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Local and Remote Functional Connectivity of Neocortex Under the Inhibition Influence

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Abstract: The current paper focuses on a relatively new and promising area of the study of EEG transformations during brain information processing based on the reduction of the signal to the discrete quasi-stationary segment sequences which may reflect individual brain microstates or discrete operations. In this framework, the complex brain functions require integration of several operations throughout the whole neocortex. However, the role of inhibitory brain systems in such processes is still unsettled.

The effects of a single dose (30μg/kg) of lorazepam on the operational activity of neuronal populations and on the temporal binding between them were examined in a double-blind randomized crossover placebo-controlled study with 8 healthy volunteers. EEG measures at 20 channels were evaluated on two occasions: (1) eyes closed, (2) eyes open. In short, we conducted a two-by-two factorial study where one factor manipulated $GABA_{ergic}$ neurotransmission (lorazepam versus placebo), while the other factor was simply brain state (eyes closed versus eyes opened). We were primarily interested in the main effect of lorazepam.

In the present study, a connection between the mesoscopic level, described by the local functional processes (neuronal assemblies or populations) and the macroscopic level, described as a sequence of metastable brain states (remote functionally synchronized neuronal populations) was established. The role of inhibitory brain systems facilitated by lorazepam in the operational dynamics of neuronal populations and in the process of EEG structural synchrony (topological peculiarities) was addressed for the first time. It was shown that GABA signalling reorganized the dynamics of local neuronal populations and the remote functional connectivity between them.

Keywords: Binding problem; Neuronal populations; Neural Assemblies; Synchronization; Operational/structural synchrony; EEG; Brain operations; GABA; Lorazepam; Inhibition

Introduction

The aim of the present study was to clarify the role of inhibitory brain systems in shaping the temporal dynamics of local neuronal populations (*local functional connectivity*) within the neocortex using established pharmacological manipulations. We also wanted to estimate *remote functional relations* among distributed cortical areas as indexed by EEG segment synchrony under the influence of inhibitory mechanisms. In particular, we wish to address the principal topological profile of EEG segment synchrony and metastable states during inhibition induced by $GABA_{ergic}$ changes. To achieve these goals, we used a previously established analytic framework (quasi-stationary segments and segment synchrony) within which we could characterize key statistical properties of induced EEG activity.

The brain is an example of a distributed environment without centralized control within it (Fingelkurts and Fingelkurts, 2001a). Although classical theories of central information processing interpret the brain as a passive, stimulus-driven device, modern approaches emphasize the constructive nature of brain processing (for the review see Arbib and Erdi, 2000; Engel et al., 2001). Recently there has been a shift towards explaining cognitive functions in terms of the joint behavior of large neuronal populations that are dynamically bound (von der Malsburg, 1981; Gray and Singer, 1989; Varela et al., 2001; Revonsuo, 2001). Several experimental studies have proposed that a crucial aspect of any cognitive function is a considerable potential multivariability of neuronal networks, which can simultaneously integrate and segregate the activities of multiple distributed cortical areas (for the review see Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2001b). In this framework it is suggested that local specific neuronal populations perform elementary operations whereas complex functions require the integration of several such operations throughout the whole neocortex (Luria, 1980; Tononi and Edelman, 1998; Nunez, 2000; Bressler and Kelso, 2001).

Although there have been many attempts to integrate local and large scales of brain activity within a common theory, no such comprehensive theory has yet been established. Very often top-down models suffer from superficial treatment of local processes such as neuronal populations (or cell assemblies). Similarly bottom-up models frequently neglect essential large-scale influences (Nunez, 2000).

The current study employed a relatively new and increasingly used approach for the analysis of EEG/MEG transformations during brain information processing based on the reduction of the signal to the sequence of individual quasi-stationary segments which may reflect the sequence of discrete brain *operations* (Kaplan et al., 1997; Kaplan, 1998; Lehmann

et al., 2000; for the review see Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2001b, 2003). It is assumed that such operations are the elementary units of informational processing embodied in the time-spatial organization of local neuronal populations – *local functional connectivity* (von der Malsburg, 1999). In contrast, complex functions of behavior and cognition may originate in the periods of short-term metastable states of the brain (for the review, see Kelso, 1991; Friston, 2000; Bressler and Kelso, 2001; Freeman, 2003). This metastability (when the number of degrees of freedom of the neural networks are maximally decreased) is the result of temporal binding of operations going on in different brain areas – *remote functional connectivity* (Kaplan 1998; Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2001b, 2003). One may note that the metastability principle extends the Haken synergetics rules (Haken, 1983), which aim to compress the effective number of degrees of freedom in complex systems to a few "order parameters" or variables that adequately approximate system dynamics at large scales (Haken, 1999). More precisely, metastability extends them to situations where there are neither stable nor unstable states, only coexisting tendencies (Kelso, 2002). Thus, within the framework of this methodology, the presented approach may offer a plausible link between macroscopic and mesoscopic levels of brain descriptions: it permits analysis of remote (metastable states) as well as local interactions (neuronal assembly operations) of neocortex activity simultaneously.

As in many other approaches utilizing the temporal binding mechanism (for the review see von der Malsburg, 1999), in the present one (*EEG Operational Architectonics*), it is implicitly supposed that temporal binding of neurons within neuronal populations and/or binding of neuronal populations into a single composite whole (spatial-temporal pattern) is achieved through the combined action of excitatory connections. However, in our initial effort to study the large-scale functional connectivity during inhibition influence through the measure of EEG structural synchrony (SS), we showed that functional connectivity of the cortex significantly increases under the lorazepam administration (Fingelkurts et al., 2004a). It is interesting that such unexpected process was accomplished not through decoupling of neuronal populations activity (about decoupling processes see Fingelkurts et al., 2003a). However, the role of inhibitory systems in the operational dynamics of local neuronal populations and in their contribution to large-scale synchrony remains unclear. Although it is an important issue, its study has been limited largely to theoretical investigations (Ermentrout and Cowan, 1980; von der Malsburg and Schneider, 1986; Sakai at al., 1997; von der Malsburg, 1999; Wright et al., 2001; Pinto and Ermentrout, 2001).

In order to answer the questions addressed above, we used $GABA_{ergic}$ agonist lorazepam, for which modulation on EEG is well documented (Link et al., 1991 among others).

Lorazepam belongs to the benzodiazepines family and its pharmacological actions are mediated by facilitation of $GABA_{ergic}$ neurotransmission by potentiating GABA-induced chloride flux at the $GABA_A$-benzodiazepine receptor complex (Villar et al, 1990). The facilitation of $GABA_{ergic}$ system results in the inhibition of brain functions (Di Lazzaro et al., 2000). Thus, by using lorazepam, we can analyze the consequences of inhibition on (1) the operational dynamic of neuronal populations, and on (2) the EEG structural synchrony between different cortical areas. The latter is especially important since there have been no studies of topological picture of cortical functional connectivity under benzodiazepines administration.

Materials and methods

Subjects

Eight non-smoking healthy human subjects (4 males, 4 females between the ages of 20 and 29 years, all right-handed) participated the study. All the subjects studied gave informed written consent and institutional ethical committee approval was obtained. Before inclusion the subjects underwent a medical examination and laboratory tests of blood to exclude physical or mental health problems. They were also screened for mental problems by SCL-90 (Derogatis et al., 1973; Holi et al., 1998). All subjects reported being mild or moderate social drinkers (not more than five drinks/week.). The subjects reported having used no medications for 2 weeks prior to the study. Subjects' weights averaged 65.9 kg (range: 54-76 kg). The subjects were instructed to avoid alcohol for at least 48 h, and caffeine for 12 h prior to the recordings. All subjects arrived at the laboratory at approximately 7:45 a.m. after an overnight fast. A catheter was placed in the right antecubital vein for drug injection. Subjects underwent either lorazepam (Ativan® 4 mg/ml, Wyeth Lederle) 30 μg/kg or placebo (saline) injection in a randomized, double-blind, placebo-controlled, cross-over design study. The EEG recording was started 5 min after the infusion. All experimental sessions were carried out between 08:00 h and Noon, and the two sessions (lorazepam or placebo) were separated by one week.

Trial design

Following electrode placement and instruments calibration, a subject was seated in a comfortable chair in a dimmed registration room and the experimental procedure was explained. To reduce muscle artifacts in the EEG signal, a subject was instructed to assume a comfortable position and to avoid movement. A subject was instructed to look straight in front of him/her (in the case of eyes open) and to avoid unnecessary eye movements. The behavior of a subject was observed on a TV monitor throughout the experiment.

Subjects underwent EEG registration, 10 minutes in duration (eyes closed and open condition 5 min each). Two continuous 5-min trials of EEG data were recorded to cover the entire 10 min. In each trial, the subjects were required to alternate between open and closed eyes conditions, with the starting condition counterbalanced across subjects.

EEG registration

All recordings were performed in a magnetically and electrically shielded room (Euroshield, Eura, Finland) in the BioMag Laboratory, Helsinki University Central Hospital. Electric spontaneous brain activity was recorded with a 60-channel EEG data acquisition system (Neuromag Vectorview, Helsinki, Finland) with a frequency band of 0.06 to 86 Hz (sampling rate 300 Hz).

EEG was recorded with an electrode cap according to the International 10/20 extended system and the nose electrode was used as reference. The impedance of recording electrodes was monitored for each subject with an impedance meter prior to data collection; this was always below 5 kΩ. Vertical and horizontal electro-oculograms were recorded. Epochs containing artifacts due to eye blinks, significant muscle activity, and movements on EEG channels were automatically rejected. The presence of an adequate signal was determined by visually checking each raw signal on the computer screen after the automatic artifacts rejection.

Data processing

A full EEG streams contained 10-min continuous signal (eyes closed and open, 5-min each) for lorazepam and placebo. EEG streams were split into 4 distinct groups: lorazepam-eyes-closed, lorazepam-eyes-open, placebo-eyes-closed, placebo-eyes-open (five 1-min signals for each group). Further, data processing was performed separately for each 1-min

signal. Due to the technical requirements of the tools which were later used to process the data, EEGs from 20 electrodes ($F_{7/8}$, Fz, $F_{3/4}$, $T_{3/4}$, $C_{5/6}$, Cz, $C_{3/4}$, $T_{5/6}$, Pz, $P_{3/4}$, Oz, $O_{1/2}$) were analyzed with a converted sampling rate of 128 Hz.

After resampling and prior to the nonparametric adaptive segmentation procedure, each EEG signal was bandpass filtered in the alpha (7-13 Hz) and beta (15-21 Hz) frequency bands. These frequency bands were chosen because it has been well documented that benzodiazepines significantly increase power in the fast (14-21 Hz) wavebands while reducing power in the midrange (7-13 Hz) (see Mandema et al., 1992 among others).

