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New Perspectives in Pharmaco-Electroencephalography

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Abstract: Recent research emphasizes that majority of brain disorders and psychiatric problems are accompanied by disruption in the temporal structure of brain activity. From this perspective, disruption is viewed as a disorder of the metastable balance between large-scale integration and independent processing in the brain, in favor of either independent or hyper-ordered processing. This paper proposes that the future of psychopharmacology lies in its ability to design the psychotropic drugs which can restore the normal temporal structure and metastable structure of brain activity. Quantitative electroencephalography (QEEG) is one of the key complex technologies utilized in psychopharmacology for this purpose. However, conventional approaches for EEG analysis used in clinical practice are not suitable for studying temporal structure of brain activity. To overcome this limitation, and in order to reveal dynamic and temporal characteristics of brain activity, the advanced analysis of EEG micro-structure should be used.

Key words: brain dynamics, EEG micro-structure, functional connectivity, lorazepam, mental disease, metastability, psychiatry, psychopharmacology, psychotropic drugs, temporal activity.

Abbreviations:
ERD/ERS – event related desynchronization / event related synchronization
ERP – event related potential
GABA – gamma amino butyric acid
GFP – global field power
MEG – magnetoencephalography
QEEG – quantitative electroencephalography

1. Introduction

Recent advances in basic brain and neuro-medical sciences have inevitably led researchers to a new understanding of brain and mental health – at all levels of brain organization it is the balance of autonomy and connectedness that sustains health (Buchman, 2002; the Complexity and Dynamics of Human Health Conference supported by the European Commission, 2001). Consequently, disease is a process with a change in the *dynamics* from what is normal, rather than regularity or irregularity of those dynamics (Glass, 2001). Indeed, recent research emphasizes that the majority of brain disorders and psychiatric/mental problems are accompanied by disruption in the *temporal* structure of brain activity (Dawson, 2004), where this temporal structure could be either more irregular (uncorrelated randomness) or more regular (excessive order) than normal (Glass, 2001; Buchman, 2002). However, in general, the role of temporal and dynamic aspects in brain disorders and psychiatry is often ignored. Most current studies are designed in a way that they avoid the temporal structure of the phenomenon under investigation (VanRullen and Koch, 2003). On the contrary, other than temporal aspects of brain functioning have been intensively studied and discussed in an appropriate literature. Thus, the purpose of the present review was to emphasize the role and importance of metastable and temporal organization of brain activity for psychopharmacology.

2. Metastable regime and temporal organization of the brain

One group of evidence for this came from studying healthy subjects. It has been suggested that the operational elements of behavioral and mental activity in norm are originated in the periods of *short-term spatio-temporal patterns (metastable states)* in the activity of the whole brain and its individual subsystems (see reviews Kaplan, 1998; Fingelkurts and Fingelkurts, 2001; 2003). In this metastable regime (Fig. 1), the brain operates in a state that allows both integration and segregation of function (Friston, 1997; Bressler and Kelso, 2001): individual neuronal networks are dynamically balanced in their tendency to function autonomously and their tendency for coordinated activity (Bressler, 2003). Together, these processes reflect the temporal and spatial organization of the brain. Thus, the disruption in brain metastability and temporal dynamic is suggested as a contributing factor to the disorganization syndrome (which has long been deemed to be a condition of impaired cognitive association) in many psychiatric and brain diseases (Haig et al, 2000; Dawson, 2004). From this perspective, then, disorganization is viewed as *a disorder of the metastable balance* between large-scale integration and independent processing in the cortex, in favor of either independent or hyper-ordered processing (Bressler, 2003). As an example, one predicted

consequence would be that large-scale patterns of neural population coordination – to be measured in patients – would be diminished and disjointed, when compared to normals. This supposition was confirmed in the pilot studies with schizophrenic patients (Kaplan and Borisov, 2002). Generally, the wide range of mental illnesses is associated with temporal breakdown in the brain activity (Dawson, 2004). This strengthens the point that time is an important etiological factor underlying mental illness.

