is given next.

Epilepsy is a neurophysiological disorder characterized by seizures, and usually related to unconsciousness and other motor, sensitive, and sensorial phenomena. These seizures lead the patient to a state where he can not control his actions. Causes of an epileptic seizure are anxiety, stress, and annoyance, among others. Investigations of single neurons have shown that the characteristic membrane potential changes do not occur under normal conditions. These disturbances, reflecting pathological processes, are in EEG visible, mostly in form of sharp waves or spike-wave complexes (Wolf, 2003).

Epilepsy can be successfully treated with appropriate medication or surgery in most of the cases. However, there is a number of cases (approx. 20-40%) where such intervention is not possible or is not sufficient, e.g. due to resistance to medication (Wolf, 2003). Therefore, other supplementary techniques such as neurofeedback have been being applied for decades, offering other possibilities to the patients (see chapter 2.5).

It is not unusual for people who have epilepsy to have additional memory, attentional, or language problems, depending on the epilepsy type. Epilepsy can reduce the attentional speed of information processing or attention span, i.e., the amount of information that can be processed at any given moment, as the result of impairment in the ability to store or consolidate new information. Epilepsy has significant effects on retrieval from declarative memory and semantic information (Barr, 2006). Furthermore, research evidence and clinical practice indicate that patients with epilepsy are at elevated risk of episodic memory problems. Additionally, antiepileptic drugs, surgery, mood, seizures, age at onset and duration can influence negatively these cognitive functions (Wolf, 2003; Thompson, 2002).

2.5 Neurofeedback: Definition and Components

In general terms, a brain-computer interface (BCI) is a system that makes the communication between brain and computer possible. BCI systems are based on brain electric signals and do not require the use of peripheral nerves or muscles for communication. Neurofeedback (or EEG-biofeedback) can be considered as a part of the BCI research. The term neurofeedback indicates the operant conditioning of EEG rhythms and is based on the self-regulation of brain responses. Technically, neurofeedback is characterized by a modulation of the instantaneous activity and providing an acoustic or visual feedback in real time. Here it is important to give an online feedback to the subject, enabling him/her the possibility to influence the current mental activity condition over time. By means of auditory and visual rewards, like sounds or pictures on the monitor, the desired effect can be improved. After several neurofeedback sessions, subjects will be able to influence (voluntarily and/or by command) brain processes learned during the sessions (Evans and Abarbanel, 1999).

From the psychological point of view, neurofeedback (also called neurotherapy) has been demonstrated to be a successful supplement to medication and surgical therapies, providing further improvement in many neurological diseases, such as attention deficit disorders, epilepsy, depression, addictive disorders, and strokes, among others (cf. review in Evans and Abarbanel, 1999). Particularly, in the area of epilepsy therapy, a great deal of research was carried out in the past decades, which tried to find the most suitable feedback parameters for reducing the frequency of epileptic seizures (Sterman, 1981; Kotchoubey et al., 1999; Ivanova et al., 1999a, 1999b).

Fig. 2.5 shows the basic components of a neurofeedback system. The stimulation task leads the subject through the training session as it gives him/her commands with the action to be performed. The EEG activity elicited by the subject is recorded by the acquisition system. A control unit, represented by the corresponding responsible of the measurement that monitors the measurement in a control computer, manages both the stimulation task and the acquisition system. The acquired data are then processed online and the significant physiological features are extracted and prepared for feedback. Last but not least, the feedback provides the control parameter to the subject. This feedback, as well as the stimulation task, is as a rule acoustic, visual or acoustic-visual.

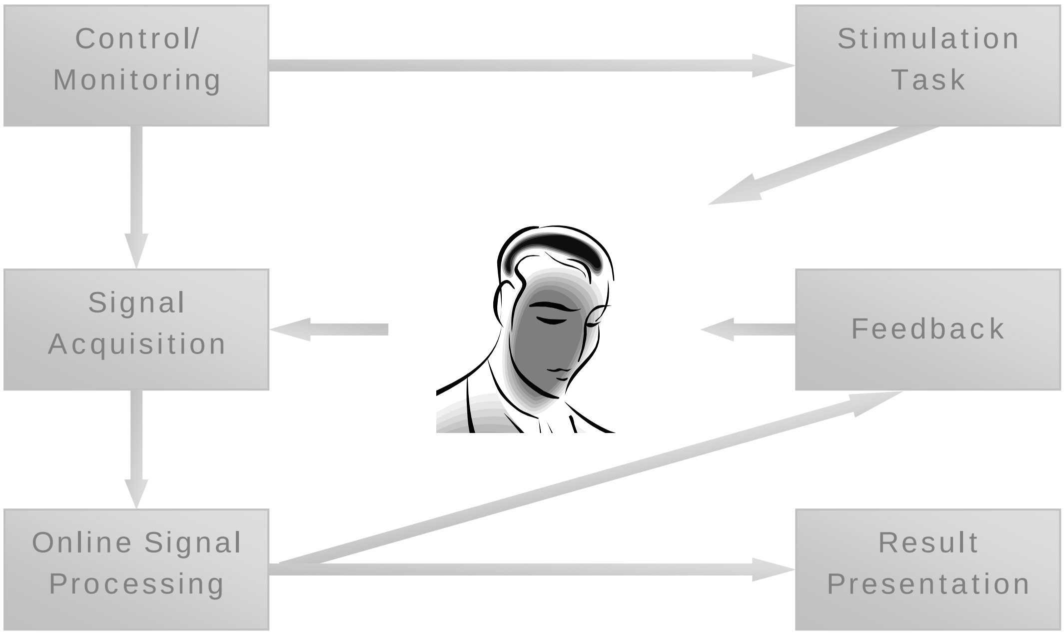


Fig. 2.5 Basic schema of a neurofeedback system.

Chapter 3

State of the Art

In this chapter, a historical background of the most commonly used neurofeedback techniques to date as well as their applications for the treatment of neurological diseases are given. Afterwards, a selection of methods for extraction and quantification of cognitive-induced brain activity is critically reviewed. Time-variant methods for univariate analysis are especially stressed, because of their importance for reflecting the rapid changes that characterize cognitive functions over time.

3.1 Neurofeedback: Historical and Methodical Background

Traditionally, the enhancement of alpha waves has been the most frequently used strategy in neurofeedback. Joe Kamiya was one the first researchers to demonstrate that human subjects could learn to control their brainwaves consciously when provided with feedback on their brain activity (Kamiya, 1968, 1969). In the USA, Sterman and co-workers began to apply neurofeedback on epilepsy patients to enhance their level of waves within the 12-15 Hz frequency range, the so-called SMR. The SMR is related to inhibitory processes (Sterman and Macdonald, 1978; Sterman, 1981). A modified version of this protocol, combining the training to enhance the SMR over the rolandic area with a reduction of the theta and delta activities, has been replicated in other laboratories (Lubar and Bahler, 1976; Psatta, 1983). Meanwhile in Europe, an approach based on SCP has been established (Rockstroh, 1982). Epilepsy patients, who show slow negative potentials shortly before they have a seizure, are suggested to have a deficit in the suppression of negative potentials. After SCP training, patients are able to control voluntarily these potentials (Rief and Birbaumer, 2000; Kotchoubey et al., 1999). Both approaches (SMR- and SCP-based) have been shown to be effective, reducing the frequency and intensity of epileptic seizures.

Neurofeedback has been applied not only in epilepsy, but also in a broad range of neurobiological disorders. For example, neurofeedback training has been historically shown to be an appropriate and efficacious adjunctive treatment for attention deficit hyperactivity disorder. In such a protocol, the patient is trained to increase the activity in the SMR or beta range and to decrease theta activity in order to improve attention (Lubar et al., 1995; Kaiser and Othmer, 1997). Peniston and Kulkovsky have proposed a protocol based on training of the ratio alpha-theta (the so-called Peniston-Kulkovsky protocol). The protocol that was originally proposed for the treatment of post-traumatic stress disorders and alcoholism has been later extended to other addictive disorders (Peniston and Kulkosky, 1999). Neurofeedback protocols for patients with dissociative identity disorder have also been proposed (Brownback and Mason, 1999; Manchester et al., 1998), where different bands at different localizations are trained, depending on the diagnosis. An alpha asymmetry protocol has been suggested for the treatment of depression, where patients are taught to compensate the alpha asymmetry in frontal areas (Baehr et al., 1999; Rosenfeld, 2000). Gosepath and colleagues (2001) have applied neurofeedback on a group of patients suffering from tinnitus. The protocol consisted in increasing the alpha activity at the same time that beta is decreased. The patients responded positively to the treatment as the tinnitus strain was reduced.

In addition to BP and amplitude-based measures, measures that take the chaotic behavior of the brain into consideration can also be applied in neurofeedback. For example, the fractal dimension has been recently proposed as feature for neurofeedback. In a pilot study, healthy controls learned to decrease the fractal dimension of their EEG (Bashashati et al., 2003). Nevertheless, the computational load was high and the feedback was refreshed every one second.

The question remains, however, unclear to what extent the training of individuals to modify the activity in a particular frequency band will specifically influence the cognitive performance. In this way, first studies have recently shown a limited improvement in cognitive performance in a control group after neurofeedback training of the SMR (Vernon et al., 2003). In the same study, neurofeedback training of absolute theta amplitude values failed. In another pilot study on healthy controls, neurofeedback training to decrease absolute power in the theta range also failed and neither improvement in cognitive performance, nor decrement of theta activity was achieved. Nevertheless, subjects showed some improvement in cognitive performance after neurofeedback training of absolute upper alpha power (Hanslmayr et al., 2005). This improvement is in accordance with the studies of Klimesch and co-workers, who have suggested a direct relationship between higher power in the upper alpha range in the resting state and good performance (Klimesch et al., 2001b).

3.2 Overview of Cognitive-Induced Brain Activity Analysis

The present review does not attempt to offer a complete list of the available methods for processing of biomedical signals but instead to provide the reader with an up-to-date overview of available methods for the analysis of cognitive processes. Depending on the issue being studied, different procedures are used for the analysis of cognitive-related brain activity. In this section, only literature on induced brain activity as far as it is relevant to the present context is reviewed. For a better understanding, a division between time- and frequency-based methods is made.

3.2.1 Time Domain Analysis

Historically, the study of univariate event-related PLA has been the focus of cognitive research. PLA is mostly represented by the ERP. They are usually calculated by averaging the segmented raw signal across trials. In this way, the NPLA is minimized and the ERP, due to its phase-locked property, is enhanced. For a broad revision of the application of the ERP in different cognitive areas, see (Fabiani et al., 2000).

In order to quantify the NPLA too, the ERD/ERS method, proposed originally by Pfurtscheller and Aranibar (1977) can be used. It is based on the calculation of the BP during the post-stimulus interval, related to a resting state. ERD/ERS has often been applied as a method for quantification of event-related brain oscillations in a considerable number of studies in different research fields (cf. review in Pfurtscheller and Lopes da Silva, 1999a). When the estimated measure is given as z-transformed power value, it is called event-related BP (ERBP; Klimesch, et al., 1998b).

The use of adaptive approaches for quantification of event-related brain oscillations is also possible. Schack and Krause (1995) proposed an adaptive recursive estimation (ARE) for the quantification of ERD/ERS during the performance of a WM task. Adaptive algorithms have the advantage that they can capture the dynamic and rapid changes in the signal better.

However, the methods cited above ignore the difference between PLA and NPLA, i.e., no distinction between the evoked and induced activities is made. The use of the intertrial variance (IV; Kalcher and Pfurtscheller, 1995) technique makes this distinction possible. The IV method has been applied to the study of event-related brain oscillations during information processing tasks (Yordanova and Kolev, 1998a) and item recognition (Burgess and Gruzelier, 1997, 2000), among others. When the estimated measure is given as z-transformed power value, it is called induced-BP (Klimesch et al., 1998b).

Signal processing methods based on blind source decomposition can also be used for separating the NPLA from other unwanted components (i.e., ERP, ocular and muscular artifacts, etc.). The goal of blind source separation is to recover independent source signals after linear combination. In this category falls the independent component analysis (ICA) technique. The ICA is a signal processing technique that can decompose multichannel data into spatially fixed and temporally independent components (Jung et al., 2001). ICA has been also suggested as a method to improve the estimation of ERD/ERS (Foffani et al., 2004). In order to evaluate event-related changes in brain dynamic, a moving-window can be introduced (Makeig et al., 2000). However, the ICA needs a training data-set for the estimation of coefficients. If the training data-set is too small, the temporal independence of the components cannot be assured (Jung et al., 2001).

3.2.2 Time-Frequency Analysis

In order to analyze a signal also for its frequency content, time-frequency methods can be applied for their conversion into the frequency domain. The main advantage of time-frequency approaches is that no a priori selection of the frequency band is needed.

The most common method for converting a signal into the frequency domain is the Fourier transform (FT). To obtain a time-frequency representation of event-related brain activity, the short-time FT (STFT) can be used (Gabor, 1946). This approach is based on the fast FT (FFT) and requires a sliding time window (for obtaining the time resolution) and a window function (for avoiding the leakage effect), which is multiplied with the signal segment defined by the time window. The STFT represents a sort of compromise between the time- and frequency-based views of a signal. The drawback is that once a particular length for the time window is chosen, that window is the same for all frequencies. Makeig (1993) introduced a normalized measure based on the STFT called event-related spectral perturbation (ERSP). The ERSP can be considered a generalization of the ERD/ERS because it is not limited to a narrow frequency band but involves the full-spectrum. The ERSP measures necessarily include the spectral energy of the ERP. A similar approach is the so-called task-related power (TRPow). The difference between the TRPow and the previous method is that the TRPow is based on spectral power analysis of EEG signals during the steady-state task performance. Since the resulting activation patterns are related to ‘task’-performance rather than to a single ‘event’, these data are referred to as ‘task-related’ rather than ‘event-related’ (Gerloff et al., 1998).

Another possibility to obtain a spectro-temporal representation of ERD/ERS is to perform an analysis based on the Hilbert transform. In such an approach, the so-called analytic signal, i.e. the signal envelope rather than the squared signal amplitude for a particular frequency band, is calculated. With help of the FFT and a band-pass filtering either in time or in frequency domain, the analytic signal specifies the amplitude and phase as a function of time and frequency (Clochon et al., 1996).

FT-based approaches have the disadvantage that, when calculated over time, the temporal resolution is the same for all frequencies, i.e. the temporal and frequency resolutions are dependent. However, sometimes it might be desirable to recognize sharp high-frequency discontinuities, while at the same time examining the lower frequencies in detail. This requires looking at the signal at different scales and multiple resolutions. The wavelet transform accomplishes this requirement: the higher the central frequency, the shorter the window duration. In a cognitive-related context, (Morlet) wavelets have been used for the analysis of data acquired during the performance of WM tasks (e.g. in Tallon-Baudry et al., 1998; Howard et al., 2003).

Paradoxically, in a recent comparative study, the STFT-, Hilbert, and wavelet-based approaches yielded similar results. The results demonstrated that the three techniques are in fact formally equivalent when using the class of wavelets that is typically applied in spectral analyses, contrary to the increased acceptance of the notion that Hilbert- or wavelet-based analyses are in some way superior to FT-based analyses (Bruns, 2004). Nevertheless, all of these methods need a data block in order to estimate the parameters and, thus, a point-by-point calculation is only possible with high overlapping values, which increases the computational load considerably.

The stationarity problem of the FFT for long segments can be avoided if adaptive recursive estimation is used instead of a window. This can be achieved with a time-variant estimation of the power spectrum based on an adaptive discrete FT (ADFT; Helbig et al., 2002). Advantages of this method are that the spectrum of a selected frequency can be calculated independently without the necessity for evaluating the whole spectrum and that, due to its recursive characteristic, it can be calculated for each time point. These two characteristics contribute to minimize the computational load.

When compared with non-parametric methods, the use of parametric spectral analysis methods based on time-varying models can offer a better time-frequency resolution. In this way, approaches based on adaptive autoregressive (AAR) or autoregressive moving average (ARMA) models have been used for cognitive applications. In the past decade, different methods based on AAR algorithms have been introduced for the estimation of the dynamics of ERD/ERS (Hiltunen et al., 1999; Schlögl et al., 1997, 2000). Furthermore, ARMA-based methods can also be used for studying rapid and elemental cognitive processes. The time-varying parameter estimation problem can be solved by using a Kalman smoother approach. Recently, such a parametric approach has been proposed for the offline quantification of ERS (Tarvainen et al., 2004). Another parametric method for the quantification of ERD in the time-frequency plane is the matching pursuit algorithm. This approach, based on the average of energy distributions of single EEG trials, uses dictionary functions for decomposition of the signal in an iterative procedure (Durka et al., 2001). However, the integration of parametric methods in the field of neurofeedback is difficult mainly because these methods are very sensitive to EEG patterns and artifacts and depend highly on several parameters (model order, update coefficients), which are not always easy to adjust. Moreover, when compared with BP algorithms, the latter have been demonstrated to yield superior and more robust results than AAR algorithms (Guger et al., 2003).

Table 3.1 summarizes the methods mentioned above. The classification in segment-based and point-by-point calculation methods reflects the lack of algorithms able to separate PLA and NPLA in each time point for online systems.

Table 3.1 Overview of methods for quantification of cognitive-induced brain activity.

	NPLA	PLA+NPLA
Segment-based --- Offline	IV *(Kalcher and Pfurt., 1995)* IBP *(Klimesch et al., 1998b)* ICA *(Foffani et al., 2004)* ERSP *(Makeig, 1993)*	Hilbert *(Clochon et al., 1996)* TRPow *(Gerloff et al., 1998)* Wavelet *(Tallon-Baudry et al., 1998)* Matching Pursuit *(Durka et al., 2001)* Kalman *(Tarvainen et al., 2004)*
Point-by-point --- Online		ERD/ERS *(Pfurtscheller et al., 1977)* ARE *(Schack and Krause, 1995)* AAR *(Schlögl et al., 1997)* ERBP *(Klimesch et al., 1998b)* ADFT *(Helbig et al., 2002)*

Chapter 4

Problem Analysis: Psychological and Methodical Issues

As mentioned in the introduction chapters, the biomedical engineering field is a multidisciplinary one. When analyzing problems in this field, both the medical and the technical facets must be considered and understood. In the context of this work, the psychological and methodical aspects of the existing neurofeedback techniques are discussed next. Afterwards, the requirements that methods for the online signal processing of induced brain activity have to fulfill, in the scope of a neurofeedback application based on cognitive parameters, are analyzed. Finally, the objectives of this work are exposed.

4.1 Psychological Aspects

From a psychological point of view, cognitive functions are particularly important for patients suffering from neurological diseases to ensure successful integration at school and workplaces. Especially in epilepsy, good memory function is important for patients to manage and monitor their disease, take their medication, and record seizures. Contrary to attentional and sensorimotor functions, a successful medication-based therapy leads to a slow and minor recovery of the cognitive functions. Hence, a complete treatment program for people with epilepsy should not only try to control seizures, but also try to reduce the distress caused by attention and memory impairments. Although impaired memory is a common problem that can be considered as a possible factor for academic, occupational and social difficulties in patients with epilepsy, direct therapy for memory deficits associated with epilepsy is rarely attempted (cf. review in Shulman and Barr, 2002; Engelberts et al., 2002).

The use of new emerging supplementary therapy techniques, e.g. neurofeedback, has helped to increase the rate of successful treatments for epilepsy. The objective of most existing neurofeedback approaches is the reduction of the seizure frequency or at least keeping the seizure under control as far as possible. Nevertheless, little attention has been paid to the improvement of cognitive impairments. Recently, first attempts to use neurofeedback training for cognitive purposes have been reported. These attempts failed, at least in part, when trying to train theta band activity and it was not possible to increase the cognitive performance. Only a limited improvement was achieved after training of the upper alpha band (Hanslmayr et al., 2005) and SMR (Vernon et al., 2003).

Regarding the relationship between brain and memory, event-related brain activity in the theta, alpha and gamma frequency bands have been demonstrated to play an important role in memory performance. Furthermore, differences in the quantification of induced brain activity (ERD/ERS phenomenon) between patients suffering from different neurological diseases and healthy controls have been associated with memory impairments. However, because the conditions and characteristics of different diseases are singular, each patient population must be examined in order to determine specific deficits and needs.

4.2 Methodical Aspects

From a methodical point of view, the current neurofeedback techniques are based on an increase, decrease or combination of the absolute (‘tonic’) activity in one or more frequency bands to compensate or correct a(n) deficit/excess in comparison with healthy subjects. Nevertheless, neurofeedback training for enhancement of cognitive performance has partially failed when using such a protocol. Cognitive neurofeedback training of absolute activity in the theta band was not effective to change the post-stimulus power during post-training cognitive measurements (Hanslmayr et al., 2005). The possible reason for this negative finding may lie in the lack of an appropriate methodology. In this way, the relationship between memory performance and event-related induced brain activity should be taken into consideration. As reviewed in section 2.3, relative measures, as relation between pre- and post-stimulus intervals, are mostly used instead of absolute ones for extraction and quantification of memory-related features. Furthermore, application of repetitive transcranial magnetic stimulation in a period preceding a task has been recently shown to enhance cognitive performance. This improvement was due to not only changes in power within the pre-stimulus (reference) interval, but also changes in the post-stimulus (test) interval (Klimesch et al., 2003). This finding confirms the hypothesis that changes in both pre- and post-stimulus EEG activities are possible.

Synchronization phenomena occur in narrow and selected frequency bands for cognitive and memory demands in particular. If the frequency band is chosen too wide, changes produced in other frequency bands can influence the result. For example, synchronization and desynchronization can appear at the same time in alpha and theta band during task performance and could cancel each other out if the frequency bands are not strictly defined. For this reason, frequency selectivity is a crucial aspect of every methodology.

