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Review Paper

How is the brain working? Research on brain oscillations and connectivities in a new "Take-Off" state

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ABSTRACT

The present report is a trial to survey analysis and applications of brain oscillations in cognitive impairment for opening the way to a new take off in research on brain oscillation. Although the number of papers related to brain oscillations rapidly increases, it is important to indicate the common principles governing the functioning of brain oscillations in the brain and body. Research scientists need a global view on the types of analysis, applications and existing oscillations.

Further, scientists dealing with brain oscillations must have some knowledge from theoretical physics, system theory, and also general philosophy. The neuroscientists working on brain oscillations can mentally integrate several papers in the present report, and try to discover new avenues to augment knowledge on brain functions. A new take off in the search of brain oscillations indicates the strong need to survey this brunch of neuroscience in a broad panoply of science.

1. Introduction

> *Everything in the universe could be explained in terms of a few intelligible systems and simple approaches, upon which the stars and the earth and all visible worlds may have been produced.*
>
> [*Renée Descartes*]

The philosophic views of René Descartes are found relevant in research of physics, chemistry, and astrophysics. These views are also valid in neuroscience. New trends in neuroscience are based on the above concept. In the present special issue, 19 contributions are included, which could provide a new take off in the understanding of EEG–brain oscillations and their spectral connectivity. Possibly a "Big Bang" will occur in neuroscience literature based on brain–body oscillations and connectivity.

The present report aims to introduce 19 steps that may aid in a new take on EEG–oscillation analysis. This may, in turn, open new avenues to prepare efficient responses to the following questions:

a) How does the brain work?
b) Can we better understand the functionality of the brain by extending the Brodmann areas with connectivity concept?[1]
c) What can we learn from the "Broken Brain"?
d) Is the brain a dynamic syncytium and memory a continuum in time space?

1.1. What is the place of psychophysiology in the interdisciplinary sciences and brain oscillations?

Can interdisciplinary approaches again gain terrain?

What is psychophysiology, and what is physiology? Are there bridges between physics, physiology and psychophysiology? Do we again need a common language in the 21st century?

Psychophysiology is an integrated field of physiology and neuroscience. Through electrophysiological and neuroimaging techniques, it establishes methodologically essential and crucial links for the investigation, understanding and mapping of brain functions. Psychophysiology looks at basic cognitive, emotional and motivational processes as well as normal and pathological conditions. Further, psychophysiologists are scientists integrating scopes of several disciplines.

Can the four "P's": *Physics*, *Physiology*, *Psychology* and *Physiology* provide a common language or common links? I favor the following view: A union between biophysics, (which combines realms of physics, physiology and molecular biology) and psychology is indispensable. Both disciplines are inseparable.

In the 19th century, an experimental biophysicist named Hermann von Helmholtz unified the four P's. He not only launched predictions, but also provided a strong empirical foundation by raising questions

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[1] CLAIR means: connected-coherence, linked, associative and integrative responses.

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and trying to find experimental evidences. In the 20th century, C.F. Hayek launched a very important theoretical frame, but did not perform genuine experiments since he was an economist (i.e. a theoretician).

In the first half of the 20th century, the field of psychology went through a magnificent breakthrough with the works of Karl Lashley, Donald Hebb, and B.F. Skinner, just to mention a few. Marcel Proust and Henri Bergson combined philosophy and psychology to open the way to the concept of episodic memory. Hans Berger, Ramon ŷ Cajal and Lord Sherrington launched breakthroughs in neurological sciences. Parallel to this, a magnificent breakthrough took place in physics with Henri Poincarré, Albert Einstein and the Copenhagen School with work of Niels Bohr, Werner Heisenberg, Max Born, and E. Schrödinger.

New steps included the evolution of molecular biology with Jacques Monod, cybernetics by Norbert Wiener, synergetics by Hermann Haken, study of dissipative structures by I. Prigogine, and catastrophe theory by René Thom. New approaches to cognitive processes have been very successful by the use of fast computers, fMRI, MEG and PET.

At the century of René Descartes (1596–1650) and of Blaise Pascal (1623–1662) tools for measuring the "Thinking Processes" were not available. Now, we have some of them.

Are the progresses in science now powerful enough to describe the processes of mind? Mankind achieved important steps, although we will never be able to completely solve the problem of brain body and mind incorporation. However, we must have to continue to research and ask further questions.

In the twentieth century, the structure of the atom was successfully illuminated, but the processes of thought continued to seem illusive. Has the time come to tackle common concepts from all branches of science and philosophy?

The Ionian philosophers Anaxagoras, Leucippus, and Democritus of the fifth century B.C. postulated that all matter is made of a set of particles, which were atoms to denote their presumed invisibility. Their concept of a world made up of invisible, incompressible eternal atoms in motion is best known through the writings of the Latin poet Lucretius (98 to 55 B.C.)

2. The contributions of this special issue point to a big change in the study of brain oscillations

The papers in the present special issue are chosen in order to orient the readers to the analysis of multiple oscillations via multiple strategies. In particular, the transition from healthy brain to diseased brain opens the possibility to discover the important relation between oscillations and neurotransmitters. Additionally, we have new possibilities to study the anatomy of the intact brain and the brain with injuries. Brain imaging methods such as MRI and DTI are very efficient complimentary tools understanding avenues in brain functioning.

In the last two decades, the analysis of brain oscillations is one of the most important developing research areas in neuroscience literature. This type of progress has opened the way to generation of publications that analyze less important details and do not contain new breaking progresses. Lord Kelvin stated, "every science is measurement, but every measurement is not science." We should somewhat change these last words: Every measurement does not belong to important new breaks in science.

