

Polunina A.G., Davydov D.M. (2004) EEG spectral power and mean frequencies in early heroin abstinence. Progress in neuropsychopharmacology and biological psychiatry. V.28 (1) pp. 73-82.

## **EEG SPECTRAL POWER AND MEAN FREQUENCIES IN EARLY HEROIN ABSTINENCE**

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## Abstract

The purpose of the present study was to investigate cumulative heroin effects on brain functioning by studying relationships between EEG spectral power and mean frequencies and heroin abusing history. Eyes closed resting EEG data were collected from the 19 monopolar electrode sites in 33 heroin abusers and 13 age-matched healthy volunteers. The mean age of the patients was  $23.1 \pm 4.5$ , the duration of daily heroin abuse (DDHA) ranged from 4 to 44 months, the i.v. doses of heroin ranged from 0.04 to 1.00 g/day, the abstinence length ranged from 6 days to 4.5 months. GLM repeated measures procedure revealed a significant group effect on the distribution of the mean power spectrum between bands and mean frequencies in almost all analyzed derivations. Further analysis demonstrated that these intergroup differences were diversely related to at least three aspects of heroin taking history. Frequency shifts in alpha2 range, most prominent in frontal and central derivations, were related to duration of daily heroin consumption. Slowing of alpha1 mean frequency, most prominent in central, temporal and occipital derivations, was registered mainly in heroin addicts who abused high doses of the drug. Spectral power characteristics of brain electrical activities in our patient population were strongly predicted by abstinence length. The present results give grounds to suppose that chronic heroin taking induces neuronal oscillation frequency changes, that may contribute to the development of antisocial trends and some semantic processes disturbances in these patients. Supplementary neurophysiological deficit is characteristic for heroin addicts, who takes high doses of the drug, however, its relation to heroin abusing remains unclear. Pronounced desynchronization is observed in acute heroin withdrawal, and spectral power characteristics tend to normalize almost completely during several weeks of abstinence.

Keywords: Abstinence; Drug abuse; EEG; Heroin; Opiate

Abbreviations: Duration of daily heroin abuse (DDHA); Electroencephalography (EEG); General Linear Model (GLM)

## Introduction

Chronic heroin intake induces changes in central nervous system functioning that clinically manifest as tolerance, sensitization and dependence symptoms (London et al., 1996). Whether adverse effects of regular heroin abusing on human brain extend beyond these widely recognized phenomena remains a subject of discussion. Indeed, some methodological issues in this field are still poorly resolved.

### Methodological issues

When current heroin addicts or patients receiving psychotropic treatment are compared to healthy controls, intergroup differences in brain functioning are usually found (Gritz et al., 1975; Shufman et al., 1996; Bauer, 1998; Rogers et al., 1999; Ornstein et al., 2000; Briun et al., 2001). Whereas studies evaluating drug and medication free populations of heroin abusers often do not find deviations in functioning of central nervous system in these patients (Costa and Bauer, 1997; Bauer, 1998; Gerra et al., 1998). Moreover, when current heroin users or patients receiving psychotropic treatment are compared to abstinent subjects, the former usually demonstrate severer brain functions impairment (Gritz et al., 1975; Shufman et al., 1996; Bauer, 1998). At least two explanations for these discrepancies may be given. First, acute effects of psychotropic drugs alter brain functioning in patients receiving treatment or current drug users. And/or, heroin abusers who are able to maintain abstinence without supportive psychotropic treatment constitute quite special population, that is not enough representative. Indeed, two studies, that evaluated both patient groups, reported significantly less years of heroin use in abstinent subjects compared to methadone-maintained patients (Gritz et al., 1975; Bauer, 1998). The third one, where current heroin users and abstinent subjects were evaluated, demonstrated less prominent but the same intergroup differences in heroin taking history (Shufman et al., 1996). Thus, heroin abusers who are able to maintain long-term complete abstinence seem to constitute a special population. Speculatively, these patients may be more protected from adverse cumulative effects of heroin on brain, and probably this allows them to enter treatment earlier and maintain sobriety longer compared to the general population of heroin addicts. In this context, current heroin abusers or patients entering treatment seem to represent the general population of heroin addicts better.

Another methodological problem in research for the cumulative heroin effects on the central nervous system is how to separate the latter from the brain dysfunctions, caused by other factors. Besides acute withdrawal or psychotropic treatment effects, altering of brain functions in heroin users may be related to comorbid psychiatric conditions (ex., antisocial personality disorder, depressive disorder, etc.) or other premorbid brain dysfunction (Kaplan et al., 1994; Ling et al., 1996); risky life-style with high prevalence of non-fatal opiate overdoses (Darke et al., 1996; Seal et al., 2001), strokes (Gorelick, 1990; Andersen and Skullerud, 1999), head traumas, chronic infections and malnutrition (Ling et al., 1996); cumulative effects of all psychotropic drugs abused throughout life (ex., alcohol, cannabis, cocaine, amphetamine, etc.); and to acute or cumulative effects of substances contaminating street heroin (ex., MPTP, lead, etc.) (Ling et al., 1996). In these circumstances, intergroup differences between heroin addicts and normal controls should be confirmed by statistical relationships of the deviated neurophysiological variables with drug abusing history. Significant relationship between a variable of interest and the duration of heroin using or, to a lesser extent, the amount of heroin used gives serious evidence to suppose adverse cumulative heroin effect as the underlying cause of brain functioning changes in heroin addicts. However, only two of known to us studies demonstrated both intergroup effect and significant relationships between the deviated neurophysiologic variables and the duration of heroin intake.

