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Review Paper

Best method for analysis of brain oscillations in healthy subjects and neuropsychiatric diseases

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ABSTRACT

The research related to brain oscillations and their connectivity is in a new take-off trend including the applications in neuropsychiatric diseases. What is the best strategy to learn about functional correlation of oscillations? In this report, we emphasize combined application of several analytical methods as *power spectra, adaptive filtering* of Event Related Potentials, *inter-trial coherence and spatial coherence*. These combined analysis procedure gives the most profound approach to understanding of EEG responses. Examples from healthy subjects, Alzheimer's Diseases, schizophrenia, and Bipolar Disorder are described.

1. Introduction

The brain is a dynamic system, and brain function has several manifestations. Electrical activity in electroencephalography (EEG) frequencies is one of the most important markers of function. In the present report, we will explain methods of signal analysis for understanding brain functions. Not only are there electrical oscillatory activities to correlate with brain functions, but also are the links between several structures necessary to indicate performance of brain functions. In a recent paper, Başar and Düzgün (2016–in this volume) indicate the necessity of extending the concept of Brodmann. Therefore, in the present report, we will present the application of this concept.

The present report will also describe some methods, concepts, and strategies to be used in comparative analyses of brain oscillations in healthy subjects and in neuropsychiatric diseases. It provides a general overview of the methods reported in the present volume and does not aim to cover all strategies related to systems theory that are applied across the brain research literature. The strategies and methods applied are examples of reflecting the innate organization of the brain "*The whole brain work*". The title of the present paper seems to indicate best methods for the analysis of brain oscillations. However, there are no best methods in this type of analysis. According to our longstanding experience, there are "better" or "more adequate" strategies to jointly apply in search of functional correlates of brain oscillations and/or in detection of diseases.

Brain oscillations as functional building blocks in sensory–cognitive processes have gained tremendous importance in recent decades. Research also shows that event-related oscillations (ERO) are highly modified in pathological brains, especially in patients with cognitive impairment. The major aim of the present study is to show that, in pathological states of the brain, multiple brain oscillations in the "whole cortex" are altered. The identification of clinical biomarkers requires large spectra of mathematical parameters and multiple strategies. The oscillatory changes in *multiple frequency windows* and the whole cortex should be taken into consideration by analyzing relevant changes in the amplitude of *function-related oscillations*, together with *multiple connectivity deficits*. At the end of the paper, we will present highlights for neurophysiological explorations in diagnostics, drug application, and progressive monitoring of diseases.

We start by emphasizing that there are important functional and interpretational differences between spontaneous EEG, sensory evoked oscillations, and EROs. In the analysis of spontaneous EEG, only sporadic changes of amplitudes from hidden sources are measured. Sensory evoked oscillations reflect the property of sensory networks activated by a simple sensory stimulation. Event-related (or cognitive) oscillations manifest a modification of sensory and cognitive networks triggered by a cognitive task (see Fig. 1).

It is evident that, by performing and comparing all types of analyses, a large number of permutations are possible, thus giving rise to a wider spectrum of interpretations related to the *differentiation of diseases*, *progress of diseases*, and modifications upon *application of medication*. The final aim of the present report, as presented in the last section, is therefore to indicate that a valid analysis of brain electrical potentials

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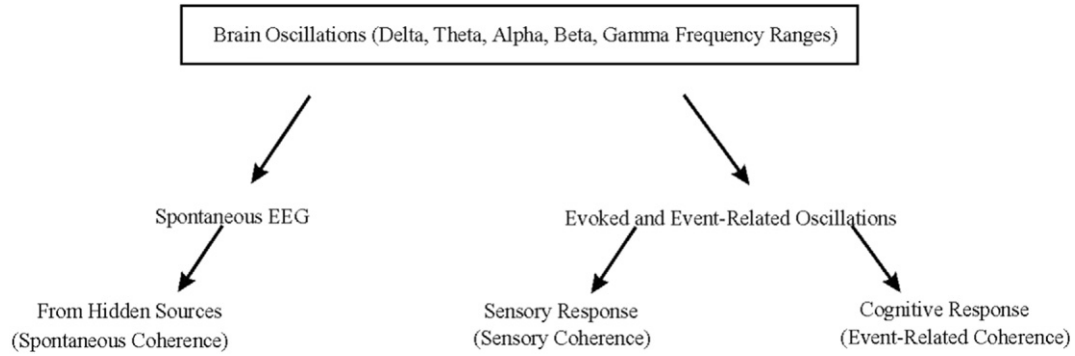

Fig. 1. A schematic presentation of differentiation in search of biomarkers related to brain oscillations (modified from Başar et al., 2013).

in search of biomarkers can be achieved only by successive application of analysis tools and should not be reduced to the search of a given frequency range or a given stimulus modality.

It is also fundamental to note that comparison of results obtained upon application of sensory signals and cognitive inputs is extremely important: In diseases such as Alzheimer's Disease (AD), schizophrenia, Mild Cognitive Impairment (MCI) and Bipolar Disorder (BD), patients show cognitive deficits depending on the state of illness, age, and cultural differences. Accordingly, cognitive deficits can be demonstrated only after comparing results upon sensory and cognitive signals (see papers by Basar-Eroglu et al., 2013; Yener and Başar, 2013a; Özerdem et al., 2013).

The methods outlined in Table 2 can be applied step-by-step or in a random sequence; some of the methods can be omitted, depending on the application possibilities in patients. This also depends on the research priorities of different laboratories. Therefore, we do not aim to demonstrate all possible applications; we will give only a few examples. Several useful applications are presented in this special issue (see Vecchio et al., 2013; Basar-Eroglu et al., 2013; Yener and Başar, 2013a; Özerdem et al., 2013).

2. Why do we apply several mathematical signal analysis methods together?

At the turn of the 20th century, a very important concept was introduced in the study of brain functions. The relevant cytoarchitectural search by Brodmann in several brain areas was associated with appropriate brain functions. The so-called Brodmann areas provide relevant information to globally understand brain functions. At the end of the 20th century, especially after personal computers began being used in all neuroscience laboratories, research scientists started to use several brain imaging techniques. Starting with the quantitation of EEG and event-related potentials in the present paper, we performed a review of relevant systems theory methods for understanding of the fine structures of the distribution in the whole cortex.

As we learn from the surveyed references presented in this report, the neural electrical responses upon stimulation of the brain are selectively distributed. The brain response oscillations can be measured in several areas of the cortex; however the amplitude in different frequencies and phase-locking strands vary according to the type of stimulation. There are also delays following stimuli related to electrode locations and type of applied stimulations. In other words, brain function, which is dependent on sensory and cognitive tasks, shows dynamic nature. When we review several imaging techniques and strategies that will be presented in next section, it is recognized that Brodmann areas alone cannot manifest the brain function distributed in the whole brain. Accordingly, it is a necessity to analyze several EEG response components in the whole cortex.

Besides the selectivity of distributed event-related oscillations, it is not possible to correlate a given brain function with a single structure of the cortex. The connectivity between several brain areas is also very relevant to define the function of the brain. Upon a given stimulation, there are oscillatory responses in more than one single structure.

Because of this fact, we consider brain function as the joint activity of several areas. The link between several areas can be measured anatomically and electrically. One of the methods used is spectral connectivity, i.e. the computing of coherence function.

There are several steps from single neural doctrine to the understanding of the whole brain. Roy John has introduced the concept of "hyperneuron", and J. Fuster developed the concept of "cognits" to demonstrate the importance of neural ensembles in brain functioning. Başar et al. (2014) have presented a new model that is structured by the research of selectively distributed and superimposed event-related oscillations. Further, the connectivity between various brain structures is included in the so-called CLAIR areas. The expressions of CLAIR are a symbolic presentation of the words "coherence-time, links, association, integration and, responsiveness". In these new publications, a few examples are provided for the use of the CLAIR model.

In the present paper, we therefore propose that the use of an ensemble of adequate methods is necessary to develop the CLAIR model to be used as an extension to the Brodmann model.

3. Why application of several methods and strategies is important in the search for biomarkers

Fig. 2 illustrates new approaches and strategies in functional neuroscience. The methods range from indirect means of measuring changes in cerebral blood flow in local regions of the human cortex [Functional Magnetic Resonance Imaging (fMRI)], or changes in the electrical activity of the human brain with EEG-recording with multiple electrodes, to the use of chronically implanted multiple electrodes in primates. According to Mountcastle (1998), measurement using large populations of neurons is presently the most useful experimental paradigm used in perception experiments. fMRI has the disadvantage of low temporal resolution, and long distance measurements cannot yet be performed with multiple microelectrodes. Therefore, measurements of *macro-activity* (EEG/ERP and Magnetoencephalography (MEG)) seem to be the most appropriate method to measure the dynamic properties of memory and of integrative brain function.

Since neuroscientists have come to the general conclusion that large numbers of different brain regions must cooperate in any brain function, the analysis of relationships between different regions of the brain is becoming increasingly important.

In the following section, we will briefly discuss the outcomes of methods and strategies shown in Fig. 2. The expression *strategy* refers here to the combined application of several methods, in parallel or sequentially.

1) Studies at the single-cell level have been of great importance in elucidating the basic physiological mechanisms of communication

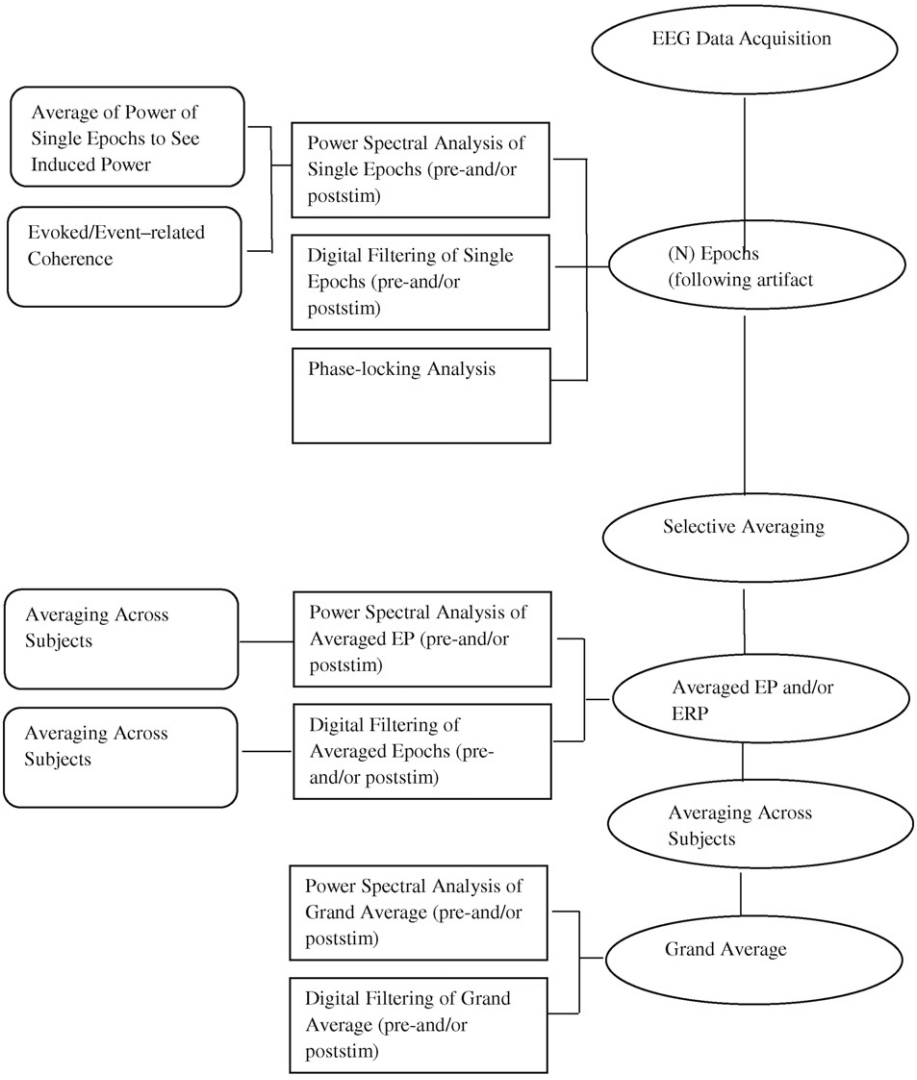

Fig. 2. Approaches and strategies in functional neuroscience (modified from Başar, 2004).

between cells (Mountcastle, 1998; Eccles, 1973). However, the importance of these studies for understanding integrative brain functions is questionable since, during the integrative processes, the whole brain is involved, as Ross Adey (1966, 1989); and Adey et al. (1960) merely underlined, and the new trends in neuroscience clearly emphasize (see also Freeman, 1999).

2) Positron emission tomography is an invasive procedure applied to patients. It has large temporal resolution in the range of half an hour and offers no possibility for dynamic measurements at the level of microseconds.

Fig. 3 illustrates a more advanced version of the Biological Systems Analysis and Brain Dynamics Research Programs, with the methods of thought or research principles being separately displayed. The rationale to develop a research program was based on ways to elucidate the black box (the brain).

3) The methods incorporating analyses of EEG/ERPs (and especially ERO) and functional magnetic resonance imaging (fMRI) provide further excellent strategies to illuminate brain functions, since they cover dynamic changes in the brain and the morphological structure. *Magnetoencephalography* and study of magnetic evoked fields (MEF) greatly increase the spatial resolution in comparison to EEG and ERP. Accordingly, these methods are likely to provide excellent results in future applications.

4) The new strategies are interwoven with the use of relevant mathematical and psycho-physiological strategies. These are:

   i) Mathematical and systems theoretical approaches including, in recent decades: a) the concepts of *chaos*, *entropy*; b) modeling with *neural networks*, interpretation of *frequency domain approach*, new approaches utilizing wavelet analysis and spatial and temporal coherences;

   ii) Psychological strategies with the use of behavioral paradigms and application of neuropsychological tests (Karakaş et al., 2002, 2003);

   iii) An important strategy, not included in Fig. 2, is recording with chronically implanted intra-cranial electrodes in the animal brain.

The application of combined strategies in all these fields has led to new horizons for understanding the integrative functions of the brain, especially of memory function. The role of memory in the human mind and behavior cannot be overemphasized, since very few aspects of higher nervous function could operate successfully without some memory contribution; perception, recognition, language, planning, problem solving and decision-making all rely on memory (Damasio and Damasio, 1994). In order to achieve relevant progress in functional

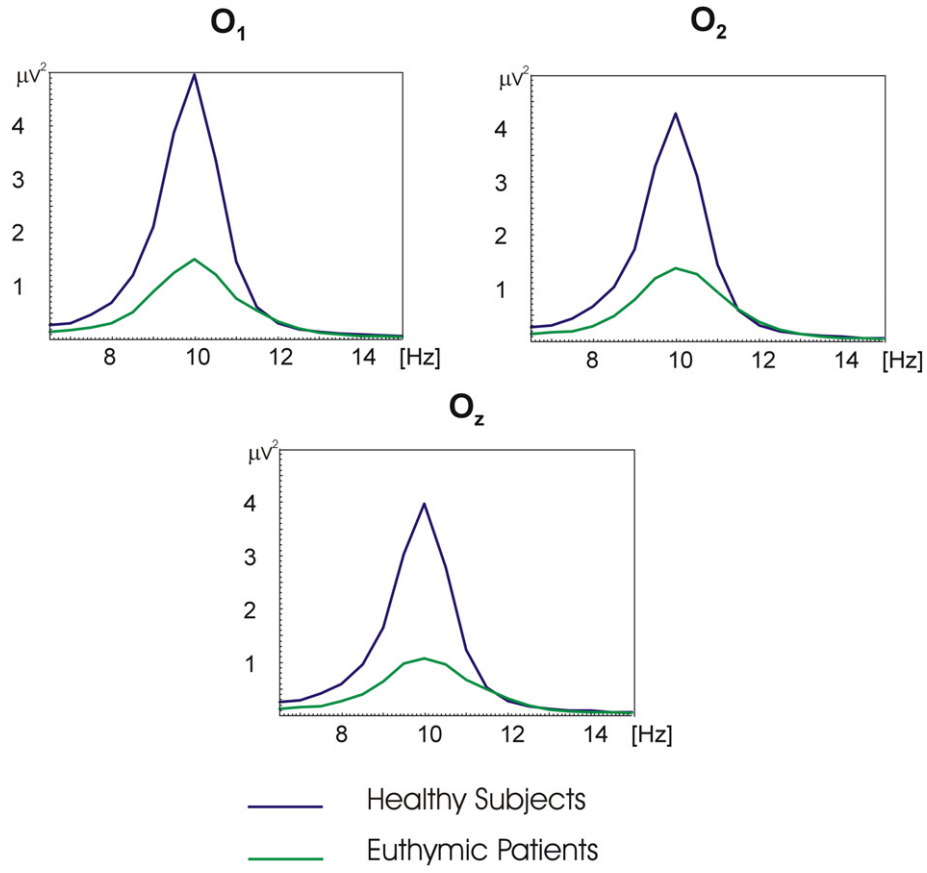

Fig. 3. Brain dynamics research program (modified from Başar, 1998).

neuroscience, it became fundamental to apply several methods together (Freeman, 1999). However, the application of all strategies in every laboratory is not yet possible. Fig. 2 further illustrates the levels of basic CNS-functions (right side) and the applied domains (left side). Functions such as *sensory detection*, *movement*, and *memory* can be successfully analyzed using individual methods or strategies from several research domains, such as *evolution*, *aging*, *pathology* and *pharmacology* (use of drugs or pharmacological agents in pathological states).

