Brain oscillations as biomarkers in neuropsychiatric disorders: following an interactive panel discussion and synopsis

Görsev G. Yener\textsuperscript{a,b,*} and Erol Başar\textsuperscript{b}

\textsuperscript{a}Brain Dynamics Multidisciplinary Research Center, and Departments of Neurosciences and Neurology, Dokuz Eylül University, İzmir 35340, Turkey
\textsuperscript{b}Brain Dynamics, Cognition and Complex Systems Research Center, Istanbul Kültür University, Istanbul 34156, Turkey

ABSTRACT

This survey covers the potential use of neurophysiological changes as a biomarker in four neuropsychiatric diseases (attention deficit hyperactivity disorder (ADHD), Alzheimer’s disease (AD), bipolar disorder (BD), and schizophrenia (SZ)). Great developments have been made in the search of biomarkers in these disorders, especially in AD. Nevertheless, there is a tremendous need to develop an efficient, low-cost, potentially portable, non-invasive biomarker in the diagnosis, course, or treatment of the above-mentioned disorders.

Electrophysiological methods would provide a tool that would reflect functional brain dynamic changes within milliseconds and also may be used as an ensemble of biomarkers that is greatly needed in the evaluation of cognitive changes seen in these disorders. The strategies for measuring cognitive changes include spontaneous electroencephalography (EEG), sensory evoked oscillation (SEO), and event-related oscillations (ERO). Further selective connectivity deficit in sensory or cognitive networks is reflected by coherence measurements.

Possible candidate biomarkers discussed in an interactive panel can be summarized as follows: for ADHD: (a) elevation of delta and theta, (b) diminished alpha and beta responses in spontaneous EEG; for SZ: (a) decrease of ERO gamma responses, (b) decreased ERO in all other frequency ranges, (c) invariant ERO gamma response in relation to working memory demand; for euthymic BD: (a) decreased event-related gamma coherence, (b) decreased alpha in ERO and in spontaneous EEG; for manic BD: (a) lower alpha and higher beta in ERO, (b) decreased event-related gamma coherence, (c) lower alpha and beta in ERO after valproate; and for AD: (a) decreased alpha and beta, and increased theta and delta in spontaneous EEG, (b) hyperexcitability of motor cortices as shown by transcortical magnetic stimulation, (c) hyperexcitability of visual sensory cortex as indicated by increased SEO theta responses, (d) lower delta ERO, (e) lower delta, theta, and alpha event-related coherence, (f) higher theta synchrony and higher alpha event-related coherence in cholinergically treated AD subjects.

In further research in the search for biomarkers, multimodal methods should be introduced to electrophysiology for validation purposes. Also, providing the protocols for standardization and harmonization of user-friendly acquisition or analysis methods that would be applied in larger cohort populations should be used to incorporate these electrophysiologic methods into the clinical criteria. In an extension to conventional anatomical, biochemical and brain imaging biomarkers, the use of neurophysiologic markers may lead to new applications for functional interpretations and also the possibility to monitor treatments tailored for individuals.

\textsuperscript{*}Correspondence to: Dr. Görsev G. Yener, M.D., Ph.D., Department of Neurology, Dokuz Eylül University Medical School, Balçova, İzmir 35340, Turkey. Tel.: +90 232 412 4050; Fax: +90 232 277 7721; E-mail: gorsem.yener@deu.edu.tr
20.1. Introductory remarks

Publications on cognitive processes by means of brain oscillations have increased within the neuroscience literature in the past 20–30 years. However, there are relatively few studies related to cognitive impairment within the literature, dating only from the beginning of the last decade. Accordingly, the trend to use “biomarkers” is relatively recent.

The official US National Institutes of Health’s definition of a biomarker is: “a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Biomarkers can provide an objective basis for diagnosis, treatment selection, and outcome measures (Fig. 1; Wright et al., 2009).

A conference/workshop related to brain oscillation in neuropsychiatric diseases took place in Istanbul in May 2011 as a first conference during which diseases such as Alzheimer’s disease (AD), mild cognitive impairment (MCI), schizophrenia (SZ), bipolar disorders (BD), attention deficit hyperactivity disorder (ADHD) and their neurophysiologic strategy modalities were jointly referenced and discussed. The present interactive survey is mostly based on the results and closing panel discussion of this conference. It also covers part of discussions, advice or remarks of lecturers, and important hints from papers of the present Supplement 62 and also relevant knowledge from previous publications.

During the panel discussion, Claudio Babiloni gave an extended and useful synopsis of discussions, and Giovanni Frisoni gave important hints and described goals for establishing brain oscillations as biomarkers in neuropsychiatric disorders based on his experience of MRI techniques. Paolo M. Rossini stated that in the next 10 years it will be very valuable to develop a low-cost, user-friendly biomarker that can be applied widely to many neuropsychiatric disorders.

The brain does not respond in a homogenous and standard manner to stimulations. The responses are highly dependent on topology, age, states, and pathology. The spontaneous electroencephalographic oscillations, evoked oscillations, event-related oscillations (EROs) and event-related coherences are selectively distributed. Accordingly, the organizers suggested that new, reliable hypotheses and biomarkers could be pronounced only after performing or surveying a wide spectrum of measurements, as described in the following section.

20.1.1. Cardinal view on multiple analysis of brain oscillations

It is necessary to emphasize that there are important functional differences between spontaneous electroencephalography (EEG), sensory evoked oscillations (SEOs), and EROs. In the analysis of spontaneous EEG, only sporadically changes of amplitudes from hidden sources are measured. SEOs reflect the property of sensory networks activated by a sensory stimulation. Event-related (or cognitive) oscillations manifest modification of sensory and cognitive networks, both triggered by a cognitive task (Fig. 2).

An important brain mechanism underlying cognitive processes is the exchange of information between brain areas. The oscillatory analyses of isolated brain areas are important (Başar et al., 1999), but not sufficient to explain all aspects of information processing within the brain. Therefore, in addition to local changes in brain dynamics, dynamics of connectivity between different brain areas must be investigated for a description
Coherence is the synchrony between neuronal activities in different parts of the brain. 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.