As we will explain in the next section, during the last 45 years one of coauthors (E.B.) has been involved in several types of experimental research and theoretical achievements in the field of brain oscillations. According to this longstanding experience, we can evaluate which new steps in neuroscience research could elicit new avenues leading to a gigantic new take-off in the field.

3. Surveys in the special issue

3.1. Multiple methods

More than eighty years has been past since the discovery of Hans Berger. According to Herrman et al. (2016-in this volume), most cognitive processes have been linked to at least one of the traditional frequency bands in the delta, theta, alpha, beta, and gamma ranges. Although the existing wealth of high-quality correlative EEG data led many researchers to believe that brain oscillations promote various sensory and cognitive processes, a causal role can only be demonstrated by directly modulating such oscillatory signals. Hermann et al. (2016-in this volume) highlight several methods to selectively modulate neuronal oscillations, including EEG-neurofeedback, rhythmic sensory stimulation, repetitive transcranial magnetic stimulation (rTMS), and transcranial alternating current stimulation (tACS). The modulation of neuronal oscillations demonstrates causal links between brain oscillations and cognitive processes, leading to obtain important insights on human brain function.

3.2. A methodological survey of oscillation analysis and strategies

The paper by Başar et al. (2016-in this volume-a) is an account of methods such as evoked/event-related spectra, evoked/event-related oscillations, coherence analysis, and phase-locking. The report does not aim to cover all strategies related to the systems theory applied in brain research literature. However, the essential methods and concepts mentioned in this paper are applied to multiple important disease states such as Alzheimer's disease (AD), schizophrenia (SCZ), and bipolar disorder (BD). Such disease examples demonstrate fundamental findings in the search for neurophysiological biomarkers in cognitive impairment. An overview of the results clearly demonstrates that it is obligatory to apply the method of oscillations in multiple EEG frequency windows to search functional biomarkers and to detect the effects of drugs. Again, according to the summary of results in AD and BD patients, multiple oscillations and selectively distributed recordings must be analyzed and should include multiple locations. Selective connectivity between selectively distributed neural networks has to be computed by means of spatial coherence. Therefore, in designing a strategy for diagnostics and application of (preventive) drugs, neurophysiological information should be analyzed within a framework including multiple methods and multiple frequency bands. The application of drugs/neurotransmitters gains a new impact with the analysis of oscillations and coherences. A more clear and differentiated analysis of drug effects can be attained in comparison to the application of the conventional wide-band evoked potential (EP) and event-related potential (ERP) applications.

4. Alpha band is not "idling of the brain"

As early as 1980, Basar demonstrated the functional relevance of alpha activity (Başar, 1980). The same author showed that the EEG is not a noise signal and that alpha does not manifest the "idling of the brain." All contributions of the present issue indicate the same trend.

5. Importance of delta window in cognitive processes

In the last decade, neuroscience literature focused on the brain's oscillatory responses. The studies on human delta (0.5–3.5 Hz) oscillatory responses in cognitive paradigms date back to 1984. Pilot studies of Başar and Stampfer (1985) and Stampfer and Başar (1985) showed that delta oscillatory responses were involved in "perception, attention, learning, decision and working memory."

The manuscript by Güntekin and Başar (2016-in this volume) comprehensively reviews the studies looking at delta oscillatory responses. This paper focuses on delta responses that impact on cognitive stimulation in healthy subjects and in diseased subjects with different pathologies, namely Alzheimer's disease, mild cognitive impairment (MCI), bipolar disorder, schizophrenia and alcoholism. Further delta oscillatory responses to presentation of faces, facial expressions, and affective pictures are reviewed. Cross-frequency couplings of delta oscillations with higher frequency windows are also included in the review.

The conclusion of this review includes several important remarks, including that delta oscillatory responses are involved in cognitive and emotional processes. Decrease of delta oscillatory responses could be a general electrophysiological marker for cognitive dysfunction (Alzheimer's disease, MCI, bipolar disorder, schizophrenia and alcoholism). The pre-stimulus activity (phase or amplitude changes in delta activity) has an effect on post-stimulus EEG responses.

6. Complexity of the gamma band

A great number of publications demonstrated the importance of the gamma activity between 25 Hz and 48 Hz. However, according to the current research, this frequency band has fine structures. New measurements with multiple experimental strategies can possibly eliminate the diversity of interpretations related to functionality in the gamma band. A typical example is behavior, the responses to Alzheimer patients in the three different subgamma bands (see paper by Başar et al., 2013; Başar et al., 2016-in this volume-b).

7. Connectome concept

Spectral connectivity in EEG plays an important role in several brain functions. According to Güntekin and Başar (2010) the application connectivity-concept to evoked and event related oscillations provides more information related to cortical performance. In recent years, great attention has been focused on the evaluation of quantitative EEG and/or event related potentials on clinical studies (Rossini, 2009; Başar et al., 2010; Yener and Başar, 2013).

Babiloni et al. (2016-in this volume) describe with sufficient details and effectivity the use of resting EEG as a biomarker in MCI and AD subjects. The study includes analysis of power spectral density correlation with MRI results (volume reduction). Further, the connectivity changes in this pathological conditions, the decrease of spectral coherence in alpha rhythms is frequently cited in literature. Babiloni emphasizes that low frequency alpha coherence was negatively correlated to collagenic lesion across the MCI subjects.

The report of Babiloni is an efficient work to show the usefulness of brain connectivity in resting states. Furthermore, it is to mention that in diseases, the connectivity between various structures can show crucial differences and discordances. For example, event related connectivity in the gamma coherence band shows increase of gamma coherences whereas alpha, delta, and theta coherences are highly decreased in Alzheimer's disease. The topology of the brain connectivity is also shown by means of graph theory in MCI and Alzheimer's disease subjects. The application of graph theory to AD research provided quite interesting results. It has been shown a loss of 'small-world' network properties in AD patients as revealed by the resting state EEG and MEG rhythms (Stam et al., 2007, 2009).