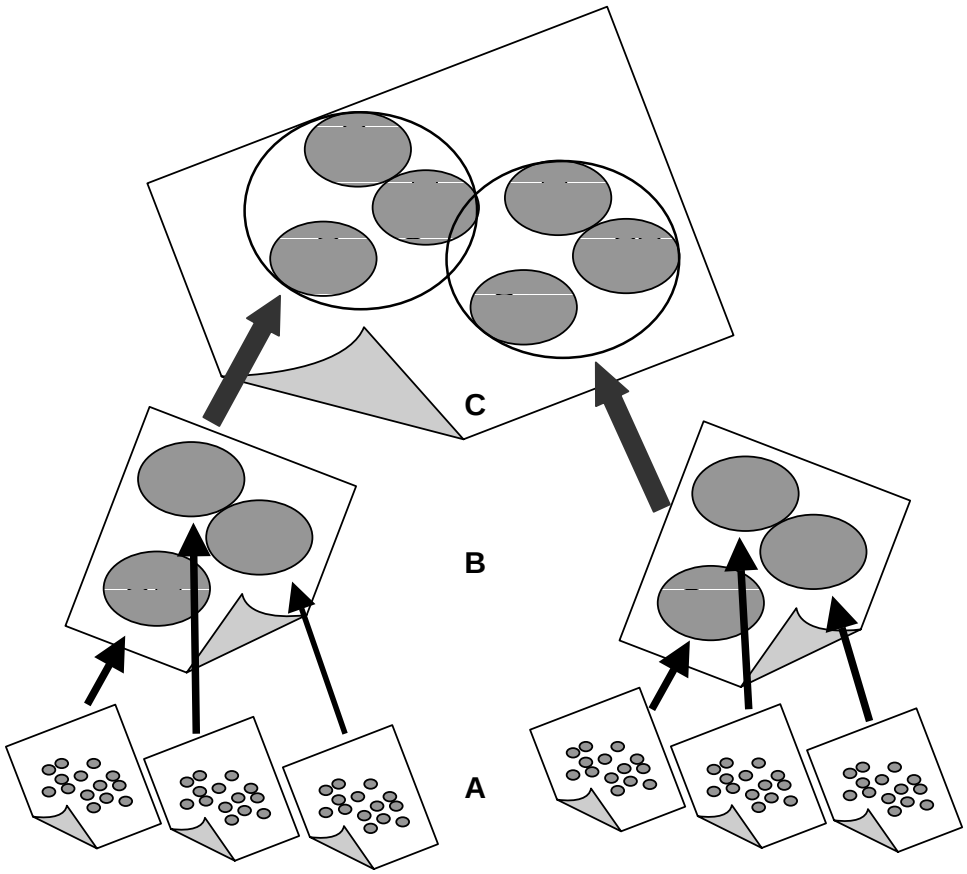

Figure 1. Schematic illustration of metastability principle of brain functioning. *A*, Individual neurons can quickly become associated (or dis-associated) by synchronizing their activity and giving rise to transient assembles. Each of these functional assembles represent discrete elemental brain operations or local microstates. *B*, The temporal synchronization of the activity of several such neuronal assemblies gives rise to operational modules, which characterized by a new level of brain abstractness – metastable brain states. *C*, Operational modules may be further synchronized (on the other temporal scale) to form new operational modules of even larger abstractness from the initial brain state. Also the reverse process is possible – when complex operational modules is decomposed to several simpler ones. For a complete argumentation, see Fingelkurts and Fingelkurts, 2003.

Taken together, these findings and analytical studies suggest that the future of psychopharmacology lies in its ability to design such psychotropic drugs, which can *restore the normal* temporal structure and metastable organization of brain activity. This approach seems more physiologically adequate to integrative, nonstationary and self-organized nature of brain processes and fits with a new understanding of the dynamical nature of brain diseases, where *"lesions in time"* become more evident especially at earlier stages of disease, than *"lesions in structure"* (Tirsch et al., 2004). In this context, it is important to study *how* different brain and mind pathologies alter the temporal structure and metastable regimen of brain activity and *how* different psychotropic drugs can modify temporal structure of brain activity in healthy subjects and patients.