Neurofeedback applications are real time systems and thus they must operate in single-trial modus. Moreover, as indicated in section 2.5, providing immediate feedback to the subject makes effective learning possible. Some of the quantification methods mentioned in chapter 3, however, either do not fulfill the requirement of online ability or are not suitable for single-trial purposes because of their iterative nature. Although, the use of a time window to get a temporal resolution (e.g. in the ICA method) is possible, the computational effectiveness of these methods can be reduced considerably because of the level of resources needed. If the delay is too long, the subject will not be able to identify and follow his current mental state with the feedback signal he is receiving, and this would make the system inefficient. Besides the algorithm velocity, the dynamic of a system must also be taken into consideration when choosing an optimal algorithm for the selected method. Since the quality of the feedback is crucial to the effectiveness of the learning process, the dynamic properties of the chosen algorithm must be kept so that they reflect the activity of interest accurately.

Another very important issue of debate is the level of interference of the PLA. Most of the methods reviewed in chapter 3 do not distinguish between PLA (evoked) and NPLA (induced). When the averaging technique is used (e.g. for the calculation of the ERP), the NPLA tends to disappear, if it does not have enough signal-to-noise ratio (SNR). Since we are focusing on single-trial analysis, this effect does not occur but the evoked activity can still play an important role. Nevertheless, to obtain a separation of the different event-related brain components, which are spatiotemporally overlapped, is a difficult task in single-trial modus. Therefore, the remaining question is whether the presence of the evoked activity in single-trial significantly influences the quantification of the NPLA during the performance of cognitive and memory tasks in particular.

In addition to the separation of activities originating in the brain, one is confronted with other sources of interferences, e.g. artifacts. Therefore, effective measures must be taken to shield the system from undesirable sources. The system has to be robust and able to deal with even poorer SNR values, which are already small in the EEG.

4.3 Objectives

Based on the fundamentals presented in chapters 2 and 3, and the problem analysis of the previous section, the objectives of the current thesis can be derived. The main objective is to develop a new methodology for online processing of induced brain activity. This methodology will be the basis for further cognitive-based neurofeedback applications, which should allow the patient to learn how to reproduce an optimal response to determined memory task demands. As argued in the previous section, the methodology must take into consideration the relationship between memory and event-related brain activity, as characterized by induced changes within determined frequency bands.

In terms of biomedical engineering, the goal of this work can be divided into two main parts, reflecting the experimental and methodical analysis, and the design steps of the development process:

- The selection of an appropriate parameter for further neurofeedback purposes. This task includes the realization of multichannel measurements on healthy controls and epilepsy patients in order to gain experimental data and build a reference database. The subsequent signal analysis from normal and pathological data, acquired during the performance of selected stimulation paradigms, is crucial. The objective of the experimental studies is to extract and quantify specific indicators as well as to determine the topography of EEG rhythms and cognitive event-related components that can differentiate both populations. For these purposes, comparisons of time courses and mapping examinations of the obtained results are needed. Afterwards, and before a quantification method is chosen for further applications, tests and comparisons of different algorithms for quantifying the selected parameter and for their online ability should be done. Analyses not only of the dynamic characteristics, but also of the computational load must be completed.

- The development of a methodology based on the selected cognitive parameter. The methodology must include not only the necessary steps for the extraction and quantification of the selected parameter, but also a general strategy or procedure for managing the experiment. The new approach must fit the requirements and features of the selected parameter. At the same time, and due to the broad spectrum of cognitive processes, the method must also be flexible to allow not only modifications depending on task constraints, but also subject-specific adjustments, i.e., the chosen variables must be adaptable in order to optimize the effectiveness of the process. The solution should be as easy as possible in order to facilitate its implementation and, thus, application.

The evaluation of the medical relevant parts, the interpretation of findings and the validation of the obtained results will be carried out in cooperation with partners of the neurophysiology and neuropsychology areas.

Chapter 5

Experimental Data

Several cognitive tasks, belonging to a series of measurements completed at the Institute of Biomedical Engineering and Informatics (BMTI) at the Technische Universität Ilmenau, were selected for the experimental analyses carried out in this work. Tasks for studying cognitive and memory features in particular were included. The next sections contain the acquisition system used for the measurements, the groups of subjects and the experimental tasks.

5.1 Data Acquisition

EEG recordings with 28 monopolar channels (Ag/AgCl electrodes) were acquired according to the International 10-20 System. However, for keeping consistency in all analyses, only 26 channels were considered due to changes in the electrode montage during the series of measurements (Fig. 5.1). The linked mastoids were used as reference. Vertical and horizontal bipolar electrooculogram signals (VEOG and HEOG, respectively) were recorded to register ocular activity.

The Synamps amplifier system of Neuroscan® was used for data acquisition. The signals were low-pass filtered (70 Hz) and sampled at 500 Hz. The electrode impedances were kept below 5 KΩ in all measurements. The raw data were downsampled to 125 Hz to reduce the computational load during the analysis. For stimulation, the software STIM® was used.

For all measurements, the subject was sitting in a comfortable chair with arms in a light darkened room. For visual tasks, a PC monitor was put in front of the subjects at a distance of approx. 1.5 m and at the height of their head. Acoustic tasks were completed with help of two desktop speakers. These conditions, as well as the start time of the session, were kept constant for all measurements.

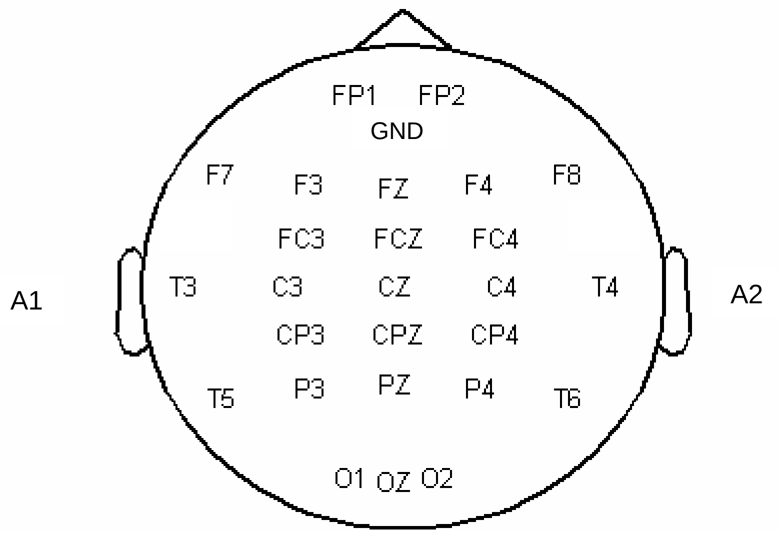


Fig. 5.1 Electrode positions used in the analyses (10/20 System).

5.2 Subjects

Data of 21 patients with refractory epilepsy (15 males, 6 females; focal or focal secondary generalized epilepsy; 37.14±11.11 years old; age range: 19–56 years old) were used for the different studies of this work. Patients did not suffer from additional cognitive or psychological disorders, e.g. depression. The selection criteria were no changes in medication and no seizures in the last weeks.

In order to collect data for comparison, data of 21 voluntary healthy subjects without previous neurological history were employed. The Subjects were between 17 and 57 years old (12 males, 9 females; 36.67±10.71 years old) and belonged to the control group of the series of measurements.

5.3 Experimental Paradigms

Because cognitive and neural processes occur between the stimuli and the behavioral responses, the selected paradigms involve the presentation of appropriate stimuli that systematically elicit the cognitive processes being investigated. Therefore, data acquired in two different cognitive tasks were employed for several studies during the completion of this work: an auditory oddball task, for examining alterations of event-related responses to different stimuli; and a modified version of the Sternberg task, for the study of WM processes.

In the oddball task (Fig. 5.2), standard tones of 1 KHz (100 ms duration) were presented once every 4.1 s with a 2 KHz target tone occurring randomly in 20% of the trials. Subjects were instructed to respond by pressing a button, as rapidly as possible, after the target stimulus was presented. Participants were required to keep their eyes closed during the task. The trials with the correct response were considered in this work. The pre- and post-stimulus intervals of both cases (target and non-target stimulus) were assigned for analysis.

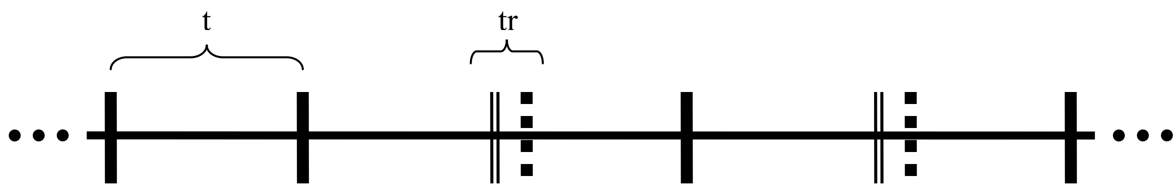


Fig. 5.2 Time sequence of the oddball paradigm: ▬, standard tone; ═, target tone; ■ ■ ■, subject response; t = 4.1 s; tr = response time.

Because of the importance of attaining new measurements of cognitive tasks on healthy controls and patients with refractory epilepsy, a modified version of the classical Sternberg paradigm (Fig. 5.3) was programmed (STIM-software) by the presenting author for the cognitive series of measurements. The Sternberg paradigm is one of the most used paradigms in the memory psychology (Sternberg, 1966). It involves a random series of four different one-digit numbers displayed singly on the screen every 1.3 s. There follows a delay, a warning signal, and then the test digit. The subject has to press two distinct buttons to confirm whether or not the test digit was within the previous list. A feedback on the screen (green or red circle) informs the subject whether the response was correct or not. The trial ends with an attempt to recall the series in order. The event that indicated the beginning of the retention interval was assigned for the analysis. Only trials with the correct response were considered for analysis.

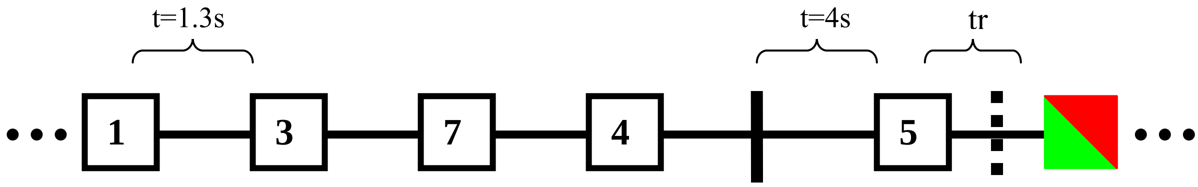


Fig. 5.3 Time sequence of the Sternberg paradigm: ▬, start of the retention interval; ■ ■ ■, subject response; tr = response time.

Chapter 6

Experimental and Methodical Analyses of Cognitive-Induced Brain Activity

The first part of the current chapter is devoted to the experimental studies completed, the signal processing methods applied and the results obtained. Afterwards, different online algorithms for quantification of the selected feature are evaluated.

6.1 Quantification of Abnormal Cognitive-Induced Brain Activity

Based on the oddball task described in chapter 5, an experimental study was carried out in order to compare the cognitive performance of both populations (controls and patients). The aim of the study was to find out a method that could quantify a possible abnormal cognitive function in a group of patients with refractory epilepsy.

The possible features that can be extracted from the EEG data are numerous. Which feature is extracted depends basically on two aspects: the task realized, and the method used for signal processing. The former determines which features are elicited and the latter which of the elicited features are extracted and quantified. Based on the discussions in chapters 2 and 3, the ERD/ERS method was used in this study because of its proved efficiency for quantifying cognitive-induced EEG features (e.g., Klimesch et al. 1996; Burgess and Gruzelier, 2000). As mentioned in previous sections, cognitive brain processes are related to alterations in specific frequency bands of the EEG. For example, attention and WM processes are associated with activity changes in the theta band (see section 2.3) that can be quantified by the ERD/ERS method. In order to check whether ERD/ERS is a valid parameter for quantifying cognitive-related differences between healthy controls and patients with refractory epilepsy, their performances during the oddball paradigm described in chapter 5 were examined.

6.1.1 Extraction of the Specific Frequency Band

The frequency band of interest was extracted by means of a digital band-pass filter. Two kinds of filter were taken into consideration at the beginning of this work: filters of finite (FIR) and infinite (IIR) impulse response. The main feature of the FIR filters is that they can have exactly linear phase, i.e. no phase shift is present. On the other hand, IIR filters can achieve a sharper transition between band edges than FIR filters can with the same number of coefficients. In other words, IIR filters need a considerable smaller order than FIR filters for fulfilling the same specifications. Thus, they require less computing time. The disadvantage of IIR filters is that they introduce a phase shift (Parks and Burrus, 1987). For the study of event-related brain responses, it could be assumed that FIR filters have advantage about IIR filters. Nevertheless, a zero-phase digital filtering technique can be used for correcting the phase distortion and making the use of rapid IIR filters for experimental studies possible. In this way, the input data are filtered in both the forward and the reverse directions. After filtering in the forward direction, the filtered segment is reversed and then fed into the filter again (see Fig. 6.1). The resulting data segment has precisely zero-phase distortion. This can be accomplished with the help of the Matlab command “filtfilt” (Mathworks, 2006). In addition to the forward-reverse filtering, this command minimizes start-up and ending transients by matching initial conditions.

Considering all these aspects, an IIR filter was chosen for the analysis. The behavior of an IIR filter can be represented in terms of its frequency response by using the z transform (Oppenheim and Schafer, 1999). The transfer function of the IIR filter is the ratio of the z transforms of the a(k) and b(k) terms:

$$H(z) = \frac{Y(z)}{X(z)} = \frac{\sum_{k=0}^{Q} b(k) \cdot z^{-k}}{1 - \sum_{k=1}^{M} a(k) \cdot z^{-k}} , \qquad (6.1)$$

where Q and M are the orders of numerator and denominator, respectively; H(z) denotes the discrete transfer function of the filter; b(k) and a(k) are the coefficient vectors.

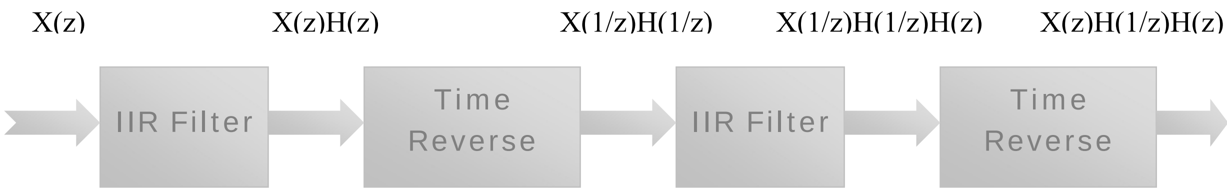


Fig. 6.1 Zero-phase digital filtering by processing the input data in both the forward and the reverse directions.

The defining relationship between the input and output variables for an IIR filter is given by the following difference equation (Parks and Burrus, 1987):

$$y(n) = \sum_{k=1}^{M} a(k) \cdot y(n-k) + \sum_{k=0}^{Q} b(k) \cdot x(n-k) \ , \qquad (6.2)$$

where x and y are the order of input and output vectors, respectively.

The second summation in eq. 6.2 is the moving average of the present plus past Q values of the input. The first term is a weighted summation of the previous M output values. For this reason, IIR filters are also called recursive filters.

Among the IIR filters, an elliptic filter was selected. Elliptic filters need a lower filter order, when compared with other IIR filters, e.g., Chebyshev or Butterworth filters. Moreover, elliptic filters allow the adjustment of several parameters (bandwidth, transition edges, pass-band deviation (ripple), and stop-band attenuation). The filter specifications were: at least 50 dB of attenuation in the stop-band, 1 dB maximum ripple in the pass-band, and band transition of 0.5 Hz. Considering the role of the different frequency bands in cognition, band-pass filters for the following frequency ranges were applied for calculation: theta (4-7.5 Hz), lower alpha (8-10 Hz), upper alpha (10-12 Hz) and gamma (36-44 Hz). Depending on the frequency band chosen, filter orders between 10 and 12 were obtained. To avoid filter instability, filters were tested to have all coefficients in the unit circle.

6.1.2 Segmentation

To extract the signal parts of interest from the continuous EEG measurement, a segmentation process was accomplished. Only the relevant parts were saved and the rest of the measurement rejected. In this way, the segmentation function contributes to the data size reduction too. After filtering, the data were segmented according to the selected stimulus. The duration of both pre- and post-stimulus intervals for segmentation was 2 s. The pre- and post-stimulus intervals were not only long enough so that the activity of interest fell completely within, but also short enough so that no overlapping between consecutive stimuli occurred. In this study, the responses of the subjects during the oddball paradigm were analyzed for both conditions, i.e., target and standard (non-target) stimuli. These responses were analyzed separately.

6.1.3 Artifact Correction

Artifacts are the main source of interferences and distort the signal components of interest. Particularly in frontal areas, artifacts caused by rapid eye movements are often present in the signal. An option to avoid these artifacts is to reject the contaminated trials. However, when studying event-related brain responses, if most of the trials are contaminated, either the measurement must take longer, with the corresponding fatigue of the subject, or too few sweeps remain for the subsequent analysis. Hence, the use of correction methods to correct or minimize artifacts seems more meaningful. Particularly, to correct ocular artifacts, an efficient sweep-based method consisting of a standardization using mean and standard deviation values was used (Ivanova et al., 2003). Because the signal is filtered previously, no trend correction is needed. The goal is to subtract the undesired components, weighted by a correlation factor. The method can be applied to a matrix of K channels and is calculated individually for each sweep j:

$$x_{k,j}^{cor} = \frac{x_{k,j} - \bar{x}_{k,j}}{\mathrm{std}(x_{k,j})} - \rho\left(x_{k,j}, EOG_{k,j}\right) \cdot \frac{EOG_{k,j} - \overline{EOG_{k,j}}}{\mathrm{std}(EOG_{k,j})} \quad , \tag{6.3}$$

where $x_{k,j}$ is the original signal of the k^{th} channel and within the j^{th} sweep, x^{cor} is the corrected signal x, $\bar{x}$ is the mean value of the signal x, std(x) represents the standard deviation of the signal x, EOG (electrooculogram) is the artifact channel, and ρ is the correlation factor between the signal and the EOG-channel.

The correlation factor is calculated according to the following formula:

$$\rho_{k,j}(n) = \frac{\sum_{n=1}^{N}\left(x_{k,j}(n)\cdot EOG_{k,j}(n)\right)}{N-1}, \tag{6.4}$$

where N is the number of points in each sweep.

In this study, ocular artifact correction was successively applied for reducing the influences of both VEOG and HEOG channels.

6.1.4 Quantification of the Non-Phase-Locked Activity

In this study, the NPLA was determined using the ERD/ERS method. Desynchronization or deactivation means that the BP is negative compared to the reference interval. Conversely, synchronization or activation indicates that the BP is positive compared to the reference interval. For the sake of simplification, the term ERD will be used for denoting the quantification parameter. After pre-processing, the signal is squared and averaged across trials separately for each experimental condition and for each subject:

$$P = \frac{1}{J}\sum_{j=1}^{J} P_j \ ; \quad P_{ref} = \frac{1}{K}\sum_{n=n_0}^{n_0+K} P_n \ , \tag{6.5}$$

where P is the BP of the test interval, averaged across J trials, and P_{ref} is the BP of the reference interval for a given frequency band, averaged over K samples.

In order to reduce the variance of the output signal, averaging within consecutive time windows of 125 ms was carried out. Then, the ERD is defined as the percentage BP change of a specific frequency band in a test interval, calculated with respect to an assigned reference interval (Pfurtscheller, 1999):

$$ERD(\%) = \frac{P - P_{ref}}{P_{ref}} \cdot 100 \, . \tag{6.6}$$

The common BP calculation contains, however, both PLA and NPLA components. In order to minimize the PLA, the IV method can be used for the quantification of ERD (Kalcher and Pfurtscheller, 1995). The filtered data is squared previous subtraction of the average across trials. The resulting IV can be considered as the induced BP (IBP) averaged across trials:

$$P = IV = \frac{1}{J-1}\sum_{j=1}^{J}\left\{x_j - \overline{x}\right\}^2 , \tag{6.7}$$

where J is the total number of trials, x_j represents the jth trial of the band-pass filtered data, $\overline{x}$ is the mean of the test interval over all trials (i.e., the PLA).

In this study, the first second was assigned as the reference interval. The algorithm was implemented using matrices including all channels for optimal computation. The calculation steps for the ERD estimation are graphically displayed in Fig. 6.2.

