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Reorganization of the Composition of Brain Oscillations and Their Temporal Characteristics in Opioid Dependent Patients

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Abstract

In the present study, we examined the composition of electroencephalographic (EEG) brain oscillations in broad frequency band (0.5-30 Hz) in 22 opioid-dependent patients and 14 healthy subjects during resting condition (closed eyes). The exact compositions of brain oscillations and their temporal behavior were assessed by the probability-classification analysis of short-term EEG spectral patterns. It was demonstrated that EEG of patients with opioid dependence was characterized by (a) significant reorganization of brain oscillations with increase in the percentage of beta- and mostly fast-alpha-rhythmic segments, (b) longer periods of temporal stabilization for alpha and beta brain oscillations and by shorter periods of temporal stabilization for theta and polyrhythmic activity when compared with control subjects, and (c) right-sided dominance (significantly larger relative presence of particular spectral patterns in EEG channels of the right hemisphere). These effects were widely distributed across the cortex with the maximum magnitude in the occipital, right parietal, temporal, and frontal areas. Taken together the present study suggested (a) an allostatic state with neuronal activation, and (b) high sensitivity of the right hemisphere to adverse opioid effects.

Key words: Electroencephalogram (EEG); Multiple brain oscillations; Opiates; Opioid addiction; Opioid dependence; Probability-classification analysis; Short-term spectral patterns.

Abbreviations:

CC – Correlation Coefficients
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders
DDOA – Duration of Daily Opioids Abuse
EEG – Electroencephalogram
FFT – Fast Fourier Transform
ICA – Independent Component Analysis
PCP – Probability Classification Profile
SP – Spectral Pattern
SCID – Structured Clinical Interview

1. Introduction

Drug addictive behavior may emerge from the dynamic activity of entire neural networks rather than from any single brain structure. Indeed, recently brain is seen as a massively interactive, dynamic system, without centralized control which displays a characteristic metastability around certain homeostatic levels (for the reviews on metastability, see Kelso, 1995; Fingelkurts and Fingelkurts, 2004). In this context drug addiction 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 adaptive process of achieving stability through change, a stability that is not within the normal homeostatic range (McEwen, 1998). Recently, allostatic alteration of brain function through stress-related mechanisms has been identified as one component of the pathway to addiction (Koob and Le Moal, 2001).

Here, the electroencephalogram (EEG) provides a satisfactory measure for accessing integrative brain functions and large-scale dynamic of the brain activity (with a temporal resolution in the order of milliseconds) associated with health and pathology (Livanov, 1977; Nunez, 2000). Indeed, spontaneous activity at the cortical level does reflect different neurological states and functional properties of neuronal assemblies (Lopes da Silva, 1991; Fingelkurts et al., 2004a). Thus, EEG studies of opioid abusers have revealed the increase of beta (Costa and Bauer, 1997; Franken et al., 2004) and alpha (Shufman et al., 1996; Davydov and Polunina, 2004; Polunina and Davydov, 2004) activities in addictive brain. However, EEG analysis in these studies had a serious limitation: spectral analysis was based on averaging of EEG parameters across extended periods of time and/or broad fixed frequency bands. It was demonstrated that the total power spectrum does not characterize each of the individual power-spectra for each EEG segment (Fingelkurts et al., 2003a, 2004b). As such, averaging of the EEG signal may not only mask temporal dynamics of EEG characteristics, but may also lead to ambiguous data interpretation (Fingelkurts et al., 2002, 2004b, for the review see Kaplan, 1998). Hence, when examining the average brain electromagnetic parameters, it is not clear whether the observed phenomenon is real (not the "virtual" result of averaging procedure) and typical for the whole analyzed signal. Moreover, according to Dumermuth and Molinari (1987), total EEG power may be affected by polyrhythmic disorganized activity (a mixture of activity of small neuronal subpopulations each with its own mode (Tirsch et al., 2000)). In this case different indices and parameters of EEG may suffer from the influences of such activity, instead of reflecting true rhythmic activity.

Additionally, in all studies related to EEG spectral analysis in opioid abusers, the frequency bands were predefined and taken in isolation from each other. This does not permit researchers to examine the behavior of the actual/natural composition of brain oscillations involved. At the same time, brain functions are indeed represented by multiple oscillations (Basar et al., 2000).

In connection to this, it seems reasonable to examine the actual composition of brain oscillations and their temporal behavior in a broad frequency band (0.5-30 Hz) in EEG of patients with opioid dependence. To assess the exact composition of brain oscillations and their temporal dynamics one should use a robust, model-independent technique which (a) considers EEG nonstationarity, (b) does not need averaging procedure and prior knowledge about the underlying dynamics, and (c) produces results which are ease to interpret in terms of their neurophysiological correlates. The probability-classification analysis of short-term EEG spectral patterns (SP) (Kaplan et al., 1999; Fingelkurts et al., 2003a) satisfies all these criteria. This analysis results in temporal dynamics of short-term EEG SPs and their probability classification profile (PCP).

It was demonstrated that PCP is highly stable over time (Fingelkurts et al., 2006a) and provides adequate and detailed description of electromagnetic brain activity during health (Kaplan et al., 1999; Fingelkurts et al., 2003a,b) and pathological brain conditions (Fingelkurts et al., 2000; 2006b). Additionally, PCP is sensitive to drug effects on brain dynamics (Fingelkurts et al., 2004b). Another advantage to using PCP is that polyrhythmic/disorganized EEG activity is automatically isolated in a separate class, and thus does not affect classes with true rhythmic activity (Fingelkurts et al., 2003a). At the same time, class with polyrhythmic/disorganized activity in its turn could be also subjected to analysis. This is justified since it was reported that the ratio of polyrhythmic/disorganized activity in EEG spectrum is strongly influenced by genetic factors (Meshkova, 1988), and as was explored in our early work (Fingelkurts et al., 2003a, 2004b) the amount of polyrhythmic/disorganized activity in EEG is dependent on functional brain state.

The aim of the present study was to investigate the actual composition of brain oscillations and their temporal behavior in a broad frequency band (0.5-30 Hz) in EEG of patients with opioid dependence during resting condition. Considering that repeated exposure to opiates induces a widespread remodeling of cortical regions (Hyman and Malenka, 2001; Robinson et al., 2002) and more generally might result in the allostatic state around new homeostatic levels of the brain (Koob and Le Moal, 2001), we predict that EEG of opioid

abusers would have a considerable reorganization of the composition of brain oscillations and altered temporal characteristics.

The present study is a first part of a longitudinal research program. This program was aimed to explore the actual composition of brain oscillations and their temporal behavior in current opioid addicts, entering the hospital unit for withdrawal and evaluation for methadone treatment program. The study of the actual composition of brain oscillations and their temporal behavior during withdrawal and after methadone treatment will be published elsewhere (Fingelkurts et al., in submission).

