

Clinical significance of electroencephalographic abnormalities in heroin addicts: systematic review

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Summary

The present review is the result of a systematic attempt to collect and analyze all the available contemporary data on neurological and psychophysiological aspects of EEG changes in heroin addicts. These data offer valuable objective insights into clinically significant encephalopathic and/or disintegrative processes in these patients. Thirteen computer EEG studies published since 1995 have been analyzed. It can be concluded that the sensitivity of computer EEGs to heroin-induced brain alterations is comparable with other contemporary neuroimaging techniques. In any case, precise recommendations for their use in regular medical practice must await further extensive research in this field.

Key Words: EEG - Heroin - Brain - Addiction - Electric activity

Introduction

Chronic heroin abuse induces significant changes in the central nervous system of human and animal individuals. Common consequences of chronic opioid consumption include addiction, tolerance to certain effects of the drug and the induction of dependence, with withdrawal symptoms after the discontinuation of drug administration. The weakening of ethical and moral attitudes, carelessness and self-centredness along with a loss of elementary self-preservation are other well-known symptoms of personality changes, which necessarily progress in each heroin addict. At present, the

neural mechanisms through which this “heroin encephalopathy” syndrome develops are incompletely understood. In their review of the neuropathology of heroin abuse, Büttner and colleagues ^[10] concluded that chronic heroin per se does not induce gross brain alterations. On the other hand, a set of abnormalities in receptor/second messenger systems was consistently demonstrated in the frontal and temporal cortex of chronic heroin addicts at several postmortem studies. Subcellular damage to frontal cortex neurons and astrocytes was also reported in these cohorts of patients ^[19, 32]. Animal studies confirmed opioids’ capacity to remodel the density of dendritic spines in many brain regions and so affect their synaptic input ^[24, 31]. Structural alterations in meso-limbic dopamine neurons were also found in the brains of rats treated chronically with morphine ^[36]. Hence, morphological studies consistently supply evidence that chronic opioid consumption induces characteristic brain alterations which probably underlie most psychopathological symptoms in this problematic patient population.

Seventy per cent of heroin addicts demonstrate prominent qualitative abnormalities in EEG recordings soon after heroin withdrawal ^[9, 20, 25]. The latter include marked EEG desynchronization, along with large amounts of low-amplitude “theta-delta” waves in central regions. During the first 3-6 months after complete withdrawal of the drug, many patients demonstrate dramatic normalization of brain electric activity ^[9, 20]. However, residual changes are still commonly observed. Some qualitative abnormalities in brain oscillations may be of clinical value. For instance, patients with paroxysmal/epileptiform bursts at frontocentral regions often take significantly lower intravenous dosages of heroin than patients with epileptiform activity in posterior brain regions ^[29]. The mechanisms of the latter phenomenon are unclear. It is likely that differences in epileptogenic and anticonvulsant cerebral opiate systems influence the course of drug abuse and other behaviours in heroin addicts.

Even a visual analysis of EEG recordings of heroin abusers may therefore give some information about the dynamics of withdrawal-related electrophysiological processes in the brain, or about individual abnormalities which may affect drug abuse behaviour. It is reasonable to expect that computer methods for analyzing electric activity in the brain may offer a range of new opportunities for elucidating the sources and clinical significance of EEG abnormalities in this patient population.

During the last decade, psychophysiology has made considerable advances in clarifying the functional role of rhythmic neuronal oscillations in cognitive processes ^[5, 37]. It has been shown that delta, theta, alpha, beta and gamma EEG frequency bands subserved various different cognitive processes. Slow (delta and theta) EEG oscillations indicate the involvement of widespread multineuronal networks in a cognitive operation, whereas faster (alpha, beta and gamma) frequency bands operate on more direct and/or localized interneuronal associations. Thus, deviations in EEG frequency distribution from normal values may provide an objective parameter for the disturbances in a certain type of cognitive process in a concrete individual.

In contrast to alcoholism or psychostimulating drug abuse, only a few quantitative studies have addressed spontaneous or elicited EEG abnormalities in chronic heroin users.

The aim of the present systematic review has been to collect and analyze all available contemporary data on neurological and psychophysiological aspects of EEG changes in heroin addicts, which might provide valuable objective information about clinically significant encephalopathic and/or disintegrative processes in these patients.