In resting EEG analysis, only sporadically occurring coherences from hidden sources are measured. 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 and cognitive networks triggered by a cognitive task. Accordingly, the cognitive response coherences comprehend activation of a greater number of neural networks.

Fig. 1. Biomarkers are useful for detecting the risk factors, screening, or treatment monitoring. (Modified from Wright et al., 2009.)

Fig. 2. A schematic presentation of differentiation in brain oscillations.
that are most likely not activated or less activated in the EEG and pure sensory evoked coherences. Therefore, event-related coherences and ERO merit special attention in 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 in future to provide a deeper physiological understanding of distributed functional networks and, in turn, the possibility of determination of markers for medical treatment. Fig. 3 presents a schema for connectivity underlying sensory evoked coherence responses following simple sensory stimuli and event-related coherence responses following a cognitive task. It is not possible to define clear-cut boundaries for these neural groups that are differentiated upon application of sensory stimulation or upon cognitive stimulation. This schema indicates that there are neural populations, mostly responding to sensory signals, and other populations responding to only cognitive stimulation. Further, there is some overlap or plasticity among these networks. It is also possible that neural groups are not separated into different structures but co-exist also in given structures. These are selectively distributed neuron clusters capable of responding to sensory/cognitive inputs. It is also expected that following sensory stimulation, cognitive neural clusters would remain silent, whereas a cognitive stimulus (i.e., target signal in oddball paradigm) would excite both sensory and cognitive neural clusters. Certainly in the case of cognitive impairment, cognitive neural clusters would be more affected, in turn, giving rise to less unclear responses. Moreover, reduced response amplitude can result from either non-responding neural units or non-phase-locked response activity.

Fig. 3 illustrates only one local area. However, isolated brain networks can explain only a limited activity. In addition to these local activities, it is important to emphasize the selective connectivity between neural elements of these networks and, more important, differential connectivity between distant areas of the brain (e.g., frontal, limbic, and parietal connections) (Fig. 4). In the case of AD, the number of neural clusters responding to cognitive stimulus is greatly reduced. Additionally, we observe a selective connectivity deficit between

---

**Fig. 3.** Neural assemblies involved in sensory and cognitive networks. Cognitive networks (here shown by magenta lines) probably contain sensory neural elements, but also involve additional neural assemblies, as shown by magenta circles. Sensory network elements are illustrated by blue squares and connections by blue lines. It is expected that sensory signals trigger activation of sensory areas, whereas cognitive stimulation would evoke both neural groups reacting to sensory and cognitive inputs.
distant neural networks (see Güntekin et al., 2008; Başar et al., 2010).

20.2. Interactive panel discussion, chaired by Görsev G. Yener and Erol Başar

The following section summarizes the interactive panel discussion.

Dean Salisbury stated that psychologists build models in order to understand complex behaviors. However, the model must be biologically realistic. Working with patients, neuroscientists look for abnormalities in the biological system; we therefore learn to constrain the model, based on these abnormalities. This provides a greater understanding of how our complex cognition is represented in the real brain. However, when we consider the clinical aspects in terms of potential benefits for patients, or discuss biomarkers, we need to differentiate between the larger class, which are state-dependent and may index a change or current functioning, and endophenotypes, which are trait related. In future, we aim to define complex endophenotypes using a multi-dimensional approach across the diagnostic categories; such a multivariate analysis of patterns of ERO and ERPs would allow classification of different sub-categories within neuropsychiatric disorders. That is the link with neurotransmitter abnormalities; therefore, if we can construct multi-dimensional profiles and link them with underlying neurotransmitter abnormalities, we can develop individualized treatments.

During this interactive discussion, three main questions were discussed.

20.2.1. Question 1: After discussing the electrophysiological details of schizophrenia, AD, BDs, MCI, ADHD, etc., can we develop an ensemble of biomarkers for these disorders, and what should we be doing to translate those valuable methods into clinical practice?

Giovanni Frisoni stated that “the case of Alzheimer’s disease (AD) is particularly favorable to develop neurophysiologic markers, because we have a reasonable hypothesis for the causes.” Current biomarkers have various degrees of validation — a dynamic process that is ongoing. Therefore, it is possible to develop neurophysiological markers, using the already validated markers as a proof of convergent validity for diagnosis or for disease progression. Future research on neurophysiological biomarkers should therefore start from the current position, with an existing framework and biomarkers against which to validate new markers.

Markers that were discussed are for diagnosis — structural, metabolic, or CSF changes. However, one may also need markers to track disease progression, to check whether a drug is effective. Some markers may be used for diagnostic and also tracking purposes, but others may not change much over time, and so are poor markers to track disease progression (Fig. 1 and Table 1).

AD is more favorable to develop electrophysiological biomarkers. Different degrees of validation occur for these biomarkers. Structural, metabolic, and CSF markers (i.e., static) are already available for AD. Further, dynamic markers are important for tracking or progression of disease or monitoring
drug effects, since disease-modifying drugs are being widely studied in AD. In AD, Michael Weiner has launched a major project called the Alzheimer’s disease neuroimaging initiative (ADNI), to follow patients with cognitive disturbances over time (every 6 months, 5 years to date), including a number of biomarkers (biological and imaging) (Weiner et al., 2012). The ADNI project has clarified much about the progression of the disease. The most obvious proposal would be to add neurophysiological markers and study how they change with time and to what extent they agree with the other markers (Karow et al., 2010; Polikar et al., 2010; Walhovd et al., 2010; Jack et al., 2011). Many years ago, the biomarker field of AD was similar to that of schizophrenia. Table 1 summarizes a few AD biomarkers.

Michael Koch commented that biomarkers could open a venue for very early therapeutic intervention, including some neuropsychiatric diseases, where the course of progression is not as rapid as in AD or Parkinson’s disease. There is widespread agreement that biomarkers must be reliable not only in differentiating diseases, but also in predicting the course of the disease, thereby allowing therapeutic intervention at the pre-symptomatic stage.