2. Methods

2.1. Subjects

The study included a total of 22 opioid-dependent patients (Table 1A) and 14 healthy subjects (Table 1B), served as control. Patients were hospitalized for 2 weeks in a drug-withdrawal unit before starting methadone maintenance therapy. Criteria for such therapy at Helsinki University Central Hospital included minimum age of 20 years, 4 years of documented i.v. opioid abuse, and failure of institutional or long-lasting out-patient withdrawal therapy, which also served as criteria for the present study inclusion. Exclusion criteria for methadone maintenance therapy were uncontrolled polysubstance abuse, physical or psychiatric illness that made routine therapy impossible, and alcohol dependence. In the present study, additional exclusion criteria for both patients and controls were major head trauma, chronic neurologic illness or ongoing medication for neurologic symptoms. Each participant was evaluated by brain MRI, and participants showing lesions indicating vascular pathology or brain injury were excluded.

Some patients reported irregular (episodic) use of benzodiazepines (15 patients), cannabis (5 patients), and amphetamine (5 patients) when heroin was not available. However, street buprenorphine and heroin were the only drugs used by the patients regularly (daily) for several years (at least 4).

Psychiatric diagnoses of patients and controls (Table 1) were explored using Structured Clinical Interviews I and II (SCID I and II) (First et al., 1994a,b) that afford detailed information according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994). One patient had negative HCV-AB and HbsAg tests. All patients studied were negative for HIV-AB test. One patient refused to be tested for HIV. Patients had no neurological complaints. Controls were volunteers from the staff of the

Institution, and no control had any experience with illegal drugs but all had drunk alcohol on social occasions. However, none met criteria of abuse of or dependence on alcohol. Controls did not fulfill any criteria for DSM-IV disorders on SCID I or II. Even though patients group had in average smaller number of years of education than control group, the difference was nonsignificant (Table 1). The study was accepted by the Ethics Committees of Helsinki University Central Hospital and all the subjects studied gave informed written consent before enrolling in the study.

Table 1. Groups demographics.

A. Patients

Subject ID	Subject Sex	Subject Hand	Age	Education (years)	Years of abuse	Dayley dose of heroin (g)	Dayley dose of buprenorfine (mg)	DSM-IV axis I Diagnosis	DSM-IV axis II Diagnosis
1	F	R	38	8	20	1.5	8	Opioid & benzodiazepin dependence	Antisocial
2	M	R	28	10	8	1	16	Opioid & benzodiazepin dependence	Antisocial
3	F	R	46	10	10	0.1	0	Opioid dependence	Antisocial, features of obsessive-compulsive, avoidant, depressive
4	F	R	36	11	6	1	0	Opioid dependence	Antisocial, borderline, features of paranoid, schizoid, obsessive-comp
5	F	R	41	9	26	1	16	Opioid & benzodiazepin dependence	Borderline, features of obsessive-compulsive, antisocial, and avoidant
6	M	R	21	12	4	0.2	16	Opioid dependence	Antisocial
7	M	R	36	9	8	1	0	Opioid & benzodiazepin dependence	Borderline, features of paranoid, obsessive-compulsive
8	M	R	25	12	8	0.5	14	Opioid & benzodiazepin dependence	Antisocial, borderline, features of obsessive-compulsive
9	M	R	35	12	5	1	4	Opioid dependence	Antisocial, borderline
10	M	R	32	11	5	0.4	8	Opioid dependence	Antisocial, features of obsessive-compulsive, paranoid
11	F	L	34	13	7	0.2	8	Opioid & benzodiazepin dependence	Antisocial
12	M	R	30	13	10	1.5	10	Opioid & benzodiazepin dependence	Antisocial, borderline, features of paranoid, schizotypal, obsessive-com
13	M	R	34	12	9	0.5	4	Opioid dependence	Antisocial, features of passive-aggressive, paranoid
14	F	R	29	12	12	1	0	Opioid & benzodiazepin dependence	Antisocial, features of borderline, obsessive-compulsive
15	F	R	33	14	12	1	8	Opioid dependence	Antisocial, features of obsessive-compulsive
16	M	R	24	10	7	1	4	Opioid & benzodiazepin dependence	Borderline
17	M	R	43	9	26	0.1	0	Opioid & benzodiazepin dependence	Features of borderline, antisocial, and narcissistic
18	M	R	29	12	10	0.05	4	Opioid & benzodiazepin dependence	Antisocial, borderline
19	M	L	30	10	8	2	32	Opioid & benzodiazepin dependence	Antisocial
20	M	R	36	12	7	0.5	2	Opioid & benzodiazepin dependence	Antisocial
21	M	R	35	10	20	0.2	8	Opioid & benzodiazepin dependence	Antisocial, features of borderline, paranoid, schizotypal
22	F	R	25	10	8	1.2	8	Opioid & benzodiazepin dependence	Antisocial, features of obsessive-compulsive
Average			32.7	11	10.7	0.8	7.7		
Standard deviation			6.3	1.6	6.4	0.5	7.6		

B. Healthy subjects

Subject ID	Subject Sex	Subject Hand	Age	Education (years)	Years of abuse	Dayley dose of heroin (g)	Dayley dose of buprenorfine (mg)	DSM-IV axis I Diagnosis	DSM-IV axis II Diagnosis
1	F	R	25	12	-	-	-	-	-
2	M	R	33	15	-	-	-	-	-
3	M	R	30	15	-	-	-	-	-
4	M	R	31	15	-	-	-	-	-
5	F	R	36	12	-	-	-	-	-
6	F	R	37	10	-	-	-	-	-
7	F	R	39	12	-	-	-	-	-
8	F	R	23	13	-	-	-	-	-
9	F	R	43	12	-	-	-	-	-
10	M	R	39	15	-	-	-	-	-
11	F	L	30	15	-	-	-	-	-
12	F	R	43	19	-	-	-	-	-
13	M	R	27	15	-	-	-	-	-
14	M	R	30	12	-	-	-	-	-
Average			33.3	13.7					
Standard deviation			6.4	2.3					

F - Female, M - Male, L - Left, R - Right

Before the EEG-study patients gave the urine samples twice a week for minimum of six weeks to exclude other substance abuse than opioids. EEG was registered on the day of admission. The patients were investigated on the day of admission and all had abused opiods (buprenorphine or heroin) during twelve hours before EEG registration; the dosages were the patients' usual dosages (see Table 1A). This permitted us to investigate patients while abusing opioids without a contribution of withdrawal symptoms: to our knowledge there are only two such EEG-studies (Feinstein, 1975; Shufman et al., 1996). None of the patients in the present study had a withdrawal syndrome at the time of EEG registration, verified by Gossop test (Gossop, 1990).

2.2. Trial design

Following electrode placement and instruments calibration, a subject was seated in a comfortable chair in a dimmed room and the experimental procedure was explained. The EEG recording was started at Noon. To reduce muscle artifacts in the EEG signal, a subject was instructed to assume a comfortable position, to avoid movement, and to look straight in front of him/her (even though the eyes were closed). The behavior of a subject was observed on a TV monitor throughout the experiment. Each subject underwent five minutes EEG registration with eyes closed.