Estimation of the local functional interrelations. Local functional interrelations were estimated in two stages. At the first stage, the adaptive level segmentation of local EEGs was performed. It has been recognized recently that an observed piecewise stationary process like an EEG is characterized by different statistical features at different time intervals and thus, can be seen as being "glued" from several quasi-stationary segments (Brodsky et al., 1999; Fell et al., 2000; Kaplan and Shishkin, 2000). Each of these quasi-stationary segments is formed by a random stationary process with some particular probabilistic characteristics which remain relatively constant within a segment (Kaplan et al., 2001). It is assumed that these segments measured by EEG may be a reflection of the discrete operations of the brain (Fingelkurts and Fingelkurts, 2001b, 2003). The aim of the segmentation was to divide the EEG-signal into quasi-stationary segments by estimating the intrinsic points of "gluing" (in mathematical statistics this problem is known as the change-point problem; see Brodsky and Darkhovsky, 1993). These instants (the transient phenomena) within short-time window when EEG amplitude significantly changed were identified as rapid transition processes (RTP) (Kaplan et al., 1997; Fingelkurts and Fingelkurts, 2001b). RTP is supposed to be of minor length comparing to the quasi-stationary segments, and therefore can be treated as a point or near-point (Fingelkurts and Fingelkurts, 2001; see also Kaplan and Shishkin, 2000).

The method for identifying RTPs (algorithm SECTION1.0®, Human Brain Research Group, Moscow State University) 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 recordings[1]. A more detailed explanation of the current version of this methodology and procedure of segmentation can be found in recent publications (Fingelkurts and Fingelkurts, 2001b, Fingelkurts et al., 2003a; see also Fingelkurts et al., 2004a – Methods and Appendix A, for an operational principles behind the RTPs). To estimate RTPs, comparisons were made between the ongoing EEG amplitude absolute values averaged in the test window (6 points=39 msec) and the EEG amplitude absolute values averaged in the level

window (120 points=930 msec). These values yielded the best results in revealing segments within the signal (according to a previous study, Fingelkurts, 1998; Borisov, 2002). The decision to use short-time windows was based on the need to track non-stationary transient cortical processes on a sub-second time scale. With this technique, the sequence of RTPs with statistically proven ($P < 0.05$, Student *t*-test) time coordinates has been determined for each EEG channel individually for each 1-min epoch.

At the second stage, after quasi-stationary segments (indexed by RTPs) were obtained, several characteristics (attributes) of 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 estimates. The attributes are:

1. *Average amplitude* (A) within each segment (μV^2) – as generally agreed, indicates mainly the volume or size of neuronal population: indeed, the more neurons recruited into assembly through local synchronization of their activity, the higher will be the amplitude of corresponding to this assembly oscillations in the EEG (Nunez, 2000).
2. *Average length* (L) of segments (msec) – illustrates the functional life span of neuronal population or the duration of operations produced by this population: since the transient neuronal assembly functions during a particular time interval, this period is reflected in EEG as a stabilized interval of quasi-stationary activity (Fell et al., 2000; Kaplan and Shishkin, 2000).
3. *Coefficient of amplitude variability* (V) within segments (%) – shows the stability of local neuronal synchronization within neuronal population or assembly (Truccolo et al., 2002).
4. *Average amplitude relation* (AR) among adjacent segments (%) – indicates the neuronal assembly behavior – growth (recruiting of new neurons) or distraction (functional elimination of neurons) (Kaplan and Borisov, 2003).
5. *Average steepness* (S) among adjacent segments (estimated in the close area of RTP) (%) – shows the speed of neuronal population growth or distraction (Kaplan and Borisov, 2003).

Segment attributes were averaged across five 1-min EEG epochs for each subject separately for each EEG channel and condition (lorazepam and placebo, eyes closed and open). After this, the data for each condition was averaged across all subjects (separately for each EEG channel).

As in the previous work (Kaplan et al., 2002; Kaplan and Borisov, 2003), the comparison of the same segment attributes between different conditions (placebo, lorazepam, eyes open and closed) was performed using Wilcoxon matched pairs *t*-test.

Estimation of the remote functional connectivity. Remote functional connectivity was estimated by calculation of the index of EEG structural synchrony. The index of structural synchrony (ISS) was estimated through synchronization of rapid transition processes (RTP) between different EEG channels. This procedure (algorithm JUMPSYN1.0® Human Brain Research Group, Moscow State University) reveals the functional (operational) interrelationships between cortical sites as distinct from those measured using correlation, coherence and phase analysis[2] (Kaplan and Shishkin, 2000). Each RTP in the reference EEG channel (the channel with the minimal number of RTPs from any pair of EEG channels) was surrounded by a "window" (from –3 to +4 digitizing points on each side of the RTP point) of 55 msec. It was taken that any RTP from another (test) channel coincided if it fell within this window. The window of 55 msec encompasses 70–80% of all RTP synchronizations (Fingelkurts, 1998; Borisov, 2002). The index of structural synchrony (ISS) for pairs of EEG channels was estimated using this procedure. More details of the current algorithm and paradigm of RTPs synchronization are described elsewhere (Fingelkurts and Fingelkurts, 2001b; Fingelkurts et al., 2003a,b). Here we only note that to arrive at a direct estimation of a 5% level of statistical significance of the ISS ($P < 0.05$), computer simulation of RTPs synchronization was undertaken based on random shuffling of segments marked by RTPs (500 independent trials). These share the properties of the experimental data (number of RTPs in each EEG channel of analyzed pair, number of segments, and number of windows of synchronization), but the time coordinates of RTPs were altered randomly in each trial so as to destroy the natural temporal structure of the data. Justification for this approach can be found in Fingelkurts et al. (2004a). However, other approaches are also possible (see for example Bullmore et al., 2001).

As a result of 500 times repeated random reshuffling of the time segments, marked by RTPs, the stochastic level of RTPs coupling (ISS_{stoh}) and the upper and lower thresholds of ISS_{stoh} significance (5%) were calculated. These values represent an estimation of the maximum (by module) possible stochastic rate of RTPs coupling (confidence levels). Thus, only those values of ISS which exceeded the upper (active coupling) and lower (active decoupling) thresholds of ISS_{stoh} have been assumed to be statistically valid ($P < 0.05$) and used for further analysis. Thus, the ISS tends towards zero where there is no synchronization between the EEG segments and has positive or negative values where such synchronization

exists. Positive values indicate 'active' *coupling* of EEG segments (synchronization of EEG segments were observed significantly more often than expected by chance), whereas negative values mark 'active' *decoupling* of segments (synchronization of EEG segments were observed significantly less than expected by chance). From a qualitative perspective, the (de)coupling of EEG segments corresponds to the phenomenon of synchronization of brain operations or Operational Synchrony – OS (Fingelkurts and Fingelkurts, 2003).

Using pair-wise analysis, structural synchrony (SS) was identified in several channels (more than two). These are described as operational modules – OM (Fingelkurts and Fingelkurts, 2001a,b, 2003). OM means that the set of the cortical areas participated in the same functional act during the period analyzed. The criterion for defining an OM was a set of EEG channels in which each channel forms a paired combination (with high values of ISS) with all other EEG channels in the same set; meaning that all pairs of channels in an OM have to have significant index of structural synchrony. The number of cortical areas recruited in OM was described as "the order of areas recruitment."

Separate computer maps of the ISS values were created for each subject and for each 1-minute EEG under different experimental conditions. The problem of multiple comparisons between maps cannot easily be overcome due to the large number of electrode pairs (Rappelsberger and Petsche, 1988) in the SS maps. This problem is common to all studies which require multiple comparisons between maps (Weiss and Rappelsberger, 2000; Razoumnikova, 2000). The comparisons that have been made should therefore be considered descriptive rather than confirmatory (Stein et al., 1999). To have valid results, the changes to the maps were only considered relevant if these changes consistently appeared in most of the EEG epochs and subjects (85-100%) under the same experimental conditions.

Results

Spectral data confirmed main previous findings on lorazepam-induced changes in the EEG for all subjects (not shown in the present paper, see Fingelkurts et al., 2004b). In light of this consistency we may suppose that the group of subjects used in the present work was representative.

In the present study we examined two frequency bands: alpha (7-13Hz) and beta (15-21Hz). In order to study local functional interrelations, we analyzed the rapid transition processes (RTP) in the EEG amplitude (which are the markers of boundaries between quasi-stationary segments) for each EEG channel. Also, the number of EEG segment attributes (A,

L, V, AR and S, see Material and Methods section) was analyzed. Remote functional connectivity (EEG structural synchrony – SS) was studied by estimation the synchronization of segments between different EEG channels. From a qualitative perspective, the SS process corresponds to the phenomenon of synchronization of brain operations or operational synchrony – OS (Fingelkurts and Fingelkurts, 2003). Data were obtained under two conditions and two functional states: lorazepam and placebo for eyes open and closed.

Local functional processes

This part of the study focused on the analysis of the local interactions within transient neuronal assemblies (or populations).

General analysis of the EEG segment attributes. In order to estimate the general dynamic range of the EEG segment attributes, the distribution of the values for each of the segment attributes was obtained for each subject and for the whole group (since all subjects showed very similar results).

Figure 1 illustrates the distributions of values of segment attributes obtained from 40 EEG epochs for 8 subjects (placebo, eyes closed). Corresponding data are presented separately for averaged posterior and anterior EEG channels within alpha frequency band (7-13 Hz). For each 1-minute EEG recording it was found about 200-270 segments for alpha activity and 240-280 segments for beta activity.

