Application of Brain Oscillations in Neuropsychiatric Diseases
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Chapter 2

Brain's alpha, beta, gamma, delta, and theta oscillations in neuropsychiatric diseases: proposal for biomarker strategies

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ABSTRACT

Brain oscillations have gained tremendous importance in neuroscience during recent decades as functional building blocks of sensory–cognitive processes. Research also shows that event-related oscillations (EROs) in "alpha," "beta," "gamma," "delta," and "theta" frequency windows are highly modified in pathological brains, especially in patients with cognitive impairment. The strategies and methods applied in the present report reflect the innate organization of the brain: "*the whole brain work.*" The present paper is an account of methods such as evoked/event-related spectra, evoked/ERDs, coherence analysis, and phase-locking. The report does not aim to cover all strategies related to the systems theory applied in brain research literature. However, the essential methods and concepts are applied in several examples from Alzheimer's disease (AD), schizophrenia, and bipolar disorder (BD), and such examples lead to fundamental statements in the search for neurophysiological biomarkers in cognitive impairment.

An overview of the results clearly demonstrates that it is obligatory to apply the method of oscillations in *multiple electroencephalogram frequency windows* in search of functional biomarkers and to detect the effects of drug applications. Again, according to the summary of results in AD patients and BD patients, multiple oscillations and selectively distributed recordings must be analyzed and should include multiple locations. *Selective connectivity between selectively distributed neural networks* has to be computed by means of *spatial coherence.* Therefore, by designing a strategy for diagnostics, the differential diagnostics, and application of (preventive) drugs, neurophysiological information should be analyzed within a framework including multiple methods and multiple frequency bands. The *application of drugs/neurotransmitters* gains a new impact with the analysis of oscillations and coherences. A more clear and differentiated analysis of drug effects can be attained in comparison to the application of the conventional wide-band evoked potential and event-related potential applications.

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The interpretation of results in AD, schizophrenia, and BD (patients mostly with damaged cognitive neural networks) becomes most efficient by joint analysis of results on oscillatory responses and coherences obtained by means of *cognitive tasks*. In these diseases, strong cognitive impairment is observed; the use of spectra therefore allows cognitive deficits to be seen more clearly upon application of stimulation involving a cognitive task.

The report concludes by presenting highlights for neurophysiological explorations in diagnostics, drug application, and progressive monitoring of such diseases.

KEYWORDS

Electroencephalography (evoked, oscillations); Event-related (systems theory, power spectrum, time–frequency analysis); Phase-locking (delta, theta, alpha, beta, gamma, coherence); Alzheimer's disease; Bipolar disorder; Schizophrenia (lithium, acetylcholine)

2.1. Introduction

Brain oscillations as functional building blocks in sensory–cognitive processes have gained tremendous importance in the recent decades. Research also shows that event-related oscillations (EROs) 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 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.

The present report will present some methods, concepts, and strategies of use in analyzing brain oscillations 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 reflecting the innate organization of the brain: "*the whole brain work.*"

The report also includes a critical view providing an orientation for readers with an interest in reviewing the results emerging from reports contained in the present volume. The presented analyses will serve as proposals and do not constitute a systematic review. The review should be considered rather as a workshop, showing the utility of the applied analyses. The examples provide a summary of statistically significant and previously published results. We have chosen examples from our research groups, as the data can easily be displayed.

Our research group has published a series of papers related to methods of brain oscillations over a period of more than 40 years; accordingly, we aim to describe core ideas for using methods of electroencephalogram *(EEG)/ERO* analysis (see also Başar et al., 1975a–c, 2001a; Başar, 1980, 2011; Güntekin and Başar, 2010).

We also have to emphasize that there are important functional and interpretational differences between EEG, 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 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

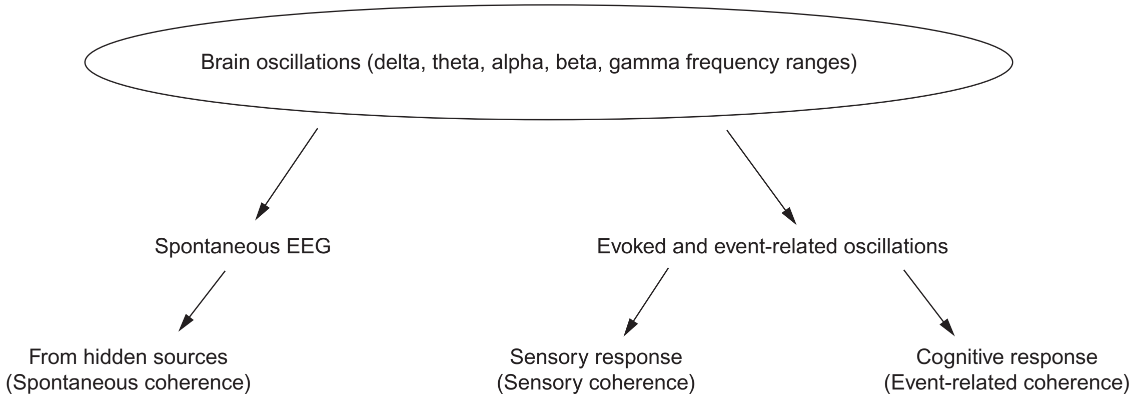

Fig. 1. A schematic presentation of differentiation in search of biomarkers related to brain oscillations.

aim of the present report, as presented in the last section, is therefore to indicate that a valid analysis of brain electrical potentials in search of biomarkers can be achieved only by successive application of analysis tools and should not be reduced to the search to a given frequency range or to 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 as Alzheimer's disease (AD), schizophrenia, mild cognitive impairment (MCI), and bipolar disorder (BD), patients show cognitive deficits depending on the state of illness, ages, and also cultural differences. Accordingly, cognitive deficits can be demonstrated only after comparing results upon sensory and cognitive signals (see papers by Başar-Eroğlu et al., Özerdem et al., 2013, this volume and Yener and Başar (a)).

The methods outlined in Table 1 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 volume (see Başar-Eroğlu et al., Özerdem et al., Vecchio et al., Yener and Başar (a)).

2.2. Why application of several methods and strategies is important in search of biomarkers

Fig. 2 illustrates new approaches and strategies in functional neuroscience. The usefulness of an *"ensemble of methods"* should be emphasized, since the application of single methods has severe shortcomings for understanding integrative brain functions. 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. However, 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/event-related potentials (ERP) and magnetoencephalography) 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

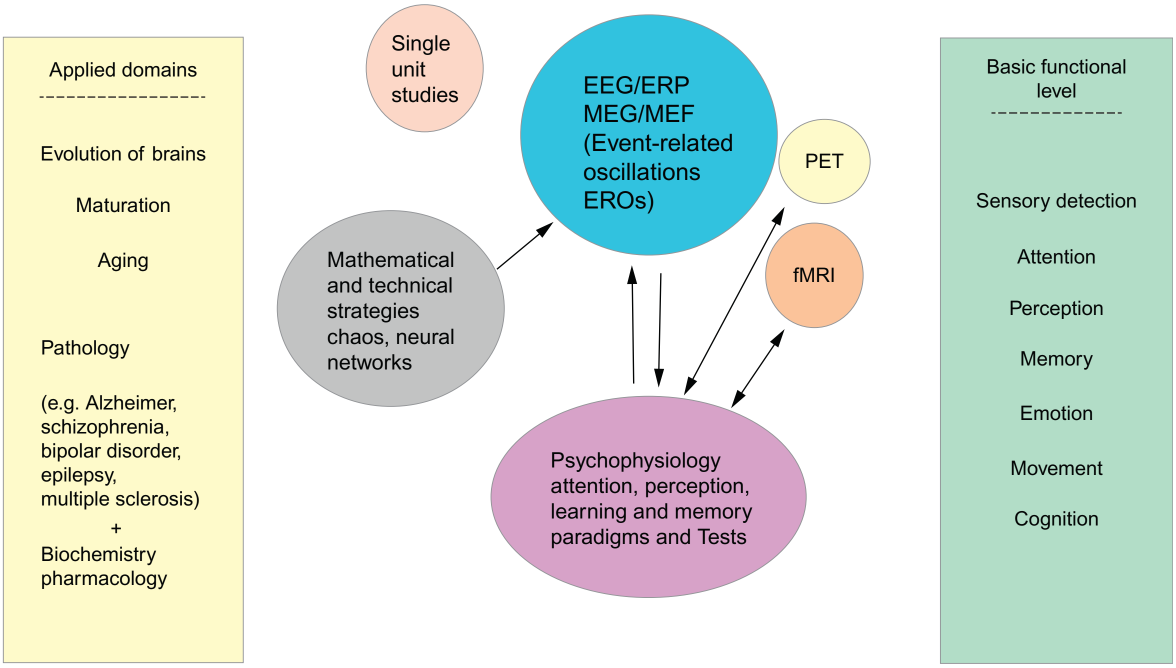

Fig. 2. New approaches and strategies in functional neuroscience (modified from Başar, 2004).

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. 1. 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 between cells (Eccles, 1973; Mountcastle, 1998). However, the importance of these studies for understanding integrative brain functions is questionable since, during the integrative processes, the whole brain is involved, as Adey et al. (1960) and Adey (1966, 1989) 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 a large temporal resolution in the range of half an hour and offers no possibility for dynamic measurements at the level of microseconds.

