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Alpha Rhythm Operational Architectonics in the Continuum of Normal and Pathological Brain States: Current State of Research

Andrew A. Fingelkurts* and Alexander A. Fingelkurts

BM-Science – Brain and Mind Technologies Research Centre, Espoo, Finland

Abstract

In the present study, we explore the operational architectonics of alpha activity in different normal and pathological brain states. Aggregated analysis of a set of diverse previously conducted EEG/MEG experimental studies was performed within the same methodological and conceptual framework. It was shown that the characteristics of short alpha activity periods (segments), as well as the spatial structural synchrony of alpha activity, changed considerably in accordance with the type of brain functional state, stimulation, cognitive task, pharmacological influence, and the type of pathology. The results of this study suggest that particular neurophysiological pattern(s) of cortex alpha activity indicates a resting state network, which is characterized by well-defined structure in both the temporal as well as the spatial domain. The optimal functional state of the brain depends upon a delicate metastable balance between local specialized processes and their global integration. Excess or lack of either component would be a deviation from the optimal condition and can lead to pathology. The fact that all observed results were significantly different from surrogate EEG data reflects a non-occasional nature of spatio-temporal dynamics in the operational architectonics of alpha activity. Better understanding of the specific ways in which disrupted dynamics of different characteristics of alpha-generating neuronal assemblies (and their functional connectivity) may underlie neuro/psychopathology might suggest new targets for therapeutic agents.

Key words: alpha rhythm, EEG, MEG, brain operations, metastability, neurophysiological pattern, resting state, default mode, synchronization, functional connectivity, psychopathology.

1. Introduction

This paper presents an overview of the current state of research in operational architectonics of alpha rhythm followed by an aggregated analysis of a set of diverse previously conducted EEG/MEG experimental studies of alpha activity in the continuum of normal and pathological brain states. In this study we look at the individual results of different studies within the same theoretical framework – Operational Architectonics of brain functioning (see Section 2) – instead of looking at different results of each individual study within the scope of each study. Such methodological approach

enables us to reveal peculiarities and generalities of operational architectonics of alpha rhythm across continuum of different states, conditions and tasks which cannot be seen within individual studies.

The brain is a system within which billions of nerve cells (neurons) in discrete local areas work in a massively parallel fashion, each on its individual tasks without any centralized supervision. At the same time, these neurons are able to self-coordinate their activity by forming so-called functional neuronal assembles and a hierarchy of such assemblies in order to cognitively and/or phenomenally (subjectively) present sensual inputs as coherent perceptions of the world, create internal images and conscious thoughts (for the recent review, see Fingelkurts et al., 2009; see also Gray & Singer, 1989; Singer, 1993; Eichenbaum, 1993; Varela, 1995; Edelman and Tononi, 2000; Bressler and Kelso, 2001; Varela et al., 2001; Triesch and von der Malsburg, 2001; Fingelkurts and Fingelkurts, 2001, 2005; Bressler, 2002; Stam, 2006; Freeman, 2007).

A neuronal assembly is a set of neurons that are able to synchronize their sub-threshold oscillations (excitatory/inhibitory postsynaptic potentials – EPSPs/IPSPs), leading to a coherent activity of the whole assembly (Nunez, 2000; Buzsaki, 2004). This notion goes back to Hebb (1949); however, the classical (Hebbian) neuronal assemblies are too slow and may not be suitable for cognitive operations (for a discussion, see Fingelkurts and Fingelkurts, 2005).

Modern understanding of neuronal assemblies stresses their functional nature, which is at scales both coarser and finer compared to classical assemblies (von der Malsburg, 1999). The idea is that large masses of neurons can quickly become functionally associated or disassociated, thus giving rise to *transient* assemblies (Friston, 2000; Triesch and von der Malsburg, 2001), which are thought to execute the basic operations of informational processing (Kaplan and Borisov, 2003; Averbeck and Lee, 2004). The overall pattern of neuronal assemblies' correlated activity persists over some temporal interval, is very sensitive to fluctuations, and it can be swiftly rearranged during rapid transitional periods (Kirillov and Makarenko, 1991). As has been demonstrated in vitro, the intervals of correlated activity are manifested in the oscillatory waves, which are the result of neuronal clustering (Leznik et al., 2002; Buzsaki, 2004). Thus, the behavior of neuronal assemblies is highly dynamic, most likely nonlinear and can be traced through EEG oscillations (Freeman and Vitiello, 2005; Kaplan et al., 2005; Stam, 2006; Freeman, 2007).

Each neuronal assembly individually presents only a partial aspect of the whole object/scene/concept (Singer et al., 1997), while the wholeness of 'perceived' or 'imagined' is brought into existence by joint (synchronized) operations of many functional and transient neuronal assemblies in the brain (for extensive discussion, see Fingelkurts et al., 2009; see also Bressler and McIntosh, 2007). The recombination of neuronal assemblies in new configurations makes it possible

to present a practically infinite number of different qualities, patterns, objects, scenes and concepts – even those, with which we have never been acquainted before (Fingelkurts and Fingelkurts, 2004).

The synchronization of dynamical neuronal assemblies into more complex spatial-temporal patterns is also highly dynamical (Stam, 2006). Therefore, both neuronal assemblies, as well as their complex constellations can be conceived of as dynamical systems. Any dynamical system is characterized by its *state* and *dynamics* (Stam, 2006).

The *state* of a dynamical system is a complete description of its present characteristics. Although, a "complete description" may not always be directly obvious, in practice, what is required, is that we choose a number of observables (measurable variables) which relate to all relevant properties of the system (Stam, 2006). In the context of the present paper we are interested in the dynamics of neuronal assemblies and synchronization among them, therefore the important and relevant variables would constitute *size*, *life-span* and *stability* of neuronal assemblies. Additionally, we are interested in knowing (a) whether neuronal assemblies tend to *grow* or *disassemble* with time, (b) the *speed* of these processes and (c) what is the *number* and *strength* of functional connections among neuronal assemblies.

Dynamics can be defined informally as the systematic change in the process of a system over time (Stam, 2006). Therefore, our interest lies in tracing the dynamical changes in the neuronal assemblies and in the interrelations among them along different normal and pathological brain states.

Both, the activity of neuronal assemblies and their dynamical interactions are "hidden" in the complex nonstationary structure of biopotential (electroencephalogram, EEG) brain field (for the reviews, see Fingelkurts and Fingelkurts, 2001, 2004, 2005; Kaplan et al., 2005).

2. EEG, neuronal assemblies and their operations

EEG (as well as magnetoencephalography, MEG) is a method well-suited to study the behavior of neuronal assemblies and their interactions within large-scale networks, because it measures a highly organized macro-level electrophysiological phenomenon in the brain, which captures the operations of large-scale cortical networks and which is remarkably correlated with both behavior and cognition (Nunez, 2000; John, 2002; Freeman, 2003; Kaplan et al., 2005; Fingelkurts and Fingelkurts, 2005), and eventually with consciousness (Fingelkurts et al., 2009).

One important feature of EEG signal is the presence of more or less regular oscillations in different frequency bands. The "oscillatory" nature of EEG signal has given rise to a classification of EEG activities into different frequency bands (Stern and Engel, 2005): delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30 Hz and higher). These basic EEG bands are

assumed to reflect different functional processes in the brain (Klimesch, 1999b; Steriade, 2000; Basar et al., 2000, 2001a,b, 2004; Fingelkurts et al., 2003a, 2007a) as well as the activity of different neuronal assemblies (Buzsaki, 2004; Buzsaki and Draguhn, 2004).

EEG waves recorded from the scalp are integrated excitatory and inhibitory post-synaptic potentials (EPSPs/IPSPs) of neuronal membranes. Since they reflect extracellular currents caused by synchronized neural activity within the local brain volume (John, 2002), the EEG signal within *quasi-stationary (nearly stable) segments* can be presented as the envelope of the probability of non-random coherence (so called a "common mode" or a "wave packet," Freeman and Vitiello, 2005) in the neuronal masses near to the recording electrode (Fingelkurts and Fingelkurts, 2008). Even though the cells that comprise an assembly under the electrode may be spatially intermixed with cells in other neuronal assemblies performing different computational tasks, they are separated by different time-scale coherence (EEG frequencies variability, Basar, 2005). Therefore, it is possible to consider one EEG quasi-stationary segment as the *single event* in the EEG-phenomenology, which reflects the *operation* of a related neuronal assembly (Fingelkurts and Fingelkurts, 2001).

Within the duration of one such segment, the neuronal assembly that generates the oscillations is supposed to be in the steady quasi-stationary state (Brodsky et al., 1999). The *rapid transition processes* (RTP) occurring in the continuous EEG activity mark the boundaries between quasi-stationary segments for this activity. Because the major contributor to temporal modulation of the variance and power of the EEG signal is the sharp change in its amplitude (Truccolo et al., 2002), the identification of RTPs can be reduced to detecting the moments of rapid statistically significant decrease or increase of EEG amplitude (see Aim and methodological aspects section). The transition from one segment to another reflects the changes of the neuronal assembly microstate or changes in the activity of the two or more neuronal assemblies (Fingelkurts and Fingelkurts, 2001, 2005, 2008; Kaplan et al., 2005; Freeman and Vitiello, 2005). This is the *first (low) level* of **Operational Architectonics framework** of brain functioning (for a complete description, see Fingelkurts and Fingelkurts, 2001, 2004, 2005, 2006, 2008; Fingelkurts et al., 2009).