3. Pharmaco-electroencephalography

Quantitative electroencephalography (QEEG) is one of the key complex technologies utilized for this purpose. QEEG scanning is a computerized statistical technique used to measure objectively precise electrophysiological activity in particular regions of the brain and relations between them (Duffy et al., 1994). Unfortunately, conventional approaches for EEG analysis usually used in the clinical practice are not suitable for studying temporal structure of brain activity. The reason for that is multifold: (i) Spectral EEG parameters are usually derived from averaged EEG power spectra, based on extended periods of time and/or broad fixed frequency bands for a specific lead. However, the averaging of the EEG signal masks the *dynamic* and *temporal* structure of EEG (Fig. 2), and often may lead to ambiguous data interpretation (Fingelkurts et al., 2003a). (ii) It is well known that an EEG signal is extremely *NONstationary* (Fell et al., 2000). However, invariants usually used in EEG studies, such as the mean spectrum, average ERP and ERD/ERS, coherency, fractal dimensions, Lyapunov exponents and others have a sense only for *stationary* dynamics (Landa et al., 2000). Thus, regardless of how powerful or statistically significant the different estimations of these measures may be, there might be difficulties in the meaningful interpretation of these if they are not matched to their piecewise stationary structure (Fingelkurts et al., 2002). (iii) Practically all existed measures of brain functional connectivity do not directly estimate metastability and have several limitations in that they do not take into account the nonstationary nature of the EEG data, require long periods of analysis, and use linear mathematical models of the signal which, for the brain, is not typically the case (Landa et al., 2000).