Methods

A preliminary search for the relevant publications was conducted using the Pubmed database with the following set of key words: “EEG AND (addiction OR dependence OR abuse) AND (heroin OR opioid OR morphine OR opiate)”. The main search was based upon appropriate references in relevant review or original articles. Publications were selected for the analysis if they fulfilled the following criteria: (1) original reports, (2) published since 1995, (3) pertinent to computer EEG studies on spontaneous or elicited electric activity in chronic heroin addicts without gross neurological or psychiatric deficits; and (4) reports that compared brain electric activity in heroin addicts with that of healthy controls. Thirteen appropriate publications by six research groups were found and included in the present systematic review. The features of the studies that have been analyzed are shown in Table 1.

Results

The techniques used for the registration and analysis of spontaneous and event-related brain electric activity differed in studies analyzed; this made direct comparisons impossible. Nevertheless, some consistent and similar findings were reported by different research groups and are presented here.

Most EEG parameters were, in fact, normal in heroin addicts 2-3 months after complete opioid withdrawal. These parameters included: (1) absolute spectral power in 5-8 frequency bands ^[11, 17], (2) relative spectral power ^[11, 35], (3) intrahemispheric and interhemispheric coherence in eight (excluding gamma) frequency bands ^[17], (4) amplitude of some types of elicited potentials ^[6, 8, 16], (5) latency of elicited brainstem auditory potentials ^[2], visual potentials ^[6] and P300 component of cognitive elicited potentials ^[7, 27].

Some of the parameters named above were abnormal in patient cohorts with a shorter length of abstinence. For instance, two studies showed a deficit in alpha2 power during the first weeks after heroin withdrawal, with a strong trend towards normalization in patients with a longer period of abstinence ^[30, 35]. An excess of beta2 activity was demonstrated in two heroin addict cohorts at the same interval after withdrawal ^[17, 30]. The rapid recovery of beta oscillations after a longer period of abstinence was observed in our patient population, too. Thus, prominent disturbances in absolute or relative spectral power are characteristic only for early heroin abstinence, and were no longer recorded after 2-3 months of opioid withdrawal. Most studies failed to find any significant differences in the amplitude and/or latency of short and intermediate

Table 1. Characteristics of the studies reviewed

Study	Group	Patients	Mean age	Years of heroin use	Abstinence	Parameters analyzed
Shufman et al., 1996	1	Current addicts (n=20)	32.5	4.5	no	Relative power at O1-Cz (resting EEG)
	2	Ex-addicts (n=20)	33.0	3.5	>2 weeks	
Costa & Bauer, 1997		Ex-addicts (n=19)	31.7	-	2.9 months	Absolute and relative power at 9 midline leads (resting EEG)
Bauer, 1998	1	Ex-addicts (n=21)	33.2	10.6	3 months	Pattern shift visual elicited potentials (N75 and P100) at O1 and O2
	2	Methadone-maintained, HIVnegative	40.1	17	no	
Bauer, 2001	3	Methadone-maintained, HIVpositive	41.8	23.8	no	Amplitude and latency of P300 component of cognitive potentials in 15 leads
		Ex-addicts (n=29)	33.6	9.9	3 months	
Arzumanov et al., 2001		Addicts in detoxification (n=60)	-	-	-	Latency of elicited brainstem auditory potentials Amplitude and latency of P300
Papageorgiou et al., 2001		Ex-addicts (n=20)	31.1	9.0	>6 months	Latency of P600 component of cognitive potentials in 15 leads

Table 1. Characteristics of the studies reviewed						
Study	Group	Patients	Mean age	Years of heroin use	Abstinence	Parameters analyzed
Bauer et al., 2002		Ex-addicts (n=29)	32.3	10.8	3.2 months	Amplitude of slow potentials (waveform between 500 and 950 ms) in 15 leads
Arzumanov et al., 2003		Ex-addicts (n=20)	18	0.5 - 3	>2 weeks	Amplitude and latency of N200 and P300
Franken et al., 2003		Ex-addicts (n=19)	33.5	9.0	>2 weeks	Amplitude of P3 and slower potentials at heroin-cued and neutral stimuli in 11 midline leads
Franken et al., 2004		Ex-addicts (n=18)	32.4	9.0	>2 weeks	Absolute and relative power in 21 leads, intrahemispheric (Fp1/O1, Fp2/O2) and interhemispheric (F7/F8, T3/T4, T5/T6) coherence
Papageorgiou et al., 2004		Current addicts (n=20)	29.6	9.3	no	Amplitude and latency of P300 in 15 leads
Polunina & Davydov, 2004		Addicts in detoxification (n=33)	21.7	1.5	6 - 141 days	Spectral power and mean frequencies in 19 leads (resting EEG)
Davydov & Polunina, 2004		Addicts in detoxification (n=33)	21.7	1.5	6 - 141 days	Resting EEG spectral power and mean frequencies in 19 leads, along with cognitive tests

latency elicited potentials several months after heroin withdrawal.