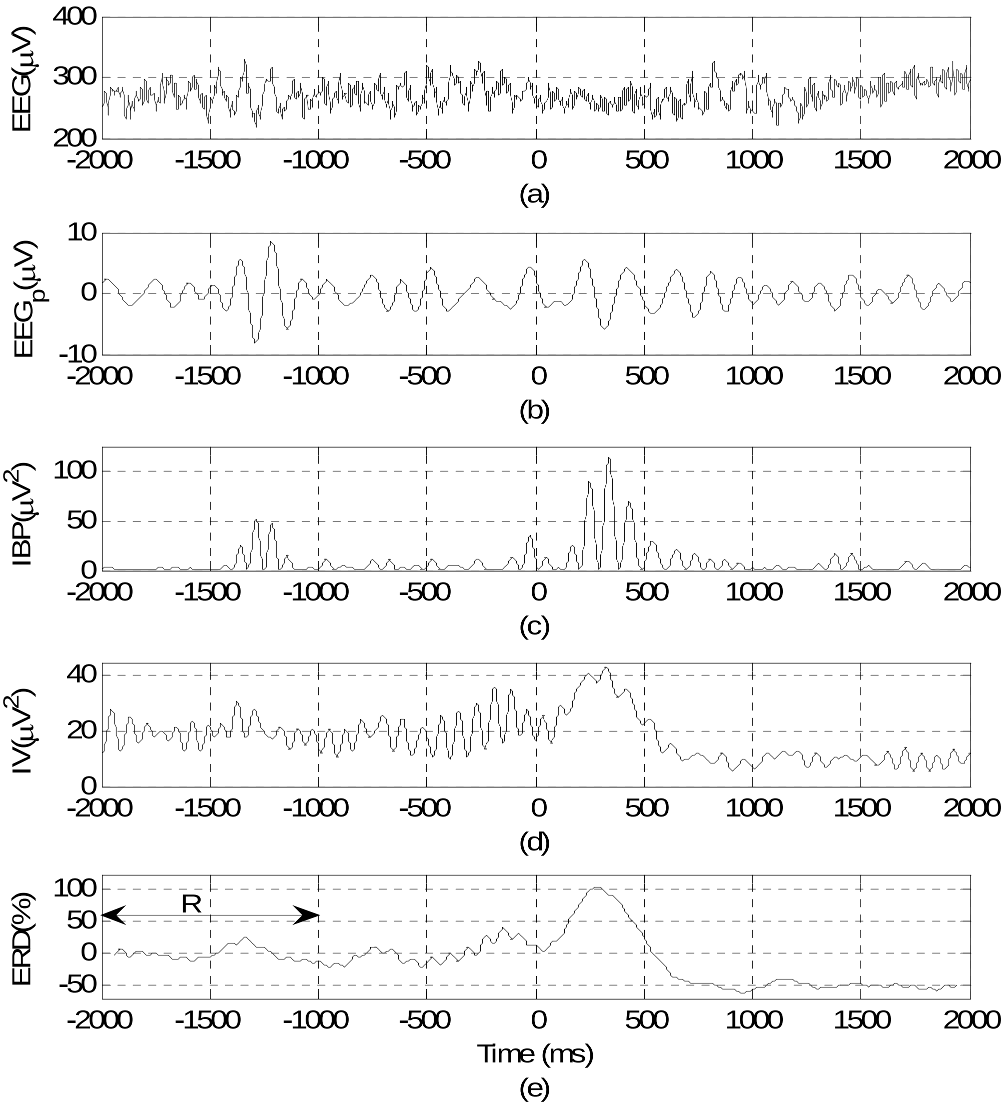


Fig. 6.2 Calculation steps of the induced ERD for the theta band (oddball task; FCZ electrode). From top to bottom: (a) raw signal (a single trial); (b) preprocessed signal (EEG$_p$); (c) IBP of the single trial; (d) IV (IBP averaged across all trials); (e) ERD. R: reference interval. “0” corresponds to the stimulus presentation.

6.1.5 Behavioral Measures

Besides the ERD time courses, the reaction times (RT) were also measured. The RT were calculated as the time difference, averaged across trials, between the stimulus presentation and the subject response (button pressing):

$$\mathrm{RT} = \frac{1}{J}\sum_{j=1}^{J} \mathrm{tr}_j - \mathrm{ts}_j \ , \tag{6.8}$$

where tr and ts are the time points for subject response and stimulus presentation, respectively; J is the number of averaged trials.

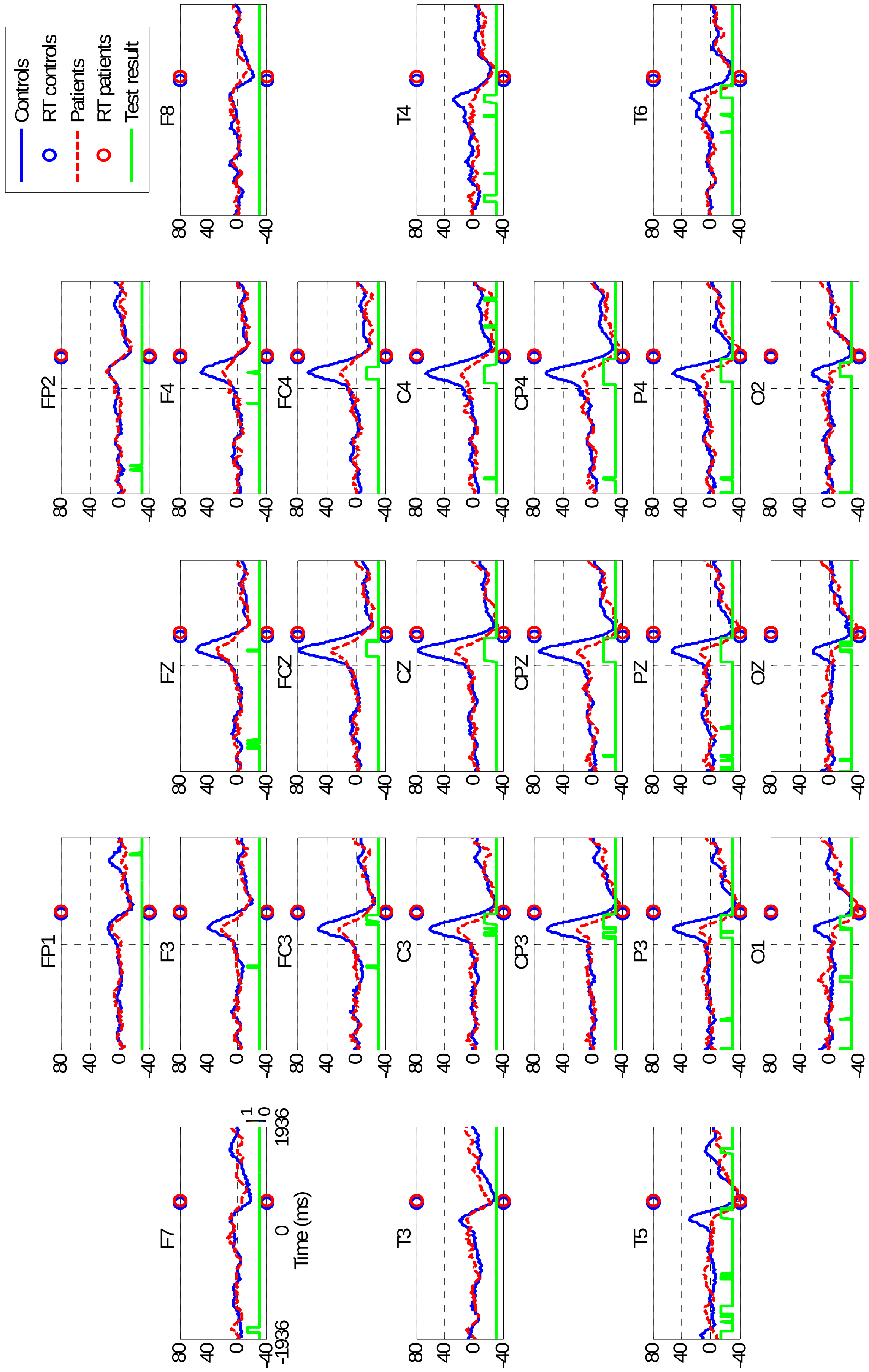
6.1.6 Results

The performances of both populations were statistically evaluated at each time point (Wilcoxon rank sum test for independent samples, $p<0.05$). Among the analyzed frequency bands, differences[1] in the ERD time courses between the control and patients group were found in the theta band for both target (Fig. 6.3a) and non-target responses (Fig. 6.3b). Healthy controls showed an increase of theta-ERS (about ~300 ms) as response to the stimulus presentation. For non-target stimuli, this post-stimulus theta increase was observed mostly at fronto-central sites, whereas for the target case, the increase was higher in amplitude and spread to almost all sites. In the epilepsy group, however, this increase was significantly smaller at many locations in both cases. Fig. 6.4 shows the mapping sequences for the two cases (target and non-target stimuli) of the control (Fig. 6.4a and 6.4c) and the patient (Fig. 6.4b and 6.d) groups. Each map represents the mean value of 152 ms.

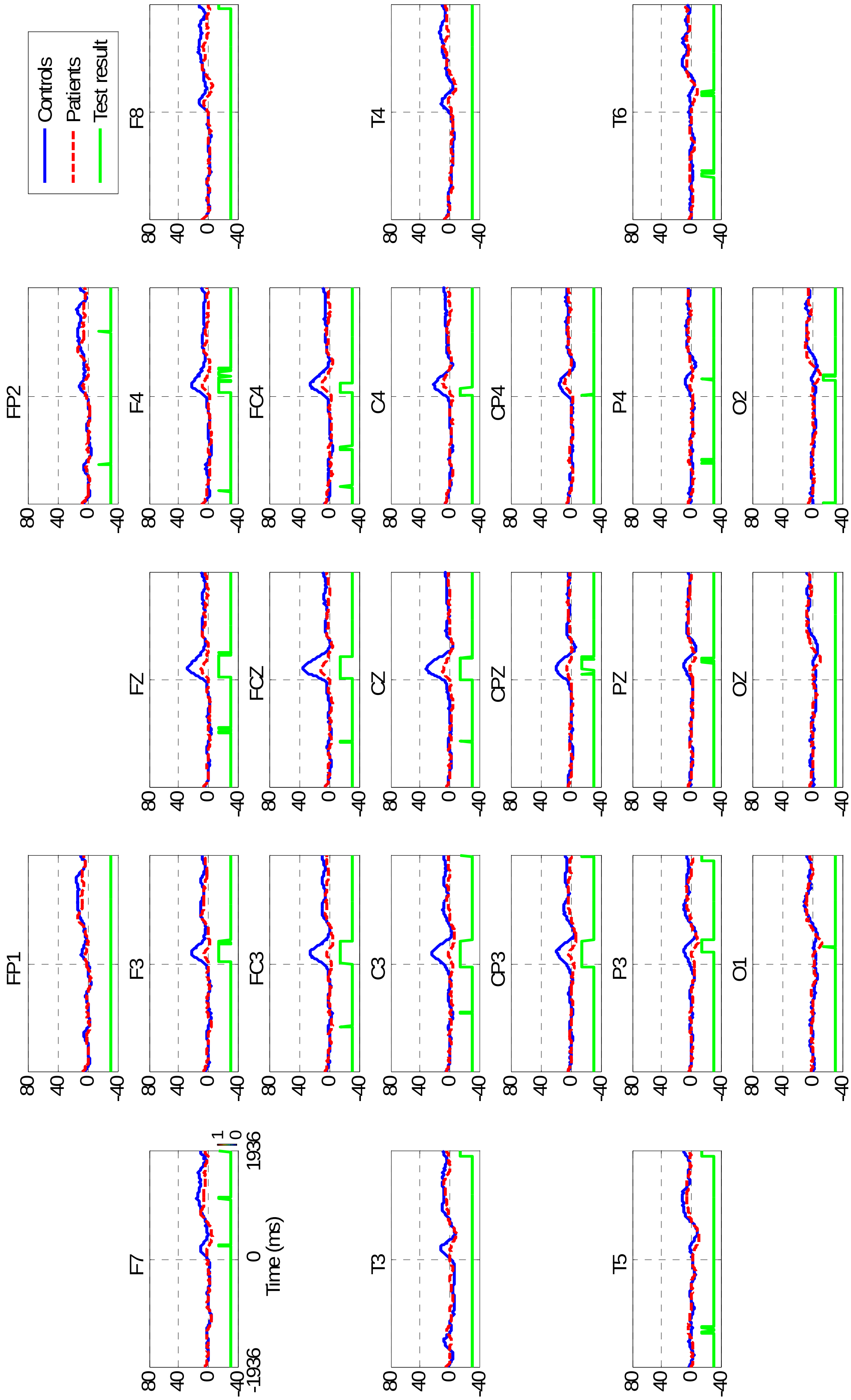
In the upper alpha band, ERD was significantly higher in the control group in parietal and occipital areas but only for the non-target case. On the other hand, no relevant differences were observed in the lower alpha and gamma ranges. The results obtained for these three frequency bands can be found in Appendix.

The RT to the target stimulus were longer in patients (618±212 ms) than in controls (562±209 ms), reflecting probably slower information processing. However, this difference was not statistically significant ($p<0.05$).

[1] Some partial results have been presented in two international conferences (Pérez et al., 2003a, 2003b).


Controls
RT controls
Patients
RT patients
Test result
FP1
FP2
F7
F3
FZ
F4
F8
FC3
FCZ
FC4
T3
C3
CZ
C4
T4
CP3
CPZ
CP4
T5
P3
PZ
P4
T6
O1
OZ
O2
ERD(%)
Time (ms)
-1936
0
1936
80
40
0
-40
1
0

(a)


Controls
Patients
Test result
FP1
FP2
F7
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FZ
F4
F8
FC3
FCZ
FC4
T3
C3
CZ
C4
T4
CP3
CPZ
CP4
T5
P3
PZ
P4
T6
O1
OZ
O2
ERD(%)
Time (ms)
-1936
0
1936
80
40
0
-40
1
0

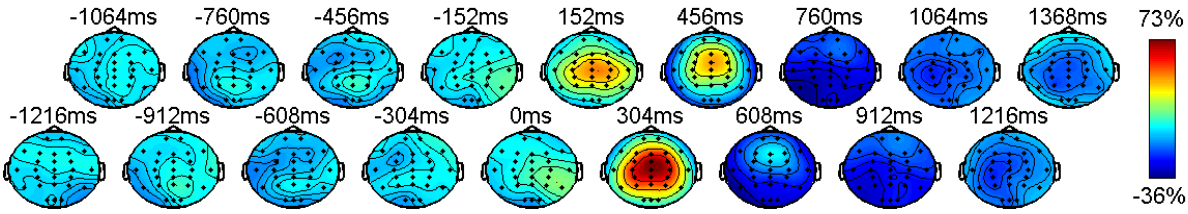
(b)

Fig. 6.3 (Pages 42-43) Comparison of ERD time courses (theta band) between the control (solid blue line) and the epilepsy groups (dashed red line) for the oddball task. The y-scale on the left (see electrode F7) indicates the ERD in percentage. The green line shows the test result at each time point. The y-scale on the right indicates the test result ("0", no significant; "1", significant). The time "0 ms" corresponds to the stimulus presentation. (a) Target case: red and blue circles represent the averaged RT of patients and controls, respectively. (b) Non-target case.

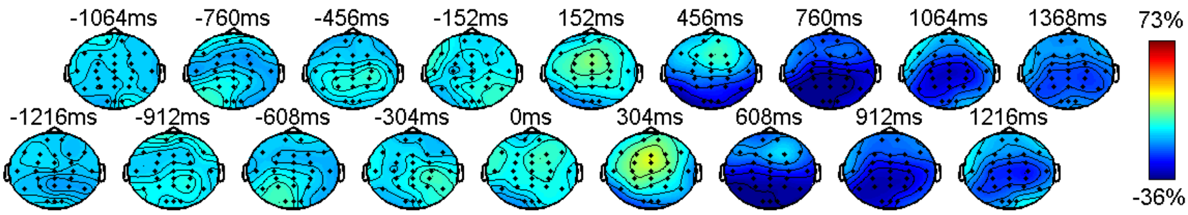
6.1.7 Discussion

In this section, the ERD time courses of both patient and control groups during the performance of an auditory oddball task were analyzed. The results showed that the theta activity observed in fronto-central positions in healthy controls is not linked to movement responses, since it was present not only in the target case, but also in the non-target case, in which no motor response was required. The results indicating a theta increase (ERS) in the control group conform to the findings of other similar studies (Yordanova and Kolev, 1998a; Doppelmayr et al., 1998a). The ERS over the frontal cortex in the post-stimulus interval is correlated with WM processes (cf. review in section 2.3). Some researchers have suggested that the encoding of new information might be reflected by theta oscillations in complex hippocampocortical feedbacks loops and have linked this activity to the WM system (Klimesch et al., 1996). This finding, together with the results obtained for the upper alpha band, could be in line with the "double dissociation" hypothesis of Klimesch (1999). To confirm this hypothesis, examination of the BP levels in the pre-stimulus interval is required.

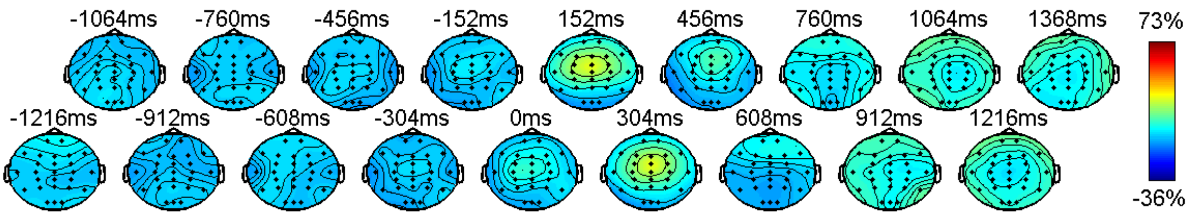
In a previous study, ERD had been shown to be a valid parameter for quantification of motor impairments in epilepsy patients. An abnormal reactivity of the central cortical "mu" and beta rhythms was reported in epilepsy patients; it was suggested to indicate that the interactions between the motor areas might be different in epileptic patients with focal motor seizures (Derambure et al., 1999). The observed differences in the theta and upper alpha bands for the patients group (Fig. 6.2-6-3) point out a possible additional dysfunction in epilepsy. The abnormal reactivity found in patients could be related to impairment during WM task performance. However, further analysis may be required for determining the differences between the target and the non-target cases.



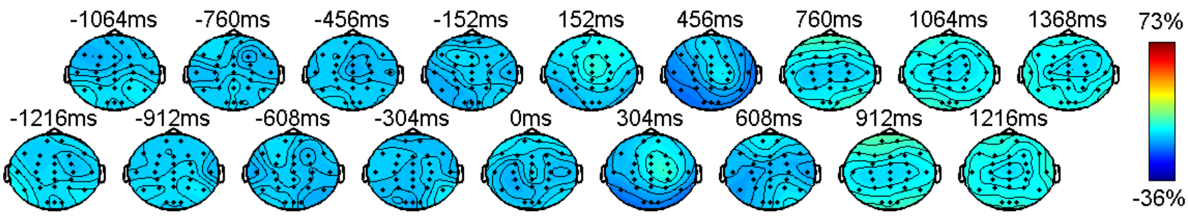
(a)



(b)



(c)



(d)

Fig. 6.4 Mapping sequences of the ERD time courses in the theta band for the oddball task. From top to bottom: target stimulus in controls (a) and patients (b); non-target stimulus in controls (c) and patients (d). "0 ms" corresponds to stimulus presentation. Red and blue values represent ERS and ERD, respectively.

Furthermore, small differences in the RT between both populations were found. These findings are in accordance with those found in other neurological diseases. For example, in a clinical study during performance of several WM tasks and based on behavioral measures

(RT, among others), Baddeley and colleagues (2001) found that Alzheimer patients were clearly impaired in contrast to normal elderly subjects, whose capacity for dividing attention was not reliably poorer than for young subjects. Similar results have been obtained in other diseases as aphasia (Starr and Barret, 1987) or cirrhosis (Sexena et al., 2001).

Summarizing, in sight of the results obtained in the previous sections, the diagnostic value of the ERD as quantitative cognitive parameter is confirmed. This choice was motivated by several factors: first, the ERD method based on the IV approach was able to extract and quantify the NPLA independently from the PLA; second, the ERD feature was able to distinguish the epilepsy group from the healthy controls during cognitive task performance. Moreover, its condition of relative power estimation, by means of normalizing values, helps to reduce the effect of the inter-individual variability of absolute spectral power values. This makes comparative analyses possible. Finally, due to its ease of calculation, ERD is expected to be suitable for online calculation.

6.2 Topographical Distribution of Band Power at Resting State

In the previous section, EEG differences in the post-stimulus interval were found between both populations during cognitive task performance. In order to examine to what extent the absolute BP (‘tonic’ activity) plays an important role, the topographical distribution of EEG frequency bands at open- and closed-eyes resting conditions was evaluated. From each subject, one minute of data was taken per condition.

6.2.1 Methods

The EEG was analyzed by calculation of the BP in the same four EEG bands as in section 6.1 (theta, lower alpha, upper alpha and gamma) after ocular artifact correction. In addition to BP values, the ratio closed-to-open eyes was calculated. The ratio provides information about the relative changes when passing from one condition to the other. The topographical distributions of both populations were statistically investigated (Wilcoxon rank sum test for independent samples, $p<0.05$). In order to prevent the presence of outliers and to keep the required continuity of the distribution, the censoring type II (the highest and lowest values were excluded; Sachs, 1992) was applied to each sample. For mapping, median values were used because of the skewness of the distribution.

6.2.2 Results

The results[2] showed differences between the both populations in three of the frequency bands analyzed (Fig. 6.5). In the theta band (4-7.5 Hz), the BP in patients was significantly higher at all electrodes for both conditions. In the lower alpha range (8-10 Hz), significant differences were found only in the open-eyes condition. These differences were located at all electrode positions. For the upper alpha band, differences at the electrodes F4, F8, FC4, T3 and T5, for the open-eyes condition, and at Pz, for the closed-eyes condition, were observed. In the gamma band, no significant differences were found in any of the conditions.