The *second (high) level* of Operational Architectonics describes the temporal synchronization of different brain operations (*operational synchrony*) simultaneously executed by different local and transient neuronal assemblies. Such synchronization of operations gives rise to a new level of brain abstractness – *metastable brain states* (Fingelkurts and Fingelkurts, 2004). These metastable brain states or functional *Operational Modules* (OM), as we name them, underlie the realization of brain complex (and composite) macro-operations: cognitive percepts, phenomenal objects, and reflective thoughts (for a review, see Fingelkurts et al., 2009). At the EEG level the OM phenomenon is expressed via synchronization of EEG quasi-stationary segments (indexed by Structural Synchrony,

ISS) obtained from different brain locations (Fingelkurts and Fingelkurts, 2001, 2005) (see Aim and methodological aspects section).

Even though all frequency bands of the human EEG may have some functional significance and could be linked with specific processes (Knyazev, 2007), the most pronounced (and studied) EEG rhythm in the consciously waking and healthy adult is the alpha rhythm. In this paper we will limit our analysis only to the dynamics of alpha activity[1]. Below is a brief explanation of why we choose alpha rhythm for our analysis.

3. Significance of Alpha rhythm

Alpha rhythm was first observed and described by a German psychiatrist, Hans Berger (1929). Since then it has been estimated that 90% of people have alpha activity in resting but awake EEG and in 60% of people EEG alpha rhythm dominates (Stern and Engel, 2005). Therefore, alpha activity is the most common component of the human brain's electrical activity (Basar and Guntekin, 2006), while theta dominates in the EEG of lower mammals (Sainsbury, 1998) and delta in the reptilian EEG (Gonzalez et al., 1999). Alpha band has the best test-retest reliability if compared with other EEG bands and, therefore, it can be treated as an intra-individually stable trait (Gasser et al., 1985). Additionally, quite often minor pathological abnormalities first manifest themselves by subtle changes exactly in the alpha rhythm (Debener et al., 2000; Knyazev et al., 2005). One of the important indicators of abnormality is a slowing of the alpha peak frequency or alpha activity asymmetry (Jelic et al., 2000; Hughes and Crunelli, 2005; Pogarell et al., 2006). For example, convergent evidence from numerous electrophysiological studies on major depression stresses a key role for the anterior alpha rhythm asymmetry—the so-called cognitive anterior model of depression (for review, see Coan and Allen, 2004; Davidson, 2004). Decrease in the alpha activity power was considered as one of the most pronounced changes in the EEG of patients with schizophrenia (Morihisa et al., 1983; Sponheim et al., 2000; Strelets et al., 2003). It has been well-documented that the most consistent changes in EEG of opioid addicts and during early abstinence were also observed in alpha frequency range (for the review, see Polunina and Davydov, 2004). And finally, in the context of the current interest in the subject of neurophysiological constituents of consciousness

[1] When the experimental data on the operational architectonics of other frequency bands across different brain states, experimental conditions, and brain pathologies will be accumulated, they will be integrated with the current data on the alpha frequency rhythm and will be published in a separate article. Readers interested in an in-depth discussion of operational architectonics of other but alpha frequency bands (however, in a limited number of brain states or pathologies) are advised to refer to the following publications: delta activity in hypnosis study (Fingelkurts et al., 2007d) and sleep study (not published); theta activity in major depression study (Fingelkurts et al., 2007b), hypnosis study (Fingelkurts et al., 2007d) and sleep study (not published); beta activity in audio-visual perception study (Fingelkurts et al., 2003b), opioid dependence study (Fingelkurts et al., 2006) and abstinence study (Fingelkurts et al., 2007c); and gamma activity in hypnosis study (Fingelkurts et al., 2007d) and sleep study (not published).

(Revonsuo, 2006), alpha activity which has been a major and a most stable component of the EEG may provide a proper window into the relation between neurophysiology and consciousness (Shaw, 2003).

Classically, alpha rhythm has been considered as an "idling-rhythm" of the brain, although recent studies signify that alpha is more than just an "empty-running" rhythm (for functional correlates see Klimesch, 1999a; Basar et al., 2001a; Nunez et al., 2001), which may accompany psycho-physiological and top-down processing events (Lehmann, 1989; Von Stein and Sarnthein, 2000). Indeed, it is evident that if one accepts the classical model that alpha is blocked in those areas of the brain that are involved in information processing then it will be difficult to find any consistent patterns except for very simple types of mental activity (Shaw, 2003; see also Knyazev, 2007).

Rhythmic activity in this frequency band (8-13 Hz) is most likely an emergent property of interacting thalamic, thalamo-cortical and cortical networks (Lopes da Silva et al., 1980; Klimesch, 1999a; Nunez et al., 2001). Even though some researchers describe alpha as a single widespread activity, while others distinguish separate alpha generators, the majority consider scalp recorded alpha activity as the summation of many localized alpha generators which are either synchronized or independent depending on the time and task (for the review see Klimesch, 1999a,b; Nunez et al., 2001; Shaw, 2003; Knyazev, 2007).

Recently, alpha activity has been associated with the so called "default mode" of brain functioning, when the presence of functionality is ongoing in the *resting state* and attenuated when resources are temporarily reallocated during goal-directed behaviors (Raichle et al., 2001). The alert eyes closed resting state is very much an active state, during which there is a dynamic circulation of neural activity in connected cortical, reticular and thalamo-cortical loops (Thatcher et al., 1994).

4. Resting state

The resting brain state constitutes a *reference baseline*, relative to which all cognitive and physiological brain states should be considered. This view dominated electrophysiological studies for a long time; however, the concrete evidence came from the extensive work of Raichle et al. (see Raichle and Snyder, 2007). Indeed, the resting human brain consumes 20% of the body's energy (even though it represents only 2% of total body mass), most of which is used to support ongoing neuronal signaling (Lennie, 2003; Shulman et al, 2004; Raichle and Mintun, 2006). On the contrary, task-related increases in neuronal metabolism are usually small (less than 5%) when compared with the large resting energy consumption (Raichle and Mintun, 2006). Therefore, if one hopes to

understand how the brain operates, he/she must take into account the component that consumes most of the brain's energy: spontaneous neuronal activity during resting brain state.

Even though not universally accepted (Morcom and Fletcher, 2006), it has been proposed that the brain's default mode during resting state supports an internal "narrative" (Gusnard et al., 2001), the "autobiographical" self (Buckner and Carroll, 2007), "stimulus independent thought" (Mason et al., 2007), "mentalizing" (Frith and Frith, 2003) and "self-projection" (Buckner and Carroll, 2007). The latter includes aspects of prospection, episodic memory, and "theory of mind" (Flavell, 1999).

Patterns of spontaneous activity during rest state could thus serve as a functional reference baseline, providing a priori hypotheses about the way in which the brain will respond across a wide variety of task conditions and/or brain states.

5. Aim and methodological aspects

The aim of the present study was to explore the operational architectonics of alpha activity in different normal and pathological brain states. For this purpose we have performed aggregated analysis (do not mix with meta-analysis) of a set of diverse previously conducted experimental studies within the same methodological and conceptual framework. These studies are: a) audio-visual perception study (Fingelkurts et al., 2003b), b) working memory study (Fingelkurts et al., 2003c), c) benzodiazepine study (Fingelkurts et al., 2004a,b), d) sleep study (not published), e) major depression study (Fingelkurts et al., 2007b), f) opioid dependence study (Fingelkurts et al., 2006), g) abstinence study (Fingelkurts et al., 2007c), and h) schizophrenia study (Borisov et al., 2005a,b). The rationale for such integration is grounded in several premises: Each research program produces large amounts of information during years. Researchers need efficiently integrate existing information by combining the results of many different studies to arrive at a better estimate of empirical truth. Further, such methodological approach establishes whether scientific findings are consistent and can be generalized across populations, settings, conditions, states or tasks and treatment variations, or whether findings vary significantly by particular subsets. Finally such aggregated analysis limits bias of individual studies and, hopefully, will improve reliability and accuracy of generalized conclusions.

All experiments were undertaken with the understanding and written consent of each subject, with the approval of the appropriate local ethics committees, and in compliance with national legislations and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki).

Readers interested in an in-depth discussion and the technical details of each of these studies are advised to refer to the provided references. Here we shall briefly describe some central aspects of each study and characteristics of the computational techniques used.

5.1. Audio-visual perception study (see details in Fingelkurts et al., 2003b)

A 306-channel MEG was recorded for 7 healthy, right-handed adult subjects (mean age 28) during the auditory, visual and audio-visual stimulation (talking face) using an oddball task.

The stimuli consisted of meaningless disyllables (vowel-consonant-vowel) uttered by a female speaker. Stimulus sequences consisted of frequent (p = 0.85) congruent stimuli (standards) and infrequent deviant congruent (p = 0.05) and incongruent (p = 0.05) stimuli for audio-visual stimulation. Target congruent stimuli (p = 0.05) were presented to be able to check that subjects were consciously attending to the stimuli. The visual and auditory stimulations contained only the relevant visual and auditory components of these stimuli respectively.

The magnetoencephalograms (MEGs) were recorded continuously in a magnetically shielded room with a 306-channel whole-head device. The data were digitized at 300 Hz. The passband of the MEG recordings was 0.06-100 Hz. About 100 responses of the subjects to each deviant stimulus and about 2000 responses to standard stimuli were collected. Gradiometer signals from 20 MEG locations which roughly correspond to the extended EEG 10-20 International system ($F_{7/8}$, F_z, $F_{3/4}$, $T_{3/4}$, $C_{5/6}$, C_z, $C_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, O_z, and $O_{1/2}$) were analyzed.

In this study we examined poststimulus MEG data (still face, no sound), which is assumed not to be influenced by any artifact of the stimulus-events themselves. Categorized data (poststimulus intervals) were extracted with respect to the preceding stimulus (belonging to post-standard, or post-deviant-congruent, or post-deviant-incongruent intervals). The output of this procedure was a sequence of concatenated MEG data, sorted stimulus-wise. In the end, the full MEG streams were split into 3 distinct groups for the following conditions: audio-visual condition; auditory condition, and visual condition.