In summary, according to G. Frisoni, M. Koch, D. Salisbury, and A. Özerdem, biomarkers can be classified based on specific functions:

<table>
<thead>
<tr>
<th>AD markers</th>
<th>For diagnosis</th>
<th>For progression</th>
<th>For drug effects</th>
<th>Non-invasiveness</th>
<th>Low cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid PET</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>CSF</td>
<td>+</td>
<td>±</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Structural MRI</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Electrophysiology</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; FDG-PET: fluoro deoxy glucose positron emission tomography; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

20.2.2. Biomarkers in schizophrenia

According to Ayşegül Özerdem, in psychiatry, we need biomarkers to differentiate between disorders rather than clearly defining patients from healthy controls. This is difficult, given the diagnostic criteria we are using. However, it may help to investigate dimensions: studying schizophrenia or bipolar patients together to see how they differ over time, for example, in terms of electrophysiological parameters. Another approach for early diagnosis would be to study the at-risk population or their first-degree relatives, to track potential electrophysiological characteristics; next focus on this issue and associate it with clinical pathology; then follow up subsequent treatments (see
Onitsuka et al., this volume). According to Dan Mathalon, most of the psychiatric disorders, whose pathophysiology we still do not know well, have a neurodevelopmental basis meaning that we know that things are not normal even before the full development of the disorder is evident. Therefore, biomarkers would allow us to detect risk and to develop strategies for early intervention, because some intervention strategies may not be effective later, beyond this early window of opportunity.

Görsev G. Yener commented on these arguments as follows: “In schizophrenia or mild cognitive impairment (MCI), we may see subtle neurophysiological changes or symptoms in the early sub-clinical era. The real challenge will be developing electro-physiological methods that are inexpensive, non-invasive and user-friendly. This might help to screen wider populations and to prevent AD progression at the earliest possible stage. The epidemiological results indicate that the expansion of AD worldwide is increasing every year, and a delay of several years in the development of AD would refuse the cost.”

According to G. Frisoni, there is a lack of a biomarker for the diagnosis of schizophrenia, as it is now based on the clinical criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 2000). Previously, we knew very little about AD, except that there were “dementias”; this is gradually broken down into more detailed classifications, that may also be a useful approach in schizophrenia. For example a diagnostic marker to differentiate between schizophrenia sub-types is needed in that case.

Even though BD and schizophrenia are considered as separate neuropsychiatric entities, they share several common susceptibility genes and overlap in the confirmed linkages (Onitsuka et al., in this volume). Altered neural oscillation and synchronization can be an index of cognitive dysfunction. Studies reported larger neural oscillations and increased phase-locking in BD than healthy controls or schizophrenia. Schizophrenia subjects exhibited delayed neural oscillations and decreased phase-locking compared with healthy controls.

20.2.2. Question 2: Can we learn about cognitive impairments after application just by knowing some dynamic factors that are influenced by the disease and by looking at the disease itself; can we learn about these disorders?

Investigating the pathophysiology of neuropsychiatric diseases by means of brain oscillations can lead to an understanding of how the brain can be so disorganized that it results in this complex system of symptoms. For many researchers, this could be a more interesting topic than their potential use as biomarker as commented by Judith Ford.

The following section summarizes the analysis presented by Claudio Babiloni during the discussion on standardization, harmonization, and continuous dialogue with clinicians which is the new frontier for our field. My work and that of several others is to follow the ADNI data collection standards and to have a common language to organize and analyze the data; to link EEG oscillations in resting state in AD with respect to biomarkers, according to the most advanced standards by ADNI.

Cognitive neuroscience studies: attention and many other cognitive functions. The field now regards the cognitive functions in a refined way that focuses on sub-functions and work is ongoing to relate our EEG oscillations to this modern view of our consciousness, etc. We have a very powerful approach to capture the transmission of information within the brain at several sites according to several oscillatory codes. Translational studies to align our various EEG markers with the concept of markers in the different fields of neurological pathologies are extremely important. Further, if we are able to go beyond the limitations of EEG, like low spatial resolution, we can precisely localize the networks used for these oscillations, such as theta networks, because there are probably specific networks using specific codes or combinations of codes. So we need neuroimaging to capture, with higher spatial resolution, the cortical and subcortical networks in the brain, and studies with transition models
to capture and validate oscillatory phenomena. Therefore, a multimodal approach to the study of clinical and cognitive neuroscience is crucial. An important contribution of this conference is to demonstrate the progress of several innovative multimodal studies (Rossini and Ferreri, this volume). These multimodal approaches include Professor Rossini’s transcortical magnetic stimulation and EEG studies, structural connectivity studies and EEG prepulse inhibition as a model of link between brain and peripheral nervous system, and neurovegetative response to the brain as described by Başar et al. (2010).

Babiloni does not view EEG alone: the purpose of his work is not simply collecting EEG data, but is primarily to dialogue with others, providing multimodal methods including neuropsychology on AD, rather than abstract theories. This is the real core of the ongoing multi-center work on EEG to break into the AD frontier and research.

20.2.3. Question 3: Would it be possible to propose some common neurophysiologic grounds? What might be the methodological necessities? Harmonized spontaneous EEG and a standardized approach to ERP and brain oscillations?

Robert Barry found that the proposal is good in principle, but very difficult to implement in practice. According to him, it is difficult to find commonalities between researchers investigating differing issues. There may be potential benefits from basic resting EEG, functional magnetic resonance imaging (fMRI). However, if one asks what might be an appropriate paradigm, these paradigms each have different efficiencies in different disorders. Therefore, there would be limited efficiency benefits from all researchers attempting to collect data on everything.

According to Dean Salisbury, we cannot simply rely on resting EEG. In psychiatry, attempts have already been made to base diagnosis and subtyping solely on quantified EEG patterns, but the results were disappointing. Therefore, any proposed approach must be multimodal, but there are difficulties in reaching agreement. To be practical, it must be relatively inexpensive, so the use of fMRI or MRI in all cases is questionable; imaging technologies would be used in AD cases, but practical implementation must consider any method’s inherent financial costs.