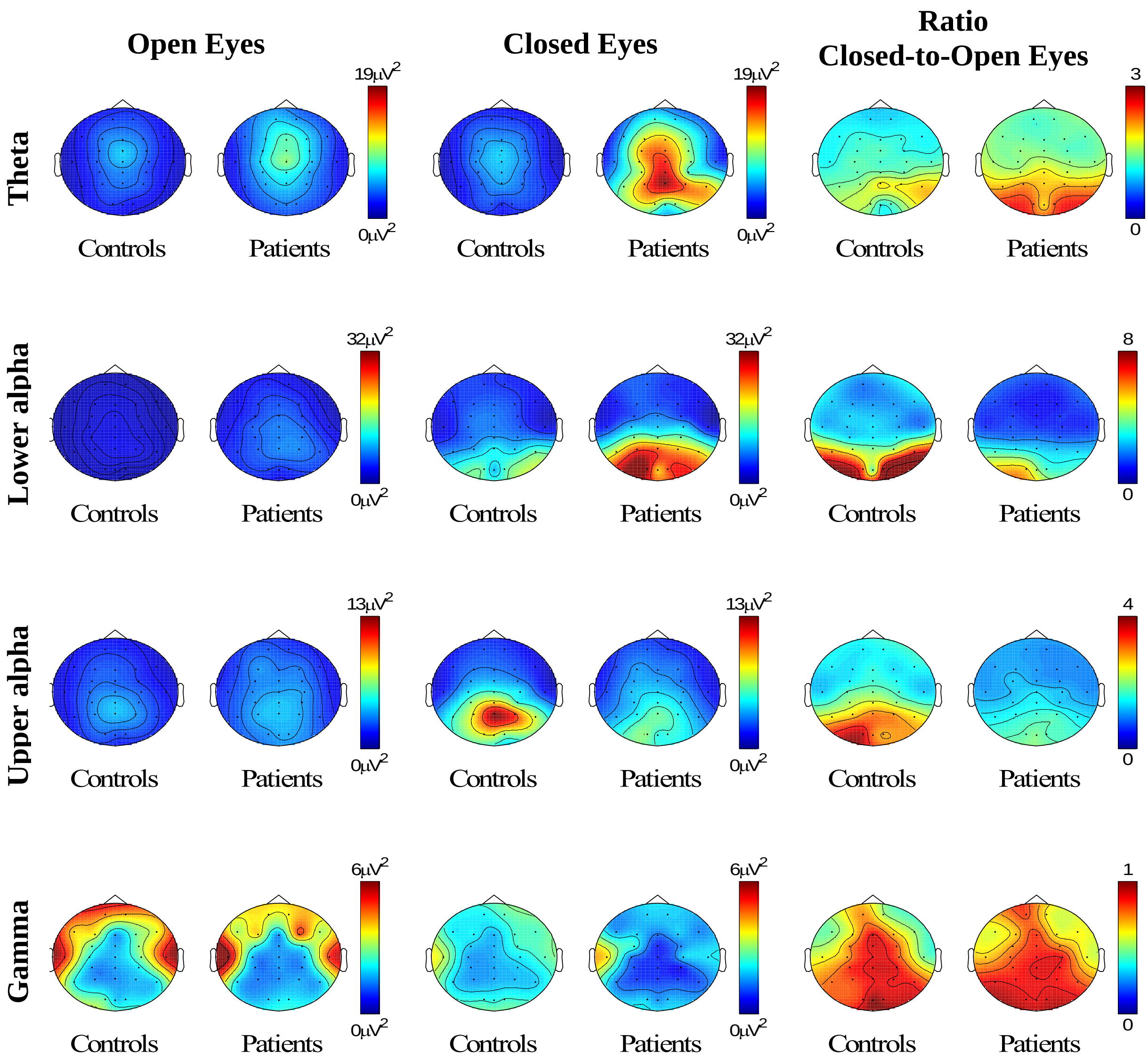


Fig. 6.5 BP-mappings from controls and epilepsy patients at resting state for the theta, lower alpha, upper alpha, and gamma bands. From left to right: open-eyes condition, closed-eyes condition, and ratio closed-to-open eyes.

[2] Some partial results have been presented in an international conference (Pérez et al., 2005).

Regarding the ratio closed-to-open eyes, significant differences were seen only in the alpha ranges. In the lower alpha band, the differences were observed at the electrodes FP2, F3, F4, F7, F8, Fz, FCz, FC3, FC4, Cz, C3, C4 and CP4. In the upper alpha range, the differences were located at all electrodes except F3, T3 and T4 (Fig. 6.5).

6.2.3 Discussion

The analysis of the BP levels during resting state yielded interesting results. The absolute theta BP was higher in the epilepsy than in the control group, particularly at fronto-central electrodes. Doppelmayr et al. (1998a) have suggested a hypothesis based on a double dissociation ('tonic' vs. 'phasic', and theta vs. alpha; see section 2.3) for explaining the relationship between memory performance and brain activity. Task performance depends not only on the activity in the post-stimulus interval but also on the absolute BP in the pre-stimulus interval. Based on this hypothesis, the lower theta-ERS found in patients during an oddball task (see section 6.1.6) could be explained at least in part through the increased theta power at resting state. Regarding the alpha ranges, the results obtained are not conclusive. The expected differences in the upper alpha band in parietal areas were statistically confirmed but only for the closed-eyes condition. The results of both ranges differ from each other. The differences observed in the alpha ranges shall be further investigated in order to determine their physiological significance.

6.3 Comparison of Online Algorithms for the Event-Related De-/Synchronization

The results of the previous sections suggest that event-induced brain activity, as quantified by the ERD method, can be a valid parameter for future neurofeedback purposes. However, the ERD can be computed by means of different algorithms of very different nature. To choose the optimal algorithm for the online quantification of the ERD, the dynamic properties of four algorithms for ERD calculation were compared.

6.3.1 Synthetic Data and Materials

The simulated data were generated with a sampling rate of 128 Hz. The test signal consisted in three sinus waves of 6, 10 and 20 Hz, respectively, and Gaussian noise (SNR = 20 dB). These frequencies were selected as exemplarily values of cognitive relevant frequency bands. The test signal contained a step function modulated in amplitude, so that within the interval 0-10 s the amplitude equaled 5 μV; within 10-20 s the amplitude was 10 μV; within 20-30 s the amplitude returned to 5 μV; and, then, the amplitude was set to 0 μV (see Fig. 6.6).

The algorithms were implemented in Matlab-Simulink and a Pentium III 1 GHz with 384 MB RAM was used for computation.

6.3.2 Online Quantification of the Event-Related De-/Synchronization

Based on the literature reviewed in section 3.2, four algorithms were chosen to study their possible use for future neurofeedback purposes, two in the time domain and two in the frequency domain. Because of the online condition of the process and, unlike the offline version that was segment-based, ERD is calculated in real time for each time point:

$$ERD(t) = \frac{P(t) - P_{ref}}{P_{ref}} \cdot 100 \ , \tag{6.9}$$

where P(t) is the BP in the test interval at the t^{th} time point, and P_{ref} is the BP in the reference interval for a given frequency band.

The first algorithm (from now onward, the squaring-filtering (SF) algorithm) is based on the calculation of the BP by squaring and additional smoothing by low-pass FIR-filtering of the resulting signal. The instantaneous power is calculated as follows (Cohen, 1995):

$$P(t) = x(t)^2 , \tag{6.10}$$

where x(t) is the filtered signal, and P(t) is the BP in the test interval at the t^{th} time point.

The advantage of this algorithm is that no transformation in the frequency domain is needed and, therefore, the computational time and time delay are minimal. However, the use of the smoothing filter reduces the advantages of saving time during the power calculation.

The second algorithm implemented is based on an ARE of the mean and the second statistical moment (Grieszbach and Schack, 1991; Schack and Krause, 1995):

$$M(t) = M(t-1) + c_1 \cdot (x(t) - M(t-1)), \tag{6.11}$$

where M(t) is the adaptive-recursive mean, x(t) is the filtered signal, and c_1 is the adaptation constant for the mean.

The power estimation is obtained by calculating the adaptive-recursive second statistical moment (i.e., the variance but using a divisor of n rather than n-1) of the previously mean-free signal (the adaptive-recursive mean value is subtracted):

$$x'(t) = x(t) - M(t), \tag{6.12}$$

$$P(t) = E(t) = E(t-1) + c_2 \cdot \left(x'(t)^2 - E(t-1)\right), \tag{6.13}$$

where E(t) is the second statistical moment, and c_2 is the adaptation constant for the variance.

A different way to calculate the BP is by means of the envelope curve. The calculation of the envelope can be obtained with help of the Hilbert transform. In the time domain, the Hilbert transform is defined as the convolution product:

$$\mathrm{h}(\mathrm{t}) = \mathrm{x}(\mathrm{t}) * \frac{1}{\pi \cdot \mathrm{t}}, \tag{6.14}$$

where x(t) is the filtered time series, and h(t) is the Hilbert transform of the time series x(t).

In the frequency domain, the Hilbert transform can be computed for successive segments or epochs (of length N) as follows (Clochon et al., 1996):

$$h(t) = F^{-1}\{F\{x(t) \cdot (-i) \cdot sign(f)\}\}, \tag{6.15}$$

where F is the Fourier-operator, i is the imagery root, and f is the frequency.

The original (real) signal x(t) is complemented with the imagery h(t), obtained from the Hilbert transform. The power is then calculated as the squared modulus of the envelope of the original signal:

$$P(t) = |y(t)|^2 = x^2(t) + h^2(t). \tag{6.16}$$

In order to obtain the same time resolution as with the other algorithms, a sliding window was applied. In this way, only the central point of the analysis window is yielded. Hence, the output signal will be N/2 points delayed. The use of the sliding window has the advantage that the border effects, due to the FT, are reduced and no smoothing filter is needed. On the other hand, the calculation of the Hilbert transform for every time point can increase the computational time considerably.

Alternatively, the band-pass filtering before the Hilbert transform can be done via multiplication with a transfer function (window) in the frequency domain. However, this second approach provides poorer results. A detailed comparison of different versions of the Hilbert algorithm can be found in (Schilz, 2004).

The stationarity problem of the FT, due to the non-stationary property of the EEG signal, can be avoided by using the ADFT proposed by Helbig (Helbig et al., 2002). This approach is based on an adaptive-recursive mean estimation:

$$X(n,t) = \frac{X(n,t-1)}{W^n} + c \cdot \left(x(t) \cdot W^{n \cdot (N-1)} - \frac{X(n,t-1)}{W^n} \right), \tag{6.17}$$

$$W = e^{\frac{-i2\pi}{N}} \quad \text{n = 0, 1, ..., N-1}, \tag{6.18}$$

where c is the adaptation constant; W is the unit root; n is the index of the analysis window; and N is the number of points in the analysis window.

To obtain comparable results, the same filters (band-pass: Butterworth 6^{th} order and 2-Hz-wide pass-band; smoothing filter: 32-point) were used for all the algorithms. Only the Hilbert approach did not need any smoothing filter after the BP calculation. For the frequency-based algorithms, the length of the analysis window was 128 samples. Therefore, the frequency resolution was 1 Hz. The interval from 4-8 s was selected as the reference interval, so that power estimations were normalized to this segment.

6.3.3 Results of the Comparative Study

Fig. 6.6 shows the results[3] of the four implemented algorithms for comparison of quality after calculation of the ERD upon the simulated signal described in the section 6.3.1. Although the responses of all four algorithms are close to the ideal behavior, several differences were found with regard to the dynamic properties.

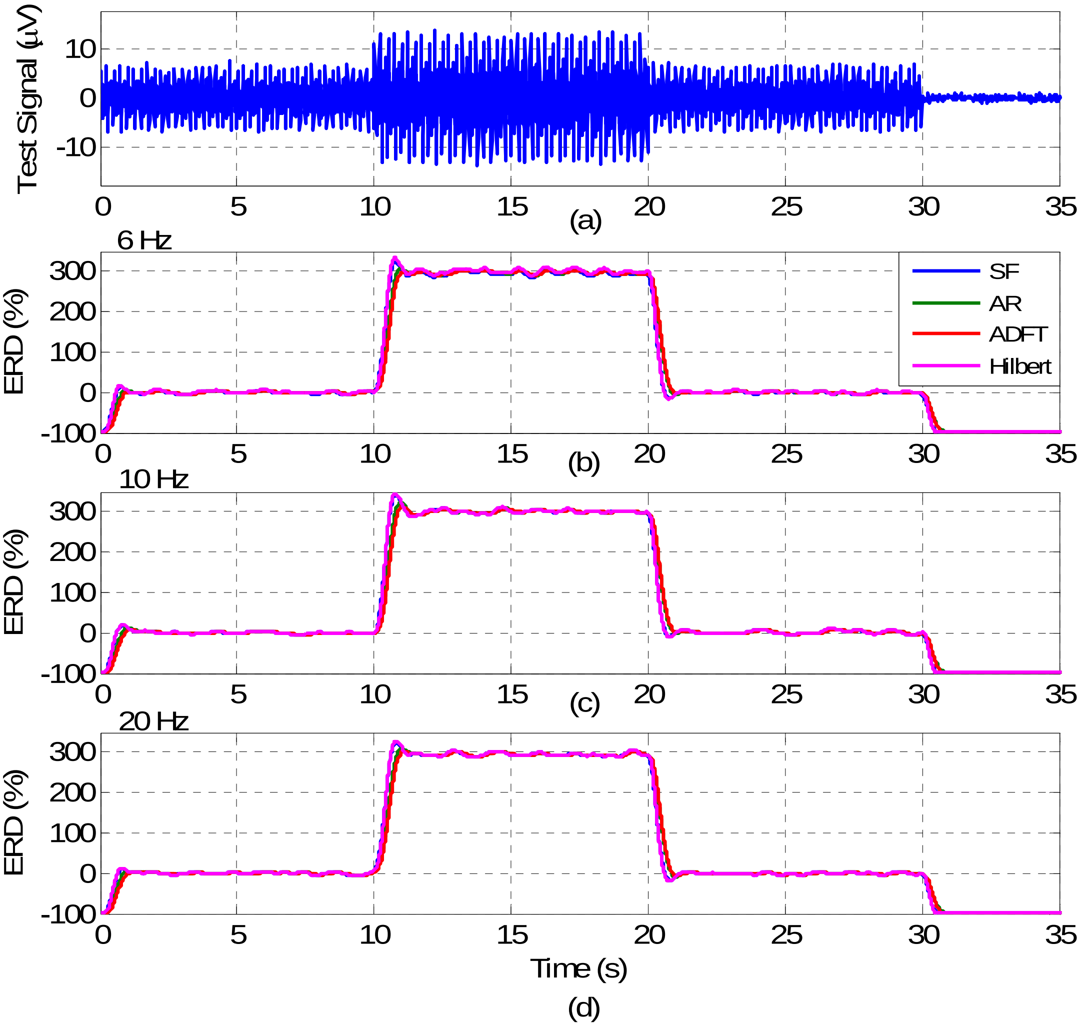


Fig. 6.6 Results of the ERD analysis on simulated data for the SF- (blue), ARE- (green), ADFT- (red) and Hilbert-based (magenta) ERD-algorithms. (a) Simulated test signal. Second to fourth rows: Estimated ERD time courses for the frequencies 6 (b), 10 (c) and 20 Hz (d), respectively.

[3] Some partial results have been published in (Pérez et al., 2004).

The results depend on the adjustment of the variables in a great manner. The adaptation constants as well as the order of the smoothing filters were set to obtain comparable performances (see Table 6.1). A detailed analysis of the value adjustment and optimization of the adaptation constants and filter orders can be found in (Schilz, 2004). Higher values of the former would increase the variance, over- and undershoot values but would decrease the rise and fall times. An opposite effect holds true for the smoothing filters: the higher the order is, the lower the variance but the longer the time delay is. Regarding the dynamic properties, the SF- and Hilbert-based algorithms have the shortest rise and fall times. However, their over- and undershoot values are higher when compared with the adaptive algorithms. On the other side, the ADFT and the Hilbert approach have the lowest and highest variance values in all frequencies, respectively.

Table 6.1 Parameter comparison of online ERD-algorithms for the frequencies 6, 10 and 20 Hz.

	SF (Smoothing = 32)			**ARE** (Smoothing = 32; c_1=0.05; c_2=0.05)			**Hilbert approach** (nfft = 128)			**ADFT** (Smoothing = 32; nfft = 128; c=0.04)		
	6 Hz	10 Hz	20 Hz	6 Hz	10 Hz	20 Hz	6 Hz	10 Hz	20 Hz	6 Hz	10 Hz	20 Hz
Rise time (in ms)	477	445	461	617	594	617	461	445	469	664	641	672
Overshoot (rise)	24	42	26	8	24	11	34	47	28	0	13	3
Variance 1*	26	16	12	14	11	10	32	19	10	12	9	9
Fall time (in ms)	406	398	406	563	563	555	398	398	398	578	586	578
Undershoot (fall)	-16	-9	-18	-6	-1	-9	-17	-11	-20	-3	-0	-6
Variance 2*	8	18	5	5	16	4	9	19	6	4	15	3

* Variance in the intervals 13-18 s (Variance 1) and 23-28 s (Variance 2).

Concerning the computational load, the SF algorithm is the fastest algorithm and needs only 27 μs for each point calculation, followed by the ARE with 31 μs, and the ADFT-algorithm with 33 μs. The Hilbert Transform-based algorithm is the slowest with 66 μs. These values confirm the online suitability of all the ERD-algorithms analyzed. However, they are not conclusive and depend on the Matlab-libraries used. Thus, additional comparison is needed in order to optimize these times.

6.3.4 Discussion

For the purpose of investigating ERD as a possible quantitative parameter for future online applications, it is not sufficient that this feature is able to distinguish between the epilepsy and control groups. Therefore, the dynamic properties and the online suitability of the ERD method were examined by comparing several ERD-algorithms.

ERD is a feature based on the course of the BP level within a narrow frequency band over time and, thus, band-pass filtering is needed. Because no ideal filter exists, a compromise between algorithm velocity, phase shift and accuracy of the results was taken. Velocity is a critical parameter since the system must work in real time. The phase must be as linear as possible for avoiding waveform distortion. The pass-band edges must be accurate enough for extracting exactly the activity of the desired frequency band. The use of a FIR filter was refused because of the higher order needed to fulfill the specifications and its consequent slow response for online data processing: To obtain the same filter properties as the IIR filter described in section 6.1.1, an FIR filter of order 424 would be needed (equiripple filter). When working online, the double filtering explained in section 6.1.1 cannot be carried out because of its segment-based algorithm condition. Another option could be to correct the phase shift by means of filters for phase compensation. Here an all-pass filter can be used. This procedure is also called equalization. However, the adjustment of compensator filters is difficult and depends of many parameters.

Based on the computational times obtained, it can be concluded that all the algorithms analyzed can be used for online purposes. These times are sufficiently low even if more channels are measured at the same time, e.g., VEOG channels or neighbor channels for calculation of bipolar or source derivation montages. However, depending on the algorithm, the quality of the resulting signal differed slightly. For the first time, the ADFT was used for the calculation of ERD. As compared with other frequency-based algorithms, the ADFT offers a point-by-point estimation. The ADFT and ARE, thanks to its adaptive recursive condition, yielded low over- and undershoot values.

In the present case, based on the results obtained and its parameter-free condition, the SF-based approach was selected for future neurofeedback applications. However, depending on both of the kind of signal and the application, further comparative analyses may be required for choosing the optimal algorithm in each case.

In conclusion, the findings of this chapter support the possible exploitation of parameters based on ERD for diagnostic and therapy evaluation purposes in a cognitive field. The algorithms analyzed did not contemplate the distinction between evoked and induced activity yet, since the aim of the comparative study was to find the best ERD-algorithm for the purposes of this work. The next step will be to include this parameter in an ERD-based methodology, where this distinction shall be considered and evaluated, among other aspects.

Chapter 7

Methodology for the Online Extraction and Quantification of Cognitive-Induced Brain Activity

Considering both of the psychophysiological significance of induced brain activity and the necessity for its online processing, a methodology for its online extraction and quantification is proposed. In order to increase applicability, the methodology is functionally organized in two main stages, namely initialization and computation, and two subsidiary sub-processes or pre-stages, namely preprocessing and decision making. The details and modus operandi of each stage are elucidated next. Afterwards, several aspects of the proposed methodology are evaluated based on cognitive studies.

7.1 Subsidiary Processes or Pre-Stages

7.1.1 Preprocessing

The SNR of the EEG signal in single-trial is often too low for achieving sufficient signal quality. Moreover, since we focus on activity within the theta band over frontal areas, EEG artifacts such as those caused by ocular movements are present on the signal. For this reason, measurements must be taken in order to obtain a reliable extraction of the desired features. These measurements include: montage selection, for improving the SNR; filtering, for extracting the specified data features of interest; and artifact correction, for minimizing the influence of undesired sources. The next subsections describe the procedures integrated in the preprocessing step.

7.1.1.1 Source Derivation

In order to improve the estimation quality and to get reference-free channels, the source derivation method proposed by Hjorth based on the Laplacian operator can be used (Hjorth, 1980; Thickbroom et al., 1984). This montage is calculated by subtracting the weighted average of the potentials at the four (Hjorth 5-point approach) or eight (Hjorth 9-point) nearest neighbors from the potential value at the selected electrode (Fig. 7.1):

$$V_i^T = V_i - \sum_{j=1}^{J} V_j \cdot D_{ij} \, , \tag{7.1}$$

where V_i is the measured potential at the ith electrode, V_i^T is the transformed potential at the ith electrode, Vj represents the potential at the jth surrounding neighbor, and

$$D_{ij} = \frac{\frac{1}{d_{ij}}}{\sum_{\substack{j=1 \\ i \neq j}}^{G} \frac{1}{d_{ij}}} \, , \tag{7.2}$$

where d_{ij} is the distance from the ith to the jth electrode, and G the number of the surrounding electrodes.