These MEG data were included in the current analysis of EEG data based on the previous studies where it has been shown that EEG and MEG signals registered in parallel form the same subjects have practically identical composition of spectral characteristics and their percent ratio for both EEG and MEG (Fingelkurts et al., 2004c). Additionally it has been consistently demonstrated that spatial resolution of EEG might be compatible with MEG. It has been shown that EEG and MEG offer comparable spatial resolutions on the order of several millimeters (Cohen et al., 1990; Ingber, 1991).

For example, dipole localization accuracy of 7-8 mm for EEG and 3 mm for MEG has been demonstrated using a human skull phantom (Leahy et al., 1998).

5.2. Working memory study (see details in Fingelkurts et al., 2003c)

A 20-channel EEG was recorded for 9 healthy, right-handed adult subjects (aged 20–29) during the modified Sternberg's memory task. The memory set (encoding) consisted of four auditorily presented stimuli. The frame set (retrieval) size was kept constant and consisted of one stimulus.

The stimuli consisted of 24 auditory verbs (spoken with a female voice). A total of 192 four-verb memory sets were constructed such that each of the verbs had to occur with equal frequency and only once in the same memory set. In 50% of the cases, the frame set verb was among the previously presented four-stimulus block. In total, there were 192 trials, which were presented to the subjects in a pseudorandomized order. The experiment was designed in such a way that it was possible to test separately resting, waiting, encoding, keeping-in-mind, and identification short-term periods of the memory task.

In the present study 16 EEG channels ($F_{7/8}$, $F_{3/4}$, F_z, $T_{3/4}$, $C_{3/4}$, C_z, $T_{5/6}$, $P_{3/4}$, and $O_{1/2}$) were used for the analysis. Raw EEG signals were recorded with a frequency band of 0.3 to 70 Hz. The impedance of the recording electrodes was always below 5 kΩ. The full EEG streams were split into 5 distinct segments: resting period, waiting period, encoding period, keeping-in-mind period, and identification period.

5.3. Benzodiazepine study (see details in Fingelkurts et al., 2004a,b)

Eight nonsmoking healthy, right-handed human subjects (aged 20-29) participated in the study. Subjects underwent either lorazepam (Ativan® 4 mg/ml, Wyeth Lederle) 30 μg/kg or placebo (saline) injection in a randomized, double-blind, placebo-controlled crossover design study. The EEG recording was started 5 min after the infusion. Two sessions (lorazepam or placebo) were separated by 1 week.

Subjects underwent continuous 10 min (eyes closed and open condition 5 min each) EEG registration with 20 electrodes ($F_{7/8}$, F_z, $F_{3/4}$, $T_{3/4}$, $C_{5/6}$, C_z, $C_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, O_z, and $O_{1/2}$) according with International 10/20 extended system. The impedance of the recording electrodes was always below 5 kΩ. All EEG streams were split into four distinct groups: lorazepam-eyes-closed, lorazepam-eyes-open, placebo-eyes-closed, placebo-eyes-open.

5.4. Sleep study (not published)

Nine young subjects participated in the study. Six one-minute EEGs were recorded during Stage 2 and Stage 3 of NREM sleep during the first half of the night. The impedance of the recording electrodes was always below 5 kΩ. In the present study EEGs from 20 electrodes ($Fp_{1/2}$, $F_{7/8}$, F_z, $F_{3/4}$, $T_{3/4}$, C_z, $C_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, O_z, and $O_{1/2}$; the International 10/20 extended system) were analyzed.

5.5. Major depression study (see details in Fingelkurts et al., 2007b)

Twelve medication-free depressed outpatients (mean age 43 years, all right-handed) and ten sex- and age-matched nonsmoking healthy controls (mean age 42 years, all right-handed) participated in the study. All subjects underwent a Structured Diagnostic Interview (SCID) for DSM-III-R. All depressed outpatients met the DSM-III-R criteria for a major depressive episode. They also had a score of at least 18 on the 17-item Hamilton Depression Rating Scale (HAM) at the time of the study procedure (the group mean HAM score was 24). All controls were free from psychiatric illnesses and the mean HAM score for the control group was 0.5.

Subjects underwent EEG registration according to the International 10/20 extended system, 20 minutes in duration with eyes closed. The impedance of the recording electrodes was always below 5 kΩ. In the present study EEGs from 20 electrodes ($F_{7/8}$, F_z, $F_{3/4}$, $T_{3/4}$, $C_{5/6}$, C_z, $C_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, O_z, and $O_{1/2}$) were analyzed. EEG data were split into two distinct groups: “depressive” and “control.”

5.6. Opioid dependence study (see details in Fingelkurts et al., 2006)

The study included a total of 22 right-handed opioid-dependent patients (aged between 21 and 46 years) and 14 right-handed controls (men age 33 years). All patients had abused opioids for 4–26 years (mean 11 years). Self-reported daily dose was 0.05–2 g for intravenous administration of heroin and 2–32 mg for intravenous administration of buprenorphine. All 22 patients met DSM-IV criteria for opioid dependence, while healthy controls did not fulfill any criteria for DSM-IV disorders on Structured Clinical Interviews I and II. Neuropsychologic tests showed normal intelligence in all subjects.

The patients were investigated on the day of admission, and all had abused opioids within 12 h before EEG registration; the dosages were the patients’ usual dosages. None of the patients had a withdrawal syndrome at the time of EEG registration, as verified by a Gossop test. Each subject

underwent 5 min of EEG registration with eyes closed. The impedance of the recording electrodes was always below 5 kΩ.

In the present study EEGs from 20 electrodes ($F_{7/8}$, F_z, $F_{3/4}$, $T_{3/4}$, $C_{5/6}$, C_z, $C_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, O_z, and $O_{1/2}$) were analyzed. EEG data were split into two distinct groups: "opioid" and "control."

5.7. Abstinence study (see details in Fingelkurts et al., 2007c)

In the study 13 right-handed, opioid-dependent patients (mean age 32 years) and 14 controls (mean age 33 years) participated. All patients had abused opioids for 4–26 years (mean 10 years). Self-reported daily dose was 0.05–1.2 g for intravenous administration of street heroin and 2–16 mg for intravenous administration of street buprenorphine. All patients met DSM-IV criteria for opioid dependence, while all controls did not fulfill any criteria for any DSM-IV disorder.

At the time of the EEG assessment, patients had been abstinent for 12–15 days. The severity of withdrawal syndrome was verified by Gossop test. Each subject underwent 5 min of EEG registration with eyes closed. The impedance of the recording electrodes was always below 5 kΩ.

In the present study EEGs from 20 electrodes ($F_{7/8}$, F_z, $F_{3/4}$, $T_{3/4}$, $C_{5/6}$, C_z, $C_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, O_z, and $O_{1/2}$) were analyzed. EEG data were split into two distinct groups: "withdrawal" and "control."

5.8. Schizophrenia study (see details in Borisov et al., 2005a,b)

In this study 45 medication-free adolescents (mean age 12 years) with schizophrenic disorders (infant schizophrenia, schizotypical and schizoaffective disorders) with similar symptoms and 39 healthy adolescents (mean age 12 years) participated. The diagnoses of all patients were provided by qualified psychiatrists from the Mental Health Research Center of the Russian Academy of Medical Sciences.

Each subject underwent 1-2 min of EEG registration with 16 electrodes ($F_{7/8}$, $F_{3/4}$, C_z, $C_{3/4}$, $T_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, and $O_{1/2}$) during resting state with closed eyes. The impedance of each electrode was monitored for each subject with an impedance meter prior to data collection; this was always below 5 kΩ.

5.9. Signal data preprocessing

Epochs containing artifacts due to eye blinks, significant muscle activity and movements on EEG/MEG channels were automatically rejected. The presence of an adequate signal was determined by visual checking each raw signal on the computer screen after the automatic artifacts rejection.

Each EEG/MEG signal was bandpass-filtered (Butterworth filter of the sixth order) in the alpha (8–13 Hz) frequency band. Phase shifts were eliminated by forward and backward filtering. Additionally, because of the technical requirements of the tools that were later used to process the data, all EEG/MEG data were re-sampled with a converted sampling rate of 128 Hz. This procedure should not affect the results since 128 Hz sampling rate meets the Nyquist Criterion (Faulkner, 1969) of a sample rate greater than twice the maximum input frequency for the alpha activity and is sufficient to avoid aliasing and preserve all the information about alpha activity in the input signal. This method was considered sufficient since the sampling rate of the source signals was significantly higher practically in all studies (in some studies it was 128 Hz initially) than of the one required.

5.10. Estimation of the local functional interrelations

Local functional interrelations were estimated in two phases. At the first phase, the adaptive level segmentation of local EEGs/MEGs was performed by means of *RTPseg* tool (BM-Science, Finland). Each 1-min EEG/MEG epoch was segmented using method of identification of rapid transition processes (RTPs) in the EEG/MEG amplitude. This method is based on the automatic selection of level conditions in accordance with a given level of the probability of "false alerts" and carrying out simultaneous screening of all EEG/MEG channels (for detailed methodological description, see Fingelkurts and Fingelkurts, 2008). With this technique, the sequence of RTPs with statistically determined ($p < 0.05$, Student's t-test) time coordinates has been determined for each EEG/MEG channel individually for each 1-min EEG/MEG epoch. The theoretical concepts behind this analysis are described elsewhere (Fingelkurts and Fingelkurts, 2001, 2004, 2005, 2006; Kaplan et al., 2005).