2.3. EEG registration

All recordings were performed in a electromagnetically 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 600 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 and each channel prior to data collection; this was always below 5 kΩ. Vertical and horizontal electro-oculograms were recorded. The presence of an adequate signal was determined by visually checking each raw signal on the computer screen.

2.4. Data processing

EEG components containing artifacts due to eye blinks, significant muscle activity, and movements were automatically removed by means of ICA (Independent Component Analysis) procedure (Hyvärinen et al., 2001). After removing artifact-related components, the back projection of remaining components originating from brain was performed (Joyce et al., 2004). The algorithm is implemented as "The FastICA package for MATLAB" freely available online http://www.cis.hut.fi/projects/ica/fastica/ .

A full artifact-corrected EEG streams contained 5-min continuous signal (eyes closed) for each patient and control subject. EEG data were split into 2 distinct groups: "opioid" and "control." Further, data processing was performed separately for each 1-min portion of the signal. Due to the technical requirements of the tools which were later used to process the data, 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, $O_{1/2}$) were analyzed with a converted sampling rate of 128 Hz.

After resampling and prior to spectral analysis, each EEG signal was bandpass-filtered in the 0.5-30 Hz frequency range. This frequency range was chosen because approximately 98% of spectral power lies within these limits (Thatcher, 2001). Individual power spectra were calculated in the range of 0.5–30 Hz with 0.5-Hz resolution (61 values), using FFT with a 2-sec Hanning window shifted by 50 samples (0.39-sec) for each channel of 1-min EEG. These values proved the most effective for disclosing oscillatory patterns from the signal according to previous studies (Levy, 1987; Kaplan, 1998, for details, see Fingelkurts et al., 2006b). Sliding spectral analysis compensated for the effects of windowing, permitted us not to lose information from residual activity, and improves statistical confidence of the results. Additionally, a shift in 50 samples permitted us to obtain a relatively high resolution (0.39-sec) of the boundaries of the EEG segments with temporally stabilized oscillatory activity.

As a result, the total number of individual SPs for each channel of 1-min EEG was 149. These SPs formed the multitude of the objects for further classification procedure. The compositions of brain oscillations (in terms of EEG SPs) were estimated with the help of a probability-classification analysis of the short-term EEG SPs (*SPclass* tool). SPclass is an advanced clean re-implementation of the SCAN tool (described in detail in Fingelkurts et al., 2003a). SPclass algorithms overcome various numerical limitations which existed in its predecessor and modify and extend its functionality as follows:

During the first stage, sequential single EEG SPs were adaptively classified in each channel of 1-min EEG using a set of standard SPs. This crucial step of generating the set of standard SPs was earlier done in a manual, time-consuming and rather empirical and arbitrary manner. With the new algorithm, the SPclass tool generates these standard SPs automatically from the EEG data itself using specially designed heuristics and Pearson's correlation coefficients (CC): A pool of SPs (n = 536 400) was built from all the SPs of the entire EEG signal (all locations) for all subjects (patients and control). From this pool, all identical SPs with peaks in the same frequencies were counted. The peak-detection was based on normalizing the SP to within-SP relative percentages of magnitude, where acceptance is achieved when the peak exceeds a given (60%) percent-magnitude (100% corresponds to the magnitude of the highest peak within the SP). The set of identical SPs with the highest count was the most likely candidates to form the "set of standard SPs." Only those SPs with minimum cross-CC were selected. Thus, the standard set included 32 SPs.

As a result of the adaptive classification technique, each current SP was labeled according to the index of the class to which it belongs. Hence, each EEG signal was reduced to a sequence of individually classified SPs.

At the second stage, PCPs of SPs for each channel of 1-min EEG in each subject were calculated. These PCPs were calculated by taking the relative number of cases of an SP type as a percentage of the total amount of all SPs within each EEG channel – presented as the histogram of relative presence of each SP type. PCPs were averaged across 110 (for opioid abusers) and 70 (for healthy control) 1-min EEG signals separately for each EEG channel. It was expected that these PCPs would make it possible to illustrate in detail (in SP description) the composition of brain oscillations and their percent ratio.

2.5. Statistics

In order to reveal any statistically significant differences in the relative presence of each SP type in PCPs between opioid abusers and control subjects the Wilcoxon test was used separately for each type of SPs presented in the PCP. Statistical significance was assumed when $P < 0.05$ (only statistically significant values are displayed). Since we intended to assess each variable in its own right, no Bonferroni correction was applied (for the problems associated with Bonferroni adjustments, see Rothman, 1990; Perneger, 1998).

However, in the case where we examined spatial distribution of significant differences 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 $P = 5\%$.

Surrogate data were used to control for the neural (non-random) origin (Ivanov et al., 1996) of the temporal dynamics of SPs. Surrogate signals had identical parameters with the original signals but do not have temporal correlations: each channel of the actual EEG was subjected to a randomized mixing of SPs. In such a way, the natural dynamics of the SP sequence within each EEG channel was completely destroyed, but the percentage ratio between different types of SPs remained the same. This modified EEG was described as "random".

An asymmetry score was computed by estimating a statistically significant difference between SP type's relative presence in PCP for all sites that have symmetrical left and right locations (O_1 and O_2, and so on).

3. Results

3.1. General description of EEG for opioid abusers and control subjects

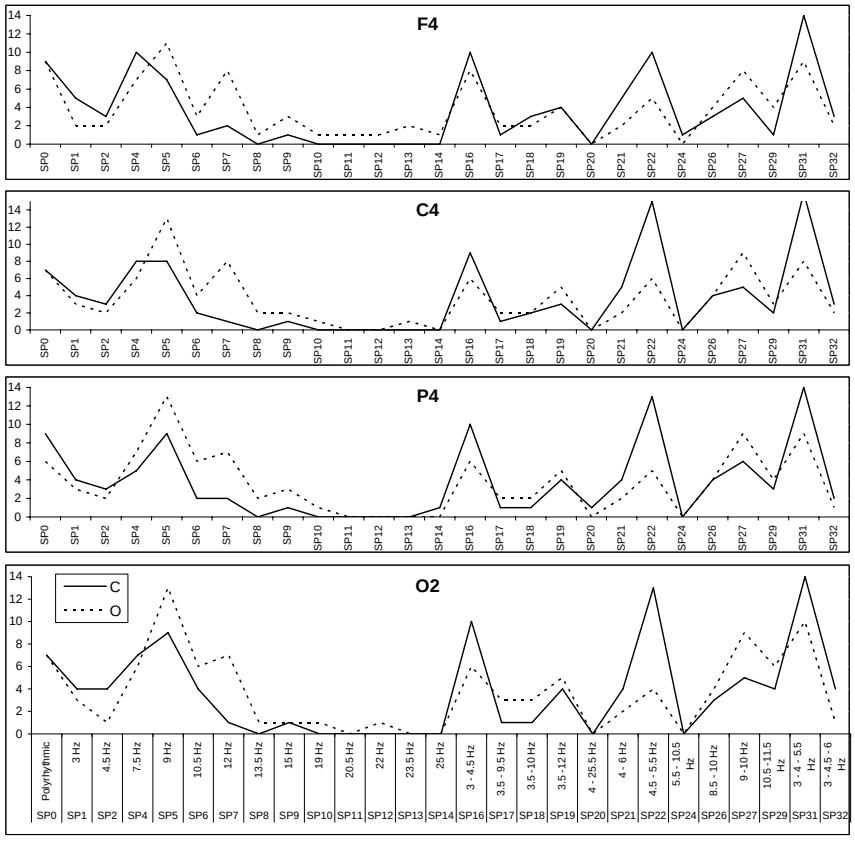
For both opioid abusers and control subjects all EEG channels were characterized by similar sets of SP types dominant in the PCPs (Fig. 1A). The spatial distribution of brain oscillations was generally consistent with that revealed in earlier studies: a significant ($P < 0.05$) increase for alpha- and decrease for delta- and theta-rhythmic EEG segments in frontal-to-occipital direction was observed (Fig. 1A).

