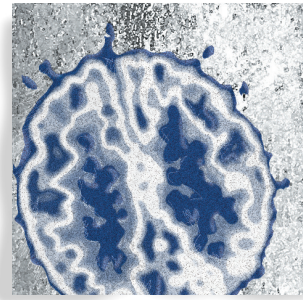


## *Brain oscillations in neuropsychiatric disease*

Erol Başar, PhD



*The term “brain (or neural) oscillations” refers to the rhythmic and/or repetitive electrical activity generated spontaneously and in response to stimuli by neural tissue in the central nervous system. The importance of brain oscillations in sensory-cognitive processes has become increasingly evident. It has also become clear that event-related oscillations are modified in many types of neuropathology, in particular in cognitive impairment. This review discusses methods such as evoked/event-related oscillations and spectra, coherence analysis, and phase locking. It gives examples of applications of essential methods and concepts in bipolar disorder that provide a basis for fundamental notions regarding neurophysiologic biomarkers in cognitive impairment. The take-home message is that in the development of diagnostic and pharmacotherapeutic strategies, neurophysiologic data should be analyzed in a framework that uses a multiplicity of methods and frequency bands.*

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**Keywords:** *oscillation; bipolar disorder; schizophrenia; alpha; beta; gamma; theta; delta; phase synchrony*

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### Introduction

The term “brain (or neural) oscillations” refers to the rhythmic and/or repetitive electrical activity generated spontaneously and in response to stimuli by neural tissue in the central nervous system, the discovery of which is generally credited to Hans Berger (1873-1941), the recorder of the first electroencephalogram. The role of brain oscillations as functional building blocks in sensory-cognitive processes has gained tremendous importance in recent decades. Event-related oscillations (ERO) in the alpha, beta, gamma, delta, and theta frequency windows are highly modified throughout the cortex in pathologic brains, in particular from patients with cognitive impairment. However, they can only be characterized as clinical biomarkers by using a wide range of strategies and mathematical parameters. The oscillatory changes in multiple frequency windows and whole cortex should be taken into consideration by analyzing relevant changes in the amplitude of function-related oscillations, together with multiple connectivity deficits.

The aims of this article are threefold:

- To briefly describe the main methods used in the brain research literature, such as evoked/event-related spectra, ERO, coherence analysis, and phase locking; to illustrate their clinical applications using the example of bipolar disorder (BD); and to show how this might

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## Selected abbreviations and acronyms

<b>AFC</b>	<i>amplitude frequency characteristics</i>
<b>EEG</b>	<i>electroencephalogram</i>
<b>EP</b>	<i>evoked potential</i>
<b>ERP</b>	<i>event-related potential</i>
<b>ERO</b>	<i>event-related oscillation</i>
<b>FFT</b>	<i>fast Fourier transform</i>
<b>fMRI</b>	<i>functional magnetic resonance imaging</i>
<b>MEF</b>	<i>magnetic evoked field</i>
<b>MEG</b>	<i>magnetoencephalography</i>
<b>PET</b>	<i>positron emission tomography</i>

inform the search for neurophysiologic biomarkers in cognitive impairment.<sup>1</sup>

- To explain the importance, for the design of (differential) diagnostic strategies and (preventive) drug schedules, of analyzing neurophysiologic information in a framework that includes multiple methods and frequency bands.
- To propose a practical approach to the analysis and interpretation of brain oscillations.

See *Box 1* for a glossary of key terms used.

Comparisons between the results of many types of analyses, in particular those employing sensory signals

and cognitive inputs, yield a wide spectrum of interpretations relating to disease differentiation, disease progression, and response to medication. In Alzheimer's disease, schizophrenia, mild cognitive impairment, and BD, cognitive deficit varies with illness stage, patient age, and cultural considerations, meaning that cognitive deficits can only be demonstrated after comparing results from sensory and cognitive signals.<sup>2,4</sup>

The methods outlined in *Table 1* can be applied stepwise or randomly; some can be omitted, depending on their feasibility in particular patients. Their deployment also depends on the research capabilities of different laboratories. We shall describe only a few examples of the possible applications that we have discussed extensively elsewhere.<sup>2,4,6</sup>

## Strategic and methodological importance of oscillations

Once it was established that any given brain function presupposes cooperation between multiple regions, the analysis of inter-regional relationships became increasingly important. We shall briefly discuss the results of such analyses achieved using various methods and strategies.