The previously developed spatio-temporal non-negative ICA method for EEG sources is now extended to a state space model. This allows the estimation of EEG source effective connectivity via Granger Causality (EEG–GC). Normative data for the Cuban Human Brain Mapping database (comprising high resolution EEG, MRI and DWI) was obtained. There was a statistically significant correspondence between DDWI-based anatomical connectivity and EEG–GC. The pitfalls of using scalp EEG for connectivity studies as well as the usefulness of the new method for evaluating neuropathology are evaluated.

8. CLAIR (connected-coherence, linked, associative and integrative responses)

Since the beginning of the last century, the localization of brain function is presented by Brodmann areas, or maps corresponding to anatomic organization. They are used in order to give a global idea of cortical structures for given sensory and cognitive functions. In the last few decades, the analysis of brain oscillations gained high importance due to their correlation to brain functions. Moreover, the use of the spectral connectivity provides information on dynamic connectivity between various structures. However, according to Luria (Luria, 1966), brain responses have dynamic features, making structural localization almost impossible. Brain functions are very difficult to localize and need joint analysis of oscillation and event related coherences. In the present special issue, a model called "CLAIR" is described to extend and possibly to replace the concept of the Brodmann areas. To design a perfect functioning CLAIR model requires years. However, the beginning step is provided in the present special issue.

9. Cognitive impairment

Around 2000 applications of brain oscillations in cognitive impairment have been identified. Most studies were performed on either schizophrenia or the application of 40 Hz steady state stimulation. Most of the changes were noted in the gamma band. However, application of the multiple oscillations was mostly disregarded. Our group was also involved in research on cognitive impairment. In 2005, 2007 and 2011, we organized three conferences and workshops in Izmir and Istanbul. The last conference (2011) covered diseases such as MCI, Alzheimer diseases, schizophrenia, bipolar disorder and ADHD. We have also edited the discussion of the final round table. Yener and Başar (2012) Brain oscillations in multiple frequency windows can be used as physiological markers for recognition of diseases and progression of the diseases. Spatial coherences in diseases may be helpful in analyzing integrative brain functions, and thus are important for future research.

Applications in cognitive impairment together with application of drugs open the way to understand the web of oscillations and neurotransmitters. In the last decade, a new application field has emerged, with a focus on "the broken brain." In this field, brain functioning has been studied by looking at diseases, application of drugs, and changes due to degenerations of focal brain areas.

Spontaneous EEG activity, sensory evoked oscillations, and event related oscillations should be analyzed in parallel when solving a new problem. Using only one of these measurements can be misleading.

10. The new gamma window

Although the gamma frequency window attracts major interest in the study of brain oscillations, there are controversial results in a great number of publications. Başar (2013) explains measured trends and controversial findings in detail (Başar-Eroğlu et al., 1991; Schürmann et al., 1997; Sakowitz et al., 2001; Başar, 2013; Başar et al., 2016-in this volume-b). In this report, several examples demonstrate that gamma oscillations, increases, and decreases can be correlated with several functions. Additionally, a recent publication has demonstrated that several peaks in the power spectrum of gamma window have different frequencies. The existence of phase coupling of these frequencies demonstrates that gamma response has a fine structure. Analysis of this fine structure reveals an increase of gamma connectivity in Alzheimer's patients. If the results can be analyzed and interpreted in a systematic way, the model of gamma response will open new avenues for correlating brain function with gamma responses. These results provide a new take-off point in the field of brain oscillations.

11. Broken brain: conformity and controversies in oscillations and connectivity

While describing brains with cognitive impairment such as schizophrenia and bipolar disorder, Andreasen (1985) was the first to use the expression, "Broken Brain." In such brains, several neuro-anatomical and neuro-chemical changes have been identified. Such changes lead to physiological modifications. Neural activity in different brain structures is modified, leading to changes in the frequency and amplitudes of oscillations. Further, depending on the nature of the disease the connectivity may also be altered (Başar et al., 1998; Başar-Eroğlu et al., 2001; Başar et al., 2016-in this volume-b). Changes in frequency, amplitude, and spatial coherence (*connectivity*) of oscillations are mostly caused by alterations of neurotransmitter release. The ensemble of these measurable parameters gives a general picture of oscillatory activity and also connectivity in the brain. Probably, the degree of neurotransmitter release is a causal factor in modification of oscillatory behavior in the brain (See also Koch et al., 2016-in this volume; Sanches and Ehlers, 2016-in this volume).

In the present special issue, we also partly aim to describe brain oscillations and spectral connectivity in neuropsychiatric diseases. In the following, we will outline some highlights from three types of diseases: Alzheimer's disease, bipolar disorders, and schizophrenia.

a) *Delta response*: In cognitive impairment, the most important and conform changes in delta response are observed approximately 400 ms following the target stimulation in the oddball paradigm. A decrease in this late delta response was observed in AD patients, BD patients, and SCZ patients. Additionally, a late delta decrease is also observed in mild cognitive impairment (MCI). However, this decrease in delta response is less ample and less significant in comparison to Alzheimer's patients. In Fig. 1, delta responses in healthy subjects are illustrated. A gradual decrease of delta response from healthy subjects to MCI and AD responses is clearly demonstrated in bipolar disorders and SCZ; the decrease in the delta response is also significant.