Bauer (1998) reported significant delays in the N75 and P100 components of pattern shift visual evoked potentials in methadone-maintained patients compared to healthy controls. The delay in N75 latency was significantly correlated with years of heroin use in this patient group ( $n=22$ ;  $r_{\text{partial}} = 0.58$ ,  $p<0.02$ ), but not with abstinence length or methadone blood levels. The author interpreted the results as “reflecting an adverse effect of chronic opioid dependence on neural transmission within primary visual areas of the brain”.

We found significant differences in performance on ‘Tower of London’ test in heroin abusers with daily heroin use duration more than 1.5 years compared to healthy matched controls (Briun et al., 2001). No significant intergroup effect was determined when patients with shorter heroin taking history were compared to both mentioned above patient and control groups. Effective solutions in this neuropsychological probe inversely correlated with daily heroin use duration ( $n=38$ ;  $r_{\text{partial}} = -.34$ ,  $p<.05$ ), and this relationship reached maximum when patients with low psychomotor speed were

excluded from the analysis ( $n=23$ ;  $r = -.54$ ,  $p<.01$ ). Hence, these data give grounds to suppose, that chronic heroin exposure impairs planning functions, that are mostly mediated by prefrontal cortex (Shallice, 1982; Owen et al., 1990).

Probably, the issue of major importance in research for cumulative heroin effects is how to define a 'heroin abuse duration'. Indeed, heroin taking history may vary considerably in different cases. Often patients report the date when they tried heroin for the first time as the 'duration of heroin intake'. However, it takes from days to months, sometimes even years, to start regular (daily) heroin use in different individuals. Moreover, frequently heroin users make efforts to stop drug taking, and intermittent abstinence periods may also last from weeks to years. Therefore, it seems to be critically important to explore drug taking history of these patients thoroughly in order to exclude periods of irregular use or intermittent abstinence from the analysis of the potential chronic heroin abuse effects.

Hence, keeping in mind all mentioned issues, we studied cumulative heroin effects on brain functioning in heroin abusers, who entered treatment not long before the investigation and therefore received psychotropic medication. In order to separate cumulative heroin effects from other adverse premorbid and concomitant factors, including current medication treatment effects, we confirmed intergroup differences by the analysis of the relationships between the variables of interest and heroin abusing history. The term 'heroin abuse duration' in this study means the sum of the periods, when patients used heroin regularly (daily).

#### EEG studies in heroin abusers populations

Few studies investigated qualitative and quantitative EEG changes in heroin abusers. Qualitative changes were observed in more than 70% of heroin addicts in early abstinence period and included low voltage background activity with diminution of alpha rhythm, increase in beta activity and large amount of low amplitude "theta-delta" waves in central regions (Benos and Kapinas, 1980; Olivennes et al., 1983; Gekht et al., 2003). Considerable or even complete normalization of the qualitative EEG characteristics in most follow-up tracings being obtained during the first 3-6 months of abstinence was reported (Gekht et al., 2003).

Some quantitative changes were also reported in methadone-maintenance patients (Gritz et al., 1975), current heroin addicts and subjects in heroin abstinence less than 80 days (Shufman et al., 1996]. Gritz et al. (1975) demonstrated significant

slowing of alpha rhythm peak frequency in 10 methadone patients and the same trend in 10 abstinent subjects (a median of abstinence 2 months). Shufman et al. (1996) detected an increase in relative alpha1 (8.0-9.5 Hz) power and deficit in relative alpha2 (9.5-12 Hz) power in 20 current heroin users; and increase in relative delta (0.5-4.0 Hz) power and the same deficit in relative high alpha (9.5-12 Hz) power in 7 heroin ex-addicts with abstinence duration 15-80 days. In the same study no intergroup differences were revealed when EEG spectral power of 13 ex-addicts with abstinence duration more than 80 days was compared to healthy controls. Costa and Bauer (1997) did not find any deviation in absolute or relative power levels in 19 abstinent heroin-dependent subjects (mean abstinence 3.0 months) either.

Thus, the most consistent changes in EEGs of heroin addicts were observed in alpha range and included deficit in alpha activity in early heroin abstinence. The latter abnormality appears to reverse considerably when heroin intake is stopped for several months, and therefore it may be viewed as acute withdrawal effect.

No relationships between spontaneous EEG variables and duration of heroin abuse or amount of the drug used were reported. However, only Gritz et al. (1975) analyzed both EEG spectral power and peak frequencies in a small patient population and only in two posterior derivations (P3-O1 and P4-O2), whereas other investigators published only spectral power data (Shufman et al., 1996; Costa and Bauer, 1997).

The purpose of the present study was to investigate cumulative heroin effects on brain functioning by studying relationships between EEG spectral power and mean frequencies and heroin abusing history.

## Methods

### Groups studied

Thirty three heroin abusers (all males) were recruited from the Moscow Research Practical Center of Prevention of Drug Addiction. All the patients injected heroin intravenously (i.v.) daily for at least four months and were receiving in-patient treatment in the Drug and Alcohol Dependency Unit during the period of the evaluation. Thirteen healthy male volunteers with no history of alcohol or drug abuse or dependence were chosen to match the drug abuse group as closely as possible for age and years of education. Written informed consent was obtained from patient and control subjects.