At the same time, the comparative analysis of PCPs for opioid abusers and control subjects demonstrated that (a) the number of SP types observed in PCPs was significantly larger ($P < 0.00001$) in opioid abusers when compared with control subjects (Fig. 1B), and (b) there were unique SP types associated only with opioid addiction: SP8 (main peak at 13.5 Hz), SP10 (19 Hz), SP11 (20.5 Hz), SP12 (22 Hz), and SP13 (23.5 Hz) (Table 2).

Although EEGs for both opioid abusers and control subjects were mostly characterized by the same dominant SP types (Fig. 1A), opioid abusers and control subjects differed from each other according to the probability estimation of the occurrence of these SP types in PCPs.

3.2. Characteristics of opioid-induced EEG changes

In general, opioids affected the activity in all EEG channels: there was no a single EEG channel without statistically significant differences in the relative presence of at least 42% of SP types in PCPs between opioid abusers and control subjects. At the same time, different cortical areas were characterized by different number of SP types which demonstrated statistically significant difference in their relative presence in PCPs, thus indicating the magnitude of the opioids effect. Hence, occipital (O1, O2, Oz), right parietal (P4), right temporal (T4, T6) and frontal (F3, F4, Fz) EEG channels were maximally affected ($P < 0.0002$) by opioids - the number of SP types which demonstrated statistically significant difference in their relative presence in PCPs between opioid abusers and control subjects reached in these EEG channels up to 75% from all observed SP types (not shown).



A

Number of SP types observed in EEG

EEG channel	C	O
O1	18	18
O2	18	21
Oz	18	19
P3	19	20
P4	20	20
Pz	18	20
T3	18	20
T4	17	21
T5	19	19
T6	18	20
C3	18	22
C4	18	21
Cz	17	21
C5	18	21
C6	20	22
F3	19	23
F4	19	24
Fz	19	23
F7	19	23
F8	21	23
Mean	18.55±1.0	21.05±1.6

C - Control
O - Opioid abusers

B

Figure 1. Probability-classification profiles (A) and the number of spectral pattern (SP) types (B) typical for EEG of opioid dependent and control subjects. Data averaged across 110 EEGs for opioid abusers and 70 EEGs for control subjects. For (A): O_2 = occipital, P_4 = parietal, C_4 = central, and F_4 = frontal EEG channels placed at the right hemisphere of the brain. The *x*-axis displays the labels (numbers) of the standard SP from 0 (polyrhythmic SPs) to 32 and their main frequency peaks. The *y*-axis displays the share of the

corresponding SPs in the percentage from the total number of the classified SPs. A line graphic was chosen instead of a bar for the ease of comparison. (Note that *x*-axis consists of 33 discrete values, all the in-between values are meaningless). Only those SPs which presented in probability-classification profiles of all EEG channels are presented.

Comparative analysis of the PCPs demonstrated that EEG under opioid influence was characterized by a larger percentage of theta1-alpha1- [SP17 (main peaks at 3.5 and 9.5 Hz)], alpha1- [SP5 (9 Hz)], alpha2- [SP7 (12 Hz), SP8 (13.5 Hz)], alpha1-alpha2- [SP27 (9-10 Hz)], beta1- [SP9 (15 Hz), SP10 (19 Hz)], and beta2- [SP11 (20.5 Hz), SP12 (22 Hz), SP13 (23.5 Hz)] rhythmic segments, and by a smaller percentage of theta2- [SP2 (4.5 Hz)], broad theta- [SP16 (3-4.5 Hz), SP22 (4.5-5.5 Hz), SP31 (3-4-5.5 Hz)], and theta2-beta2- [SP20 (4-25.5 Hz)] rhythmic segments when compared with the control subjects ($P < 0.05$–$P < 0.000001$ for different channels) (Table 2).

Table 2. Spectral pattern types which demonstrated statistically significant (*Pcorrected* < 0.002-*Pcorrected* < 0.000001) difference between opioid abusers and control subjects.
Data averaged across 110 EEGs for opioid abusers and across 70 EEGs for control subjects.

Brain oscillation	SP type	Main peak (Hz)	EEG channels (%)	Topographical distrbution
C > O				
Theta2	SP2	4.5	55	O1,O2,Oz,Pz,C3,C5,T8,F3,Fz,F7
	SP16	3 - 4.5	90	O1,O2,Oz,P3,P4,Pz,P7,P8,C3,C4,Cz,C5,C6,T7,T8,F3,Fz,F7
Broad theta	SP22	4.5 - 5.5	100	distrubuted across all EEG channels
	SP31	3 - 4 - 5.5	100	distrubuted across all EEG channels
Theta2-beta2	**SP20**	**4 - 25.5**	20	P4,C6,F3,Fz
C < O				
Theta1-alpha1	SP17	3.5 - 9.5	40	O1,O2,Oz,P4,P8,F4,C4
Alpha1	SP5	9	70	O2,Oz,P3,P4,Pz,P8,C3,C4,Cz,C5,T8,F3,F4,Fz
Alpha2	SP7	12	100	distrubuted across all EEG channels
	SP8	**13.5**	80	O2,Oz,P4,Pz,P8,C3,C4,Cz,C5,T7,T8,F3,F4,Fz,F7,F8
Alpha1-alpha2	SP27	9 - 10	90	O1,O2,Oz,P3,P4,Pz,P7,P8,C4,Cz,C5,C6,T7,T8,F3,F4,Fz
Beta1	SP9	15	45	P4,Pz,P7,Cz,C5,T8,F4,Fz,F8
	SP10	**19**	80	O1,O2,Oz,P4,Pz,P8,C3,C4,Cz,C5,C6,T7,T8,F3,F4,Fz
	SP11	**20.5**	25	F3,F4,Fz,F7,F8
Beta2	**SP12**	**22**	35	O2,T8,F3,F4,Fz,F7,F8
	SP13	**23.5**	55	C3,C4,Cz,C5,C6,T8,F3,F4,Fz,F7,F8

C = Control subjects; O = Opioid dependent subjects; SP = Spectral patterns; Hz = Frequency; "SP type" column represents the labels of spectral pattern types; "EEG channels" column represents the number (in %) of EEG channels where relative presence of a given SP type demonstrated statisically significant difference between opioid abusers and control subjects; Bold indicates unique spectral pattern types for opioid abusers and control subjects

The main effects of opioids described above were distributed across the whole cortex and were detected mostly in the majority of EEG channels (*Pcorrected* < 0.002–*Pcorrected* < 0.000001 for different channels) (Table 2).