### Box 1

- **Alpha response:** Oscillatory component of an evoked potential (EP) in the 8-13 Hz frequency range.
- **Amplitude frequency characteristics (AFC):** The spectra of evoked responses in the frequency domain potentials.
- **Coherence analysis:** A mathematical approach to examining the relationship between signals or data sets.
- **Event-related oscillations (ERO):** These include event-related potentials (ERP) and induced rhythms.
- **Event-related potential (ERP):** The measured brain response resulting directly from a specific sensory, cognitive, or motor event
- **Evoked frequency response:** Dominant maximum in amplitude frequency characteristics.
- **Delta response:** Oscillatory component of an evoked potential in the 0.5-3.5 Hz frequency range.
- **Gamma response:** Oscillatory component of an evoked potential in the 30-60 Hz frequency range.
- **Magnetoencephalography:** A research and clinical imaging technique for measuring the magnetic fields produced by electrical activity in the brain.
- **Neural oscillation:** Rhythmic or repetitive neural activity in the central nervous system.
- **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. They include induced alpha, beta, and gamma oscillations that may relate to specific aspects of information processing. In the additive EP model, non phase-locked activity includes the background electroencephalogram (EEG). Separate approaches are used to analyze non phase-locked, phase-locked and non-locked EEG responses.
- **Oddball paradigm:** An EP research technique in which trains of usually auditory or visual stimuli are used to assess neural responses to unpredictable but recognizable events. The subject is asked to react by counting incidences of target stimuli that are hidden as rare occurrences amongst a series of more common stimuli.

## Single-cell studies

These have been of great importance in elucidating the basic physiologic mechanisms of intercellular communication.<sup>7,8</sup> However, their importance for understanding integrative brain functions is questionable since by definition such functions involve the whole brain.<sup>9-12</sup>

## Positron emission tomography (PET)

PET is a nuclear medicine technique that produces a three-dimensional image of functional processes. Temporal resolution (the data acquisition refresh rate) is much longer (from 30-40 seconds to minutes with four-dimensional PET) than with electrophysiologic techniques.

## Electroencephalography (EEG), event-related potentials (ERP), event-related oscillations, functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and magnetic evoked fields (MEF)

Strategies incorporating analyses of these investigations are excellent for illuminating brain functions as they cover dynamic changes in the brain and morphological structures. In particular, MEG and MEF greatly increase spatial resolution in comparison with EEG and ERP, making them excellent, among other purposes, for presurgical localization, and are therefore likely to yield ground-breaking results in future applications.

### Four key methods:

- Power spectral density of the spontaneous electroencephalogram
- Evoked spectra (fast Fourier transform analysis of sensory evoked potentials (elicited by simple light, tone signal, etc)
- Event-related spectra (fast Fourier transform analysis of an event-related potential, eg, target or nontarget signal during an oddball paradigm)
- Phase locking, phase synchrony

### Five ancillary methods:

- Cross-correlation
- Cross-spectrum
- Electroencephalographic coherence
- Evoked coherence
- Event-related coherence

**Table I.** The ensemble of systems theory methods.

## Mathematic and psycho-physiologic strategies

The above are interwoven with the use of the following mathematic and psycho-physiologic strategies:

- Mathematic and systems theory approaches drawing on the concepts of chaos and entropy, and using neural network modeling, frequency domain analysis, wavelet analysis, spatial coherence and temporal coherence,
- Psychologic strategies using behavioral paradigms and neuropsychologic tests,<sup>12-13</sup>
- Recordings from electrodes chronically implanted in animal brain.