(3) The methods incorporating analyses of EEG/ERPs (and especially EROs) and fMRI provide further excellent strategies to illuminate brain functions, since they cover dynamic changes in the brain and the morphological structure. The MEG and study of magnetic evoked fields (MEFs) 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 psychophysiological 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 intracranial electrodes in the animal brain.

In order to achieve relevant progress in functional 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 central nervous system (CNS) functions (right side) and the applied domains (left side). Functions such as *sensory detection, movement,* and *memory* can be successfully analyzed by 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). 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).

2.3. 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 following hypothesis:

The EEG consists of the activity of an ensemble of generators producing rhythmic activity in several frequency ranges. These oscillators are usually active in a random way. However, by application of sensory stimulation, these generators are coupled and act together in a coherent way. This synchronization and enhancement of EEG activity gives rise to "evoked" or *"induced"* rhythms. *Evoked potentials (EPs), representing ensembles of neural population responses, were considered to be a result of the transition from a disordered to an ordered state. The compound ERP manifests a superposition of evoked oscillations in the EEG frequencies, ranging from delta to gamma ("natural frequencies of the brain" such as delta (0.5–3.5 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (15–28 Hz),* and *gamma (30–70 Hz).* (See publications by Başar, 1980; Klimesch et al., 1997; Yordanova and Kolev, 1998; see also reports in Başar and Bullock, 1992; Gurtubay et al., 2004; Buszáki, 2006.)

There are several strategies available for measuring cognitive changes, including spontaneous EEG, sensory evoked oscillation, and EROs. The term "sensory evoked" implies responses elicited upon a simple sensory stimulation, whereas "event-related" indicates responses elicited upon a cognitive task, generally an oddball paradigm. Further selective connectivity deficit in sensory or cognitive networks is reflected by coherence measurements. When a simple sensory stimulus is used, a sensory network becomes activated and "sensory evoked coherence" can be measured between brain regions, whereas an oddball task initiates activation in both a sensory network and an additional cognitive network, and then "event-related coherence" can be measured.

In the following, some rules and concepts are presented:

(1) Intrinsic oscillatory activity of single neurons forms the basis of the natural frequencies of neural assemblies. Oscillatory activity of the neural assemblies of the brain consists of the *alpha, beta, gamma, theta,* and *delta* frequencies. These frequencies are the natural frequencies and thus the real responses of the brain (Başar et al., 2001a–c).

(2) Morphologically different neurons or neural networks are excitable upon sensory–cognitive stimulation in the same frequency range of EEG oscillations; the type of neuronal assembly does not play a major role in the frequency tuning of oscillatory networks. Research has shown that neural populations in the cerebral *cortex, hippocampus*, and *cerebellum* are all tuned to the very same frequency ranges, although these structures have completely different neural organizations (Eckhorn et al., 1988; Llinás, 1988; Singer, 1989; Steriade et al., 1992; Başar, 1998, 1999). It is therefore suggested that brain networks in the whole brain communicate by means of the same set of frequency codes of EEG oscillations.

(3) The brain has *response susceptibilities*. These susceptibilities mostly originate from its intrinsic rhythmic activity, i.e., its spontaneous activity (Başar, 1980, 1983a,b; Narici et al., 1990; Başar et al., 1992). A brain system responds to external or internal stimuli with those rhythms or frequency components that are among its intrinsic (natural) rhythms. Accordingly, if a given frequency range does not exist in its spontaneous activity, it will also be absent in the evoked activity. Conversely, if activity in a given frequency range does not exist in the evoked activity, it will also be absent in the spontaneous activity. However, in the presence of high pre-stimulus activity, aftercoming post-stimulus activity enhancement will not be adequate for eliciting a significant response upon a stimulus application.

(4) There is an inverse relationship between EEG and ERPs. The amplitude of the EEG thus serves as a control parameter for responsiveness of the brain, which can be obtained in the form of EPs or ERPs (Jansen et al., 1993; Rahn and Başar, 1993; Başar, 1998; Barry et al., 2003; Başar et al., 2003).

(5) This characteristic and the concept of response susceptibility led to the conclusion that the oscillatory activity that forms the EEG governs the most general transfer functions in the brain (Başar, 1990).

(6) Oscillatory neural tissues that are selectively distributed in the whole brain are activated upon sensory–cognitive input. The oscillatory activity of neural tissues may be described through a number of response parameters. Different tasks, and the functions that they elicit, are represented by different configurations of parameters. Due to this characteristic, the same frequency range is used in the brain to perform not just one but *multiple functions*. The response parameters of the oscillatory activity are as follows: enhancement (amplitude), delay (latency), blocking or desynchronization, phase-locking, phase changes, prolongation (duration), degree of coherence between different oscillations, degree of entropy (Pfurtscheller, 1997, 2001; Neuper and Pfurtscheller, 1998a,b; Başar et al., 1999a,b; Miltner et al., 1999; Pfurtscheller et al., 1999, 2006; Schürmann et al., 2000; Kocsis et al., 2001; Rosso et al., 2001, 2002; Başar, 2004).

(7) The number of oscillations and the ensemble of parameters that are obtained under a given condition increase as the complexity of the stimulus increases, or as the recognition of the stimulus becomes more difficult (Başar, 1980, 1999; Başar et al., 2000, 2001a).

(8) Each function is represented in the brain by the superposition of the oscillations in various frequency ranges. The values of the oscillations vary across a number of response parameters. The comparative polarity and phase angle of different oscillations are decisive in producing function-specific configurations. Neuronal assemblies do not obey the *all-or-none* rule that the single neurons obey (Karakaş et al., 2000a,b; Klimesch et al., 2000a,b; Chen and Herrmann, 2001).

(9) The *superposition principle* indicates synergy between the alpha, beta, gamma, theta, and delta oscillations during the performance of

sensory–cognitive tasks. Thus, according to the superposition principle, integrative brain function operates through the combined action of multiple oscillations.

ESSENTIAL FEATURES OF THE "WHOLE BRAIN" WORK IN INTEGRATIVE BRAIN FUNCTION AS CONSEQUENCE OF THE ABOVE RULES

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,b; Karakaş et al., 2000a,b; Klimesch et al., 2000b; Chen and Herrmann, 2001).
2. The parallel activation of oscillations in gamma, beta, alpha, theta, and delta responses upon exogenous or endogenous inputs is 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,b, 2000, 2001a,b). 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,b; Miltner et al., 1999; Schürmann et al., 2000; Kocsis et al., 2001).
6. Inverse relationship between EEG and ERPs: EEG is a control parameter for responsiveness of the brain.

2.4. Ensemble of systems theory methods

2.4.1. Systems theory methods

In order to analyze the dynamics of brain oscillatory processes, several mathematical methods are applied. Table 1 summarizes the methods included in the "systems theory" of brain-state analysis.

More refined methods were also incorporated in order to analyze evoked brain activity, including the combined EEG–EP analysis, and wavelet analysis methods (Başar et al., 1999c, 2001a; Demiralp et al., 1999; Quiroga et al., 2001a, b). Our group first applied the system theory methods to brain waves by using the conventional methods. Later, our group has also applied new methods such as *wavelet entropy* (Quiroga et al., 1999; Rosso et al., 2001). In addition to the systems theory methods, newly emerging methods of analyzing EROs include studies of nonlinearities and the incorporation of the concept of chaos, which aim to further increase understanding of the properties of the system.

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 there are also a variety of measures derived from them, including important coupling measures such as coherence or phase synchrony. Başar et al. (1999c), Demiralp et al. (1999), and Başar (2011) compared wavelet transform techniques and conventional Fourier analysis in the human and cat brains and showed the

TABLE 1

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

equivalence of these techniques. 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 analysis also yield equivalent results in practical applications to neuronal signals.

2.4.2. Some fundamental remarks

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 sensory and cognitive event)* (Başar, 1980, 1998).

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, 1980; Röschke et al., 1995; Yordanova and Kolev, 1997), or the event-related and evoked power spectra. The AFCs 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. 3. Further, Fig. 3 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 EP and ERPs in the