At the second phase, after quasi-stationary segments (indexed by RTPs) were obtained for each EEG/MEG channel, several characteristics (attributes) of EEG/MEG segments (Kaplan and Borisov, 2003) were calculated. These attributes reflect different aspects of local processes in the cortex and thus permit assessing the mesolevel description of cortex interactions (interactions within transient neuronal assemblies) through large-scale EEG/MEG estimates (Fingelkurts et al., 2004b). These attributes are: (1) average amplitude within each segment (microvolts), – as generally agreed, indicates mainly the volume or size of neuronal assembly – the more neurons recruited into assembly through local synchronization of their activity, the higher the amplitude of corresponding to this assembly oscillations in the EEG/MEG (Nunez, 2000; Klimesch et al., 2005). (2) Average length of

segments (milliseconds) – illustrates the functional life-span of neuronal assembly or the duration of operation produced by this assembly. Because the transient neuronal assembly functions during a particular time interval, this period is reflected in EEG/MEG as a stabilized interval of quasi-stationary activity (Fingelkurts et al., 2004b). (3) Coefficient of amplitude variability within segments (%) – shows the stability of local neuronal synchronization within neuronal assembly (Truccolo et al., 2002). (4) Average amplitude relation among adjacent segments (%) – indicates neuronal assembly growth (recruitment of new neurons) or disassembling (functional elimination of neurons) (Fingelkurts et al., 2004b). (5) Average steepness among adjacent segments estimated in the close area of RTP (%) – shows the speed of neuronal assembly growth or disassembling (Fingelkurts et al., 2004b).

5.11. Estimation of the remote functional connectivity

Remote functional connectivity was estimated by calculation of the index of EEG/MEG structural synchrony (ISS) by means of *RTPsyn* tool (BM-Science, Finland). The ISS was estimated through synchronization of RTPs between different EEG/MEG channels. This measure reveals functional (operational) interrelations between cortical sites different from those measured by correlation, coherence and phase analysis (for detailed methodological description, see Fingelkurts and Fingelkurts, 2008). In brief, each RTP in the reference EEG/MEG channel (the channel with the minimal number of RTPs from any pair of EEG/MEG channels) was surrounded by a short "window" (in milliseconds). Any RTP from another (test) channel was considered to coincide if it fell within this window. The ISS tends toward zero where there is no synchronization between the EEG/MEG segments and has positive or negative values where such synchronization (or dis-synchronization) exists. Positive values indicate "active" coupling of EEG/MEG segments (synchronization of EEG/MEG segments is observed significantly more often than expected by chance; $p < 0.05$, random shuffling, computer simulation), whereas negative values mark active decoupling of segments (synchronization of EEG/MEG segments is observed significantly less than expected by chance; $p < 0.05$, random shuffling, computer simulation). From a qualitative perspective, coupling of EEG/MEG segments corresponds to the synchronization of operations executed by local neuronal assemblies or operational synchrony (OS) (Fingelkurts and Fingelkurts, 2001, 2005, 2006).

Using pairwise analysis, ISS was identified in several channels (more than two). These are described as operational modules (OMs) (Fingelkurts and Fingelkurts, 2004, 2005, 2008). OM means that the set of the cortical areas participated in the same functional act during the analyzed period. The criterion for defining an OM is a sequence of the same synchrocomplexes (SC), where SC is a set

of EEG/MEG channels in which each channel forms a paired combination with high values of ISS with all other EEG/MEG channels in the same SC; meaning that all pairs of channels in an SC have to have statistically significant ISS (see Fingelkurts and Fingelkurts, 2008).

5.12. Statistics

For each analyzed condition, group-EEG/MEG-segment-attribute averages and respective standard deviations were calculated in the following manner: (a) first, per-subject individual averages were calculated for each segment attribute across all EEG/MEG registrations and all channels; (b) second, group averages were calculated for all data pooled together for each studied condition separately. Similarities in the initial per-subject averages indicate if the results between the subjects are consistent for each condition, and only then if the consistency exists, would it be justified to pool all individual data together for each condition. All subjects in each group (condition) had very similar values in the EEG/MEG segment attributes, which was reflected in small values of standard deviations. This justifies the pulling of all data within the same condition together to characterize the group. As in previous works, the comparison of the same segment attributes between different group conditions was performed using Wilcoxon *t*-test, as only the difference between pairs of states was of interest.

The differences in the number and strength of EEG/MEG structural synchrony patterns between different conditions were assessed using the Wilcoxon *t*-test as in the majority of the functional connectivity studies (for the overview, see Weiss and Rappelsberger, 2000). At first all EEG/MEG synchronized patterns were averaged for all subjects within nine categories of functional connectivity ($short_{left/right}$, $short_{anterior/posterior}$, $long_{left/right}$, $long_{anterior/posterior}$, and $long_{interhemispheric}$) per condition, separately for the number of functional connections and for the strength of these connections. Since the absolute number of possible functional connections within each category was different, the percentage of them per category was calculated. During the final stage an average of all the categories was calculated. Thus only average values for all statistically valid functional connections were used for further analysis. This makes the difference in the number of channels (20 and 16) irrelevant for this study.

Since we intended to assess each variable in its own right and the difference between pairs of states was of interest, no Bonferroni correction was applied. However, in the case where we compared several conditions at a time, a Bonferroni correction was made in order to control for repeated observations of the same measures. *P* corrected is the value required to keep the number of false positives at $P = 5\%$.

For eyes closed and open rest conditions, data were averaged from all experimental studies with observations weighted inversely to their variance. In weighted average of the results, larger trials have more influence than their smaller counterparts because small studies are more prone to chance deviations (Bevington and Robinson, 2002). Eyes closed resting condition served as a common reference state against which all other conditions were contrasted[2].

Additionally, surrogate data were used to control for the non-random origin of the dynamics of different EEG characteristics, which is commonly applied as direct probing of a signal for its non-occasional nature (Ivanov et al., 1996).

Although it is often claimed that volume conduction is the main obstacle in interpreting EEG data in terms of brain connectivity, it has been shown previously through modeling experiments that the values of the ISS are sensitive to the morpho-functional organization of the cortex rather than to the volume conduction and/or reference electrode (for relevant details, we refer the reader to Kaplan et al., 2005; Fingelkurts and Fingelkurts, 2008).

6. Results and discussion

To study the dynamical changes in operational architectonics of alpha rhythm, which occur in normal functional brain states and during different pathological conditions, we will contrast them with the common reference state – resting condition with closed eyes. The "awake resting state" is usually defined as a "baseline" of brain activity that is distinct from both sleep and any type of task involving explicit perception, memory or other cognitive activity (Laufs et al., 2003).

6.1. Local functional connectivity of alpha rhythm in norm

Figure 1 presents the mean values of EEG/MEG segment attributes that characterize different features of neuronal assemblies for all EEG/MEG locations and subjects for each functional state/condition. Corresponding data are presented separately for five features of neuronal assemblies (see Aim and methodological aspects section). The rest condition with closed eyes was taken as a reference functional state. To the right side from this reference state there are eight functional states/conditions with gradually increasing cognitive loading (rest condition with opened eyes being the lowest

[2] Such reference condition (been a weighted average of all resting control conditions from all experimental studies) allows us to compare different groups in which subjects with different ages (middle aged depressed patients, thirty-year old opiate addicts, 12 year old schizophrenic patients) participated. Thus, this reference condition is normalized for the age factor.

cognitive loading; and retrieval with open eyes – the highest cognitive loading). To the left side from the reference state there are two functional states with decreased arousal/wakefulness (lorazepam and NREM sleep).