Progress in functional neuroscience is only achievable using a combination of methods.<sup>12</sup> However, not all strategies can be applied in every laboratory.

## Suggested steps in the application of oscillatory dynamics

Pointers to the functional significance of brain oscillations emerge from the analysis of responses to well-defined events (ERO phase- or time-locked to a sensory or cognitive event). Such oscillations can be investigated, among other approaches, using frequency domain analysis of ERP based on the following hypothesis:

The EEG consists of the activity of an ensemble of oscillators generating rhythmic activity in several frequency ranges. Oscillator activity is usually random. However, sensory stimuli can be used to couple these oscillators so that they act together in a coherent way. This synchronization and enhancement of EEG activity gives rise to evoked or induced rhythms. Evoked potentials (EP), representing ensembles of neural population responses, are considered the result of a transition from a disordered to an ordered state. Compound ERP manifest a superposition of evoked oscillations in the EEG frequencies ranging from delta to gamma. Natural brain frequencies are denoted as alpha: 8-13 Hz; beta, 18-25; theta: 3.5-7 Hz; delta: 0.5-3.5 Hz, and gamma: 30-70 Hz.<sup>15-20</sup>

When the stimulus signal contains a cognitive task the evoked oscillations are considered as ERO. There are several strategies available for measuring cognitive changes, including spontaneous EEG, sensory-evoked oscillations, and ERO. The term "sensory-evoked" implies responses elicited by simple sensory stimulation, whereas "event-related" indicates responses elicited by a cognitive task, generally an oddball paradigm.

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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, whereas an oddball task initiates activation in a sensory network and additionally in a related cognitive network.

## Ensemble of systems theory methods

Several mathematic methods and systems theory approaches are used to analyze the dynamics of brain oscillations (*Table I*). We describe four such methods in more detail below. Spectral signal analysis constitutes one of the most important and most commonly used analytical tools for evaluating neurophysiologic signals.

### Some fundamental remarks

#### *Time-locked and or phase-locked methods*

Responses of a specific frequency after stimulation can be identified by computing the amplitude-frequency characteristic (AFC) of the averaged ERPs,<sup>15,22-23</sup> or event-related and evoked power spectra. The AFC and event-related power spectra describe the brain system's transfer properties, eg, excitability and susceptibility to respond, by revealing resonant as well as salient frequencies. The AFC does not simply represent the spectral power density characterizing the transient signal in the frequency domain but the predicted behavior of the system (brain) assuming sinusoidal modulated input signals of defined frequencies were applied as stimulation. Since it reflects 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 most preferred oscillations of the system during the response to a stimulus.

In order to calculate the AFC, ERP are first averaged and then transformed to the frequency domain using a one-sided Fourier transform (Laplace transform).<sup>15,24</sup> Brain oscillations in response to stimulation have helped to advance the analysis. First of all, in order to perform Fourier analysis of brain responses, an averaging procedure is applied to the data of healthy subjects and patients. Following artifact rejection, selective averaging is performed. The averaged potentials (EP and/or

ERP) are then analyzed using a fast Fourier transform (FFT) and single epochs are digitally filtered based on the cut-off frequencies of the evoked power spectra. Lastly the data are averaged across subjects to produce a grand average. Another option is power spectral analysis of the grand average with adaptive digital filtering.

## Examples of changes in the electroencephalogram and event-related oscillations

### Power spectral analysis of the spontaneous electroencephalogram

Power spectral analysis of spontaneous EEG activity is one of the most successfully applied methods for identifying biomarkers. *Figure 1* shows the grand averages of power spectra in 18 bipolar euthymic subjects (red) and 18 healthy controls (black) in the alpha frequency range for the eyes closed recording session from occipital locations ( $O_1$ ,  $O_z$ , and  $O_2$ ): the power spectrum in the euthymic subjects ranged up to  $1 \mu V^2$  across all electrodes but up to  $4.8 \mu V^2$  for  $O_1$ ,  $4 \mu V^2$  for  $O_z$ , and  $4.5 \mu V^2$  for  $O_2$  in the controls.