According to Giovanni Frisoni, the progress of the AD research resulted from the effort to organize researchers from multiple sites to generate definitive data sets. That facilitated the discovery of patterns across different imaging modalities, to the extent that these patterns are now useful for clinicians. There are other similar trends that should be encouraged: there are initiatives to conduct multi-site collection of schizophrenia data in clinically high-risk youths; as a result, large samples are rapidly being generated. This addresses a long-standing problem in our field, where the literature is dominated by studies using small samples that fail to be replicated. This problem of replication is compounded because our fields examine conditions that are inherently complex, abnormal, and heterogeneous. In the process of addressing this, we must change the process of science. It is not easy to agree on commonly applicable paradigms, but some changes are occurring, where researchers collect data that are beneficial for the wider research field. Such multi-site, large-sample studies will be necessary in order to deliver results that are of use to clinicians.

Robert Barry provided the following comments: “Listening to the presentations, it seems we are ignoring the state of the patients when they come to be assessed. Some of the differences in alpha that were presented may relate to the fact that patients may be highly anxious for a diagnosis or treatment. So some of the results we are observing are related to anxiety, not the disease itself. We should be considering universally applicable methods that would
screen out some of those issues and lead to more robust results. One simple and cheap add-on might be the use of skin conductors, which showed huge differences between patients and controls in ADHD.”

20.3. Open discussion

20.3.1. Summary by Claudio Babiloni

Some speakers presented an intriguing view of the brain rhythms in the resting state condition. This condition can be conceptualized as a spontaneous fluctuation in brain arousal along the time axis. This apparently simple state of the brain is very rich in information about, and the mechanisms of, neural synchronization and coordination within cortico-cortical and subcortical-cortical circuits modulating the brain arousal time by time. The speakers have shown that specific brain dynamics of the resting stage, the “default” state, express a sort of inhibition in the processing of stimuli coming from the external world and form a crucial bias in the subsequent response of the brain to external stimuli. For example, the specific phase of the brain oscillatory activity in the prestimulus period can affect the timing of the brain response to a given external stimulus, the selective involvement of the neural networks, and the relative ability of these networks to process information in order to represent events/operative states, and memories.

It has also been confirmed that brain rhythms at particular alpha frequencies (about 8–10 Hz) are related to arousal and are modulated in amplitude by caffeine. In the resting state, other brain frequencies are able to be associated with the global personality of children in the development of state; these preliminary results need to be confirmed. However, this is a positive indication that several people with different personalities and methods of processing information are characterized by particular features of the neural synchronization in the brain, together with a different functional coupling of EEG rhythms between cortical populations (“functional connectivity”) as a mode to gate the transfer of signals/information across neural circuits.

Evaluation of resting state brain rhythms enlightens physiological and pathological aging and global cognitive status of the subjects. On the one hand, it has been shown that particular resting state alpha rhythms (about 8–10 Hz) are reduced in amplitude in association with brain atrophy and global cognitive status in subjects with MCI and AD. In the same vein, pathological delta rhythms (1–4 Hz) increase as a function of the disease, at least at group level. The power reduction of the alpha rhythms along the disease progression would be slowed by cholinesterase inhibitors (Donepezil) in AD patients responding to long-term therapy of 12 months, suggesting some relationship among resting state alpha rhythms, aging, and integrity of the cholinergic neuromodulation systems. Of note, intriguing analogies between AD and major depression are suggested by the finding of reduced resting state alpha rhythms in patients with depression during asymptomatic periods. On the other hand, it has been shown that, in AD patients, the power of delta rhythms is abnormal not only in the resting state, but also in response to “oddball” target stimuli as a function of the treatment with cholinesterase inhibitors (Yener et al., 2007). Impaired processing of the “oddball” target stimuli would also be related to an abnormal coupling of the EEG oscillations from delta to alpha frequencies. This is a promising neurophysiological approach to the exploration of brain function in developmental age, physiological, and pathological aging, as well as psychiatric disorders.

20.3.2. Schizophrenia

In the workgroup on schizophrenia, several speakers reviewed the state of the art in relation
to the neurophysiological basis of the generation of brain gamma (<35 Hz) rhythms. A key role would be played by fine neural circuits modulated by agonists and antagonists (i.e., ketamine) of glutamate neurotransmission and NMDA receptors. Interesting original evidence has been presented in both human and animal models.

Some interesting evidence has been presented about the relationship between atrophy of the temporal lobe and abnormal EEG oscillations in oddball paradigms in schizophrenic patients, although some open issues and contrasting results suggest that the variability of the disease endophenotypes may prevent the definition of a common picture about the particular abnormalities of the brain synchronization mechanisms in schizophrenia. In this regard, the relationship between features of EEG rhythms and genotyping merits specific discussion. Some speakers have shown EEG procedures to unveil the relationships between specific endophenotypes, EEG oscillatory activity, and the progression of schizophrenia. Specifically, there would be some invariant individual features of gamma rhythms along the progression of schizophrenia from the first episode onward, and these features appear to be common to people of the same family, in terms of determining whether they depend on genetics. This is promising for a future classification of patients with different forms of the disease, possibly in relation to genetic features.

20.3.3. EEG markers in schizophrenia

Another important input from the schizophrenia workgroup was the evaluation of candidate EEG markers for schizophrenia (resting state, “oddball,” etc.) in young healthy subjects who underwent to a reversible and innocuous pharmacological procedure to induce some mental states resembling positive schizophrenia symptoms. The results showed that such a procedure is not able to induce, “tout court,” the typical EEG picture of schizophrenia. Only a minority of EEG markers was affected by the experimental manipulation, with only slight relationships with the subjects’ mental state, in agreement with the idea that schizophrenia cannot be captured by simple pharmacological “challenge” models. However, the general methodological approach based on surrogate EEG endpoints seems to be quite promising for drug discovery in schizophrenia.