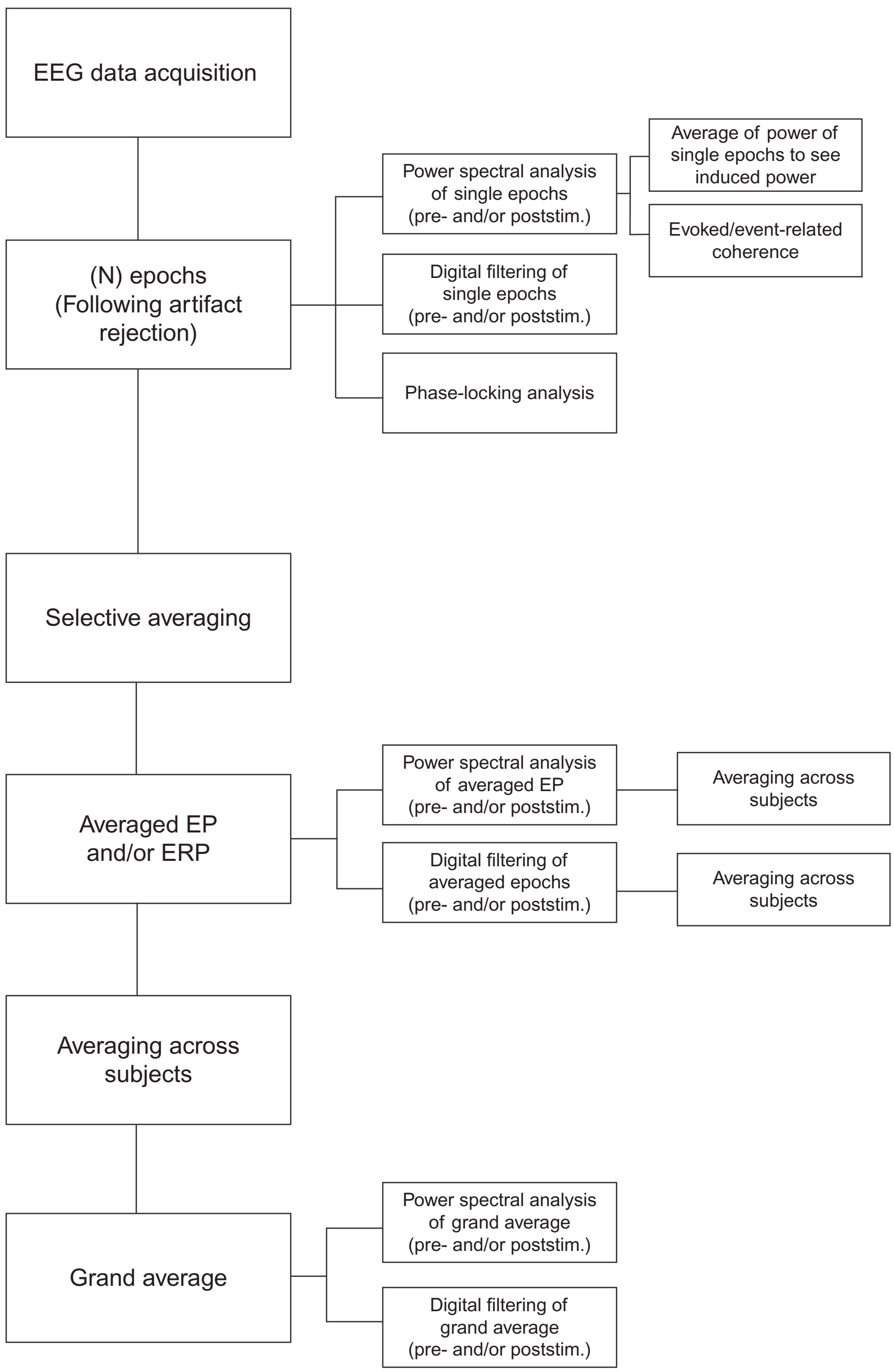

Fig. 3. Combined time and frequency domain analysis of EEG–EP epochs (modified from Schürmann and Başar, 1994; Başar et al., 2000).

conventional nomenclature of electrophysiology analysis. However, brain oscillations upon application of stimulation have been now a relevant progress in the analysis. First of all, 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 single epochs. A grand average is also applied by performing averaging across subjects. Another option is power-spectral analysis of grand average, in which adaptive digital filtering of grand average is performed.

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

2.5.1. 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, this volume). Fig. 4 represents the grand averages of power spectra of 18 healthy (indicated by black line) and 18 bipolar euthymic subjects (red 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. 4, 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. (2012b). Only the prominent decrease of alpha power illustrated in Fig. 4 could possibly serve as a neurophysiological marker in BD. Additionally, the disappearance of event-related theta power in BD may also be a relevant change; this will be explained in the next sections.

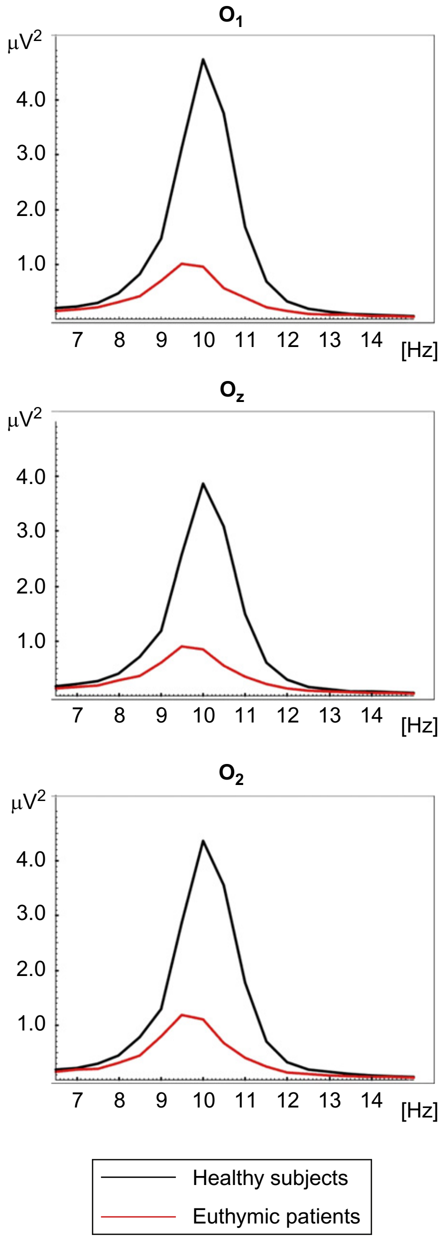

Fig. 4. Mean eyes-closed power values for occipital electrodes (modified from Başar et al., 2012b).

2.5.2. Analysis of evoked and event-related spectra

As seen in Fig. 5, in the grand average of post-stimulus power spectrum upon stimulation of

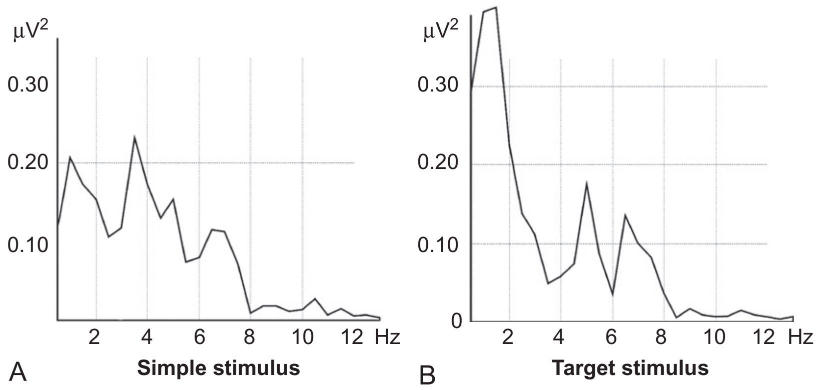

Fig. 5. Grand average of power spectra of auditory evoked (A) and event-related responses (B) over left frontal (F_3) location. Target stimuli (B) create increased amplitudes than simple sensory stimuli (A) in the delta frequency range in healthy subjects.

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 (for further information, see Başar, 2004). Doppelmayr et al. (1998) and Dumont et al. (1999) also suggested that narrow-band filtered analyses may be more informative for obtaining task specific parameters of the responses.

Accordingly, each subject's averaged evoked and ERPs 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 high as event-related delta response. Changes are markedly higher upon cognitive load. This is most possibly 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.

2.5.3. Differentiated changes of theta responses in BD

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

Slow (4–6 Hz) and fast (6–8 Hz) theta responses behaved differently during oddball paradigm in patients with BD. Fast theta responses (6–8 Hz) almost disappeared in euthymic BD patients (Atagün et al., 2011).

Application of digital filters in the analysis of neuropsychiatry patients requires refinement with the use of adaptive filters selected according to the cut-off 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 is also especially the case following drug applications.

2.5.4. 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. 7 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.

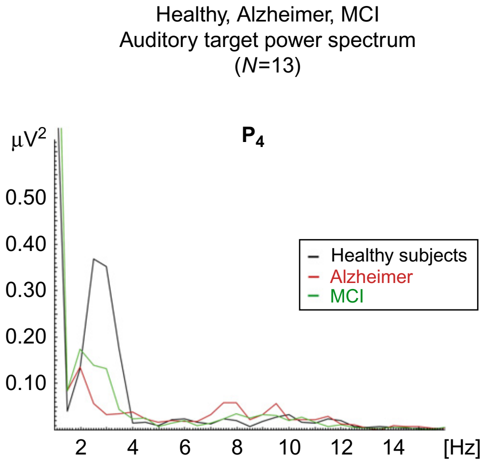

Fig. 7. Event-related spectral analysis of healthy control subjects, mild cognitive impairment (MCI), and Alzheimer's disease (AD).

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. 8 illustrates adaptively filtered frontal and parietal EROs 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. 6) and in schizophrenia in measurements upon inputs with cognitive task.

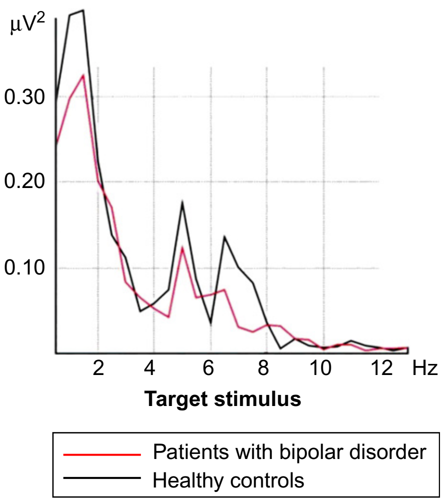

Fig. 6. Grand average of power spectra of auditory event-related responses over left frontal (F_3) location in bipolar disorder subjects and healthy controls upon auditory oddball stimulation (modified from Özerdem et al., 2013, this volume).