### Clinical assessment and selection principles

General physical, neurological and psychiatric evaluations were done to exclude patient and control subjects with lifetime history of a major medical disorder (hepatic, neurological, etc.), head injury resulting in loss of consciousness for more than 5 min., heroin overdoses resulting in hospitalization to intensive care unit for more than one day, seizures or other paroxysmal states (including drug-related paroxysms), HIV infection or a major psychiatric illness (schizophrenia, bipolar disorder, etc.). A blood sample was drawn from each patient during the period of in-patient treatment. HIV-serology was negative, and a standard CBC and serum transaminase levels were in normal ranges in all included cases.

Detailed drug histories were taken prior to evaluation. Only the periods of regular (daily) heroin use were included into the analysis. Thus, patients who used heroin daily for at least 4 months (range 4 - 44 months) were included.

The doses of heroin per day and the last date of heroin intake were also inquired. The average dose of heroin per day, that was taken through the week before complete withdrawal, was included into the analysis. The abstinence period was counted from the date, when regular (daily) heroin intake was stopped.

Almost all patients reported irregular (episodic) use of cannabis, ecstasy, pervitin-ephedrone (home-made stimulant drug). Most of the patients reported excessive use of barbiturates, benzodiazepines and tramadol when heroin was not available. Five patients used alcohol excessively in the same circumstances. However,

heroin was the only drug used by the patients regularly (daily) for several months or years.

At the admission all patients signed the regimen consent that included twenty-four-hour stay at the unit and limitation of outside contacts to one-two non-addicted persons (usually patient's parents). The further refusal to follow these points lead to discharge from the unit. This allowed to prevent using illicit drugs during the inpatient treatment. However, patients received psychotropic medication treatment for decreasing cravings. The prescribed drugs and dosages varied in each case and could include neuroleptics, antidepressants, benzodiazepines and/or carbamazepine. In order to evaluate medication sedation, the Digit Symbol test from the Wechsler Adult Intelligence Scale (Wechsler, 1955) was administered to the patients and healthy controls as a probe sensitive to the administered drugs sedative effects (Mattila et al., 1988; Lynch et al., 1997; Busto et al., 2000).

#### EEG recordings and analysis

Eyes closed resting EEG data were collected from the 19 monopolar electrode sites of the International 10/20 system (Fp1/Fp2, F3/F4, C3/C4, P3/P4, O1/O2, F7/F8, T3/T4, T5/T6, Fz, Cz, Pz), referred to linked earlobes. A differential eye channel was used for the detection of eye movements. EEG signal was amplified using EEG machine (Neurokartograph-4, MBN) with bandpass filter settings 0.5 and 100 Hz and a 50-Hz notch filter. All signals were digitized online at a sampling rate of 256 Hz and with a resolution of 12 bits. Electrode impedances were below 5 K $\Omega$ . Each recording comprised 7 min.

The resulting time series were inspected visually for body movements, eye blinks, eye movements, EMG, ECG, rheogram and loose electrodes artifacts. Intervals identified as disturbed by artifacts were excluded from the spectral analysis. Thus, 96 $\pm$ 15 (range 76 - 132) sec artifact-free epochs were available per individual. Additionally, EMG frequency range (65-80 Hz) was used as a covariate when high-frequency (beta1 and beta2) bands were analyzed in artifact-free epochs.

Finally, 4 sec with 50% overlap epochs were obtained from artifact-free EEG tracings and submitted to a Fast Fourier Transform. For each of the 19 monopolar derivations absolute power and mean frequency were computed for the delta1 (1-2Hz), delta2 (2-4Hz), theta1 (4-6Hz), theta2 (6-8 Hz), alpha1 (8-10 Hz), alpha2 (10-13 Hz), beta1 (13-20 Hz) and beta2 (20-30 Hz) frequency bands. Additionally,

absolute power and mean frequency for the delta (1-4 Hz), theta (4-8 Hz) and alpha (8-13) bands were calculated.

### Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 11 for Windows on a PC computer. Several power variables and days of abstinence did not meet parametric test assumptions, therefore all power measures and abstinence length were log transformed to reduce distribution skewness. Delta1, delta2, theta1 and theta2 mean frequencies in most derivations did not meet parametric test assumptions after transformation either, therefore in the latter case only non-parametric tests were used. All derivations were analyzed separately.

First, the data were statistically treated using General Linear Model (GLM) repeated measures procedure in order to test null hypotheses about the effects of a group as a between-subjects factor and effects of frequency bands as a within-subjects factor on absolute power or mean frequency variables. Then Linear Regression analyses were performed in attempt to elucidate the cause of power or frequency changes among heroin abusers. For regression analyses, five predictor variables were entered into a simultaneous regression model: months of daily heroin use, grams of heroin per day, days of abstinence, age and digit symbol performance. When beta-coefficients associated with any of the former three predictors attained significance, further comparisons with healthy controls were conducted. For this purpose patients were divided into subgroups as: (1) subgroup with duration of daily heroin abuse 4-16 months (n=17) and subgroup with duration of daily heroin abuse 19-44 months (n=16); (2) subgroup with dose of heroin per day 0.04-0.33 g (n=17) and subgroup with heroin dose 0.50-1.00 g per day (n=16); and (3) subgroup with abstinence 6-14 days (n=23) and subgroup with abstinence 15-141 days (n=10). One-way ANOVAs with post hoc Bonferroni multiple comparisons and non-parametric Kruskal-Wallis tests with separate Mann-Whitney U analyses were used where appropriate.