Event-related spectra in the alpha frequency range are also drastically reduced in BD.<sup>25</sup> Only the marked decrease in alpha power shown in *Figure 1* could possibly serve as a neurophysiologic marker in BD.

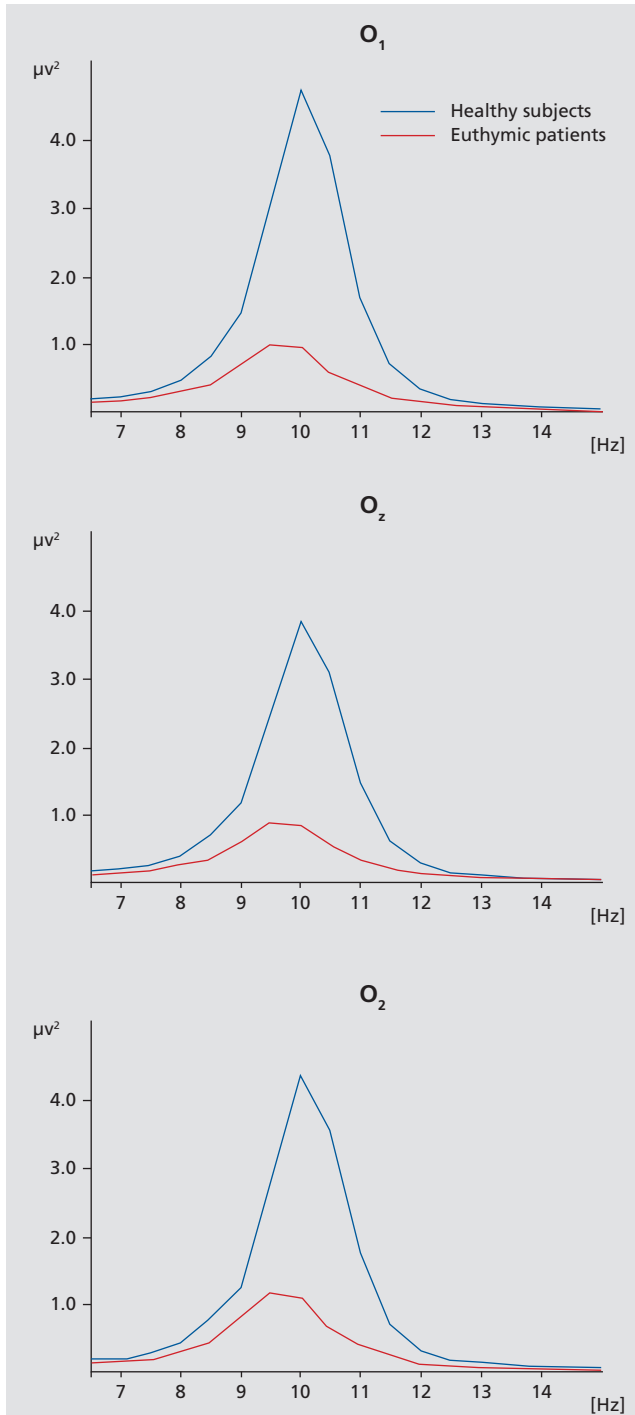
### Phase locking in the gamma band in healthy subjects

In inter-trial coherence plots of EROs (*Figure 2a and 2b*), the general time course and frequency composition are completely changed.

1) a) At the  $O_2$  location there are phase-locked components at 400 ms and 600 ms in addition to phase locking at around 100 ms. b) Moreover, the frequencies of phase-locked oscillations increase to over 40 Hz (200 ms periodicity), indicating superposition with the 5 Hz frequency band.

There are abundant phase-locked response components in comparison to sensory evoked responses in *Figure 2b*.

2) Responses at the F4 location are similar to those at  $O_2$ . There is 10 Hz periodicity at 100-200 ms with lower frequencies around 30 Hz, whereas at around 600 ms we find solid phase locking (0.45) with a frequency higher than 40 Hz.