20.3.4. Hyperconnectivity

One of the most interesting findings of the schizophrenia session concerned “hyperconnectivity.” One of the speakers showed that schizophrenic patients were characterized by “paradoxical” occipital EEG oscillatory responses to auditory “oddball” targets in two different experiments (Başar-Eroğlu et al., 2011). This is further evident that schizophrenia patients can display maladapted hyper-connectivity; it has been speculated that, in these patients, abnormal auditory information is distributed and triggers excitation in the occipital visual cortex, possibly producing abnormal visual imagery or visual processing. This intriguing working hypothesis will need to be tested with control experiments in schizophrenic patients to evaluate possible relationships between the “paradoxical” occipital EEG oscillatory responses to auditory “oddball” targets and structural neuroimaging indexes (i.e., tractography, diffusion tensor imaging).

20.3.5. Neurotransmitters

The symposium also addressed a new frontier for the study of EEG oscillations and neurotransmitters, namely EEG investigations of BDs. In this regard, the first preliminary results were presented on brain oscillations and major depression. ERO and coherence studies in AD also showed decreased delta and theta responses and widely diminished cortico-cortical coherences in alpha, theta, and delta ranges. Among those parameters, frontal theta phase-locking and alpha fronto-parietal coherence values were
sensitive to medication effects, as reported by Yener and Başar (2010) and Güntekin et al. (2008). An intense discussion was developed about how EEG may help identify the relationship between the neural synchronization mechanisms at the basis of transfer of information between areas and mood regulation as reflected by the generation of EEG oscillations.

### 20.3.6. General conclusion

A general conclusion was that the EEG community must continue to inform the discussion with clinicians about the kind of evidence required to test the particular contribution of EEG oscillatory markers for early diagnosis and prognosis, individualized management, therapy monitoring, and drug discovery in psychiatric and dementia patients. Besides, understanding the brain plasticity and its underlying functional and structural components has been challenged by new neurophysiological techniques within the past 10 years as summarized by Rossini and Ferreri (this volume). There is a need for a deeper dialogue with cognitive neuroscientists using fMRI and transcranial magnetic stimulation in order to investigate the correlation between EEG oscillations and fine brain topography of hemodynamic responses and excitatory/inhibitory neurotransmitter systems. Furthermore, a deeper dialogue is necessary with cognitive psychologists involved in the fine modeling of subtypes of attention (i.e., endogenous, reflexive, exogenous, orienting, etc.) and memory (i.e., procedural, episodic, semantic), to evolve the experimental designs to be used in our EEG studies. The future role of EEG oscillations in clinical and cognitive neuroscience depends on this dialogue. The same is true for the future of clinical and cognitive neuroscience itself. Indeed, EEG oscillations are the main emerging property of the resting state and working brain. The pathway is still long but quite exciting.

After Claudio Babiloni’s summary, Giovanni Frisoni stated that “as a physician, my feeling is that neuroscientists working on brain oscillations have a great tool available, but the cross-talk with clinicians is crucial to understand how to apply this tool. For most clinicians, the neuroscience vocabulary is challenging and, previously, waveforms were difficult for physicians to interpret. The great expansion of neuroimaging within the last year allows the function to be plotted onto the anatomy, making it more recognizable for clinicians. It requires effort from all parties to use the appropriate language to communicate with each other. In AD, the great initiatives are large and multinational. This group should be expanded to mirror such approaches; if neurophysiology enters that mainstream, it could contribute enormously to the understanding of the disease and to patient treatment.”

### 20.4. Candidate electrophysiological biomarkers for several neuropsychiatric disorders

#### 20.4.1. Attention deficit hyperactivity disorder (ADHD)

ADHD is a condition in which a person (usually a child) has an unusually high activity level and a short attention span. People with the disorder may act impulsively and may have learning and behavioral problems. Several reports consistently reported increased gamma oscillatory responses (Perez et al., Taylor et al., Yordanova et al., all in this volume) and elevation of delta and theta along with diminished alpha and beta responses in spontaneous (resting) EEG (Monastra et al., 2001; Barry et al., 2003). One of the difficulties with ADHD is a tendency for over-diagnosis. Barry and Clarke (in this volume) suggest the theta:beta ratio as a potential biomarker for ADHD. As they state, it seems to be sensitive to medication, as improved symptoms following medication are linked to a reduction in the theta:beta ratio. An updated general model of coherence anomalies in ADHD children, based on Barry and Clarke (this volume), also indicates a wide range of regional connectivity anomalies in this disorder.
20.4.2. Schizophrenia

Schizophrenia is a psychotic disorder (or a group of disorders) marked by severely impaired thinking, emotions, and behaviors. Increased dopaminergic activity in the mesolimbic pathway of the brain is a consistent finding. The mainstay of treatment is pharmacotherapy with antipsychotic medications; these primarily work by suppressing dopamine activity.

Gamma activity induced in response to task-relevant and irrelevant auditory oddball stimuli in medicated schizophrenics showed a significant decrease in comparison to controls (Haig et al., 2000). Later other reports confirmed the reduced gamma (Wynn et al., 2005; Başar-Eroğlu et al., 2007; Spencer et al., 2008) independent of medication (Minzenberg et al., 2010), and also reduction in delta, theta, and alpha frequency bands (Başar-Eroğlu et al., 2009) in schizophrenia patients. Başar-Eroğlu et al. (2011) indicated an overexcitability of neuronal networks in schizophrenia as shown by their findings showing elevated gamma responses at both anterior and occipital sites to auditory stimuli. They also showed a less prominent anterior alpha response to simple sensory auditory input, which probably indicates less efficient processing, similar to reduced alpha responses for non-target stimuli in oddball paradigm in schizophrenia subjects (see Başar Eroğlu et al., this volume).

Herrmann and Demiralp (2005) reviewed the literature on the alterations of gamma oscillations (between 30 and 80 Hz) during the course of neuropsychiatric disorders and based on a study by Lee et al. (2003). They suggested that in schizophrenic patients, negative symptoms correlate with a decrease in gamma responses, whereas a significant increase in gamma amplitudes is observed during positive symptoms such as hallucinations.

Auditory steady-state response (ASSR) power and phase-locking to gamma range stimulation were found to be reduced in patients with schizophrenia. In a review by O’Donnell et al. (this volume), alterations of ASSRs in schizophrenia, schizotypal personality disorder, and first-degree relatives of patients with schizophrenia were reported. ASSRs are usually reduced in power or phase-locking in patients with schizophrenia following 40-Hz stimulation. Possibly, delayed phase synchronization and reduction in 40-Hz power in schizophrenia could be also considered as biomarkers.