4. Some established rules in the application of oscillatory dynamics

The functional significance of oscillatory neural activity begins to emerge from the analysis of responses to well-defined events (*ERO that is phase- or time-locked to a sensory or cognitive event*). Among other approaches, it is possible to investigate such oscillations by frequency domain analysis of ERP, based on the hypothesis and rules outlined in Basar (2013) and in this special issue. We recommend the reading of Başar-Eroglu et al. (1993); Başar-Eroğlu et al. (1999), Başar-Eroglu et al. (1991) Başar-Eroglu et al. (2001), Sakowitz et al. (2001), Schürmann et al. (1997); and Başar et al. (1998).

In the following table, we summarize essential features (Table 1).

5. Ensemble of systems theory methods

5.1. Systems theory methods

In order to analyze the dynamics of brain oscillatory processes, several mathematical methods are applied. Table 2 summarizes the methods included in the 'systems-theory' of brain-state analysis.

Table 1
Essential features of the "Whole Brain" work in integrative brain function as consequence of the above rule.

According to Başar (2006, 2011), all structures of the brain work in concert during sensory–cognitive processes. This overall coordination of oscillatory processes is based on a type of super-synergy, which comprises an ensemble of at least six mechanisms working in parallel upon sensory–cognitive input. It is proposed that the coexistence and cooperative action of these interwoven and interacting sub-mechanisms shape the integrative brain functions.
The sub-mechanisms and/or related processes are as follows:

1. The "superposition" is the parallel activation of electrical activity in alpha, beta, gamma, theta, and delta bands during integrative functional processes of the brain (Başar et al., 1999a, 1999b; Karakaş et al., 2000a, 2000b; Klimesch et al., 2000; Chen and Herrmann, 2001).
2. The parallel activation of oscillations in gamma, beta, alpha, theta and delta responses upon exogenous or endogenous inputs are selectively distributed oscillations in the brain. These responses are manifested with the occurrence of multiple parameters such as *phase-locking enhancement*, *delay*, *blocking* (*desynchronization*), and *prolongation* (Başar, 1980, 1999; Başar et al., 1999a, 1999b, 2000, 2001a, 2001b). The ensemble of oscillations and amplitude of oscillations and coherence values between different brain areas usually increase as the complexity of the stimulation increases or the recognition of the stimulus becomes more difficult.
3. Temporal and spatial changes of entropy in the brain (Quiroga et al., 1999; Yordanova et al., 2002).
4. Temporal coherence between cells in cortical columns contributes to the simple binding mechanism (Eckhorn et al., 1988, Gray and Singer, 1989).
5. Varying degrees of spatial coherence occur over long distances as parallel processing (Başar, 1980, 1983a, 1983b; Miltner et al., 1999; Schürmann et al., 2000; Kocsis et al., 2001).
6. Inverse relationship between EEG and event-related potentials: EEG is a control parameter for responsiveness of the brain.

Table 2
The ensemble of systems theory methods.

a) Power spectral density of the spontaneous EEG
b) Evoked spectra (FFT analysis of the sensory evoked potential elicited by simple light, tone signal, etc.)
c) Event-related spectra (FFT analysis of an ERP, for example target or non-target signal during an oddball paradigm).
d) Phase-locking, phase synchrony
e) Cross correlation
f) Cross spectrum
g) EEG coherence
h) Evoked coherence
i) Event-related coherence
k) Inter-trial coherence

Among the applications described in the following sections, spectral signal analysis constitutes one of the most important and most commonly used analytical tools for the evaluation of neurophysiological signals. It is not only amplitude and phase that are of interest, but also a variety of measures derived from them, including important coupling measures such as coherence or phase synchrony. Demiralp et al. (1999); Başar et al. (1999c); and Başar (2011) compared wavelet transform techniques and conventional Fourier analysis in human and cat brains and showed the equivalence of these techniques (see also Appendices A.1 and A.2). A most fundamental comparison of various spectral techniques was performed by Bruns (2004), comparing the three classical spectral analysis approaches: Fourier, Hilbert, and wavelet transform. Although recently there seems to be increasing acceptance of the notion that Hilbert- or wavelet-based analyses might be superior to Fourier-based analyses, Bruns (2004) demonstrated that the three techniques are formally (i.e. mathematically) equivalent when using the class of wavelets that is typically applied in spectral analyses. Moreover, spectral amplitude serves as an example that Fourier, Hilbert, and wavelet analyses also yield equivalent results in practical applications on neuronal signals.

More refined methods were also incorporated in order to analyze evoked brain activity, including the combined EEG–EP analysis and

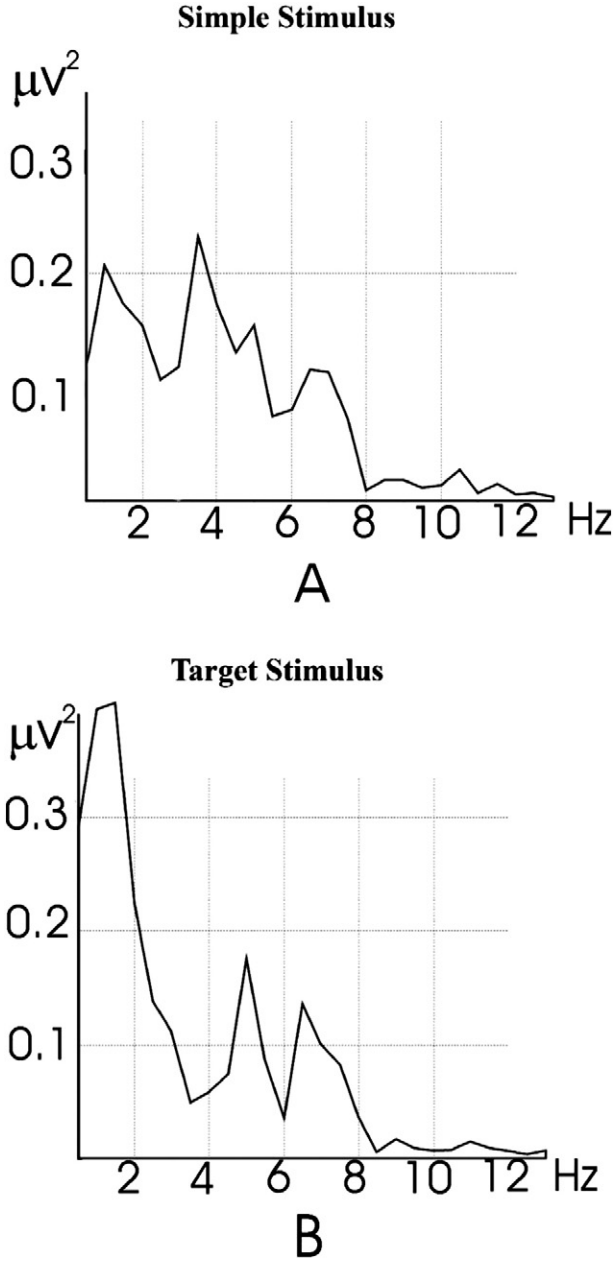

Fig. 4. Combined time and frequency domain analysis of EEG–EP epochs (modified from Schürmann and Başar, 1994; Başar et al., 2000).

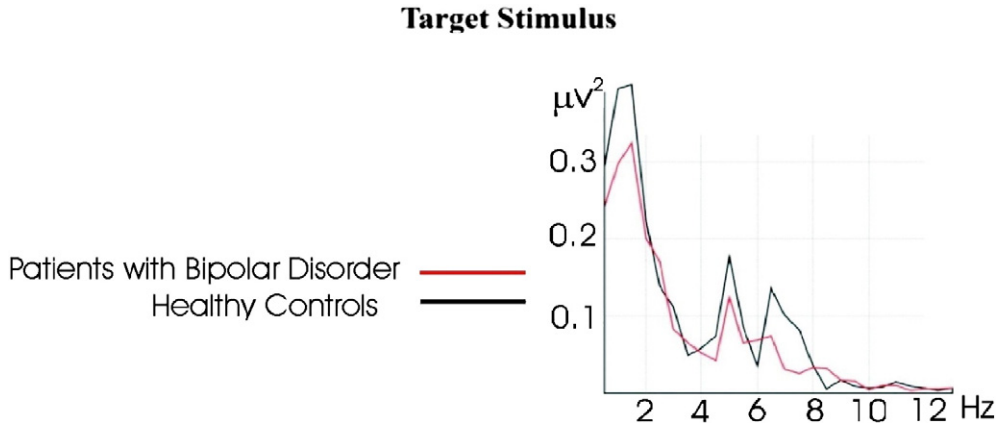

Fig. 5. Mean values of power spectrum for occipital electrodes in eyes-closed condition (modified from Başar et al., 2012).

wavelet analysis methods (Quiroga et al., 2001a, 2001b; Başar et al., 1999c, 2001a; Demiralp et al., 1999). Our group first applied system theory methods to brain waves using conventional methods. Later, our group also applied new methods such as *wavelet entropy* (Rosso et al., 2001; Quiroga et al., 1999). In addition to the systems theory methods, newly emerging methods of analyzing ERO include studies of nonlinearities and the incorporation of the concept of chaos, which aim to further increase understanding of the properties of the system.

5.2. Some fundamental remarks

Time-locked and/or phase-locked methods show that the responses of a specific frequency after stimulation can be identified by computing the amplitude frequency characteristics (AFCs) of the averaged ERPs (Başar, 1972, 1980; Başar and Ungan, 1973; Başar and Özesmi, 1972; Röschke et al., 1995; Yordanova and Kolev, 1997) or the event-related and evoked power spectra. The AFC and event-related power spectra describe the brain system's transfer properties, e.g., excitability and susceptibility to respond, by revealing resonant as well as salient frequencies. Therefore, it does not simply represent the spectral power density characterizing the transient signal in the frequency domain but also the predicted behavior of the system (brain) if sinusoidal modulated input signals of defined frequencies were applied as stimulation. Since it reflects the amplification in a given frequency channel, the AFC is expressed in relative units. Hence, the presence of a peak in the AFC or post-stimulus spectra reveals the *resonant frequencies* interpreted as the preferred oscillations of the system during the response to a stimulus. In order to calculate the AFCs, the ERPs were first averaged and then transformed to the frequency domain by means of one-sided Fourier transform (Laplace transform, see Solodovnikov, 1960; Başar, 1980), as shown in Fig. 4. Further, Fig. 4 illustrates the proposed ensemble of systems-theory analysis methods in search of neurophysiological markers in healthy subjects and neuropsychiatric patients. A core stage in this ensemble of methods is the recording of electrical potentials, known as evoked potential and event-related potentials in the conventional nomenclature of electrophysiology analysis. First, in order to perform Fourier analysis of brain responses, an averaging procedure is applied to data from healthy subjects and patients. Following artifact rejection, selective averaging is performed. The averaged potentials (EP and/or ERP) are then analyzed with FFT and, according to the cut-off frequencies of evoked power spectra, digital filtering is applied to compound evoked potentials. A grand average is also applied by performing averaging across subjects. Another option is power-spectral analysis of the grand average, in which adaptive digital filtering of the grand average is performed.

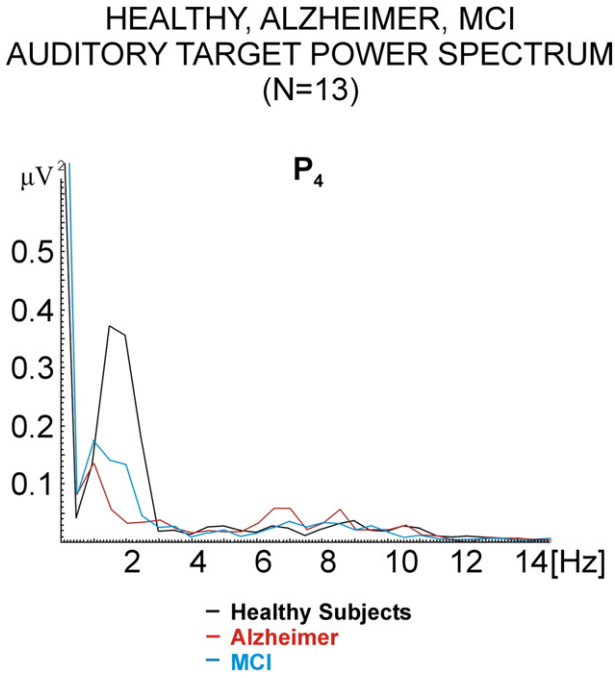

Fig. 6. Grand average of power spectra of auditory evoked (A) and event-related (target) responses (B) over left frontal (F_3) location. Target stimuli (B) create greater increases in amplitudes than simple sensory stimuli (A) in delta frequency range in healthy subjects (modified from Başar et al., 2013).

6. Changes in EEG and ERO by means of some examples

6.1. Power spectral analysis of spontaneous EEG

Power spectral analysis of EEG spontaneous activity is one of the most successfully applied methods in the search for biomarkers (see Vecchio et al., 2013). Fig. 5 represents the grand averages of power spectra of 18 healthy (indicated by blue line) and 18 bipolar euthymic subjects (green line) in the alpha frequency range for the eyes-closed spontaneous EEG recording session for occipital locations (O_1, O_z, and O_2). As seen from Fig. 5, within the alpha frequency range, the power spectrum of healthy subjects reaches up to 4.8 μV^2 for O_1; 4 μV^2 for O_z and 4.5 μV^2 for O_2 electrodes, while that of euthymic subjects reaches up to 1 μV^2 for all occipital electrodes.

Event-related spectra of bipolar patients in the alpha frequency range are also drastically reduced, as recently shown by Başar et al.

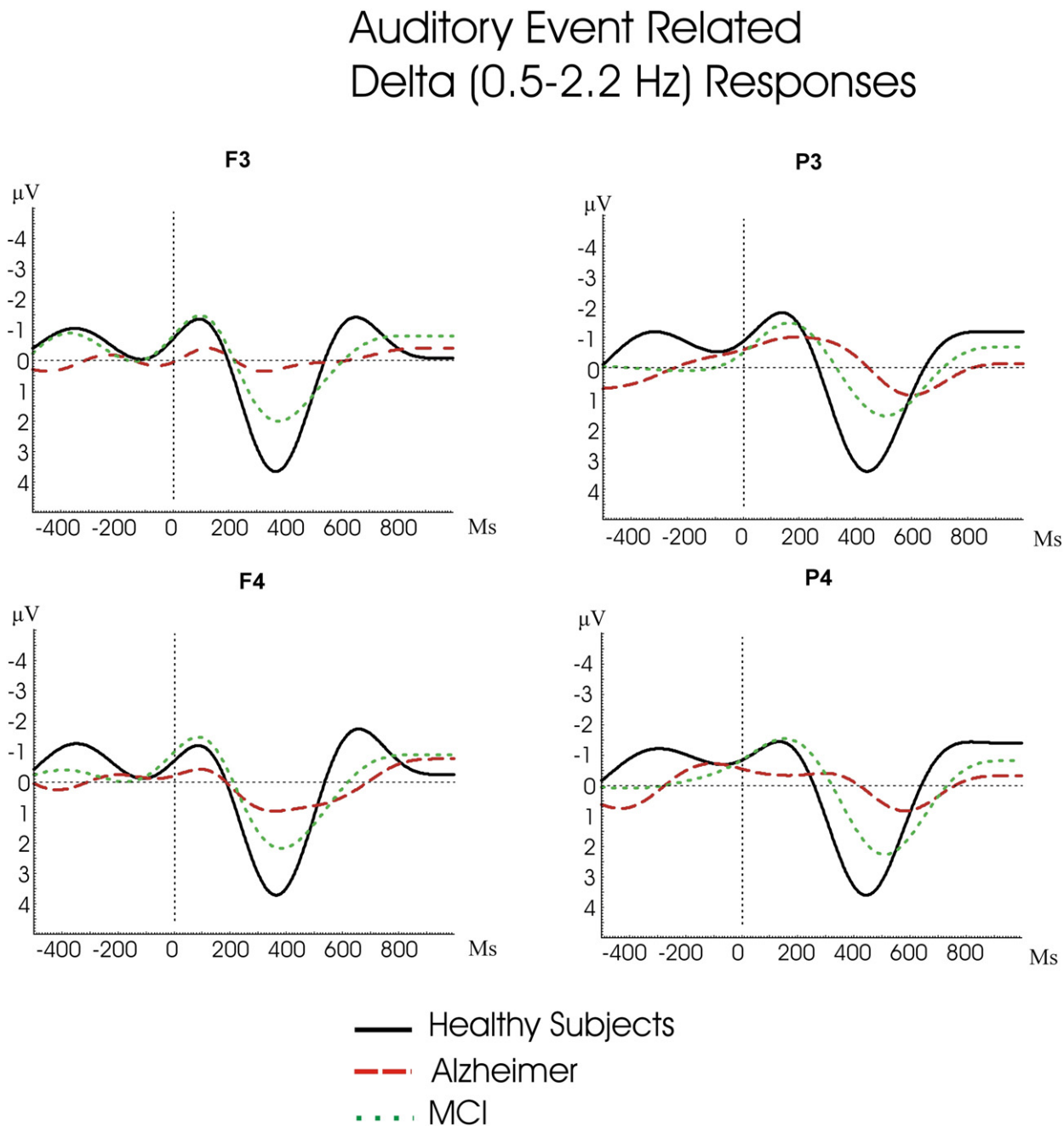

Fig. 7. Grand average of power spectra of auditory event-related responses over left frontal (F_3) location in bipolar disorder subjects and healthy controls upon auditory oddball stimulation (modified from Özerdem et al., 2013).