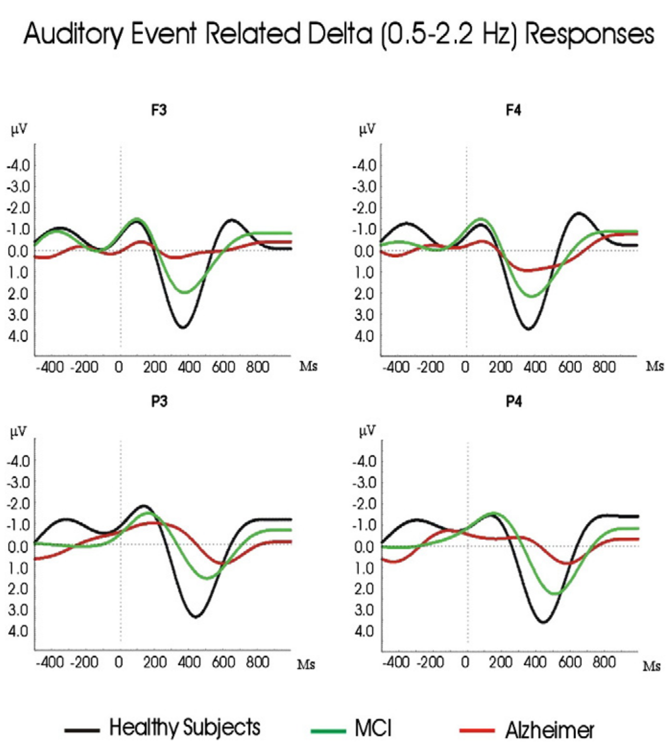

Fig. 1. MCI and AD continuity is prominent in auditory ER (Event Related) delta oscillatory activity, showing gradually decreasing delta amplitudes and delayed delta peak responses among healthy subjects, MCI, and mild Alzheimer subjects. (Modified from Yener et al., 2011).

b) There is also a decrease of theta response in Alzheimer's patients compared to healthy subjects (Yener et al., 2008). Moreover, upon medication with acetylcholine esterase, theta response is again regular and increased.
In BD and SCZ, we also observed reduced theta responses. Further, it is known that in BD, the fast theta response between 5 Hz and 8 Hz is almost abolished, whereas the slow theta component is almost intact (Atagün et al., 2013).
c) *Alpha response*: In AD disease, the spontaneous alpha activity (resting EEG) is modified to lower frequencies in alpha band (Babiloni et al., 2016-in this volume). Spectral connectivity in the alpha frequency band is reduced in AD compared to healthy subjects. In SCZ, alpha spontaneous activity is slightly reduced, whereas in bipolar patients, spontaneous activity is 80% reduced (Başar et al., 2012, 2016-in this volume-b).
d) Beta responses in bipolar patients are highly increased upon application of target stimulation. Interestingly, beta response on bipolar subjects is also increased upon application of lithium (Atagün et al., 2013; Başar et al., 2016-in this volume-b).
e) Gamma responses belong to mostly analyzed oscillatory responses in SCZ. In most cases, a reduction of gamma responses is observed (Uhlhaas and Singer, 2006). Several other studies show similar results (Başar and Güntekin, 2013). Only one paper discusses the slight increased and sustained gamma activity in SCZ patients during application of a cognitive task with varying difficulties (Başar-Eroğlu et al., 2007).
f) A crucial decrease of gamma coherence above 40 Hz is observed in BD patients upon application of target stimuli in the oddball paradigm. Although cases of cognitive impairment show highly reduced gamma responses, we observed an important controversy in Alzheimer's patients. Upon application of target signal in an oddball paradigm, the gamma response is recorded at around 400–600 ms in AD. Additionally, spectral connectivity is highly increased between frontal and parietal locations. This finding shows that the gamma coherence is not only decreased in cognitive impairment, but also can be increased in Alzheimer's disease.
g) Alzheimer's patients respond to an oddball target light stimulation (i.e. cognitive load) with a delayed gamma burst in comparison to healthy subjects. Late cognitive gamma response occurs at approx. 400–600 ms. This delay can be analyzed by considering the frequency structure of the gamma band.

12. Biomarkers for detection and progression of diseases

12.1. Correlation of delta oscillation with MRI volumetry

In the report by Yener et al. (2016-in this volume-a,b) delta ERO responses at the frontal, central and parietal regions, and MRI frontal volume showed significant group differences between MCI and healthy elderly. In the MCI and healthy control (Hc) subject groups, a positive correlation was found between frontal delta EROs following oddball rare targets and frontal volume as measured by structural MRIs. These results suggest that frontal delta target EROs are important factors in cognitive processes of aged people, and are related to frontal neurodegeneration in the continuum between normal and amnestic MCI subjects. This suggests that EEG markers are candidates for possible future screening of large populations of elderly subjects at risk of AD (Fig. 2).

13. Genetics and event related oscillations

According to Enoch et al. (2002), electrophysiological phenotypes, including resting EEG power, ERP amplitude, ERO power, EEG coherence,

