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Reorganization of the Composition of Brain Oscillations and Their Temporal Characteristics during Opioid Withdrawal

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Abstract
Majority of the opioid-dependence and withdrawal studies are dominated with many inconsistencies and contradictions. One of the reasons for such inconsistencies may be methodological while performing EEG analysis. To overcome methodological limitations, in the present study we examined the composition of electroencephalographic (EEG) brain oscillations in broad frequency band (0.5-30 Hz) in 13 withdrawal opioid-dependent patients and 14 healthy subjects during resting condition (closed eyes). The exact compositions of brain oscillations and their temporal behaviour were assessed by the probability-classification analysis of short-term EEG spectral patterns (SPs). It was demonstrated that early withdrawal had a generalized effect: the activity in all EEG channels was affected nearly equally. EEG of withdrawal patients was characterized by (a) different dominant SP types (had unique SP types which describe beta frequency band), (b) increased number of SP types observed in each EEG channel, (c) a larger percentage of alpha$_2$-, beta-, and poly- rhythmic activity, and by a smaller percentage of delta-, theta-, and alpha$_1$- rhythmic activity, (d) predominantly right-sided asymmetry, and (e) longer periods of temporal stabilization for alpha and beta brain oscillations and by shorter periods of temporal stabilization for theta activity when compared with control subjects. When taken together, these findings suggest a considerable reorganization of composition of brain oscillations, which reflects a disorganization process and an allostatic state with neuronal activation in EEG of opioid withdrawal patients.

Keywords Opioid dependence; Opioid withdrawal; Electroencephalogram (EEG); Multiple brain oscillations; Short-term spectral patterns; Probability-classification analysis

Introduction

The present study is the second part of a longitudinal research program, which aims to explore actual composition of brain oscillations and their temporal behaviour in current opioid addicts entering the hospital unit for withdrawal and evaluation for methadone treatment. In our previous study (Fingelkurts et al., 2006c), we reported that electroencephalogram (EEG) of patients with opioid dependence was characterized by significant reorganization of brain oscillations and changes in their temporal features. The results supported the concept of allostatic state of addiction (Koob and Le Moal, 2001). Allostatic state is defined as adaptive stability through change, a stability that is not within the normal homeostatic range (McEwen, 1998). In the present study, we examined how actual composition of brain oscillations and their temporal behaviour would change during early withdrawal in the same opioid-dependent patients.

Even though majority of the opioid-dependence studies are made with the usage of withdrawal patients (Benos and Kapinas, 1980; Olivennes et al., 1983; Shufman et al. 1996; Polunina et al., 2003; Franken et al., 2004; Polunina and Davydov, 2004), the field is dominated with many inconsistencies and contradictions: (a) some researchers found changes only in $beta_2$-frequency band in withdrawal opioid-dependent patients (Franken et al., 2004), when others demonstrated changes in other than $beta_2$-frequency bands (Gritz et al., 1975; Benos and Kapinas, 1980; Olivennes et al., 1983; Shufman et al., 1996; Polunina and Davydov, 2004) and (b) significance of increased beta-power in withdrawal opioid-dependent patients is not known (Franken et al., 2004).

One of the reasons for such inconsistencies may be the usage of averaging procedures while performing EEG analysis and the fact that the frequency bands are usually predefined and taken in isolation from each other (for other reasons such as differences in withdrawal length and drug doses, see Polunina and Davydov, 2004). As a result, the observed phenomenon may be a "virtual" result of the averaging procedure (Fingelkurts et al., 2003a, 2004), which does not characterize the majority of individual EEG segments. Thus, the averaging of the EEG signal may not only mask the dynamics of EEG characteristics, but also may lead to ambiguous data interpretation (Fingelkurts et al., 2002, 2004). Predefined frequency bands (the usual practice in EEG studies) do not permit researchers to examine behaviour of the actual/natural composition of brain oscillations involved. At the same time, it has been shown that brain functions are represented by superimposed multiple brain oscillations in many frequency bands (Basar et al., 2000; for the review, see Basar et al.,

2004). Moreover, total EEG power may be affected by polyrhythmic disorganized activity (Dumermuth and Molinari, 1987). In this case, different indices and parameters of EEG may suffer from the influences of such activity, instead of reflecting true rhythmic activity.

In connection to this, it seems reasonable to examine the actual composition of brain oscillations and their temporal behaviour in a broad frequency band (0.5-30 Hz) in EEG of opioid-dependent patients during early withdrawal. To assess the exact composition of brain oscillations, their percent ratio and temporal dynamics, one should use a robust and model-independent technique, which considers EEG non-stationarity, does not need previous knowledge about the underlying dynamics and produces results that are easy 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 probability classification profile (PCP): short-term power spectra are computed from a long EEG time series; then the individual power spectra are classified using a set of reference spectra; subsequently, the relative occurrence of each class is determined, resulting in PCP for each electrode and subject.

It was reported 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), and is a sensitive index reflecting drug effects on brain dynamics (Fingelkurts et al., 2004, 2006c). Another advantage to using PCP is that polyrhythmic disorganized 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 could be also subjected to analysis. This is justified since it was reported that the ratio of polyrhythmic disorganized activity and rhythmic components in EEG spectrum is strongly influenced by genetic factors (Meshkova, 1988), and as explored in our early work (Fingelkurts et al., 2003a, 2004, 2006b) the amount of polyrhythmic disorganized activity in EEG is dependent on functional brain state and/or task.

Hence, the aim of the present study was to investigate the actual composition of brain oscillations and their temporal behaviour in a broad frequency band (0.5-30 Hz) in EEG of opioid-dependent patients during early withdrawal. Considering that noradrenaline excess during early withdrawal (a) causes opiate physical dependency (Maldonado, 1997; Devoto et al., 2002) and withdrawal symptoms (Valmana, 1999), (b) produces changes in EEG (Cape

and Jones, 1998) and (c) more generally might result in the allostatic state around new homeostatic levels of the brain (Koob and Le Moal, 2001), we hypothesize that EEG of opioid abusers during early withdrawal would be characterised by a considerable disorganization. Such disorganization can be expressed as increased number of SP types, increased amount of polyrhythmic activity (PA) and altered temporal characteristics.

Methods and materials

Subjects

The study included a total of 13 right-handed, opioid-dependent patients, eight men and five women aged between 21 and 41 years of age (32 ± 5 years) and 14 controls, six men and eight women (age 33 ± 5 years). 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 outpatient 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 and neurologic illness.