## Results

### Demographic and heroin use history analyses

In order to emphasize relationships between demographic characteristics and duration of daily heroin use in this patient population, the demographic and heroin use data are presented for two patient subgroups with different duration of daily heroin abuse and healthy control group (Table 1).

Differences in age and psychomotor speed among the groups were detected. Subjects with duration of daily heroin abuse less than 18 months (DDHA<18) were somewhat younger than healthy controls, nevertheless, were equivalent in years of education. Heroin abusers with duration of daily heroin abuse more than 18 months (DDHA>18) were well matched with the controls in both age and education. Both heroin abusers subgroups showed significantly lower psychomotor speed in Digit Symbol test in comparison to controls. Dose of i.v. heroin per day and abstinence duration were equivalent in both patient subgroups.

Besides Digit Symbol performance, no other intergroup differences were found, when subgroups with different doses or abstinence length were compared with healthy controls. All patient subgroups were characterized by significantly lower psychomotor speed compared to healthy controls.

Spearman rank-order correlations between duration of daily heroin abuse, dose and abstinence duration were not significant. There was a trend for age and duration of daily heroin abuse to correlate ( $R=.338$ ,  $p=.055$ ). Spearman rank-order correlations between Digit Symbol performance and age, years of education, duration of daily heroin abuse, dose and abstinence duration were not significant in the patient group. However, Digit Symbol performance correlated with age in the control group ( $R=-.586$ ,  $p=.045$ ).

### General Linear Model repeated measures analyses

Comparison of the patient group ( $n=33$ ) to the healthy controls ( $n=13$ ) using GLM repeated measures procedure revealed a significant group effect on the non-linear (order 5 contrast) distribution of the mean power spectrum between bands in all analyzed derivations ( $F_s = 5.87 - 18.99$ ,  $p_s=.020 - .000$ ). Example of group-averaged power spectra distributions in F4 derivation is presented in Fig. 1.

Group effect in GLM repeated measures analysis of mean frequencies distribution reached significance in all derivations except C3,T5, T6 and Fz (order 5 contrasts  $F_s = 4.28 - 10.00$ ,  $ps=.044 - .003$ ). Example of group-averaged data in F4 derivation are presented in Fig. 2.

Thus, in almost all derivations the spectral power characteristics and mean frequencies distributed between bands differently in heroin abusers compared to controls. However, these differences might be related to diverse factors, therefore the further analysis was conducted.

#### Relationships between duration of daily heroin abuse and EEG variables

The most consistent relationships between DDHA and EEG variables were found in the alpha range mean frequencies analysis (Table 2). Positive relationship between alpha frequency and daily heroin abuse duration reached significance in Fp1, Fp2, F3, F4, C3, C4, F8, Pz (adjusted R squares = .095 - .127, betas = .353-.396,  $ps=.049 - .028$ ). However, when patient subgroups were compared to normal controls the differences reached significance only in separate alpha1 and alpha2 bands analyses. Mean alpha1 frequency tended to be somewhat slower in patients and this trend reached significance only in subgroup DDHA<18 months compared to controls in Fp1, P4, O2, T3 and T4 ( $F_s=3.80-5.15$ ,  $ps=.030-.010$ ,  $ps$  after Bonferroni correction = .044-.008). Whereas mean frequency in alpha2 band was significantly faster in DDHA>18 months compared to controls in most derivations (Fp1, Fp2, F3, F4, C3, C4, P3, O1, F8, T3, T4, Fz, Cz ;  $F_s=3.75-6.27$ ,  $ps=.032-.004$ ,  $ps$  after Bonferroni correction = .049-.004).

In slow wave range, DDHA predicted positively delta1 power in P4, and negatively mean delta frequency in T3 and mean theta frequency in F7 (adjusted R squares = .132 - .209, betas = (-.355) - (-.481),  $ps=.039 - .006$ ). In beta1 range, DDHA related positively to beta1 power at Fp2 and P4, and negatively to mean frequency at T6 and P4 (adjusted R squares = .092 - .397, betas = (-.350) - .397,  $ps=.050 - .035$ ). ANOVAs of slow wave and beta bands demonstrated intergroup differences only in beta2 mean frequencies. The latter was significantly faster in O1 and O2 in subgroup DDHA>18 months compared to controls ( $F_s=5.09$  and  $5.57$ ,  $ps=.010$  and  $.007$ ,  $ps$  after Bonferroni correction = .017 and .006).

### Relationships between doses of heroin per day and EEG variables

The most consistent relationships between amount of heroin used per day and EEG variables were found in alpha1 mean frequencies and beta1 power analyses (Table 3). Dose of heroin per day related negatively to mean alpha1 frequencies in Fp2, C3, C4, F8, T3, T4, T5 and T6 (adjusted R squares = .107 - .168, betas = (-.370) – (-.442), ps=.040-.013). ANOVAs confirmed slowing of alpha1 band activity in subgroup with heroin doses 0.5 – 1.0 g compared to healthy controls in Fp1, C3, C4, P4, O1, O2, F7, T3, T4, T5, T6, Fz (Fs=3.19-7.53, ps=.050-.002, ps after Bonferroni correction = .050-.002).

Amount of heroin used per day before withdrawal predicted positively beta1 and beta2 power, that reached significance for beta1 power almost in all derivations except P3, O1 and O2; and for beta2 power only in three derivations (C4, F8 and Pz) (adjusted R squares = .239 - .327, betas = .327-.580, ps=.047-.001).