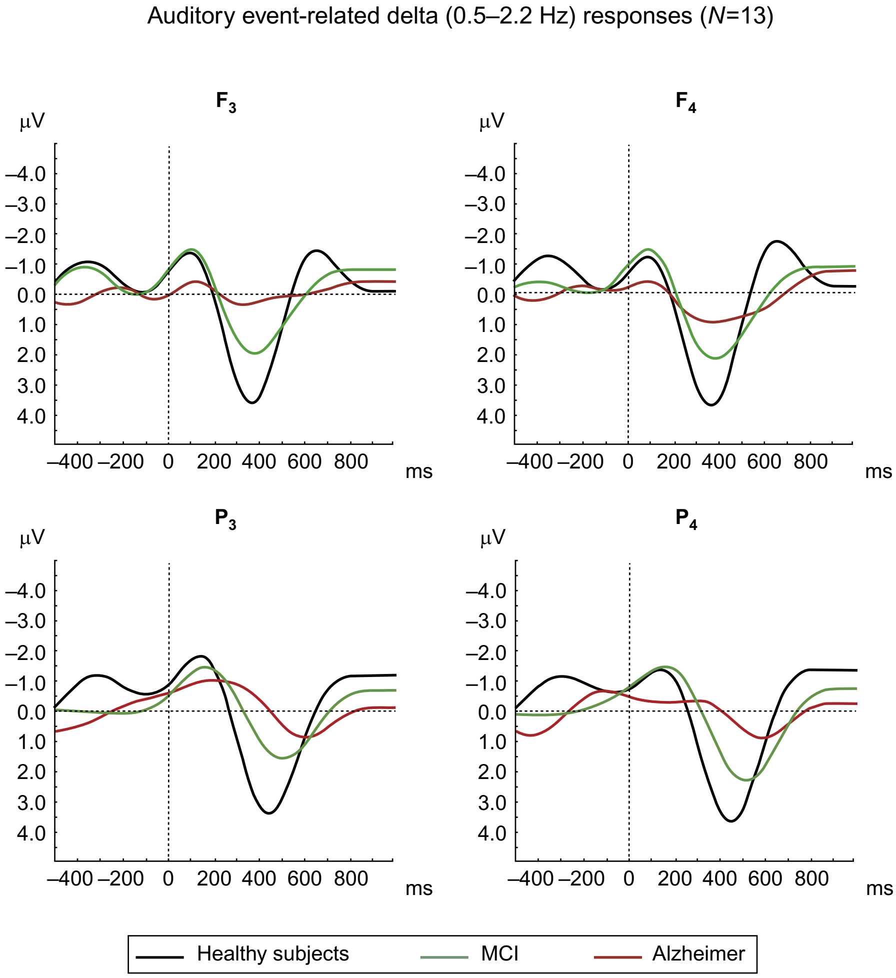

Fig. 8. MCI and AD continuity is prominent in auditory event-related delta oscillatory activity. Results show gradually decreasing delta amplitude and increasing delta peak latency among healthy elderly subjects, MCI, and mild-stage Alzheimer subjects (MCI: mild cognitive impairment, AD: Alzheimer's disease).

For AD, there are specific biomarker methods related to structural changes in the CNS. Those methods are described by Lovestone (2009), Vecchio et al. (2013, this volume), and Yener and Başar (2013a, this volume).

2.6. 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 deficit in selective connectivity.

An important brain mechanism underlying cognitive processes is the exchange of information between brain areas (Güntekin et al., 2008; Başar et al., 2010). The oscillatory analyses of isolated brain areas alone are not sufficient to explain all aspects of information processing within the brain. Therefore, for a description of neurophysiological mechanisms underlying cognitive deficits

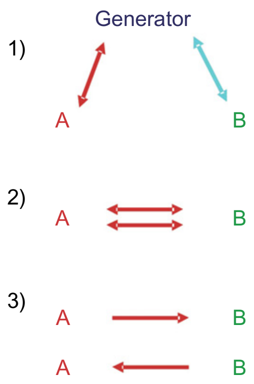

Fig. 9. A description of possible underlying mechanism of coherence between two structures (see text).

of neuropsychiatric diseases, connectivity dynamics between different brain areas must be investigated (Sharma et al., 2013, this volume; Yener and Başar, 2013a,b, this volume).

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; (3) one of the structures, A or B, drives the other (Fig. 9).

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

2.6.1. 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. Jelic et al. (2000), Babiloni et al. (2006, 2007, 2009), and Rossini et al. (2006) published core results on spontaneous EEG coherence in MCI patients. Hogan et al. (2003), Zheng-yan (2005), Yener et al. (2007, 2008, 2009), Güntekin et al. (2008), Dauwels et al. (2009), and Başar et al. (2010) published results on evoked/event-related coherence in AD 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 the 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) 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 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-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 the hints for the preserved visual-sensory network in contrast to damaged visual cognitive network in mild AD.

Fig. 10 illustrates the histogram of mean Z values for delta frequency range upon application of "simple light" stimuli for all electrode pairs. Fig. 11 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. 11 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. 10 shows that the evoked delta coherence

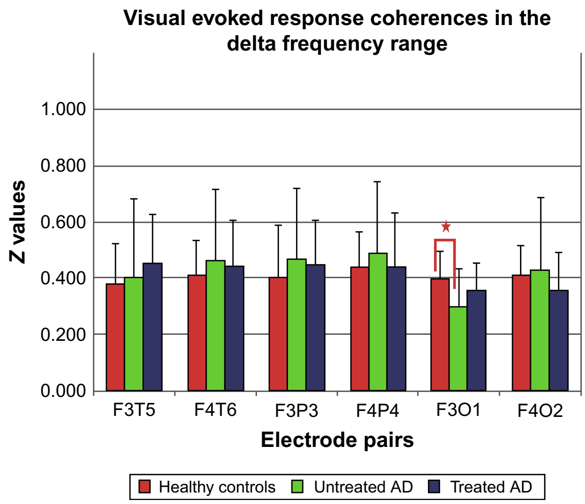

Fig. 10. Mean Z values of healthy control, treated AD, and untreated AD subjects for delta frequency range upon simple light stimuli. "*" sign represents $p < 0.01$ (modified from Başar et al., 2010).

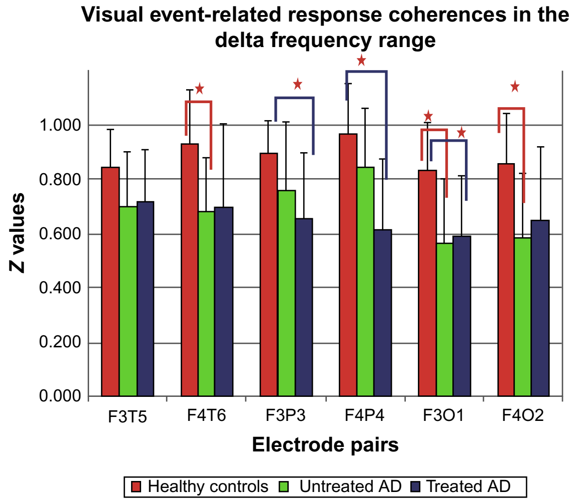

Fig. 11. Mean Z values of healthy control, treated AD, and untreated AD subjects for delta frequency range upon target stimuli. "*" sign represents $p < 0.01$ (modified from Başar et al., 2010).

upon "simple light" is not as 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. 12 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. 13 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. 13 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 Fig. 12 illustrates, 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 12 and 13

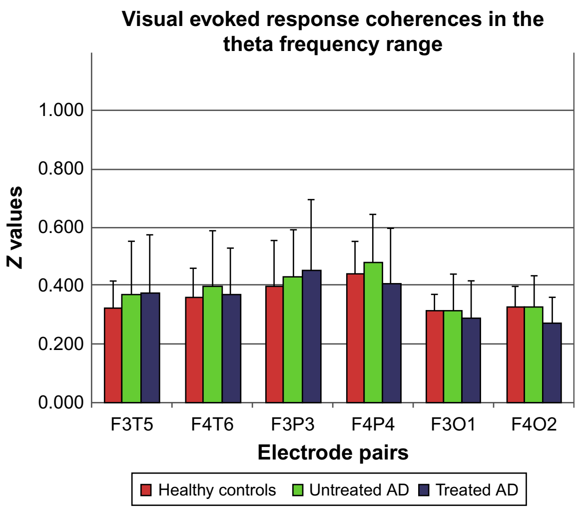

Fig. 12. Mean Z values of healthy control, treated AD, and untreated AD subjects for theta frequency range upon simple light stimuli (modified from Başar et al., 2010).