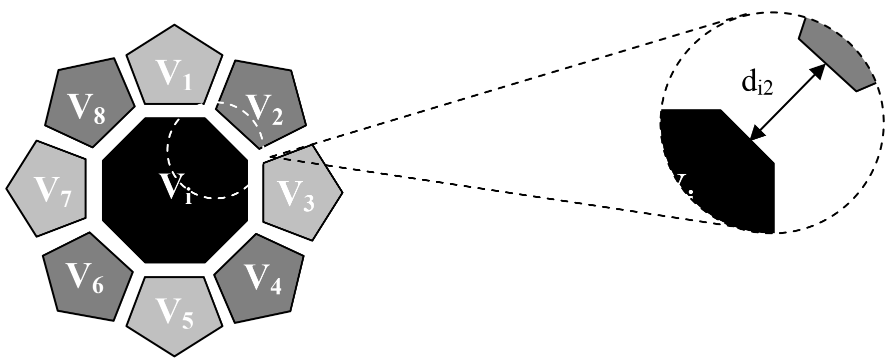


Fig. 7.1 Graphical representation of the source derivation technique. The transformed potential results from a linear combination of the surrounding electrodes.

In the present case, source derivation improves the SNR and, compared with unipolar and bipolar montages, reduces influences of components originating at the references electrodes and outside the observed sources, respectively (Hjorth, 1980). Nevertheless, this montage can cause some disadvantages. If the activity in a determined electrode spread out to the neighbor ones, this could distort the estimation. Depending of the frequency band, a possible spatial phase shift could appear and must be taken into consideration. Another drawback is that the number of available electrodes is reduced, since the outer electrodes are removed from the montage.

7.1.1.2 Filtering

After montage selection, band-pass filtering is applied to extract the frequency band of interest (Fig. 7.2). Considering the relationship between induced brain activity and memory processes, the filter is designed to filter the activity of the theta band (4-7.5 Hz).

The elliptic IIR filter used for the offline analysis was discarded because of its higher non-linear phase property and the impossibility to apply the zero-phase digital filtering technique used in section 6.1.1. For online purposes, a Butterworth filter was used instead. Among the IIR filters, the Butterworth provides the best phase relationship.

7.1.1.3 Artifact Correction

As exposed in section 6.1.3, artifacts due to ocular movements are present in EEG measurements, especially at frontal areas, and their contaminating effect must be minimized. However, most of the methods used for offline studies are not suitable for real time systems. Instead, online artifact correction methods (Kisser, 2002) must be used. Furthermore, additional measures can be introduced for specific artifact minimization, e.g., setting of limits for EEG-channel amplitude.

7.1.2 Decision Making

Previous studies have pointed out the important role of the pre-stimulus interval for the post-stimulus activity elicited by the event, meaning that a stable absence or presence of an EEG rhythm is a prerequisite for eliciting or attenuating it, respectively (Doppelmayr et al., 1998a; Blankertz et al., 2003; Fingelkurts et al., 2002). In the same way, the estimation of the ERP pattern within the initialization phase (see section 7.2) can be improved if a selective stimulation procedure is applied (Başar et al., 1998). Taking these as basis, a second pre-stage called decision making was included. In this sub-process, the condition(s) for the release of the next trial is(are) determined: after the corresponding preprocessing, trials will be released only when the BP within the last second satisfies a task constraint (Fig. 7.2). The BP level during resting state plus the standard deviation (STD) was chosen as the task constraint. The decision-making module is introduced before both the initialization and the computation stages.

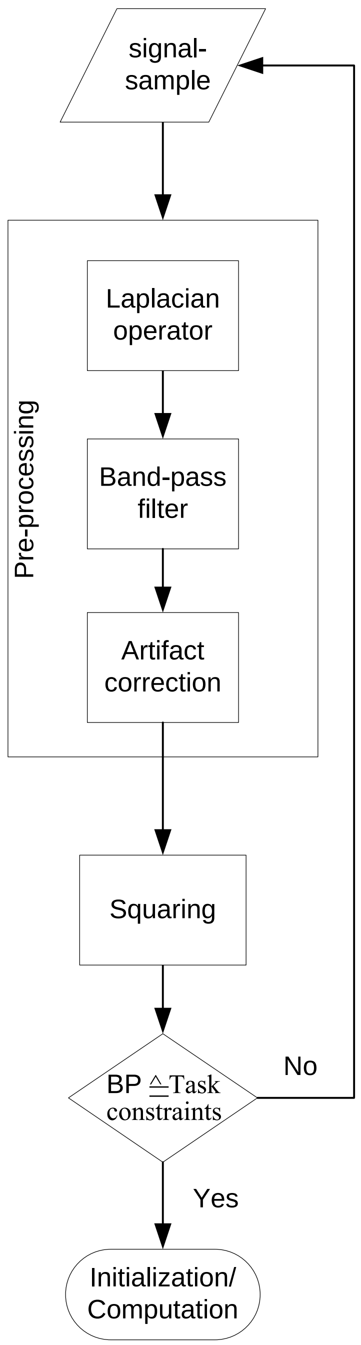


Fig. 7.2 Block diagram of the decision-making module. After EEG preprocessing, the condition for releasing the trial is evaluated. When the condition is fulfilled, then the procedure continues with the next stage (initialization or computation).

7.2 Initialization Stage

In the initialization stage, the ERP pattern in the specific frequency band is estimated using the selective stimulation method cited above. Based on the success of this estimation, the conditions for the further development of the process are evaluated.

7.2.1 Estimation of the Evoked Activity

Focusing on the event-induced theta activity over frontal areas in this study, the P300 was taken as a reference ERP for the analysis. The P300 is the most prominent cognitive ERP peak with high delta but also theta band component and, consequently, with a great influence in this band (Yordanova and Kolev, 1998b). An ERP-pattern is calculated for each type of trigger and condition by averaging the signal across trials. As the measure of the signal quality, the STD is calculated at each time point across the trials acquired up to time. The procedure is repeated until the STD at each time point of the trial is below a given threshold. A minimum of 15 trials was set. The adjustment of the threshold was subject-specific and set equal to the STD value calculated during the resting state. It must be noted that, due to intra-individual variability of the ERP, the ERP pattern must be re-estimated for each new measurements session. Therefore, a possible use of databases containing subject-specific ERP features is excluded.

7.2.2 Cancel Condition

When the threshold condition is fulfilled, each trial as well as the ERP pattern are evaluated to confirm pattern stability. If the latency and/or amplitude variability is high, or the P300 is absent, then computation shall be completed without its subtraction. On the contrary, if the ERP pattern is positively evaluated, it is stored for the computation stage and the initialization stage finishes (Fig. 7.3). Conversely, if the threshold is not reached in a fixed number of trials, the suitability of the process for the subject must be evaluated, i.e., examination of EEG features (e.g., stability, power level) and/or readjustment of parameters must be carried out. In case of positive evaluation, parameter computation shall be performed without subtraction of the estimated ERP. Otherwise, the process is canceled (Fig. 7.3).

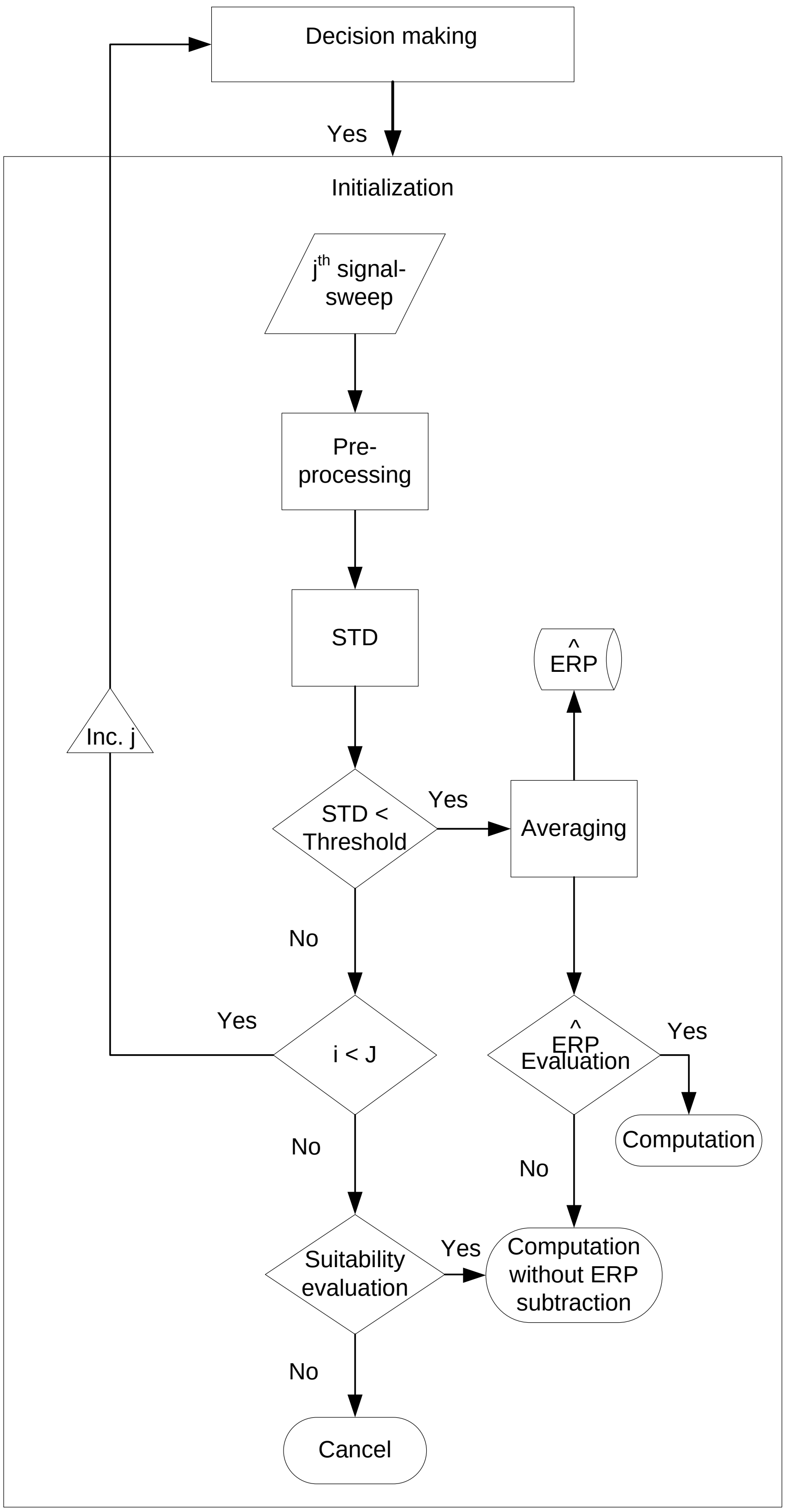


Fig. 7.3 Block diagram of the initialization stage. The $E\hat{R}P$ in the selected frequency band is calculated only if the STD is below a given threshold during the first J trials. Otherwise, the suitability of the process for the subject is evaluated. In case of a positive evaluation, no $E\hat{R}P$ is stored and the procedure is continued without $E\hat{R}P$ subtraction.

7.3 Computation Stage

After initialization, the computation stage starts. In this stage, the induced brain activity is quantified after the trial is released by the decision-making stage. Fig. 7.4 shows the steps sequence of this stage.

7.3.1 Event-Related De-/Synchronization

For the quantification of the cognitive-induced brain activity, the SF algorithm for the ERD calculation method is employed, according to the results of the previous comparative study. The resulting signal is the one to be utilized for the feedback control:

$$ERD_n(\%) = \frac{P_n - P_{ref}}{P_{ref}} \cdot 100\,, \tag{7.3}$$

where P_n is the BP at the n^{th} point of the trial, and P_{ref} is the BP in the reference interval for a given frequency band.

As exposed in chapter 6, the common BP calculation contains both evoked and induced components. Therefore, the evoked activity is subtracted via point-by-point operation, if the ERP pattern was successfully estimated in the initialization stage. The estimated IBP is assigned as the square of the difference:

$$P_n = \left| x_n - \bar{x}_{n_{INIT}} \right|^2, \tag{7.4}$$

where P_n is the estimated IBP at the n^{th} point of the current trial, and $\bar{x}_{n_{INIT}}$ is the mean at the n^{th} point averaged over the trials calculated in the initialization stage, i.e. $\mathrm{E\hat{R}P}\,(n)$.

Special attention must be paid to the point-by-point subtraction, which must start synchronous to the stimulus presentation. Fig. 7.5 shows an example of the calculation steps for obtaining the induced brain activity.

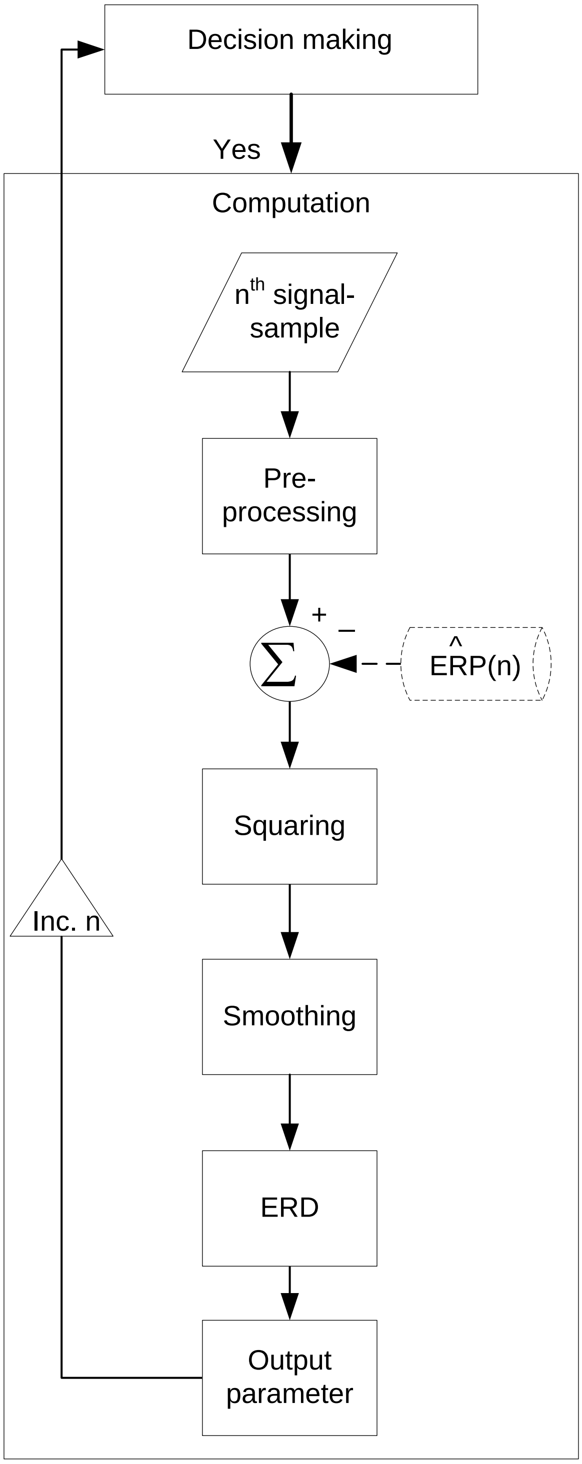


Fig. 7.4 Block diagram of the computation stage. After the sweep is released in the decision-making stage, ERD is calculated either without $\hat{ERP}$ subtraction or, if it was successfully estimated in the initialization stage, with its subtraction.

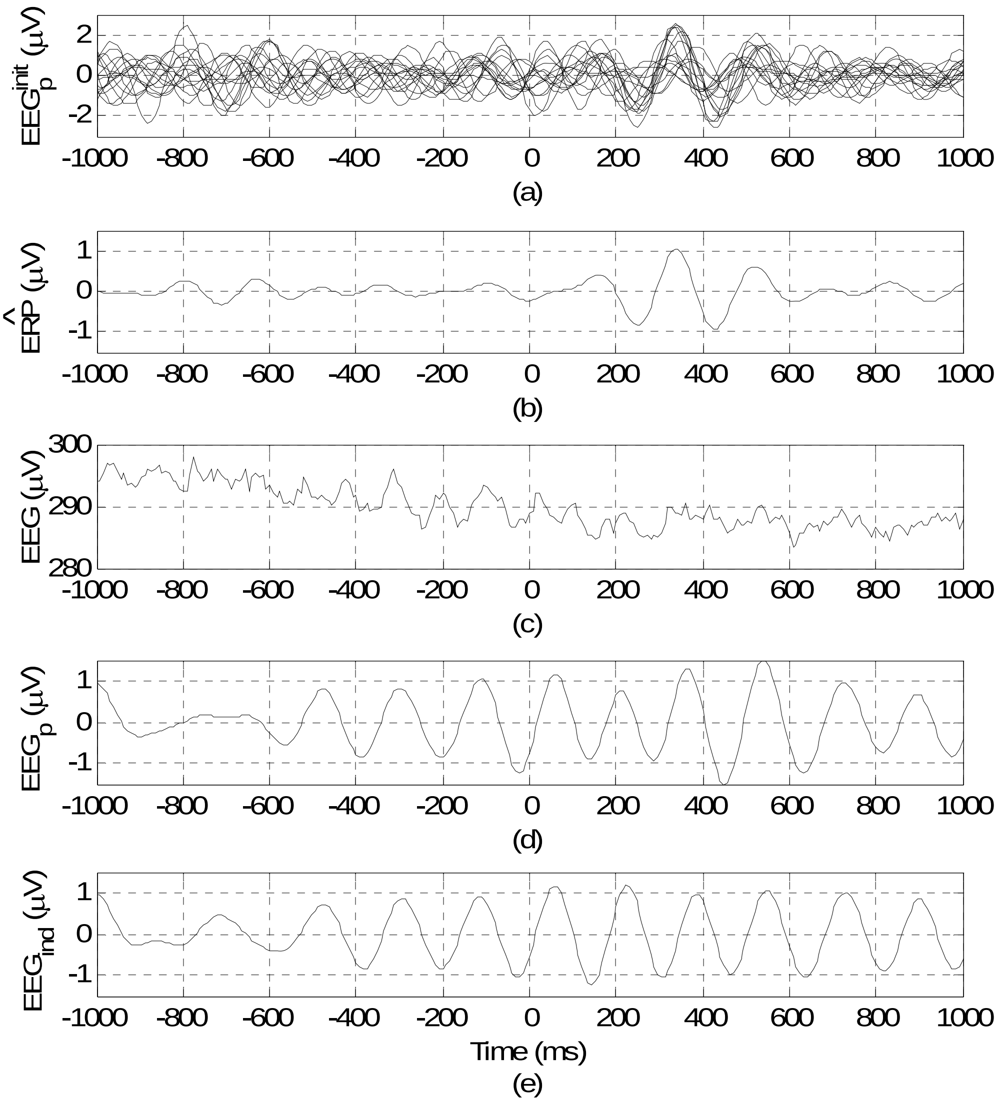


Fig. 7.5 Calculation steps of the induced EEG activity for the theta band (oddball task; FCZ electrode). From top to bottom: (a) EEG_p^{init} denotes all the pre-processed trials of the initialization stage used for ERP estimation; (b) $\hat{ERP}$ is the estimated ERP, obtained after ensemble averaging of EEG_p^{init}; (c) EEG represents the raw EEG signal (single trial) to be analyzed; (d) EEG_p denotes the preprocessed EEG trial, including both evoked and induced activities; (e) and EEG_{ind} is the induced EEG activity, after the subtraction of $\hat{ERP}$. "0" corresponds to the stimulus presentation.

7.3.2 Setting the Reference Interval

As defined in the section 3.2.1, ERD represents the BP at each time point referred to an inactive reference interval. Therefore, the selection of the reference interval is important for the final result. This interval can be determined based on different criteria. A possibility is to set as reference interval a data segment recorded previously to the computation stage, e.g. within the initialization stage, where subjects are sitting and relaxed with their sight fixed on the monitor, where later the control parameter will be presented. The averaged BP calculated over this resting state interval (e.g., during 1 minute) would be the P_{ref}. During the resting state, no ERP is present, so the BP calculated in this interval equals the IBP. The advantage of this approach is that recording during a long time period (e.g. 1 min), the influence of artifacts or short brain activation are minimized. However, the longer the session is, the more tired the subject becomes. This can lead to changes in the potential values of the subject during the session and, thus, to inaccurate ERD values.

Another possibility is to re-calculate the reference interval in the short pause between trials, so that the reference interval always refers to the current potential values. This approach has the disadvantage that, if an artifact occurs, its influence increases for short intervals. Additionally, to ensure brain inactivity during the selected interval becomes difficult because the conditioning process is still going on.

A better solution is to consider a combination of both approaches: before the computation stage begins, the reference interval is determined; and, after each trial, the reference interval is updated. In the case that an extreme deviant value is obtained, e.g. higher than a given threshold, this value is considered as artifact; it will be disregarded and the previous reference value will remain until the next trial. However, this threshold must be empirically set. If the threshold value is set too high, then artifacts are let through. Conversely, if the value chosen is too low, then any minimal change in the reference interval will be assumed an artifact. Disadvantages are that possible overlaps of two consecutive trials can occur. In this case, the reference interval would lie partially or completely in the preceding sweep and would not be a valid reference for the current trial. This effect could be minimized, but not eliminated, if the whole trial is chosen as reference for the ERD calculation (Brunner et al., 2004).

7.4 Results

First, the importance of choosing an appropriate electrode montage was examined. Three different electrode montages were compared: unipolar, Hjorth 5-point, and Hjorth 9-point.

In order to optimize the duration of the session, i.e. to extend the duration of the computation stage, the time used for both the initialization stage and the fulfillment of the task constraints should be optimized. Because of the simulation condition of the study, the feature *bad trials* was included in the analysis. The term *bad trials* refers to those trials that did not fulfill the task constraints and, thus, were not considered for the analysis. The results show that the number of *bad trials* was higher with the unipolar montage than with Hjorth's montages in both tasks (see Tables 7.1 and 7.2) and, thus, the duration of both initialization and computation stages increases considerably.