Other relationships included combined delta power in C4, combined theta power in C4 and Cz, and beta2 frequency in Cz (adjusted R squares = .136 – .349, betas = (-.384) – .609, ps = .027 and .000).

### Relationships between abstinence length and EEG variables

Except delta and theta1 bands, power variables strongly depended on abstinence length in our patient population. As abstinence became longer, theta2 power in Fp1, Fp2, P3, P4, O2, F8, Pz (adjusted R squares = .101 - .209, betas = .361-.486, ps=.046-.006), alpha1 power in Fp1, Fp2, F8, T5, Cz, and combined alpha power in O1 and O2 (adjusted R squares = .092 - .141, betas = .350-.412, ps=.050-.021) increased, whereas beta1 power in Fp2, F3, F4, C3, C4, F7, F8, T3, T4, T5 (adjusted R squares = .248 - .302, betas = (-.362)-(-.459), ps=.043-.006) and beta2 power in all derivations except P3, O2 and T6 (adjusted R squares = .119 - .382, betas = (-.386)-(-.637), ps=.032-.000) decreased. In addition, one-way ANOVAs revealed group effects when alpha and beta power were compared. Subgroup with abstinence less than two weeks was characterized by significant deficit in alpha power at the Fp1, Fp2, F3, F4, F7, F8 and T4 and significantly greater beta1 power at the Fp1, Fp2, F3, F4, C3, C4, F7, F8, T3, T4, T5, Fz and Cz leads and beta2 power at each lead in comparison to normal controls (Fs=3.19-14.63, ps=.000-.051, ps after Bonferroni correction =.000-.052). Decrease in beta2 power with abstinence prolongation seemed to occur faster and to be more complete in comparison to beta1 band. Indeed, subgroup with abstinence

more than two weeks had a statistical trend to differ from normal controls in beta1 power in eight derivations, and this trend reached significance at Fp1 and O2 (ps=.034 and .015). Whereas beta2 power had a trend to be lower in patients with longer abstinence in comparison to shorter abstinence group, and this trend reached significance at F7 and F8 (ps=.004-.027).

Combined theta and beta1 mean frequencies were also predicted by abstinence length. Mean combined theta frequency increased in Fp1, F3, F4, C3, P4, O1, O2, F7, F8, T5, T6, Fz, Cz and Pz (adjusted R squares = .133 - .291, betas = .369-.561, ps=.046-.001) and mean beta1 frequency decreased in Fp1, Fp2, F3, F4, C3, C4, F7, F8, T5, Fz, Cz (adjusted R squares = .095 - .221, betas = (-.353) – (-.502), ps=.049-.006) as abstinence became longer. The latter was confirmed by the significant slower beta1 frequency in subgroup with longer abstinence compared to recent abstainers in the same derivations plus T3 and T4 (Fs=3.64-8.62, ps=.038-.001, ps after Bonferroni correction = .038-.000). However, group effect in comparison to healthy controls reached significance only in C3 and P4 for longer abstainers (ps after Bonferroni correction = .043 and .039).

## Discussion

The distribution of spectral power and mean frequencies characteristics between bands was significantly different in our heroin abusers population compared to healthy controls; and these differences were most prominent in alpha and beta ranges. As further analysis demonstrated, these intergroup differences could be attributed to the influence of at least three factors: duration of daily heroin abuse, amount of heroin used per day before withdrawal and acute withdrawal effects. In the context of the research for cumulative heroin effects on human brain functioning, the most interesting findings in this study included the relationships between duration of daily heroin abuse and EEG variables changes.

### Daily heroin abuse duration

Daily heroin abuse duration consistently predicted the combined alpha mean frequencies in the frontal-central derivations. In addition, the DDHA>18 months group differed significantly from the healthy controls by higher alpha2 mean frequencies in the same derivations plus anterior temporal and left posterior derivations. Relationships between duration of daily heroin abuse and frequency shifts in delta, theta and beta ranges were also observed in a small number of derivations. And only in two derivations (Fp2 and P4) delta1 and beta1 power was predicted by DDHA. Thus, the duration of daily heroin abuse related much stronger to EEG frequency shifts compared to power variables changes in our patient population; and this effect was most prominent in alpha2 band. Given the correlations between EEG mean frequencies and event-related brain potentials (ERP) component peak latencies, as well as those between EEG power and ERP component amplitude [Intriligator and Polich, 1995], these findings are consistent with the results of the ERP study of Bauer (1998), mentioned in introduction.

Alpha2 mean frequency (9.5-12.5 Hz) positively correlates with P300 latency in healthy individuals ( $r=.55$ ,  $p<.01$ ) (Intriligator and Polich, 1995). Deckel et al. (1996) found that fast alpha activity (10.9-12.4 Hz) in frontal regions was predictive of the antisocial personality disorder diagnosis and the childhood problem behaviours in subjects with no history of substance abuse. Klimesch et al. (1998) showed that fast alpha (10.4-12.4 Hz) activity reflects semantic processes that are related to cognitive tasks performance.

Thus, the long-term shifts in alpha2 frequency range correlating with duration of daily heroin intake may reflect neuronal oscillation frequency changes, that contribute to the development of antisocial trends and some semantic processes disturbances in persons who chronically abuses heroin. This cumulative effect of the opioid seems not to be easily reversible at least within the first months of abstinence. Speculatively, opioids ability to remodel the density of dendritic spines and thus to affect the synaptic inputs may be assumed as an underlying cause of long-term neuronal oscillation frequency changes in chronic heroin abusers (Morozov and Bogolepov, 1984; Robinson et al., 2002).