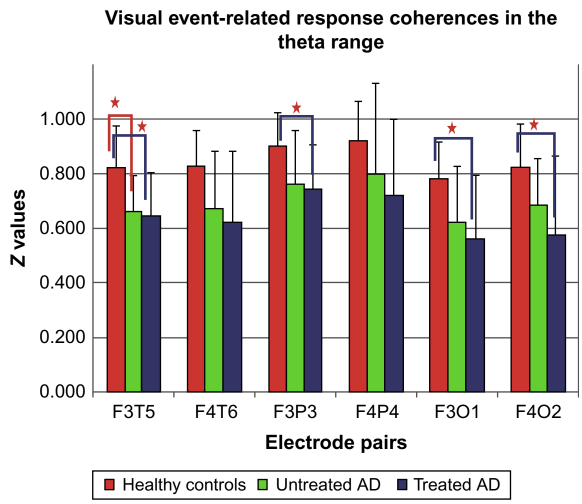

Fig. 13. Mean Z values of healthy control, treated AD, and untreated AD subjects for theta frequency range upon target stimuli. "*" sign represents $p < 0.01$ (modified from Başar et al., 2010).

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 future, as a biomarker in diagnostics of AD patients (see also Yener and Başar, 2013a, this volume).

2.6.2. 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 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. 14A and B depicts the grand average of visual event-related coherence in 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).

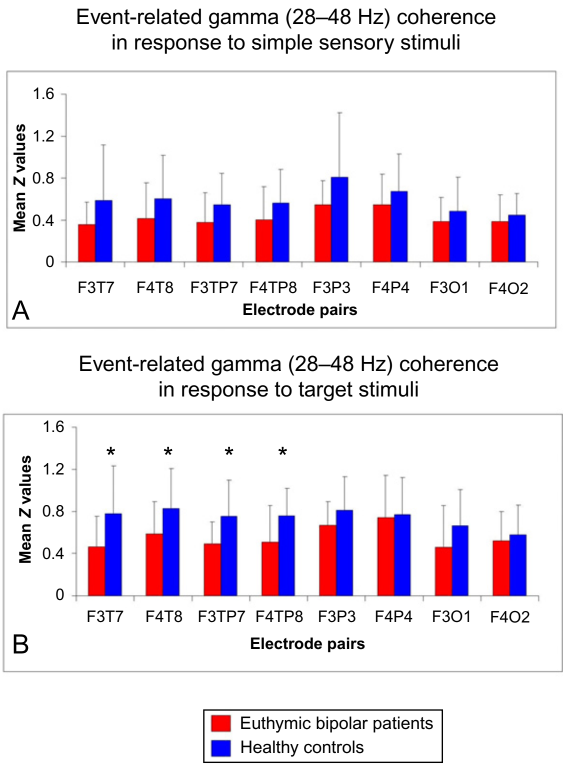

Fig. 14. Mean Z values for sensory evoked (A) and target (B) coherence in response to visual stimuli at all electrode pairs. "*" sign represents $p < 0.05$ (modified from Özerdem et al., 2011).

Oscillatory responses to both target and nontarget stimuli are manifestations of working memory (WM) 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.

2.7. Event-related delta, theta, and gamma oscillations in schizophrenia patients during N-back working memory tasks

A more differentiated visual event-related response paradigm in comparison to a simple oddball paradigm was applied to healthy subjects and schizophrenia patients by Schmiedt et al. (2005) and Başar-Eroğlu et al. (2007). The authors used the paradigm derived from classic N-back tasks under varying WM load. It consisted of three tasks: a simple choice reaction task (serving as a control), easy WM task (1-back), and hard WM (2-back) task.

Fig. 15 shows grand-average ERPs and the corresponding event-related gamma oscillations during the three tasks in patients and controls. In healthy subjects, the gamma amplitude increased gradually from control task to hard WM task. The event-related gamma activity significantly differed between tasks, indicating higher gamma amplitude values during the hard WM task compared to the control task. The ERPs were not filtered in the delta frequency range. However, the strong contribution of delta component to the ERPs is easily seen. The WM tasks usually trigger large delta responses in healthy subjects. Such large delta responses are not observed in schizophrenia patients upon WM tasks. The reduced theta responses in all three tasks and at all locations in patients were also reported (Schmiedt et al., 2005). In contrast, the gamma activity was higher in schizophrenia patients than in healthy subjects and remained constant regardless of task demand.

These results show increases of evoked and induced gamma, since enhanced gamma activities can be observed in both pre- and poststimulus time windows. This modulation of gamma activity seems to be related to increased cognitive load (Fig. 16, lower panel). The results in healthy subjects further suggest a task-related allocation of attentional processes with increased WM load. In contrast, the patients did not show a modulation of gamma activity with varying task demands. Accordingly, these results could be interpreted as a consequence of impairment in focused attention. Another possible interpretation is that higher gamma activity in patients could be related to cortical hyper-excitability, as suggested by Eichhammer et al. (2004) and Spencer et al. (2004).

Most studies on auditory steady-state evoked gamma responses showed reduced gamma response

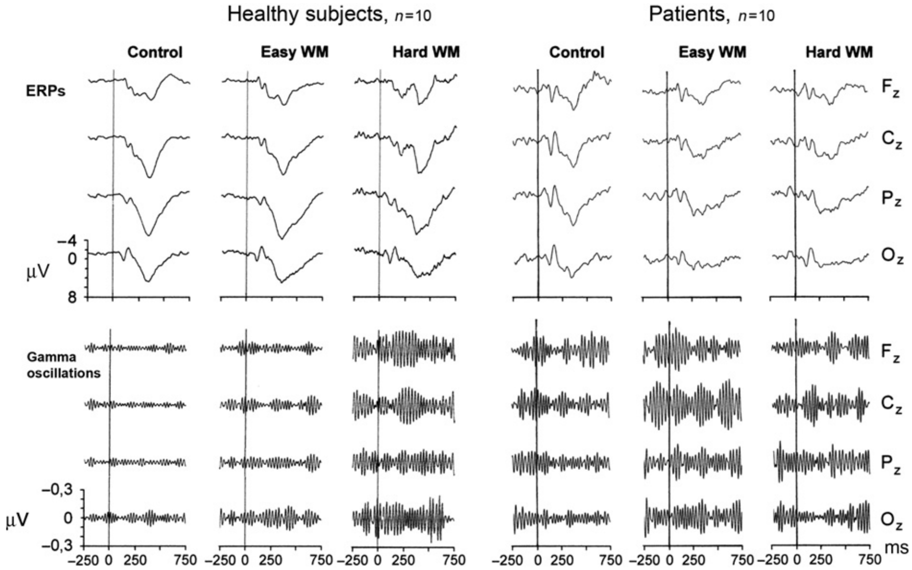

Fig. 15. Grand-average event-related oscillations (ERPs) in healthy controls (left upper panel) and in schizophrenia patients (right upper panel) during N-back tasks under varying working memory (WM) demands. $T = 0$ represents the stimulus onset. Lower panel shows grand-average gamma activities corresponding to the upper panel (modified from Başar-Eroğlu et al., 2007).

oscillations in schizophrenia patients compared to healthy controls. To our knowledge, there is only one study in which previous findings of reduced steady-state gamma band synchronization in schizophrenic patients were not directly replicated (Hong et al., 2004). On the other hand, event-related gamma responses in schizophrenia patients in comparison to healthy subjects show contradictory results in cognitive paradigms. In auditory oddball paradigms, previous authors mostly evaluated event-related gamma responses in two different time windows (early and late time window). Some studies showed that early evoked gamma band responses did not show significant group differences. However, schizophrenic patients showed reduced evoked gamma band responses in late latency range stimuli (Haig et al., 2000; Gallinat et al., 2004). Other studies (Lee et al., 2001; Slewa-Younan et al., 2004; Symond et al., 2005; Lenz et al., 2010) reported that schizophrenia subjects showed lower early-gamma phase synchrony compared to healthy subjects. Some recent studies reported increased gamma response in schizophrenic subjects compared to healthy controls upon application of an auditory paradigm. Başar-Eroğlu et al. (2011) reported that passive listening to stimuli was related to increased single-trial gamma power at frontal sites. Flynn et al. (2008) reported that, in first-episode patients, gamma phase synchrony was generally increased during auditory oddball task processing, especially over left centro-temporal sites in the 800 ms post-stimulus time window. Further research is needed to make robust conclusions on gamma response in auditory oddball paradigm in schizophrenia.

2.8. 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

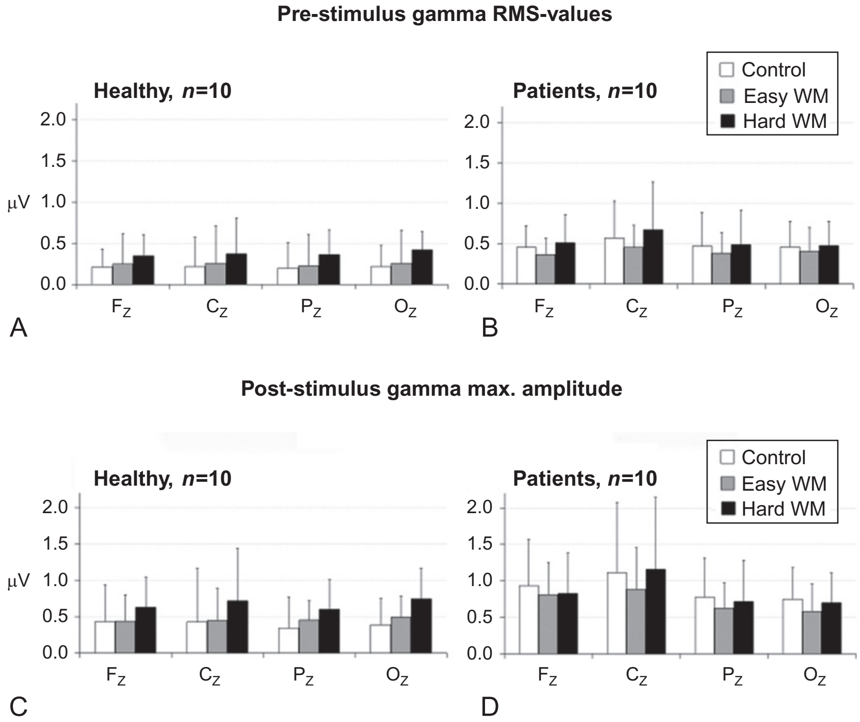

Fig. 16. Upper panel represents pre-stimulus RMS gamma values in healthy subjects and in schizophrenia patients in the three tasks. Lower panel shows post-stimulus maximal gamma amplitudes (modified from Başar-Eroğlu et al., 2007).