**Figure 1.** Eyes closed mean power values for occipital (O) electrodes. Modified from ref 25: Başar E, Güntekin B, Atagün Mİ, Turp Gölbaşı B, Tülay E, Özerdem A. Brain's alpha activity is highly reduced in euthymic bipolar disorder patients. *Cogn Neurodyn.* 2012;6:11-20. Copyright © Springer 2012

### Differentiated changes in target responses in bipolar disorder

Evoked and event-related slow and fast theta oscillations in response to an auditory stimulus were studied in 22 euthymic drug-free patients with BD I ( $n=19$ ) or BD II ( $n=3$ ). A two-tone oddball task was used, with frequent 1600-Hz target tones, and infrequent 1500-Hz non-target tones. The tones were presented in a random sequence at 3-7 second intervals. The subjects were instructed to keep a mental count of the number of 1600 Hz target tones. A FFT was applied to the 0-800 ms period after stimulus onset.

Slow (4-6 Hz) and fast (6-8 Hz) theta responses behaved differently during the oddball paradigm in euthymic BP patients. Fast theta responses (6-8 Hz) almost disappeared<sup>26</sup> (Figure 3).

Application of digital filters to the analysis of neuropsychiatry patients requires refinement using adaptive filters chosen according to the cutoff frequency in power spectra instead of rigid filters in the conventional frequency ranges. Sometimes a peak is missed or else it shifts to other frequencies in patients, especially after drug administration.

### Selective connectivity deficit

There are several forms of connection between different structures in the brain. The connectivity that can be measured using wavelet coherence function in healthy subjects is well defined, in contrast to the deficit in selective connectivity displayed by patients whose substructures are anatomically or physiologically disrupted.

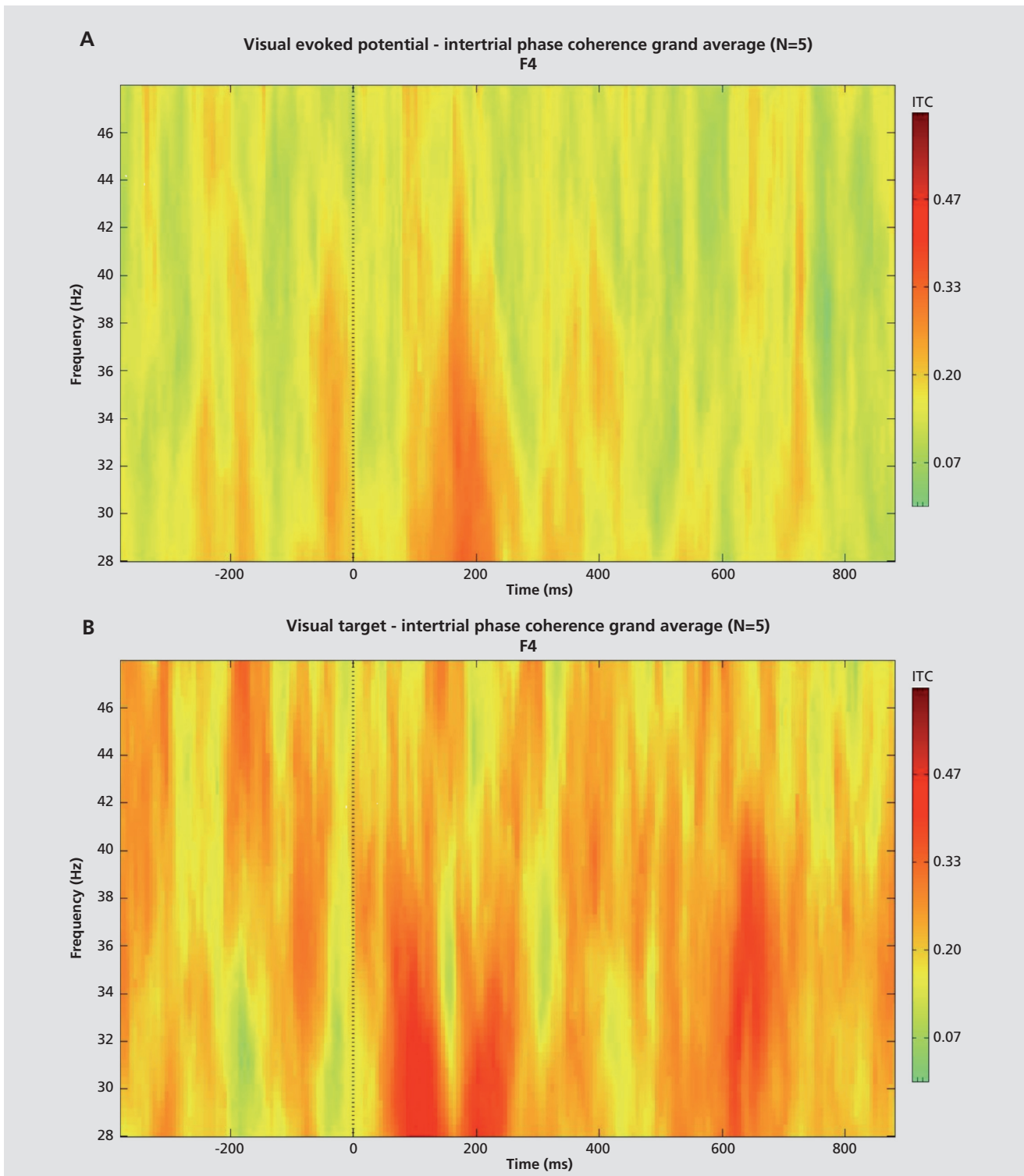
An important brain mechanism underlying cognitive processes is the exchange of information between brain areas.<sup>27-28</sup>