#### Heroin dose per day

Statistical relationships between neurophysiological variables and amount of heroin used per day before withdrawal may have at least three possible explanations. First, neurophysiological variable changes most prominent in drug abusers with high doses are due to the severity of acute withdrawal in these patients. This seems to be true for the positive relationship between heroin doses and beta1 power in our patient population, as beta1 power was also inversely related to the abstinence length.

Secondly, high amount of heroin used per day may induce more extensive cumulative effect on brain functioning. Thus, slowing of electrical activity in alpha1 frequency range in central, temporal and occipital derivations, that was observed in patients with heroin doses 0.5 – 1.0 g per day, may be considered under this suggestion. However, slowing of alpha1 mean frequency in almost the same derivations was also found in patients with shorter daily heroin abusing period (DDHA<18 months) compared to healthy controls. The latter finding favours the third possible explanation – premorbid brain dysfunction, that contributes to malignant pattern of heroin consumption. Indeed, the data of this study do not allow to make clear conclusion about the possible origin of alpha1 band frequency slowing in our patients who injected high doses of the drug. Probably, the combination of both factors may play a role.

Interestingly, the same slowing of alpha rhythm in patients with daily heroin doses more than 0.5 gram compared to heroin abusers with lower doses ( $8.9 \pm 0.8$  Hz vs  $10.3 \pm 2.0$  Hz,  $p < .05$ ) was observed by us in the other patient population with somewhat shorter daily heroin abusing duration ( $12.2 \pm 8.0$  months) (Gekht et al., 2003). Slowing of alpha rhythm in methadone-maintained and abstinent heroin

addicts was also found by Gritz et al. (1975), however, no dose effect was reported in this study. Thus, slowing of alpha activity in posterior derivations seems to be common in heroin abusers especially when high doses of heroin are taken.

It is worth to mention, that in contrast to alpha2 band, alpha1 mean frequency correlates with P300 latency negatively ( $r=-.59$ ,  $p<.01$ ) (Intriligator, Polich, 1995). This alpha frequency range reflects non-specific selective attention processes (expectancy), whereas as mentioned above alpha2 band physiological correlates are specific semantic processes (Klimesch et al., 1998). Hence, the present findings suggest that individuals who daily abuse high doses of heroin have broader cognitive deficits compared to less intensive abusers. This is consistent with our neuropsychological findings in the same heroin addicts population (Briun et al., 2002).

#### Abstinence duration

Power variables in our patients population were strongly related to abstinence length and seemed to be a consequence of acute withdrawal. EEGs of heroin abusers registered during the first two weeks after withdrawal were characterized by pronounced desynchronization with excesses of beta power and deficits of alpha power. These electrical activity disturbances subsided within the next several weeks of abstinence along with increase in theta2 power, although the latter parameter deviations remained in the normal range. Mean frequencies shifts also occurred during the course of heroin abstinence. Interestingly, that theta and beta1 mean frequencies remained in normal ranges during the first two weeks after heroin withdrawal. Nevertheless, theta mean frequencies increased, and beta1 mean frequencies decreased in most anterior and central derivations as abstinence became longer.

Sala et al. (1995) reported very similar spectral power dynamics in rats given chronic morphine: a progressive decrease in mean total spectral power accompanied by a significant increase in delta and beta and a decrease in theta and alpha power between the last day of morphine and the first 3 days of abstinence. Complete normalization of total and bands spectral power was confirmed in this study at the 3, 6, 9 and 12 months follow-ups.

The dynamics and characteristics of spectral power changes within the early opiate withdrawal suggest the participation of catecholamine imbalances, especially

noradrenaline and perhaps to a lesser degree dopamine, that are widely recognized as a main cause of opiate physical dependency symptoms (Bassareo et al., 1995; Maldonado, 1997; Devoto et al., 2002). Relationships between theta and beta frequencies shifts and neurotransmitter imbalances characteristic for heroin withdrawal remain unclear.

### Limitations of the study

The main limitation of the present study was impossibility to determine medication treatment effects directly. Methadone is not available in Russia, and various treatment regimens are used. We included sedation measure (psychomotor speed) into regression model for controlling treatment effects, however, ideally, doses of the medication used in a single drug treatment regimen should be used as covariant.

Our patients had diverse life and drugs taking histories including number of non-fatal overdoses, nutrition pattern, non-opioid drugs using, etc. Therefore, more detailed drugs abusing history and examination are needed in future studies in order to determine possible cumulative influence of concomitant to heroin abuse adverse factors on the brain functioning in these patients.

Nothing is known about contaminant substances, that might also be taken daily with heroin injections. However, at the period of the study, street heroin in Moscow was quite pure, as may be seen from relatively low doses. Nevertheless, cumulative effects of contaminants on brain functioning in heroin abuses is not completely excluded.

### Conclusion

The present results demonstrated frequency shifts in alpha2 range, most prominent in frontal and central derivations, in heroin abusers who used heroin for at least eighteen months. This gives grounds to suppose that chronic heroin taking induces neuronal oscillation frequency changes, that may contribute to the development of antisocial trends and some semantic processes disturbances in these patients. Slowing of alpha1 mean frequency, most prominent in central, temporal and occipital derivations, was also observed in heroin addicts, who used high doses of the drug, however, its relation to heroin abusing remains unclear. Pronounced desynchronization is characteristic for acute heroin withdrawal, and spectral power tend to normalize almost completely during several weeks of abstinence.