3.3. Relationships between duration of daily opioids abuse and the number of SP types

The duration of daily opioids abuse (DDOA) predicted positively the number of SP types observed in PCPs and the percentage of polyrhythmic SPs: with the increase of DDOA, (a) the number of SP types increased ($r = 0.98$, $P < 0.005$, Spearman rank order correlation) and (b) the percentage of polyrhythmic SPs increased ($r = 0.79$, $P < 0.05$, Spearman rank order correlation).

3.4. Interhemisphere asymmetry in the EEG for opioid abusers and control subjects

In general, for opioid abusers and control subjects, interhemisphere asymmetry (*Pcorrected* < 0.002–*Pcorrected* < 0.0001, indexed by statistically significant difference in relative presence of SPs in PCPs) was observed in the majority of homologous EEG-channel pairs (not shown). Only F3-F4 homologous EEG-channels pair did not reveal any interhemisphere asymmetry. Opioid abusers had more EEG-channel pairs with right-side-dominance asymmetry (significantly larger relative presence of particular spectral patterns in EEG channels of the right hemisphere) than EEG-channel pairs with left-side-dominance asymmetry (significantly larger relative presence of particular spectral patterns in EEG channels of the left hemisphere) ($P < 0.05$), whereas control subjects had the opposite results ($P < 0.05$) (not shown).

3.5. Temporal stabilization of the spectral patterns under opioids influence

The temporal stabilization of SP types was evaluated by computing the average number (for all EEG channels) of successive *m* EEG epochs of the same SP type (including polyrhythmic spectra – the type "0"), where *m* is the range from 1 to 149, and was then described as a "block". In this case the particular block length reflects the particular period of temporal stabilization of brain oscillations. The results of this analysis are summarized in Figure 2.

EEG of opioid abusers was characterized by smaller index values for short periods of temporal stabilization ($P < 0.05$–$P < 0.01$ for different block lengths) and greater index values

for long periods of temporal stabilization ($P < 0.05$–$P < 0.001$ for different block lengths) when compared with EEG of control subjects (Fig. 2).

However, it is obvious that even in the absence of any correlation between the EEG SPs there should be a temporary stochastic stabilization of the SPs, which may reflect merely occasional combinations of SP types. As control for the neural origin of temporal dynamics of SPs, "random" EEG (an EEG with a random mix of different SP types separately for each channel) was used. From Figure 2, it can be seen that the actual EEG data substantially differed from the "random EEG" ($P < 0.01$-$P < 0.0001$ for different block lengths).

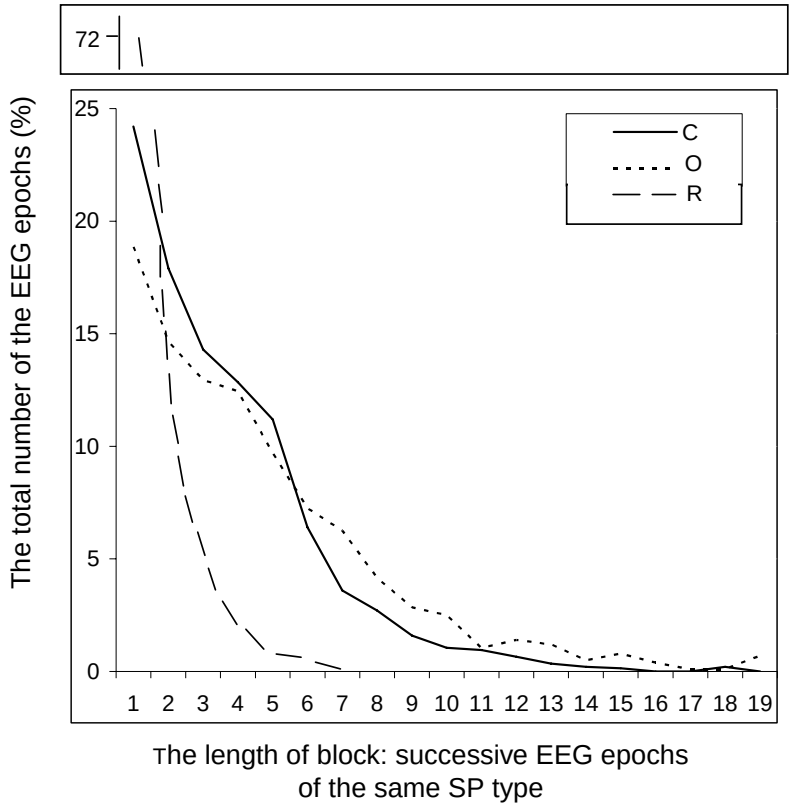


Figure 2. The average number (for all EEG channels, *n* = 20) of successive *m* EEG epochs of the same SP type (including polyrhythmic spectra) (the *y*-axis), where *m* is the range from 1 to 149 (the *x*-axis). The values are presented as a percentage of the total number of the epochs in all EEGs, for 22 opioid-dependent patients (n = 16 390) and 14 control subjects (n = 10 430). C = control subjects; O = opioid-dependent patients; R = "Random EEG" = EEG which natural sequence of spectral pattern types has been completely removed in each individual channel; SP = spectral patterns**.**

Does specific type of brain oscillations (in terms of SPs) maintain a particular period of temporal stabilization? To answer this question we analyzed the maximum periods of temporal

stabilization for all SP types which were found in PCPs for EEG of opioid abusers and EEG of control subjects (Fig. 3).

The maximum periods of temporal stabilization for SP types presented in Figure 3 as block length were recalculated in time-scale. This analysis demonstrated that the brain "maintains" the stabilization period of neural activity between 2 and 5.12 sec (for different SPs) for both opioid abusers and control subjects (Fig. 3). The longest maximum periods of temporal stabilization for opioid abusers were found for alpha and beta activity, whereas for control subjects the maximum period of temporal stabilization was the longest for polyrhythmic and theta activity.