### Decreased event-related gamma coherence in euthymic bipolar patients

Özerdem et al<sup>29</sup> studied 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 20 euthymic drug-free BD patients and 20 sex- and age-matched healthy controls. The coherence values of the left and right intra-hemispheric electrode pairs ( $F_3-T_3$ ,  $F_3-TP_7$ ,  $F_3-P_3$ ,  $F_3-O_1$  and  $F_4-T_4$ ,  $F_4-TP_8$ ,  $F_4-P_4$ ,  $F_4-O_2$ ,



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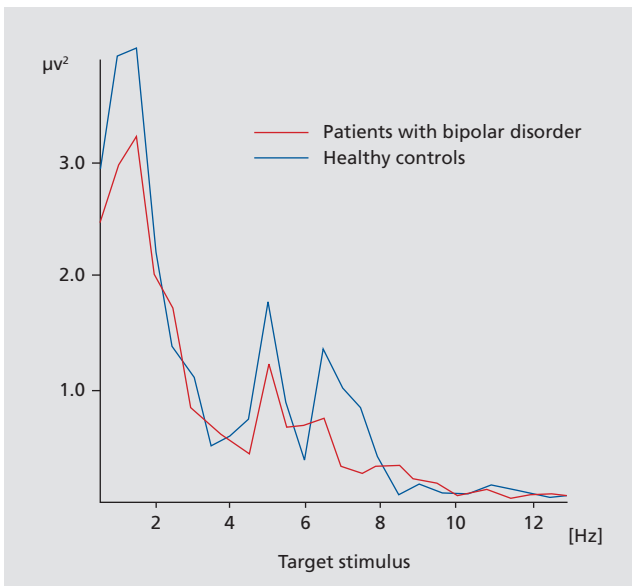


**Figure 2.** The grand average plots of inter trial phase coherence as grand average of 5 subjects.

respectively) were compared between the groups. BD patients showed bilaterally diminished long-distance gamma coherence between frontal and temporal as well as between frontal and temporo-parietal regions compared with healthy controls. The reductions in gamma coherence between the electrode pairs were statistically significant.