The number of ERP patterns estimated in the initialization stage with source derivation montages was slightly higher when compared with the unipolar montage. In the oddball task, one (unipolar), three (Hjorth 5-point), and three (Hjorth 9-point) ERP patterns were excluded after evaluation (not included in Table 7.1). In the Sternberg task, the number of patterns excluded was one, five, and four, respectively (not included in Table 7.2). Thus, the subtraction of the ERP was carried out in 11% (unipolar), 28% (Hjorth 5-point), and 22% (Hjorth 9-point) of the cases in the oddball task. The rates in the Sternberg task were 11% for all montages. Furthermore, the number of trials necessary for ERP estimation was in general shorter in the oddball task. Tables 7.1 and 7.2 include the values obtained for the oddball and Sternberg tasks, respectively.

The STD values of the ERP patterns obtained during the initialization stage were examined. Because the activity ranges of the three montages differ considerably, the STD values were divided to the BP range of each subject to obtain the percentage values (STDn; Tables 7.1 and 7.2). In the auditory task, the STDn values remained below 1% for all montages. In the visual task, however, the STDn mean value for the unipolar montage was 1.4%.

Table 7.1 Parameter comparison (oddball task) for the unipolar, Hjorth 5-point and Hjorth 9-point montages.

	Estimated ERP	**Trials needed for ERP**	**STD (µV)**	**STDn (%)**	**BP (µV)**	**Bad trials**	**Success rate (%)**
Unipolar	2 (11%)	16.00	4.25	<1	2325	16	68
Hjorth 5-point	5 (28%)	16.00	1.02	<1	181	3	68
Hjorth 9-point	4 (22%)	16.50	1.27	<1	273	3	70

Table 7.2 Parameter comparison (Sternberg task) for the unipolar, Hjorth 5-point and Hjorth 9-point montages.

	Estimated ERP	Trials needed for ERP	STD (µV)	STDn (%)	BP (µV)	Bad trials	Success rate (%)
Unipolar	2 (11%)	20.00	4.55	1.4	496	13	70
Hjorth 5-point	2 (11%)	16.00	1.06	<1	170	2	76
Hjorth 9-point	2 (11%)	16.75	1.36	<1	200	2	76

Additionally, the individual trials processed in the computation stage were visually analyzed for examining the success rate of the process. In this way, the ERD time courses of both estimations (common and induced ERD) containing 1 s pre- and post-stimulus intervals from different subjects during different tasks are exemplarily plotted in Fig. 7.6. According to Klimesch et al. (1998a), it is expected that these activities are equal under conditions where evoked activity is absent. This is observed regularly in the pre-stimulus interval, where no ERP is present. On the other hand, in the post-stimulus interval, where P300 occurs, different cases were observed. In most of the trials, the P300 influences considerably the estimation and was successfully minimized (case I; Fig. 7.6a-b). In case II, the difference between both ERD estimations was minimal (Fig. 7.6c-d), probably due to higher BP levels at resting state. In case III (Fig. 7.6e-f), overcorrection was observed due to influence of the P300 characteristics. Again, the results obtained with the source derivation montages were better than with the unipolar montage in both tasks (see Tables 7.1 and 7.2).

In order to examine to what extent the minimum of trials for ERP estimation influences in the results, the process was repeated setting this value to 10 trials. The success rates decreased in all montages, except for the unipolar one in the Sternberg task (76%). Moreover, the following values were obtained: 59% (unipolar), 67% (Hjorth 5-point), and 69% (Hjorth 9-point), for the oddball task; 70% (Hjorth 5-point), and 73% (Hjorth 9-point), for the Sternberg task. Paradoxically, the number of ERP patterns estimated in the oddball task was higher (17%) for the unipolar montage but remained equal for the Laplacian ones, when compared with the preceding values. For the Sternberg task, the ERP estimations increased to 22% in both Laplacian montages. Regarding the STDn values, it must be noted that they remained in all cases <1%, excepting for the unipolar case in the Sternberg task (1.8%).

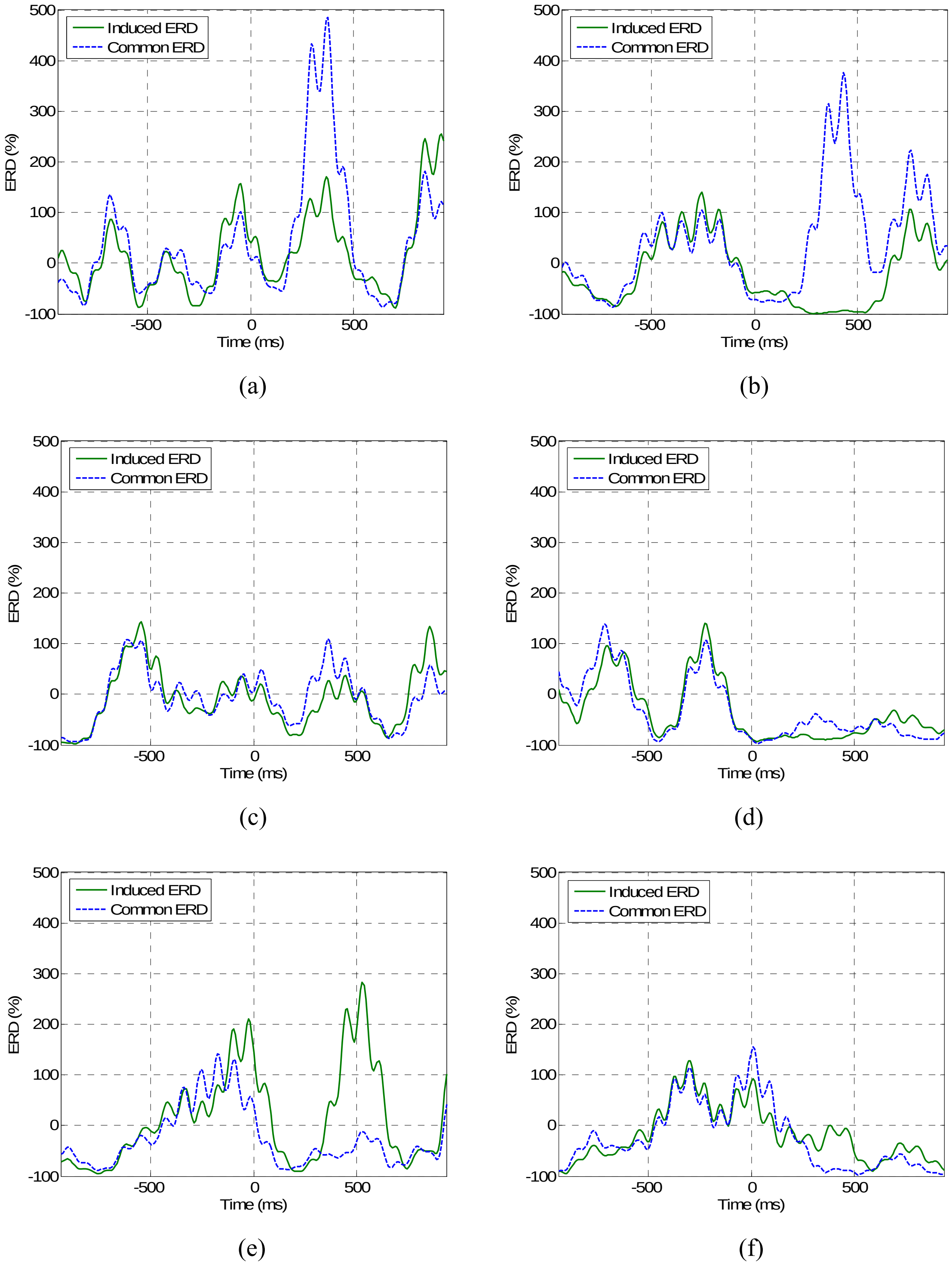


Fig. 7.6 Theta-ERD time courses at FCz (Hjorth 5-point) of single trials of different subjects during task performance. Case I: (a) oddball task (subject 2); (b) Sternberg task (subject 5). Case II: (c) oddball task (subject 13); (d) Sternberg task (subject 7). Case III: (e) oddball task (subject 16); (f) Sternberg task (subject 13). “0” corresponds to the stimulus presentation.

7.5 Discussion

In this section, several key issues by the online quantification of cognitive-induced brain activity are discussed. The use of source derivation instead of unipolar montage reduces the number of bad trials and, thus, the duration of the session. The number of bad trials can also be reduced by softening the task constraints, e.g. increasing the BP threshold. However, more artifacts might not be detected and, thus, the process efficacy could decrease.

Using a threshold based on STD values, ERP patterns were estimated in approx. 11-28% of the cases. In this issue, the role of the electrode montage chosen is minor. The question arises, however, whether this rate can be improved when choosing different parameters, e.g. SNR values reflecting the relationship between pre- and post-stimulus intervals. The estimation of the ERP pattern, in our case the P300 component, could be improved by using some denoising methods based, e.g., on consecutive averages or on wavelets. Consecutive averages of a few trials can be used in order to solve the problem of habituation and tiredness when having large number of trials. However, this is not appropriate when the intertrial ERP variability is high (Holm, 2004). In this case, the computation stage is carried out without ERP subtraction. On the other hand, it has been shown that denoising improves the differentiation of the ERP from the background EEG in most of the trials (Quian Quiroga, 2000). These advantages could significantly reduce the minimum number of trials necessary for the ERP estimation, especially in case of high artifact presence. In another study, Demiralp et al. (1999) correlated one single wavelet coefficient with the P300 response and used its sign for discriminating between trials with and without P300. As a result, they achieved better averages of the P300 component. Whether such techniques are feasible for their possible integration in the proposed methodology will be topic of future research.

Regarding the separation of the evoked and induced activities in single-trial, some conclusions can be summarized. The success rates in the Sternberg task were superior to the oddball task, corresponding to the quality of P300 in the different tasks. As expected, the success rates decreased in most of the cases when the number of trials for ERP estimation was reduced.

Concerning the procedure for minimizing the ERP during the computation stage, several approaches have been considered in this study. A possible solution to avoid the undesired influence of the ERP is to ignore the interval in which it occurs, in our case, the first 500 ms of the post-stimulus interval. However, this approach has certain disadvantages. First, P300 is a parameter with high inter-individual variability. Several studies have shown that patients suffering from different diseases have retarded P300, even over 500 ms (Polich et al., 1986; Idiazábal et al., 2002). Therefore, setting a time boundary for this parameter is not viable. Second, also related to the first problem, it is not recommendable to ignore a long time interval of the trial, because the induced activity could be restricted. Hence, assuming the presence of the P300 component in a trial, we opted to assign the subtraction interval as the maximal duration of a trial during the computation stage.

Another important issue of debate is the variability of the P300. It has been widely studied in relation with habituation effects due to task increases and stimulus train. The habituation effect of the P300 component is not an obvious effect. Habituation occurs mainly with long recording sessions (cf. review in Holm, 2004). A related issue is the occurrence probability of the P300. This fact could partially explain the results displayed in Fig. 7.6e-f. However, this question remains still an unsolved problem and shall be focus of further research.

Appropriate preprocessing is an essential part of the method, helping to achieve the conditions required for the subsequent signal processing. The module-based structure of the procedure (Fig. 7.2-7.4) allows modification or, if necessary, exclusion/inclusion of modules individually. For example, in case of patients with absent or deviant ERP, subtraction of the ERP should be switched off to avoid reinforcing false components. This fact underlines the necessity of individual pre-examinations to check the appropriateness of the process for a given case.

Chapter 8

General Discussion and Future Research

The empirical data to guide treatment of memory and attentional disorders in patients with epilepsy is scarce but mostly with positive results (cf. review in Shulman and Barr, 2002). For example, Engelberts (2002) showed in a study for assessing the effectiveness of cognitive rehabilitation for attention deficits in focal seizures has shown that patients with active epilepsy benefited more than did the seizure-free patients. However, the neurofeedback research for the improvement of cognitive functions based on electrophysiological changes in the brain by means of neurofeedback is limited and mostly inadequate. From the biomedical engineering point of view, there was a necessity for looking for appropriate processing methods of the corresponding cognitive-related signals. For this work, the cognitive-induced brain activities in the theta, alpha and gamma bands were chosen as the signals of interest, since they have been suggested to play an important role in memory performance (see section 2.3).

Among the results of the experimental EEG studies reported in chapter 6, the findings observed in the theta and upper alpha bands were the most relevant. The short-lasting post-stimulus theta-ERS found in the control group is in line with the literature and related to WM performance. Since the patient group showed a deviation in post-stimulus ERS as well as in the BP level at resting state, the subsequent studies were focused on this band. Similar results were obtained for the upper alpha band. However, the post-stimulus differences in parietal and occipital areas were restricted to the non-target case. Concerning the upper alpha BP at resting state, the expected higher values at posterior sites could only be confirmed for the Pz electrode during the closed-eyes condition. As mentioned in chapter 3, ERD in the upper alpha range has also been related to memory functions, especially to semantic memory tasks.

Hence, further analyses are needed in order to investigate the question whether activity in this band can be a suitable feature for future neurofeedback applications. In such a case, other preprocessing measures should be taken, e.g., the correction of muscular artifacts coming from back and neck instead of ocular ones, etc.

After selecting the frequency band of interest, two options are conceivable: either to consider only the absolute BP level, suggesting working with the absolute ('tonic') BP level in the theta band in order to achieve a higher ERD value; or to consider the relationship between resting state and task performance by using a relative measure. Current approaches of neurofeedback are based on absolute measures of brain activity that do not take the relationship between pre- and post-stimulus activities into consideration. As reviewed in section 2.3, first attempts for training absolute theta BP for cognitive improvement have failed. However, the exact causes that led to the unsuccessful attempt are not known. It might be hypothesized that too few sessions were made or that the protocol was not appropriate. This last hypothesis would support the suggestion of using relative measures instead of absolute ones. In order to reduce the effect of the high inter-individual variability of absolute power values, and to avoid a continuous system subject-adaptation for improving the effectiveness of the neurofeedback training, relative power values can be computed by "normalizing" values. Hence, ERD was then selected as a valid parameter for quantifying cognitive-induced brain activity. Although the ERD method has often been used in BCI systems based on motor-related activity, its possible integration in neurofeedback applications as electrophysiological indicator of cognitive-induced processes had not been examined yet.

The analysis of the memory-related brain activity in the frequency domain has several advantages in comparison with the typical analysis in the time domain: first, the full-spectrum can be studied and, second, there is no limitation to a certain narrow frequency band. These advantages can be used for adjusting individually the frequency band of interest. Several studies have demonstrated that the use of individually adjusted frequency bands for extracting event-related BP measures has advantages over the common analysis within fixed frequency bands because of the inter-individual high variability in frequency distribution (Doppelmayr et al., 1998b; Klimesch et al., 1994). Hence, since these examinations are made before the therapy, the calculation of the whole spectrum is not necessary in the final application.

In the framework of this work, surface recordings of the brain electrical activity were made by means of the EEG technique. Because of its higher time resolution, the EEG is an experienced tool for the study of cognitive processes. However, it could be interesting to extend the term neurofeedback to other techniques in order to increase not only its availability and universality but also its functionality and application fields. In this way, the fMRI and PET techniques provide information on the increases in blood flow accompanying neuronal activation with relatively high spatial resolution (in mm range). First studies for using fMRI as a tool for providing neurophysiological feedback have been reported. deCharms and colleagues used the information acquired by real-time fMRI to guide learning of increased brain activation during repeated biofeedback training of imagery motor action. Subjects were able to voluntarily control a target brain region in real-time, during task performance (deCharms et al., 2004). The main disadvantage is that the temporal resolution is limited by the velocity of the haemodynamic changes (Matthews, 2001). The processing of the data requires about 2 s, the biologically inherent haemodynamic delay requires about 2 s and 4-6 s to reach its peak value after neural activation (Menon and Goodyear, 2001; deCharms et al., 2004). Because of the widespread availability of the fMRI technology, its improvement in temporal resolution, and the necessity for a higher spatial resolution of the brain functionality, it may get a major role in future applications.

Next steps are the implementation and optimization of the developed methodology in the existing neurofeedback system, and the design of an appropriate training paradigm. Contrary to standard neurofeedback protocols, which are based in long-lasting intervals (of more seconds), and considering that the ERS in the theta band is mostly present as a relative short-lasting event-related brain oscillation, a paradigm based on changes between ERS and ERD or a baseline seems more meaningful. The task has a twofold goal: first, the enhancement of theta synchronization (or greater desynchronization, in the case of the upper alpha band) with respect to the resting state; and, second, an improvement of the RT during memory performance can be expected. As demonstrated in the study of Jausovec and Jausovec (2004), shorter RT, i.e. such responses occurred in the immediate interval after stimulus presentation, have been shown to be characteristic from high-IQ subjects. Hence, this kind of paradigm should help to improve RT during memory performance as well.

Because a paradigm irremediably elicits more than one cognitive process, the paradigm must be specific for eliciting so few cognitive processes as possible at the same time.

Otherwise, the extraction and quantification of the signal of interest becomes difficult because the processes overlap to each other. For example, when using averaging techniques, e.g. for ERP estimation, overlapping processes can lead to a balance of diverse task-related EEG changes rather than actual principal processes (Fingelkurts et al., 2002). Because more components are overlapped, they are even more difficult to separate in single-trial. Particularly, the P300 component is an overlap of more components with the same latency or amplitude and has a high inter-individual variability (Mecklinger, 1992; Polich, 1989). Considering the theory of a phase-resetting as origin of specific ERP components, such as the P300, the distinction between evoked and induced activity, as defined in the previous sections, becomes problematic. Strictly speaking, one could argue that since the phase resetting is evoked by the stimulus, the induced activity 'becomes' evoked activity for a short period of time. This indicates that the distinction between evoked activity and induced activity is a relative distinction rather than an absolute one (Bastiaansen and Hagoort, 2003).

A possible solution to avoid this issue is to use an asynchronous approach. In such an approach, there is no trigger or event as signal to demand a response from the subject. Therefore, it is to expect that no evoked activity appears. The subject can freely start the specific task, i.e., the control is not system-initiated but user-initiated. However, the difficulty falls on the fact that it requires that the system can detect when the EEG control is intended and when it is not (Mason and Birch, 2000; Millán and Mouriño, 2003).

Regarding the task itself, a possibility is to increase ERS up to a given threshold and then to decrease it down to zero. With this approach, the subjects learn to distinguish between the two states, extending their ERD limits, but without consideration of the speed factor. A better approach suggests several changes between ERS and the baseline in each sweep (adjustable according to difficulty level), in the same ranges that the theta ERS usually changes. In case of a positive reaction of the subject, the sweep can be extended (increase of the difficulty grad). By using an adaptive reference interval, as proposed in section 7.3.2, the possible changes of the baseline or reference interval during the session can be observed and, therefore, the resulting signal will reflect the current brain behavior.

After the paradigm is designed and implemented, and before neurotherapy methods are introduced in the praxis, the effectiveness of the process must be confirmed by means of pilot and clinical studies on healthy controls.

In further studies, measurements on epilepsy patients must be completed. Finally, the therapy evaluation and the validation of the obtained results will be carried out in cooperation with partners of the neurophysiology and neuropsychology areas.

Chapter 9

Summary

In terms of biomedical engineering, this thesis started from the necessity of further research in the signal processing of electrophysiological indicators of cognitive and memory processes in particular. The studies concentrated on the cognitive-induced brain activity, since it had been suggested to play an important role in memory performance.

The first objective of this work dealt with the determination of appropriate electrophysiological indicators for the quantification of memory processes. For accomplishing this aim, the topic was subdivided into two main issues:

- the finding of a suitable parameter to distinguish between populations with normal and impaired memory performance, and

- the development of an efficient algorithm for the online implementation of the selected parameter.

In order to find the solution to the first problem, data of a group of healthy controls and a group of patients with refractory epilepsy acquired during performance of an auditory oddball task were analyzed and statistically compared. The event-related de-/synchronization (ERD/ERS) was used as the quantification method, since it has been shown to be a valid electrophysiological cognitive parameter, especially for working memory (WM) processes (Burgess and Gruzelier, 2000). Significant differences in the theta band were found between both populations. The results showed large amplitudes of theta-ERS occurred as response to the stimulus presentation in healthy controls, with maximal peak amplitude at fronto-central electrodes. In the epilepsy group, however, this increase of theta-ERS was significantly lower.

In the upper alpha band, differences at parietal and occipital sites were also observed but only for the non-target stimulus. These findings pointed out a possible additional dysfunction in epilepsy that may be related to WM processes. ERD depends not only on the post-stimulus activity elicited by the corresponding stimulus but also on the activity at the resting state (i.e., the pre-stimulus interval). To confirm the hypothesis of ERD as an adequate quantitative parameter, the significance of the BP levels during resting state was also evaluated. The results showed significant differences on the EEG topography at resting state between controls and epilepsy patients. The theta BP at resting state was lower in the control than in the epilepsy group in both open- and closed-eyes conditions. An opposite effect was observed in the lower alpha band, but only for the open-eyes condition. These findings validated the hypothesis that task performance depends on the activity not only in the post-stimulus but also in the pre-stimulus interval. In sight of the results obtained, and because ERD measures consider both pre- and post-stimulus activities, this method was confirmed as a valid cognitive parameter for the purposes of this work.

The second aim was motivated by the fact that an appropriate algorithm for online calculation is required for a potential integration of the ERD method in future neurofeedback applications. Hence, a comparative study was carried out in order to examine the dynamic characteristics and resources demands of different algorithms for ERD computation. All of the examined algorithms (squaring-filtering (SF) approach, adaptive-recursive estimation (ARE), adaptive discrete Fourier transform (ADFT), and Hilbert approach) fulfilled the requirements of online suitability. In the present case, and due to its better dynamic properties and parameter-free condition, the SF-algorithm was chosen fur further analysis. However, depending on the software-technical implementation, further comparative analyses may be required for an additional adjustment of each algorithm.