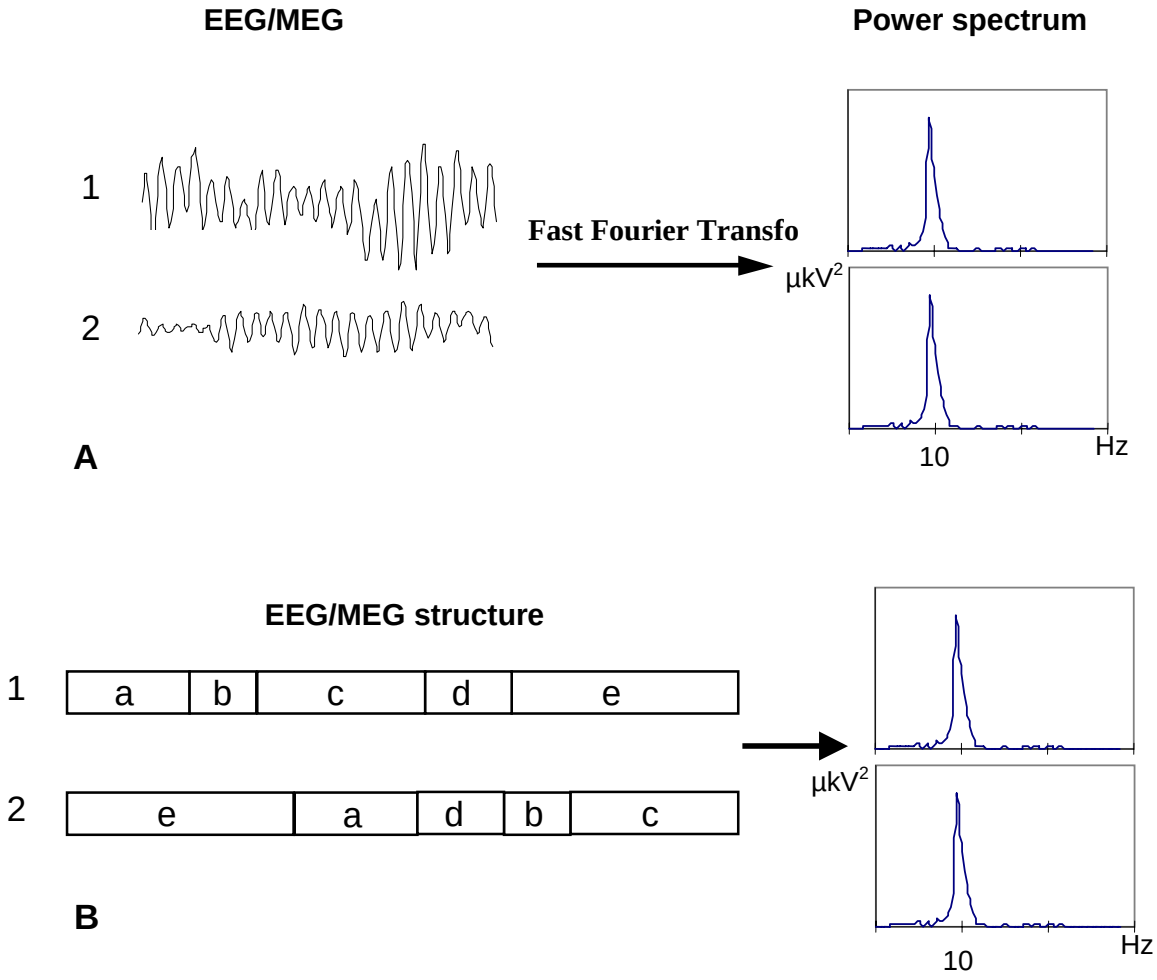

Figure 2. Schematic illustration of the averaging procedure for obtaining the EEG/MEG power spectrum or other characteristics. 1 and 2 are EEG/MEG signal with different temporal structure; however, the calculation of the mean power spectrum for these signals leads to identical results (*A*). The average power spectrum of a signal predominantly reflects an influence of high-amplitude segments of the EEG/MEG and the low-amplitude ones may be totally obscured. Different temporal structure of the signals 1 and 2 may contain the same set of elemental blocks; mean characteristics of such signals would be virtually the same (*B*).

4. Micro-structural EEG analyses

In order to overcome the numerous limitations of conventional EEG analysis based on averaging procedures, and to reveal *dynamic* and *temporal* characteristics of brain activity, the advanced analyses of EEG (or MEG) *micro-structure* were introduced (McEwen and

Anderson, 1975; Barlow, 1985; Lehman et al., 1987; Jansen and Cheng, 1988; Jansen, 1991; Kaplan, 1998; Hilfiker and Egli, 1992; Inouye et al., 1995; Koenig et al., 1999; Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2001; Durka et al., 2002; Fingelkurts et al., 2003a,b,c,d). These approaches include either fixed-interval or adaptive segmentation of the signal under investigation. Adaptive segmentation in its turn consists of (i) parametric segmentation based on autoregressive models (Bodenstein and Praetorius, 1977; Bodunov, 1985; Gath et al., 1992) or on scaling models (Deistler et al., 1986), and (ii) nonparametric segmentation (Michael and Honchin, 1979; Skrylev, 1984; Creutzfeldt et al., 1985; Shishkin et al., 1997; Fell et al., 2000). Segmentation procedures allow revealing the micro-structure of local EEG/MEG signals, where each quasi-stationary segment corresponds to the local stabilized miscrostate (Fig. 3 A, B). Similar piecewise stationary structure of the EEG/MEG signal has been found also for the whole biopotential field, resulting in the sequence of distinct microstates (segments of EEG/MEG field) of the whole brain (Lehmann, 1971, 1991; Lehmann et al., 1987). More recent technique for estimation of brain microstates includes measure of brain metastability by means of synchrony between local segmental EEG/MEG descriptions (Fig. 3 C; Kaplan et al., 1997; Fingelkurts and Fingelkurts, 2001; 2004). These approaches allow revealing the (i) individual microstates of various types in accordance with the number of stationary EEG/MEG segments (either local or of the whole brain field); (ii) relative presence of the individual EEG/MEG segments of each type and the peculiarities of their alternation in the analyzed signal; (iii) mean duration of each microstate (EEG/MEG segment); (iv) appearing of the new types of microstates and disappearing of the existing ones. These variables can then be further analyzed as function of the experimental condition or pharmacological influence. It is obvious that psychopharmacological agents may alter one or many of these variables in different manner without changes in averaged characteristics of the signal.