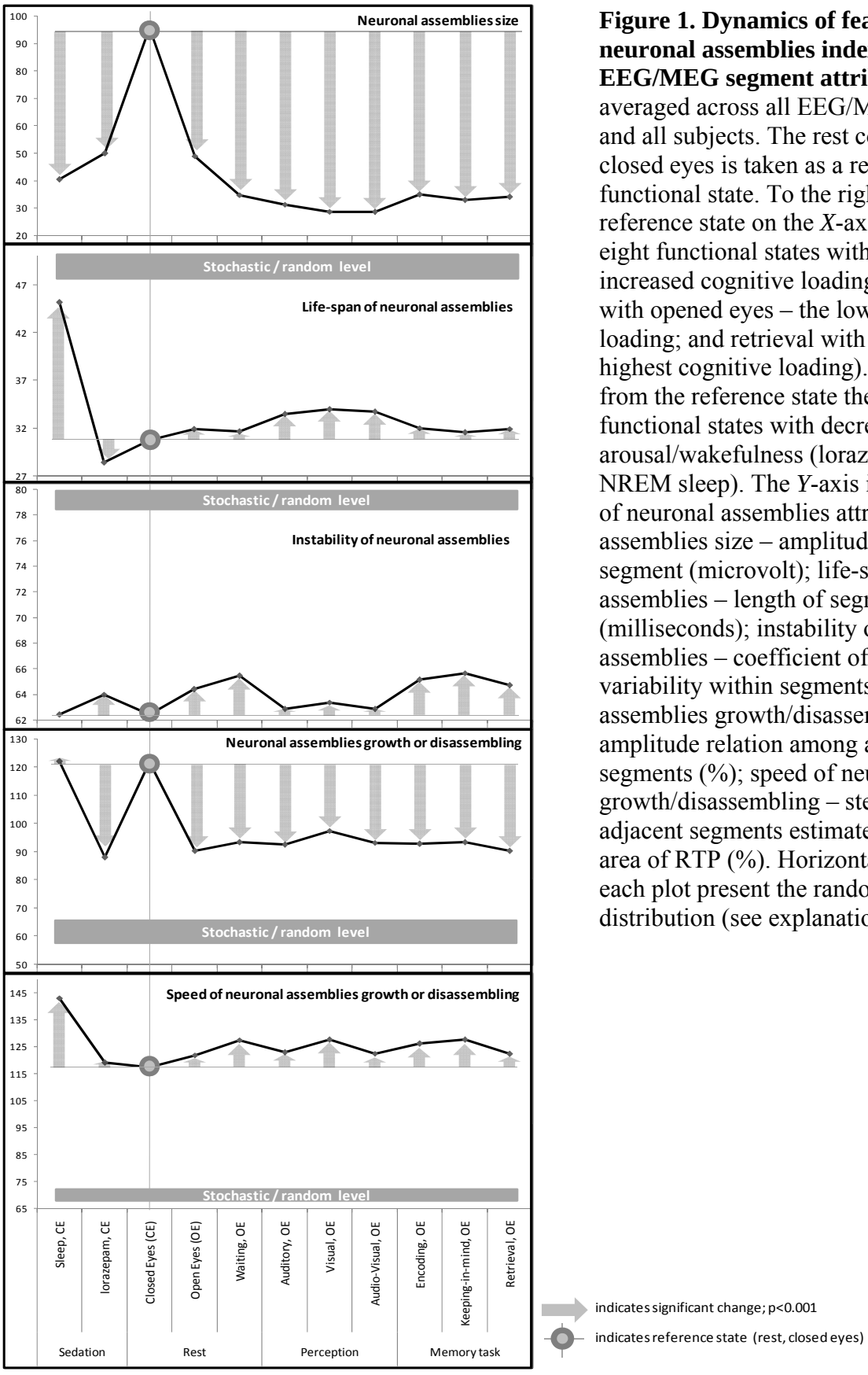

Figure 1. Dynamics of features of neuronal assemblies indexed by EEG/MEG segment attributes. Data averaged across all EEG/MEG channels and all subjects. The rest condition with closed eyes is taken as a reference functional state. To the right side from this reference state on the *X*-axis there are eight functional states with a gradually increased cognitive loading (rest condition with opened eyes – the lowest cognitive loading; and retrieval with open eyes – the highest cognitive loading). To the left side from the reference state there are two functional states with decreased arousal/wakefulness (lorazepam and NREM sleep). The *Y*-axis indicates values of neuronal assemblies attributes: neuronal assemblies size – amplitude within each segment (microvolt); life-span of neuronal assemblies – length of segments (milliseconds); instability of neuronal assemblies – coefficient of amplitude variability within segments (%); neuronal assemblies growth/disassembling – amplitude relation among adjacent segments (%); speed of neuronal assemblie growth/disassembling – steepness among adjacent segments estimated in the close area of RTP (%). Horizontal grey bars for each plot present the random level distribution (see explanation in the text).

One can see that the size of neuronal assemblies was largest ($p_{corrected} < 0.05$) during the reference state – rest condition with closed eyes (Fig. 1). This may be interpreted that during resting state, when there are no any active tasks or actions present, the degrees of freedom of the cortex become low (Stam, 2006) and this state is characterized by the presence of large neuronal assemblies which are formed by recruiting new neurons through the mechanism of local synchronization (see below). Considering that there is a finite pool of neurons in each section of the cortex (Van Ooyen, 2001), if large functional assemblies dominate, then there are fewer possibilities for small populations to be organized in the same cortex section. This indicates competitive and cooperative relationships between local neuronal assemblies in the neocortex (von der Malsburg, 1999) even in the resting state.

Both, cognitive loading and sedation were characterized by an abrupt drop in the size of neuronal assemblies in the cortex (Fig. 1). However, the neurophysiological meaning of this common effect is different for cognitive loading and sedation. For the cognitive loading, this observation can be easily interpreted through an increased independence of brain processes (effort to maintain a state of alertness) needed to anticipate, perceive, and process different external stimuli, and execute particular tasks (e.g. memory). Indeed, in agreement with the general understanding, many neuronal assemblies with distributed parallel processing are active, when mental activation (attention, perception, memory) takes place (Mesulam, 1990; Nunez, 2000). This idea is in line with the results derived from studies on EEG complexity (Stam, 2006), where increased EEG dimensional complexity (an increased independence of information processing) was found in conditions characterized by notable overall mental activation or cognitive workload (Molle et al., 1996; Pritchard and Duke, 1992). The minimal size ($p_{corrected} < 0.05$) of neuronal assemblies was observed during perception functional states (Fig. 1), allowing a fast parallel information processing mode to simultaneously execute numerous processes from sensory "channels" (Basar, 1983; Knyazev, 2007). However, during the memory condition the size of neuronal assemblies slightly (but significantly; $p < 0.001$) increased, probably indicating the need for a stronger support of concrete cognitive operations of encoding, retaining, and retrieval (Fingelkurts et al., 2003c).

The decrease of the size of neuronal assemblies during sedation (low arousal), although counterintuitive at first sight, might be the result of GABA inhibition (in both cases: lorazepam and NREM sleep) onto the dendrites of excitatory cells (Semyanov, 2003). Indeed, lorazepam-induced $GABA_A$ receptor-mediated inhibitory postsynaptic potentials (IPSPs), which originate in dendrites,

can impair propagation of glutamatergic EPSPs to the cell body, resulting in the functional elimination of neurons from the neuronal assembly (see below). In the case of NREM sleep condition, cortical neurons are under the pressure exerted by $GABA_{ergic}$ thalamic reticular neurons (Steriade and Timofeev, 2003). Additionally, during dreams (which may occur in NREM) the neuronal assemblies are expected to be smaller than in a waking condition because no strong external stimuli are engaging large numbers of neurons (Greenfield, 2002).

The life-span of neuronal assemblies increased significantly ($p < 0.001$) in all functional states and conditions with cognitive loading, when compared with the reference state (Fig. 1). Among these states, the minimal life-span ($p_{corrected} < 0.05$) was characteristic for the waiting and memory conditions with open eyes. Considering previous findings that the life-span of neuronal assemblies (indexed by the length of EEG quasi-stationary segments) correlates with the speed of brain operations (indexed by the reaction times) (Fingelkurts et al., 2003b; Fingelkurts et al., 2007d), we may speculate that shortening of life-span of neuronal assemblies during active waiting and memory conditions reflects the shortening of brain operations and intensification of cognitive processing (Knyazev, 2007). Furthermore, this also stresses the relationship between attention (which is present in active waiting) and working memory (Bressler and Tognoli, 2006).

Although pharmacological sedation resulted in decreased ($p < 0.001$) life-span of neuronal assemblies, the even lower arousal condition (NREM sleep) increased the life-span of neuronal assemblies significantly ($p < 0.001$) and reached a much longer duration compared to conditions with cognitive loading (Fig. 1). This observation reflects the extreme prolongation of neuronal assemblies' operations and thus seems to be responsible for the well-established slowing of cognitive performance during sleep (Steriade, 1992; Coenen, 1998). This interpretation is also consistent with the phenomenological experiences (dreams) of the participant subjects in the study. When mental images or sensations have occurred involuntarily in the mind of subjects during NREM stages of sleep, they were characterized as static and simple (Noreika et al., 2006).

Active waiting and memory conditions were characterized by the highest ($p_{corrected} < 0.05$) instability of neuronal assemblies, while neuronal assemblies during NREM sleep and to some extent during auditory and audio-visual perception functional states were the most stable (Fig. 1). Generally these findings indicate that moderate cognitive loading and the need to memorize and process information shift the cortex into a dynamical and unstable mode of functioning, whereas NREM sleep and relatively stereotypical perception activity can be still supported by stable neuronal assemblies. Indeed, NREM mentation is considered as nonprogressive – the mind seems to be running in place (Hobson, 1988); and auditory, visual and audio-visual perception is usually regarded as quite ordinary and trivial activities (Fingelkurts et al., 2007a).

All functional states with cognitive loading and pharmacological sedation resulted in functional elimination of neurons from neuronal assemblies, reaching a maximum disassembling rate during lorazepam administration (Fig. 1). Only NREM sleep functional state was characterized ($p < 0.001$) by the recruitment of new neurons in the neuronal assemblies (Fig. 1), thus indicating the tendency of growth of neuronal assemblies in the cortex. The speed of functional elimination or recruitment of neurons in neuronal assemblies was higher in all functional states than in the reference state (rest condition with closed eyes) and reached a maximum value during NREM sleep (Fig. 1). This may be interpreted such that in all studied conditions, the shifts between brain operations were completed more abruptly and that there existed a transition to a more differential organization of functional relations in the cortex outside the resting state, which is identified as a relatively "passive" state (Gusnard and Raichle, 2001).

One should also note that the described dynamics of all characteristics of neuronal assemblies differed significantly from random levels of related dynamics calculated for a randomly altered EEG (Fig. 1, grey horizontal bars). Using the procedure of random mixing of amplitude values within EEG signal, the relative values of (a) life-span (length of quasi-stationary EEG segments), (b) instability (coefficient of EEG amplitude alternations within segments), (c) growth/disassembling (the coefficient of segment amplitude relations between neighboring EEG segments), and (d) speed of growth/disassembling (steepness of abrupt change in amplitude between neighboring EEG segments) were estimated in average for all EEG channels and subjects and the result was compared with correspondent values of real (non-modified) EEG (Fig. 1). The values of the mixed ("random") EEG were significantly higher ($p_{corrected} < 0.00 - p_{corrected} < 0.00001$ for life-span and $p_{corrected} < 0.000001$ for instability of neuronal assemblies) and lower ($p_{corrected} < 0.000001$ for neuronal assemblies growth/disassembling and the speed of these processes) when compared with the actual EEG. These findings indicate that the dynamics of the parameters of neuronal assemblies observed in the present study had a non-occasional character.

6.2. Remote functional connectivity of alpha rhythm in norm

Figure 2 presents mean values of the number and strength of functional connections for all EEG pair combinations that characterize remote functional connectivity between neuronal assemblies (see Aim and methodological aspects section). Corresponding data are organized the same way as in Fig. 1 and are presented separately for different functional states/conditions.

Strength of functional connectivity between neuronal assemblies decreased significantly ($p < 0.001$) during those functional states and conditions which were characterized by cognitive loading

and during NREM sleep, when compared with the reference state – resting condition with closed eyes (Fig. 2). These findings mark a weak communication among neuronal assemblies located in different cortex areas during functional states/conditions, characterized by some level of cognitive loading. Such state of the cortex would allow some level of flexibility with a fast reorganization of synchronized neuronal assemblies into different combinations (operational modules) in order to phenomenally (subjectively) present large number of possible objects, scenes or operations of variable complexity (Fingelkurts et al., 2009).