Previously, Mathalon’s and Ford’s groups showed that the early evoked gamma band response to tones is poorly synchronized in schizophrenia (Roach and Mathalon, 2008), which is consistent with other reports of abnormalities in the early auditory gamma oscillatory responses in chronic schizophrenia patients (for a review, see Gandal et al., 2012). Gamma responses of young schizophrenia patients show decreased evoked power (Perez et al., this volume) and diminished phase-locking of gamma responses (Roach et al., this volume).

According to Taylor et al. (this volume), it seems likely that the early auditory gamma band responses would be reduced in schizophrenia. Roach and Mathalon (2008) suggested that wavelet parameters might play a role in the detection of group differences and reported reduced phase-locking of early auditory gamma band responses in this disorder.

The relationship between long-range fronto-posterior connectivity and local brain activity in the frontal and posterior areas is investigated by Sharma et al. (this volume). They show that abnormal functional connectivity in the fronto-posterior brain network in schizophrenia is not necessarily characterized by a global reduction of connectivity, but can either be increased (during rest) or decreased (during cognitive control), depending on the stage of the task. The sensory and frontal areas of schizophrenia patients showed reduced evoked activity and the posterior association cortex during later target evaluation and perceptual processes are more strongly reduced in schizophrenia. Fronto-posterior coherence was reduced in patients as early as 100 ms. These results indicate
that connectivity disturbances may be a more fundamental deficit in schizophrenia and may manifest very early during cognitive control. This may also have an implication for the later local evoked activity, where connectivity impairments that manifested earlier could drive impairments in the later local activity.

20.4.3. Bipolar disorders

BD is not a single disorder, but a category of mood disorders defined by the presence of one or more episodes of abnormally elevated mood, clinically referred to as mania. Individuals who experience manic episodes also commonly experience depressive episodes or symptoms, or mixed episodes which present the features of both mania and depression (Bowden, 2007). The event-related oscillatory responses in various types of BDs and their response to valproate were investigated by Özerdem et al. (2008a,b, 2010). In their reports in 2008a, investigating bipolar manic and medication-free patients, they reported significantly higher occipital beta and lower occipito-frontal alpha EROs than healthy controls. After treatment with valproate, alpha ERO responses in BD patients were significantly lower. Başar et al. (2011) reported the decrease of alpha frequency band both in spontaneous EEG and sensory evoked oscillatory responses. This group concluded that alpha response is the universal operator in the brain. Increased occipital beta response in mania may be compensatory to the dysfunctional alpha operation. Its reduction after valproate may be through modulation of glutamatergic and GABAergic mechanisms. Their study on the effects of valproate euthymic and medication-free bipolar patients showed a diminished delta responses (Özerdem et al., 2008b). Later reports by the same research group have indicated decreased event-related gamma coherence both in euthymic BD (Özerdem et al., 2011) and manic BD (Özerdem et al., 2010) as another possible candidate of biomarker.

The results presented by Özerdem et al. (in this volume) and by Başar et al. (2011) suggest that the crucial decrease of alpha power, the increase of beta activity, the high reduction of long distance visual event-related gamma coherence in euthymic BD patients are candidate biomarkers in this disease.

Hall et al. (2011) examined whether or not gamma band oscillations constitute endophenotypes of BD by testing BD patients, monozygotic BD twins, unaffected relatives, and healthy subjects using the auditory oddball task. Patients with BD exhibited reduced gamma band power, whereas these changes were not observed in clinically unaffected relatives. Therefore, these responses do not appear to be an eligible criterion for endophenotypes of BD (Hall et al., 2011). Oribe et al. (2010) investigated evoked neural oscillations at 20–45 Hz and found that subjects with BD exhibited greater power in evoked neural oscillations in response to speech sounds compared to healthy subjects and schizophrenia subjects; and schizophrenia patients exhibited delayed evoked neural oscillation peak- and phase-locking to speech sounds. Their study implied that the evoked neural oscillation to speech sounds provided a useful index to distinguish BD from schizophrenia (Onitsuka et al., in this volume).

20.4.4. Alzheimer’s disease

AD is the most common form of dementia, a neurological disease characterized by loss of mental ability severe enough to interfere with normal daily activities of living. In the normal aging, a reduction in total brain volume is seen; the reduction in the cortical gray matter volume in AD is more severe than in healthy controls and ranges between 8% and 9% and hippocampal loss is 8%, and olfactory/orbitofrontal cortex shows 12–15% loss. The pattern of cortical atrophy in mild AD is similar to that in prodromal AD, but the loss
is more severe in the direct hippocampal pathway and sensorimotor, visual, and temporal cortices (Prestia et al., this volume). These morphometric changes are reflected in many electrophysiological measurements. In resting EEG studies (Babiloni et al., 2011; for a review, see Lizio et al., 2011), when healthy controls, MCI, and AD subjects were classified according to spectral EEG coherence and other EEG features, the successful discrimination rates of controls from mild AD were as 89–45%, from MCI to AD 92–78%, and the conversion of MCI subjects to AD 87–60%. The most sensible parameters of resting state EEG were cortical delta/theta and alpha rhythms, fronto-parietal coherence and computation of the directed transfer function that were abnormal in amnesic MCI and AD subjects (Vecchio et al., this volume).