Generally, the techniques within the micro-structural frame of analysis are very sensitive to temporal structure of the EEG-signal, account the nonstationary nature of this signal, do not contain averaging techniques, and have special tests for non-random/non-occasional nature of the signal. These techniques provide new insights into the nature of human brain functioning in the norm and pathology (Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2001) and under the influence of psychotropic drugs (Kaplan et al., 1996; Fingelkurts et al., 2004a,b). Indeed, the intimate dynamic micro-structure of the EEG is rich in information on the underlying cellular and intercellular processing, brain states, localization, forms of cooperativity and the stages of brain development (Bullock, 1997). Finally, the methods which are sensitive to dynamical metastable and temporal properties of EEG permit researchers,

probably for the first time, to monitor and design psychotropic drugs which should restore an optimal range of metastability and temporality in the brain (as an example for development of a new psychotropic drug, see Kaplan et al., 1996). Of special interest in this context is the suggestion that cognition is intrinsically temporal (Shanon, 2001) and the temporal organization of consciousness is an important phenomenon in clinical assessment and treatment planning (Dawson, 2004).

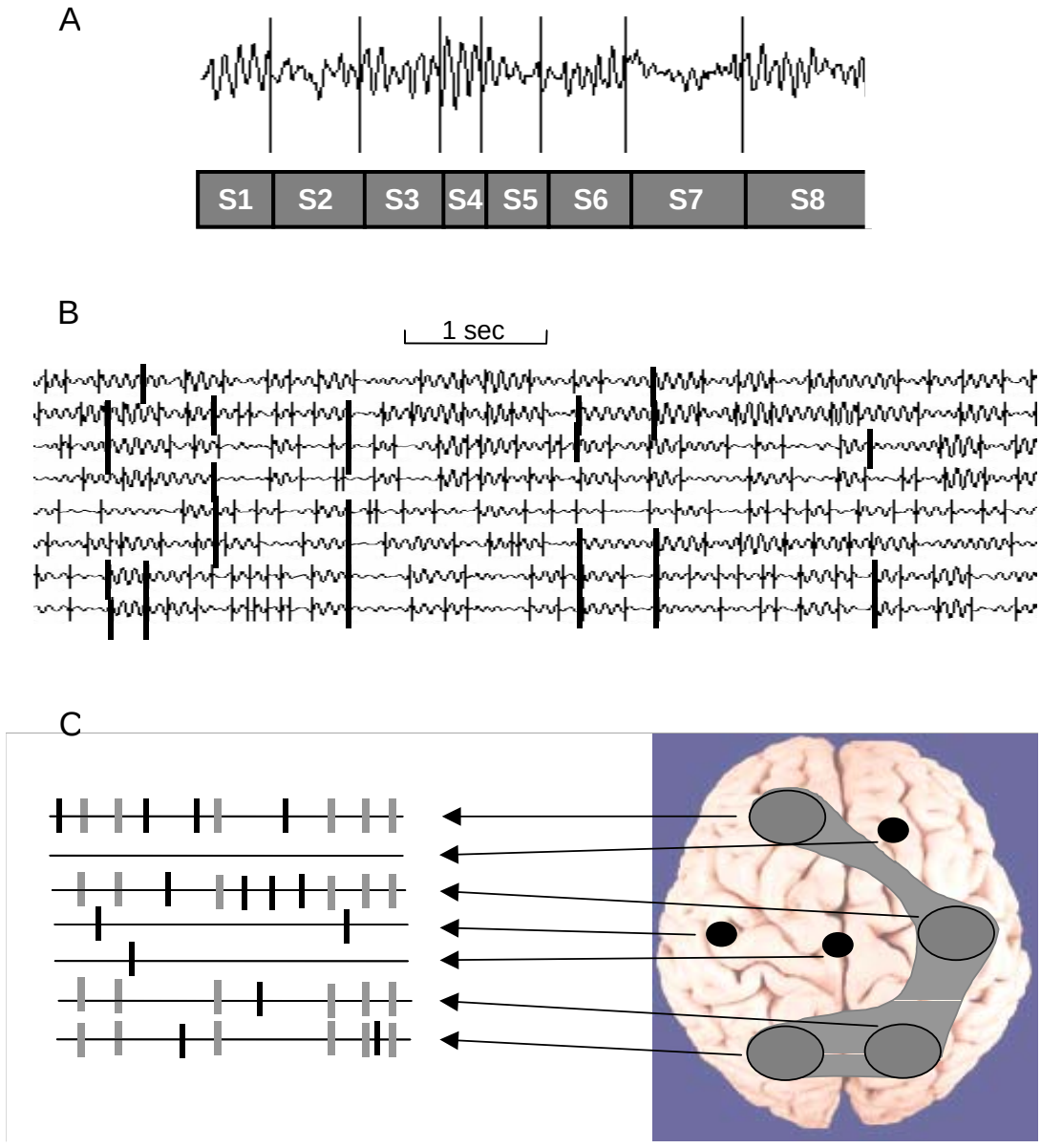

Figure 3. EEG/MEG segmentation (modified from Fingelkurts et al., 2004. © Int. J. Neuroscience). *A*, Piecewise stationary structure of EEG/MEG signal may be presented as a result of "gluing" of quasi-stationary segments with different probability characteristics (Fell et al., 2000). *S1*, *S2*, …*S8* – sequence of EEG/MEG segments. *B*, As a typical example, 8 EEG channels filtered in alpha frequency band with automatically detected boundaries (shown as vertical lines) between quasi-stationary segments are presented. It can be seen that some segments' boundaries in different EEG channels appeared simultaneously (shown as thick vertical lines). *C*, Metastable spatial-temporal pattern – operational module (scheme). In the result of operational synchrony process, the metastable brain states are emerged which accompany the realization of brain complex macrooperations (Fingelkurts and Fingelkurts, 2001; 2003). Seven schematic EEG/MEG channels (horizontal lines) with automatically detected boundaries (shown as vertical lines) between quasi-stationary segments are presented. Temporally synchronous boundaries between different EEG/MEG channels are shown as thick vertical lines. Exactly these EEG locations form the operational module (grey shape on the cortex background).