(2012). Only the prominent decrease of alpha power illustrated in Fig. 5 could possible serve as a neurophysiological marker in BD. Additionally, the disappearance of event-related theta power in BD may be also a relevant change; this will be explained in the next sections.

6.2. Analysis of evoked and event-related spectra

As seen in Fig. 6, in the grand average of post-stimulus power spectrum upon stimulation of target stimuli, two different theta frequency peaks were detected in the healthy control group, in the 0.5–15 Hz frequency range for both slow theta (4–6 Hz) and fast theta (6–8 Hz). Adaptive digital filtering was applied to these identified frequency ranges. Adaptive filtering of the response provides a major advantage that subsystems of the system might be selectively removed to obtain isolation. Isolation of the filters separately may lead to choosing the amplitude and frequency characteristics of the filters. Ideal filters may be applied without phase shifts. In addition, the method also allows the definition of filters with exact characteristics and regulating them adequately according to the amplitude characteristics of the system

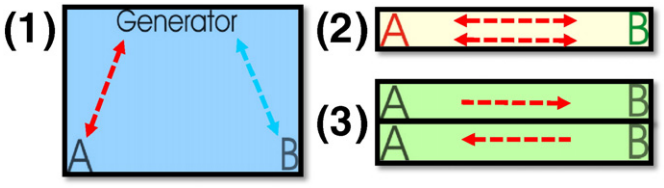

Fig. 8. Event-related spectral analysis of healthy control subjects, mild cognitive impairment (MCI), and Alzheimer's disease (AD).

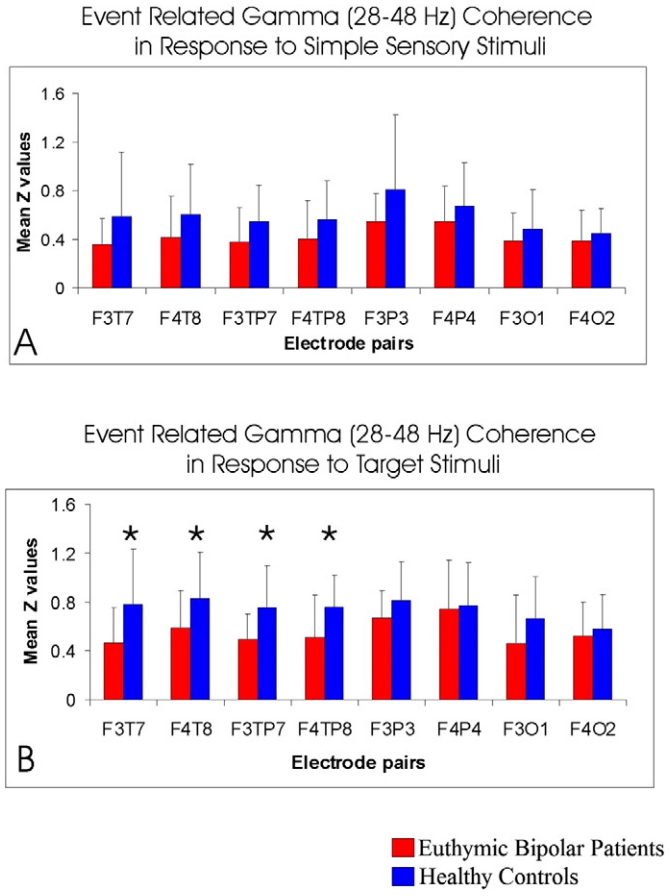

Fig. 9. MCI and AD continuity is prominent in auditory event-related delta oscillatory activity. Results show gradually decreasing delta amplitude and increasing delta peak latency among healthy elderly subjects, MCI, and mild-stage Alzheimer subjects (MCI: mild cognitive impairment, AD: Alzheimer's disease).

(for further information, see Başar, 2004; Doppelmayr et al., 1998; Dumont et al., 1999).

Accordingly, each subjects' averaged evoked and event-related potentials were digitally filtered in slow theta (4–6 Hz) and fast theta (6–8 Hz) frequency ranges. The maximum peak-to-peak amplitudes for each subject's averaged slow theta (4–6 Hz) and fast theta (6–8 Hz) responses were analyzed; that is, the largest peak-to-peak value in these frequency ranges in terms of μVs found in the time window between 0 and 500 ms.

The event-related (target) response shows a highly increased delta response (1.5 Hz) in comparison to sensory evoked delta. It is of further interest that two different responses are recorded upon simple auditory versus target stimuli in healthy subjects: Slow theta (4 Hz) and fast theta (7 Hz).

It is important to note that the delta response to sensory stimulation is not as high as the event-related delta response. Changes are markedly higher upon cognitive load. This is most probably because in healthy subjects and patients, the sensory–cognitive stimulation activates a larger number of neural populations in comparison to the effect of pure sensory stimulation. Further, it is important to analyze the changes in two different windows: the selection of digital filters in the conventional 4–7 Hz filter limits could lead to crucial information lost in this example.

6.3. Differentiated changes of theta responses in bipolar disorder

Evoked and event-related slow and fast theta oscillations in response to auditory stimulus were studied in 22 euthymic, drug-free patients with bipolar disorder.

As seen from Fig. 7, slow (4–6 Hz) and fast (6–8 Hz) theta responses behaved differently during the oddball paradigm in patients with bipolar disorder. Fast theta responses (6–8 Hz) almost disappeared in euthymic BD patients (Atagün et al., 2013).

Application of digital filters in the analysis of neuropsychiatry patients requires refinement with the use of adaptive filters selected according to the cutoff frequency in power spectra rather than predefined filters in the conventional frequency ranges. Sometimes a peak is missed or shifted to other frequencies in patients; this also is especially the case following drug applications.

6.4. AD and MCI delta responses: frequency shift, amplitude decreases and delays

In order to compare cognitive responses between healthy subjects and AD patients, a further study used a two-tone auditory oddball task. We confined our attention to the delta frequency range, as this frequency band shows major reduction in AD patients. Fig. 8 shows a comparative analysis of event-related power spectra computed by means of FFT applied to oddball target tones. Healthy subjects show a maximum around 2 Hz, whereas in MCI and AD subjects, the frequency of the response is decreased to approximately 1 Hz. These results can be immediately interpreted as a frequency slowing in MCI and AD patients during cognitive performance in comparison to healthy subjects.

According to the cut-off frequency (0.5–2.2 Hz) of the target responses, the transient target responses were analyzed in frontal and parietal locations with adaptive digital filters.

Fig. 9 illustrates adaptively filtered frontal and parietal ERO of healthy, MCI, and AD subjects in the delta frequency range. In all locations, delta responses of healthy subjects show peak-to-peak response amplitudes around 4–5 μV, whereas delta responses of MCI subjects have only the half value, at around 2 μV. Frontal and parietal delta responses of AD patients were extremely low. A delay in peak delta ERO response and a gradual decrease in amplitude of delta ERO response across healthy control subjects, MCI, and AD patients can be noted. This delay is much more pronounced in parietal locations.

A decrease in delta response is also observed in euthymic bipolar patients (Fig. 7) and in schizophrenia patients in measurements upon inputs with cognitive tasks.

For Alzheimer's disease, there are specific biomarker methods related to structural changes in the central nervous system (CNS). Those methods are described by Lovestone (2009), Vecchio et al. (2013); and Yener and Başar (2013a).

7. Selective connectivity deficit

There are several connections between different structures of the brain. The connectivity that can be measured by means of coherence function in healthy subjects is well defined, whereas patients in whom some given brain substructures are anatomically or physiologically disrupted display deficits in selective connectivity.

An important brain mechanism underlying cognitive processes is the exchange of information between brain areas (Başar et al., 2010; Güntekin et al., 2008). The oscillatory analysis of isolated brain areas alone is not sufficient to explain all aspects of information processing within the brain. Therefore, for a description of neurophysiological mechanisms underlying cognitive deficits of neuropsychiatric diseases, connectivity dynamics between different brain areas must be investigated (Yener and Başar, 2013b; Sharma et al., 2013).

According to Bullock et al. (2003), increased coherence between two structures, namely A and B, can be caused by the following processes: (1) structures A and B are driven by the same generator; (2) structures A and B can mutually drive each other; and (3) one of the structures, A or B, drives the other (Fig. 10).

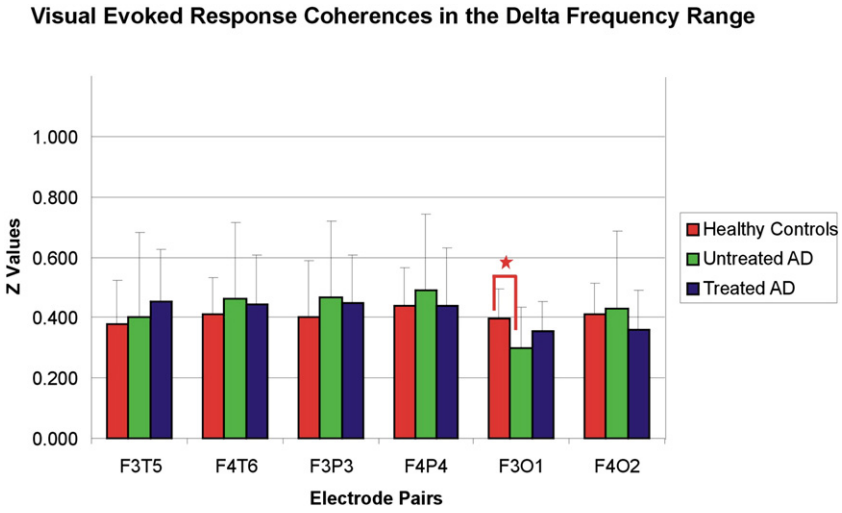

Fig. 10. A description of possible underlying mechanism of coherence between two structures (see text).

In the following section, two examples of the selective connectivity deficit in AD and BD patients will be presented.

7.1. Decrease of event-related gamma coherence in euthymic bipolar patients

Özerdem et al. (2011) studied the cortico-cortical connectivity by examining sensory-evoked coherence and event-related coherence values for the gamma frequency band during simple light stimulation and visual oddball paradigm in euthymic drug-free bipolar patients. The study group consisted of 20 drug-free euthymic bipolar patients and 20 sex- and age-matched healthy controls. Groups were compared for the coherence values of the left (F_3–T_3, F_3–TP_7, F_3–P_3, F_3–O_1) and right (F_4–T_4, F_4–TP_8, F_4–P_4, F_4–O_2) intra-hemispheric electrode pairs and showed significantly diminished bilateral long-distance gamma coherence between frontal and temporal as well as between frontal and temporo-parietal regions compared to healthy controls.

However, no significant reduction in sensory-evoked coherence was recorded in the patient group compared to the healthy controls. The decrease in event-related coherence differed topologically and ranged between 29% (right fronto-temporal location) and 44% (left fronto-temporo-parietal location). Fig. 11A and B depict the grand average of visual event-related coherence in the gamma frequency (28–48 Hz) band in response to target stimuli between the right (F_4–T_8) and left (F_3–T_7) fronto-temporal electrode pairs in euthymic bipolar patients (n = 20) compared with healthy controls (n = 20) (Özerdem et al., 2011).

Oscillatory responses to both target and non-target stimuli are manifestations of working memory processes. Therefore, the coherence decrease in response to both types of stimuli indicates inadequate connectivity between different parts of the brain during a cognitive process, in comparison to pure sensory signal processing.

7.2. Decrease of event-related coherence in Alzheimer patients

Several research groups have already published a number of studies related to analysis of oscillatory dynamics in MCI and AD patients. Babiloni et al. (2006, 2007, 2009), Jelic et al. (2000), and Rossini et al. (2006) published core results on spontaneous EEG coherence in MCI patients. Zheng-yan (2005), Hogan et al. (2003), Başar et al. (2010), Güntekin et al. (2008), Yener et al. (2007, 2008, 2009), and Dauwels et al. (2009) published results on evoked/event-related coherence in Alzheimer's disease patients. At this point, it is vital to emphasize that there are important functional differences between "*EEG coherence*", "*evoked coherence*" and "*event-related coherence*". In EEG analysis, only sporadically occurring coherences from hidden sources can be measured. Sensory evoked coherences reflect the property of sensory networks activated by a sensory stimulation. Event-related (or cognitive)

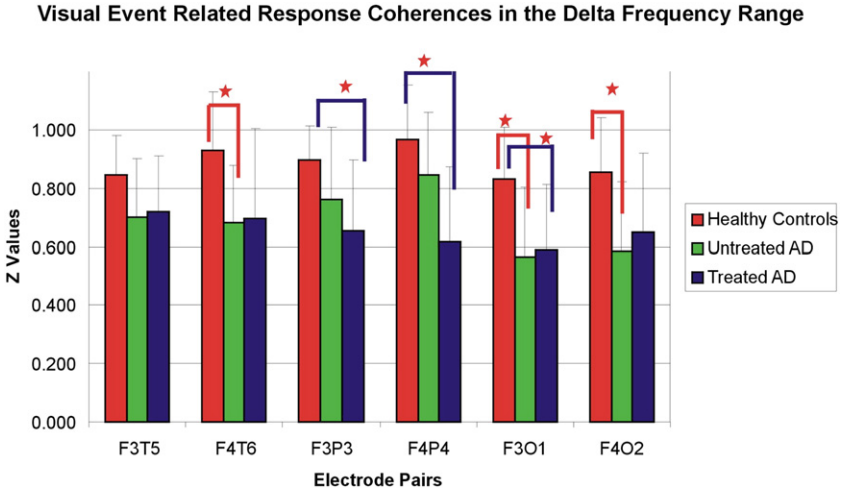

Fig. 11. Mean Z values for sensory evoked (11A) and target (11B) coherences in response to visual stimuli at all electrode pairs. "*" sign represents $p < 0.05$ (modified from Özerdem et al., 2011).

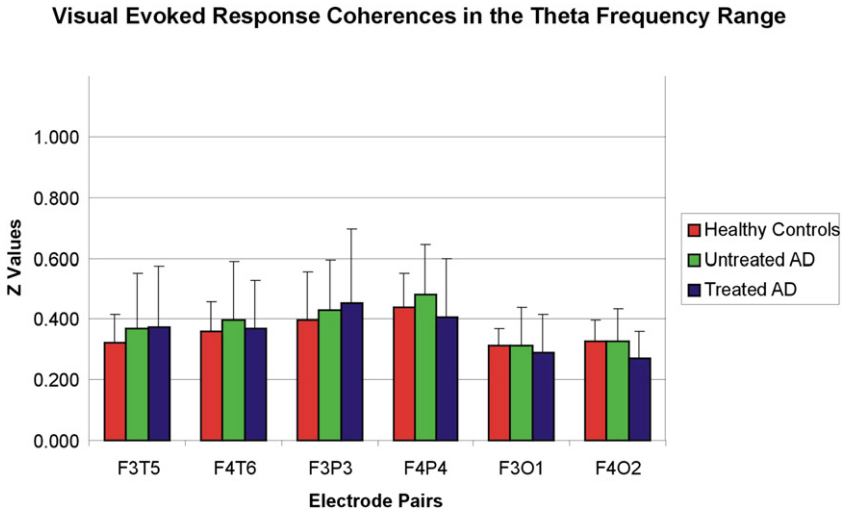

Fig. 12. Mean Z-values of healthy controls, treated AD, and untreated AD subjects for delta frequency range upon simple light stimuli. "*" sign represents $p < 0.01$ (modified from Başar et al., 2010).

coherences manifest coherent activity of sensory and cognitive networks triggered by a cognitive task. Accordingly, the cognitive-response coherences comprise activation of a greater number of neural networks that are most possibly not activated, or less activated, in the EEG and sensory-evoked coherences. Therefore, event-related coherence merits special attention. Particularly in AD patients with strong cognitive impairment, it is relevant to analyze whether medical treatment (drug application) selectively acts upon sensory and cognitive networks manifested in topologically different areas and in different frequency windows. Such an observation may provide, in the future, a deeper understanding of the physiology of distributed functional networks and, in turn, the possibility of determination of biomarkers for medical treatment.

