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

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1. Introduction

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

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

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

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

It is evident that, by performing and comparing all types of analyses, a large number of permutations are possible, thus giving rise to a wider spectrum of interpretations related to the *differentiation of diseases*, *progress of diseases*, and modifications upon *application of medication*. The final aim of the present report, as presented in the last section, is therefore to indicate that a valid analysis of brain electrical potentials in search of biomarkers can be achieved only by successive application of analysis tools and should not be reduced to the search of a given frequency range or a given stimulus modality.

It is also fundamental to note that comparison of results obtained upon application of sensory signals and cognitive inputs is extremely important: In diseases such as Alzheimer's Disease (AD), schizophrenia, Mild Cognitive Impairment (MCI) and Bipolar Disorder (BD), patients show cognitive deficits depending on the state of illness, age, and

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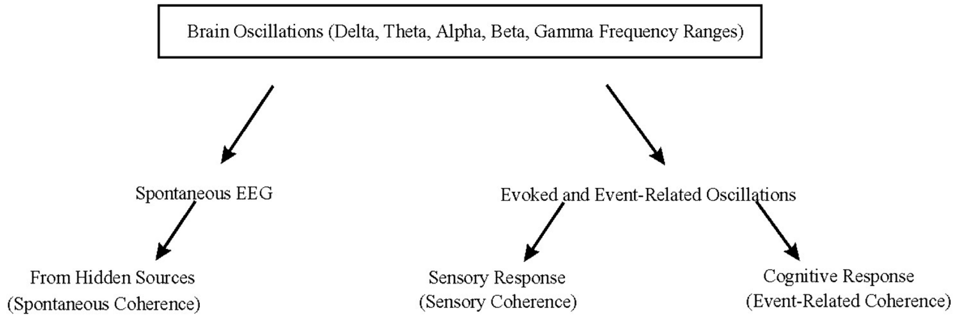

Fig. 1. A schematic presentation of differentiation in search of biomarkers related to brain oscillations (modified from Başar et al., 2013).

cultural differences. Accordingly, cognitive deficits can be demonstrated only after comparing results upon sensory and cognitive signals (see papers by Basar-Eroglu et al., 2013; Yener and Başar, 2013a; Özerdem et al., 2013).

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

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

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

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

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

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

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

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

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

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

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

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

1) Studies at the single-cell level have been of great importance in elucidating the basic physiological mechanisms of communication between cells (Mountcastle, 1998; Eccles, 1973). However, the importance of these studies for understanding integrative brain functions is questionable since, during the integrative processes, the whole brain is involved, as Ross Adey (1966, 1989); and Adey et al. (1960) merely underlined, and the new trends in neuroscience clearly emphasize (see also Freeman, 1999).
2) Positron emission tomography is an invasive procedure applied to patients. It has large temporal resolution in the range of half an hour and offers no possibility for dynamic measurements at the level of microseconds.

   Fig. 3 illustrates a more advanced version of the Biological Systems Analysis and Brain Dynamics Research Programs, with the methods

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