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What does the broken brain say to the neuroscientist? Oscillations and connectivity in schizophrenia, Alzheimer's disease, and bipolar disorder

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ABSTRACT

The application of the concept and methods of brain oscillations has been an important research area in neurosciences. In the last decades, besides the application in cognitive processes, the study of changes in brain oscillations in diseases has also become an important focal point of research. In the present paper, some remarkable examples in three different diseases are taken into consideration: 1) schizophrenia (SZ), 2) Alzheimer's disease (AD), 3) bipolar disorders (BD).

In the current literature, decreased oscillations in cortical recordings are observed in most of the pathologies. For example, decrease of gamma activity in SZ, decrease of delta activity in almost all diseases, as well as frequency shifts in alpha and the lower frequencies were recorded. However, there are also paradoxical cases in which an increase of oscillatory activities is observed. In BD, whereas alpha activity is greatly decreased, a huge increase of beta activity is observed. Or, in SZ, a paradoxical increase of gamma activity can be observed during cognitive loading. We also observed paradoxical changes in the analysis of connectivity. In AD, we find that alpha, delta, and theta coherences between distant parts of the cortex are greatly decreased, whereas in the gamma band, event-related coherences attain very high values.

The comparison of the results and paradoxical changes in diseases may lead to important conclusions related to the web of oscillations and neurotransmitters. In turn, we could gain new insights to approach "brain function", in general.

1. Introduction

This paper aims to give a global, but efficient, orientation for electrophysiological description of brain dysfunction for special cases, including unexpected results, controversies, and conformities in oscillatory dynamics. Examples are chosen from three encountered diseases: schizophrenia, Alzheimer's disease, and bipolar disorder.

The concepts and methods of brain oscillations in healthy subjects have invaded neuroscience literature over the past twenty years; they are used to learn the functioning of the healthy brain and observe changes in different subjects (Başar et al., 1998; Başar-Eroglu et al., 1991, 1993, 2001; Sakowitz et al., 2001; Schürmann et al., 1997). These methods can also be used as biomarkers for recognition of diseases, differentiation of diseases, and progression in diseases.

In the present comparative report, we attack another important problem: Are there any shared mechanisms in these very common neuropsychiatric disorders? What are similar oscillatory reactions? Are there clear controversies? Can the obtained results serve to differentiate neuropsychiatric diseases? In future discussions, an ensemble of results from already published work and additional new results can provide a type of brainstorming for electrophysiological understanding in diseases.

The seemingly paradoxical or unexpected results in pathology could, in the future, provide new avenues or keys to understand more differentiated brain functions. Different diseases are results of modified neurotransmitter release (see also Koch et al., in this volume; Sanchez-Alaveza and Ehlers, in this volume; Başar and Düzgün, in this volume). Accordingly, in the synopsis of the present report, we will tentatively describe possibilities to discover new windows for the analysis of oscillations and connectivity. The present report does not cover a comprehensive view of oscillations in diseases; for that, we refer to (Başar et al., 2013; Yener and Başar, 2013b).

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The authors of the present report have published approximately fifty reports and reviews on brain oscillations in diseases such as multiple sclerosis, Alzheimer's disease, schizophrenia, Parkinson's disease, and bipolar disorder. Because of this, it was possible to select a number of paradoxical findings, controversies, or similarities between the diseases in consideration.

In this manuscript, we want to emphasize some common and differential patterns of electrophysiological changes in three common neuropsychiatric entities, namely schizophrenia (SZ), Alzheimer's disease (AD), and bipolar disorder (BD). Our new results on alpha spectral power of SZ and its comparison with BD plus event-related gamma coherences of AD will be presented and discussed in light of our and other groups' earlier findings.

1.1. Characteristics of "bipolar disorder", "schizophrenia" and "Alzheimer's disease"

1.1.1. What is bipolar disorder?

Bipolar disorder is a lifetime illness which follows a relapsing and remitting course. Manic or depressive episodes relapse in an unpredictable manner. Between the symptomatic episodes is the well-being state called "euthymia". Symptoms of both manic and depressive episodes involve several domains such as mood, energy, motor activity, sleep, appetite, thought, and cognition. Recent years have witnessed documentation of a subclinical course with sleep and circadian rhythm disturbances, emotional dysregulation, and cognitive impairment between the full-blown mood episodes (Leboyer and Kupfer, 2010).

Bipolar disorder is one of the leading causes of disability worldwide (Murray and Lopez, 1996). Bipolar disorder types I and II together reach a 4.4% prevalence rate (Merikangas et al., 2007), which is considerably higher than the l% prevalence of another severe psychiatric disorder, schizophrenia. Data shows large disturbances in neurocognition during the different stages of bipolar disorder. Attention and memory deficits, impairment in verbal recall and fine motor skills, and disturbance of sustained attention is evident during depressive episodes. Attention, complex processing, memory, and emotional processing are dysfunctional in mania (Goldberg and Chengappa, 2009). Cognitive deficits remain even during euthymia, where response inhibition, set-shifting, executive function, verbal memory, sustained attention, processing speed, visual memory, and verbal fluency have been shown to be disturbed (Bora et al., 2009). Such a wide range of cognitive disturbances involves dysfunction of neural circuits that run between pre-frontal and striatal structures, with further projections to the thalamic nuclei (Vawter et al., 2000), and includes those that regulate cognitive, emotional, and social behavior. Recently, a fronto-temporal- and fronto-limbic-related cognitive impairment has been defined as a cognitive endophenotype (Bora et al., 2009).