All patients had abused opioids for 4–26 years (10 ± 5 years). Self-reported daily dose was 0.05–1.2 g for i.v. street heroin and 2-16 mg for *i.v.* street buprenorphine. Almost all patients reported irregular (episodic) use of cannabis, amphetamine, and alcohol for short periods earlier in their lives. Some patients reported use of benzodiazepines (8 patients), cannabis (5 patients), buprenorphine (10 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 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). All patients met DSM-IV criteria for opioid dependence, whereas eight patients met also DSM-IV criteria for benzodiazepine dependence. Patients fulfilled no other DSM-IV criteria aside from substance abuse on axis I;

all met DSM-IV criteria of axis II diagnosis (American Psychiatric Association, 1994) for personality disorders. The most common was antisocial personality disorder, diagnosed in all except one patient, who nonetheless had some features of antisocial personality disorder. Six patients also fulfilled criteria for borderline personality disorder. One patient had negative HCV-AB and negative HbsAg tests. All patients studied were negative for HIV-AB test. One patient refused to be tested for HIV. 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 of the controls met criteria for abuse of or dependence on alcohol. Controls did not fulfill any criteria for DSM-IV disorders on SCID I or II. All patients and some of the controls were habitual smokers and all participants were habitual coffee-drinkers. Even though patients group had in average smaller number of years of education than control group, the difference was non-significant. 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.

Trial Design

At the time of the EEG assessment, patients had been abstinent for 12-15 days. For a withdrawal period, patients were visited frequently (i.e., twice per week) and unpredictably for the purpose of detecting relapse or continued withdrawal via urine and breath screening. Blood tests were also done if there was a suspicion of relapse. After 2 weeks of withdrawal before starting EEG registration, urine and blood tests were made to make sure of opiod withdrawal and exclude other illicit drug abuse. The severity of withdrawal syndrome was verified by Short Opioid Withdrawal Scale (SOWS) or Gossop test (Gossop, 1990). SOWS is a 16 items scale with acceptable validity and reliability. The 16 items of SOWS are diarrhoea, stomach cramps, palpitation, agitation, irritability, dysphoria, anxiety, craving, muscle cramp, muscle tension, yawing, coldness, nausea, aches and pains, runny eyes, and sleep problems. Each item was assessed on four point Likert scale ranging from 0 (none) to 3 (severe). For the management of withdrawal symptoms in patients, lofexidine was used three times per day (0.2-0.4 mg). It does not reduce cravings, but is effective in reducing the symptoms associated with opiate withdrawal, such as chills, sweating, stomach cramps, diarrhoea, muscle pain, runny nose and eyes (Washton et al., 1983). Lofexidine is an anti-adrenergic drug; it does not give rise to withdrawal symptoms of its own (Strang et al., 1999).

The subjects were instructed to avoid smoking and caffeine for 12 h before EEG recording. Following electrode placement and instruments calibration, a subject (patient or healthy control) was seated in a comfortable chair in a dimmed registration 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 and to avoid movement. A subject was instructed also 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 5-min EEG registration with eyes closed.

Vigilance of the subjects was controlled by (a) the presence in EEG of sleep spindles, which naturally appear during drowsiness (Rechtschaffen and Kales, 1968), (b) occipital decrease of alpha activity and (c) slow, pendular eye movements. Criteria for sleep spindles detection: frequency 13-15 Hz; time duration 0.5-2.5 s, that is, one should be able to count at least 6 or 7 distinct waves within the half-second period; peak-to-peak amplitude above 15 mkV (Rechtschaffen and Kales, 1968). Visual and spectral analysis of EEG did not reveal any sleep spindles or diminution of occipital alpha activity (see also Fig. 2). Several EEG epochs contained eye movements - they were rejected from the analysis.

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 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 each electrode 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. The presence of an adequate signal was determined by visually checking each raw signal on the computer screen.

Data Processing

EEG components containing artifacts because of 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 the brain was performed (Joyce et al., 2004). It 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 two distinct groups: "withdrawal" and "control." Further, data processing was performed separately for each 1-min portion of the signal. Because of 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 before 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). Because EEG is widely referred to as non-stationary signal with varying characteristics (Kaplan and Shishkin, 2000; see also Fingelkurts and Fingelkurts, 2001), brain oscillations are expected to be dynamic in nature. To capture such changing dynamics, the data series were divided into overlapping windows. Thus, 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-s Hanning window shifted by 50 samples (0.39 s) for each channel of 1-min EEG. These values proved the most effective for disclosing oscillatory patterns from the signal according to previous studies (Kaplan, 1998; Levy, 1987, 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 s) of the boundaries of the EEG segments with temporally stabilized oscillatory activity.

As a result, the total number of individual SP for each channel of 1-min EEG was 149 (Fig. 1). 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, see Fingelkurts et al., 2006c). Considering that detail description of this analysis was published elsewhere

(Fingelkurts et al., 2003a), here we are highlighting only the most important steps. In short, this analysis was undertaken in two stages (Fig. 1).