Event-related oscillations have also shown that mild AD subjects differ from healthy controls. Polikar et al. (2007) used ERO frequency bands to classify AD and healthy controls by means of an automated program. They found oscillatory responses of 1–2 and 2–4 Hz at Pz, and 4–8 Hz at Fz, and 2–4 Hz at Cz were the most valuable classifiers for AD subjects from healthy controls. By means of these four parameters, they reported a sensitivity rate of 77% and a specificity rate of 81%. Later studies reported a consistent decrease in fronto-central delta responses upon either visual (Yener et al., 2008) or auditory oddball stimulation (Caravaglios et al., 2008; Yener et al., 2012). Frontal theta responsiveness has been also reported, either following visual (Yener et al., 2007) or auditory oddball (Caravaglios et al., 2010) paradigm. In their study, Caravaglios et al. (2010) reported that a decreased theta responsiveness in a late time window later than poststimulus 250 ms. Diminished event-related coherence values have been reported in AD in delta, theta, and alpha ranges in fronto-parietal connections. Regarding the medication effects, the alpha event-related coherence (Güntekin et al., 2008) and theta phase-locking (Yener et al., 2007) seem to improve in AD subjects with cholinergic treatment. The most sensible ERO parameters seem to be delta and theta oscillatory responses over fronto-central regions, and fronto-parietal coherences in alpha, theta, and delta frequencies (Başar et al., 2010; Yener and Başar, Ch. 16, this volume). When electrophysiological markers are used in combination with structural MRI, SPECT, and PET markers, a comprehensive data fusion analysis may provide a more accurate analysis taking into account important variables such as validity, costs, invasiveness, and availability of the procedures in the epidemiological studies (Vecchio et al., this volume).

A chart summarizing the possible biomarkers and related neurotransmitters in mentioned neuropsychiatric disorders has been shown in Fig. 5.

20.4.5. Polymorphism

The works of Porjesz et al. (2005) and of Rangaswamy and Porjesz (2008), related to AD and a cholinergic receptor gene (CHRM2), are important, since their findings suggest the possible role of CHRM2 in the generation and modulation of evoked oscillations. Theta and delta EROs depend on the level of acetylcholine (muscarinic activation). M2 receptors inhibit presynaptic release of acetylcholine, leading to inhibition of irrelevant networks. Muscarinic receptors are particularly concentrated in the forebrain and possibly serve to maintain the effective balance of relevant/irrelevant networks, hence, directly influencing P300 generation (Frodl-Bauch et al., 1999). According to the work of the Porjesz group (Begleiter and Porjesz, 2006), the results with the CHRM2 gene and brain oscillations strongly support the role of acetylcholine in the generation of N200 (theta oscillations) and in the P300 component (delta and theta oscillations). The function of acetylcholine has been demonstrated with regard to stimulus significance (Perry et al., 1999),
selective attention (Mitrofanis and Guillery, 1993), and P300 generation (Callaway et al., 1983).

Thus, genes are important for the expression of the endophenotype (brain oscillations) and help in the identification of genes that increase the propensity to develop alcohol dependence and related disorders (Begleiter and Porjesz, 2006). From the summary of the research publications of Begleiter and Porjesz and their research teams, it can be clearly stated that studies of neuroelectric endophenotypes offer a powerful strategy for identifying the genes that can create susceptibility to develop psychiatric disorders and provide novel insights into etiological factors.

### 20.5. Neurotransmitters and experimental studies

#### 20.5.1. Neurotransmitters

It is important to remark that such neurotransmitter-related agents are often used as medication in certain diseases. It was long thought that a given neuron released only one kind of neurotransmitter, but today many experiments have shown that a single neuron can produce several different neurotransmitters. Below, four of the best-known transmitters that are involved in functions in both the central and the peripheral nervous systems are described; and neurotransmitters that play a role in major
neuropsychiatric disorders mentioned in this volume are listed in Fig. 5.

Acetylcholine is a widely distributed, excitatory neurotransmitter that triggers muscle contraction and stimulates the excretion of certain hormones. In the central nervous system, it is involved in, for example, wakefulness, attentiveness, anger, and aggression.

Norepinephrine is a neurotransmitter that is important for attentiveness, emotion, sleeping, dreaming, and learning. It is also released as a hormone into the blood, where it causes blood vessels to contract and the heart rate to increase. Norepinephrine plays a role in mood disorders such as manic depression.

Dopamine is an inhibitory neurotransmitter involved in controlling movement and posture. It also modulates mood and plays a central role in positive reinforcement and dependency. The loss of dopamine in certain parts of the brain causes the muscle rigidity typically present in Parkinson’s disease.

GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter that is widely distributed in the neurons of the cortex. GABA contributes to motor control, vision, and many other cortical functions. Some drugs that increase the level of GABA in the brain are used to treat epilepsy and to calm the trembling of patients suffering from Huntington’s disease. GABAergic interneurons, which are the core component of corticolumbic circuitry, were found to be defective in the cerebral cortex of bipolar patients (Benes and Berretta, 2001). GABA spreads in neural networks involved in cognitive and emotional processing and modulates noradrenergic, dopaminergic, and serotonergic local neural circuitry (Brambilla et al., 2003). Several studies revealed low plasma (Kaiya et al., 1982; Berrettini et al., 1983) or cortical (Bhagwagar et al., 2007) GABA activity or altered genetic expression of GABA (Guidotti et al., 2000) in BD. Low GABA activity was thought to be a genetically determined trait creating a vulnerability which, with the contribution of environmental factors, can lead to the development of either mania or depression. It is also important to note that GABAergic activity is reciprocally regulated by dopamine, hyperactivity of which also plays a role in mania (Yatham et al., 2002). Alterations in the modulation of the dopamine system may trigger the appearance of a defective GABA system (Benes and Berretta, 2001). It is important to emphasize the web of theta activity on the GABAergic and cholinergic inputs from the septum. In vivo studies suggest that the hippocampal theta rhythm depends on GABAergic and cholinergic inputs from the septum (Stewart and Fox, 1990; Brazhnik and Fox, 1997) and requires an intact hippocampal CA3 region (Wiig et al., 1994). The cholinergic inputs to the hippocampus are distributed on both the pyramidal and interneuronal cells (Frotscher and Léranth, 1985), while the GABAergic inputs selectively contact the hippocampal interneurons (Freund and Antal, 1988). Later work in vitro on septo-hippocampal cocultures showed that CA3, but not CA1, exhibited theta-like oscillations driven by septal muscarinic synaptic inputs (Fischer et al., 1999). This suggests that the hippocampus is locally capable of regulating the frequency of theta, independent of the septal inputs. Valproate was shown to augment the ability of atypical antipsychotic medications to increase dopamine (DA) and acetylcholine (ACh) efflux in the rat hippocampus and medial prefrontal cortex (Huang et al., 2006). It was also shown to lead to a significant reduction in presynaptic dopamine function in manic patients.