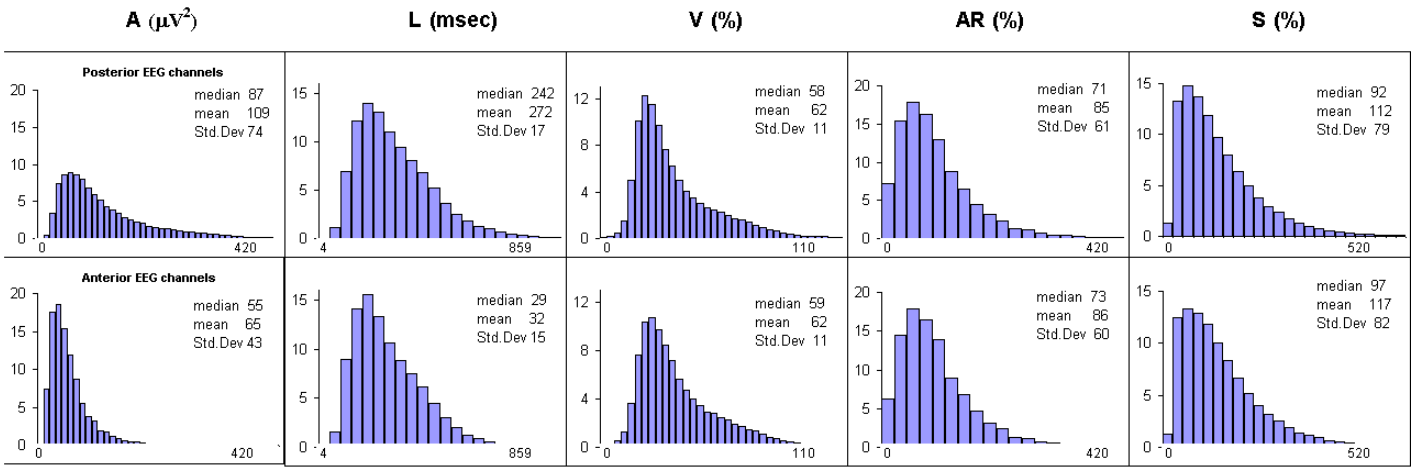


Figure 1. **The distributions of EEG segment attribute values** (averaged across 40 EEGs for 8 subjects, placebo-closed eyes). Corresponding data are presented separately for averaged posterior (upper row) and anterior (lower row) EEG channels within alpha frequency band.
A – average amplitude within each segment, L – average length of segments, V – coefficient of amplitude variability within segments, AR – average amplitude relation among adjacent segments, S – average steepness among adjacent segments.

Figure 1 indicates that all segment attributes had monomodal and asymmetrical distributions with the peak of histograms shifted to smaller values (for A_{post}=50-60 μV^2, A_{ant}=30-40 μV^2; $L_{post/ant}$=156-234 msec; $V_{post/ant}$=50-60 %; $AR_{post/ant}$=40-60 %; $S_{post/ant}$=40-60 %). There were no statistically significant differences between different EEG channels for the same segment attributes except the amplitude attribute, which in the anterior EEG channels was more asymmetric when compared with posterior (Fig. 1). Very similar dependence was found for placebo in eyes-open condition and for lorazepam in both eyes-closed and eyes-open conditions for alpha and beta frequency bands (data not shown). Obtained results demonstrated that different experimental conditions did not influence the distributions of EEG segment attributes except amplitude attribute in alpha frequency band for which the peak of histograms was shifted to smaller values under lorazepam condition when compared with placebo (Fig. 1).

Together, these results imply that different EEG segment attributes may be mutually inter-correlated. To address this question, the Pearson correlation coefficients (*rr*) between series of values of different EEG segment attributes were calculated for each of the EEG channel separately and for all EEG channels altogether (Table 1). As an example, data are shown for the placebo-eyes-closed condition (alpha band). Table 1 I illustrates *rr* between different EEG segment attributes for each of two separate EEG channels, while Table 1 II presents *rr* between different EEG segment attributes when all EEG channels were considered together. In all cases, the correlation was estimated between different attributes of the segments that were expressed at the same time.

Table 1. Pearson correlation coefficients (rr) and mean errors between dynamical series of values of EEG segment attributes.

I
Separate channels

	A	L	V	AR	S
A		-	-0.5±0.02	0.79±0.012	-
L	-		-	-	-
V	-0.6±0.02	-		-	-
AR	0.86±0.013	-	-		-
S	-	-	-	-	

F3

II
All channels

	A	L	V	AR	S
A		0.15±0.1	-0.45±0.02	0.8±0.01	-
L			-	0.33±0.03	0.22±0.034
V				0.19±0.1	0.35±0.03
AR					0.76±0.01
S					

O1

Left table illustrates rr for separate EEG channels while right table presents rr when all EEG channels considered together. The sign ± indicates mean error.

A - avarage amplitude within each segment
L - average length of segments
V - coefficient of amplitude variability within segment
AR - average amplitude relation among adjacent segments
S - average steepness among adjacebt segments

O1 - left occipital EEG electrode, F3 - left frontal EEG electrode.

Significant correlations for separate EEG channels were observed only for AxV (rr = -0.5, P<0.05) and AxAR (rr = 0.79, P<0.05) segment attributes. Note that average amplitude and average length of the segments as well as other segment attributes were uncorrelated between each other (Table 1 I). This means that the majority of changes in the dynamics of the EEG segment attributes were determined not by their mutual interrelations, but rather by external factors. Obtained results were very similar in all experimental conditions (placebo, lorazepam) and for open and closed eyes for both frequency bands (alpha and beta).

In contrast to rr for separate EEG channels, topographic factor results in the emergence of significant correlations between almost all attributes of EEG segments (Table 1 II). The strongest values of correlations were observed for AxAR (rr = 0.8, P<0.05) and for ARxS (rr = 0.76, P<0.05). At the same time, A and S were uncorrelated between each other. As with separate EEG channels, observed regularities were very similar in both experimental conditions (placebo, lorazepam) and for eyes-open and eyes-closed within both alpha and beta frequency bands.

Dynamics of the average values of EEG segment attributes. Total averaging of all the values within each attribute category has no functional purpose, since there are EEG segments with both high and low amplitude. Hence, it is more meaningful to estimate the average values of

segment attributes for different EEG amplitude classes (separately for alpha and beta frequency bands). Earlier it was already shown that such quartile analysis is very informative (Kaplan et al., 2002). In the present work three amplitude classes were obtained: first and third classes contained 25% segments with lowest and highest EEG amplitude correspondingly, while second class contained 50% of the rest of the segments (medium EEG amplitude) (Table 2). In this manner, the segments within these three classes reflect different degree of local synchronization of the neurons within a particular cortical location.

Corresponding data presented separately for three amplitude classes (I - low, II - medium and III - high).

	A						L						V						AR						S					
	I		II		III		I		II		III		I		II		III		I		II		III		I		II		III	
	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE
O1	53	0.3	121	0.6	253	1.4	273	0.4	273	0.3	273	0.5	70	0.3	60	0.2	54	0.1	96	1.9	78	0.9	85	1.7	129	2.3	106	1.3	96	1.7
O2	46	0.3	109	0.5	254	1.7	281	0.4	281	0.3	270	0.5	69	0.3	60	0.2	54	0.1	97	1.9	82	1	81	1.6	129	2.3	109	1.3	96	1.7
Oz	51	0.3	113	0.5	238	1.5	281	0.4	273	0.3	270	0.5	70	0.3	60	0.2	54	0.1	97	1.8	78	0.9	81	1.6	130	2.3	103	1.2	91	1.6
P3	40	0.2	81	0.3	191	1.4	273	0.4	250	0.3	270	0.4	72	0.3	60	0.2	55	0.1	99	1.7	80	0.9	85	1.5	135	2.3	111	1.3	103	1.8
P4	44	0.2	94	0.4	217	1.7	273	0.4	250	0.3	271	0.5	71	0.3	60	0.2	54	0.1	95	1.6	78	0.9	87	1.6	130	2.1	105	1.2	100	1.8
Pz	43	0.2	67	0.2	227	1.7	265	0.4	250	0.3	271	0.4	71	0.3	61	0.2	55	0.1	95	1.7	82	1	85	1.6	131	2.3	112	1.3	97	1.7
T5	34	0.2	68	0.3	137	1	273	0.4	242	0.3	261	0.4	72	0.3	61	0.2	56	0.1	98	1.6	78	0.8	91	1.6	135	2.2	108	1.2	115	1.9
T6	33	0.2	63	0.2	153	1.2	265	0.4	250	0.3	250	0.4	71	0.3	61	0.2	55	0.1	93	1.6	79	0.9	88	1.5	130	2.2	108	1.2	107	1.9
C3	33	0.2	68	0.3	125	0.9	273	0.4	234	0.2	265	0.3	72	0.3	61	0.2	56	0.1	98	1.6	77	0.8	93	1.5	133	2.1	108	1.2	121	2
C4	34	0.2	76	0.3	145	1.1	265	0.4	250	0.3	250	0.4	71	0.3	61	0.2	55	0.1	94	1.6	79	0.9	94	1.6	132	2.2	109	1.3	117	2
Cz	39	0.2	76	0.3	150	0.9	273	0.4	250	0.3	263	0.4	72	0.3	61	0.2	55	0.1	100	1.7	79	0.9	95	1.5	137	2.2	109	1.2	120	2
C5	30	0.1	57	0.2	111	1	273	0.4	226	0.2	250	0.3	73	0.3	61	0.2	57	0.1	98	1.5	74	0.8	93	1.5	138	2.2	104	1.2	121	1.9
C6	27	0.1	54	0.2	117	1	257	0.4	242	0.3	273	0.4	69	0.2	62	0.2	56	0.1	93	1.5	78	0.9	91	1.5	129	2.2	109	1.2	117	2
T3	30	0.1	55	0.2	106	0.9	273	0.4	29	0.2	250	0.3	73	0.3	61	0.2	57	0.1	96	1.5	72	0.7	91	1.4	132	2.1	102	1.1	120	1.9
T4	31	0.2	69	0.3	175	2.2	273	0.4	250	0.3	253	0.4	71	0.3	61	0.2	58	0.2	97	1.6	84	0.9	95	1.5	130	2.1	114	1.3	125	2.1
F3	27	0.1	51	0.2	101	1	281	0.4	234	0.2	250	0.3	73	0.3	61	0.2	57	0.1	103	1.7	75	0.8	97	1.6	142	2.4	104	1.2	121	1.9
F4	27	0.1	51	0.2	98	1.1	281	0.4	234	0.3	250	0.3	72	0.3	61	0.2	57	0.2	100	1.6	74	0.8	97	1.6	136	2.2	103	1.2	125	2
Fz	33	0.2	62	0.2	121	0.8	273	0.4	242	0.3	273	0.3	72	0.3	61	0.2	56	0.1	100	1.7	75	0.8	96	1.5	135	2.2	104	1.2	122	2
F7	20	0.1	36	0.1	76	0.9	273	0.4	226	0.2	260	0.3	73	0.3	61	0.2	58	0.2	98	1.5	73	0.8	99	1.6	133	2	101	1.1	128	2.1
F8	22	0.1	41	0.1	80	0.8	273	0.4	234	0.2	250	0.3	73	0.3	61	0.2	57	0.2	99	1.5	75	0.8	100	1.6	136	2.1	104	1.2	130	2.1
Av	35	0.2	71	0.3	154	1.2	273	0.4	236	0.3	261	0.4	71	0.3	61	0.2	56	0.1	97	1.6	78	0.9	91	1.5	133	2.2	107	1.2	114	1.9
	p<0.01						p<0.01						0.01<p<0.001						p<0.01						p<0.01					

M - mean values, SE - standard error, Av - average values for all channels togerther.
For A, L, V, AR, S see Table 1.