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.

2.8.1. Application of cholinergic drugs in AD patients

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, gamma, etc., oscillations that may relate to specific aspects of information processing. In the framework of the additive model of EPs, 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 (AChEIs). 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. 17 and 18). Moreover,

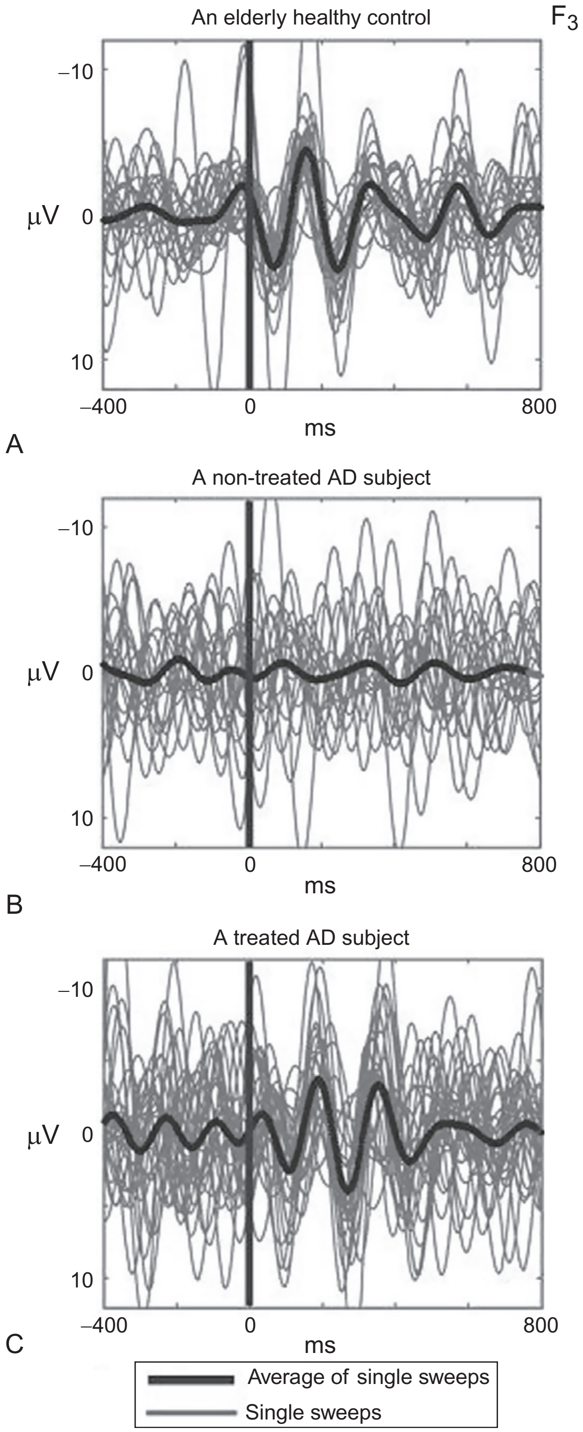

Fig. 17. Examples from each group showing single sweeps to the target stimuli elicited by a classical visual oddball paradigm recorded from F_3 scalp electrode. The thick black line indicates the average of single sweeps, and the thin gray lines show each single sweep for the subject. (A) An elderly healthy control. (B) A non-treated Alzheimer subject. (C) A treated (cholinesterase inhibitor) Alzheimer subject (modified from Yener et al., 2007).

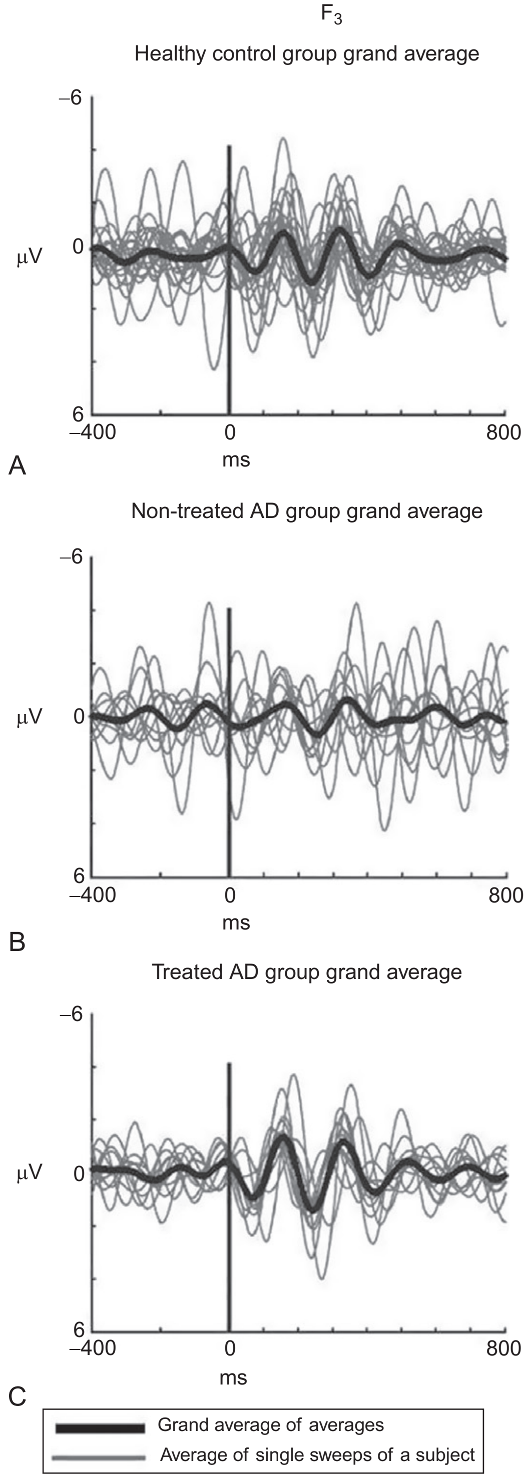

Fig. 18. Decreased visual event-related theta phase locking in AD. The thick black line represents the grand-average response of each group to the target stimuli elicited by a classical visual oddball paradigm and the thin gray and thin lines show averages of single sweeps from each subject (modified from Yener et al., 2007).

cholinergically treated AD group and healthy control did not differ from each other.

There are several methods to analyze the changes in phase locking (for further reading, see Tallon-Baudry et al., 1996; Yordanova and Kolev, 1997, 1998; Herrmann et al., 1999; Ergen et al., 2008; Vinck et al., 2011).

2.8.2. Application of lithium in BD patients

In a study by Özerdem et al. (2013, this volume) 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. 19 depicts 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 patients under lithium monotherapy.

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 BD.

2.9. 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 possibly not activated or less activated in the EEG or in pure sensory evoked coherences (see papers by Yener and Başar, 2013a,b, this volume). Therefore, *event-related coherences* and EROs 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 in 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 2 describes the possibilities to apply methods of oscillatory analysis in post-stimulus responses and the ensemble of significant results. Table 3 provides a similar overview of biomarkers in BD. 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 4 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, this volume). Spontaneous EEG alpha activity was 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).