Başar et al. (2010) compared visual sensory-evoked and event-related coherences of patients with Alzheimer's-type dementia (AD). A total of 38 mild, probable AD subjects (19 untreated, 19 treated with cholinesterase inhibitors) were compared with a group of 19 healthy controls. The sensory-evoked coherence and event-related target coherences were analyzed for all frequency ranges for long-range intra-hemispheric (F_3–P_3, F_4–P_4, F_3–T_5, F_4–T_6, F_3–O_1, F_4–O_2) electrode pairs. The healthy control group showed significantly higher values of event-related coherence in "*delta*", "*theta*" and "*alpha*" bands in comparison to the *de novo* and medicated AD groups upon application of target stimuli. In contrast, almost no changes in event-related coherences were observed in beta and gamma frequency bands. Furthermore, almost no differences were recorded between healthy and AD groups upon application of simple light stimuli. Besides this, coherence values upon application of target stimuli were higher than sensory-evoked coherence in all groups and in all frequency bands ($p < 0.01$). These results give hints for a preserved visual-sensory network in contrast to a damaged visual cognitive network in MCI.

Fig. 12 illustrates the histogram of mean Z-values for delta frequency range upon application of "simple light" stimuli for all electrode pairs; Fig. 13 provides a histogram of mean Z-values for delta frequency range upon application of "target" stimuli for all electrode pairs. In both figures, red bars represent the mean Z-values for healthy subjects, whereas green bars represent untreated AD subjects, and blue bars represent treated AD subjects. Fig. 13 shows that the healthy subjects had higher delta response coherence compared to both untreated and treated AD subjects upon application of target stimuli for all electrode pairs. The mean Z-value of healthy subjects is 40–50% higher than AD patients in most of the electrode pairs upon application of "target" stimuli. Fig. 12 shows that the evoked delta coherence upon "simple light" is as not high, and almost no difference was recorded between healthy controls and AD subjects except for slightly lower F_3–O_1 delta sensory evoked coherence in AD.

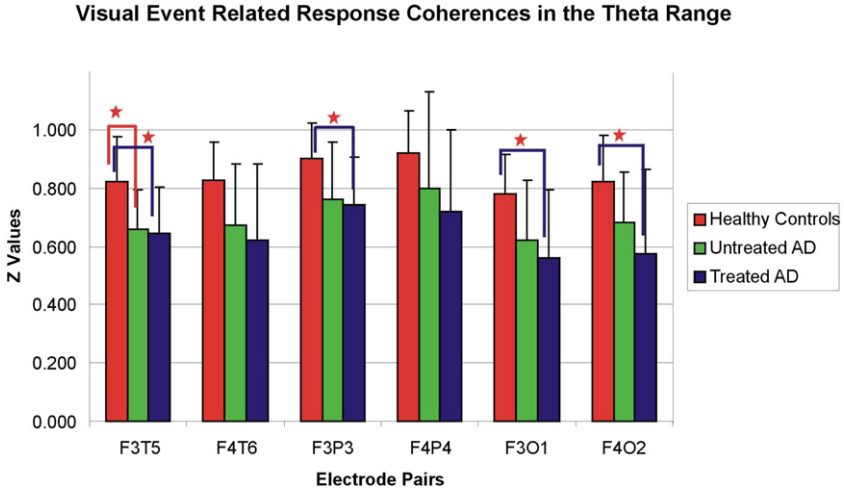

Fig. 13. Mean Z-values of healthy controls, treated AD, and untreated AD subjects for delta frequency range upon target stimuli. "*" sign represents $p < 0.01$ (modified from Başar et al., 2010).

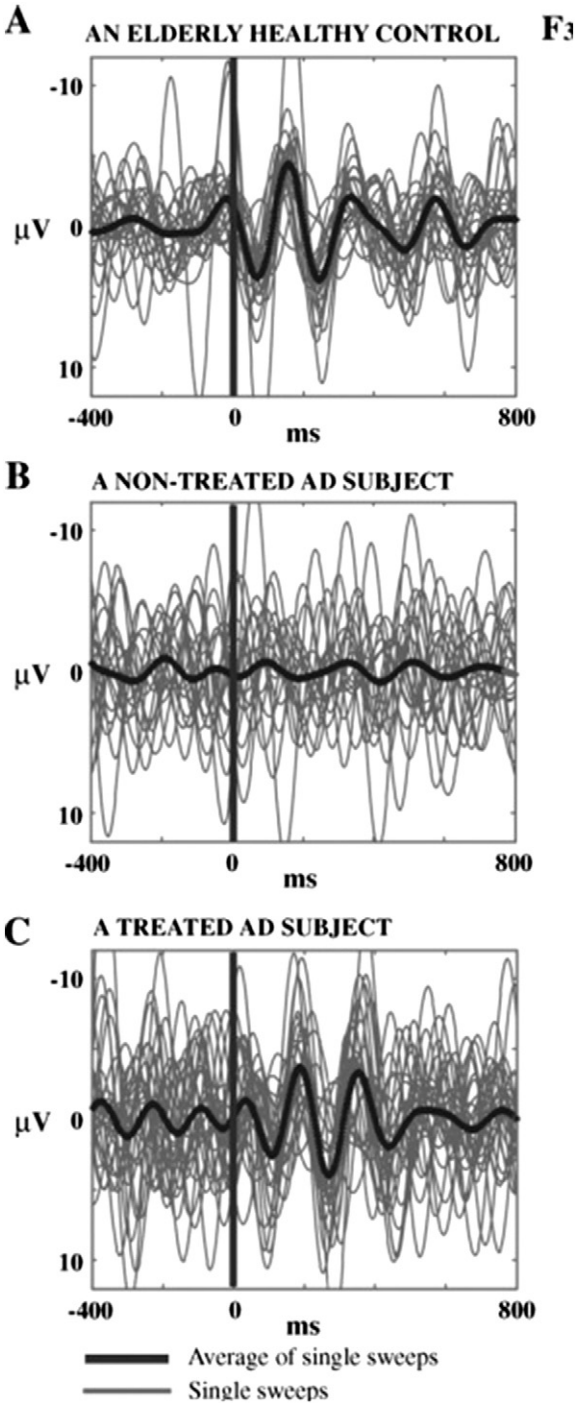

Fig. 14. Mean Z-values of healthy controls, treated AD, and untreated AD subjects for theta frequency range upon simple light stimuli (modified from Başar et al., 2010).

Fig. 14 shows no difference in mean Z-values for theta frequency range upon application of "simple light" stimuli for all electrode pairs between healthy controls and AD subjects. Fig. 15 shows mean Z-values for theta frequency range upon application of "target" stimuli for all electrode pairs. Both figures show the mean Z-values for healthy subjects (red bars), untreated AD subjects (green bars), and treated AD subjects (blue bars). Fig. 15 shows that the healthy subjects had higher theta response coherence compared to both untreated and treated AD subjects upon application of target stimuli for all electrode pairs. The mean Z-value of healthy subjects is 30–40% higher than AD patients in most of the electrode pairs upon application of "target" stimuli. As Figs. 12 and 13 illustrate, the mean Z-values upon application of simple light are between 0.3 and 0.48, while upon application of "target stimuli" the mean Z values increase to 0.9. Comparison of Figs. 14 and 15 shows that the sensory-evoked theta coherence upon "simple light" is not as high as event-related coherence, and no difference was recorded between healthy controls and AD subjects.

The results show evidence for the existence of separate sensory and cognitive networks that are activated either on sensory or cognitive stimulation. The cognitive networks of AD patients were highly impaired in comparison to networks activated by sensory stimulation. Accordingly, analysis of coherences upon cognitive load may serve, in the future, as a biomarker in diagnostics of AD patients (see also Yener and Başar, 2013a).

8. Analysis of drug/neurotransmitter application

The following two examples show how drug applications significantly influence event-related (and/or evoked) brain oscillations.

A special responsiveness of the frontal lobe in the theta frequency range has been demonstrated in a time prediction task in humans (Başar-Eroğlu et al., 1992) and in a paradigm with regular omitted stimuli in cats (Demiralp et al., 1994). In these studies, the theta responsiveness in frontal lobes was interpreted as an indication of the function of the hippocampal–fronto-parietal system during cognitive processes.

8.1. Application of cholinergic drugs in AD patients

8.1.1. Phase-locked and non-phase-locked activity

Non-phase-locked activities contain evoked oscillations that are not rigidly time-locked to the moment of stimulus delivery. These are, for example, induced alpha, beta, and gamma. oscillations that may relate to specific aspects of information processing. In the framework of the additive model of evoked potentials, non-phase-locked activity includes the background EEG. For analysis of only non-phase-locked or both phase-locked and non-phase-locked EEG responses, specific approaches have been used. Phase-locked activity is suggested to include all types of event-related brain potentials. For quantification of the phase-locked activity, the averaging procedure is usually applied, whereby the phase-locked responses are enhanced and the non-phase-locked ones are attenuated.

Yener et al. (2007) investigated the phase-locking of visual event-related theta oscillations in frontal locations in two groups of AD and elderly controls. It was hypothesized that the non-treated AD would show weaker phase-locking of theta oscillations than both controls and the AD group treated with acetylcholine esterase inhibitors (AChEI). The results indicated that, at the F_3 location, the non-treated AD patients had a weaker theta response than both the control and treated AD groups. This result was related to the reduced phase-locking in this group (Figs. 16 and 17). Moreover, the cholinergically treated AD group and healthy controls did not differ from each other.

There are several methods to analyze the changes in phase-locking (for futher reading, Tallon-Baudry et al., 1996; Herrmann et al., 1999; Ergen et al., 2008; Yordanova and Kolev, 1997, 1998; Vinck et al., 2012).

8.2. Application of lithium in bipolar disorder (BD) patients

In a study by Özerdem et al. (2013), both drug-free euthymic patients and patients on lithium monotherapy had higher beta responses compared to healthy controls. However, the responses from the lithium-treated patients were significantly higher than both drug-free patients and healthy controls. Fig. 18 depicts grand-averages of event-related beta responses in left (F_3) and right (F_4) frontal electrode

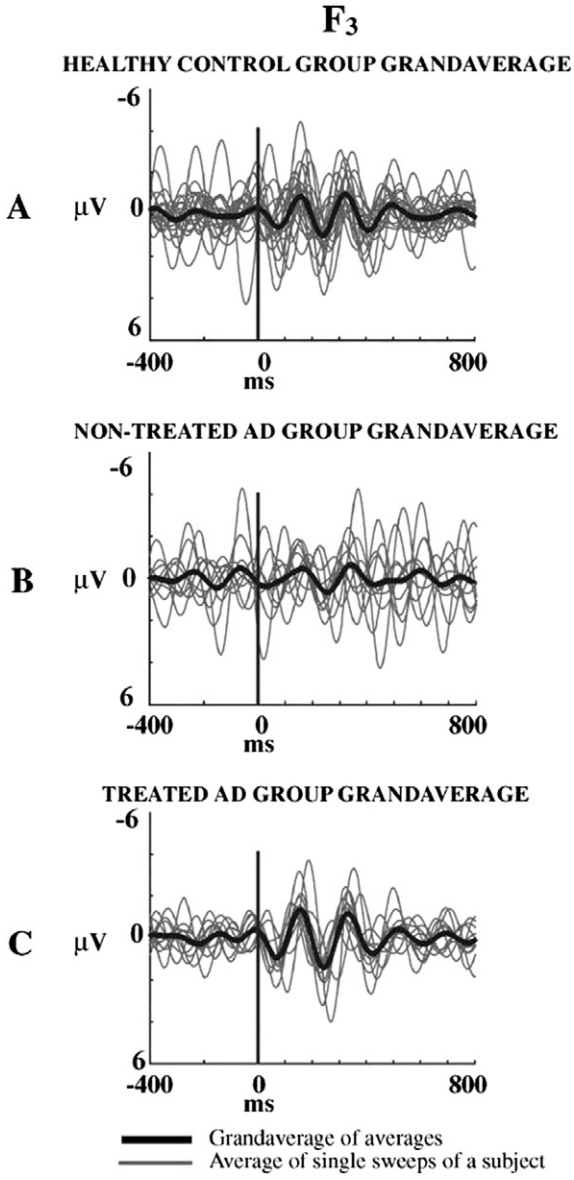

Fig. 15. Mean Z-values of healthy controls, treated AD, and untreated AD subjects for theta frequency range upon target stimuli. "*" sign represents $p < 0.01$ (modified from Başar et al., 2010).

sites in (from top to bottom) healthy controls, euthymic drug-free patients, and patients under lithium monotherapy.

In Fig. 19, event-related spectra upon auditory target stimulation oddball paradigm are shown. Here we also have comparative analyses with three different stimuli. The power spectrum of healthy subjects has spectral responses at around 16 Hz and 20 Hz. Medication-free patients do not show higher responses without application of medication; however, upon application of lithium, an immense increase of beta power around 20 Hz is observed. Other frequency responses around 14–17 Hz and 22 Hz are recorded. In other words, lithium causes a high increase in all beta responses.

Lithium is known to have a neuroprotective effect through changes in the activity of pro- and anti-apoptotic proteins (Machado-Vieira et al., 2009). This finding is important from the point of view that these are lithium-responsive patients and this lithium sensitivity of beta responses may be of crucial importance in tracking treatment response in patients with bipolar disorder.

9. Example of event-related inter-trial coherence (ITC) in the gamma frequency window

The ITC method is used in order to indicate whether a stimulation elicits phase-locked responses or time-locked responses. When single trial responsiveness is congruent, the inter-trial coherence is high. In neuroscience literature, there exist several applications of this method. Certainly, it is relevant to choose a broad frequency window for a perfect analysis of multiple oscillatory responsiveness to stimulation. However, in this report, we will give only an example in the gamma frequency window. Recently, we proposed (Başar, 2012) a new type of analysis taking into account that in the gamma frequency window three or four phase-locked responses do exist. Further, we have shown that several phase-locked gamma responses are superimposed depending on the modality of the stimulations.

As seen in Fig. 20, in the early time-window (0–200 ms), although visual target stimulation elicited greater gamma-phase locking than simple light stimulation, they both have high inter-trial coherence. On the contrary, late responses to a single light stimuli do not show relevant phase-locking whereas visual target stimulation elicits several phase-locked responses in the time periods of 400 ms, 600 ms, and 800 ms. This means that the cognitive processes take a longer time by multiple phase-lock processing. Başar et al. (2016, 2015) interpreted that the late phase-locked responses are responses of association areas of the cortex.

10. How to present ensembles of neurophysiological markers describing cognitive deficits and connectivity deficits

EEG analysis only measures sporadically occurring coherences from hidden sources. Sensory evoked coherences reflect the degree of connectivity (links) between sensory networks activated only by a sensory stimulation. Event-related (or cognitive) coherences manifest coherent activity of sensory–cognitive networks triggered by a cognitive task. Accordingly, the cognitive response coherences comprise activation of a greater number of neural networks that are most probably not activated or less activated in the EEG or in pure sensory-evoked coherences (See papers by Yener and Başar, 2013a, b). Therefore, *event-related coherences* and *event-related oscillations* merit special attention for analysis of results from patients with cognitive impairment. In particular, in AD patients with strong cognitive impairment, it is relevant to analyze whether medical treatment (drug application) selectively acts upon sensory and cognitive networks manifested in topologically different places and in different frequency windows. Such an observation may serve to increase understanding of the physiology of distributed functional networks and, in turn, the possibility of determining markers for medical treatment.