5. Application of micro-structural EEG analyses in psychopharmacology

Currently, the usage of some of these new approaches conform the idea that psychotropic drugs (in particular benzodiazepines) may significantly modify temporal structure and alter metastability of brain activity in healthy subjects. We will show only few examples. To study the effects of a single-dose (30 μg/kg) administration of the $GABA_A$ agonist lorazepam in a randomized, double-blind, cross-over, placebo-controlled study on the temporal characteristics of EEG/MEG dynamics, an *adaptive classification analysis* of the individual short-term spectral patterns was used (Fingelkurts et al., 2004a). Short-term power spectra were computed from a long EEG/MEG time series and then classified using a set of reference spectra; subsequently, the relative occurrence of each spectrum class was determined for each electrode, subject and condition. It was demonstrated that known (classical) lorazepam effect was typical for only 40% of a given EEG. Generally, lorazepam administration significantly reorganized the *microstructure* of EEG/MEG signal. Thus, lorazepam prolonged temporal stabilization periods of the particular oscillatory states suggesting a reduction of brain information processing. Additionally, the analysis showed that the brain "maintained" the stabilization period of neural activity for lorazepam between 2.8 and 7.5 sec, whereas for placebo this range was somewhat narrower: 3.6–6.7 sec. Moreover, for placebo, all EEG/MEG segments with fast-theta, delta-alpha, fast-theta–alpha and alpha activity were characterized by larger maximum periods of temporal stabilization than for lorazepam. At the same time, for lorazepam, all EEG/MEG segments with delta, slow-theta, delta–slow-theta, delta-beta and

with polyrhythmic activity were characterized by larger maximum periods of temporal stabilization than for placebo. In contrast to classical EEG analysis, micro-structural analysis demonstrated also that lorazepam caused no increase power in the independent beta rhythm. It was proved in the modeling test that the observed in classical studies effect of EEG beta rhythm increase is a "virtual" result of averaging procedures (Fingelkurts et al., 2004a). This suggests that *temporal* EEG/MEG characteristics may provide novel additional information on drug effects.