Table 2 summarizes the results of the average values of EEG segment attributes (alpha frequency band) obtained from all subjects (n=8) for each EEG channel (n=20). Corresponding data are presented separately for three amplitude classes (I, II and III). Although there were some insignificant differences between several channels, average data for all channels showed that values of L, AR and S were largest in the low (I) amplitude class and smallest in the medium (II) amplitude class (P<0.01). Values of V were largest in the low (I) amplitude class and smallest in the high (III) amplitude class (0.01<P<0.001) (Table 2). Obtained dependences were identical for both alpha and beta frequency bands for placebo and lorazepam, and for eyes open and eyes closed.

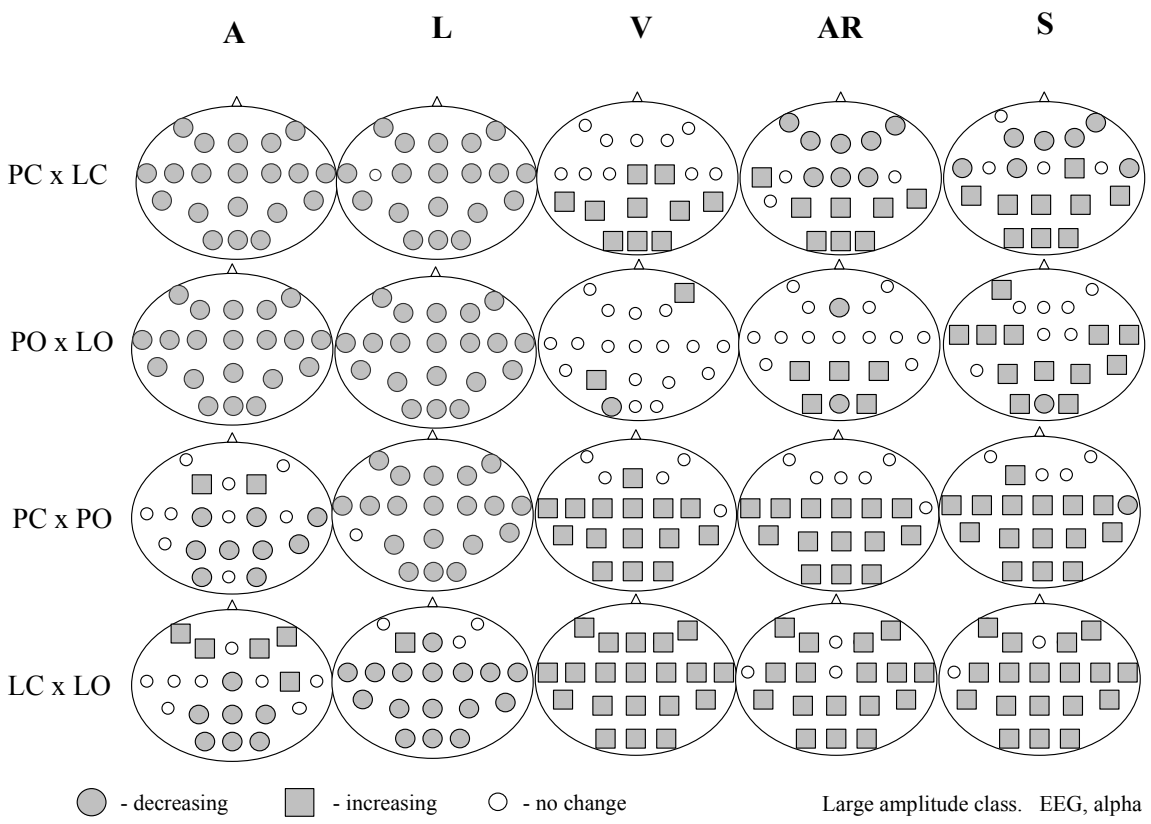
Changes in the average values of EEG segment attributes as a function of the condition. Although mutual inter-relations between different EEG segment attributes were stable and unchangeable for different experimental conditions, clear changes were observed in the average values of individual EEG segment attributes occurring together with changes in experimental conditions (placebo–lorazepam, open–closed eyes). These changes were specific for alpha and beta frequency bands.

Dynamics of EEG segment attributes for alpha activity. Figure 2 displays the maps of lorazepam-induced changes of segment attributes for alpha activity (data averaged across all subjects). Corresponding data presented separately for three amplitude classes (I, II and III) and for five pairs of experimental conditions (placebo-eyes-closed [PC] – lorazepam-eyes-closed [LC], placebo-eyes-open [PO] – lorazepam-eyes-open [LO], placebo-eyes-closed [PC] – placebo-eyes-open [PO], lorazepam-eyes-closed [LC] – lorazepam-eyes-open [PO]).

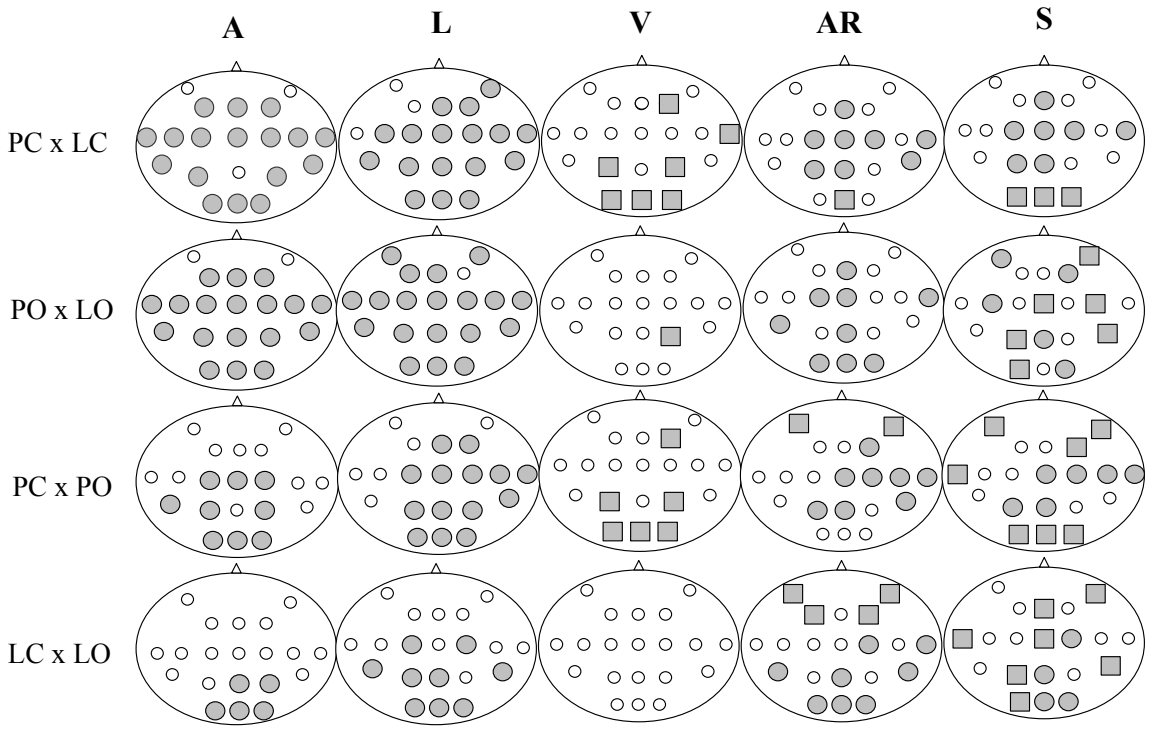
Average amplitude (A) of EEG segments decreased significantly under the lorazepam administration ($P<0.001$ for high amplitude class, $P<0.01$ for medium amplitude class, and $P<0.05$ for low amplitude class – only in the posterior cortical areas) when compared with placebo (Fig. 2). Average length (L) of EEG segments decreased by lorazepam ($P<0.001$ for high amplitude class, $P<0.01$ for medium amplitude class, and $P<0.05$ for low amplitude class – only in a few cortical areas). Note that for low amplitude class some increase in the L values was observed under lorazepam eyes open condition ($P<0.05$) when compared with placebo (Fig. 2 III).

The coefficient of amplitude variability (V) within EEG segments increased significantly by lorazepam ($P<0.05$-0.001 for different amplitude classes) mainly in the posterior right cortical areas (Fig. 2). Average amplitude relation (AR) among adjacent EEG segments increased significantly under the lorazepam administration ($P<0.01$ for high amplitude class, and $P<0.05$ for low amplitude class) mainly in the posterior right cortical areas. At the same time, AR decreased by lorazepam when compared with placebo ($P<0.05$ for medium amplitude class for central and right cortical areas, and for anterior areas for high and low amplitude classes).

Average steepness (S) among adjacent EEG segments increased significantly by lorazepam ($P<0.05$-0.001 for different amplitude classes) in posterior and right cortical areas. Also, the decrease of S was observed under the lorazepam condition ($P<0.05$ for central and frontal cortical areas) when compared with placebo (Fig. 2).