Afterwards, considering both the psychophysiological importance of induced brain activity and the necessity for its online processing, a methodology for the online extraction and quantification of cognitive-induced brain activity was developed. The procedure was functionally organized in blocks of algorithms in order to increase applicability. Several aspects, including the role of electrode montages and the minimization of the evoked activity in the effectiveness of the proposed methodology, were examined based on cognitive studies as part of the optimization process. The use of source derivation montages provided slightly superior results when compared with unipolar montage. The hypothesis that evoked activity significantly influences the measurement of the induced activity in single-trial was positively evaluated. This finding underlines the necessity of minimizing evoked components as a part of the online signal processing.

Future steps should include the implementation and optimization of the developed methodology, the design of a special training paradigm as well as a pilot study for confirming the theoretical approach proposed in this work.

In conclusion, this work contributes to the further development of the cognitive-induced brain activity research, as referred to quantitative parameters and processing algorithms for its online calculation. This work sets the methodical basis for developing neurofeedback applications based on cognitive-induced brain activity. Further interdisciplinary research in this direction is needed in order to offer new possibilities for the treatment of cognitive impairments in epilepsy and other neurological diseases.

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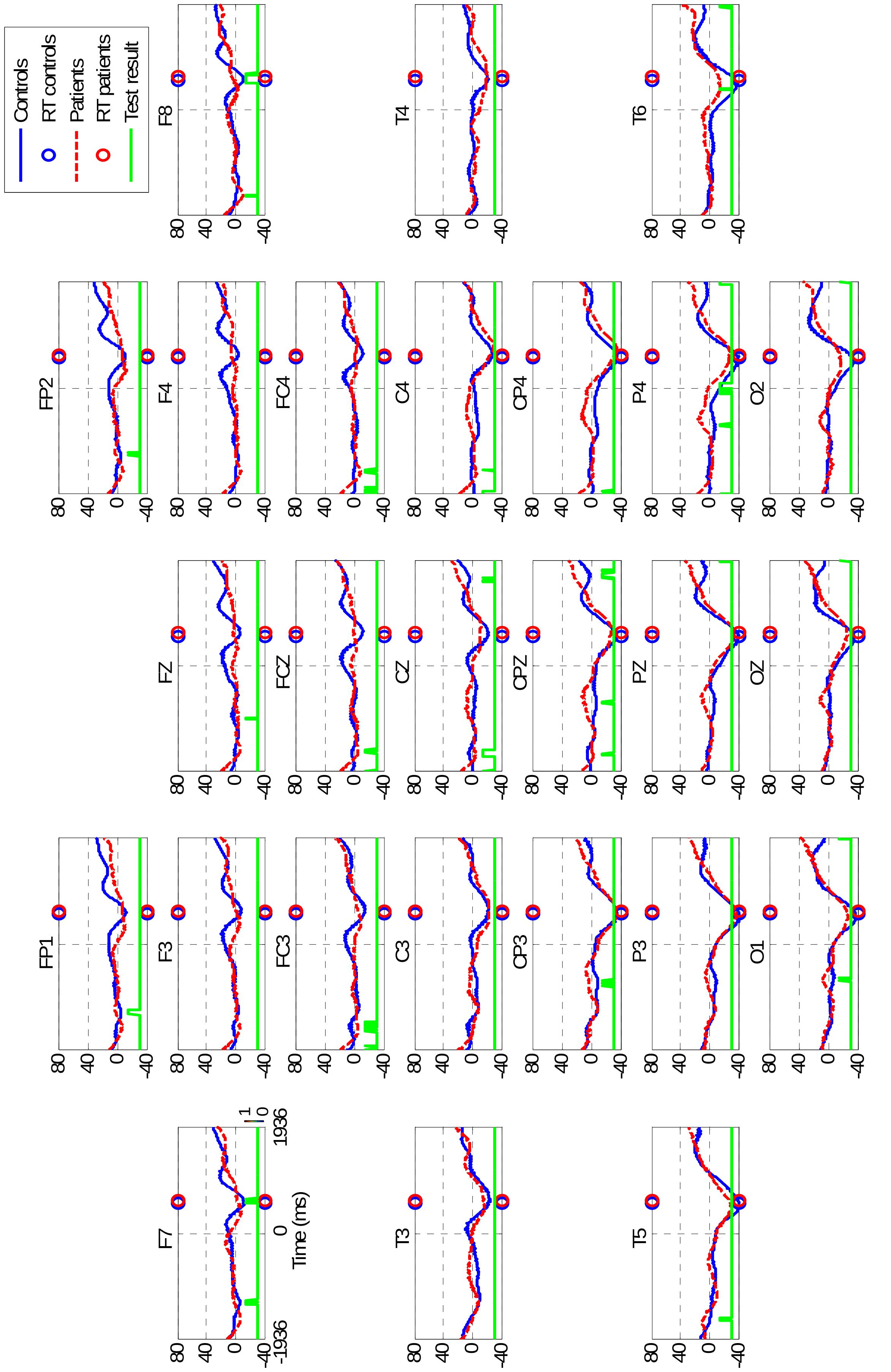
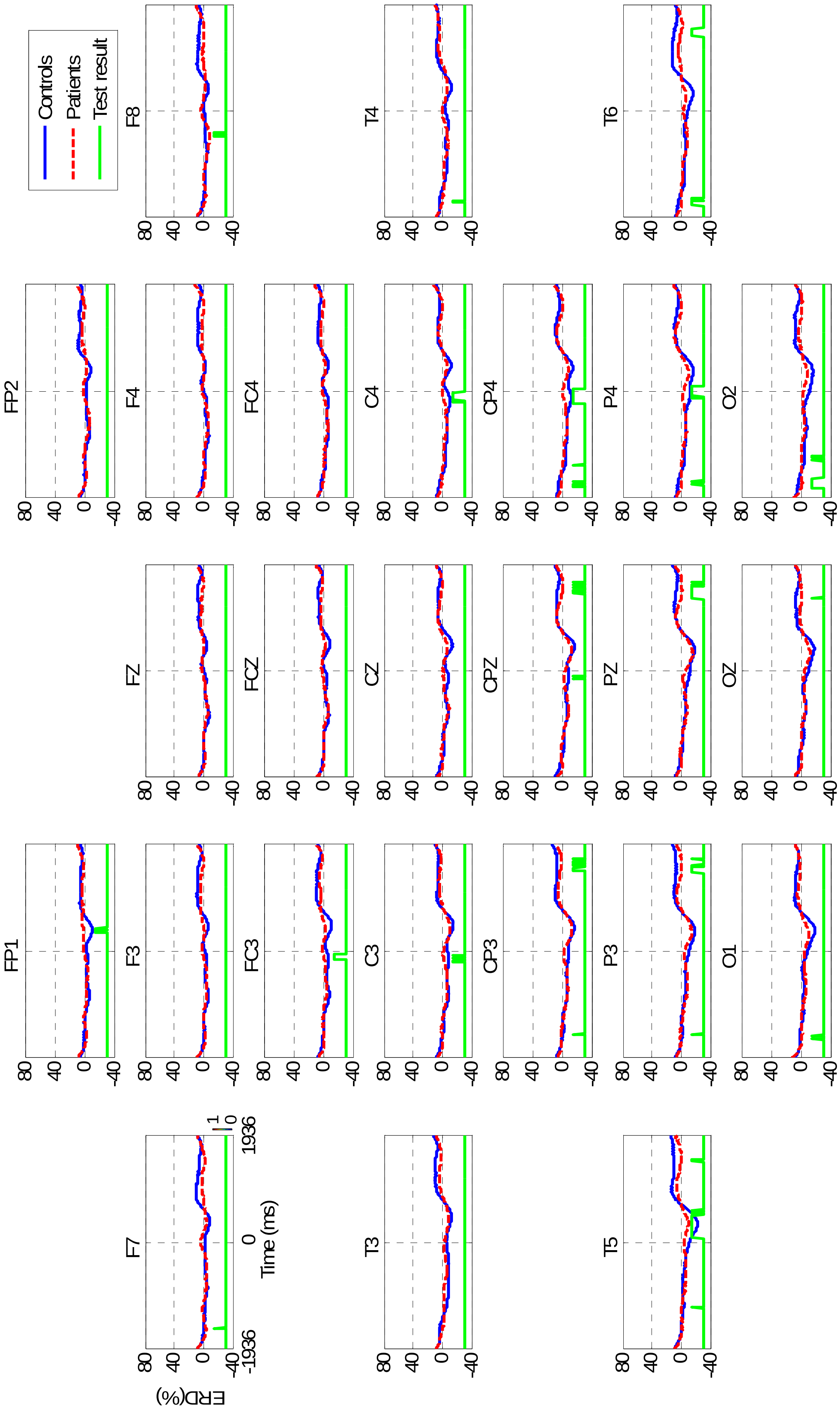
Appendix


Controls
RT controls
Patients
RT patients
Test result
FP1
FP2
F7
F3
FZ
F4
F8
FC3
FCZ
FC4
T3
C3
CZ
C4
T4
CP3
CPZ
CP4
T5
P3
PZ
P4
T6
O1
OZ
O2
ERD(%)
Time (ms)
-1936
0
1936

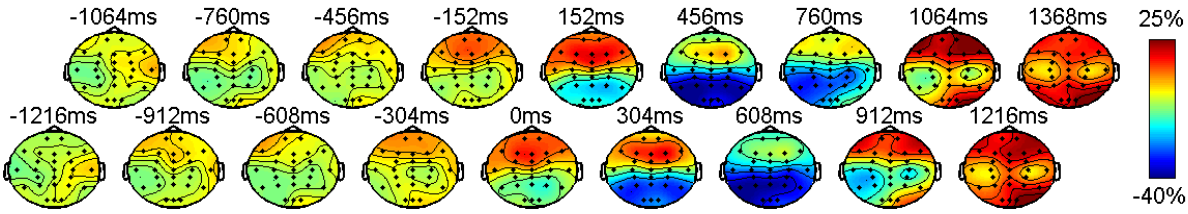
(a)



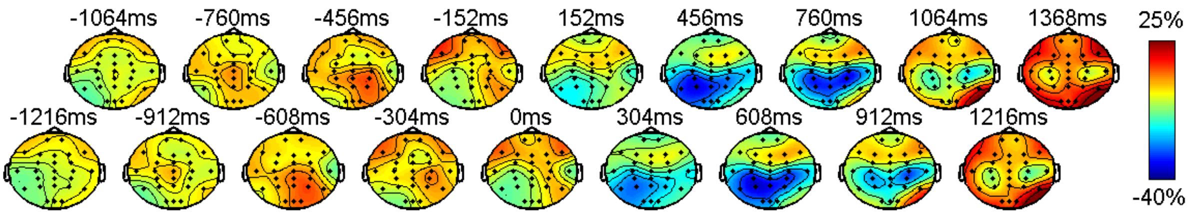
Controls
Patients
Test result
FP1
FP2
F7
F3
FZ
F4
F8
FC3
FCZ
FC4
T3
C3
CZ
C4
T4
CP3
CPZ
CP4
T5
P3
PZ
P4
T6
O1
OZ
O2
ERD(%)
Time (ms)
-1936
0
1936
80
40
0
-40

(b)

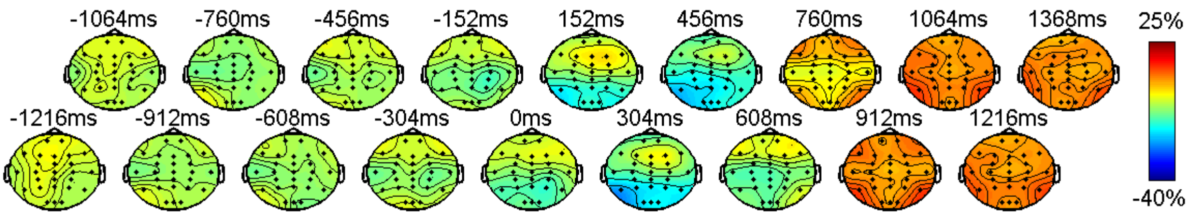
Fig. A.1 (Pages 94-95) Comparison of ERD time courses (lower alpha band) between the control (solid blue line) and the epilepsy groups (dashed red line) for the oddball task. The y-scale on the left (see electrode F7) indicates the ERD in percentage. The green line shows the test result at each time point. The y-scale on the right indicates the test result (“0”, no significant; “1”, significant). The time “0 ms” corresponds to the stimulus presentation. (a) Target case: red and blue circles represent the averaged RT of patients and controls, respect. (b) Non-target case.



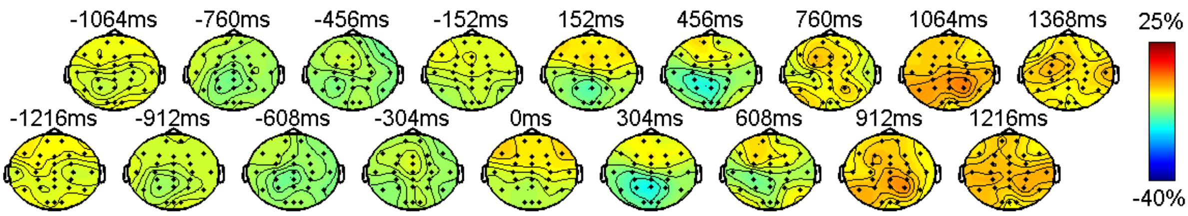
(a)



(b)

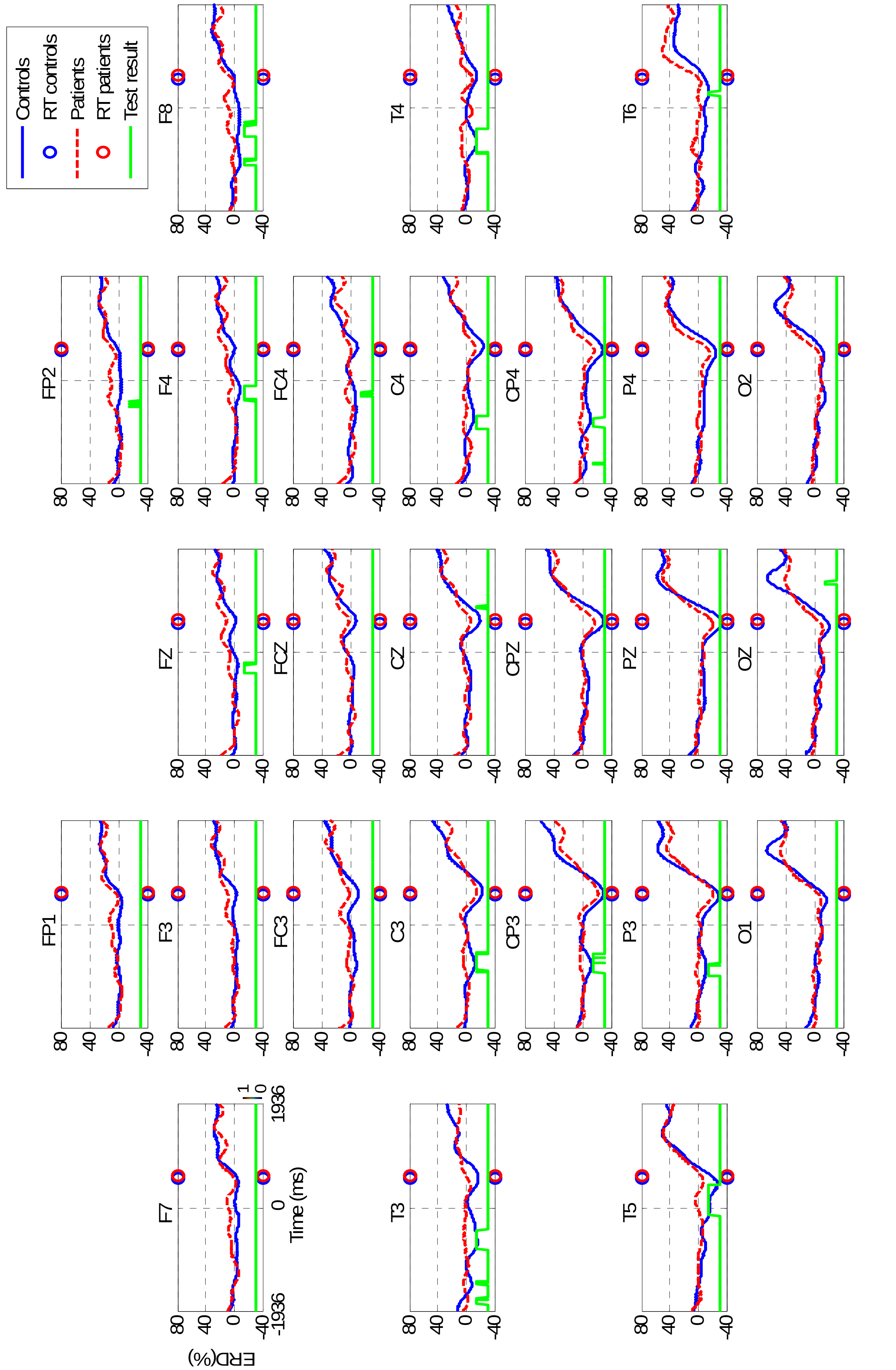


(c)

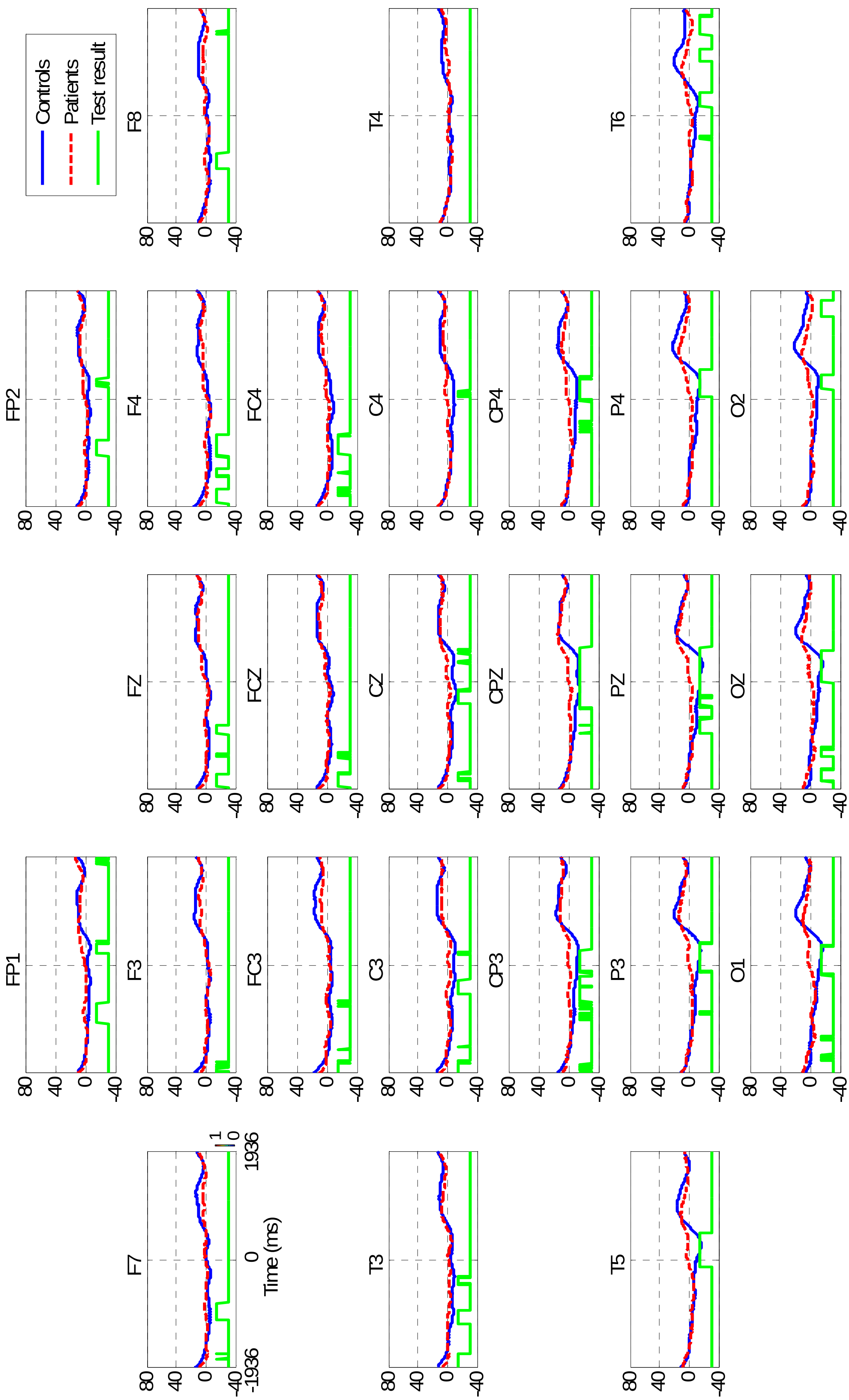


(d)

Fig. A.2 Mapping sequences of the ERD time courses in the lower alpha band for the oddball task. From top to bottom: target stimulus in controls (a) and patients (b), non-target stimulus in controls (c) and patients (d). “0 ms” corresponds to stimulus presentation. Red and blue values represent ERS and ERD, respectively.