1.1.2. What is schizophrenia?

Schizophrenia is a complex and severe mental disorder, affecting the participant's actions, perceptions, emotions, and cognitive functions (Andreasen, 1997; Gold, 2004). The lifetime prevalence of schizophrenia is approximately 1% (Lewis and Lieberman, 2000; Saha et al., 2005). Very often the illness persists for a lifetime, rendering patients dependent on the public health system. Although the onset of the disease is most common at the end of adolescence or the beginning of adulthood (Pantelis et al., 2007), the etiopathogenesis indicates that genetic predispositions and developmentally early "hits", such as social stress, enhance the probability of developing schizophrenia (Rehn and Rees, 2005). The transition into the illness is marked by pathological changes of the brain, such as regional specific losses in gray and white matter (Pantelis et al., 2007). Similar to bipolar disorder, widely distributed neural circuits seem to be altered in schizophrenia, predominantly affecting frontal, temporal, and sub-cortical structures (Pantelis et al., 2007). Cognitive deficits are apparent early, sometimes even before illness onset (Mathes et al., 2005; Wood et al., 2002), and partially deteriorate over the duration of the illness (Bora et al., 2014).

Patients with schizophrenia display heterogeneous characteristics of positive and negative symptoms. Positive symptoms mainly mirror the patient's loss of contact with reality, such as delusions (bizarre beliefs that are resilient to counterarguments), hallucinations (perceptual distortions), and disorganized thinking. Negative symptoms include the blunting or diminishment of behavior and cognitive functions as well as affective expression and experience (Andreasen, 1997).

1.1.3. What is Alzheimer's disease?

Alzheimer's disease (AD) is a neurodegenerative disease that, in its most common form, is generally found in people over 65 years old. Approximately 24 million people worldwide have dementia, of which the majority (approximately 2/3) is due to AD (Ferri et al., 2005). Clinical signs of AD are characterized by progressive cognitive deterioration, together with declining activities in daily life and by neuropsychiatric symptoms or behavioral changes.

2. Alpha activity in Alzheimer's disease, schizophrenia and bipolar disorder

Hans Berger (1929) was the first to observe alpha rhythm. It was initially considered to be the brain's "idling rhythm". Later, several authors stated that EEG was not noise and that selectively synchronized alpha oscillations in the mammalian and human brain are part of the fundamental functional signaling of the central nervous system (Başar, 1980; Lehmann, 1989; Nunez et al., 2001).

Decrease of spontaneous alpha activity is one of the common EEG parameters reported in Alzheimer's disease, bipolar disorder and schizophrenia (Itil et al., 1972, 1974; Iacono, 1982; Miyauchi et al., 1990; Sponheim et al., 1994, 2000; Alfimova and Uvarova, 2008, see Fig. 1 for a graphical summary). Since the cause and pathology behind these three diseases differ considerably, the generalization of this finding needs further exploration.

In this manuscript, we will therefore discuss the similarities and differences of reductions in spontaneous alpha activity in patients with Alzheimer's disease, bipolar disorder, and schizophrenia. As a first step, we will review some previously published results on spontaneous alpha activity in patients with bipolar disorder with respect to an accompanying, new study that includes patients with schizophrenia.

Our previous study (Başar et al., 2012) was one of the first to show that spontaneous alpha activity (8–13 Hz) is highly reduced in drug-free, euthymic patients with bipolar disorder. In this study (Başar et al., 2012), we analyzed the spontaneous EEG activity (4 min eyes closed, 4 min eyes open) of eighteen drug-free DSM-IV euthymic bipolar patients and compared it to eighteen healthy controls. The results showed that spontaneous EEG alpha power of healthy participants was significantly higher than the spontaneous EEG alpha power of euthymic patients during both the eyes open and eyes closed conditions. Fig. 2 (modified from Başar et al., 2012) specifically depicts reduced alpha power in bipolar patients at the right and left occipital region for the eyes closed condition.

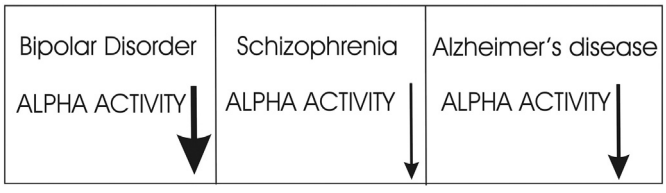

Fig. 1. Decrease of spontaneous alpha activity in bipolar disorder, schizophrenia and Alzheimer's disease.

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