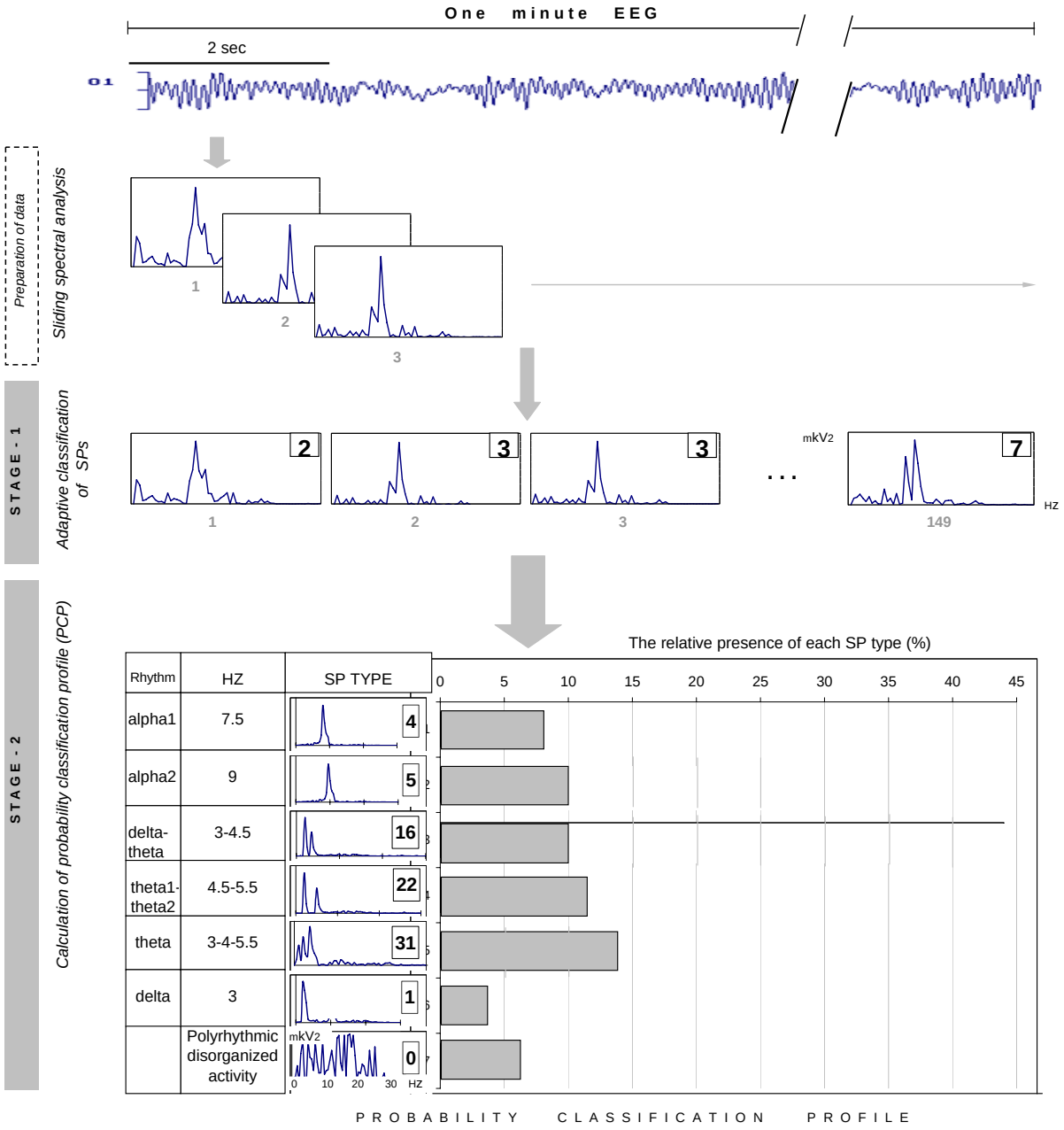


Figure 1. The scheme of the data processing. Sliding spectral analysis, adaptive classification of spectral patterns (SP) and calculation of the probability-classification profiles (PCP) were done separately for each subject and each channel of 1-min EEG. Reproduced from Fingelkurts et al., (2007).
Gray small numbers under each SP represent the running numbers from 1 to 149. The numbers in the square represent the labels – types of classified SPs. Column "Hz" represents the main dominant peak(s) in particular SP. Presented PCP illustrates the composition and percent ratio of the main brain oscillations in O_1 EEG for control subject during closed eyes condition.

During the first stage, sequential single EEG SPs were adaptively classified in each channel of 1-min EEG using a set of standard SPs, which were generated automatically from the EEG data itself (Fingelkurts et al., 2006c). As the result of this classification, each current SP was labelled according to the index of the class to which it belongs. Hence, each EEG signal was reduced to a sequence of individually classified SPs (Fig. 1).

At the second stage, PCPs of SPs for each channel of 1-min EEG in each subject were calculated (Fig. 1). 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 65 (for withdrawal patients) 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.

In addition, three indices were calculated for each subject separately for each condition and channel of each 1-min EEG:

a) The percentage of *polyrhythmic/disorganized activity* (PA), – represented by polyrhythmic SP. A polyrhythmic spectral pattern constitutes a pattern where peaks occupy a majority of the frequencies within the studied range. Such a spectral pattern indicates a mixture of activity of small neuronal subpopulations, each with its own mode (Tirsch et al., 2000).

b) Index of *non-homogeneity of classification profile* (NHCP) was estimated as a ratio of the number of SP types detected in a given 1-min EEG to the total number in the standard set (32 standard SPs – 100%). This index indicates how many different SP types participate in PCP.

c) Index of *non-stability of classification profile* (NSCP) is a percent value that reflects how the set of distinct SP types changes across the three EEG sub-segments of 20 s within a complete 1 min.

$$NSCP = \left(1 - \frac{n1 + n2 + n3}{3 * ns}\right) * 100,$$

Where, n_i, is the number of distinct SP types found in a 20-s EEG segment i; n_s is the number of SP types found in all three 20-s EEG segments. The range of this index is 0–67.

d) An *asymmetry score* was computed by estimating a statistically significant difference between relative presence of each SP type from PCP for all sites that have symmetrical left

and right locations (O_1 and O_2, and so on). Right-side-dominance would mean that relative presence of each (or majority of) SP type(s) in the right hemisphere is significantly larger than in the left one. Left-side-dominance would mean that relative presence of each (or majority of) SP type(s) in the left hemisphere is significantly larger than in the right one.

Statistics

We studied the behaviour of each type of SPs separately and did not make any conclusions *per se* about differences between PCPs. To show any statistically significant differences in the relative presence of each SP type in PCPs between withdrawal patients 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 discussion, see Perneger, 1998; Rothman, 1990).

However, in the case where we examined spatial distribution of significant differences, a Bonferroni correction was made 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 origin of the temporal dynamics of SPs, which is commonly applied as direct probing a signal for a non-random temporal structure (Ivanov et al., 1996). Surrogate signals have identical parameters with the original signals but do not have temporal correlations. Thus, 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". Even though randomization dose not account for overlapping EEG epochs, the natural temporal structure of the randomized signal was considerably destroyed. Therefore, these surrogate data were relevant for the analysis.

Results

General description of EEG during early withdrawal

Early withdrawal of opioid-dependent patients affected the activity in all EEG channels: there was no single EEG channel without statistically significant differences in the relative

presence of at least 60% of SP types in PCPs between withdrawal opioid-dependent patients and control subjects. In general, different cortical areas were characterized by very similar number of SP types, which demonstrated statistically significant difference in their relative presence in PCPs, thus indicating a generalized effect of early withdrawal (not shown).