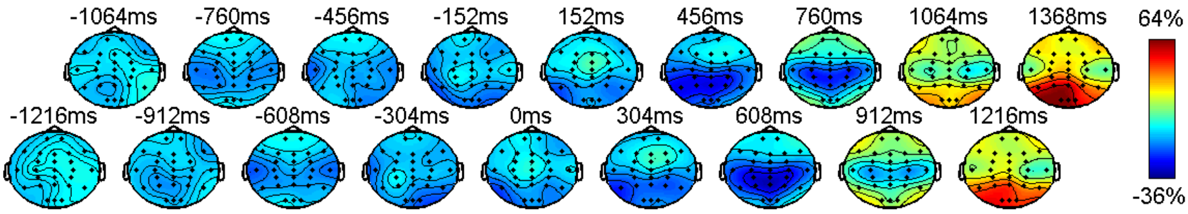

Controls
RT controls
Patients
RT patients
Test result
FP1
FP2
F7
F3
FZ
F4
F8
FC3
FCZ
FC4
T3
C3
CZ
C4
T4
CP3
CPZ
CP4
T5
P3
PZ
P4
T6
O1
OZ
O2
ERD(%)
Time (ms)
-1936
0
1936
80
40
-40

(a)

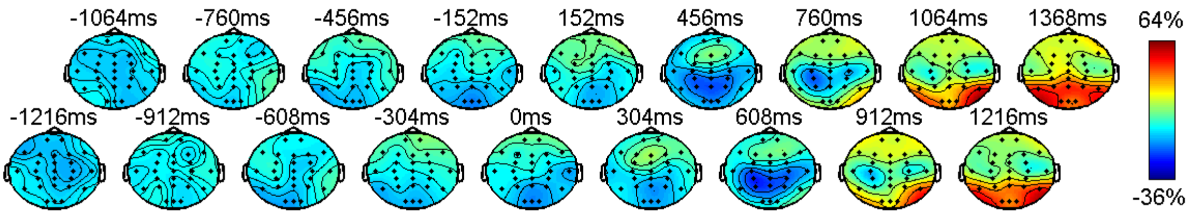

Controls
Patients
Test result
FP1
FP2
F7
F3
FZ
F4
F8
FC3
FCZ
FC4
T3
C3
CZ
C4
T4
CP3
CPZ
CP4
T5
P3
PZ
P4
T6
O1
OZ
O2
ERD(%)
Time (ms)
-1936
0
1936
80
40
0
-40

(b)

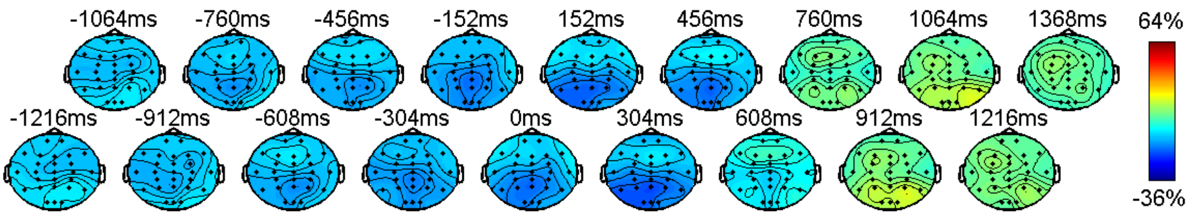
Fig. A.3 (Pages 97-98) Comparison of ERD time courses (upper alpha band) between the control (solid blue line) and the epilepsy groups (dashed red line) for the oddball task. The y-scale on the left (see electrode F7) indicates the ERD in percentage. The green line shows the test result at each time point. The y-scale on the right indicates the test result (“0”, no significant; “1”, significant). The time “0 ms” corresponds to the stimulus presentation. (a) Target case: red and blue circles represent the averaged RT of patients and controls, respect. (b) Non-target case.



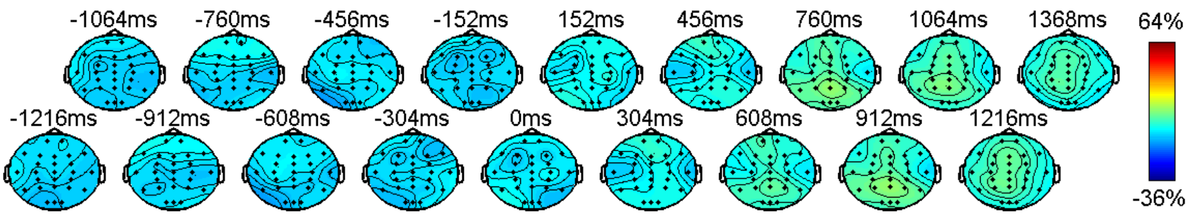
(a)



(b)

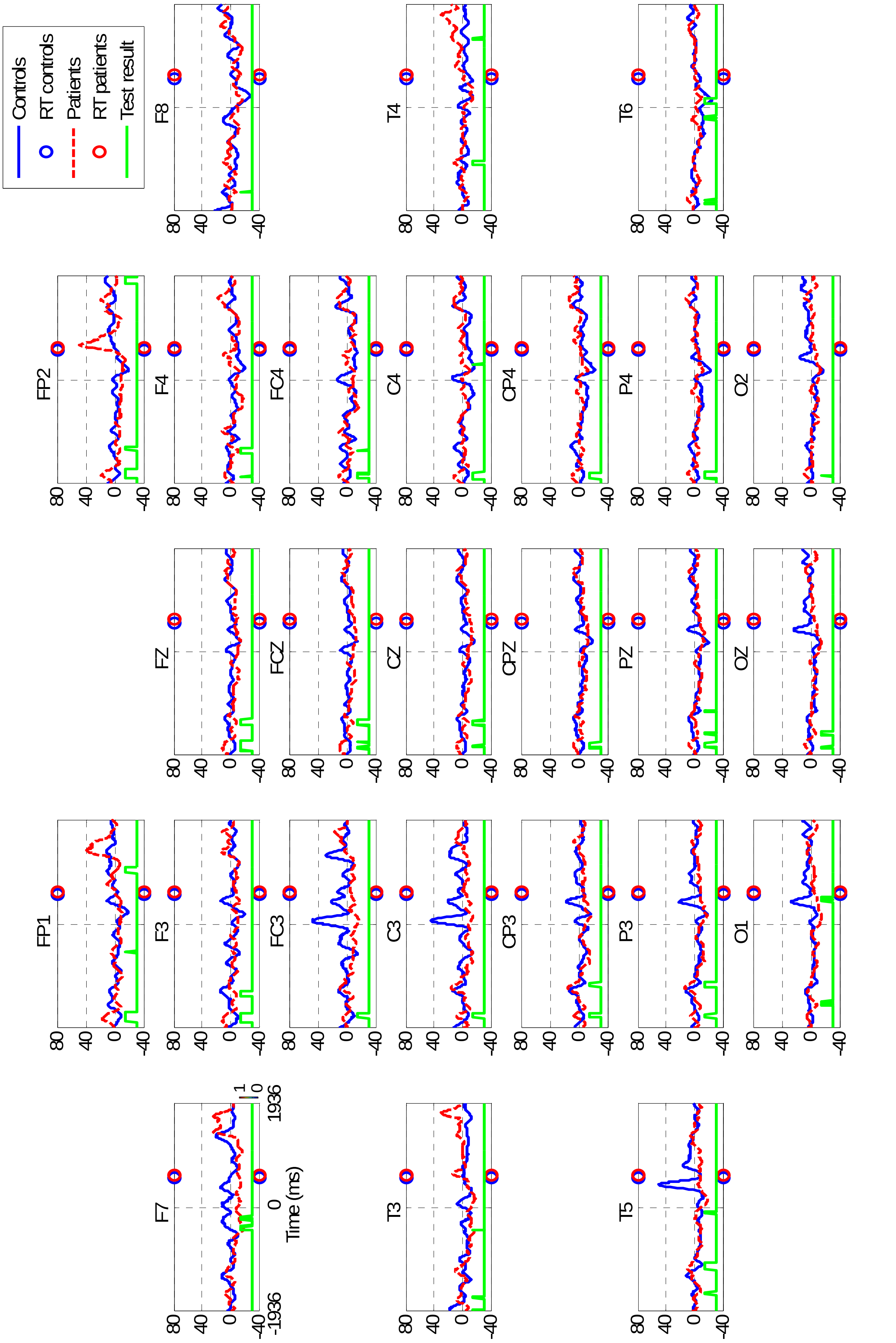


(c)



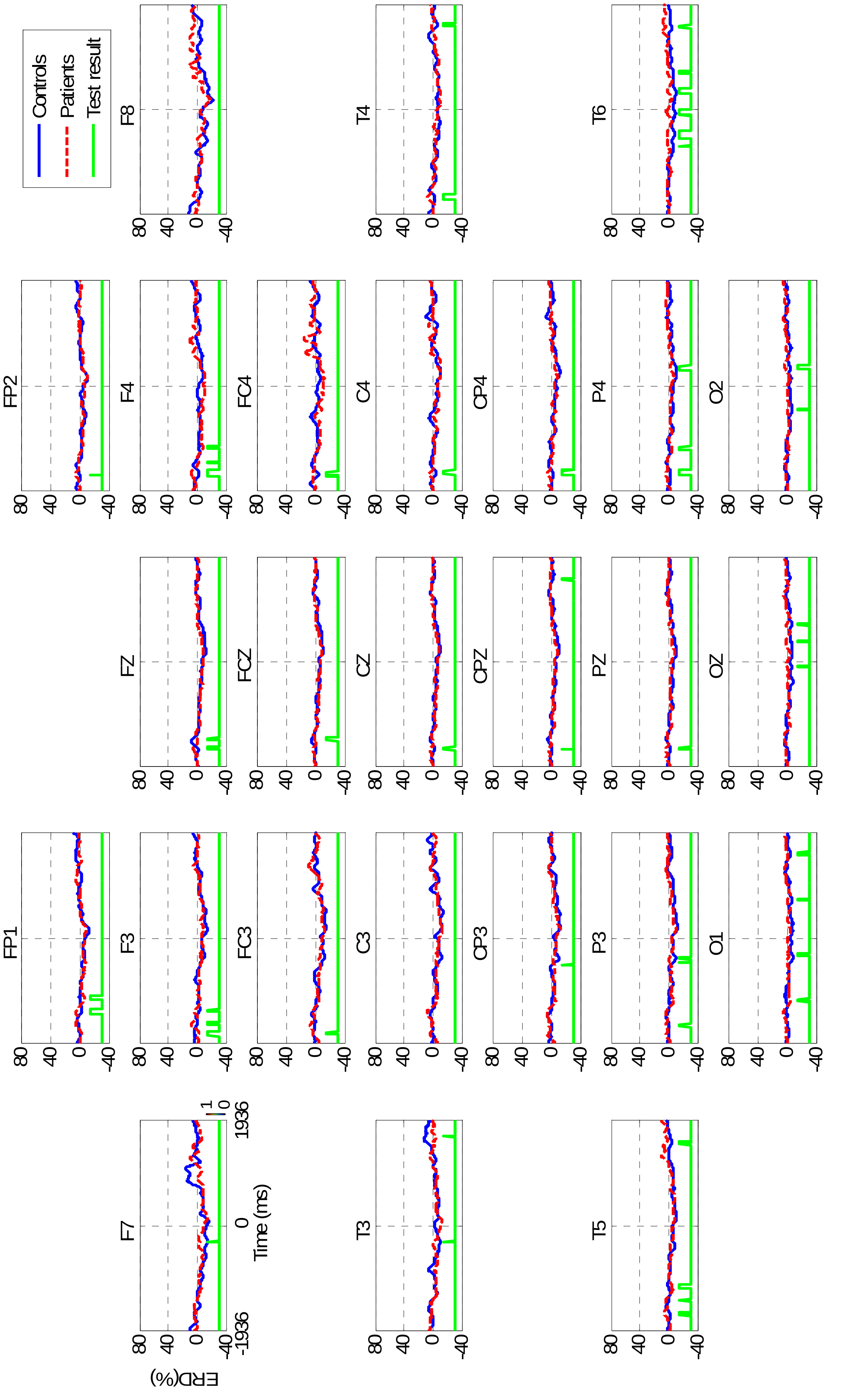
(d)

Fig. A.4 Mapping sequences of the ERD time courses in the upper alpha band for the oddball task. From top to bottom: target stimulus in controls (a) and patients (b), non-target stimulus in controls (c) and patients (d). “0 ms” corresponds to stimulus presentation. Red and blue values represent ERS and ERD, respectively.



Controls
RT controls
Patients
RT patients
Test result
FP1
FP2
F7
F3
FZ
F4
F8
FC3
FCZ
FC4
T3
C3
CZ
C4
T4
CP3
CPZ
CP4
T5
P3
PZ
P4
T6
O1
OZ
O2
ERD(%)
80
40
0
-40
-1936
0
1936
Time (ms)
1
0

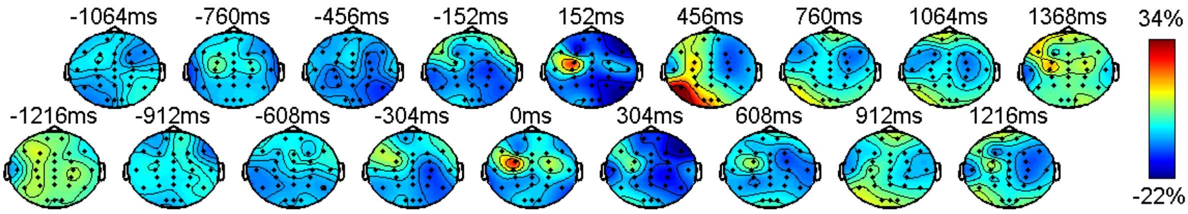
(a)



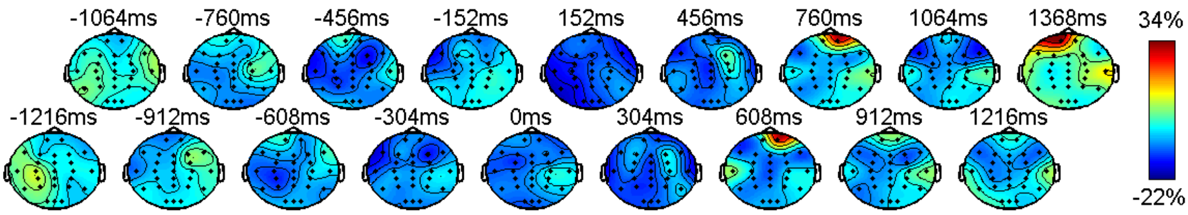
Controls
Patients
Test result
FP1
FP2
F7
F3
FZ
F4
F8
FC3
FCZ
FC4
T3
C3
CZ
C4
T4
CP3
CPZ
CP4
T5
P3
PZ
P4
T6
O1
OZ
O2
ERD(%)
Time (ms)
80
40
0
-40
-1936
0
1936
1
0

(b)

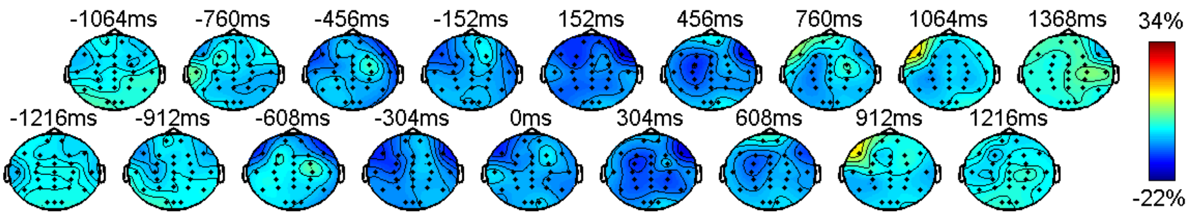
Fig. A.5 (Pages 100-101) Comparison of ERD time courses (gamma band) between the control (solid blue line) and the epilepsy groups (dashed red line) for the oddball task. The y-scale on the left (see electrode F7) indicates the ERD in percentage. The green line shows the test result at each time point. The y-scale on the right indicates the test result ("0", no significant; "1", significant). The time "0 ms" corresponds to the stimulus presentation. (a) Target case: red and blue circles represent the averaged RT of patients and controls, respect. (b) Non-target case.



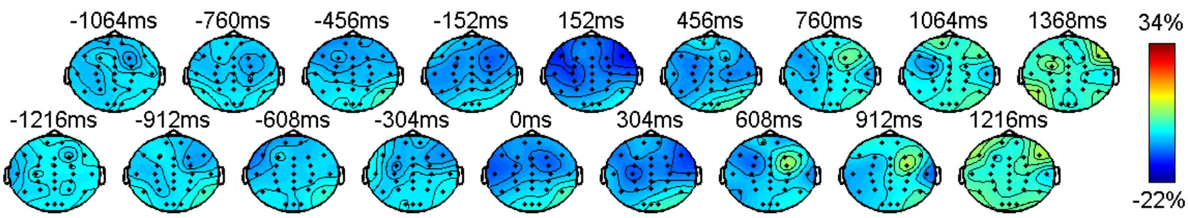
(a)



(b)



(c)



(d)

Fig. A.6 Mapping sequences of the ERD time courses in the gamma band for the oddball task. From top to bottom: target stimulus in controls (a) and patients (b), non-target stimulus in controls (c) and patients (d). "0 ms" corresponds to stimulus presentation. Red and blue values represent ERS and ERD, respectively.

Selbstständigkeitserklärung (German)

Ich versichere, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet.

Bei der Auswahl und Auswertung folgenden Materials haben mir die nachstehend aufgeführten Personen in der jeweils beschriebenen Weise unentgeltlich geholfen:

1. Dr.-Ing. Galina Ivanova (Leiterin der Forschungsgruppe)
2. Johannes Schilz (Diplomarbeit)
3. Mitglieder von „NeuroCybernetics Research Group“

Weitere Personen waren an der inhaltlich-materiellen Erstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich hierfür nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberater oder anderer Personen) in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalte der vorgelegten Dissertation stehen.

Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer Prüfungsbehörde vorgelegt.

Ich bin darauf hingewiesen worden, dass die Unrichtigkeit der vorstehenden Erklärung als Täuschungsversuch angesehen wird und den erfolglosen Abbruch des Promotionsverfahrens zu Folge hat.

Daniel Pérez Marcos

Ilmenau, 7. Februar 2006

Induced Brain Activity as Indicator of Cognitive Processes: Experimental-Methodical Analyses and Algorithms for Online Applications

Thesen

1. Die Signalverarbeitung von oszillatorischer Hirnaktivität ist ein entscheidendes Werkzeug, um die kognitiven Prozessen verstehen zu können.

2. Induzierte EEG Aktivität wird in mehreren Untersuchungen mit kognitiver Leistung assoziiert. Beispielsweise wird Aktivität in den Theta- und Alpha-Frequenzbändern in den Prä- und Post-Stimulus Intervallen mit Gedächtnisprozessen korreliert.

3. Die Gewinnung von elektrophysiologischen Parametern ist grundlegend für die Charakterisierung von kognitiven Prozessen sowie von kognitiven Dysfunktionen in neurologischen Erkrankungen.

4. Die Epilepsie ist eine neurologische Erkrankung, die durch Anfälle, meistens auf motorische und sensorische Phänomene bezogen, beschrieben ist. Allerdings treten häufig zusätzliche Störungen wie Gedächtnis-, Aufmerksamkeits-, oder Sprachprobleme auf.

5. Neurofeedback (bzw. EEG-Biofeedback) ist eine Therapiemethode, die als operante Konditionierung der Hirnaktivität betrachtet wird. Sie wird seit Jahrzehnten zusätzlich zu medikamentösen- und chirurgischen Therapien bei der Behandlung vieler neurologischer Krankheiten erfolgreich praktiziert.

6. Neurofeedback wird jedoch meist dafür angewendet, eine Anfallsreduzierung zu erzielen. Dagegen wird eine Verbesserung kognitiver Fähigkeiten selten vorgesehen. Darüber hinaus sind die aktuellen Neurofeedbackstrategien für diesen Zweck ungeeignet. Der Grund dafür sind unter anderem nicht adäquate Verfahren für die Gewinnung und Quantifizierung dieser Hirnaktivität.

7. Die kognitiven Leistungen von einer Patientengruppe (Epilepsie) und einer Probandengruppe wurden anhand der ereignisbezogenen De-/Synchronisation (ERD/ERS) Methode untersucht und statistisch verglichen. Signifikante Unterschiede wurden im Post-Stimulus Intervall im Theta bzw. Alpha Band

festgestellt. Unterschiede in diesen Frequenzbändern wurden nach Untersuchung der Bandleistung auch im Ruhezustand, d.h. im Prä-Stimulus Intervall, nachgewiesen. Diese Ergebnisse deuten eine mögliche, auf Arbeitsgedächtnis oder Aufmerksamkeit bezogene, kognitive Dysfunktion bei den Epilepsie Patienten an.

8. Anhand einer methodischen Studie wurden die dynamischen Eigenschaften von vier verschiedenen ERD-Algorithmen verglichen und ihre Onlinefähigkeit bestätigt. Ausgehend von den erhaltenen Ergebnissen wurde ein ERD-Algorithmus für zukünftige Neurofeedback Applikationen ausgewählt.

9. Basierend auf den ausgewählten Parametern wurde eine Methodik für die Gewinnung und Quantifizierung von kognitionsbezogener induzierter EEG Aktivität in Echtzeit entwickelt. Die dazugehörigen Prozeduren sind in Module organisiert, um die Prozessapplikabilität zu erhöhen. Mehrere Bestandteile der Methodik, einschließlich der Rolle von Elektrodenmontagen sowie die Eliminierung bzw. Reduktion der evozierten Aktivität, wurden anhand kognitiver Aufgaben evaluiert und optimiert.

10. Die Entwicklung einer geeigneten Neurofeedback Strategie sowie die Bestätigung der psychophysiologischen Hypothese anhand einer Pilotstudie sollen Gegenstand der zukünftigen Arbeitschritte sein.

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