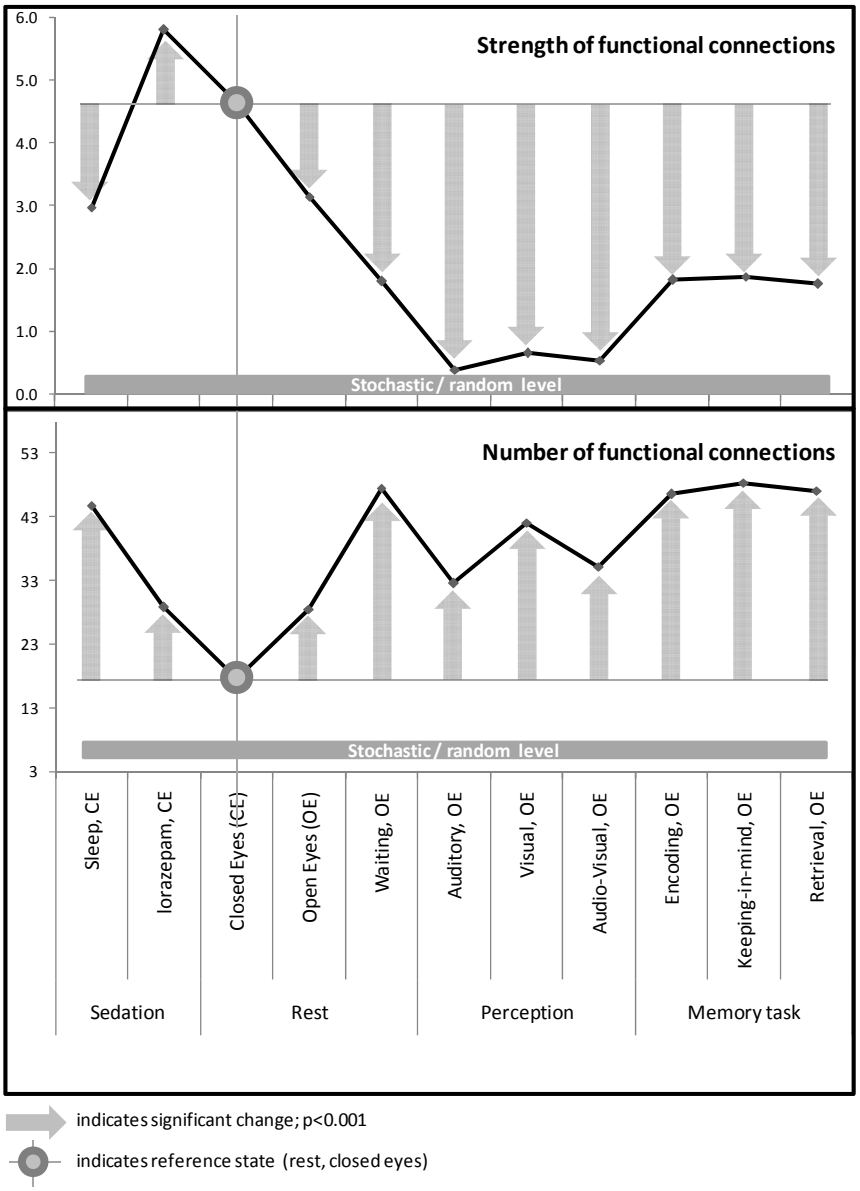

Figure 2. Number and strength of functional connections between neuronal assemblies (indexed by EEG/MEG segments coupling). Data averaged across all pairs of EEG/MEG channels and all subjects. The *Y*-axis presents values of either number or strength of functional connections. The *X*-axis is organized the same way as in the Fig. 1.

The lowest values ($p_{corrected} < 0.005$) were observed during perception functional states (Fig. 2), probably signifying the need for high degrees of freedom (high complexity; Stam, 2006) to support the multiple possible sensory stimuli and related with them expectations and goals (Skarda and Freeman, 1987; Freeman, 2007). In other words, during perception the cortex is in rather "stand by" or "fragile binding" (Stam, 2003) state (close to random level), when different neuronal assemblies retain their individuality and are ready to be engaged in the functional communication with each other when it is needed. The largest values ($p_{corrected} < 0.05$) of functional connectivity were registered during pharmacological (lorazepam) sedation (Fig. 2), indicating an inhibition of the proper expression of local neuronal assemblies' operations and, thus, been responsible for the slowing of cognitive processing and sedation (Fingelkurts et al., 2004a,b).

At the same time the number of functional connections among remote neuronal assemblies increased significantly ($p < 0.001$) for all functional states (both, with cognitive loading and with sedation) when compared with reference state (Fig. 2). The maximum number ($p_{corrected} < 0.05$) of functional connections was observed for NREM sleep, active waiting state and for the memory condition. According to the Operational Architectonics framework, although elementary brain operations are executed by individual neuronal assemblies (located in different cortical areas), complex functions require the joint operation of multiple distributed neuronal assemblies acting in concert (Fingelkurts and Fingelkurts, 2001, 2004, 2005, 2006; Fingelkurts et al., 2009). On the other hand, synchrony of operations executed by different neuronal assemblies can also represent the decrease of informational processing as in NREM sleep and benzodiazepine sedation (however, note that the strength of functional connections in these conditions was very different from the conditions characterized by the cognitive activity; Fig. 2).

It is worth noting that both these characteristics (strength and number of functional connections among local neuronal assemblies) were significantly different when compared with random level (Fig. 2). Random level of coupling was performed on so called "surrogate" EEGs in which a mixing of actual EEG channels was done in such a way that each channel was taken from different time slot, so that the natural time relations between channels in such surrogate multichannel EEG were completely destroyed. However, the number and the sequence of segments within each channel remained the same as in the actual EEG. The values for random level of strength ($p_{corrected} < 0.05$ – $p_{corrected} < 0.0005$ for different functional states) and number ($p_{corrected} < 0.001$ – $p_{corrected} < 0.0005$) of functional connections were significantly smaller than in real EEGs. These findings indicate that dynamics of the parameters of functional connectivity among neuronal assemblies observed in the present study had a non-occasional character.

6.3. Local functional connectivity of alpha rhythm during pathology

Figure 3 presents the mean values of EEG segment attributes that characterize different features of neuronal assemblies for all EEG channels and subjects for each pathological condition. Corresponding data is presented separately for five features of neuronal assemblies (see Aim and methodological aspects section). The rest condition with closed eyes in healthy subjects was taken as a reference functional state and it is indicated on the figure as a horizontal line. Pathological conditions (resting state with closed eyes) are placed on the *X*-axis in accordance with the predominantly impaired brain system: affective system – depression, opioid abuse and abstinence; executive system – opioid abuse, abstinence and schizophrenia; and memory system – abstinence. The grey area in each plot of Fig. 3 indicates the normal physiological range (distribution) of possible changes for each particular feature/parameter of neuronal assemblies (estimated from Fig. 1).

One can see that the size of neuronal assemblies increased during abstinence, opioid abuse and depression, and decreased during schizophrenia when compared with the healthy reference state – resting condition with closed eyes (Fig. 3). The largest ($p_{corrected} < 0.05$) neuronal assemblies were observed in opioid abuse and depression pathological conditions. These findings are in agreement with the predictions of Susan Greenfield (2002) and could be interpreted in the following way: such pathologies as depression, opioid abuse and abstinence are characterized by rigid plasticity of neurons; and this keeps neurons temporally synchronized into large and stable (see below) assemblies (Goldstein, 1996; Buzsaki and Draguhn, 2004). Schizophrenia, on the contrary, is characterized by facilitated neuronal recombination, which leads to disassembling of large neuronal assemblies into a set of smaller and highly unstable (see below) independent clusters of synchronous activity. This can be related to the fact that in the cortex of schizophrenic patients there is a reduction of synaptic elements and neuronal connections without a decrease in total neuronal number (Selemon, 2004). Interestingly, this attribute of the neuronal assemblies' dynamics clearly distinguishes (and/or stresses the dominance of one) between pathological conditions classified in association with impairment of affective and executive brain systems (Fig. 3).

It is important to note, that despite the fact of being significantly different from the normal healthy reference state, the schizophrenia condition (indexed by the size of neuronal assemblies) still lies within the range of possible variability of physiological norm (grey area in Fig. 3). At the same time, such pathological conditions as depression, opioid abuse and abstinence are located well outside the normal physiological range (Fig. 3). This stresses the fact that the size of neuronal assemblies reaches "true" pathological values only in depression, opioid abuse and abstinence pathological conditions, but not in schizophrenia. Therefore, we conclude that not all variables that describe a

pathological brain state in a particular disorder are always incompatible with normal brain functioning (for the same conclusion pointed the observation of dynamics of other attributes of neuronal assemblies; see below).