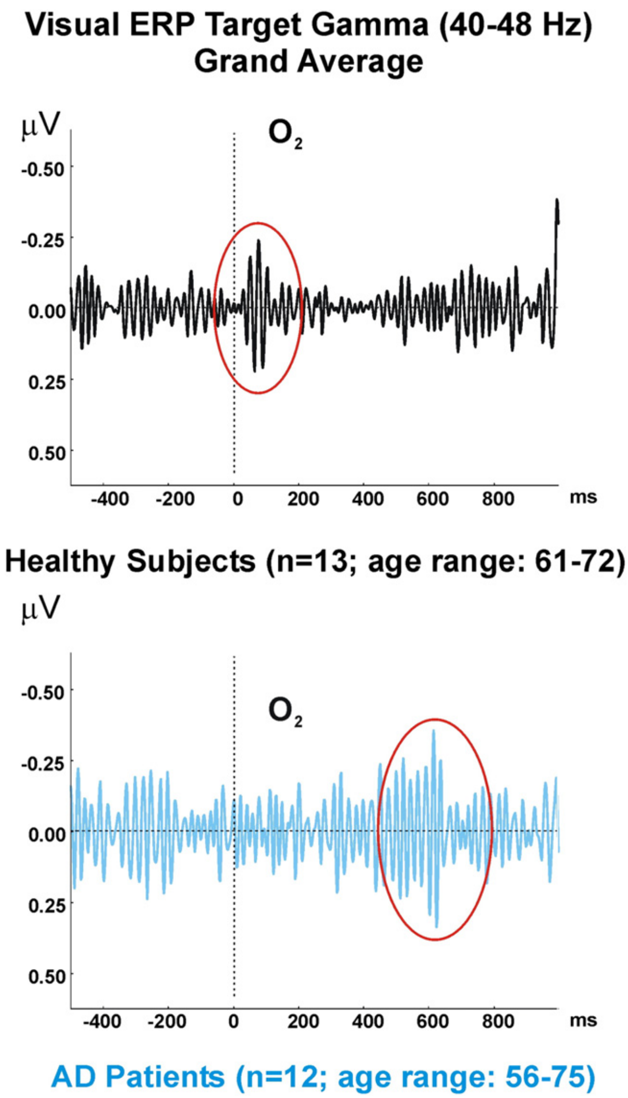

Fig. 2. Grand-average of gamma ERO responses at 40–48 Hz over the right occipital location.

and functional connectivity within EEG frequency bands, are stable traits that are moderately to highly "heritable". These phenotypes are related to psychiatric diseases, including alcoholism. These phenotypes are found in alcohol-naive biological children of alcoholics, suggesting that they may be predictors for disease vulnerability.

Genetic studies of the P300 ERP have not been as fruitful. Instead, studies have moved from time-frequency decomposition of the ERP to analyses of the underlying theta and delta event related oscillations (EROs). This approach has led to the detection of cholinergic, glutamatergic, and serotonergic results associated with electrophysiological phenotype and disease.

14. Web of neurotransmitters, drugs and oscillations

Three decades ago, Başar (1980) launched a working hypothesis stating that, "alpha, beta, gamma, theta and delta oscillations and their connectivities govern the 'whole brain work'." The event related oscillatory responses (EROs) and selective connectivity during cognitive tasks (in alpha, beta, gamma, theta and delta frequency bands) measured by scalp electrodes are highly increased compared to evoked oscillations from a pure sensory signal, depending on brain topography. Each oscillatory activity represents multiple functions, and vice versa, each function is represented by multiple oscillations. Quasi-invariant natural frequencies and neurotransmitters govern functioning in all physiological and biochemical pathways. Several brain functions are manifested by superposition of EEG–oscillations. The effects of neurotransmitters such as GABA, acetylcholine and dopamine are highly efficient in oscillatory activity. Hence, sensory-sensitive and/or cognitive-sensitive oscillatory neural networks react differentially upon stimulation modality. This electrophysiological differentiation enables efficient analysis of the brain's oscillatory responses in cognitive impairment such as MCI, Alzheimer's disease, bipolar disorders and schizophrenia. Candidates for biomarkers of these diseases are recently extensively discussed (Başar et al., 2013; Yener et al., 2007; Başar and Güntekin, 2008).

15. The cholinergic system in animal

The report by Sanches and Ehlers (2016-in this volume) indicates the importance of animal models in understanding the influence of neurotransmitters on electrical activity of the brain. Such studies are rare, but in the future, similar recordings will be extremely useful in the analysis of the "web of oscillations and neurotransmitters" to understand cognitive processes.

The cholinergic system in the brain is involved in attentional processes that are engaged for the identification and selection of relevant information in the environment and the formation of new stimulus associations. In the present study we determined the effects of cholinergic lesions of nucleus basalis magnocellularis (NBM) on amplitude and phase characteristics of event related oscillations (EROs) generated in an auditory active discrimination task in rats. Rats were trained to press a lever to begin a series of 1 K Hz tones and to release the lever upon hearing a 2 K Hz tone. A time-frequency based representation was used to determine ERO energy and phase synchronization (phase lock index, PLI) across trials, recorded within frontal cortical structures. Lesions in NBM produced by an infusion of a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) resulted in (1) a reduction of the number of correct behavioral responses in the active discrimination task, (2) an increase in ERO energy in the delta frequency bands, (3) an increase in theta, alpha and beta ERO energy in the N1, P3a and P3b ROI regions of interest (ROI), and (4) an increase in PLI in the theta frequency band in the N1 ROIs. These studies suggest that the NBM cholinergic system is involved in maintaining the synchronization/phase resetting of oscillations of different frequencies in response to the presentation of the target stimuli in an active discrimination task. This emphasizes the utility of animal models in search of neurotransmitter correlation of oscillations.

16. A pharmaco-EEG approach to oscillations

Impairments in spatial and temporal integration of brain network activity are a core feature of schizophrenia. The neural network oscillatory activity is considered fundamentally important in coordinating neural activity throughout the brain. Hence, exploration of brain oscillations has become an indispensible tool to study the neural basis of mental illnesses. However, most of the studies in schizophrenia include medicated patients. This brings to question to what extent the changes in the electrophysiological parameters are genuine illness effects, genuine drug effects or a mixture of both. Koch et al. (2016-in this volume) provide a short overview of the neuropharmacology of brain oscillations with respect to schizophrenia.