Although each individual oscillatory finding presented in different diseases in the present report can serve as a candidate biomarker, we recommend that these electrophysiological markers should not be used separately. Instead, a constellation of these electrophysiological markers should be considered as being more appropriate for diagnostic and response-tracking purposes in cognitive deficits. This approach can provide a more solid basis for application of oscillatory assessments and a substantial reduction in potential errors when assessing diagnosis and medication response. Table 3 describes the possibilities to apply methods of oscillatory analysis in post-stimulus responses and the ensemble of significant results in MCI and AD. Table 4 provides a similar overview of biomarkers in bipolar disorder. In these tables, sub-frequency (i.e., alpha 1, alpha 2, theta 1, theta 2) groups are not yet included. We expect that at least four or five additional candidate biomarkers may be discovered in future studies applying these methods. Table 5 provides a similar overview of candidate biomarkers in schizophrenia upon application of auditory sensory and auditory oddball paradigms. For more detailed information see Başar and Güntekin (2013) (*spontaneous EEG Alpha activity was

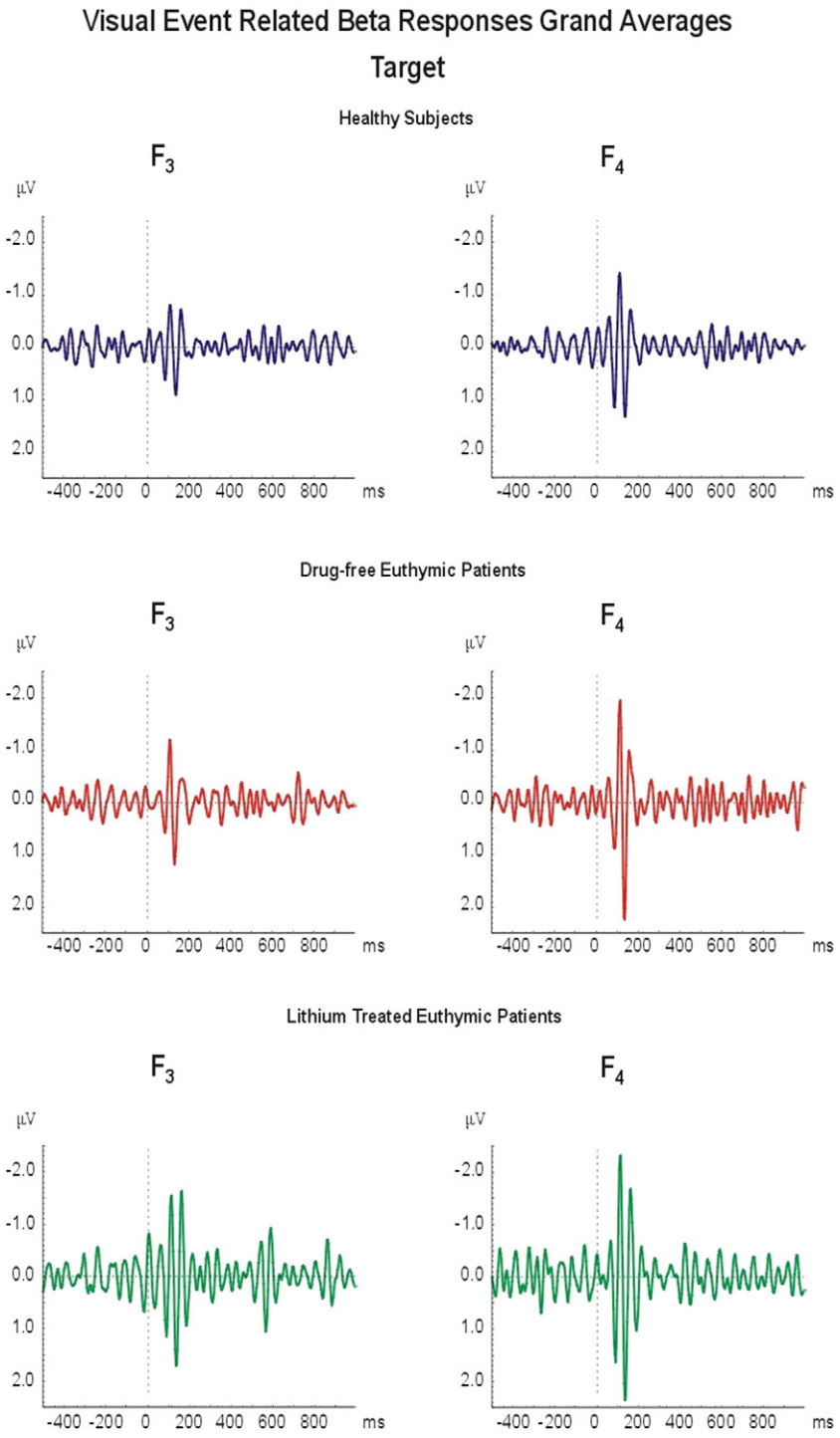

Fig. 16. Examples from each group showing single sweeps to the target stimuli elicited by a classical visual oddball paradigm recorded from F_3 scalp electrode. The thick black line indicates the average of single sweeps, and the thin gray lines show each single sweep for the subject. A: an elderly healthy control; B: a non-treated Alzheimer's subject; C: a treated (cholinesterase inhibitor) Alzheimer's subject (modified from Yener et al., 2007).

found to be lower in schizophrenia by several groups; Itil et al., 1972, 1974; Iacono, 1982; Miyauchi et al., 1990; Sponheim et al., 1994, 2000; Alfimova and Uvarova, 2008).

Similar summaries of spontaneous EEG activity must be also included in order to present a complete overview of the oscillatory manifestation of the disease under study. We also mention that Tables 3, 4 and 5 serve as examples; similar tables should be also prepared for other diseases.

There are many results combining various analysis methods in all EEG frequency windows that are relevant to the search for biomarkers. These tables describe at least 45 combinations, indicating the potential discovery and/or comparative analysis of at least five to ten biomarkers for each pathology.

11. Highlights for neurophysiological explorations in diagnostics, drug application, and progressive monitoring of diseases

In the following sections, we bring together strategies, methods, and their short results in order to provide a synopsis and proposals for efficient analysis of cognitive impairment:

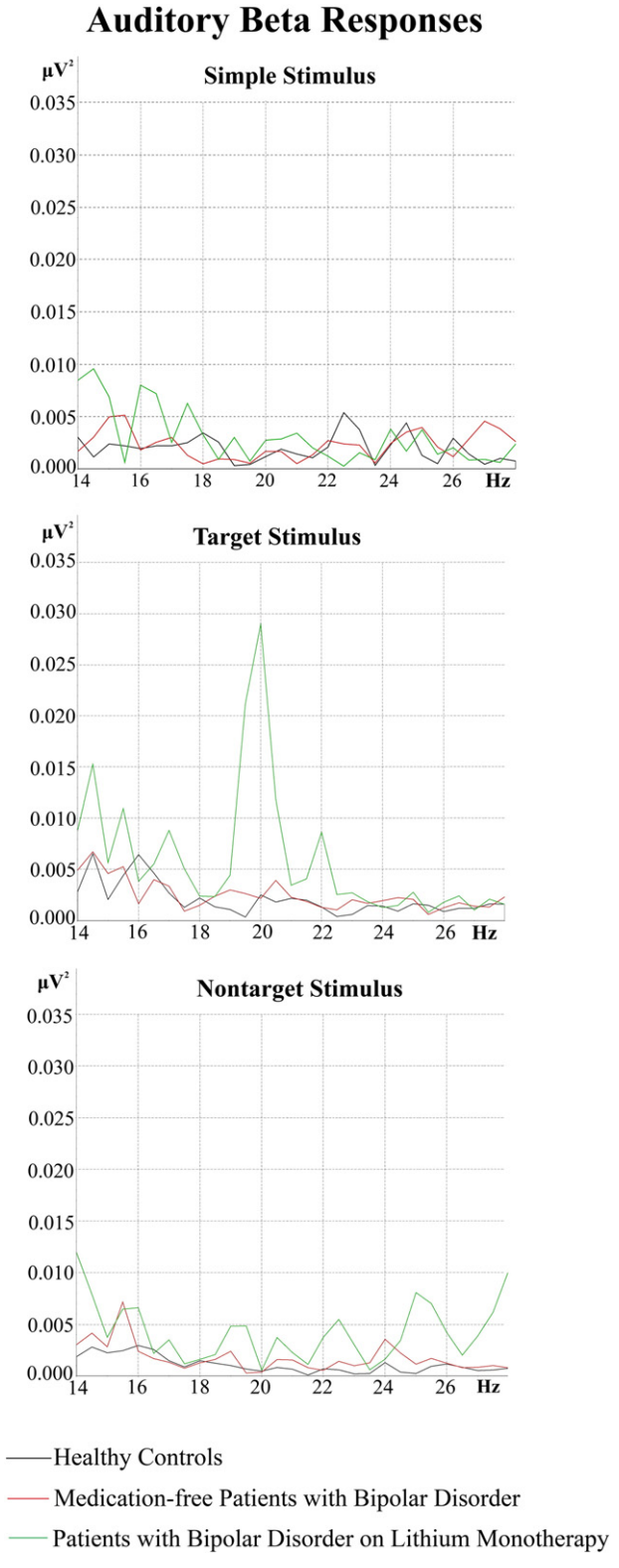

Fig. 17. Decreased visual event-related theta phase-locking in AD. The thick black line represents the grand average response of each group to the target stimuli elicited by a classical visual oddball paradigm and the thin gray lines show averages of single sweeps from each subject (modified from Yener et al., 2007).

1. The procedure of EEG (and/or MEG) oscillations allows measurement of brain dynamics related to changes in perception, memory, learning, and attention within a very short time-window of 0–500 ms. With applications of the brain imaging methods illustrated in Fig. 3, or with the application of structural biomarkers described by Yener and Başar (2013a, b), it is not possible to compare function-related alterations (especially cognitive functions) between healthy subjects and patients.
2. EEG/MEG procedures are inexpensive and noninvasive.
3. The importance of analyzing spontaneous EEG is explained with numerous examples by Vecchio et al. (2013); Yener and Başar (2013a); and Başar and Güntekin (2013).
4. *Multiple oscillations*: The present report clearly demonstrates that it is obligatory to apply the method of oscillations in *multiple EEG frequency windows* in the search for functional biomarkers and to detect the effects of drug applications (see Tables 2, 3, and 4).
5. *Selectively distributed oscillatory networks*: Again, according to the summary of results for AD, schizophrenia, and BD patients in Tables 3, 4 and 5, recordings should be analyzed for multiple oscillations and at selectively distributed sites, rather than at one location.
6. *Selective connectivity between selectively distributed neural networks* has to be computed by means of *spatial coherence*.
7. It is necessary to compare ERO (triggered by stimulations including a cognitive load) with sensory evoked oscillations (see Tables 3–5). These results show that, in AD and bipolar groups, ERO show more prominent changes in comparison to simple sensory-evoked oscillations. Moreover, event-related spatial coherences in AD and bipolar patients also show considerably more differentiation than simple sensory-evoked coherences.
8. *Importance of temporal coherence*: It is suggested that such integrative brain functions combine the actions of multiple oscillations and are a necessity for temporal coherence of perceptions and actions (Başar, 2006). The basis for these mechanisms lies in the resonance properties of cortical networks, i.e., the tendency to engage in oscillatory activity (e.g., Başar et al., 2001a, 2001b; Buszáki and Draguhn, 2004; Başar, 2008).
9. *Phase-locking*: Phase-locked activity is suggested to include all types of event-related brain potentials. The averaging procedure is usually applied to quantify the phase-locked activity, whereby the phase-locked responses are enhanced and non-phase-locked ones are attenuated. An example of phase-locking deficits in AD patients and the restoration of phase-locking is demonstrated in Section 8; Figs. 16 and 17.
10. *Frequency shift and delay* can be also indicators of cognitive impairment as explained in Fig. 9, indicating reduced delta frequency response.
11. It is recommended to standardize the causality of pre-stimulus activity when considering ERD as a cognitive biomarker (Başar and Turp Gölbaşı, 2014).
12. *Steady-state responses* (SSRs) may be used as markers; however, they are less efficient since patients cannot be analyzed upon a cognitive load. A study by Capilla et al. (2011) provides evidence that visual SSRs can be explained as a superposition of transient ERPs: These findings have critical implications in the current understanding of brain oscillations. Contrary to the idea that neural networks can be tuned to a wide range of frequencies, the findings of these authors rather suggest that the oscillatory response of a given neural network is constrained within its natural frequency range.
13. *Most analyses of cognitive impairment are in the gamma frequency band*, especially in schizophrenia. Steady-state responses, which do not encompass a cognitive paradigm, elicit decreased gamma responses, whereas the oddball paradigm evokes greatly variable gamma responses.
14. *Cognitive tasks with progressively increasing difficulty* open the way to interpreting various brain functions or insights into differentiated cognitive deficits.
    a) The superposition of decreased delta activity and enhanced gamma activity in schizophrenic patients indicates the necessity of analyzing multiple oscillations in tasks with progressive increase of difficulty. Further, application of different tasks enables the interpretation of multiple functions, such as increased

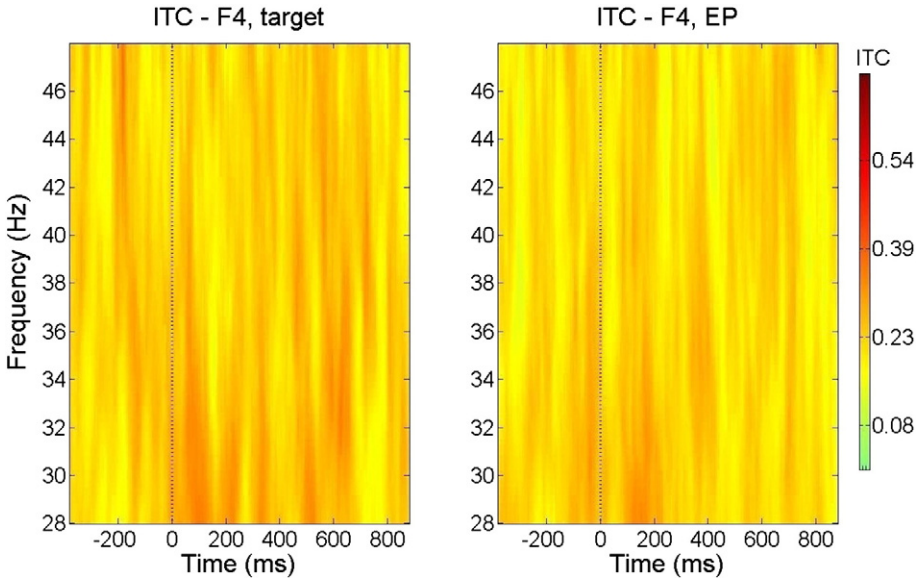

Fig. 18. Grand averages of event-related beta responses in left (F_3) and right (F_4) frontal electrode sites in (from top to bottom) healthy controls, euthymic drug-free patients, and in euthymic patients under lithium monotherapy (modified from Özerdem et al., 2013).

attention and short-term memory.

b) Through the use of tasks with a progressive increase in difficulty, it was possible to indicate that the oscillatory components (here gamma) are not decreased in diseases, and that enhancements are also observed as the increase of spontaneous delta (Vecchio et al., 2013).

c) Similarly, the work of Karakaş et al. (2000b) notably applied easy and difficult oddball tasks to healthy subjects. This application can be useful in measuring differentiability during progression of diseases, for example to analyze the progression between MCI and Alzheimer's disease.

15. Beta increases are observed in BD patients, accompanied by a major decrease of alpha. The increase of beta in BD indicates, again, that enhancements can be also observed in diseases.
16. *Application of drugs/neurotransmitters* gains new implications with the analysis of oscillations and coherences. Better-differentiated analysis of drug effects can be achieved by conventional wide band EP and ERP applications (see Section 8).
17. *The efficiency of assemblies of neurophysiological markers* in describing diseases and biomarkers is clearly emphasized in Tables 3, 4 and 5. According to Giovanni Frisoni, Michael Koch, and Dean Salisbury, in the panel described by Yener and Başar (2013b), neurophysiological markers are not only useful for diagnosis of a specific disease but also for tracking the disease, differential diagnosis, monitoring the effects of drug therapy, and identifying subtypes.
    Therefore, in designing a strategy for diagnostics, differential diagnostics, and application of (preventive) drugs, neurophysiological information should be analyzed within a framework incorporating multiple methods and multiple frequency bands, as shown in Tables 3, 4 and 5.
18. The interpretation of results in AD, schizophrenia, and BD becomes most efficient by joint analysis of results on oscillatory responses and coherences obtained by means of *cognitive tasks*.

Finally, we can conclude that the highlight for exploration of brain oscillations as biomarkers in pathology is based on three important fundamentals:

1) The innate interwoven, multifold mechanisms that constitute "whole brain work" (see Section 1; Table 1) are highly affected and modulated by diseases. Accordingly, methods for identifying biomarkers should be tailored according to relevant changes within the ensemble of innate mechanisms and should not rely only on single, specific mechanisms.
2) It is evident that such strategies must be derived from observation of pathological changes such as frequency shifts, delays, abolishment or changes of some oscillatory responses, and deficits of connectivity. These pathological changes are often structural and also due to changes in biochemical pathways or changes in release of neurotransmitters. Therefore, the use of neurophysiological markers is also useful in monitoring drug application and drug development (see Section 8).
3) It is also almost imperative to compute *evoked*- or *event-related power spectra* before deciding on the application of adaptive digital filters (see Section 6.2). Depending on the type of cognitive tasks, event-related spectra can show modification in frequency windows of ERO. Most critical is the choice of frequency windows in cognitive impairment. Patients can show highly altered frequency windows or frequency shifts. The choice of rigid filters in conventional EEG bands can lead to errors.

In this final part of the article, the outlined strategies, methods, and conclusion are based on experiences from our research group, related to Alzheimer's disease, bipolar disorder, and schizophrenia. Although the results and conclusions of our group were presented in a wide spectrum, we want to emphasize that research groups should tailor further frameworks to show ensemble of results leading to biomarkers.

The present paper is also intended to emphasize that the search for biomarkers is complicated; therefore, such work must encompass all possible combinations derived from the applications of multiple oscillatory frequencies by means of multiple methods. The search for biomarkers is certainly not limited to the content presented above and it is hoped that other groups could further develop this type of analysis.

Appendix A

A.1. Evoked coherence in cat brains

Başar (1980); Başar et al. (1979a, b) demonstrated long distance coherences in alpha, beta, theta, and delta frequency ranges in structures such as sensory cortices, the hippocampus, and brain stem, in waking and freely moving cats.