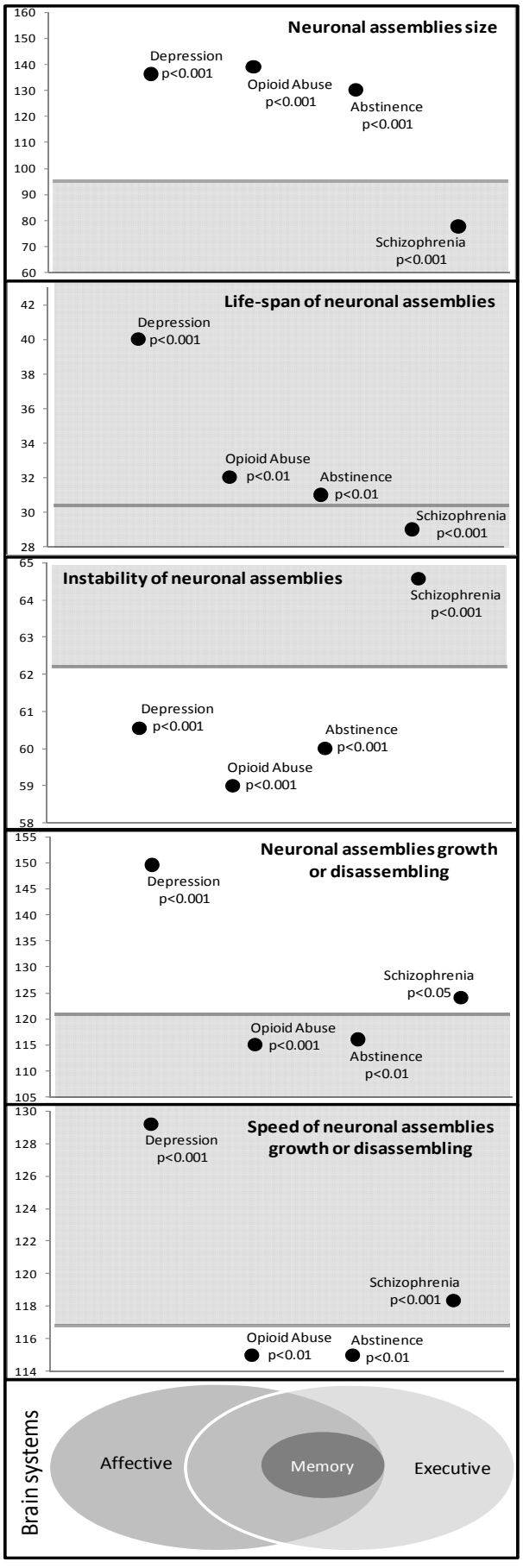

Figure 3. Dynamics of features of neuronal assemblies indexed by EEG/MEG segment attributes for different pathological conditions. Data averaged across all EEG/MEG channels and all subjects. The rest condition with closed eyes in healthy subjects is taken as a reference functional state and it is indicated on the figure as a horizontal line. Pathological conditions (resting state with closed eyes) are placed on the *X*-axis in accordance with the predominantly impaired brain system: affective system – depression, opioid abuse, and abstinence; executive system – opioid abuse, abstinence, and schizophrenia; and memory system – abstinence. The *Y*-axis is organized the same way as in the Fig. 1. Grey area in each plot of the Fig. 3 indicates the normal physiological range (distribution) of possible changes for each particular feature/parameter of neuronal assemblies (it is estimated from Fig. 1).

Life-span of neuronal assemblies followed the same rule as their sizes: increase ($p_{corrected} < 0.05$) for depression, opioid abuse and abstinence pathological states, and decrease ($p_{corrected} < 0.05$) for schizophrenia pathological state when compared with the healthy reference functional state (Fig. 3). The longest life of neuronal assemblies was characteristic for depression and the shortest – for schizophrenia. One possible explanation can be that short-lived neuronal assemblies may be responsible for the fast thoughts, lack of logical sequence (word "salad" syndrome), and derailed perceptions of schizophrenic patients (Kramer and France, 2001), while in such disorders as depression, opioid abuse and abstinence there is persistent and recurrent presence of the same train of thoughts – negative thoughts in depression that maintain depressive affect and cognition (Fossati et al., 2003) and drug-related thoughts that lead addicts to drug-seeking and drug-taking behavior (Robinson and Berridge, 2000) in opioid abuse and abstinence – which could be interpreted in terms of long-lived neuronal assemblies (Fingelkurts and Fingelkurts, 2005). Additionally, this attribute of neuronal assemblies' dynamics also sharply distinguishes (or stresses the dominance of one) between pathological conditions classified in respect with impairment of affective and executive brain systems (Fig. 3).

It is worth noting that life-span is such an attribute of neuronal assemblies which, although being significantly different from the analogous attribute in normal healthy reference state, happen to be within the range of possible variability of physiological normal values for all studied pathological conditions (grey area in Fig. 3). Therefore, we could conclude, that life-span of neuronal assemblies in depression, opioid abuse, abstinence and schizophrenia does not reach "true" pathological values, and signifies the variance of norm (in a broad sense).

The most unstable ($p_{corrected} < 0.05$) were neuronal assemblies in schizophrenia; at the same time depression, opiod abuse and abstinence conditions were much more stable ($p < 0.001$) than the healthy reference state with the most stable neuronal assemblies during opioid abuse (Fig. 3). These findings are in agreement with the dynamics of life-span of neuronal assemblies and support the provided interpretations (see above). Again, this feature of neuronal assemblies reaches "true" pathological values in depression, opioid abuse and abstinence conditions, while in schizophrenia it may be considered within the bounds of normal variability (grey area in Fig. 3).

Depression and schizophrenia were characterized by the tendency to recruit new neurons into the neuronal assemblies when compared with the healthy reference state (Fig. 3). This process was the most pronounced during depression ($p_{corrected} < 0.05$). On the contrary, opioid abuse and abstinence demonstrated functional elimination of neurons from neuronal assemblies. Such recruitment or elimination processes can probably indicate the process of compensation either for very small or very large size of neuronal assemblies (Fingelkurts et al., 2004b, 2006, 2007c). This attribute of neuronal

assemblies reaches "true" pathological values only in depression and schizophrenia, while in two other pathological conditions (opioid abuse and abstinence) this attribute can be interpreted as belonging to a variance of the norm (grey area in Fig. 3). Moreover, this attribute distinguishes between pathologies, which are associated with impairment in a single brain system, either affective or executive, or in both of them (Fig. 3).

The speed of the neurons' recruitment and/or elimination was highest ($p_{corrected} < 0.05$) during depression, followed by schizophrenia, while opioid abuse and abstinence pathological conditions were characterized by very slow speed when compared with the healthy reference state (Fig. 3). At the same time, only opioid abuse and abstinence conditions reach the "true" pathological values for the "speed" attribute of neuronal assemblies; in depression and schizophrenia this attribute is within the area of possible normal values (grey area in Fig. 3), thus indicating that it can be considered as a variance of norm for these pathological conditions. Additionally, this attribute distinguishes also between pathologies, which are associated with impairment in a single brain system, either affective or executive, or in both of them (Fig. 3).

6.4. Remote functional connectivity of alpha rhythm during pathology

Figure 4 presents the mean values of number and strength of functional connections for all EEG pair combinations that characterize remote functional connectivity between neuronal assemblies (see Aim and methodological aspects section). Corresponding data are organized the same way as in Fig. 3 and are presented separately for different functional states.

Both, strength and number of functional connections increased ($p < 0.05 - p < 0.001$) during depression and abstinence conditions, while decreased ($p < 0.01 - p < 0.001$) in opioid abuse and schizophrenia, when compared with the healthy reference state (Fig. 4). Strong functional connectivity in depression and abstinence may indicate the disordered metastable representation of semantics that depressed individuals tend to hold (Fossati et al., 2003; Fingelkurts et al., 2007b) and feeling of craving together with cognitive processes such as positive drug related expectancies and intrusive thoughts related to drugs in abstinent subjects (Franken, 2003; Fingelkurts et al., 2007c). On the contrary, decrease of functional connectivity among remote neuronal assemblies in opioid abusers and schizophrenic patients may signify a well-documented pattern of impairment in addicts (Davis et al. 2002) and schizophrenics (Tononi and Edelman, 2000) that expresses the lack of integration of different cognitive functions for effective problem solving, deficits in abstract concept formation, set maintenance, set shifting, behavioral control and problems in the regulation of affect and behavior.

From this perspective then, disorganization can be viewed as a disorder of the metastable balance between large-scale integration (remote functional connectivity) and independent processing (local functional connectivity) in the cortex (Fingelkurts et al., 2005a; Kelso and Tognoli, 2007). Both these characteristics of functional connectivity distinguish between pathological conditions dominated by one or several impaired brain systems (Fig. 3).

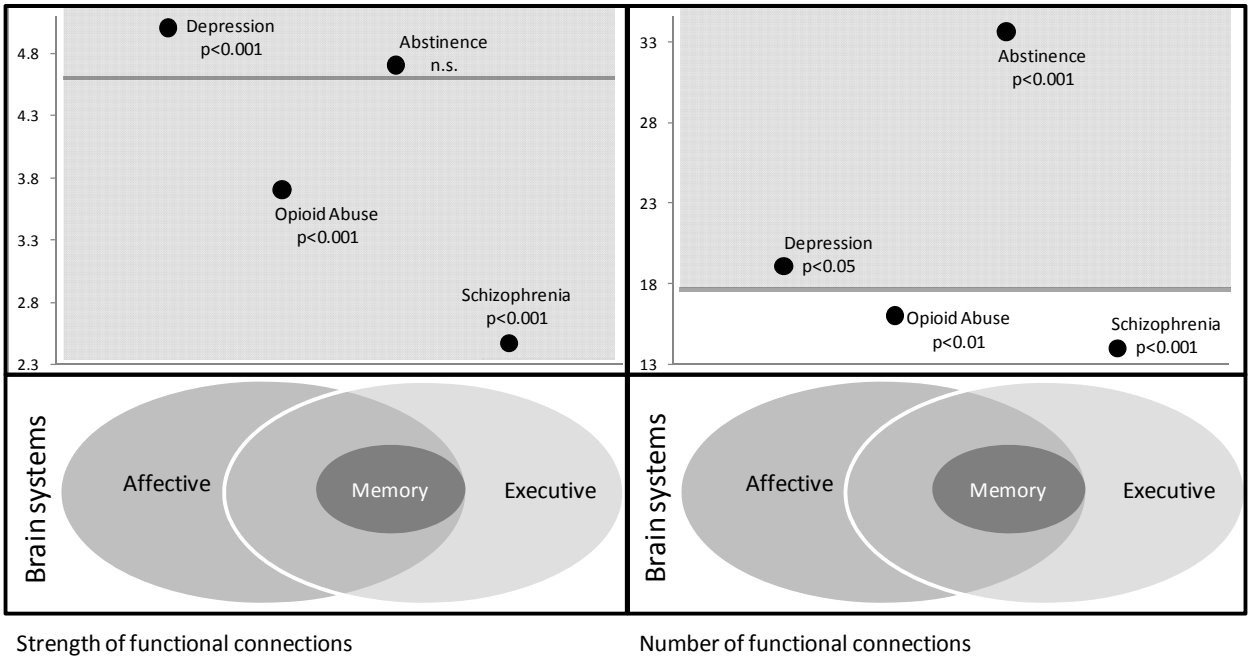

Figure 4. Number and strength of functional connections between neuronal assemblies (indexed by EEG/MEG segments coupling). Data averaged across all pairs of EEG/MEG channels and all subjects. Corresponding data are organized the same way as in the Fig. 3.