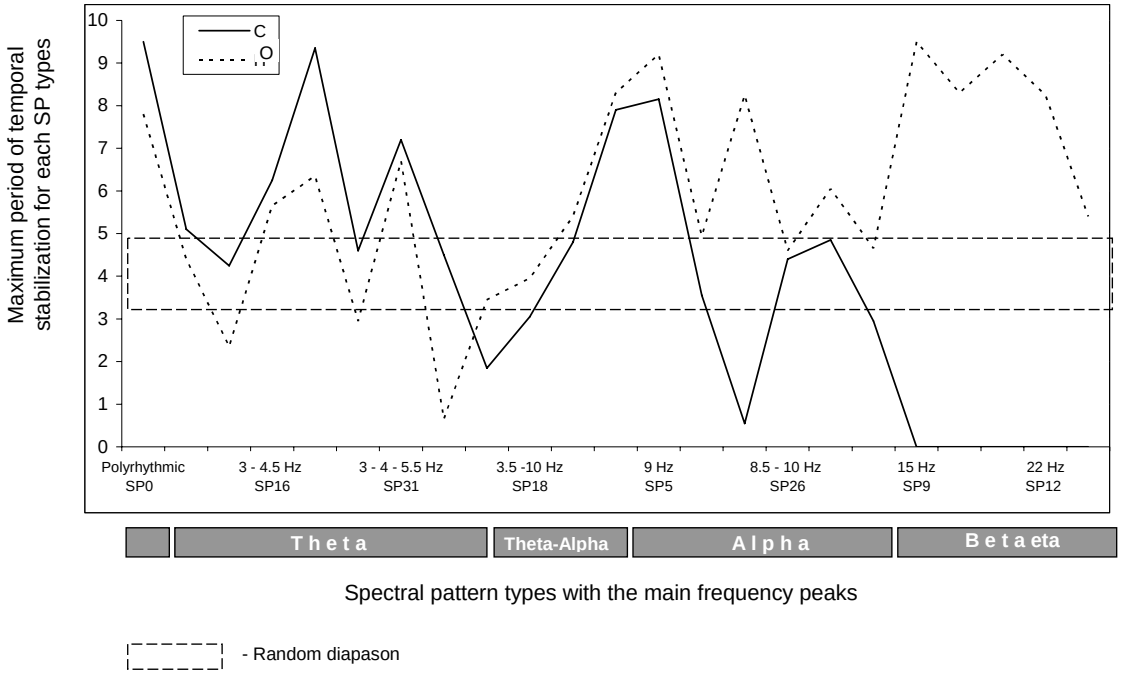


Figure 3. The maximum periods of temporal stabilization for each spectral pattern type, which was found in the EEG probability-classification profiles. The *x*-axis displays the labels (numbers) of the EEG spectral patterns (SP) corresponding to the standard SP set (including polyrhythmic spectra – type "0") and their main frequency peaks. The *y*-axis displays the maximum periods of temporal stabilization for each SP types (in terms of block length – *m* EEG epochs follow in succession without SP type change, where *m* is the range from 1 to 149). Data averaged across all subjects and all EEG channels. Horizontal dotted line bar represents random range of the maximum periods of temporal stabilization for "Random EEG" (EEG whose natural sequence of spectral pattern types has been completely removed in each individual channel). C = control subjects; O = opioid-dependent patients.

Moreover, for opioid abusers' EEG, all SPs with theta1–alpha2-, alpha1-, alpha2-, alpha1-alpha2-, beta1-, and beta2-activity were characterized by longer maximum periods of temporal stabilization than for controls EEG ($P < 0.05$-$P < 0.000001$ for different SP types). At the same time, for controls EEG, all SPs with theta2-, theta1-theta2-, and polyrhythmic activity were characterized by longer maximum periods of temporal stabilization than for opioid abusers EEG ($P < 0.05$-$P < 0.000001$ for different SP types) (Fig. 3). The duration of such periods for "random EEG" was different from the actual EEG and reached up to 2.3–2.6 sec (for different SP types) (Fig. 3).

3.6. Specificity of opioid-induced EEG changes

Considering that several patients besides opioid dependence met also DSM-IV criteria for benzodiazepine dependence, all patients were assigned to two analysis subgroups: opioid-dependent group and opioid+benzodiazepine-dependent group. Correlation analysis (Spearman rank correlations) between PCPs of these two groups revealed very high values (from 0.78 to 0.96, $P < 1.2e\text{-}05$ – $P < 1e\text{-}07$, for different EEG channels, Table 3.A). Additionally, the probability of the occurrence of particular brain oscillations and different parameters of PCPs in these two groups differed insignificantly (Table 3.B). EEG temporal characteristics in these two subgroups either coincided or differed insignificantly (Fig. 4). Thus, results of the comparison analysis between opioid-dependent and opioid+benzodiazepine-dependent subgroups conformed that opioid effects which were observed in the previous sections were dominant and characteristic.

Table 3. Comparison of opioid and opioid+benzodiazepine subgroups of patients.

A. Spearman rank correlations of probability-classification profiles for opioid and opioid+benzodiazepine subgroups of patients. Data presented for each EEG channel separately.

EEG channels	*R*	Significance	*Z*
O1	0.9	$p < 5.113e-07$	$Z = 5.0$
O2	0.9	$p < 5.113e-07$	$Z = 5.0$
Oz	0.96	$p < 1.012e-07$	$Z = 5.3$
P3	0.94	$p < 1.795e-07$	$Z = 5.2$
P4	0.93	$p < 2.088e-07$	$Z = 5.2$
Pz	0.92	$p < 3.081e-07$	$Z = 5.1$
T5	0.91	$p < 4.087e-07$	$Z = 5.1$
T6	0.93	$p < 2.323e-07$	$Z = 5.2$
C3	0.89	$p < 8.172e-07$	$Z = 4.9$
C4	0.91	$p < 3.721e-07$	$Z = 5.1$
Cz	0.91	$p < 3.555e-07$	$Z = 5.1$
C5	0.9	$p < 5.537e-07$	$Z = 5.0$
C6	0.89	$p < 7.021e-07$	$Z = 5.0$
T3	0.91	$p < 3.853e-07$	$Z = 5.1$
T4	0.78	$p < 1.283e-05$	$Z = 4.4$
F3	0.81	$p < 6.614e-06$	$Z = 4.5$
F4	0.82	$p < 5.641e-06$	$Z = 4.5$
Fz	0.94	$p < 1.84e-07$	$Z = 5.2$
F7	0.82	$p < 4.533e-06$	$Z = 4.6$
F8	0.83	$p < 3.744e-06$	$Z = 4.6$

B. The number of SP types and the probability of the occurrence of particular brain oscillations (measured as the sum of percentages of all SP types which belong to the same type of brain oscillation). Data averaged across all subjects and all EEG channels.