The spatial distribution of brain oscillations was generally consistent with that showed 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. 2A).

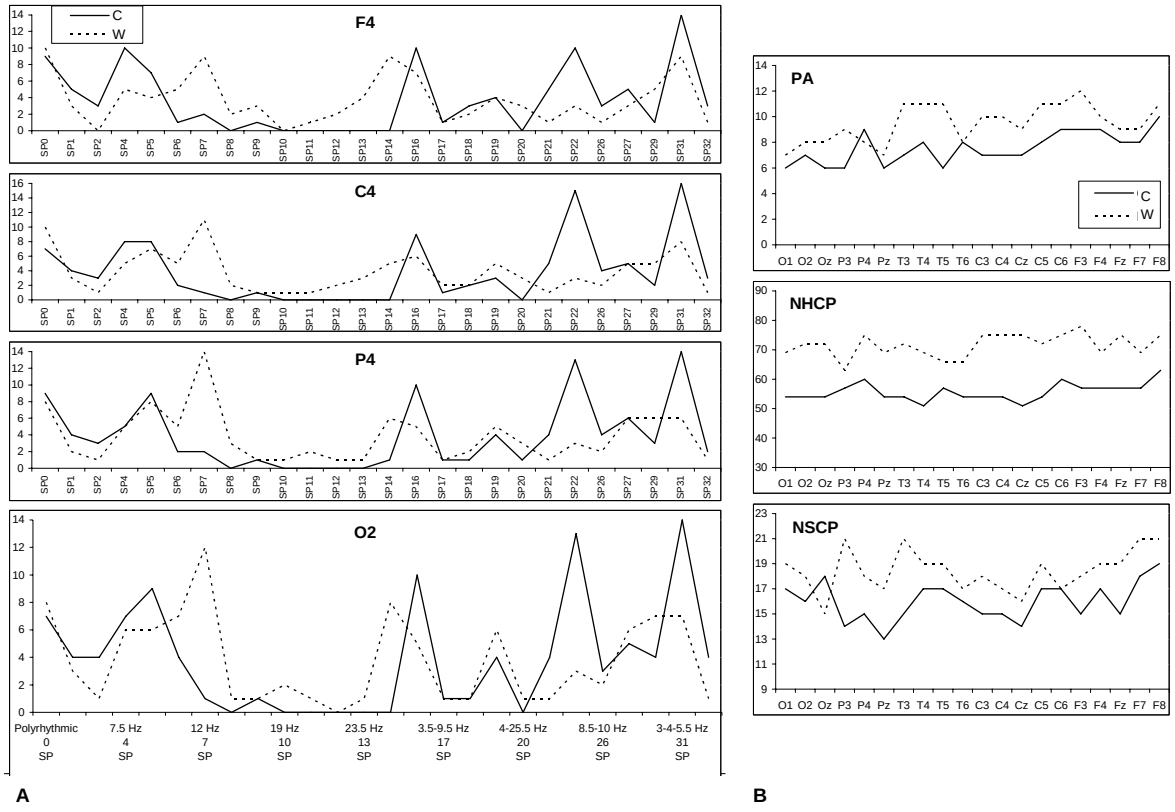


Figure 2. (A) Probability-classification profiles and (B) the percentage of polyrhythmic activity (PA), index of non-homogeneity of classification profile (NHCP), and index of non-stability of classification profile (NSCP). Data averaged across 65 EEGs for withdrawal patients and 70 EEGs for control subjects.
For (A): O_1 = occipital, P_3 = parietal, C_3 = central, and F_3 = frontal EEG channels placed at the left 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). C = control subjects; W = withdrawal opioid-dependent patients. Only those SPs which are presented in PCPs of all EEG channels are illustrated.

EEGs of withdrawal opioid-dependent patients and control subjects were characterized by different sets of SP types dominant in the PCPs (Fig. 2A). Thus, SPs with fast-alpha- [SP12 (main peak at 22 Hz)], fast-beta- [SP14 (25 Hz)] and polyrhythmic- [SP0] activity dominated in PCPs of withdrawal opioid-dependent patients, whereas SPs with theta- [SP16 (3-4.5 Hz), SP22 (4.5-5.5 Hz) and SP31 (3-4.5-6 Hz)] and slow-alpha- [SP4 (7.5 Hz) and SP5 (9 Hz)] activity dominated in PCPs of control subjects.

The comparative analysis of PCPs for withdrawal opioid-dependent patients and control subjects showed that (a) the number of SP types observed in PCPs (indexed by NHCP) was significantly larger ($p < 0.0000001$) in withdrawal opioid-dependent patients when compared with control subjects (Fig. 2B), (b) non-stability of PCPs (indexed by NSCP) was significantly larger ($p < 0.0001$) in withdrawal opioid-dependent patients when compared with control subjects (Fig. 2B) and (c) there were unique SP types associated only with early withdrawal: SP8 (main peak at 13.5 Hz), SP11 (20.5 Hz), SP12 (22 Hz), SP13 (23.5 Hz) and SP14 (25 Hz) (Table 1).

Additionally, withdrawal opioid-dependent patients and control subjects differed from each other according to the probability estimation of the occurrence of SP types in PCPs.

Characteristics of EEG changes induced by early withdrawal

Comparative analysis of the PCPs demonstrated that EEG during early withdrawal was characterized by a larger percentage of alpha$_2$- [SP6 (main peak at 10.5 Hz), SP7 (12 Hz), SP8 (13.5 Hz) and SP29 (10.5-11.5 Hz)], beta$_1$- [SP10 (19 Hz)], beta$_2$- [SP11 (20.5 Hz), SP12 (22 Hz), SP13 (23.5 Hz), and SP14 (25 Hz)], theta–beta$_2$- [SP20 (4-25.5 Hz)], and poly- rhythmic segments, and by a smaller percentage of delta- [SP1 (3 Hz)], delta–theta- [SP16 (3-4.5 Hz), SP31 (3-4-5.5 Hz) and SP32 (3-4.5-6 Hz)], theta- [SP2 (4.5 Hz), SP21 (4-6 Hz) and SP22 (4.5-5.5 Hz)] and alpha$_1$- [SP26 (8.5-10 Hz)] rhythmic segments when compared with the EEG of control subjects ($p < 0.05$–$p < 0.0000001$ for different channels) (Table 1, Fig. 2B).