Large amplitude class. EEG, alpha



Medium amplitude class. EEG, alpha

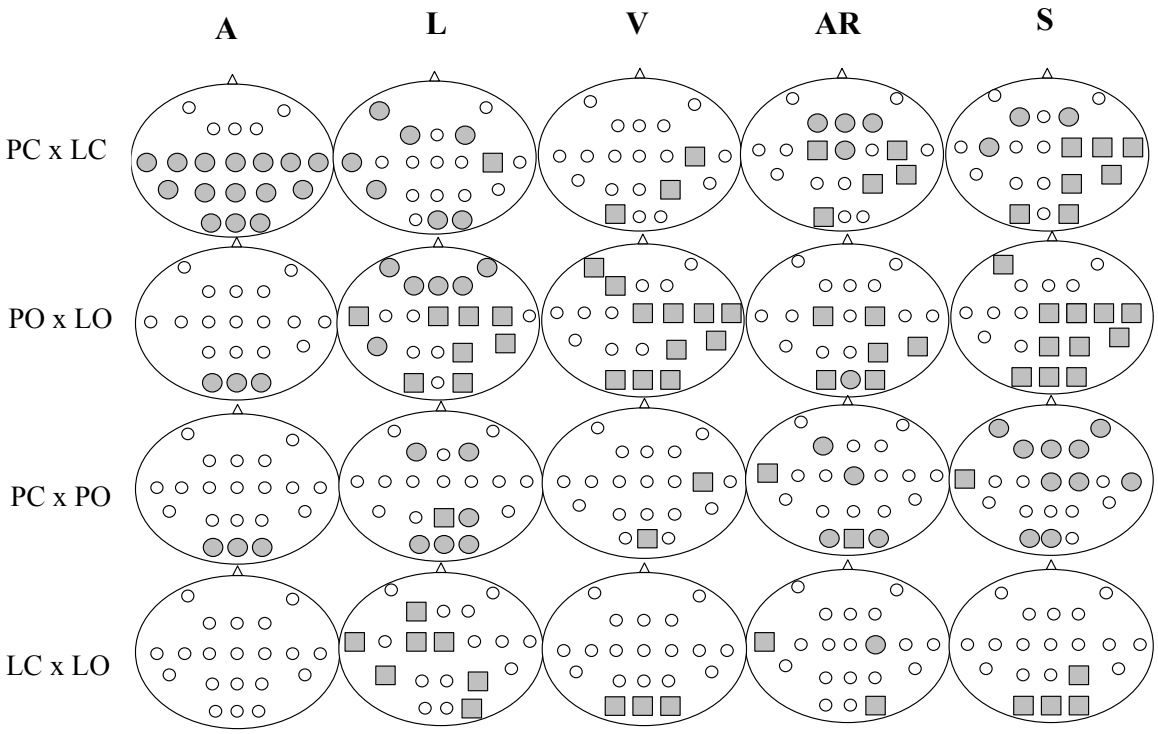
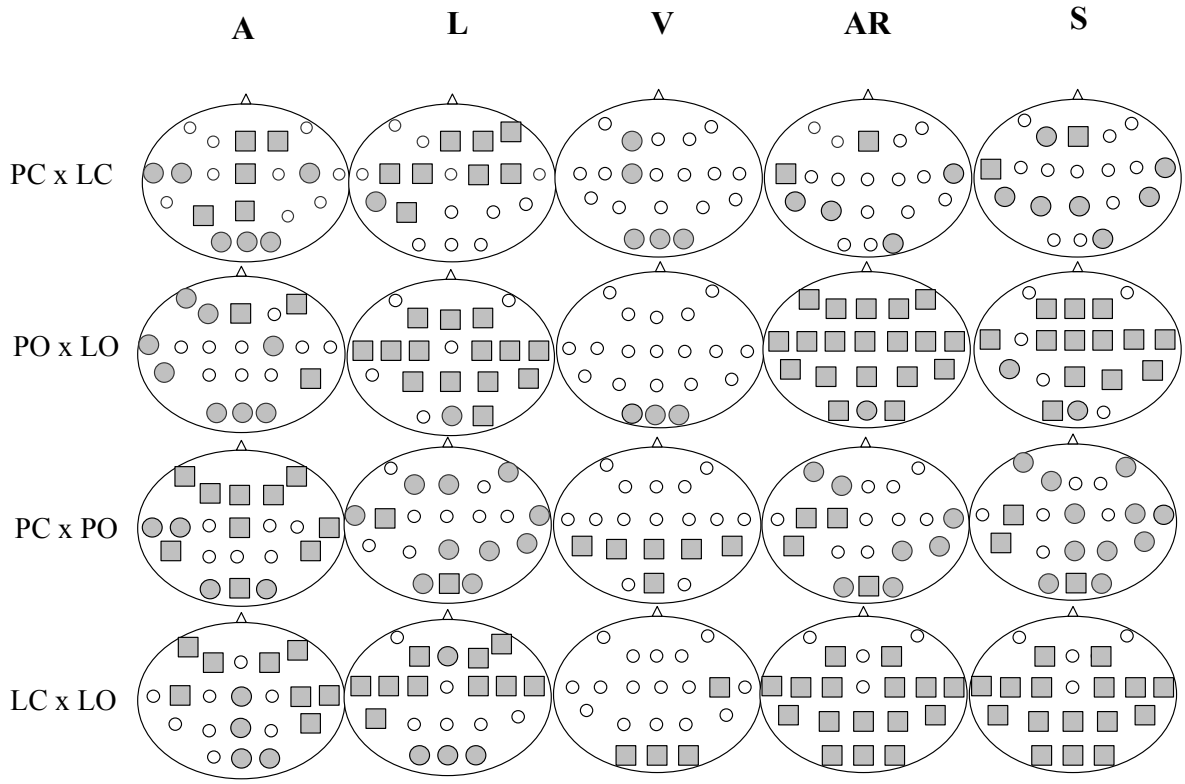


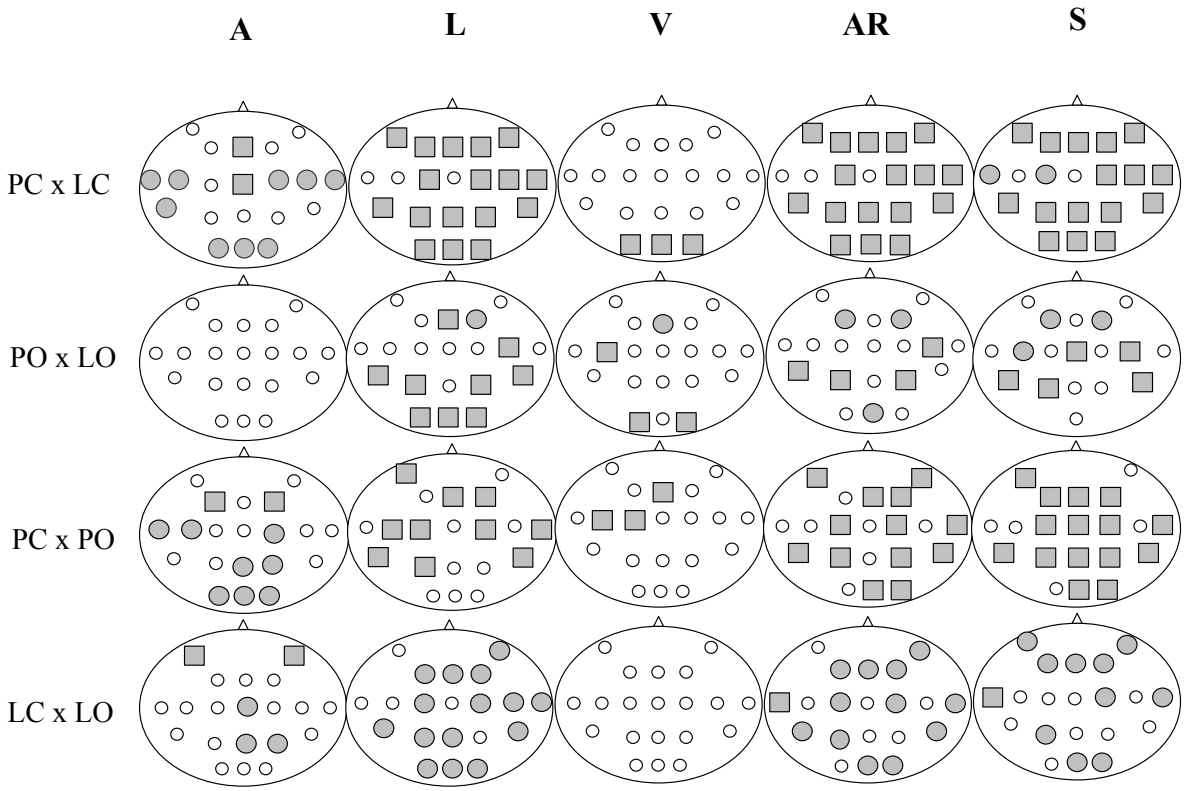
Figure 2. **The maps of lorazepam-induced changes** (after the Wilcoxon filtering) of alpha activity segment attributes for the group of subjects. Corresponding data presented separately for three amplitude classes (I – high, II – medium, and III – low) and for five pairs of experimental conditions (placebo-eyes-closed [PC] x lorazepam-eyes-closed [LC], placebo-eyes-open [PO] x lorazepam-eyes-open [LO], placebo-eyes-closed [PC] x placebo-eyes-open [PO], lorazepam-eyes-closed [LC] x lorazepam-eyes-open [LO]). EEG labels: first level of electrodes from the top – F_7, F_8; second – F_3, F_z, F_4; third – T_3, C_5, C_3, C_z, C_4, C_6, T_4; forth – T_5, P_3, P_z, P_4, T_6; fifth – O_1, O_z, O_2.

If we consider the shift in the functional state from eyes closed to eyes open for placebo and lorazepam separately, then the tendency of the eyes-open-induced changes was similar for placebo and lorazepam (Fig. 2, PCxPO and LCxLO). The majority of the significant changes were seen in the high amplitude class.

Dynamics of EEG segment attributes for beta activity. Figure 3 presents the maps of lorazepam-induced changes in the beta activity segment attributes. The construction of the figure is the same as for the figure 2.



Large amplitude class. EEG, beta



Medium amplitude class. EEG, beta

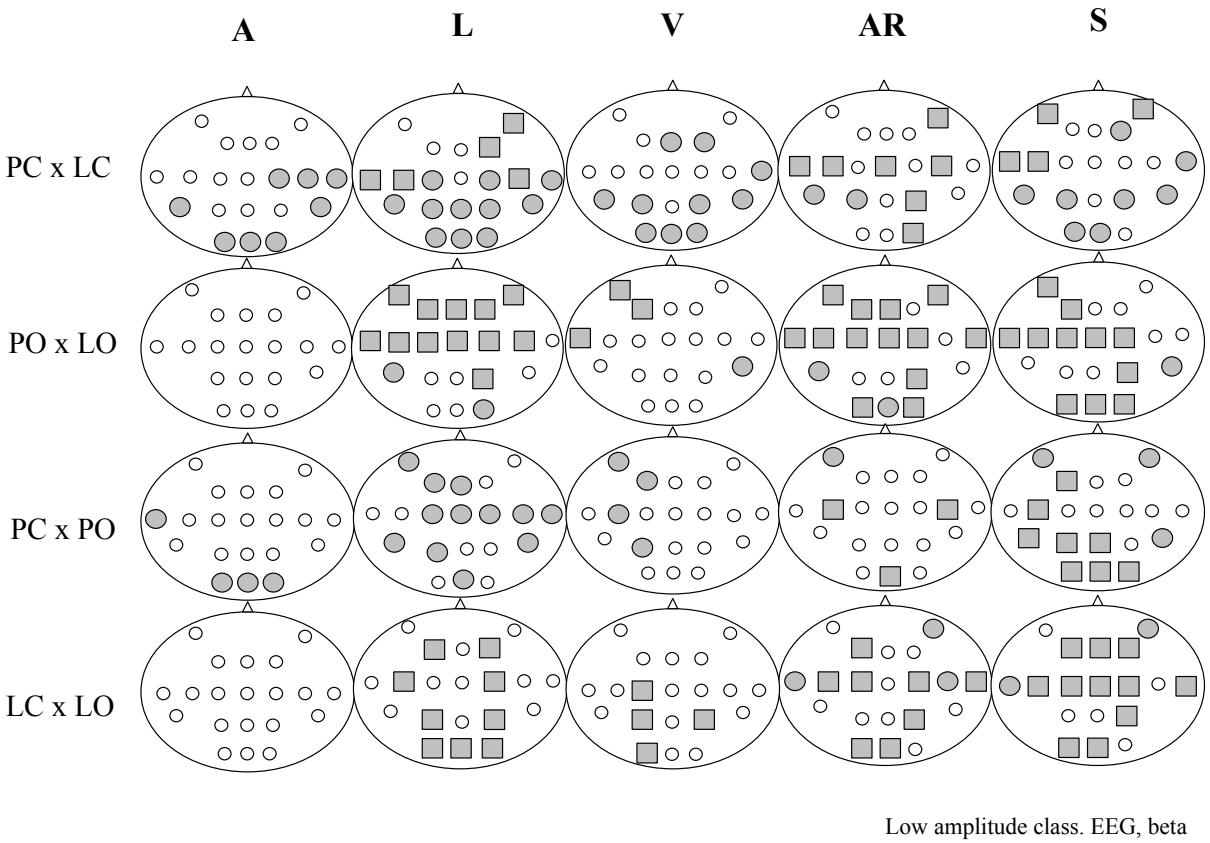


Figure 3. **The maps of lorazepam-induced changes** (after the Wilcoxon filtering) of beta activity segment attributes. Construction of this figure is the same as for the figure 2.