However, the patient group showed no significant reduction in sensory-evoked coherence compared with the healthy controls. The decrease in event-related coherence differed topologically and ranged from 29% (right fronto-temporal location) to 44% (left fronto-temporo-parietal location). *Figures 4a and 4b* depict the grand average of visual event-related coherence in the gamma frequency band (28-48 Hz) in response to target stimuli between the right (F<sub>4</sub>-T<sub>8</sub>) and left (F<sub>3</sub>-T<sub>7</sub>) fronto-temporal electrode pairs in euthymic bipolar patients ( $n = 20$ ) compared with healthy controls ( $n = 20$ ).<sup>29</sup>

Oscillatory responses to both target and non-target stimuli are manifestations of working memory processes. Therefore, the decrease in coherence in response to both stimuli points to an inadequacy of connectivity between different parts of the brain under cognitive load that in patients with cognitive impairment is greater than when they are processing purely sensory signals.

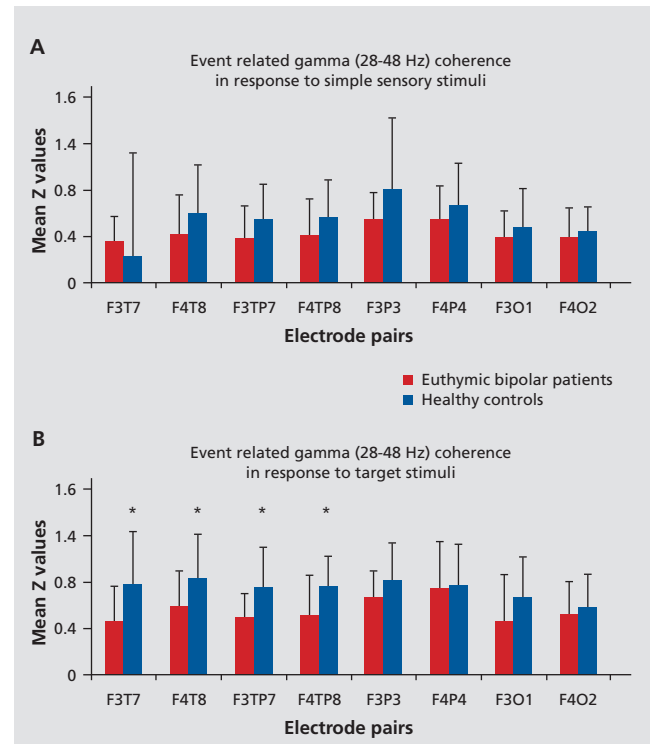


**Figure 3.** Grand average of power spectra of auditory event related responses over left frontal (F3) location in bipolar disorder subjects and healthy controls upon auditory oddball stimulation.

## Signal analysis results

The preceding analysis prompts a number of hypotheses, conclusions and lines of further enquiry:

1. Intrinsic oscillatory activity by single neurons forms the basis of the natural frequencies of neural assemblies. These natural frequencies, classified as alpha, beta, gamma, theta and delta, are the brain's real responses.<sup>30-32</sup>
2. Morphologically different neurons or neural networks respond to sensory-cognitive stimuli in the same frequency ranges 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



**Figure 4.** Mean Z values for sensory evoked (a), and target (b) coherence in response to visual stimuli at all electrode pairs. "\*" represents  $P < 0.05$ .

Modified from ref 29: Özerdem A, Güntekin B, Atagün Mİ, Turp B, Başar E. Reduced long distance gamma (28-48 Hz) coherence in euthymic patients with bipolar disorder. *J Affect Disord.* 2011;132:325-332. Copyright © Elsevier 2011

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organizations.<sup>21,33-37</sup> It is therefore suggested that whole-brain networks communicate via the same set of EEG oscillation frequency codes.