The core assumption of the so-called "pharmaco-EEG" approach is that drug effects on mental and cognitive functions are reflected in changes of quantitative EEG parameters. Hence, clinical efficacy of drugs might be predicted on the basis of the neuropharmacology of electrophysiological measures, such as brain oscillations. Vice versa, knowledge of drug effects on brain oscillations can be of essence in understanding schizophrenia. However, the current literature lacks systematic findings because of at least two problems. First, the pharmacology of most antipsychotic drugs is complex including interactions with several transmitter receptors. Second, the neuropathology of schizophrenia still has no pathognomonic signature. Even though it is presently not possible to clearly dissociate drug- and illness effects in neural oscillations, the review by (Koch et al., 2016-in this volume) emphasizes the need for future studies to foster the understanding of this relationship in schizophrenia and other neuropsychiatric diseases.

Fig. 3. The illustration describes globally the influence of few neurotransmitters in cognitive impairment.

17. Complex cortical alpha processing by means of ambiguous figures in schizophrenia

Schizophrenia is a complex mental disorder. Patients with schizophrenia show impairments in fundamental sensory and cognitive functions, encompassing the entire perception–action-cycle. This illness is a frequently used model for clinical applications of event-related oscillations.

Başar-Eroğlu et al. (2016-in this volume) analyzed the alterations of alpha activity during perception of multistable pattern (stroboscopic alternative motion) in patients with schizophrenia. Multistable visual perception is a phenomenon in which a stimulus pattern can give rise to at least two different "perceptual interpretations," i.e. the stimulus remains constant. This stimulus pattern is generally accepted to contribute to functional integration of sensory and cognitive processes and activates many oscillatory networks of different frequency bands.

The report by Başar-Eroğlu et al. (2016-in this volume) stated that the alpha activity is higher in patients during the viewing of multistable patterns in a stable period in comparison to healthy controls. On the other hand, during the reversion period, decreasing stronger alpha is observed in patients than controls. These results indicate that the higher amplitude alpha oscillations in patients during stable periods mean that patients must give more attention in order to stabilize perception. The patients have difficulty keeping the multistable pattern during the stable period.

The results indicate that patients are more influenced by the sensory information than cognitive drivers of perception. Accordingly, the presentation of ambiguous patterns could also provide a type of biomarker for differentiation of diseases (see also Başar-Eroğlu et al., 1993, 2001).

18. Ambiguous figures in children

The prefrontal cortex (PFC) is considered the primary source of attentional control during elementary visual processing. This is exemplified in perceptual ambiguity. Assuming that multistable perception activates a fronto-parietal network, Ehlers et al. (2016-in this volume) looked at the results of mature and developing cognitive systems to deduce the developmental status of underlying structures. This study looked at behavioral performances and functional EEG parameters in ten-year old subjects. Ehlers et al. (2016-in this volume) analyzed the topographical distribution, amplitude characteristics, and inter-trial variability of a reversal-related delta response that accompanies perceptual switches between the two alternative percepts of an ambiguous motion pattern. The behavioral data showed a considerably lower reversal rate within children, thus suggesting that the related mechanisms are not operating on fully-developed level. In contrast to findings in adults, the involved delta component emerges as part of an unspecific posterior activation, suggesting that a cortical specialization process has not been accomplished yet. On frontal locations the ten-year olds fail to yield a stable component during ambiguous processing. This report also underlines the ambiguous nature of cognitive processes as related to delta oscillations.

19. Beta activity and heart rate variability

Triggiani et al. (2016-in this volume) tested the hypothesis of a relationship between heart rate variability (HRV) and Rolandic mu rhythms in relaxed condition of resting state. Resting state eyes-closed electroencephalographic (EEG) and electrocardiographic (ECG) data were recorded (10–20 system) in 42 healthy adults. EEG rhythms of interest were high-frequency alpha (10.5–13 Hz) and low-frequency beta (13–20 Hz), which are supposed to form Rolandic mu rhythms. Rolandic and occipital (control) EEG sources were estimated by LORETA software. Results showed a statistically significant ($p < 0.05$, corrected) negative correlation across all subjects between Rolandic cortical sources of low-frequency beta rhythms and the low-frequency band power (LF, 0.04–0.15 Hz) of tachogram spectrum as an index of HRV. These results suggest that Rolandic low-frequency beta rhythms are related to sympathetic activity regulating heart rate, as a dynamic neurophysiologic oscillatory mechanism sub-serving the interaction between brain neural populations involved in somatomotor control and brain neural populations regulating ANS signals to the heart for on-going homeostatic adaptations.

20. A holistic approach by oscillations is interpreted by Claudio Babiloni

According to Babiloni (private communication), Erol Başar developed the new idea that the brain oscillations reflect, and are key to understanding, the complex homeostatic interactions between the brain and body visceral organs. This idea helps form the mind as a term capturing the representation of the reality and the related cognitive and affective processes. Erol Başar leads the readers to surpass the view of the mind as emerging from brain oscillatory processes, in favor of the view that the mind emerges from the multiple oscillatory processes characterizing the homeostatic interactions between the brain and body visceral organs and tissues. Basar promotes a structural and functional continuum termed "Brain–Body–Mind functional syncytium". Within such "functional syncytium", quasi-invariant nervous oscillatory processes at different frequencies would ensure a stochastic unstable transfer of (excitatory and inhibitory) signals among different brain nodes by means of neurotransmitter systems and complex biochemical pathways. In parallel, quasi-invariant myogenic slow oscillatory processes would ensure the inter-relatedness and homeostatic adaptation of body visceral organs and tissues by means of vegetative system. Afterwards, Erol Başar outlines the "life span" of such "functional syncytium" along the phylogenesis and human ontogenesis as well as its derangement in the form of Alzheimer's disease, schizophrenia, and depression. The concept of the "Nebulous Cartesian System" helps him to emphasize the chaotic nature but tight relationships among the countless dimensions of the mentioned "functional syncytium" (Başar, 2011).