The A value decreased significantly under the lorazepam in the occipital and temporal cortical areas (P<0.05-0.001 for different amplitude classes), and increased under lorazepam for the whole central axis (P<0.001 for high amplitude class), and for central and frontal cortical areas (P<0.01 for medium class) when compared with placebo (Fig. 3).

L increased significantly by lorazepam in almost all EEG channels (P<0.01) for high and low amplitude classes. In the low amplitude class, increasing was observed in anterior and central cortical areas (P<0.01) and decreasing in posterior areas, especially at eyes closed (P<0.05). V decreased by lorazepam in the occipital and several central cortical areas for high and low amplitude classes (P<0.01). At the same time, V significantly increased in the occipital (P<0.05, medium amplitude class) and right anterior cortical areas for low amplitude class (P<0.05) (Fig. 3).

Both AR and S increased in almost all EEG channels under the lorazepam intake at eyes open (P<0.001, high amplitude class) and eyes closed (P<0.01, medium amplitude class)

when compared with placebo. In addition, several channels showed increased AR (P<0.05) for low amplitude class (Fig. 3).

In contrast to the alpha activity, the shift from eyes closed to eyes open resulted in different changes by placebo and lorazepam in all beta activity segment attributes (Fig. 3, PCxPO and LCxLO).

EEG structural synchrony – remote functional connectivity

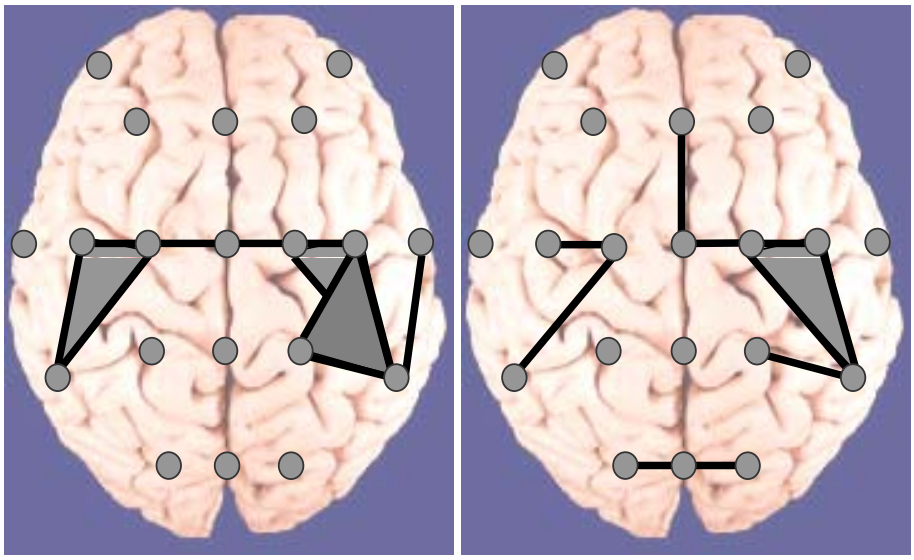
This part of the research focused on estimating the periods of mutual temporal stabilization of quasi-stationary segments in the multichannel EEG and permitted the study of remote functional connectivity of distributed neuronal assemblies.

The main finding was the absence of negative values of index of structural synchrony (ISS) in all obtained combinations of EEG channels for alpha and beta frequency bands. The percentage of the number of structurally synchronized EEGs (registered from different cortical areas) and the strength of this structural synchrony increased significantly under lorazepam when compared with placebo (details in Fingelkurts et al., 2004a).

To assess the principal topological picture of EEG structural synchrony (SS), all pair combinations of EEG channels exhibiting statistically proven SS were ranged in accordance with their rate of occurrence within all analyzed epochs in each subject and across all subjects. Only the most frequently found combinations (not less than 85% occurrence in all epochs and all subjects) were analyzed further.

Figure 4 displays the stable (unspecific) statistically significant (P<0.05) ISS values mapped onto brain schemata as connecting lines between corresponding EEG sites. These SS patterns occurred independently on condition and/or functional state and always remained the same, thus being stable.

Both alpha and beta frequency bands exhibited stable SS patterns. The majority of functional pair SS patterns occupied the central, temporal and occipital cortical areas. There were several operational modules (OMs) with "3rd order of recruitment" – three for alpha band and one for beta band (Fig. 4).



EEG/alpha EEG/beta

Figure 4. **The stable (unspecific) statistically significant (p<0.05) values of Index of Structural Synchrony (ISS)** in the alpha and beta frequency bands. The ISS values which occur more than in 85% of repetitions across all subjects are mapped onto schematic brain maps as connecting lines between the EEG channels involved. Grey areas indicate the operational modules (OM). EEG labels: first level of electrodes from the top – F_7, F_8; second – F_3, F_z, F_4; third – T_3, C_5, C_3, C_z, C_4, C_6, T_4; forth – T_5, P_3, P_z, P_4, T_6; fifth – O_1, O_z, O_2.

In addition to irrelevant, it was shown that there are also *relevant* (or specific) functional combinations of cortical areas which changed significantly during different experimental conditions and the subject's functional states. The most frequently found pattern of synchronized areas (indexed by ISS) elicited by lorazepam for eyes open or eyes closed (and comparison with placebo) are drawn on schematic brain maps for the alpha and beta frequency bands (Fig. 5).

Figure 5 indicates that maps of synchronized cortical areas (indexed by ISS) differed in placebo and lorazepam conditions. Thus, functionally connected cortical areas were more scattered along the cortex for placebo than for lorazepam condition (Fig. 5). This dependence was especially pronounced for the alpha band. Eyes-opening also resulted in significant reorganization of maps of structurally synchronized brain areas for placebo condition. This process was seen as a widening of the coupling between pairs of cortical areas in the posterior cortex (Fig. 5, PO in alpha and beta bands).

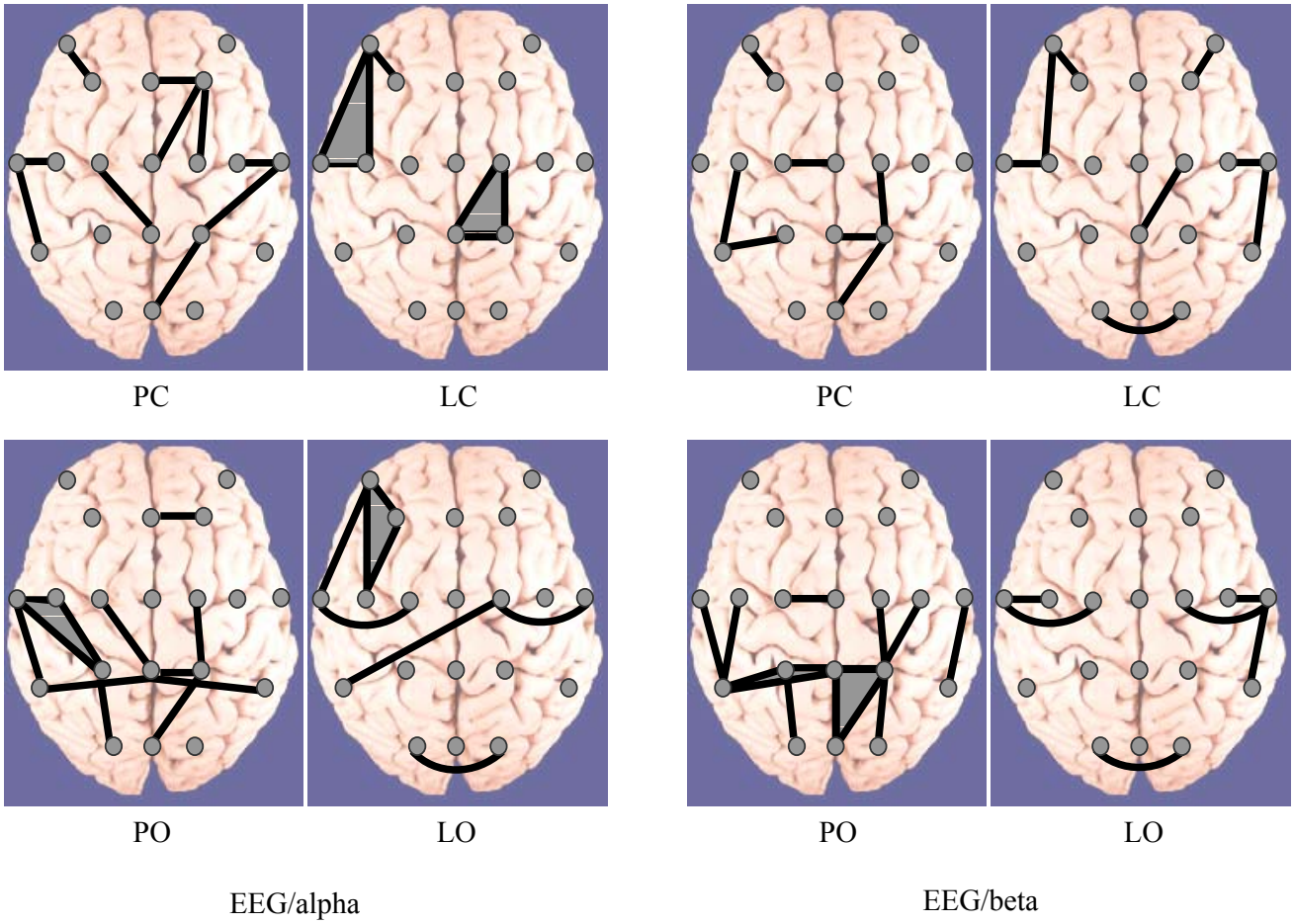


Figure 5. **The specific patterns of synchronized cortical areas** (indexed by Index of Structural Synchrony – ISS) elicited by lorazepam or placebo and by open or closed eyes in the alpha and beta frequency bands. The ISS values which occur more than in 85% of repetitions across all subjects are mapped onto schematic brain maps as connecting lines between the EEG channels involved. Grey areas indicate the operational modules (OM). EEG labels: first level of electrodes from the top – F_7, F_8; second – F_3, F_z, F_4; third – T_3, C_5, C_3, Cz, C_4, C_6, T_4; forth – T_5, P_3, P_z, P_4, T_6; fifth – O_1, O_z, O_2.
PC – placebo eyes closed, LC – lorazepam eyes closed, PO – placebo eyes open, LO – lorazepam eyes open.