The main effects of early abstinence described above were distributed across the whole cortex and were detected in the majority of EEG channels ($p_{corrected} < 0.002$ to $p_{corrected} < 0.0000001$ for different channels) (Table 1).

Table 1. Spectral pattern types which demonstrated statistically significant (*Pcorrected* < 0.002-0.0000001) difference between withdrawal patients and control subjects.
Data averaged across 65 EEGs for withdrawal patients and across 70 EEGs for control subjects.

Brain oscillation	SP type	Main peak (Hz)	EEG channels (%)	Topographical distribution
C > W				
Delta	SP1	3	55	distributed across majority of brain lobes except occipital
Delta-Theta	SP16	3-4.5	95	distributed across all brain lobes*
	SP31	3-4-5.5	100	distributed across all EEG channels
	SP32	3-4.5-6	90	distributed across all brain lobes
Theta	SP2	4.5	95	distributed across all brain lobes
	SP21	4-6	95	distributed across all brain lobes
	SP22	4.5-5.5	100	distributed across all EEG channels
Alpha1	SP26	8.5-10	75	distributed across all brain lobes
C < W				
Alpha2	SP6	10.5	70	distributed across all brain lobes
	SP7	12	100	distributed across all EEG channels
	SP8	**13.5**	85	distributed across all brain lobes
	SP29	10.5-11.5	75	distributed across all brain lobes
Beta1	SP10	19	75	distributed across all brain lobes
Beta2	**SP11**	**20.5**	65	distributed across majority of brain lobes
	SP12	**22**	75	distributed across all brain lobes
	SP13	**23.5**	85	distributed across all brain lobes
	SP14	**25**	95	distributed across all brain lobes
Theta-Beta2	SP20	4-25.5	60	distributed across majority of brain lobes

C = Control subjects; W = withdrawal patients; 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 withdrawal patients and control subjects; Bold indicates unique spectral pattern types for withdrawal patients.
* One brain lobe may contain several EEG electrodes

Interhemisphere asymmetry in the EEG for withdrawal opioid-dependent patients and control subjects

In general, for withdrawal opioid-dependent patients and control subjects, interhemisphere asymmetry ($p_{corrected} < 0.002$ to $p_{corrected} < 0.0001$, indexed by relative presence of SPs in PCPs) was observed in the majority of homologous EEG-channel pairs (not shown). Only F_3-F_4 homologous EEG-channels pair did not reveal any interhemisphere asymmetry. Withdrawal opioid-dependent patients had more EEG-channel pairs with right-side-dominance asymmetry than EEG-channel pairs with left-side-dominance asymmetry ($p < 0.05$), whereas control subjects had the opposite results ($p < 0.05$).

Temporal stabilization of the spectral patterns under early withdrawal 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 3.

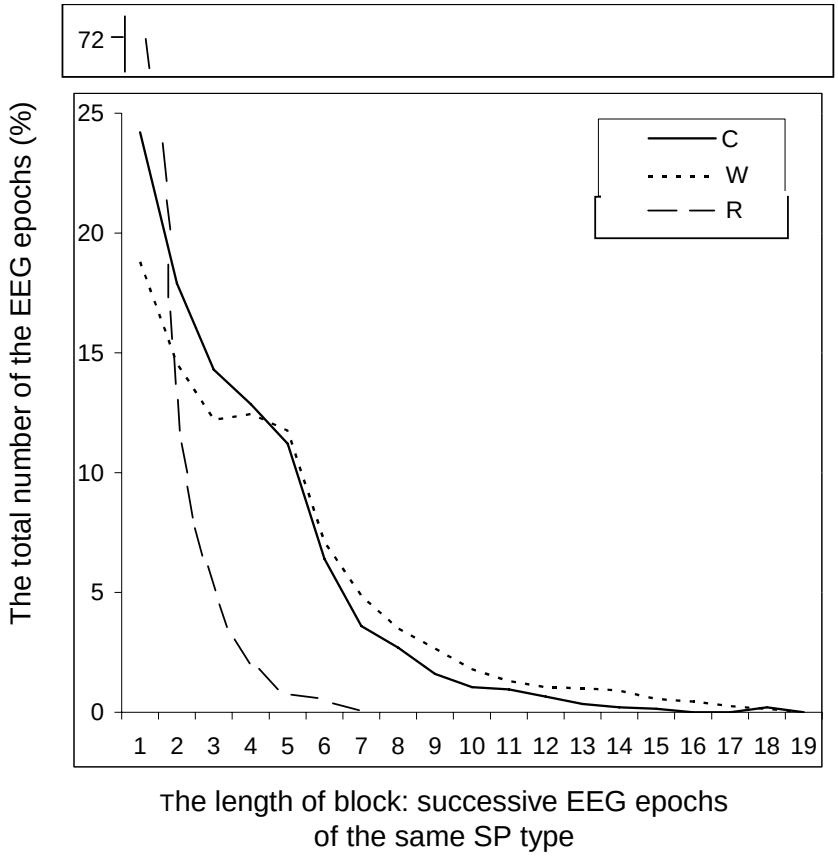


Figure 3. The average number (for all EEG channels, $n = 20$) of successive *m* EEG epochs of the same SP type (including polyrhythmic spectra) (the *y*-axis), where *m* is the range from 1 to 149 (the *x*-axis). The values are presented as a percentage of the total number of the epochs in all EEGs, for 13 withdrawal opioid-dependent patients ($n = 9\ 238$) and 14 control subjects ($n = 10\ 728$).
C = control subjects; W = withdrawal opioid-dependent patients; R = "Random EEG" = EEG which natural sequence of spectral pattern types has been removed in each individual channel.

The temporal stabilization of SPs in both EEG of withdrawal opioid-dependent patients and EEG of control subjects was similar, showing a common characteristic: this index decreased as the length of block increased. At the same time, EEG of withdrawal patients was characterized by smaller index values for short periods of temporal stabilization ($p < 0.001$ to $p < 0.0001$ for different block lengths) and greater index values for long periods of temporal stabilization ($p < 0.01$ to $p < 0.0001$ for different block lengths) when compared with EEG of control subjects (Fig. 3).

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 3, it can be seen that the actual EEG data substantially differed from the "random EEG" ($p < 0.001$ to $p < 0.00001$ for different block lengths). An excessive increase in the number of blocks of length 1 for "random EEG" may indicate a stochastic process.