The hypothesis by Başar (2011) was mainly based on findings of Barman and Gebber group in the EEG frequency range and on the results by Aladjalova (1957) in ultra slow range. Barman's view is explained below.

21. The view of Suzan Barman

Since the first recordings of sympathetic nerve activity in the 1930's, it was very clear that the activity was organized into bursts synchronized with the respiratory and cardiac cycles. Since the early studies, evidence has accumulated showing that sympathetic neural networks are quite complex and generate a variety of periodicities that range between ~0.04 and 10 Hz, depending on the physiological state, type of nerve being analyzed, age of the subject, and the species. Despite the ubiquity of sympathetic rhythms, many investigators have failed to consider this oscillatory characteristic of sympathetic nerve activity. Instead, they rely on simply quantifying changes in the level of activity to make decisions about the role of the sympathetic nervous system in mediating certain behaviors. The review by Barman (2016-in this volume) highlights work that shows the importance of including an assessment of the frequency characteristics of sympathetic nerve activity.

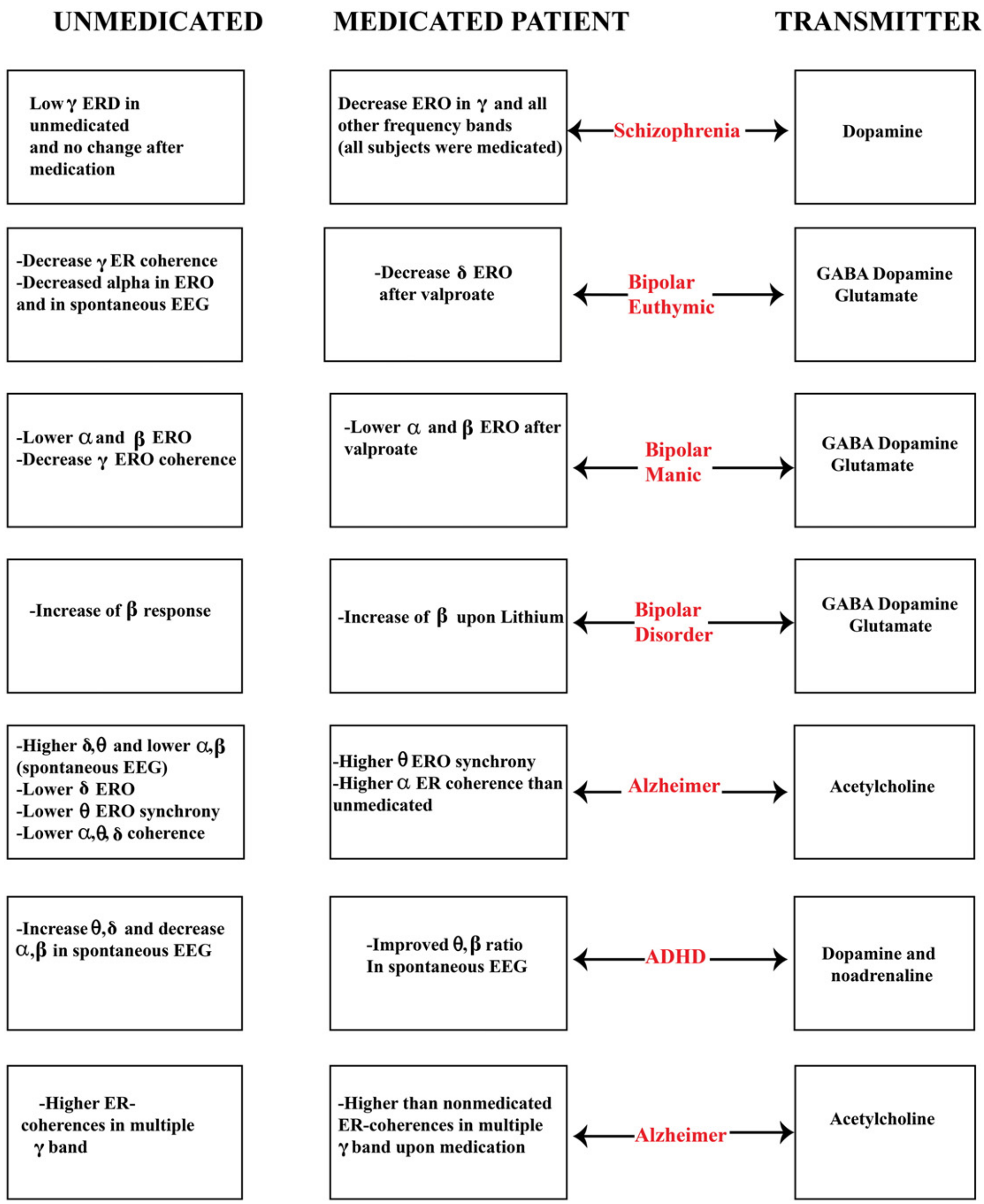

Fig. 3. After a review of articles in the present special issue and the review of the volume of by Başar et al., 2013 in Neuropsychiatric Disorders; Başar and Düzgün (in this volume-a) developed the present table globally describing the effect of some neurotransmitters in brain functions.

22. Quantum neurophysiology

The introduction of quantum theory to the brain is a new step. Tarlacı and Pregnolato (2016-in this volume) explain this development as follows:

In the past twenty years in particular, those working on quantum mechanics and neuroscience have begun to take an interest in each other's fields. In the neuroscience community, discussion started as to whether quantum physics had a place in the communication between nerve cells. In the last decade, some significant work about how quantum effects can occur in biological systems has been particularly prominent: superposition in photosynthesis, entanglement in magnetoreception, and quantum tunneling in smell perception. Besides to these effects, we also add here the opinion of Başar (2011) who suggested the necessity to use the concept of Heisenberg's S-Matrix and the Feynman diagrams in neuroscience.