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Table 1

Subject Characteristics	DDHA<18 subjects	DDHA>18 subjects	Control subjects	Test	Bonferroni post-hoc result
N	17	16	13		
Age	21.7±3.1	24.6±5.3	25.8±5.1	$F=3.5^*$	C>(DDHA<18)
Years of education	13.1±1.9	12.7±2.7	14.1±2.2	$F=1.4$	NS
Digit Symbol performance	6.6±1.4	7.1±1.7	10.3±3.0	$F=15.0^{**}$	C>(DDHA<18, DDHA>18)
Months of daily heroin use	8.76±3.48	28.68±6.96	-	$t=-10.4^{**}$	(DDHA>18)>(DDHA<18)
Grams of heroin per day	0.42±0.34	0.43±0.26	-	$t=-.154$	NS
Days of abstinence	13 (range 6-60)	12 (range 8-141)	-	$U=132.5$	NS

Abbreviations:  $F$ , ANOVA  $F$ ;  $t$ , independent samples  $t$ -test;  $U$ , Mann-Whitney test; C – controls; DDHA, duration of daily heroin abuse; NS – not significant.

\*  $p<0.05$ ; \*\*  $p<0.001$

Table 2

Relationships between duration of daily heroin abuse and EEG variables.\*

	<b>Delta1</b>	<b>Delta2</b>	<b>Tetha1</b>	<b>Tetha2</b>	<b>Alpha1</b>	<b>Alpha2</b>	<b>Beta1</b>	<b>Beta2</b>
Spectral power	↑ P4	NS	NS			NS	↑ Fp2, P4	NS
Mean frequency		↓ T3		↓ F7		↑ Fp1, Fp2, F3, F4, C3, C4, F8, Pz (P3, O1, T3, T4, Fz, Cz for alpha2 only)	↓ P4, T6	↑ O1, O2

\* Summary data are based on the results of regression (adjusted R squares = .092 - .397, betas = .353 - (-.481), ps=.050-.006) and group differences (Fs=3.80-5.57, ps=.030-.007, ps after Bonferroni correction = .044-.006) analyses.

Abbreviations: ↑, positive relationship – power or mean frequency increases as DDHA increases; ↓, negative relationship – power or mean frequency decreases as DDHA increases; NS, no significant relationships were found.

Table 3

Relationships between dose of heroin per day and EEG variables.\*

	<b>Delta1</b>	<b>Delta2</b>	<b>Tetha1</b>	<b>Tetha2</b>	<b>Alpha1</b>	<b>Alpha2</b>	<b>Beta1</b>	<b>Beta2</b>
Spectral power	↑ C4		↑ C4, Cz		NS		↑ All analyzed derivations except P3, O1, O2	↑ C4, F8, Pz
Mean frequency	NS		NS		↓ Fp1, Fp2, C3, C4, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz	NS	NS	↓ Cz

\* Summary data are based on the results of regression (adjusted R squares = .107 - .349, betas = (-.370) - .609, ps=.047-.000) and group differences (Fs=3.19-7.53, ps=.050-.002, ps after Bonferroni correction = .052-.002) analyses.

Abbreviations: ↑, positive relationship – power or mean frequency increases as dose of heroin per day increases; ↓, negative relationship – power or mean frequency decreases as dose of heroin per day increases; NS, no significant relationships were found.