GABAergic interneurons and pyramidal cells were found to build and maintain complex interconnections, which lead to large-scale network oscillations, such as theta, gamma (40–100 Hz), and ultrafast (200 Hz) frequency bands (Benes and Berretta, 2001).

Glutamate is a major excitatory neurotransmitter that is associated with learning and memory and is also thought to be associated with AD, whose first symptoms include memory malfunctions. Neurons that use GABA and glutamate as
neurotransmitters are used by more than 80% of the neurons in the brain and constitute the most important inhibition.

20.5.2. Animal models and neurotransmitters

The significance of 40-Hz activity in the brains of different mammals has been hypothesized by several authors (Freeman, 1975; Başar et al., 1987; Eckhorn et al., 1988; Başar-Eroğlu and Başar, 1991; Kaiser et al., 2008; Lenz et al., 2008) as an important coding channel in processing sensory and cognitive information in neural networks. These results further indicate a widely ranging function of the gamma component among the different classes of vertebrates and invertebrates. Bullock and Başar (1988), Schütz et al. (1992), and Başar et al. (1999) also examined the effect of transmitters such as acetylcholine, dopamine, noradrenaline, and serotonin on the isolated ganglia of Helix pomatia (snail) and showed changes in the oscillatory dynamics of these ganglia. The application of acetylcholine (ACh) induced a large increase in the theta response in the isolated visceral ganglion. Dopamine induced a crucial change in the oscillatory response, which was recorded in the gamma frequency band following the electrical stimulation in the Helix visceral ganglion.

According to Michael Koch (see in this volume), it seems that transmitters and animal models, and also the links between genetics, transmitters, and oscillations, will be very important in the near future. The challenge is to see whether a research group is able to combine these three factors. Koch states that animal models and endophenotypes of mental disorders are regarded as preclinical approaches for understanding the underlying mechanisms of these diseases, and in developing drug treatment strategies. A frequently used translational model of sensorimotor gating and its deficits in some neuropsychiatric disorders is prepulse inhibition (PPI) of startle. PPI is reduced in schizophrenia patients, but the exact relationship between symptoms and reduced PPI is still unclear. Recent findings suggest that the levels of PPI in humans and animals may be predictive of certain cognitive functions. Hence, this simple measure of reflex suppression may be of use for clinical research and the cannabinoid system will be one promising field of schizophrenia translational research.

20.6. Essences of the conference: advantages and efficiency of neurophysiological markers

Following the standard definition, a “biomarker” should differentiate the subject with a certain neuropsychiatric disorder from the healthy subject, track the progress of the disorder, or monitor the effects of medication. In the present report, three fundamental questions arose in relation to the principal theme of the utility of brain oscillations as biomarkers. Questions and/or remarks of conference participants are presented here in order to display knowledge related to brain oscillations in different brain diseases. Giovanni Frisoni’s comments related to the nature and evolution of biomarkers in AD present important criteria for successful development of electrophysiological biomarkers in addition to structural MRI and biochemical CSF biomarkers. Claudio Babiloni’s discussion presents a concise overview of the state of the art.

The advantages of electrophysiological biomarkers in comparison to other markers are as follows:

1. These methods are non-invasive.
2. They are inexpensive.
3. Neurophysiological measurements enable the description of brain dynamics.
4. These methods analyze a fast activity chain of the brain in the range of 0–500 ms.
5. The electrophysiological measurements open the possibility to record processes of perception, attention, decision making, and working memory. In other words, it is possible to learn about dynamic brain function.
At this stage, it is vital to mention that applications of ensembles of electrophysiological recording methods and strategies are important in the search for appropriate biomarkers (Fig. 6). According to the results in the present volume, both conceptual and methodological types of strategies are needed to identify biomarkers. The conceptual strategies include (a) differentiation between evoked and EROs as they possibly reflect the activities of sensory and cognitive networks, respectively; (b) differential connectivity deficit as shown by coherence measurements; (c) changes in spontaneous EEG activity; and (d) changes under medication influence.

The present report also emphasizes the importance of the link between oscillations and neurotransmitters (Fig. 5). In this report, we also indicate the possibility that several findings described in this volume can be proposed as biomarker candidates. The search of biomarkers is certainly not limited to the results of the present issue, and the reviews of O’Donnell et al., Vecchhio et al., Yener and Başar, and Başar and Güntekin (all in this volume) indicate several other possibilities.

The present volume, Supplements to Clinical Neurophysiology, Vol. 62, and the present panel report will likely be most useful in manifesting the new strong trend to develop biomarkers related to brain oscillations in at least four discussed neuropsychiatric diseases, namely, ADHD, AD, BD, and schizophrenia.

We hope that the results of this conference will contribute to better translational research. The most challenging topic would therefore be to develop user-friendly electrophysiological methods and a common ground that would allow discussion between clinicians, electrophysiologists, and other researchers.

**Abbreviations**

- Aβ42 = amyloid beta 42 peptide
- AD = Alzheimer’s disease
- ADHD = attention deficit hyperactivity disorder
- ADNI = Alzheimer’s disease neuroimaging initiative
- ASSR = auditory steady-state responses
- BACE = beta-secretase
- BD = bipolar disorder
- CSF = cerebrospinal fluid
- EEG = electroencephalography
- ERO = event-related oscillation
- ERP = event-related potential
- fMRI = functional magnetic resonance imaging
- FDG-PET = fluoro-deoxy glucose positron emission tomography

**The strategies for analysis of brain activity**

![Diagram](attachment:image.png)

Fig. 6. Analysis of brain includes combinations of default brain activity or evoked brain activity by simple sensory stimuli or event-related brain activity elicited by cognitive tasks.
HC = healthy controls
MCI = mild cognitive impairment
MRI = magnetic resonance imaging
PET = positron emission tomography
PLF = phase-locking factor
P-tau = phospho-tau protein
SZ = schizophrenia
SEO = sensory evoked oscillation
TMS = transcranial magnetic stimulation
T-tau = total tau protein

References