The strength of long distance coherence depends on stimulation modality and recording sides. During the waking stages, the synchronization

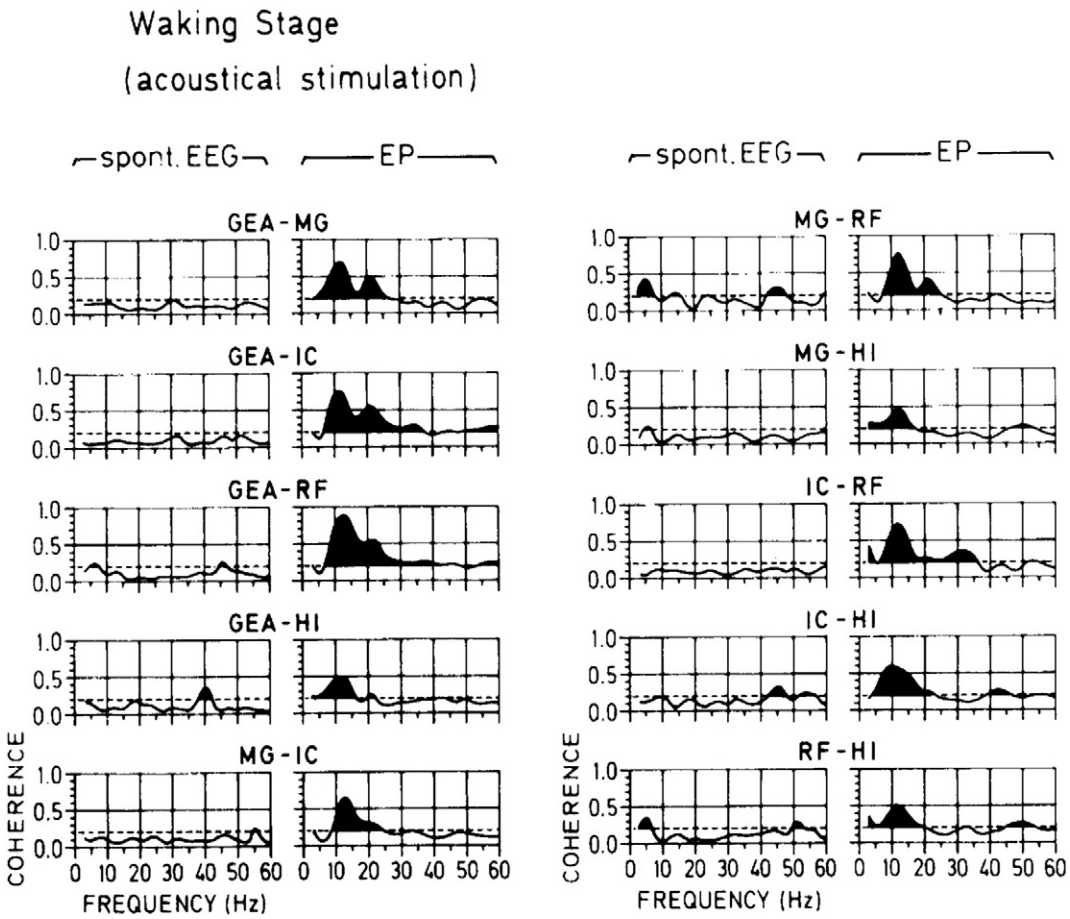

Fig. 19. Grand averages of event-related spectral analysis at beta frequency (F_4 location) (modified from Atagün et al., 2015).

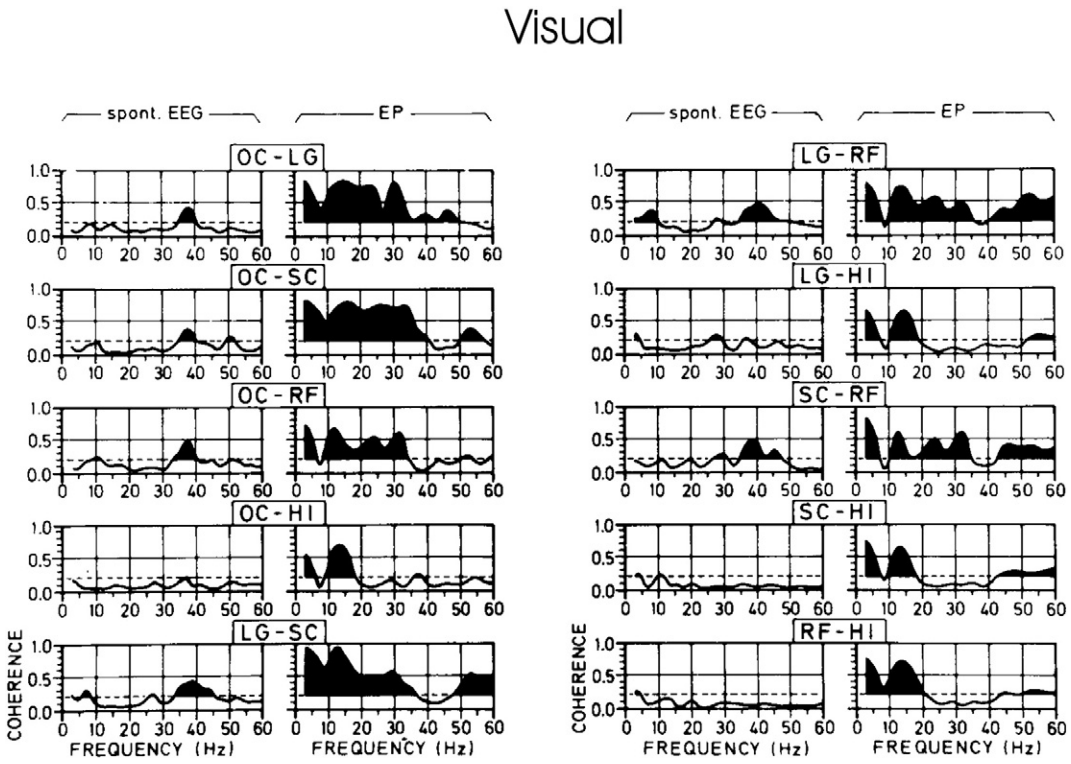

Fig. 20. Grand average of the inter-trial coherence of gamma responses in both stimulations (visual target and simple light) at F_4 location.

Table 3
Overview of studies on electrophysiological biomarker candidates in mild cognitive impairment (MCI) or Alzheimer's disease (AD). Black arrows represent the difference between un-medicated AD patients and healthy controls; red arrows represent the medicated AD patients. Empty cells remain to be analyzed.

Frequency	Power spectrum			Evoked oscillations	Event-related oscillations	Phase-locking	Coherence		
	Spontaneous EEG	Evoked power	Event-related power				EEG Coherence	Evoked coherence	Event-related coherence
Delta	↑	↑ ↔	↓↓	↔ (Yener et al., 2009, visual sensory)	↓ (Yener et al., 2008, visual oddball; Yener et al., 2012, auditory oddball)		↑ Delta coherence in progressive MCI Rossini et al. (2006)	↔ (Except F_3O_1 delta decrease) (Başar et al., 2010, visual oddball)	↓ (Başar et al., 2010; Güntekin et al., 2008, visual oddball)
Theta	↑		↓	↑ (Yener et al., 2009, visual sensory)	↔ (Yener et al., 2008, visual oddball)	↓↑ (Yener et al., 2007, visual oddball)		↔ (Başar et al., 2010, visual oddball)	↓ (Başar et al., 2010; Güntekin et al., 2008, visual oddball)
Alpha	↓			↔ (Yener et al., 2009, visual sensory)	↔ (Yener et al., 2008, visual oddball)		↓ Coherence in MCI Babiloni et al. (2010); ↓ Coherence in AD Jelic et al. (2000); Knott et al. (2000); Adler et al. (2003)	↔ (Başar et al., 2010, visual oddball)	↓↑ (Başar et al., 2010; Güntekin et al., 2008, visual oddball)
Beta	↓			↔ (Yener et al., 2009, visual sensory)	↔ (Yener et al., 2008, visual oddball)			↔ (Başar et al., 2010, visual oddball)	↔ (Başar et al., 2010; Güntekin et al., 2008, visual oddball)
Gamma				↔ (Yener et al., 2009, visual sensory)	↔ (Yener et al., 2008, visual oddball)		↑ Gamma coherence in progressive MCI Rossini et al. (2006)	↔ (Başar et al., 2010, visual oddball)	↔ (Başar et al., 2010; Güntekin et al., 2008, visual oddball)

of resonant responses from various nuclei of the cat brain in the alpha and beta frequency ranges can be demonstrated by using the coherence functions between all possible pairings of evoked activities in the structures of the auditory pathways and visual pathways. In Figs. 21 and 22, which present results of a typical experiment, the coherence in all possible pairings of the studied brain structures are illustrated. Because of limitation of the experimental parameters, it is advised to consider only evoked coherences up to approximately 30 Hz.

The coherence between spontaneous activities in all pairings of structures shows usually significant coherences. On the contrary, evoked coherences between all pairings of structures in the auditory and visual pathways are high where coherence values up to 0.8 in all structures to accurate stimuli. These results demonstrate that alpha, beta, and theta response coherences exist in subcortical long distance structures.

A.1.1. What does this long distance coherence upon stimulation mean?

We measured high response coherences upon application of the adequate stimuli in scalp electrodes of the human brain. The comparison with animal experiments clearly demonstrates that long distance alpha, beta, theta, and gamma coherence results are not due to volume conductions. Moreover, there are certainly coupled EEG oscillators in structures of the brain stem, thalamus, and hippocampus. Accordingly, processing of cognition and processing of brain function are most possibly due to synergy in whole brain work. Because of this clearly shown experimental data, it can be concluded that analysis of coherence between long distance areas can be very useful for interpretation of cognitive functions in the human brain. Another important application of the research on long distance coherence is useful for the interpretation of Brodmann maps. In a report by Başar et al. (2014), the concept of Brodmann is revised. The conclusion is that several cortical areas work jointly in a coherent way to perform a function. This extension

Table 4
Overview of studies on electrophysiological biomarker candidates in bipolar disorder. Black arrows represent un-medicated bipolar manic and euthymic patients. Green arrows show bipolar patients medicated with lithium. Empty cells have not yet been analyzed.

Frequency	Power spectrum			Evoked oscillations	Event-related oscillations	Phase-locking	Coherence		
	EEG	Evoked power	Event-related power				EEG Coherence	Evoked coherence	Event-related coherence
Delta			↓ (Atagun et al., 2014, auditory oddball)		↓ (Atagun et al., 2014, auditory oddball)				
Fast theta			↓ (Atagün et al., 2013, auditory oddball)						
Alpha	↓ Başar et al. (2012); Clementz et al. (1994)				↓ (Özerdem et al., 2008, manic BD, visual oddball)				
Beta	↑↑ (Başar et al., 2016--in this volume)				↑ (Özerdem et al., 2008, manic BD visual oddball) ↑ (Tan et al., in press, auditory oddball)				
Gamma								↔ (Özerdem et al., 2010, visual sensory)	↓ (Özerdem et al., 2010, visual oddball)

Table 5
Overview of studies on electrophysiological biomarker candidates in schizophrenia.

Frequency	Power spectrum			Filtered evoked oscillations	Filtered event-related oscillations	Phase-locking	Coherence		
	EEG	Evoked power	Event-related power				EEG Coherence	Evoked coherence	Event-related coherence
Delta						↓ Ford et al. (2008); Doege et al. (2010)			
Theta						↓ Ford et al. (2008); Doege et al. (2010)			
Alpha	↓*								↓ Koh et al. (2011) (inter-trial phase coherence)
Beta									
Gamma		↔ Spencer et al. (2008); Gallinat et al. (2004)	↓ Lee et al. (2001); Gallinat et al. (2004); Hall et al. (2011) ↑ (Başar-Eroğlu et al., 2011, single trail evoked power)		↓ Haig et al. (2000)	↓ Slewa-Younan et al. (2004); Symond et al. (2005) (decreased frontal, Lee et al., 2003; Roach and Mathalon, 2008) ↑ increased posterior synchrony Lee et al. (2003)			

of Brodmann areas in cortical organization is most probably due to long distance coherence action of reticular formation, thalamus, and hippocampus. The CLAIR model also finds support from the research of intracranial evoked coherences described in this section (Başar and Düzgün, 2016–in this volume).

A.2. Wavelet families in EEG analysis

Wavelet is an oscillatory, vanishing small wave having sharp discontinuities with time limited extend. Wavelet families have been developed into main categories such as orthogonal and compactly supported wavelets (Daubechies, Symmlet, Coiflet) and non-orthogonal and not compactly supported wavelets (complex Gauss, complex Morlet, and complex B-splines). The other wavelet family is Meyer, which is orthogonal and not compactly supported. In other words, Meyer wavelets are indefinitely differentiable. Among the wavelet families, the three different mostly used wavelet families are shown in Fig. 23.

Wavelets are used to decompose a signal into basis functions in both continuous and discrete time for analysis of non-stationary signals with variable time/frequency resolution. Therefore, wavelet transforms (WT) can be classified as continuous WT (CWT) and discrete WT (DWT). In continuous time, the Wavelet Transform (WT) is the convolution of the signal denoted by $x(t)$ with scaled and shifted versions of a wavelet prototype, so-called Mother Wavelet, in form:

$$X(\tau, s) = \frac{1}{\sqrt{|s|}} \int_{-\infty}^{+\infty} x(t) \Psi^* \left(\frac{t-\tau}{s} \right) dt$$

where the pair of (τ, s) denotes translation and scaling parameters, respectively (Mallat, 2008). This transformation can represent $x(t)$ by a good approximation, if the wavelet family, i.e. $\Psi(t)$, is designed with respect to both shape and size as well as the bandwidth of $x(t)$ regarding the instantaneous frequency of $x(t)$. Therefore, both scaling and translating parameters, in addition to the number of vanishing moments, lead the limitations of WT to obtain temporal analysis of non-stationary signals. In addition, $\Psi(t)$ has to be zero average with finite energy in form:

$$\int_{-\infty}^{+\infty} \Psi(t) dt = 0 \ \ where \ \ E = \int_{-\infty}^{+\infty} |\Psi(t)|^2 dt < \infty$$

and this wavelet has no frequency content.

The capability of WT highly depends on the selection of wavelet family in the characterization of a real signal. Not only the type of application (analysis or reconstruction, filtering, compression), but also the qualitative properties of the signal (randomness, discontinuity, periodicity, causality, sampling frequency, duration, energy, and power distribution) offer the optimality of this selection regarding the specific wavelet parameters such as regularity, symmetry, support, and smoothness determined by the number of vanishing moments. In the literature, Haar wavelets (orthonormal and orthogonal) were found to be useful for detection of changes in amplitudes, whereas Meyer wavelets (orthonormal and orthogonal) were found to be suitable for obtaining changes in the frequency of the signal (Bilen and Huzurbazar, 2002; Walter and Zhang, 1998; Walter and Shen, 2001). Besides, Daubechies wavelets (orthogonal) were used to detect the impulsive and oscillatory transient components of vibration signals (Ferroudji et al., 2012; Megahed et al., 2008).

The WT was also used to characterize the brain oscillations, so-called EEG series, generated by cerebral cortex nerve cells regarding different goals such as characterization of seizures consisting of 3-Hz spike and slow wave epileptic discharges (Adeli et al., 2003), extraction of both amplitudes and latencies of event related potentials (ERPs) in case of high Signal-to-Noise-Ratio (Quiroga and Garcia, 2003), task discrimination to capture more precise information from the cortex reactions during a cognitive task such as mathematical thinking (Sakkalis et al., 2006), chaos identification to obtain possible markers in Alzheimer's

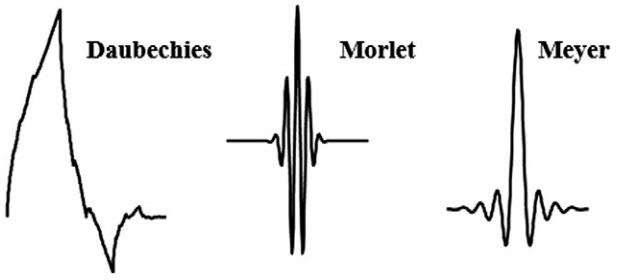

Fig. 21. A typical set of coherence functions computed from the spontaneous activities and EPs of all possible pairings of the studied brain structures during the waking stage. The scale is indicated at the bottom. Along the abscissa is the frequency from 0 Hz to 60 Hz; along the ordinate is the coherence between 0 and 1. The horizontal broken lines indicate the significance level, which is 0.2 for all plots. The area under the coherence function is darkened only if the curve surpasses this level. In order to facilitate a comparison between the coherence values computed from spontaneous and evoked parts of the EEG–EP epochs, the respective coherence functions are presented adjacently as couples for all pairings of recording electrodes (modified from Başar, 1980).