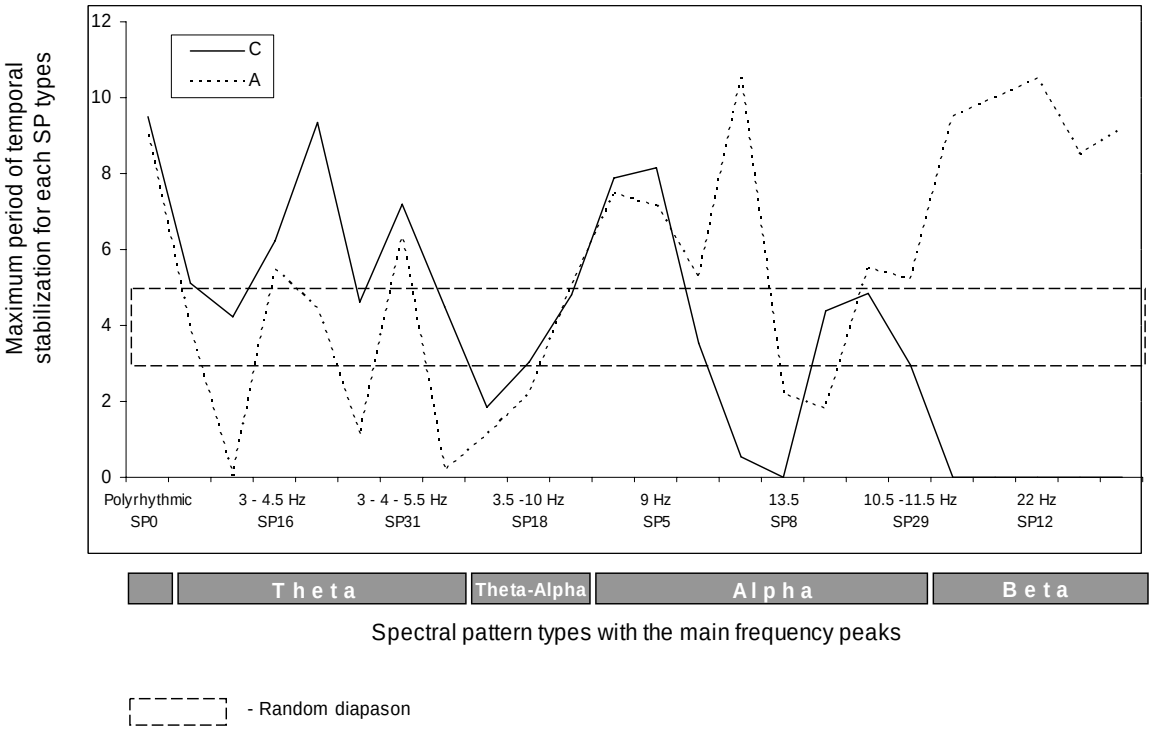
It should be noted that the analysis presented above could not show the dependence between the periods of temporal stabilization and the type of SPs. In other words, does specific type of brain oscillations (in terms of SPs) maintain a particular period of temporal stabilization? Therefore, we analyzed the maximum periods of temporal stabilization for all SP types which were found in PCPs for EEG of withdrawal opioid-dependent patients and EEG of control subjects (Fig. 4A).

The maximum periods of temporal stabilization for SP types presented in Figure 4A as block length were recalculated in time-scale. This analysis showed that the brain "maintains" the stabilization period of neural activity between 2 and 6 s (for different SPs) for withdrawal opioid-dependent patients and control subjects (Fig. 4A). The longest maximum periods of temporal stabilization for withdrawal patients were found for alpha- and beta- activity, whereas for control subjects the maximum period of temporal stabilization was the longest for theta-activity.

Moreover, for withdrawal opioid-dependent patients' EEG, all SPs with $alpha_2$-, $beta_1$- and $beta_2$-activity were characterized by longer maximum periods of temporal stabilization than for control EEG ($p < 0.05$ to $p < 0.000001$ for different SP types). At the same time, for controls' EEG, all SPs with $theta_1$-, $theta_2$-, $theta_1$-$theta_2$-, and $theta_1$-$alpha_1$- activity were characterized by longer maximum periods of temporal stabilization than for withdrawal patients EEG ($p < 0.05$ to $p < 0.000001$ for different SP types) (Fig. 4A). The duration of

such periods for “random EEG” (an EEG with a random mix of different SP types) was different from the actual EEG and reached up to 2.3–2.6 s (for different SP types) (Fig. 4A).

Finally the maximum periods of temporal stabilization (averaged across all SP types and EEG channels) were longer for withdrawal opioid-dependent patients’ EEG than for the control EEG ($p < 0.000001$) (Fig. 4B).