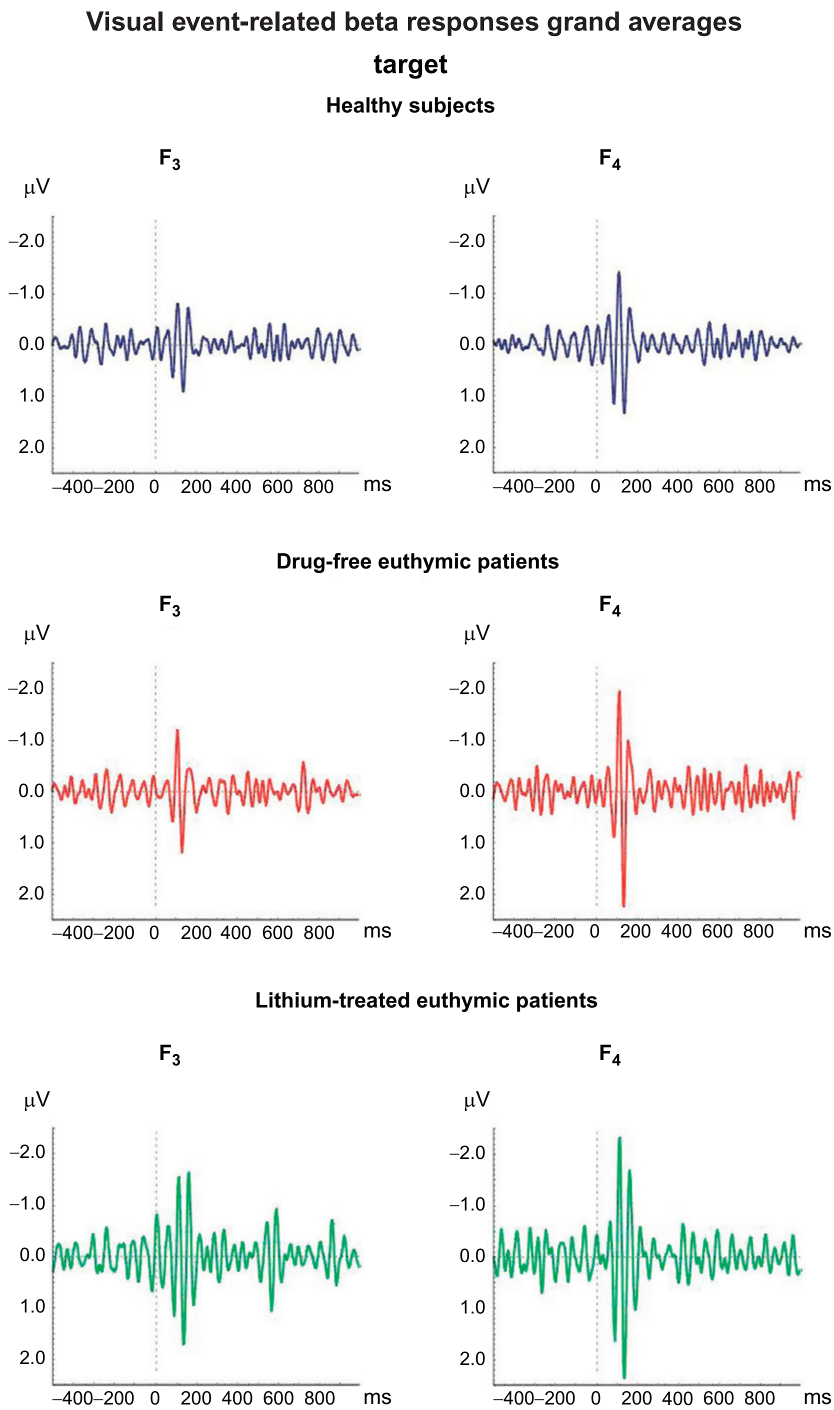

Fig. 19. Grand averages of event-related beta responses in left (F_3) and right (F_4) frontal electrode sites in (from top to bottom) healthy controls, euthymic drug-free patients, and in euthymic patients under lithium monotherapy (modified from Özerdem et al., 2013, this volume).

TABLE 2

OVERVIEW OF STUDIES ON ELECTROPHYSIOLOGICAL BIOMARKER CANDIDATES IN MCI OR AD

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)	↓ (Güntekin et al., 2008, visual oddball; Başar et al., 2010)
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)	↓ (Güntekin et al., 2008, visual oddball; Başar et al., 2010)
Alpha	↓			↔ (Yener et al., 2009, visual sensory)	↔ (Yener et al., 2008, visual oddball)		↓ α1 Coherence in MCI (Babiloni et al., 2010). ↓ α Coherence in AD (Jelic et al., 2000; Knott et al., 2000; Adler et al., 2003)	↔ (Başar et al., 2010, visual oddball)	↓↑ (Güntekin et al., 2008, visual oddball; Başar et al., 2010)
Beta	↓			↔ (Yener et al., 2009, visual sensory)	↔ (Yener et al., 2008, visual oddball)			↔ (Başar et al., 2010, visual oddball)	↔ (Güntekin et al., 2008, visual oddball; Başar et al., 2010)
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)	↔ (Güntekin et al., 2008, visual oddball; Başar et al., 2010)

Blue arrows represent the difference between unmedicated AD patients and healthy controls; red arrows represent the medicated AD patients. Empty cells remain to be analyzed.

TABLE 3

OVERVIEW OF STUDIES ON ELECTROPHYSIOLOGICAL BIOMARKER CANDIDATES IN BIPOLAR DISORDERS

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									
Fast theta			↓ Atagün et al., 2011, auditory oddball						
Alpha	↓ Clementz et al., 1994; Başar et al., 2012b				↓ Özerdem et al., 2008, manic BD, visual oddball				
Beta	↑ ↑ Başar et al., 2012a				↑ Özerdem et al., 2008, manic BD visual oddball				
Gamma								↔ Özerdem et al,. 2010, visual sensory	↓ Özerdem et al., 2010, visual oddball

Blue arrows represent unmedicated bipolar manic and euthymic patients. Green arrows show bipolar patients medicated with lithium. Empty cells have not yet been analyzed.

TABLE 4

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(a)			
Theta						↓ Ford et al. 2008; Doege et al., 2010(a)			
Alpha	↓								↓ Koh et al. 2011 (inter-trial phase coherence)
Beta									
Gamma		↔ Gallinat et al., 2004; Spencer et al., 2008	↓ 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 syncrony (Lee et al., 2003)			

Similar summaries of spontaneous EEG activity must also be included in order to present a complete overview of the oscillatory manifestation of the disease under study. We also mention that Tables 2–4 serve as examples; similar tables should also be 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 5–10 biomarkers for each pathology.

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

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

(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. 2, or with the application of structural biomarkers described by Yener and Başar (2013a,b, this volume), 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., Yener and Başar (a), Başar and Güntekin (all 2013, this volume).

2.10.1. 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 2–4).

2.10.2. Selectively distributed oscillatory networks

Again, according to the summary of results for AD, schizophrenia, and BD patients in Tables 2–4, recordings should be analyzed for multiple oscillations and at selectively distributed sites, rather than at one location.

2.10.3. Selective connectivity

Selective connectivity between selectively distributed neural networks has to be computed by means of spatial coherence. It is necessary to compare EROs (triggered by stimulations including a cognitive load) with sensory evoked oscillations (see Tables 2–4). These results show that, in AD and bipolar groups, EROs 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.

2.10.4. 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,b; Buszáki and Draguhn, 2004; Başar, 2008).

2.10.5. 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 and Figs. 17 and 18.

Frequency shift and delay can be also indicators of cognitive impairment as, explained in Fig. 8, indicating reduced delta frequency response.

It is recommended to standardize the causality of pre-stimulus activity for considering ERD as a cognitive biomarker (see Appendix).

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.

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 oddball paradigm evokes greatly variable gamma responses.

Cognitive tasks with progressively increasing difficulty open the way to interpreting various brain functions or insights into differentiated cognitive deficits, as shown in Fig. 15.

(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 attention and short-term memory.

(b) Through the use of tasks with progressive increase of 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, this volume).

(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 AD.

   (1) *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.

   (2) *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).

   (3) *The efficiency of assemblies of neurophysiological markers* in describing diseases and biomarkers is clearly emphasized in Tables 2–4. According to Giovanni Frisoni, Michael Koch, and Dean Salisbury, in the panel described by Yener and Başar (2013b, this volume), 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, application of (preventive) drugs, and neurophysiological information should be analyzed within a framework incorporating multiple methods and multiple frequency bands, as shown in Tables 2 and 3.

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 two important fundaments:

(a) The innate interwoven, multifold mechanisms that constitute "whole brain work" (see Section 2) 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.

(b) 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.

(c) It is also almost imperative to compute *evoked* or *event-related power spectra* before deciding on the application of adaptive digital filters. 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 chapter, the outlined strategies, methods, and conclusions are based on experiences from our research group, related to AD, BD, 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 present ensemble of results leading to biomarkers. The present paper is 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.

2.11. Appendix

Can event-related desynchronization be considered as a cognitive marker?

2.11.1. Further remarks related to the role of alpha in cognitive processes

The theories presented by Squire (1992), Baddeley et al. (1995), Fuster (1995, 1997), and Goldman-Rakic (1996) clearly explain the role of inborn phyletic memory (iconic, echoic) and, also, that memory states are not separable from basic brain functions. Besides remembering, memory functioning also comprehends processes of sensation, perception, and learning. Accordingly, memory theories manifested in brain oscillations could not be considered as pure top-down processes; bottom-up processes do occur in parallel or as serial processing. Sensory alpha responses in human have been described by several authors, starting with Başar (1972, 1980), Spekreijse and Van der Tweel (1972), and Başar et al. (1975a–c). In terms of the most fundamental findings, Dudkin et al. (1978) and Dinse et al. (1997) described visual evoked oscillations at the cellular level; the 10-Hz responses demonstrated by these authors were triggered by pure light signals and did not include cognitive tasks. The association of alpha activity with working memory was described by Başar and Stampfer (1985). More comprehensive and detailed studies of brain oscillations and memory were presented, in a long series of papers, by the Klimesch group, emphasizing differences between good and bad memory performers.

Recently, Klimesch et al. (2007) launched a hypothesis related to the "inhibition timing in alpha oscillations," which suggested that the event-related alpha response can be described solely in terms of suppression or event-related synchronization.

However, the alpha sensory and event-related responses were first described by Adrian (1941) and Bishop et al. (1953), who measured alpha responses upon pure sensory stimulation. In contrast, Klimesch et al. (1993, 1997) and Klimesch (1996) claimed that the vast majority of experiments correlates alpha with cognitive performance. These authors also indicate that, under certain conditions, alpha responds reliably, with an increase in amplitudes (event-related synchronization or ERS).