	O+B	O	*P*-Value
Number of SP types	25.75 (±0.85)	25.65 (±0.81)	NS
Number of unique SP types	3.15 (±1.4)	2.4 (±0.7)	NS
Theta activity	29.55 (±5.73)	32.2 (±11.03)	NS
Alpha activity	45.25 (±9.23)	41.35 (±8.49)	NS
Beta activity	5.7 (±4.91)	4.05 (±1.87)	NS
Theta-Alpha activity	9.2 (±2.48)	10.48 (±3.58)	NS
Polyrhythmic activity	7.25 (±2.1)	7.8 (±1.8)	NS

Data presented as means (± standard deviations); O+B = opioid+benzodiazepine subgroup of patients; O = opioid subgroup of patients; NS = nonsignificant difference; SP = spectral pattern

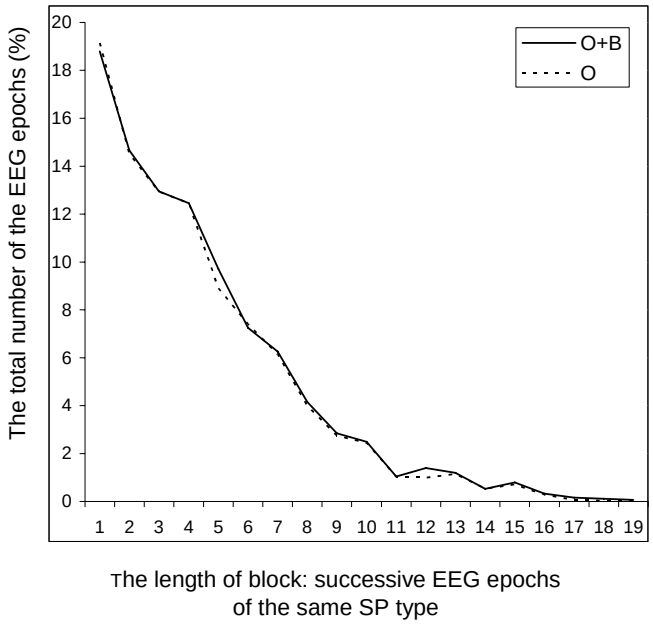


Figure 4. The average number (for all EEG channels, *n* = 20) of successive *m* EEG epochs of the same SP type (including polyrhythmic spectra) (the *y*-axis), where *m* is the range from 1 to 149 (the *x*-axis). The values are presented as a percentage of the total number of the epochs in all EEGs, for 7 opioid-dependent patients (*n* = 5 215) and 15 opioid+benzodiazepine-dependent patients (*n* = 11 175). O+B = opioid+benzodiazepine-dependent patients; O = opioid-dependent patients; SP = spectral patterns**.**

4. Discussion

Patients in the present study met criteria for opioid and opioid+benzodiazepine dependence. Both opioids and benzodiazepines have strong influence on EEG (Shufman et al., 1996; Fingelkurts et al., 2004b; Franken et al., 2004; Polunina and Davydov, 2004; Jensen et al., 2005). However, considering (a) very high correlations of PCPs for opioid-dependent and opioid+benzodiazepine-dependent subgroups of patients (Table 3.A) and (b) very high similarity of PCPs parameters (Table 3.B) and of EEG temporal characteristics (Fig. 4) between opioid-dependent and opioid+benzodiazepine-dependent subgroups of patients, the findings presented in the present study are determined mainly by opioid dependence.

4.1. Characteristics of opioid-induced EEG changes

We found that opioids affected the activity in all EEG channels. At the same time, the magnitude of the opioid effect (the number of SP types which demonstrated statistically

significant difference in their relative presence in PCPs) was different for different EEG channels. Thus, occipital (O1, O2, Oz), right parietal (P4), right temporal (T4, T6) and frontal (F3, F4, Fz) EEG channels demonstrated maximal opioids effect. This finding is consistent with other studies: Two studies demonstrated persisting prefrontal dysfunction in chronic heroin abusers (Papageorgiou et al., 2001; Lee and Pau, 2002). Perhaps chronic abuse of opiates, may lead to changes in neurotransmission present in dopamine terminals such as frontal cortex (Kalivas and Sorg, 1997). The literature facts that heroin abusers have (a) profound impairment on a test of visual pattern recognition memory which has been shown to be sensitive to temporal lobe lesions (Owen et al., 1995), (b) dysfunction in the visual-spatial domain and visual discrimination tasks (Ornstein et al., 2000), and (c) impaired planning functions, which are mostly mediated by the prefrontal cortex (Owen et al., 1990) may explain participation of temporal, occipital, parietal and frontal brain areas in opioids effect which was reported in the present study. Additionally, Kivisaari et al. (2004) using opioid-dependent subjects demonstrated cortex changes which may be related to brain atrophy located especially in frontal and temporal lobes. Concentration of opioid receptors with the maximum in frontal and temporal lobes of the brain (Pike, 1993) is also consistent with the location of EEG channels where the maximal opioid effect was observed in the present study.

An alternative explanation for the distributed opioid effects should be considered. It could be suggested that these results may be attributed to the volume conduction. This explanation seems unlikely for the following reasons: (a) the occipital and frontal EEG channels clearly showed different accentuations in opioid effect; (b) the analysis revealed that each EEG channel or small group of channels had its own specific SP set, and (c) it was shown that there is little effect of volume conduction on the shape of the spectrum below about 25 Hz and spatial filtering is significant only for frequencies above the major rhythms (Robinson et al., 2001).

Comparative analysis of the PCPs demonstrated that EEG under opioids influence was characterized by a larger percentage of beta- and mostly fast-alpha-rhythmic segments, and by a smaller percentage of theta-rhythmic segments when compared with control subjects (Table 2). These results confirm the increase of beta (Costa and Bauer, 1997; Franken et al., 2004) and alpha (Shufman et al., 1996; Davydov and Polunina, 2004; Polunina and Davydov, 2004) activity obtained earlier with the use of conventional spectral analysis methods. However, results of the present study substantially extended previously known data: opioids changed the total amount of the time (percentage of EEG segments) that particular type of brain oscillations was on, rather than changed its amplitude or power.

Previously it was demonstrated that spectral power in the EEG of heroin addicts strongly relates to abstinence length (Shufman et al., 1996; Polunina and Davydov, 2004), to DDOA (Davydov and Polunina, 2004; Polunina and Davydov, 2004), to dosages of heroin per day (Polunina and Davydov, 2004), and is mediated by opioid receptors (Greenwald and Roehrs, 2005). This means that EEG power is related to the use of opioids itself. In the present study DDOA consistently predicted the number of SP types observed in PCPs and the percentage of polyrhythmic SPs. This finding supports the conclusion of Polunina and Davydov (2004) that the DDOA related much stronger to EEG frequency shifts compared with power variable changes.

Observed in the present study (a) the increase in the number of SP types in PCPs for each EEG channel (Fig. 1B), (b) the increase in the percentage of fast-alpha-rhythmic segments (Table 2), and (c) the appearance of beta-rhythmic segments in opioid addicts (Table 2) may be associated with predisposition to substance use (Costa and Bauer, 1997), and reflect a state of cognitive or emotional (Ray and Cole, 1985), neuronal (Porjesz et al., 2002) and cortical neuronal networks (Lopes da Silva et al., 1980; Pfurtscheller and Klimesch, 1990) activation. Indeed, opioids induce neuronal activation (Lynch et al., 1990; Nutt, 1996; Schlaepfer et al., 1998). Increased neuronal activity in its turn changes the ionic environment of neurons (Heinemann et al., 1986) that can lead to increased burst firing of neurons (Jensen et al., 1994) and as consequence courses observed shift towards higher frequencies.