Another approach holds the analysis of the large-scale functional connectivity and metastability in the cortex during lorazepam inhibition influence through the new *measure of EEG structural synchrony*. This measure estimates simultaneous occurrence of the rapid transitive moments in on-going EEG generated by different brain locations – observed as sharp amplitude changes in multichannel EEG recording. It has been shown that the number of functional connections in the cortex and the strength (actual values of the measure) of these connections significantly increased under the lorazepam administration (Fingelkurts et al., 2004b). In the same study, it was found that different-sized neuronal populations (indexed by the EEG amplitude within discrete EEG segments) in alpha and beta frequency bands performed differently under lorazepam when compared with placebo (Fingelkurts et al., 2004c): For the *alpha-generated neuronal populations* it was observed that large neuronal populations exhibited a total decrease in size, functional life span (duration of EEG quasi-stationary segments), and stability (coefficient of amplitude variability) under the lorazepam administration when compared with placebo. In contrast to large neuronal populations, small populations performed the reduction in size only in several cortical areas (posterior and occipital) under the lorazepam administration, thus been stable. For the *beta-generated neuronal populations* it was found that none of the neuronal populations (large-, medium- and small-sized) increased the beta-amplitude under lorazepam administration when compared with placebo. At the same time, all neuronal populations prolonged their functional life span. This data probably reflects the prolongation of inhibitory neuronal operations and thus seems to be responsible for the well-established slowing of the cognitive performance under the lorazepam administration (Fingelkurts et al., 2004c). Generally, analysis showed that the rules of cooperation and competition act on a local scale (neuronal populations), however, the phenomenon of self-organization is, in fact, the emergence of long-distance synchrony between transient neuronal assemblies governed by globally ordered metastable states. Functionally distinct regions of the brain are considered to operate as a series of operationally synchronized modules – metastable states (Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2003;

2004), and any change in a function of a specific region is associated with a gain or loss of operational synchrony processes (Kaplan, 1998; Fingelkurts and Fingelkurts, 2001).

The currently available other studies on EEG microstate data (Lehman et al., 1987) stress also the importance of microstructural techniques. The segmentation procedure in this research was done as following: For each epoch of the signal, the global field power (GFP) was calculated. GFP describes the degree of variability of the potential map at each sampling point (Lehman et al., 1987). Only points in time corresponding to maximum GFP were taken for map constructions and segmentation. In all these maps, the locations of the positive- and negative-field extreme potential were defined as field descriptors (orientation of the field). If field descriptors change significantly over time in a new position, a new or 'different segment' is defined. In a study of neuroleptic-naïve, first-episode, acute schizophrenic patients, the duration of EEG microstates of a particular class was reduced (Koenig et al., 1999). Chronic schizophrenic patients with positive symptomatology demonstrated similar results (Strelets et al., 2003). The EEG microstates with asymmetric configuration have been shown to be dominant in patients with dementia (this dominance increase with increasing severity of the disease) (Koenig et al., 2002b). In the study of EEG microstates during the single doses of piracetam (2.9, 4.8, and 9.6 g Nootropil UCB and placebo) in a double-blind study of normal young volunteers it was shown that the dominant EEG microstates consist of a generally anterior-posterior field orientation (Lehmann et al., 1993). Recently, the normative database of EEG microstates has been published (Koenig et al., 2002a).

The studies have been reviewed here show that application of micro-structural approaches to the pharmacological data allows the detection of clear changes in the temporal and metastable structure of EEG/MEG signal as a function of psychotropic drug and brain pathology. This kind of knowledge is inaccessible through the "timeless" averaging procedures. Further investigation of temporality and metastability in patients under psychopharmacological influence is important to reveal whether the particular drug is able to restore the normal temporal and metastable structure of EEG/MEG. This knowledge will help to design the drugs which would be able to do so in a precise manner.

6. Conclusion

Although cited research provided definitely the starting point in studying the effects of psychotropic drugs by using the micro-structural EEG/MEG methods, and much more systematic research and data accumulation are needed, the practical importance of this research stream is straightforward. It is to be hoped that the usage of micro-structural approach for

EEG/MEG analysis may help to develop a more rational psychopharmacology, where a deeper neurophysiological and neuropharmacological understanding of dynamical and metastable mechanisms of brain functioning is very important and could eventually lead to creation of a new generation of psychotropic drugs and therapeutic procedures.

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