Several authors supported the hypothesis of Klimesch and co-workers. However, there are also fundamental critics of the inhibition theory. Knyazev et al. (2006) explained the essential shortcomings as follows: “The idea of inhibitory function for alpha synchronization is appealing but it raises some doubts. First, it is not clear how the same mechanism might be linked with perceptual activation, as in the case of phase-locked evoked alpha oscillations described by Başar (1998, 1999), and perceptual inhibition (as proposed for event-related alpha synchronization, ERS). Further, if ERS served a function of selective attention (e.g., inhibition of non-task-relevant perception), one would expect that relatively small cortical areas within a task-relevant zone would show ERD, whereas larger cortical areas, which are not related to the task processing, would show ERS; actually the opposite applies. Alpha ERD is usually more pronounced and widespread during first presentations of a signal or a task is stronger during more complex tasks compared to the relatively simple ones (Neubauer et al., 1999). All these observations are difficult to reconcile with the idea of lateral inhibition as a function of ERS.”

Knyazev et al. (2006) further indicated the relevance of background activity: Extensive studies by Brandt and Jansen (1991), Başar (1998, 1999), Barry et al. (2000), and other authors accumulated considerable evidence that different reactions of EEG bands could be observed, depending on background activity. According to the concept demonstrated by several authors, the ongoing EEG determines (controls) evoked activity.

Compared to the abundance of experiments dealing with alpha power measurements, relatively few studies focused on task-related shifts in alpha frequency. The experiments by Osaka (1984) showed that, only for difficult but not for easy tasks, alpha frequency increases selectively in the hemisphere that is dominant for a particular task.

The review by Ward (2003) summarized the recent evidence that synchronous neural oscillations reveal much about the origin and nature of cognitive processes such as memory, attention, and consciousness, and that memory processes are most closely related to theta and gamma rhythms, whereas attention seems closely associated with alpha and gamma rhythms. These conclusions are not in accordance with the fundamental views of Fuster (1995, 1997), Baddeley (1996), Desimone (1996), and Goldman-Rakic (1996), who demonstrated that processes of memory and attention are inseparable. This discordance is also evident in the “time inhibition hypothesis” (Klimesch et al., 2007), that omitted the important relationship between pre-stimulus activity and ERO in that model. As already stated by Rémond and Lesèvre (1967) and Walter (1950), there are several mechanisms underlying the spontaneous alpha activity and evoked/event-related alpha oscillations; according to Rémond and Lesèvre (1967), the phase angle of the alpha oscillations at the time of the stimulus plays a crucial role in the generation of evoked alpha response.

We have started a new pilot study (as yet unpublished), analyzing the qualitative and quantitative behavior of alpha activity and alpha responsiveness. Besides the phase angle described by Rémond and Lesèvre (1967), five different types of alpha process were detected in pre-stimulus alpha and post-stimulus alpha sweeps in the analysis of 17 subjects (−500 ms pre-stimulus/ +500 ms post-stimulus alpha).

In all subjects we have encountered five different groups in the pre-stimulus–post-stimulus epochs:

(1) EEG–EP sweeps showing alpha phase locking and enhancement.
(2) EEG–EP sweeps showing alpha blocking and no phase locking following stimulation.
(3) EEG–EP sweeps showing only phase locking upon stimulus onset.

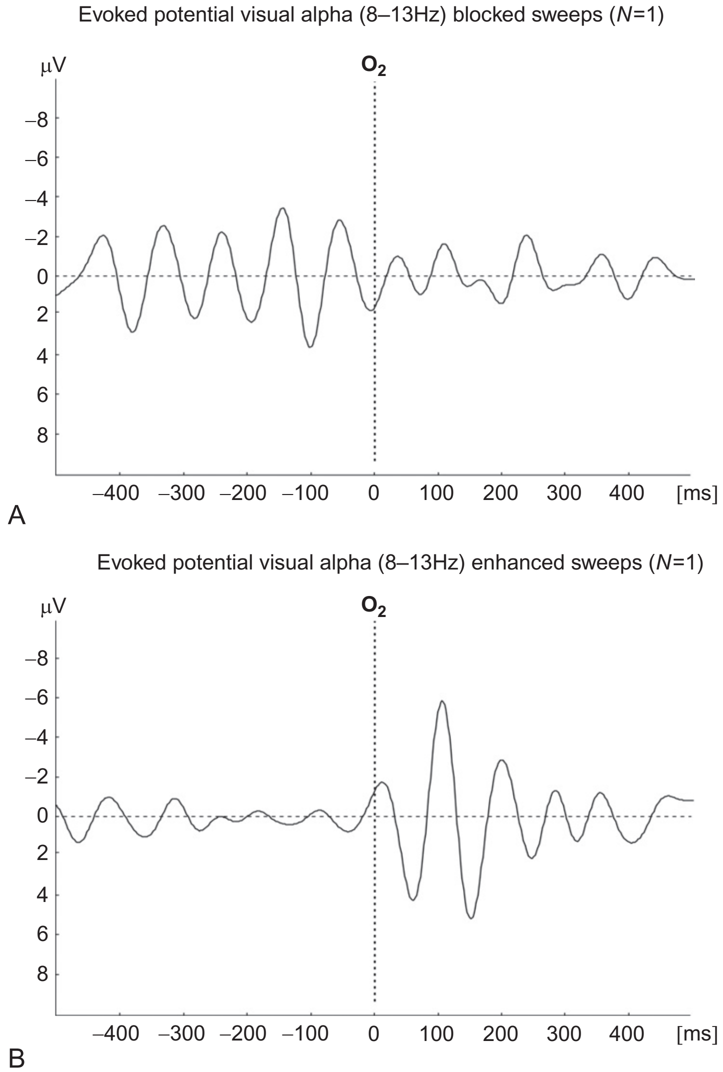

Fig. A1. Alpha blocking (A) and enhanced alpha (B) in a single subject.

(4) EEG–EP sweeps showing no enhancement and no phase locking.

(5) EEG–EP sweeps showing time locking (induced responses).

According to the above grouping of single EEG–ERP records, we have performed averaging of selected EEG–EP ensembles for each subject and further grand average of 17 subjects.

Fig. A1 shows two selective ensembles for a typical subject in which alpha blocking (A) and alpha enhancement (B) have been recorded. It is clearly seen that pre-stimulus alpha activity is high in the case of alpha blocking (ERD), whereas enhanced (ERS) is recorded only when the post-stimulus alpha activity is low.

The grand average from 17 subjects in Fig. A2 confirms the results of a typical single subject. The evaluation of five different types of responsiveness is currently in progress. The existence of these five different alpha responsiveness processes

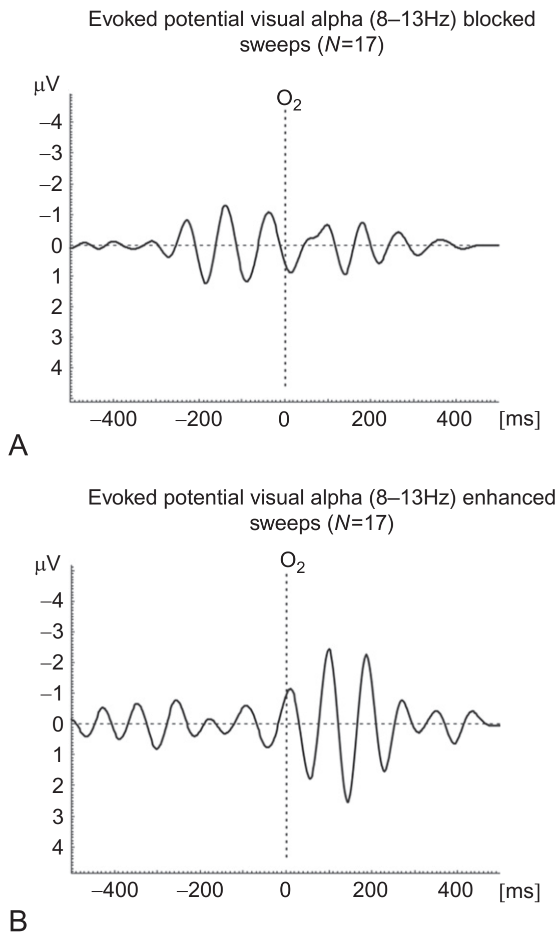

Fig. A2. Alpha blocking (A) and enhanced alpha (B) in a grand average of 17 subjects.

is encountered in all subjects. However, the distribution shows significant variability between subjects. A comprehensive analysis of this matter will be presented in a future publication.

According to the results of this appendix, it is recommended to standardize the causality of pre-stimulus activity before considering ERD as cognitive biomarker.

Abbreviations

ACh = acetylcholine
AChEI = acetylcholine esterase inhibitor
AD = Alzheimer's disease
AFC = amplitude frequency characteristic
BD = bipolar disorder
CNS = central nervous system
EEG = electroencephalography
EROs = event-related oscillations
ERPs = event-related potentials
FFT = Fast Fourier Transform
fMRI = functional magnetic resonance imaging
MCI = mild cognitive impairment
MEG = magnetoencephalography
MEF = magnetic evoked field
MRI = magnetic resonance imaging
PET = positron emission tomography
PLF = phase-locking factor
TMS = transcranial magnetic stimulation
WM = working memory

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