In contrast to the pair combinations, OMs recruiting frontal and central cortical areas were seen mostly under the lorazepam condition (Fig. 5, LC and LO alpha bend). The state of eyes open under the placebo condition was also characterized by OMs, which recruited posterior and occipital cortical areas (Fig. 5, PO in both frequency bands).

Discussion

Modern cognitive and neurophysiological studies indicate that complex brain activity requires the integration of numerous neuronal populations within widely distributed neural networks (for the reviews see Singer, 2001; Varela et al., 2001; Revonsuo, 2001). The present work is concentrated not on the neural networks *per se* (as they are understood in classical concepts – Hebb, 1949; Hayek, 1952), but rather focuses on the *functional* networks whose units (neuronal assemblies or populations) are at scales both coarser and finer than that of the classical neural networks (von der Malsburg, 1999). The idea is that large neuronal populations can quickly become associated or disassociated, thus giving rise to transient assemblies (Frison, 2000; Triesch & von der Malsburg, 2001). Kaplan and colleagues (2003) extended this idea and suggested that such transient neuronal populations may serve as the functional elements of brain activity which execute the basic operations of informational processing (for definition of "brain operation," see Fingelkurts and Fingelkurts, 2003). Cell assembly or neuronal network may indicate a group of neurons or neural masses for which correlated activity persists over substantial time intervals (Nunez, 2000; Breakspear and Terry, 2002a). At the level of EEG these intervals should be reflected in the periods of quasi-stationary activity operating in different frequency ranges (for a review see Fingelkurts and Fingelkurts, 2001b, 2003). Exactly such segments of quasi-stationarity were obtained in the present work using a segmentation approach (see Materials and methods section).

Local functional interrelations

As envisioned here, different attributes of obtained EEG quasi-stationary segments illuminate different characteristics of neuronal populations (see also Kaplan and Borisov, 2003). Together all these attributes reflect and permit the detailed investigation of the intrinsic nature of local (mesolevel) interactions in the neocortex.

Basic peculiarities of neuronal population attributes. In the present work it was observed that distributions of these attributes were similar to each other and were stable under the lorazepam or placebo administration and also for eyes open and eyes closed conditions for alpha and beta frequency bands (Fig. 1). Also, mutual inter-correlations between segment attributes were stable for different experimental conditions within both (alpha and beta) frequency bands. These findings suggest that interrelations between segment attributes are basic characteristics of EEG signal; they are enslaved within a rigid functional range and thus are independent from

the current functional state and/or lorazepam influence (at least in the concentration tested). These data confirm the findings on segment structure of alpha activity during rest (Kaplan et al, 2002) and cognitive performance (Kaplan and Borisov, 2003). However, the stability of interrelations between segment attributes under the lorazepam influence and for beta activity was shown for the first time in the present work.

The fact that segment attributes within local EEG channels did not correlate between each other but became correlated when all channels were considered together (Table 1) may suggest that morpho-functional organization of cortical areas forces distant neuronal populations to operate in a similar manner, thus limiting the temporal (within each cortical location) and topological (between locations) relationships. These data are also consistent with previous findings for segment structure of the alpha frequency band for resting conditions (Kaplan and Borisov, 2003). Here one may ague that the finding of correlated segment attributes between EEG channels may be the result of volume conduction, since as it is sometimes claimed that EEG is a distorted copy of the cortical potential distribution due to the poor conductivity of the skull. However, we have shown in our previous work through modeling experiments that the values of the ISS are sensitive to the morpho-functional organization of a cortex rather than to the volume conduction (Fingelkurts, 1998; Kaplan et al., 2000; Borisov, 2002). In fact, all techniques for EEG transformation have their particular merits and limitations, and no agreement on a preferred solution is established at present (Hagemann et al., 2001). However, the ISS measure can accurately reflect local and global cortical function due to its independence from the averaged power spectrum of the signal and reference electrode (Kaplan and Shishkin, 2000; Borisov, 2002; Fingelkurts et al., 2003b).

To achieve physiologically plausible granularity in the analysis, all segments were grouped into three amplitude classes: high, medium and low. It was supposed that high amplitude class would correspond to the large-size neuronal populations, and medium and low amplitude classes would correspond to the medium- and small-size neuronal populations correspondingly. Such division permits independent analysis of neuronal populations of different size in a particular cortical location (Kaplan et al., 2002).

It was observed in the present study that the functional life span (L) of neuronal populations and the speed (S) of construction of new neuronal populations (AR) were highest for small neuronal populations and smallest for medium-size neuronal populations (Table 2). In contrast to this, the largest neuronal populations were the most stable (Table 2, see also Table 1 for negative correlation of AxV). These dependences were common for both frequency bands and for lorazepam and placebo, therefore indicating the basic character of

interrelations between the parameters of different-size neuronal populations. The functional role of this phenomenon is yet to be determined.

Lorazepam-induced changes in the attributes of neuronal populations. At the same time, the individual attributes of different-size neuronal populations were sensitive to the lorazepam influence as well as to the functional state of the subjects (open/closed eyes). Thus, in this study it was found that different-size neuronal populations within alpha and beta frequency bands performed differently under lorazepam when compared with placebo (Fig. 2, 3). To simplify the analysis, in this study alpha- and beta-generated neuronal populations are considered separately, because it has been shown that excitatory pyramidal neurons seem to participate mainly in alpha responses (Jones et al., 2000) while inhibitory interneurons are mostly responsible for higher (beta, gamma) frequencies (Porjesz et al., 2002). However, one need keeps in mind that in the brain excitatory and inhibitory neurons are highly interconnected and that both types of neurons contribute to different frequency ranges (Whittington et al., 1997; Traub et al., 2000; Tiesinga et al., 2002; Shu et al., 2003).

Alpha-generated neuronal populations. For the alpha-generated neuronal populations it was observed that large neuronal populations exhibited a total decrease in size (A), functional life span (L) and stability (V, mainly in posterior cortical areas) under the lorazepam administration when compared with placebo. Instability of such populations was reflected in the high speed (S) that new neurons were recruited into the new neuronal populations (AR), probably indicating the process of compensation for the smaller size of large neuronal populations under lorazepam when compared with placebo (Fig. 2 A). Most likely these findings reflect two sides of the same process of GABA inhibition which depends on the spatial distribution (compartmentalization) of the interneurons within excitatory cells (Semyanov, 2003). Thus, the increased inhibition onto the dendrites of the excitatory cells accompanied by the reduction of the size of neuronal population, while the decreased inhibition on the excitatory cell axons (governed by the inhibitory-inhibitory connections) may lead to the recruitment of new neurons (Paulsen and Moser, 1998). Indeed, $GABA_A$ receptor mediated inhibitory postsynaptic potentials (IPSPs) which originate in dendrites can impair propagation of glutamatergic EPSPs to the cell body. Thus, dendritic GABAergic synapses regulate excitatory “input” to the soma (Semyanov, 2003).

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. At the same time, some of these neuronal populations increased their functional life span

under lorazepam when compared with placebo (Fig. 2 C). This means that small neuronal populations throughout the entire cortex were not as influenced by the inhibition process as large populations and thus were stable. One explanation for that may be found in the proportion of different subunits in the heterogeneous $GABA_A$ receptor population or the small amount of $GABA_A$ receptors in such populations (Semyanov, 2003). This supposition is supported indirectly by the fact that occipital cortical areas have more GABA receptors (Wang et al., 2000) than other cortical areas. Recall that only posterior and occipital neuronal populations decreased in size and were unstable (Fig. 2 C) under the lorazepam administration. Exactly these cortical areas performed fast process of the organization of new neuronal populations. Another explanation for the stability observed in the small neuronal populations may be found in the work of Tiesinga et al. (2002). They suggested that for a neuronal population to be stable, it should have a robust termination mechanism that terminates the population bursts when enough neurons are in the refractive state. Without such a mechanism, the neuronal population would settle into an asynchronous state when each neuron fired in each own regime (Fellous and Sejnowski, 2000). Probably GABA-signalling mediates this mechanism when the neuronal assembly reaches a particular size.

It is interesting that eyes opening resulted in the strongest changes in large neuronal populations in both conditions (placebo and lorazepam). Almost the entire cortex became unstable (V attribute) and exhibited fast (S attribute) recruitment of new neurons (AR attribute) into the new neuronal populations (Fig. 2 A). These data confirm previous results on segment structure of the alpha activity during eyes-closed/open conditions (Kaplan et al., 2002). Altogether these findings suggest that the behavior of neuronal population depends not only on intrinsic properties of neurons, but also on network properties within neuronal population. This view has also been confirmed by the results of computer simulations (Tiesinga et al., 2002). Obtained findings on the dynamic of neuronal assembly attributes indicate that GABA-influence does not result in a functional elimination of neuronal assemblies, but rather realizes in the process of their reorganization into more local and smaller neuronal assemblies. Considering that there is a finite pool of neurons in each section of the cortex (Van Ooyen, 2001), if large functional assemblies/populations dominate then there are fewer possibilities for small populations to be organized in the same cortex section. This indicates competitive and cooperative relationships[3] between local neuronal populations in the neocortex (van der Malsburg, 1999).

Beta-generated neuronal populations. Data on the beta-generated neuronal populations were some how unexpected. A well-established effect of lorazepam (like other benzodiazepines) on

EEG is a strong increase in beta power (e.g. Link et al., 1991). However, our analysis showed that none of the neuronal populations (large-, medium- and small-size) increased the beta-amplitude under lorazepam administration when compared with placebo (Fig. 3). This finding is consistent with advanced micro-structural spectral analysis of the same data where an increase in individual independent beta activity under lorazepam was not observed (Fingelkurts et al., 2004b). In this work it was shown that beta-effect in the average power spectrum most likely is "virtual" and originated from averaging the EEG segments with polyrhythmic activity. This may explain why beta-effect of the lorazepam influence has no clinical relevance (for the discussion see Fingelkurts et al., 2004b). In the present study large- and medium-size neuronal populations nevertheless increased in size only along the midline of the cortex (Fig. 3 A, B). 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 (Volkow et al., 1995).