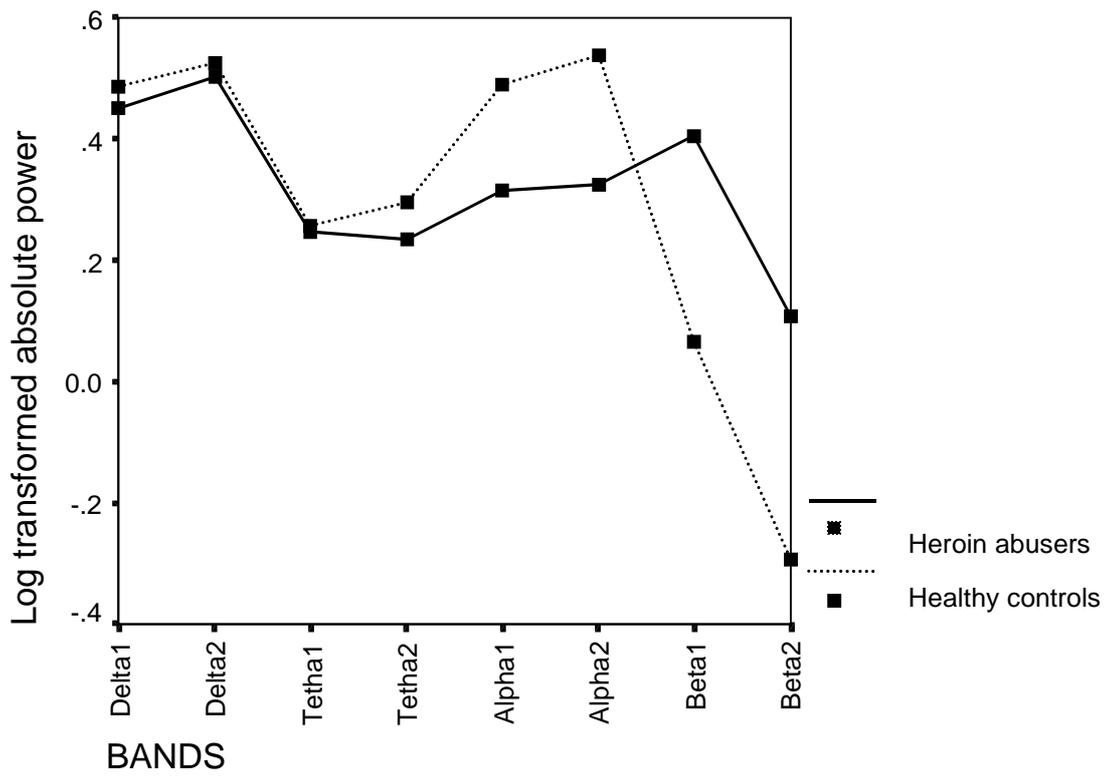
Table 4

Relationships between abstinence length and EEG variables.\*

	<b>Delta1</b>	<b>Delta2</b>	<b>Tetha1</b>	<b>Tetha2</b>	<b>Alpha1</b>	<b>Alpha2</b>	<b>Beta1</b>	<b>Beta2</b>
Spectral power	↑ T3		NS	↑ Fp1, Fp2, P3, P4, O2, F8, Pz	↑ Fp1, Fp2, F3, F4, O1, O2, F7, F8, T4, T5, Cz		↓ Fp1, Fp2, F3, F4, C3, C4, F7, F8, T3, T4, T5, Fz, Cz (P4, O1, Pz for beta2 only)	
Mean frequency	NS		↑ Fp1, F3, F4, C3, P3, O1, O2, F7, F8, T5, T6, Fz, Cz, Pz		NS		↓ Fp1, Fp2, F3, F4, C3, C4, F7, F8, T3, T4, T5, Fz, Cz	NS

\* Summary data are based on the results of regression (adjusted R squares = .092 - .382, betas = .350-(-.637), ps=.050-.000) and group differences (Fs=3.19-14.63, ps=.000-.050, ps after Bonferroni correction =.000-.052) analyses.

Abbreviations: ↑, positive relationship – power increases as abstinence length increases; ↓, negative relationship – power decreases as abstinence length increases; NS, no significant relationships were found.



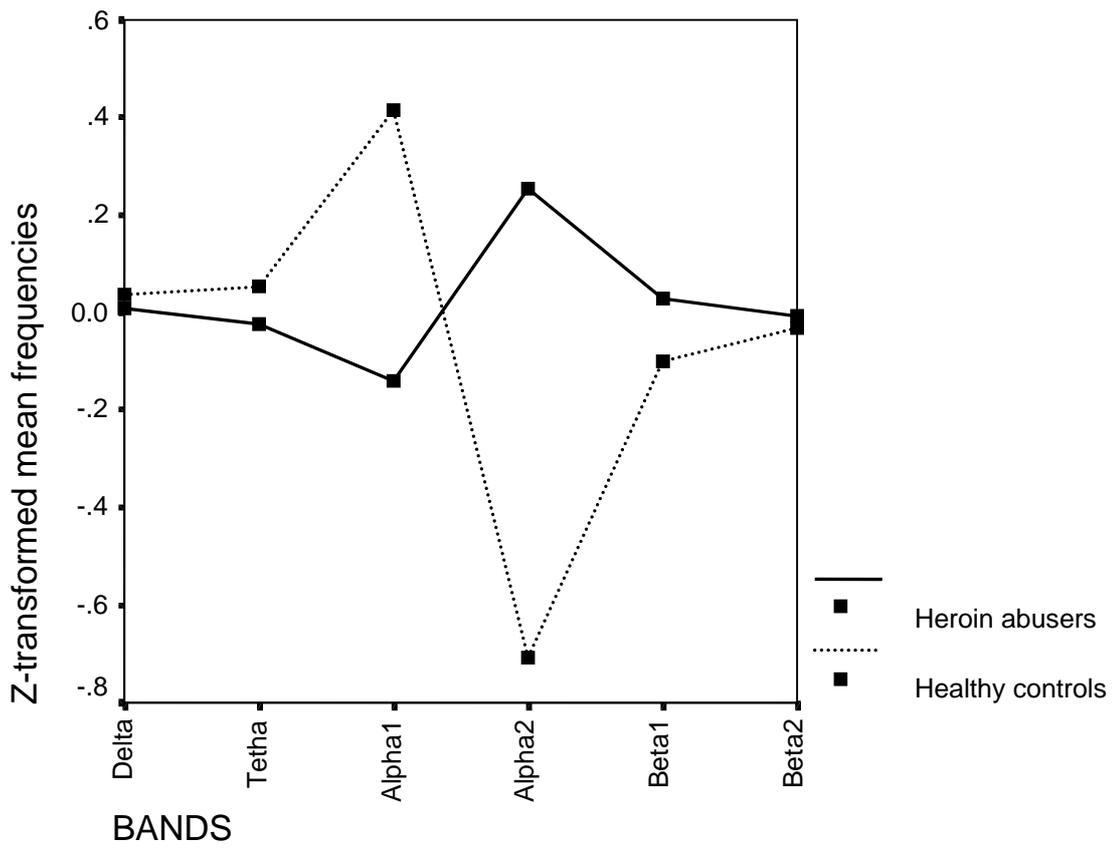


Fig. 1. Group-averaged and log-transformed power spectra at the F4 lead (GLM repeated measures procedure order 5 contrasts  $F=13.32$ ,  $p=.001$ ).

Fig. 2. Group-averaged z-transformed mean frequencies at the F4 lead (GLM repeated measures procedure order 5 contrasts  $F=4.94$ ,  $p=.031$ ).