23. Graph theory

The application of graph theory seeks to understand that the brain's connectivity in our opinion is relevant field in future. An important problem in systems neuroscience is the relation between complex structural and functional brain networks. Stam et al. (2016-in this column) use simulations of a simple dynamic process based upon the susceptible-infected-susceptible (SIS) model of infection dynamics on an empirical structural brain network. Stam used these simulations to investigate the extent to which functional interactions between any two brain areas depend upon (i) the presence of a direct structural connection and (ii) the degree product of the two areas in the structural network.

Stam et al. (2016-in this volume) found a phase transition between an inactive and a partially active state for a critical ratio $\tau = \beta/\delta$ of the transition rates in agreement with the theory of SIS models. Slightly above the critical threshold, node activity increases with degree, also in line with epidemic theory. The functional, but not the effective connectivity matrix closely resembled the underlying structural matrix. Both functional and, to a lesser extent, effective connectivity were higher for connected as compared to disconnected (i.e. not directly connected) nodes. Effective connectivity scaled with the degree product. For functional connectivity, a weaker scaling relation was only observed for disconnected node pairs. For random networks with the same degree distribution as the original structural network, similar patterns were seen, but the scaling exponent was significantly decreased especially for effective connectivity.

Even with a very simple dynamical model, it can be shown that functional relations between nodes of a realistic anatomical network display clear patterns if the system is studied near the critical transition. The detailed nature of these patterns depends on the properties of the functional or "effective connectivity" measure that is used.

24. Memory continuum: hypermemory

Hypermemory is the overlapping of all memory types in the same time space of 0.5 ms. Başar and Düzgün (2016-in this volume-a,b) shortly surveyed the relevant models emphasizing the time structure in general memory processes. These authors claim that most memory models describe serial processing, whereas memory states should occur in parallel, according to psychological evidence. Moreover, memory is not a mental construct purely from the brain, but memory performance is also structurally linked to inborn physiological functions including reflexes. In order to explain the memory as the most important brain function, it is essential to study temporal structure of memory processes. By doing this, it is proposed that all types of memories are embedded into a larger memory construct, called "hypermemory". Episodic memory, semantic memory, emotional memory, and phyletic memories are integrated in hypermemory, and parallel occurrence of all these memories occurs in short fractions of a second. Accordingly, this hypermemory embracing past, present, and future should process in a hypertime space.

25. Cognitive brain and philosophy as a method

The brain's ability to form "intuition" is one of the important aspects of brain function. The analysis of brain oscillations through studies of the present special issue may open a new way of conceptualizing the brain's functional ability in this realm.

Since the beginning of the Renaissance, the question "what is mind?" was considered by prominent philosophers such as René Descartes, Blaise Pascal, John Locke, Emanuel Kant and Henri Bergson. According to Bergson, new ideas can be the most fruitful, and they may be engendered in physiological intuition. Modern science could not be realized without this concept of Renaissance philosophers (see Başar and Düzgün, 2016-in this volume-a,b).

Accordingly this special issue includes a philosophical report by Northoff (2016-in this volume). We also emphasized the view of Henri Bergson who indicated that intuition should be considered a method in science. This view is also explained by Deleuze (1966) in a brilliant manner.

26. The integration of reasons to use the title of the special issue as "a new take-off?"

At the beginning of 1980s some monographs, edited books and special issues have been important to introduce the concepts of EEG as an important physiologic and "function correlated" signal and not "noise" (Başar, 1972; Başar and Ungan, 1973). In the second step, investigators started to describe cognitive progresses by means of event related oscillations, mostly by using single frequency windows. Presently, superposition of multiple oscillations, coherence, and event related coherences between different brain structures are also considered important parameters in understanding integrative brain function (see CLAIR Model in BD). Using strategies including multiple methods is especially emphasized.

Aims to edit around 20 reports related to brain oscillations are based on the following facts:

1. There are increased numbers of applications of EEG oscillations in various fields of neurosciences.
2. In addition to showing importance in neuroscience, EEG oscillations in the autonomic nervous system and their links recently led to important keys of brain–body functions.
3. Although originally described hypothetically, oscillations' functionality in the broken brain has been demonstrated by studies explicitly showing prominent changes of oscillatory activity in diseases.
4. Ambiguous patterns are differentiated in healthy subjects and schizophrenia.
5. The importance of using strategies with multiple methods is highly recommended, as several examples in the reports of special issue demonstrate.
6. Basic trends and methods of thoughts in physics can be translated to the study of neural oscillations. The approach to quantum neurophysiology provides one of these steps.
7. Comparative analysis of different diseases by indicating "controversies" and "conformities" may also help with more general interpretations of the fundamental question: "How does the brain work?" (3 disease papers).
8. A very important topic is the use of spatial connectivities in EEG frequency ranges to describe function. The CLAIR model brings together oscillatory connectivity in various areas of the brain and the delays of oscillatory responses. Başar and Düzgün (2016-in this volume-b) proposed to consider the CLAIR model in extension of Brodmann areas.
9. Hypermemory embracing all types of memories acting in parallel as "a continuum in the time space" is a result of the oscillatory concept.

The present special issue comprehends a number of reports, views, and theoretical concepts towards the understanding of brain functions. Further, by describing diseases with oscillatory concepts and analysis, this issue adds important value to finding biomarkers of diseases and observing progresses in diseases. We also included a new model to describe dynamic topology of brain function and of hypermemory, including all types of memories. The inclusion of papers with different contents will possibly generate a new window in a decade during which research on brain oscillations will rapidly increase. However, the "new take off" does not only refer to the increasing number of publications. Rather, we expect that the observation of new types of ideas and windows will highly add to a more profound understanding of brain functions.

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