In general, data described here appears to be inconsistent with the *very simplified* picture often proposed for benzodiazepine-induced changes in EEG, such as when the alpha activity desynchronizes and the beta activity synchronizes under benzodiazepine intake (Link et al., 1991). In the framework of the present study the periods of event-related desynchronization and event-related synchronization do not mark episodes of "active work" and "rest state" respectively, but rather are the signs of switching in the dynamics of cortical operations, which are equally *active* but differ in their processing architecture (Borisov, 2002). Our findings suggest that differences in the behavior between excitatory and inhibitory populations may vary depending on strengths of internal interactions and the size of neuronal populations. These findings my be interpreted based on the recent study of McCormick et al. (Shu et al., 2003) who showed that local cortical populations do indeed operate through a proportional balance of excitation and inhibition generated through local recurrent connections, and that the operation of such circuits can generate self-sustaining activity that can be turned on and off by synaptic inputs. Here GABA may mediate the activity of synaptic inputs shifting the balance in the favor of inhibition or excitation depending on the target neuron. Indeed, inhibiting principal cells will normally reduce network excitability, whilst inhibiting interneurons will increase network excitability (Semyanov, 2003; for the review of GABA excitatory actions, see also Freeman, 1993; Köhling, 2002). $GABA_{ergic}$ therapeutic agents do not distinguish between these two alternatives, which may explain why, on occasion, $GABA_{ergic}$ antiepileptic drugs can be also proconvulsant (Köhling, 2002). A persistent "tonic" form of GABA-signalling may also regulate cortical excitability (Semyanov et al., 2003).

Although the actual cortical networks (comprised by excitatory and inhibitory cells) are very complex (Aboitiz, 1996; Keverne et al. 1996), the approach described in this article provides a powerful tool for analyzing in a precise manner the behavior peculiarities of transient neuronal assemblies (local interactions in the neocortex), thus enabling the assessment of mesolevel brain description through large-scale measure such as an EEG.

Remote structural synchrony of neuronal populations under the lorazepam influence

The previous discussion has dealt with the spatial-temporal behavior of neuronal populations which are produced by the coupling of the nearest neighboring neurons. However, local interaction among neurons and neuronal assemblies (mesolevel) cannot be independent from remote integrative processes (macrolevel) in the cortex (Nunez, 2000). The present study points to a similar conclusion in that topological factor leads to the high values of inter-correlation between different segment attributes (see above). This means that there is also a remote coordination of distant neuronal populations, which is reflected in the EEG in the form of inter-segmental temporal binding (or unbinding) between different EEG channels (for the reviews see Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2001b). The present study assessed this self-organized process (von der Malsburg, 1998) by the index of EEG structural synchrony (see Materials and Methods section). It has been suggested that the process of operational synchrony (OS) might be reflected in the values of the index of structural synchrony – ISS (Kaplan et al., 1997; Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2001b, 2003).

Earlier we already demonstrated that all OS patterns had positive values of ISS during lorazepam influence, thus indicating the active binding process under inhibition. Moreover, the percentage and the strength of such OS patterns were higher under lorazepam when compared with placebo (for detailed discussion of these findings see Fingelkurts et al., 2004a). Thus, the temporal synchronization of operations processed by local neuronal populations within different cortical sites under the lorazepam administration suggests that inhibition may also be an efficient mechanism for synchronizing large populations of neurons, rather than a mechanism for switching off irrelevant functional connections.

Topological aspects of EEG structural synchrony under the lorazepam influence. In general, EEG structural synchrony (SS) occurs significantly more often than expected in the absence of relationships between the cortical areas from which electrical activity is derived (compare with the stochastic level of synchronization). Transient synchronization of brain operations

(indexed by structural synchrony) going on in several cortical areas may result in the construction of so-called operational modules – OMs (Kaplan, 1995; Fingelkurts and Fingelkurts, 2001b) which constitute unified and metastable neural states (Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2003). This metastability permits both regional (specialized) and global (integrative) brain dynamics depending on the balance between intracortical coupling and local independence (Friston et al., 1995; Bressler and Kelso, 2001; Bressler, 2003). It is supposed that such metastabitily is a crucial aspect of brain functioning (Frison, 2000; Fingelkurts and Fingelkurts, 2001b; 2003; Breakspear and Terry, 2002b; Freeman, 2003).

Stable spatial structures. In the present study, stable (but irrelevant to conditions) configurations of structural or operational synchrony and operational modules (OM) were observed (Fig. 4). We call such SS patterns *"basic SS structures"* and propose that these may reflect basic characteristics of the EEG field for the alpha and the beta frequency bands. This finding is consistent with our previous data on the structural synchrony of the alpha activity (Fingelkurts et al., 2003b). Such stability of the functional organization of alpha and beta frequency bands probably reflects the intrinsic spatial features of those neuronal populations, the mutual activity of which is important for constant brain tasks, such as providing and controlling vital processes of the organism (Fingelkurts et al., 2003c) and mental activity (Fingelkurts and Fingelkurts, 2001b). Even lorazepam at doses used in the present study was not able to change SS of these neuronal populations.

Both frequency bands exhibited very similar spatial structures (Fig. 4), being in line with the finding that cortical sites may also synchronize their operations between different time-scales (frequency bands). The possibility of structural synchrony between brain oscillations at different frequencies for the first time has been shown previously (Kaplan et al., 1998; Fingelkurts, 1998 and also for MEG in Fingelkurts et al., 2003a). The present data are consistent with the modern view on inter-frequency consistency as one principle of brain integrative functioning (Nunez, 1995; see also the review, Fingelkurts and Fingelkurts, 2001b). According to this theory, brain information processing takes place at multiple time scales and is mediated by temporal binding between various frequencies (see the reviews Kaplan, 1998; Nunez, 2000). This allows rapid information processing simultaneously at both local and global scales (Ingber, 1995; Nunez, 2000; Breakspear and Terry, 2002b).

Specific spatial structures. Simultaneously with irrelevant SS patterns there were relevant or specific SS patterns (Fig. 5) which changed significantly together with the experimental

conditions (placebo and lorazepam). Interestingly, operationally synchronized cortical areas marked on Fig. 5 roughly correspond to those cortical sites where the majority of parameters of the local neuronal populations changed under particular condition (Fig. 2, 3). These data support the idea that specific local networks can generate rhythms in the alpha and beta bands and such activity can occur simultaneously with global oscillations in the same frequency ranges, thus governing the functional binding of local neuronal populations (Nunez, 2000). Such phenomenon has been referred to as the self-organizing emergence of globally ordered brain states (von der Malsburg, 1998; see also Haken, 1999). The main principle lies in the moment-by-moment metastable synchronization of the on-going changes in the brain activity between different cortical areas within large-scale networks (Kaplan and Shishkin, 2000; Bressler and Kelso, 2001; Fingelkurts and Fingelkurts, 2001b, 2003). These changes (rapid transition processes) have been determined as triggering moments of the discrete operations processed in various cortical sites (Kaplan et al., 1997; see also the review Fingelkurts and Fingelkurts, 2001b).

The particular topological picture of SS maps under the lorazepam intake probably reflects heterogeneously distributed $GABA_A$ receptors in the brain (Mennini and Gobbi, 1992) and different affinities of lorazepam for the various benzodiazepine receptor subtypes (Volkow et al., 1995; Semyanov, 2003). Separate issue is the diffuse extrasynaptic $GABA_A$ receptors. Extrasynaptic $GABA_A$ receptors are found within all cellular compartments (soma, dendrites and axon), and are characterized by the specificity of their cellular and subcellular distribution (Brunig et al., 2002). Typically, extrasynaptic receptors have comparatively high affinity for GABA (Banks and Pearce, 2000; Mody, 2001). It has been suggested that extrasynaptic $GABA_A$ receptors can generate a persistent tonic current due to the ambient GABA concentration (Soltesz and Nusser, 2001). Such properties make extrasynaptic $GABA_A$ receptors ideal “detectors” of changes in electrical activities within the brain and thus, they can simultaneously change the activity of several neuronal populations (Semyanov, 2003). However, relative correspondence between anatomical regularities of benzodiazepine (as well as other pharmacological agent) receptors within the cortex and structural (or operational) synchrony needs special investigation.

Concluding Remarks

Taken together, the results of the current study (1) support the idea that in many regions of the cortex coupled excitatory and inhibitory cells comprise local neuronal networks (or

neuronal populations) which execute transient dynamic behavior (Nunez, 2000). GABA inhibition leads to a significant functional reorganization of neuronal assemblies in the cortex. However, the small-, medium- and large-size neuronal populations were affected differently by the lorazepam-mediated GABA-signalling.

(2) Analysis showed that the rules of cooperation and competition act on a local scale, however the phenomenon of self-organization is in fact the emergence of remote synchrony between transient neuronal assembles governed by globally ordered metastable states. Thus, 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), 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, 2001b). However, localized changes in neuronal assemblies governed by GABA-signalling create a particular difference in remote spatial relationships between individual regions of the brain.

(3) Thus, the present methodological approach offers a plausible link between macroscopic and mesoscopic levels of brain description: it enables to analyze simultaneously remote (functional synchrony of distributed neuronal assemblies) as well as local (transient neuronal assemblies) regularities of neocortex activity.

(4) The temporal synchronization of operations processed by local neuronal populations within different cortical sites under the lorazepam administration suggests that inhibition (or more precisely GABA-signalling) may also be an efficient mechanism for synchronizing large populations of neurons, rather than a mechanism for switching off irrelevant functional connections.

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Notes

1. The conventional parametric segmentation procedures contain internal controversies and thus have limitations. The main one is the following: segmentation into stationary fragments is impossible without construction of an adequate mathematical model, but

such a model cannot be built without previous segmentation (for discussion and review see Kaplan and Shishkin, 2000; see also Brodsky et al., 1999). To overcome such disadvantages original technology for the adaptive EEG segmentation was developed.

2. Known approaches for estimating inter-cortical connectivity inevitably come up against the problem of the nonstationary nature of the brain electromagnetic field (for the reviews see Fell et al., 2000; Kaplan and Shishkin, 2000; Fingelkurts and Fingelkurts, 2001b; Fingelkurts et al, 2004a, Appendix B).
3. Competition is defined as a process in which there are multiple participants whose behavior is governed by certain rules such that one or more of the participants emerge as victors (Van Essen et al., 1990; see also Van Ooyen, 2001 for review of independent, interdependent and interference competition).

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