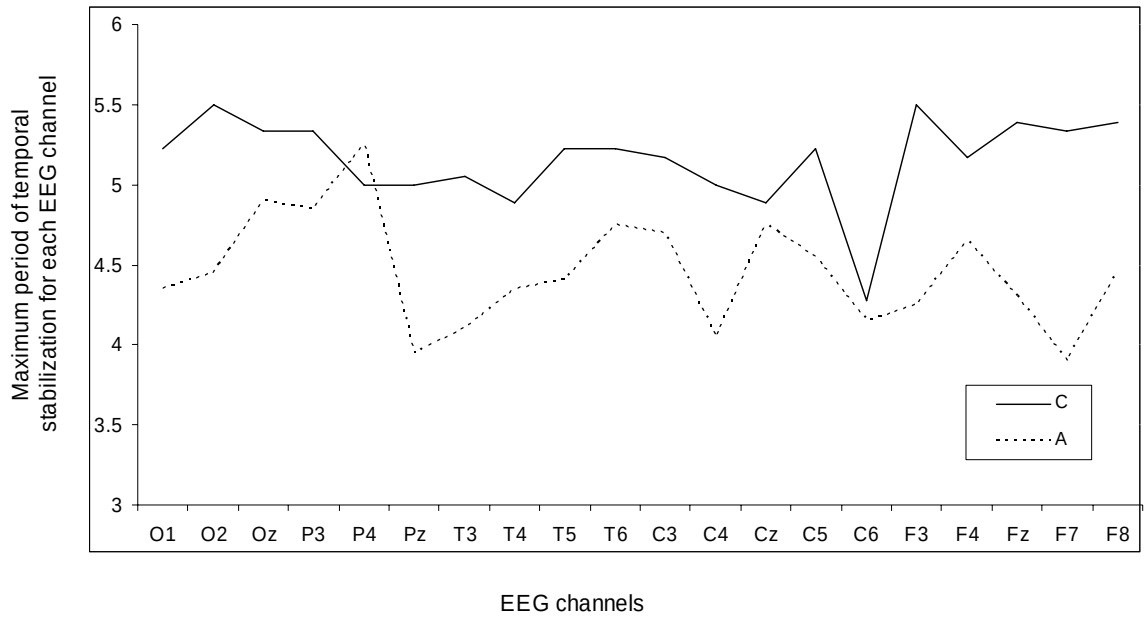


Figure 4. The maximum periods of temporal stabilization: (A) for each spectral pattern type, which was found in the EEG probability-classification profiles. The *x*-axis displays the labels (numbers) of the EEG spectral patterns (SP) corresponding to the standard SP set (including polyrhythmic spectra – 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); (B) for all EEG channels. Data averaged across all subjects and all SP types observed in the EEG probability-classification profiles. C = control subjects; W = withdrawal opioid-dependent patients.

Relationships between severity of withdrawal symptoms and EEG changes induced by early withdrawal

The severity of withdrawal symptoms was measured by Gossop test (Gossop 1990). Patients had different values on the Gossop scale. This means that withdrawal symptoms were expressed in different magnitude in different patients. Correlation analysis of EEG changes (increase of the percentage of polyrhythmic-, theta-beta-, and beta- activity) induced by early withdrawal and the values of Gossop test permitted us to reveal the dependence between some EEG changes induced by early withdrawal and the magnitude of the withdrawal symptoms (Table 2). However, only the patients with high values on Gossop scale (from 9 to 25 (n = 8)) demonstrated such correlation. Thus, it was found that as a severity of withdrawal symptoms increase, the percentage of polyrhythmic-, theta-beta-, and beta- activity increase (Spearman rank correlations: $r = 0.74$ – $r = 86$, $p < 0.05$ to $p < 0.01$, Table 2).

Table 2. Relationship between severity of abstinence symptoms and different types of EEG activity.

EEG activity	*r*	*p*
Polyrhythmic	0.81	< 0.02
Theta-beta	0.74	< 0.05
Beta	0.86	< 0.01

r = Spearman rank correlations

Discussion

Findings of the present study fully support our hypothesis that EEG of opioid abusers during early withdrawal would be characterised by a considerable disorganization.

Characteristics of EEG changes induced by early withdrawal

We found that early withdrawal of opioid-dependent patients had a generalized effect: the magnitude of EEG changes in all EEG channels was nearly equal. This means that EEG of withdrawal patients was characterized by a more homogeneous topological pattern than the control EEG. Because the main differences described in this article have been observed in all EEG channels, it appears that the distributed neuronal networks were involved in early withdrawal process. Thus, early withdrawal of opioid-dependent patients can be conceptualized as a dysfunction in distributed neural circuits, rather than local focal changes. Generally, early withdrawal was characterized by different sets of SP types dominant in the PCPs when compared with control subjects (Fig. 2A). Additionally, it caused decrease in stability of PCPs and increase in the number of SP types observed in PCPs for each EEG channel when compared with control subjects (Fig. 2B). This means that EEG during early withdrawal was more diverse (in terms of brain oscillations) than EEG of control subjects. Partly this was due to the fact that withdrawal was associated with unique SP types which describe beta frequency band (Table 1).

Comparative analysis of the PCPs demonstrated that EEG during early withdrawal was characterized by a larger percentage of $alpha_2$-, $beta_1$-, $beta_2$-, theta–$beta_2$-, and poly-rhythmic segments, and by a smaller percentage of delta-, theta-, and $alpha_1$- rhythmic segments when compared with the EEG of control subjects (Table 1, Fig. 2B). These results confirm the increase of beta activity obtained earlier with the use of conventional spectral analysis methods (Franken et al., 2004; Polunina et al., 2003; Polunina and Davydov, 2004). However, results of the present study substantially extended previously known data: early withdrawal 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. The importance of brain oscillatory states for opioid dependence was demonstrated earlier: Polunina and Davydov (2004) reported that the duration of daily opioids abuse related much stronger to EEG frequency shifts compared with power variable changes.

Observed in the present study, increase in the percentage of beta-rhythmic segments (in most cases beta-rhythmic segments were unique for abstinence) during early withdrawal (Table 1) may be associated with predisposition to substance use (Costa and Bauer, 1997), and reflect (a) a state of cognitive or emotional (Ray and Cole, 1985) and neuronal (Porjesz et al., 2002) activation and (b) an increase in alertness (Knyazeva and Vil'davskii, 1986; Bouyer et al., 1987; Bonnet and Arand, 2001) and can be interpreted as reflecting increased excitatory activity. This interpretation is consistent with the idea that the neuronal assemblies synchronized within beta-frequency band represent a general state of arousal (Porjesz et al., 2002), which is presumably more typical for short-term withdrawal patients than for healthy controls (Franken et al., 2004). Indeed, the early opioid withdrawal is characterized by catecholamine imbalances, especially noradrenaline excess (Maldonado, 1997; Valmana, 1999; Devoto et al., 2002). Noradrenaline in its turn, depolarizes and excites the cholinergic cells, and produces an increase in beta-EEG activity, a decrease in delta activity, and an increase in waking (Edmund et al., 1998).

The present study did not confirm slowing of alpha-rhythm in withdrawal opioid addicts reported earlier (Gritz et al., 1975; Gekht et al., 2003). The increase in the percentage of fast-alpha-rhythmic EEG segments during early withdrawal in the present study (Table 1) may reflect activation of cortical neuronal networks (Lopes da Silva et al., 1980; Pfurtscheller and Klimesch, 1990) and suggests an increase in alertness (as indicated by Knyazeva and Vil'davskii, 1986; Bonnet and Arand, 2001). This can be interpreted as the internalization of information processing – sort of "disconnection" of the brain from the outside world, but with increased receptiveness (readiness to respond to relevant stimuli).

Considering that alpha activity decreases during selective attention (Lopes da Silva, 1991; Steriade et al., 1990) 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 non-specific selective attention processes (Klimesch et al., 1998) correspondently, the results of the present study (Table 1) may suggest that early withdrawal alters attentional (Franken et al., 2000; Franken, 2003) and memory (Curran et al., 2001; Hyman and Malenka, 2001) mechanisms. 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 Sarnthein, 2000). Indeed, it was reported that heroin abusers directed more attentional resources towards heroin cues 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).