Considering that alpha activity decreases during selective attention (Steriade et al., 1990; Lopes da Silva, 1991) and that the activity in the theta and slow-alpha bands may be responsible for the encoding of new information (Doppelmayr et al., 1998; Klimesch, 1999) and nonspecific selective attention processes (Klimesch et al., 1998) correspondently, we may speculate that the results of the present study (Table 2) may suggest that chronic opioid abuse alters attentional and memory mechanisms. This idea is indirectly supported by the studies of Franken et al. (2000), Franken (2003), and Curran et al. (2001) (for a review, see Hyman and Malenka, 2001). Cortical activity that is not driven by external stimuli, such as in the present study, may reflect processing of internal mental context (top down processing) (von Stein and Sarntheim, 2000). Indeed, it was demonstrated that heroin abusers directed more attentional resources towards heroin cues (external or internal) compared to neutral cues (Franken et al., 2000; Lubman et al., 2000) and that opioid system is involved in attentional bias (Hernandez and Watson, 1997).

4.2. Interhemisphere asymmetry in the EEG for opioid abusers

Analysis of the interhemisphere asymmetry indexed by the relative presence of each SP type in PCPs for each homologous EEG-channel pair demonstrated that opioid abusers had predominantly right-sided asymmetry, whereas control subjects had predominantly left-sided asymmetry. This indicates that chronic opioid exposure changes interhemisphere brain asymmetry from relatively left-sided (which is species-specific for humans – mostly right-handed population; see Bragina and Dobrohotova, 1998; Annett, 1999) to relatively right-sided dominance. The main brain oscillations, which were involved in interhemisphere asymmetry for both opioid abusers and control subjects were theta1, theta2, alpha1, alpha2, beta1, and beta2. However, the combination of these brain oscillations was more diverse for opioid abusers than for the control subjects. Earlier it was already shown that alpha brain oscillations participated in interhemisphere asymmetry during chronic heroin addiction (Davydov and Polunina, 2004). Thus, chronic opioid effects on brain appeared to be stronger at the right hemisphere compared to the left one. This may suggest the higher sensitivity of the right hemisphere to adverse chronic opioid effects in comparison with the left. This idea is supported by EEG study of Papageorgiou, et al. (2001) where the authors demonstrated more severe right hemisphere dysfunction in heroin abusers. Based on the studies which demonstrated opioids' ability to remodel the density of dendrite spines and thus to affect the synaptic inputs (Morozov and Bogolepov, 1984; Robinson et al., 2002), Davydov and Polunina (2004) hypothesized that "synaptic modulation may adversely affect right hemisphere functions disproportionately greater in comparison to the left one".

4.3. Temporal stabilization of the spectral patterns under opioid influence

A single EEG spectrum illustrates the particular integral dynamics of tens and hundreds of thousands of neurons in a given cortical area at a particular point in time (Dumermuth and Molinari, 1987). Therefore, the absence of variance of a single spectrum during several analyzed epochs may suggest that in a given cortical area the same macro-regimen of neuronal pool activity is maintained during that period. This phenomenon of a temporal stabilization may be explained by the stabilization of oscillatory patterns in the brain. In the present study, EEG of opioid abusers was characterized by longer periods of temporal stabilization for alpha and beta brain oscillations and by shorter periods of temporal stabilization for theta and polyrhythmic activity when compared with control subjects (Fig. 3). Note that these estimations differed significantly in the "random EEG" that reflects the temporal stabilization

of the main dynamic parameters of neuronal activity being of the non-occasional character (Fig. 3).

Perhaps, increased stabilization periods for alpha and beta brain oscillations indicate that the brain's operations completed less dynamically and that there exists a transition to a less differential organization of spectral relations (Lindsley, 1961). All these may suggest a reduction of brain information processing and development of allostatic state - a state of chronic deviation of brain oscillations system from its normal state of operation with establishment of a new set point (Koob and Le Moal, 2001). As a result, such system is less able to cope with the demands of a constantly changing environment. Neuronal assembles operate in these conditions as resonance systems that limits their involvement in new type of activity, thus providing a dynamic rigidity. At the same time, dynamic rigidity is not permanent: opioid brain is rather characterized by fluctuations (metastability) between long periods of temporal stabilization for alpha and beta brain oscillations and short periods of temporal stabilization for theta and polyrhythmic activity.

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).

Before coming to the final conclusions, an alternative attribution of the results obtained in the present study should be considered. It could be suggested that these results may be attributed primarily to the comorbid psychiatric conditions of the patients (see Table 1A). This view seems unlikely for the following reasons: (1) The most common was the antisocial personality disorder, which was diagnosed in all except three patients, who also had some features of antisocial personality disorder. According to the literature, antisocial personality disorder is characterized by an overall reduction in alpha activity, a bilateral increase in occipital delta and theta activity (Lindberg et al., 2005), and by increased frontal left-hemisphere EEG activation (Deckel et al., 1996). These data contradict to the results of the present study (see Table 2 and Section 3.4); (2) Eleven patients also met criteria for borderline personality disorder. According to the literature this disorder is characterized by a 40-84% incidence of diffuse EEG slowing (Tanahashi, 1988; De la Fuente et al., 1998). These data contradict to the results of the present study too (see Table 2); (3) We found that as the duration (years) of daily opioid usage increase, the diversity of composition of brain oscillations increase also. Thus, even though we cannot deny the influence of comorbid

psychiatric conditions on EEG effects, above mentioned reasons together give ground to suppose that this influence was insignificant in the present study.

Considering that there is some, though not consistent, evidence for general intellectual decline in very recent or ongoing chronic opioid abuse (Grant et al., 1978; Rounsaville et al., 1982), one may explain the observed differences in resting state EEG by possible significant between-group difference in IQ. However, verbal intelligence (VIQ) which was assessed for 15 patients from our sample when they participated in another study (Rapeli et al., 2006) did not differ from healthy controls.

Therefore taken together, results obtained in the present study demonstrated reorganization of composition of brain oscillations and their temporal behavior in EEG of chronic opioid addicts. This process affected brain activity nearly in all EEG channels. At the same time, the magnitude of opioids effect was maximal in the occipital, right parietal, right temporal, and frontal areas of the cortex. Observed in the present study reorganization of composition of brain oscillations may be explained partly by opioid-dependent reorganization of neural circuitry which was reported by number of authors: Morozov and Bogolepov (1984), Sklair-Tavron et al. (1996), Robinson et al. (2002), and Kivisaari et al. (2004) and by establishment of allostatic state (Koob and Le Moal, 2001). Interhemisphere asymmetry during opioid addiction was characteristic also for all homologous EEG-channel pairs, with right-sided dominance.

5. Conclusions

Results obtained in the present study demonstrated reorganization of composition of brain oscillations and their temporal behavior in EEG of chronic opioid addicts. These results suggested that increase in the percentage and duration of beta- and mostly fast-alpha-rhythmic segments in EEG of chronic opioid addicts reflects an allostatic state with neuronal activation, and may be associated with altered attentional and memory mechanisms. Right-sided dominance in addicted brain suggested the higher sensitivity of the right hemisphere to adverse chronic opioid effects in comparison with the left.

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