3. The brain has response susceptibilities that mostly originate from its intrinsic (ie, spontaneous) rhythmic activity.<sup>15,38-41</sup> 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 from its evoked activity. Conversely, if activity in a given frequency range does not exist in evoked activity, it will also be absent from spontaneous activity.
4. There is an inverse relationship between the EEG and ERP. EEG amplitude thus serves as a control parameter for brain responsiveness in the form of EP or ERP.<sup>33,42-45</sup>
5. Combined with the concept of response susceptibility, this characteristic leads to the conclusion that EEG oscillatory activity governs most general transfer functions in the brain.<sup>46</sup>
6. Oscillatory neural tissue selectively distributed throughout the brain is activated by sensory-cognitive input. Such oscillatory activity can be described by a number of response parameters—enhancement (amplitude), delay (latency), blocking or desynchronization, prolongation (duration), degree of coherence between different oscillations, degree of entropy—that are differently configured depending on the particular task and the functions which that task elicits.<sup>47-60</sup> In other words, the brain uses the same frequency range to perform not just one but multiple functions.
7. The number of oscillations and the ensemble of parameters that are obtained under given conditions

increase as the complexity of the stimulus increases, or as recognition of the stimulus becomes difficult.<sup>15,21,61-62</sup>

8. Each function is represented in the brain by the superposition of 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. Neuron assemblies do not obey the all-or-none rule of single neurons.<sup>63-67</sup>
9. The superposition principle indicates synergy between alpha, beta, gamma, theta, and delta oscillations during the performance of sensory-cognitive tasks. Integrative brain function operates through the combined action of multiple oscillations.
10. Our results strongly support the recommendation to use several methods in multiple frequency windows when attempting to identify biomarkers that will differentiate between cognitive diseases.

## Conclusions and perspectives

Research scientists in neuropsychiatry tend to be non-selective and non concept-oriented in using only one of the methods from the ensemble of oscillatory analyses. Consequently, brain oscillations often fail to provide useful and effective results in terms of biomarker identification or cognitive deficiency screening. This paper has suggested ways of improving such analyses by emphasizing the complementarity between the different methods of brain oscillation investigation and the over-riding need to use them in combination with one another. □

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## Oscilaciones cerebrales en enfermedades neuropsiquiátricas

El término "oscilaciones cerebrales (o neurales)" se refiere a la actividad eléctrica rítmica y/o repetitiva generada espontáneamente y en respuesta a estímulos por el tejido neural en el sistema nervioso central. Cada vez es más evidente la importancia de las oscilaciones cerebrales en los procesos sensorio-cognitivos. También es claro que las oscilaciones relacionadas con eventos se modifican en muchos tipos de neuropatología, particularmente en el deterioro cognitivo. Esta revisión discute métodos como los espectros y las oscilaciones evocadas o relacionadas con eventos, el análisis de coherencia y el bloqueo de fase. Da ejemplos de aplicaciones de métodos y conceptos esenciales en el trastorno bipolar que permiten una base para las nociones fundamentales en relación con los biomarcadores neurofisiológicos en el deterioro cognitivo. El mensaje que se puede obtener es que en el desarrollo del diagnóstico y las estrategias farmacoterapéuticas, los datos neurofisiológicos deben ser analizados en una estructura que emplee una multiplicidad de métodos y bandas de frecuencia.

## Oscillations cérébrales dans les maladies neuropsychiatriques

Le terme d'« oscillations cérébrales ou neuronales » se rapporte à l'activité électrique rythmique et/ou répétitive générée spontanément et en réponse aux stimuli par le tissu neuronal dans le système nerveux central. L'importance des oscillations cérébrales dans les processus cognitivo-sensoriels devient de plus en plus manifeste. Les oscillations liées aux événements sont clairement modifiées dans de nombreux types de pathologies neurologiques, en particulier dans le déclin cognitif. Cet article analyse les méthodes comme les spectres et les oscillations évoquées/liées à un événement, les analyses de cohérence et le blocage de phase. Il donne des exemples d'application de concepts et de méthodes essentiels dans le trouble bipolaire, servant de base pour des notions fondamentales sur des biomarqueurs neurophysiologiques dans le déclin cognitif. Le message clé est le suivant : au cours du développement des stratégies diagnostiques et pharmacothérapeutiques, les données neurophysiologiques devraient être analysées dans un cadre utilisant de multiples méthodes et bandes de fréquence.

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