The present study demonstrated that the number of EEG segments with polyrhythmic activity was larger in EEG of withdrawal patients than in the control EEG. This finding is consistent with the results of our previous study, where we reported that different pathologies of the brain were characterized by increased percent of EEG segments with polyrhythmic activity (Fingelkurts et al., 2000, 2006b). Some (small) percent of polyrhythmic activity always exists in a healthy EEG (Fingelkurts et al., 2002, 2003a, 2004); however pathological processes cause its elevation (Grindel, 1973; Fingelkurts et al., 2000, 2006b). It seems that polyrhythmic activity is necessary to maintain a high level of activity in neuronal networks for sustained periods of time (Gutkin et al., 2001).

The fact that the percentage of polyrhythmic-, theta-beta-, and beta- activity predicted positively the values of Gossop test suggests a specificity of these indices and reflects the increase in EEG disorganization along with the increase in the severity of withdrawal symptoms.

When taken together, these findings suggest a considerable reorganization of composition of brain oscillations, which reflects a disorganization process in EEG of abstinent patients: (1) an increased amount of fast-alpha-, beta-, and poly-rhythmic disorganized activity, (2) an increased diversity of SPs in PCPs, and (3) a reduced stability of PCPs.

Interhemisphere asymmetry in the EEG during early withdrawal

Analysis of the interhemisphere asymmetry indexed by the relative presence of each SP type in PCPs for each homologous EEG-channel pair demonstrated that withdrawal opioid-dependent patients had predominantly right-sided asymmetry, whereas control subjects had predominantly left-sided asymmetry. This indicates that early withdrawal changes interhemisphere brain asymmetry from relatively left-sided to relatively right-sided dominance. This may suggest the higher sensitivity of the right hemisphere to adverse early withdrawal effects in comparison with the left. This idea is supported by the other EEG study (Papageorgiou et al., 2001) where the authors reported more severe right hemisphere dysfunction in the withdrawal heroin abusers.

Temporal stabilization of the spectral patterns under early withdrawal

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 analysed epochs proves 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 withdrawal patients was characterized by longer periods of temporal stabilization for alpha- and beta- brain oscillations and by shorter periods of temporal stabilization for theta activity when compared with control subjects (Fig. 3 and Fig. 4A). Note that these estimations differed significantly in the "random EEG" (EEG whose natural sequence of SP type has been completely removed in each individual channel) that reflects the temporal stabilization of the main dynamic parameters of neuronal activity being of the non-occasional character (Fig. 3 and Fig. 4A). It seems that in EEG of withdrawal patients, brain oscillations of high frequencies (above 13 Hz) in the neighbouring analysis epochs have high deterministic influence on each other. Perhaps, increased stabilization periods of SPs with this brain oscillations indicate that the brain's operations completed less dynamically in these frequencies and that there exists a transition to a less differential organization of spectral relations, where neural elements become less independent and are able to function as united informational channels (Lindsley, 1961).

Recently, it has been suggested that pathological process is a process with a change in the temporal dynamics from what is normal, rather than regularity or irregularity of those dynamics (for a review, see Fingelkurts et al., 2005). This may suggest a development of allostatic state (Koob and Le Moal, 2001) - a state of chronic deviation of brain oscillatory systems from their normal state of operation with establishment of a new set point. Withdrawal-negative affect component is dominated by decreases in dopamine and opioid peptide function (Koob and Moal, 2001). These decreases are hypothesized to contribute to a shift in reward set point (Koob and Moal, 2001) as well as recruitment of the brain stress system such as noradrenaline (Maldonado, 1997; Valmana, 1999; Devoto et al., 2002). Support for an allostatic view of drug addiction, reward regulation and EEG oscillations has been reported in Fingelkurts et al., (2006c).

Dynamic of EEG changes from opioid dependence to early withdrawal

Comparison of EEG characteristics during early withdrawal (the present study) and under opioid dependence (our previous study, Fingelkurts et al., 2006c) showed that early withdrawal is a distinct brain state in its own right, which differed from both opioid-dependence and control groups. Thus, during early withdrawal the number of SP types observed in PCPs and percentage of EEG segments with beta activity continue to increase; and percentage of EEG segments with pure-theta activity continue to decrease in the same direction as for opioid-dependence condition (see our previous study, Fingelkurts et al., 2006c). At the same time, early withdrawal showed unique changes in EEG, which were not detected for opioid-dependence. Thus, early withdrawal causes increase in (a) percentage of theta-beta- and poly-rhythmic activity, (b) instability of PCPs, and (c) the number of asymmetric SPs. Additionally, percentage of EEG segments with pure-alpha- and with theta-alpha- activity decreased during early withdrawal when compared with opioid-dependence.

Even though there are no studies on the influence of lofexidine on EEG, we cannot rule out a contribution of lofexidine effect in the described differences between early withdrawal and opioid-dependence.

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 section Subjects). This view seems unlikely for the following reasons: (1) The most common was the antisocial personality disorder, which was diagnosed in all except one patient, 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 Fig. 2, Table 1 and section ‘Interhemisphere asymmetry in the EEG during early withdrawal’); (2) Six 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 1); (3) We found that as a severity of withdrawal symptoms increase, the percentage of polyrhythmic-, theta-beta-, and beta-activity increase (Table 2). 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, which was assessed for all patients when they participated in another study (Rapeli et al., 2006) did not differ from healthy controls.

Results of this study should be considered as preliminary due to relatively small number of subjects. Further study with a larger number of patients is needed.

Conclusions

Taken together results obtained in the present study (a second part of longitudinal research program) demonstrated considerable reorganization of composition of brain oscillations and their temporal behaviour, which reflects a disorganization process and an allostatic state with neuronal activation in EEG of withdrawal patients. This process affected brain activity in all EEG channels nearly equally. Increase in the percentage and duration of beta- and fast-alpha-rhythmic segments in EEG of withdrawal patients suggested a state of emotional and neuronal activation. Right-sided dominance in withdrawal brain suggested the higher sensitivity of the right hemisphere to adverse early withdrawal effects in comparison with the left one.

We also found that as a severity of withdrawal symptoms increase, the percentage of polyrhythmic-, theta-beta-, and beta- activity increase. Such significant statistical relationship between EEG parameters and severity of opioid withdrawal gives the ground to suppose that the influence of lofexidine treatment on the study results was insignificant.

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