Despite the fact that the strength of functional connections among different remote neuronal assemblies in all studied pathological conditions was significantly different (exception was the abstinence state) from the analogous attribute in normal healthy reference state, it happens to be within the range of possible variability of physiological normal values (grey area in Fig. 4). Therefore, we could conclude, that the strength of functional connections among different neuronal assemblies in depression, opioid abuse, abstinence and schizophrenia does not reach "true" pathological values, and signifies the variance of norm (in a broad sense).

At the same time, for the number of functional connections between remote neuronal assemblies, only opioid abuse and schizophrenia were outside the normative range (grey area in Fig. 4), indicating that out of all the conditions considered only these reached "true" pathological values of cortex functional connectivity.

7. General discussion and conclusions

The rapid transitional processes (RTPs) occurring in the amplitude of a continuous alpha activity mark the boundaries between quasi-stationary segments for this activity. According to the Operational Architectonics (OA) framework each homogenous segment within alpha activity corresponds to a temporary stable microstate – an operation executed by a neuronal assembly. The transition from one segment to another reflects then the moment of abrupt switching from one neuronal assembly to another (see the example in Fingelkurts and Fingelkurts, 2008). The synchronization of these segments (alpha activity structural synchrony) between different EEG/MEG channels reflects the synchronization of different neuronal operations and constitutes the "operational synchrony" phenomenon. As a result of this process, the transient metastable states of alpha activity emerged in the form of so-called Operational Modules (OM). They are metastable because intrinsic differences in the activity between neuronal assemblies which constitute OM are sufficiently large and each neuronal assembly does its own job, while still retaining a tendency to be coordinated together. The interplay of these two tendencies (autonomy and integration) constitutes the metastable regime of brain functioning (Kelso, 1995), whereas local (autonomous) and global (integrated) processes coexist as a complementary pair, not as conflicting principles (Kelso and Engstrøm, 2006).

Using this OA framework, it has been possible to describe the main dynamical characteristics of neuronal assemblies that generate alpha activity in humans during normal and pathological brain states. It was shown that the characteristics of alpha activity segments, as well as the spatial structural synchrony of alpha activity changed considerably in accordance with the type of brain functional state, stimulation, cognitive task, pharmacological influence or pathology. However, all studied parameters of neuronal assemblies did not reach the random levels. In fact the range of "safe space" was quite large practically for all parameters, thus indicating that there is room for the variability of each particular parameter/attribute. The broader the dynamic range, the higher the probability of state/condition-related changes. This is very important as it gives the potential of representing the vast multivariability of different physiological, cognitive, behavioral and conscious states (Fingelkurts and Fingelkurts, 2004).

Based on the evidence presented in this study we may conclude that even the resting state with eyes closed (which is not directly related to identifiable sensory or motor events) involves existence of large, but short-lived neuronal assemblies, which have few (but very strong) functional connections between each other, probably reflecting a small-world functional architecture (Bullmore and Sporns, 2009). This neurophysiological pattern of cortex alpha activity indicates the resting state

network, which is characterized by significant nonlinear structure both in the temporal as well as in the spatial domain (Stam, 2006).

In connection with this we would like to suggest the following comments on the meaning of so-called alpha "synchronization" and "desynchronization". The realization of an individual brain operation demands the formation of functionally interconnected neurons in a relatively large neuronal assembly. Synchronization of neurons' activity is the main mechanism here (Fingelkurts et al., 2005b). This synchronization has a rhythmical nature (Buzsaki, 2004; Freeman and Vitiello, 2005). As a result, the formation of a neuronal assembly is accompanied by a rhythmical increase in the total potential of an assembly, whereas a disassembling of the neuronal assembly is characterized by a decrease in the total potential. Thus, the well-known phasic structure of alpha activity (or alternations of synchronization and desynchronization periods, Pfurtscheller and Lopes da Silva, 1999) mainly reflects the processes of functional formation and disassembling of cortex neuronal assemblies respectively. In this framework, periods of alpha synchronization and desynchronization do not mark episodes of "rest state" and "active work" respectively, but are signs of two equally active types of cortical processing, that differ in the way neighboring neurons interact (see also Knyazev, 2007).

The non-physiological dynamics of different parameters of neuronal assemblies and their functional relations can be studied if we go from normal to pathological brain conditions. The findings presented here suggest a loss of dynamical (but metastable) balance between local, specialized neuronal assemblies' functions and global integrative processes during different pathological conditions. It was shown that all studied pathological conditions could not reach a proper (for the healthy brain) resting state where individual neuronal assemblies (located in different brain areas), besides expressing their own functioning, are also heavily involved in a collective activity. Therefore, such optimal resting state in the brain depends upon a delicate metastable balance between local specialized processes and global integration. Excess or lack of either component would be a deviation of the optimal situation (see also, Stam, 2006; Kelso and Engstrøm, 2006; Bressler and McIntosh, 2007).

At the same time, our data pointed to the fact that not all characteristics of neuronal assemblies' dynamics and their functional interrelations in a particular pathological condition are incompatible with dynamics of normal brain functioning. In this context particular pathological condition may be conceptualized as an adapted state – a new metastable regimen of brain functioning around altered homeostatic levels (Daglish and Nutt, 2003; Kiyatkin, 2004). This adapted state is known as allostasis and is defined as an adaptive process of achieving stability through change, a stability that is not within the normal homeostatic range (McEwen, 1998). In other words allostatic state is a state of chronic deviation of brain oscillations system from the normal state of operation with establishment

of a new set point (Koob and Le Moal, 2001). As a result, such a system is less able to cope with the demands of a constantly changing environment. Recently, allostatic alteration of brain function has been identified as one component of the pathway to addiction (Koob and Le Moal, 2001, 2004), depression (Rosen and Schulkin, 2004) and schizophrenia (Schulkin et al., 1994; McEwen, 2000). For example, the mechanisms that contribute to allostasis of drug addiction are normal mechanisms for homeostatic regulation of drug reward that have spun out of the physiological range. Support for an allostatic view of reward regulation comes from increasing evidence that chronic exposure to drugs of abuse can change the "set point" for drug reward (Ahmed and Koob, 1998, 1999). In connection to this, those characteristics of dynamics of neuronal assemblies and their functional interrelations in a particular pathological condition which were statistically different from the resting reference state, but were within the range of the variability of normal functioning may be considered as potential markers of allostasis.

Hence, one needs to acknowledge, that the questions about to what extent particular disorder is "normal", in the sense that it is a simple reversible oscillation of a state of equilibrium, and to what extent it is "pathological", in the sense that it generates disease, are an extremely subtle and hazy issue (Bellavite and Signorini, 1998).

Operational architectonics, thus, provides a methodological and theoretical framework for a new field of experimental neuropathodynamics that is devoted to exploring the ways in which transient neuronal assemblies and their interactive hierarchical structures can be made to abandon the normal domain of flexible and adaptive behavior. Better understanding of the specific ways in which disrupted dynamics of different characteristics of neuronal assemblies and their functional connectivity may underlie neuro/psychopathology may also suggest new targets for therapeutic agents. Elsewhere, we have proposed that the future of psychopharmacology lies in its ability to design specific psychotropic drugs, which can restore the normal temporal dynamics of disordered features of neuronal assemblies and disordered metastable binding among them (Fingelkurts et al., 2005a). Such pharmacological agents potentially might be much more efficient than classical general compounds that are "blind" to the actual dynamic properties of neuronal assemblies and functional relations among them.

Future research should focuses on the further clarification on and classification of the behavior of neuronal assemblies across more brain states, experimental and pathological conditions, and through extension to neuronal assemblies behaving in other (besides alpha) frequency domains.

7.1. Limitations of this study

One needs to use aggregated analysis with caution because generally it has several serious limitations, which could lead to misleading results: (1) An aggregated analysis is subject to bias when only selected data are unintentionally used to favor hypothesis of a researcher; (2) Exclusion of nonpublished studies increases selection bias; (3) Aggregation of data that are significantly different from one another methodologically makes aggregated analysis less reliable; (4) Combining of data which were analyzed by different methods makes comparisons problematic; (5) Puling all data together with a high degree of variability; (6) Lack of information from individual studies can preclude the comparison of effects in predetermined subgroups or conditions.

However, the mentioned limitations of aggregated analysis might not have been realized in the present study due to the following reasons: (1) There were no selection of particular studies: All studies, including nonpublished, which investigate the operational architectonics of EEG alpha activity have been aggregated; (2) All aggregated data have been obtained using the same methodology – operational architectonics; (3) All aggregated data were analyzed by the same set of methodological tools with the same parameters; (4) Data from different conditions were not pulled together: The comparisons have been done between the set of conditions within the same methodological framework; (5) In the present study complete information about individual data sets was available for all individual studies.

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