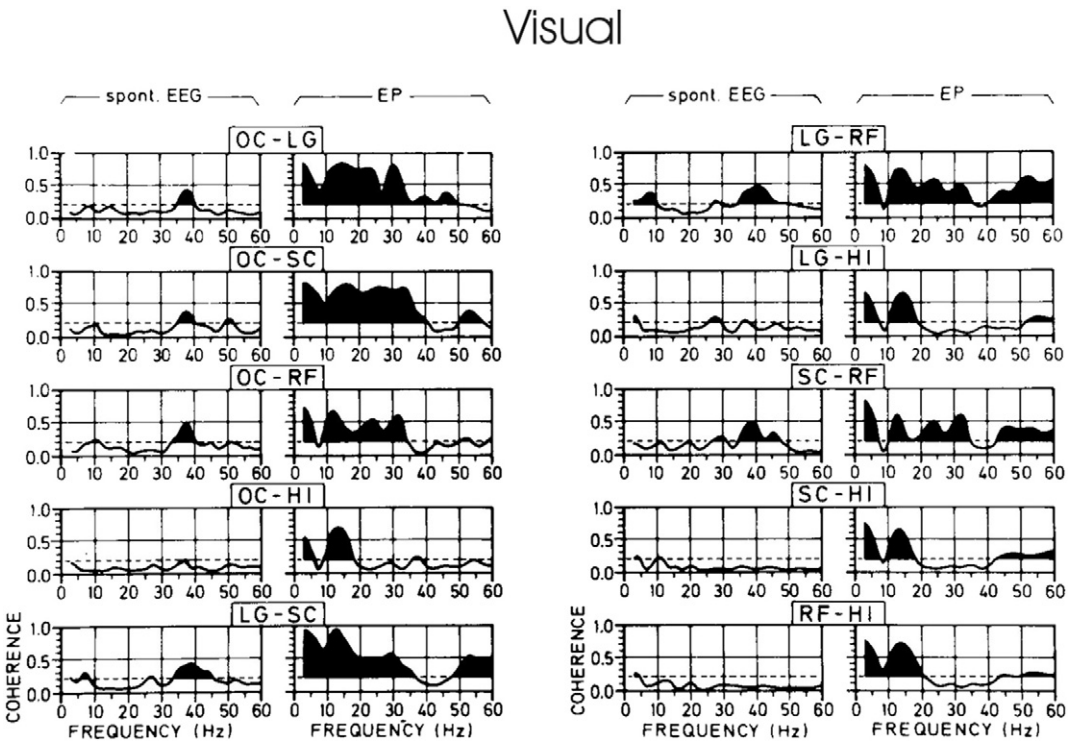

Fig. 22. A typical set of coherence functions computed from the spontaneous and visual evoked potentials of all possible pairings of the studied brain structures. The scale is indicated at the bottom. Along the abscissa is the frequency from 0 to 60 Hz; along the ordinate is the coherency between 0 and 1. The horizontal broken lines indicate the significance level, which is 0.2 for all the plots. The area under the coherence function is darkened only if the curve surpasses this level. In order to facilitate a comparison between the coherence values computed from spontaneous and evoked parts of the EEG–EP epochs, the respective coherence functions are presented adjacently as couples for all pairings of recording electrodes (modified from Başar, 1980).

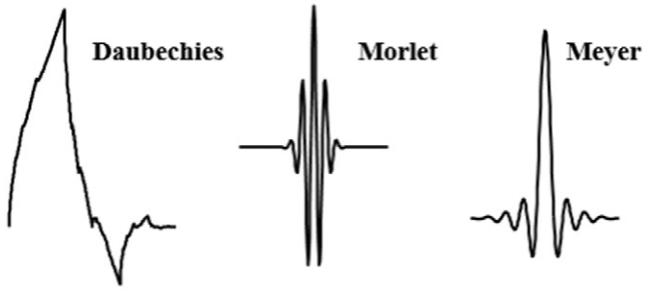

Fig. 23. Specific wavelet families.

(Adeli et al., 2008), and artifact reduction in healthy measurements (Castellanos and Makarov, 2006).

In these studies, different wavelet functions such as harmonic wavelets (Adeli et al., 2003), quadratic biorthogonal B-splines (Quiroga and Garcia, 2003), normalized complex Morlet wavelets (Sakkalis et al., 2006), and Daubechies 4-order wavelets (Adeli et al., 2008) were used with respect to both recording parameters and waveform of the EEG signal.

In all applications, the common concern is that the selection of the wavelet function is closely related to the energy and power spectra of the signal to be analyzed in conclusion.

References

Adeli, H., Zhoub, Z., Dadmehr, N., 2003. Analysis of EEG records in an epileptic patient using wavelet transform. J. Neurosci. Methods 123 (1), 69–87.

Adeli, H., Ghos-Dastidar, S., Dadmehr, N., 2008. A spatio-temporal wavelet-chaos methodology for EEG-based diagnosis of Alzheimer's disease. Neurosci. Lett. 444 (2), 190–194.

Adey, W.R., 1966. Neurophysiological correlates of information transaction and storage in brain tissue. In: Stellar, E., Sprague, J.M. (Eds.), Progress in Physiological Psychology. Academic Press, New York, pp. 1–43.

Adey, W.R., 1989. Cell membranes, electromagnetic fields, and intercellular communication. In: Başar, E., Bullock, T.H. (Eds.), Brain Dynamics: Progress and Perspectives. Springer, Berlin, pp. 26–42.

Adey, W.R., Dunlop, C.W., Hendrix, C.E., 1960. Hippocampal slow waves. Distribution and phase relationships in the course of approach learning. Arch. Neurol. 3, 74–90.

Adler, G., Brassen, S., Jajcevic, A., 2003. EEG coherence in Alzheimer's dementia. J. Neural Transm. 110 (9), 1051–1058.

Alfimova, M.V., Uvarova, L.G., 2008. Changes in EEG spectral power on perception of neutral and emotional words in patients with schizophrenia, their relatives, and healthy subjects from the general population. Neurosci. Behav. Physiol. 38 (5), 533–540.

Atagün, M.I., Güntekin, B., Ozerdem, A., Tülay, E., Başar, E., 2013. Decrease of theta response in euthymic bipolar patients during an oddball paradigm. Cogn. Neurodyn. 7 (3), 213–223.

Atagun, M.I., Güntekin, B., Masali, B., Tülay, E., Başar, E., 2014. Decrease of event-related delta oscillations in euthymic patients with bipolar disorder. Psychiatry Res. 223 (1), 43–48.

Atagün, M.I., Güntekin, B., Tan, D., Tülay, E.E., Başar, E., 2015. Lithium excessively enhances event related beta oscillations in patients with bipolar disorder. J. Affect. Disord. 170C, 59–65.

Babiloni, C., Frisoni, G., Steriade, M., Bresciani, L., Binetti, G., Del Percio, C., Geroldi, C., Miniussi, C., Nobili, F., Rodriguez, G., Zappasodi, F., Carfagna, T., Rossini, P.M., 2006. Frontal white matter volume and delta EEG sources negatively correlate in awake subjects with mild cognitive impairment and Alzheimer's disease. Clin. Neurophysiol. 117 (5), 1113–1129.

Babiloni, C., Cassetta, E., Binetti, G., Tombini, M., Del Percio, C., Ferreri, F., Ferri, R., Frisoni, G., Lanuzza, B., Nobili, F., Parisi, L., Rodriguez, G., Frigerio, L., Gurzi, M., Prestia, A., Vernieri, F., Eusebi, F., Rossini, P.M., 2007. Resting EEG sources correlate with attentional span in mild cognitive impairment and Alzheimer's disease. Eur. J. Neurosci. 25 (12), 3742–3757.

Babiloni, C., Ferri, R., Binetti, G., Vecchio, F., Frisoni, G.B., Lanuzza, B., Miniussi, C., Nobili, F., Rodriguez, G., Rundo, F., Cassarino, A., Infarinato, F., Cassetta, E., Salinari, S., Eusebi, F., Rossini, P.M., 2009. Directionality of EEG synchronization in Alzheimer's disease subjects. Neurobiol. Aging 30 (1), 93–102.

Babiloni, C., Visser, P.J., Frisoni, G., De Deyn, P.P., Bresciani, L., Jelic, V., Nagels, G., Rodriguez, G., Rossini, P.M., Vecchio, F., Colombo, D., Verhey, F., Wahlund, L.O., Nobili, F., 2010. Cortical sources of resting EEG rhythms in mild cognitive impairment and subjective memory complaint. Neurobiol. Aging 31 (10), 1787–1798.

Başar, E., 1972. A study of the time and frequency characteristics of the potentials evoked in the acoustical cortex. Kybernetik 10, 61–64.

Başar, E., 1980. EEG-Brain Dynamics: Relation Between EEG and Brain Evoked Potentials. Elseiver, Amsterdam.

Başar, E., 1983a. Toward a physical approach to integrative physiology. I. Brain dynamics and physical causality. Am. J. Physiol. 245 (4), R510–R533.

Başar, E., 1983b. Synergetics of neuronal populations. A survey on experiments. In: Başar, E., Flohr, H., Haken, H., Mandell, A. (Eds.), Synergetics of the Brain. Springer, Berlin, pp. 183–200.
Başar, E., 1999. Brain function and oscillations. II. Integrative brain function. Neurophysiology and Cognitive Processes. Springer, Heidelberg.
Başar, E., 2004. Memory and Brain Dynamics: Oscillations Integrating Attention, Perception Learning and Memory. CRC Press, Boca Raton, FL.
Başar, E., 2006. The theory of the whole-brain work. Int. J. Psychophysiol. 60 (2), 133–138.
Başar, E., 2008. Oscillations in "brain–body–mind": a holistic view including the autonomous system. Brain Res. 1235, 2–11.
Başar, E., 2011. Brain–Body–Mind in the Nebulous Cartesian System: A Holistic Approach by Oscillations. Springer, Heidelberg.
Başar, E., 2012. Multiple oscillations and phase locking in human gamma responses: an essay in search of eigenvalues. Neuroquantology 10 (4), 606–618.
Basar, E., 2013. Brain oscillations in neuropsychiatric disease. Dialogues Clin. Neurosci. 15 (3), 291–300.
Başar, E., Düzgün, A., 2016. The CLAIR model: Extention of Brodmann's areas based on brain oscillations and connectivity. Int. J. Psychophysiol. 103, 185–198 (in this volume).
Başar, E., Güntekin, B., 2013. Review of delta, theta, alpha, beta and gamma response oscillations in neuropsychiatric disorders. Suppl. Clin. Neurophysiol. 62, 303–341.
Basar, E., Özesmi, C., 1972. The hippocampal EEG activity and a systems analytical interpretation of averaged evoked potentials of the brain. Kybernetik 12, 45–54.
Başar, E., Turp Gölbaşı, B., 2014. Event related desynchronization: use as a neurophysiologic marker is restricted. Cogn. Neurodyn. 8 (6), 437–445.
Başar, E., Ungan, P., 1973. A component analysis and principles derived for the understanding of evoked potentials of the brain: studies in the hippocampus. Kybernetik 12, 133–140.
Başar-Eroğlu, C., Başar, E., Schürmann, M., Schütt, A., Strüber, D., Stadler, M., Karakaş, S., 1999. Gamma-band responses in the brain: functional significance (Ch. 26). In: Başar, E (Ed.), Brain Function and Oscillations: II. Integrative Brain Function. Neurophysiology and Cognitive Processes. Springer-Verlag, Heidelberg.
Başar, E., Demir, N., Gönder, A., Ungan, P., 1979a. Combined dynamics of EEG and evoked potentials I. Studies of simultaneously recorded EEG–EP EP-epochs in the auditory pathway, reticular formation and hippocampus of the cat brain during the waking stage. Biol. Cybern. 34 (1), 1–19.
Başar, E., Durusan, R., Gönder, A., Ungan, P., 1979b. Combined dynamics of EEG and evoked potentials II. Studies of simultaneously recorded EEG–EP EP-epochs in the auditory pathway, reticular formation and hippocampus of the cat brain during sleep. Biol. Cybern. 34 (1), 21–30.
Başar, E., Rahn, E., Demiralp, T., Schürmann, M., 1998. Spontaneous EEG theta activity controls frontal visual evoked potentials amplitudes. Electroencephalogr. Clin. Neurophysiol. 108 (2), 101–109.
Başar, E., Başar-Eroğlu, C., Karakaş, S., Schürmann, M., 1999a. Are cognitive processes manifested in event-related gamma, alpha, theta and delta oscillations in the EEG? Neurosci. Lett. 259 (3), 165–168.
Başar, E., Başar-Eroğlu, C., Karakaş, S., Schürmann, M., 1999b. Oscillatory brain theory: a new trend in neuroscience. The role of oscillatory processes in sensory and cognitive functions. IEEE Eng. Med. Biol. 18 (3), 56–66.
Başar, E., Demiralp, T., Schürmann, M., Başar-Eroğlu, C., Ademoğlu, A., 1999c. Oscillatory brain dynamics, wavelet analysis and cognition. Brain Lang. 66 (1), 146–183.
Başar, E., Başar-Eroğlu, C., Karakaş, S., Schürmann, M., 2000. Brain oscillations in perception and memory. Int. J. Psychophysiol. 35 (2–3), 95–124.
Başar, E., Özgören, M., Karakaş, S., 2001a. A brain theory based on neural assemblies and superbinding. In: Reuter, H., Schwaband, P., Gniech, K.D. (Eds.), Wahrnehmenund Erkennen. PABST Science Publishers, Lengerich, pp. 11–24.
Başar, E., Başar-Eroğlu, C., Karakaş, S., Schürmann, M., 2001b. Gamma, alpha, delta, and theta oscillations govern cognitive processes. Int. J. Psychophysiol. 39 (2–3), 241–248.
Başar, E., Güntekin, B., Tülay, E., Yener, G.G., 2010. Evoked and event-related coherence of Alzheimer patients manifest differentiation of sensory–cognitive networks. Brain Res. 1357, 79–90.
Başar, E., Güntekin, B., Atagün, I., Turp-Gölbaşı, B., Tülay, E., Özerdem, A., 2012. Brain's alpha activity is highly reduced in euthymic bipolar disorder patients. Cogn. Neurodyn. 6 (1), 11–20.
Başar, E., Başar-Eroğlu, C., Güntekin, B., Yener, G.G., 2013. Brain's alpha, beta, gamma, delta, and theta oscillations in neuropsychiatric diseases: proposal for biomarker strategies. Suppl. Clin. Neurophysiol. 62, 19–54.
Başar, E., Düzgün, A., Güntekin, B., 2014. A proposal to extend Brodmann's areas concept to a new model. Neuroquantology 12 (2), 201–209.
Başar, E., Schmiedt-Fehr, C., Mathes, B., Femir, B., Emek-Savaş, D.D., Tülay, E., Tan, D., Düzgün, A., Güntekin, B., Özerdem, A., Yener, G.G., Başar-Eroğlu, C., 2016. What does the broken brain say to the neuroscientist? Oscillations and connectivity in schizophrenia, Alzheimer's disease, and bipolar disorder. Int. J. Psychophysiol. 103, 135–148 (in this volume).
Başar, E., Tülay, E., Güntekin, B., 2015. Multiple gamma oscillations in the brain: a new strategy to differentiate functional correlates and P300 dynamics. Int. J. Psychophysiol. 95 (3), 406–420.
Başar-Eroğlu, C., Başar, E., Demiralp, T., Schürmann, M., 1992. P300-response: possible psychophysiological correlates in delta and theta frequency channels. A review. Int. J. Psychophysiol. 13 (2), 161–179.
Başar-Eroglu, C., Strüber, D., Stadler, M., Kruse, P., Başar, E., 1993. Multistable visual perception induces a slow positive EEG wave. Int. J. Neurosci. 73 (1–2), 139–151.
Başar-Eroglu, C., Demiralp, T., Schürmann, M., Başar, E., 2001. Topological distribution of oddball 'P300' responses. Int. J. Psychophysiol. 39 (2–3), 213–220.
Başar-Eroğlu, C., Mathes, B., Brand, A., Schmiedt-Fehr, C., 2011. Occipital gamma response to auditory stimulation in patients with schizophrenia. Int. J. Psychophysiol 79 (1), 3–8.
Basar-Eroglu, C., Schmiedt-Fehr, C., Mathes, B., 2013. Auditory evoked alpha oscillations imply reduced anterior and increased posterior amplitudes in schizophrenia. Suppl. Clin. Neurophysiol. 62, 121–129.
Bilen, C., Huzurbazar, S., 2002. Wavelet-based detection of outliers in time series. J. Comput. Graph. Stat. 11 (2), 311–327.
Bruns, A., 2004. Fourier-, Hilbert- and wavelet-based signal analysis: are they really different approaches? J. Neurosci. Methods 137 (2), 321–332.
Bullock, T.H., McClune, M.C., Enright, J.T., 2003. Are the electroencephalograms mainly rhythmic? Assessment of periodicity in wide-band time series. Neuroscience 121 (1), 233–252.
Buszáki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. Science 304 (5679), 1926–1929.
Capilla, A., Pazo-Alvarez, P., Darriba, A., Campo, P., Gross, J., 2011. Steady-state visual evoked potentials can be explained by temporal superposition of transient event related responses. PLoS ONE 6 (1), e14543.
Castellanos, N.P., Makarov, V.A., 2006. Recovering EEG brain signals: artifact suppression with wavelet enhanced independent component analysis. J. Neurosci. Methods 158 (2), 300–312.
Chen, A.C., Herrmann, C.S., 2001. Perception of pain coincides with the spatial expansion of electroencephalographic dynamics in human subjects. Neurosci. Lett 297, 183–186.
Clementz, B.A., Sponheim, S.R., Iacono, W.G., Besier, M., 1994. Resting EEG in first-episode schizophrenia patients, bipolar psychosis patients and their first degree relatives. Psychophysiology 31 (5), 486–494.
Damasio, A.R., Damasio, H., 1994. Cortical systems for retrieval of concrete knowledge: the convergence zone framework. In: Koch, C., Davis, J.L. (Eds.), Large-Scale Neuronal Theories of the Brain. MIT Press, Cambridge, MA, pp. 61–74.
Dauwels, J., Vialatte, F., Latchoumane, C., Jeong, J., Cichocki, A., 2009. EEG synchrony analysis for early diagnosis of Alzheimer's disease: a study with several synchrony measures and EEG data sets. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2009, 2224–2227.
Demiralp, T., Başar-Eroğlu, C., Rahn, E., Başar, E., 1994. Event-related theta rhythms in cat hippocampus and prefrontal cortex during an omitted stimulus paradigm. Int. J. Psychophysiol. 18 (11), 35–48.
Demiralp, T., Ademoglu, A., Schurmann, M., Başar-Eroğlu, C., Başar, E., 1999. Detection of P300 in single trials by the wavelet transform (WT). Brain Lang. 66 (1), 108–128.
Doege, K., Jansen, M., Mallikarjun, P., Liddle, E.B., Liddle, P.F., 2010. How much does phase resetting contribute to event-related EEG abnormalities in schizophrenia? Neurosci. Lett. 481 (1), 1–5.
Doppelmayr, M., Klimesch, W., Pachinger, T., Ripper, B., 1998. Individual differences in brain dynamics: important implications for the calculation of event-related band power. Biol. Cybern. 79 (1), 49–57.
Dumont, M., Macchi, M.M., Carrier, J., Lafrance, C., Hebert, M., 1999. Time course of narrow frequency bands in the waking EEG during sleep deprivation. NeuroReport 10 (2), 403–407.
Eccles, J.C., 1973. The Understanding of the Brain. McGraw Hill, New York.
Eckhorn, R., Bauer, R., Jordan, R., Brosch, W., Kruse, M., Munk, M., Reitboeck, H.J., 1988. Coherent oscillations: a mechanism of feature linking in the visual cortex. Biol. Cybern 60, 121–130.
Ergen, M., Marbach, S., Brand, A., Başar-Eroğlu, C., Demiralp, T., 2008. P3 and delta band responses in visual oddball paradigm in schizophrenia. Neurosci. Lett. 440 (3), 304–308.
Ferroudji, K., Benoudjit, N., Bahaz, M., Bouakaz, A., 2012. Selection of a suitable mother wavelet for microemboli classification using SVM and RF signals. Microelectronics (ICM), 24th International Conference on, 2012, pp. 1–4.
Ford, J.M., Roach, B.J., Hoffman, R.S., Mathalon, D.H., 2008. The dependence of P300 amplitude on gamma synchrony breaks down in schizophrenia. Brain Res. 1235, 133–142.
Freeman, W.J., 1999. Foreword. In: Başar, E. (Ed.), Brain Function and Oscillations. II. Integrative Brain Function. Neurophysiology and Cognitive Processes. Springer, Berlin.
Gray, C.M., Singer, W., 1989. Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proc. Natl. Acad. Sci. USA 86, 1698–1702.
Gallinat, J., Winterer, G., Herrmann, C.S., Senkowski, D., 2004. Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. Clin. Neurophysiol. 115 (8), 1863–1874.
Güntekin, B., Saatçi, E., Yener, G., 2008. Decrease of evoked delta, theta and alpha coherence in Alzheimer patients during a visual oddball paradigm. Brain Res. 1235, 109–116.
Haig, A.R., Gordon, E., De Pascalis, V., Meares, R.A., Bahramali, H., Harris, A., 2000. Gamma activity in schizophrenia: evidence of impaired network binding? Clin. Neurophysiol. 111 (8), 1461–1468.
Hall, M.H., Taylor, G., Sham, P., Schulze, K., Rijsdijk, F., Picchioni, M., Toulopoulou, T., Ettinger, U., Bramon, E., Murray, R.M., Salisbury, D.F., 2011. The early auditory gamma-band response is heritable and a putative endophenotype of schizophrenia. Schizophr. Bull. 37 (4), 778–787.
Herrmann, C.S., Mecklinger, A., Pfeifer, E., 1999. Gamma responses and ERPs in a visual classification task. Clin. Neurophysiol. 110 (4), 636–642.
Hogan, M.J., Swanwick, G.R., Kaiser, J., Rowan, M., Lawlor, B., 2003. Memory-related EEG power and coherence reductions in mild Alzheimer's disease. Int. J. Psychophysiol. 49 (2), 147–163.
Iacono, W.G., 1982. Bilateral electrodermal habituation–dishabituation and resting EEG in remitted schizophrenics. J. Nerv. Ment. Dis. 170 (2), 91–101.
Itil, T.M., Saletu, B., Davis, S., 1972. EEG findings in chronic schizophrenics based on digital computer period analysis and analog power spectra. Biol. Psychiatry 5 (1), 1–13.
Itil, T.M., Hsu, W., Saletu, B., Mednick, S., 1974. Computer EEG and auditory evoked potential investigations in children at high risk for schizophrenia. Am. J. Psychiatry 131 (8), 892–900.
Jelic, V., Johansson, S.E., Almkvist, O., Shigeta, M., Julin, P., Nordberg, A., Winblad, B., Wahlund, L.O., 2000. Quantitative electroencephalography in mild cognitive

impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol. Aging 21 (4), 533–540.
Karakaş, S., Erzengin, O.U., Başar, E., 2000a. The genesis of human event related responses explained through the theory of oscillatory neural assemblies. Neurosci. Lett. 285 (1), 45–48.
Karakaş, S., Erzengin, O.U., Başar, E., 2000b. A new strategy involving multiple cognitive paradigms demonstrates that ERP components are determined by the superposition of oscillatory responses. Clin. Neurophysiol. 111 (10), 1719–1732.
Karakaş, S., Karakaş, H., Erzengin, O.U., 2002. Early sensory gamma represents the integration of bottom-up and top-down processing. Int. J. Psychophysiol. 45, 39.
Karakaş, S., Bekçi, B., Erzengin, O.U., 2003. Early gamma response in human neuroelectric activity is correlated with neuropsychological test scores. Neurosci. Lett. 340 (1), 37–40.
Klimesch, W., Doppelmayr, M., Schwaiger, J., Winkler, T., Gruber, W., 2000. Theta oscillations and the ERP old/new effect: independent phenomena? Clin. Neurophysiol. 111 (5), 781–793.
Knott, V., Mohr, E., Mahoney, C., Ilivitsky, V., 2000. Electroencephalographic coherence in Alzheimer's disease: comparisons with a control group and population norms. J. Geriatr. Psychiatry Neurol. 13 (1), 1–8.
Kocsis, B., Viana Di Prisco, G., Vertes, R.P., 2001. Theta synchronization in the limbic system: the role of Gudden's tegumental nuclei. Eur. J. Neurosci. 13 (2), 381–388.
Koh, Y., Shin, K.S., Kim, J.S., Choi, J.S., Kang, D.H., Jang, J.H., Cho, K.H., O'Donnell, B.F., Chung, C.K., Kwon, J.S., 2011. An MEG study of alpha modulation in patients with schizophrenia and in subjects at high risk of developing psychosis. Schizophr. Res. 126 (1–3), 36–42.
Lee, Y.J., Zhu, Y.S., Xu, Y.H., Shen, M.F., Tong, S.B., Thakor, N.V., 2001. The nonlinear dynamical analysis of the EEG in schizophrenia with temporal and spatial embedding dimension. J. Med. Eng. Technol. 25 (2), 79–83.
Lee, K.H., Williams, L.M., Haig, A., Gordon, E., 2003. Gamma (40 Hz) phase synchronicity" and symptom dimensions in schizophrenia. Cogn. Neuropsychiatry 8 (1), 57–71.
Lovestone, S., 2009. Biomarkers in brain disease. Ann. N. Y. Acad. Sci. 1180, 1–124.
Machado-Vieira, R., Manji, H.K., Zarate Jr., C.A., 2009. The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis. Bipolar Disord. 11 (Suppl. 2), 92–109.
Mallat, S., 2008. A Wavelet Tour of Signal Processing. 3rd ed. Academic Press.
Megahed, A.I., Moussa, A.M., Elrefaie, H.B., Marghany, Y.M., 2008. Selection of suitable mother wavelet for analyzing power system fault transients. IEEE Power and Energy Society General Meeting — Conversion and Delivery of Electrical Energy in the 21st Century, 2008, pp. 1–7.
Miltner, W., Braun, C., Arnold, M., Witte, H., Taub, E., 1999. Coherence of gamma-band EEG activity as a basis for associative learning. Nature 397, 434–436.
Miyauchi, T., Tanaka, K., Hagimoto, H., Miura, T., Kishimoto, H., Matsushita, M., 1990. Computerised EEG in schizophrenic patients. Biol. Psychiatry 28 (6), 488–494.
Mountcastle, V.B., 1998. Perceptual Neuroscience: The Cerebral Cortex. Harvard University Press, Cambridge, MA.
Özerdem, A., Güntekin, B., Tunca, Z., Başar, E., 2008. Brain oscillatory responses in patients with bipolar disorder manic episode before and after valproate treatment. Brain Res. 1235, 98–108.
Özerdem, A., Güntekin, B., Saatçi, E., Tunca, Z., Başar, E., 2010. Disturbance in long distance gamma coherence in bipolar disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 34 (6), 861–865.
Özerdem, A., Güntekin, B., Atagün, I., Turp, B., Başar, E., 2011. Reduced long distance gamma (28–48 Hz) coherence in euthymic patients with bipolar disorder. J. Affect. Disord. 132 (3), 325–332.
Özerdem, A., Güntekin, B., Atagün, I., Başar, E., 2013. Brain oscillations in bipolar disorder in search of new biomarkers. Suppl. Clin. Neurophysiol. 62, 207–221.
Quiroga, R.Q., Garcia, H., 2003. Single-trial event-related potentials with wavelet denoising. Clin. Neurophysiol. 114, 376–390.
Quiroga, R.Q., Rosso, O.A., Başar, E., 1999. Wavelet entropy: a measure of order in evoked potentials. Electroencephalogr. Clin. Neurophysiol. 49, 299–303.
Quiroga, R.Q., Rosso, O.A., Basar, E., Schürmann, M., 2001a. Wavelet entropy in event-related potentials: a new method shows ordering of EEG oscillations. Biol. Cybern. 84, 291–299.
Quiroga, R.Q., Sakowitz, O.W., Basar, E., Schürmann, M., 2001b. Wavelet transform in the analysis of the frequency composition of evoked potentials. Brain Res. Protocol. 8 (1), 16–24.
Roach, B.J., Mathalon, D.H., 2008. Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. Schizophr. Bull. 34 (5), 907–926.
Röschke, J., Mann, K., Riemann, D., Frank, C., Fell, J., 1995. Sequential analysis of the brain's transfer properties during consecutive REM episodes. Electroencephalogr. Clin. Neurophysiol. 96 (5), 390–397.
Rossini, P.M., Del Percio, C., Pasqualetti, P., Cassetta, E., Binetti, G., Dal Forno, G., Ferreri, F., Frisoni, G., Chiovenda, P., Miniussi, C., Parisi, L., Tombini, M., Vecchio, F., Babiloni, C., 2006. Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. Neuroscience 143 (3), 793–803.
Rosso, O.A., Blanco, S., Yordanova, J., Kolev, V., Figliola, A., Schürmann, M., Başar, E., 2001. Wavelet entropy: a new tool for analysis of short time brain electrical signals. J. Neurosci. Methods 105 (1), 65–75.
Sakkalis, V., Zervakis, M., Micheloyannis, S., 2006. Significant EEG features involved in mathematical reasoning: evidence from wavelet analysis. Brain Topogr. 19 (1–2), 56–60.
Sakowitz, O.W., Quiroga, R.Q., Schürmann, M., Başar, E., 2001. Bisensory stimulation increases gamma-responses over multiple cortical regions. Brain Res. Cogn. Brain Res. 11 (2), 267–279.
Schürmann, M., Başar, E., 1994. Topography of alpha and theta oscillatory responses upon auditory and visual stimuli in humans. Biol. Cybern. 72 (2), 161–174.
Schürmann, M., Başar-Eroğlu, C., Başar, E., 1997. Gamma responses in the EEG: elementary signals with multiple functional correlates. NeuroReport 8 (7), 1793–1796.
Schürmann, M., Demiralp, T., Başar, E., Başar-Eroğlu, C., 2000. Electroencephalogram alpha (8–15 Hz), responses to visual stimuli in cat cortex, thalamus, and hippocampus: a distributed alpha network? Neurosci. Lett. 292 (3), 175–178.
Sharma, A., Weisbrod, M., Bender, S., 2013. Connectivity and local activity within the frontoposterior brain network in schizophrenia. Suppl. Clin. Neurophysiol. 62, 181–196.
Slewa-Younan, S., Gordon, E., Harris, A.W., Haig, A.R., Brown, K.J., Flor-Henry, P., Williams, L.M., 2004. Sex differences in functional connectivity in first-episode and chronic schizophrenia patients. Am. J. Psychiatry 161 (9), 1595–1602.
Solodovnikov, V.V., 1960. Introduction to the Statistical Dynamics of Automatic Control Systems. Dover Press, New York.
Spencer, K.M., Niznikiewicz, M.A., Shenton, M.E., McCarley, R.W., 2008. Sensory-evoked gamma oscillations in chronic schizophrenia. Biol. Psychiatry 63 (8), 744–747.
Sponheim, S.R., Clementz, B.A., Iacono, W.G., Beiser, M., 1994. Resting EEG in first-episode and chronic schizophrenia. Psychophysiology 31 (1), 37–43.
Sponheim, S.R., Clementz, B.A., Iacono, W.G., Beiser, M., 2000. Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia. Biol. Psychiatry 48 (11), 1088–1097.
Symond, M.P., Harris, A.W., Gordon, E., Williams, L.M., 2005. "Gamma synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? Am. J. Psychiatry 162 (3), 459–465.
Tallon-Baudry, C., Bertrand, O., Delpuech, C., Pernier, J., 1996. Stimulus specificity of phase-locked and non-phaselocked 40 Hz visual responses in human. J. Neurosci. 16 (13), 4240–4249.
Tan, D., Özerdem, A., Güntekin, B., Atagün, M.I., Tülay, E., Karadağ, F., Başar, E., 2015. Increased beta frequency (15–30 Hz) oscillatory responses in euthymic bipolar patients under lithium monotherapy. Clin. EEG Neurosci. pii: 1550059414561056 (in press).
Vecchio, F., Babiloni, C., Lizio, R., De Vico, F.F., Blinowska, K., Verrienti, G., Frisoni, G., Rossini, P.M., 2013. Resting state cortical EEG rhythms in Alzheimer's disease: towards EEG markers for clinical applications. A review. Suppl. Clin. Neurophysiol. 62, 223–236.
Vinck, M., Battaglia, F.P., Womelsdorf, T., Pennartz, C., 2012. Improved measures of phase-coupling between spikes and the local field potential. J. Comput. Neurosci. 33 (1), 53–75.
Walter, G.G., Shen, X., 2001. Wavelets and Other Orthogonal Systems. 2nd ed. CRC Press, Boca Raton, FL.
Walter, G.G., Zhang, J., 1998. Orthonormal wavelets with simple closed form expression. IEEE Trans. Signal Process. 46 (8), 2248–2251.
Yener, G.G., Başar, E., 2013a. Biomarkers in Alzheimer's disease with a special emphasis on event-related oscillatory responses. Suppl. Clin. Neurophysiol. 62, 237–273.
Yener, G.G., Başar, E., 2013b. Brain oscillations as biomarkers in neuropsychiatric disorders following an interactive panel discussion and synopsis. Suppl. Clin. Neurophysiol. 62, 343–363.
Yener, G.G., Güntekin, B., Öniz, A., Başar, E., 2007. Increased frontal phase-locking of event-related theta oscillations in Alzheimer patients treated with cholinesterase inhibitors. Int. J. Psychophysiol. 64 (1), 46–52.
Yener, G., Güntekin, B., Başar, E., 2008. Event related delta oscillatory responses of Alzheimer patients. Eur. J. Neurol. 15 (6), 540–547.
Yener, G., Güntekin, B., Tülay, E., Başar, E., 2009. A comparative analysis of sensory visual evoked oscillations with visual cognitive event related oscillations in Alzheimer's disease. Neurosci. Lett. 462 (3), 193–197.
Yener, G.G., Güntekin, B., Orken, D.N., Tülay, E., Forta, H., Basar, E., 2012. Auditory delta event-related oscillatory responses are decreased in Alzheimer's disease. Behav. Neurol. 25 (1), 3–11.
Yordanova, J., Kolev, V., 1997. Developmental changes in the event-related EEG theta response and P300. Electroencephalogr. Clin. Neurophysiol. 104 (5), 418–430.
Yordanova, J., Kolev, V., 1998. Event-related alpha oscillations are functionally associated with P300 during information processing. Neuroreport 9 (14), 3159–3164.
Yordanova, J., Kolev, V., Rosso, O.A., Schürmann, M., Sakowitz, O.W., Özgören, M., Başar, E., 2002. Wavelet entropy analysis of event-related potentials indicates modality independent theta dominance. J. Neurosci. Methods 117 (1), 99–109.
Zheng-yan, J., 2005. Abnormal cortical functional connections in Alzheimer's disease: analysis of inter- and intra-hemispheric EEG coherence. J. Zhejiang Univ. (Sci.) 6B (4), 259–264.