From a neurological point of view, it is important to determine what alterations in the central nervous system underlie poorly reversible psychopathological changes in opioid addicts. Hypothetically, these alterations might correlate with chronic heroin and remain stable over a long (several month) period of heroin abstinence. Many EEG parameters were studied in this respect, but only three of them significantly correlated with the duration of chronic heroin intake.

In our study of young heroin addicts (median age = 21.5 years) with relatively short duration of chronic heroin intake (median = 1.5 years), the mean frequency of alpha2 oscillations in frontal/central regions was significantly faster in addicts with a long history of drug abuse.

Franken et al. ^[16] studied heroin addicts with a relatively long history of drug abuse (mean = 9.0) and found a correlation between decreased beta1- and theta-coherence in lateral frontal regions (F7/F8) and chronic heroin duration. Unfortunately, the authors did not analyze coherence in frontal/medial or central derivations in this study.

Finally, Bauer ^[6] reported a significant correlation between the prolonged latency of the N75 component of visual event-related potentials and chronic heroin duration in methadone-maintained patients with an extremely long heroin abuse history (mean = 17-24 years). The same study did not register any deviation in this parameter in ex-addicts with a moderate heroin abuse duration (mean = 10.6 years).

The studies just cited, therefore, show that chronic heroin length affects brain electric activity, and two of these studies consistently reported adverse heroin effects on electric activity at frontal/central regions. However, the considerable differences in duration of drug abuse and in the EEG parameters used in three studies should be noted.

Six reports by four research groups consistently pointed to the lateralized dysfunction of cognitive processing in chronic heroin abusers (see Table 2). Two studies found a more marked slowing of cognitive elicited potential components in the right than in the left hemisphere in heroin addict cohorts ^[2, 26]. Significantly, this phenomenon was reported in right frontal/central derivations in heroin addicts 6 months after heroin withdrawal ^[26].

In our young patient cohort, we observed a significant association between the elevation of mean frequency in alpha2 oscillations in frontal/central regions and poor performance in the 'Tower of London' test (TLT is a cognitive test sensitive to prefrontal cortex dysfunction ^[34] ^[30]). When chronic heroin length was entered as a covariate, the latter variable removed alpha2 frequency at the right central lead (C4) and did not affect the strongest independent predictor of cognitive performance – alpha2 mean frequency at the left central (C3) derivation. These findings indicated that chronic heroin intake affected performance on TLT through the induced imbalances in right hemisphere neuronal networks. At the same time, a subgroup of heroin addicts, which included some patients with a long and some with a relatively short heroin history (e.g. 6 months), gave an extremely poor TLT performance and had an extremely high alpha2 mean frequency at C3 lead.

Very interesting findings were reported by Franken et al. [16], who reported significantly higher amplitudes of slow potentials in heroin addicts elicited by heroin-cued pictures than in healthy controls. These potentials were significantly more pronounced at the left central (C3) lead than at the right central (C4) one. More importantly, those high amplitudes of slow potentials at C3 were significantly correlated both with addicts' desire to use heroin and with the need for relief from their negative state, and only the latter correlation was significant at C4. The same authors reported a direct association

Table 2. Neurological and psychophysiological correlates of brain electric activity in heroin addicts
<p>Chronic heroin length correlates</p> <ol style="list-style-type: none"> 1. Frontal interhemispheric coherence decrease in beta1 and theta frequency band [Franken et al., 2004]. 2. Frontal/central increase of mean frequency of alpha2 activity [Polunina & Davydov, 2004]. 3. Prolonged latency of component N75 of pattern shift visual elicited potential [Bauer, 1998].
<p>Lateralized imbalances of cognitive processing in heroin addicts</p> <ol style="list-style-type: none"> 1. Delayed latency of cognitive elicited potentials, most prominent at right hemisphere [Arzumanov, 2001; Papageorgiou et al., 2001]. 2. Disturbances of normal interhemispheric asymmetry of cognitive stimulus processing [Arzumanov et al., 2003]. 3. Increased left intrahemispheric gamma coherence (Fp1/O1) [Franken et al., 2004]. 4. Strong association between elevated alpha2 mean frequency at central derivations (C3, Cz, C4) and poor performance on Tower of London test (planning dysfunction). This association was independent of drug abuse history at C3 and Cz, and, in contrast, was mediated by chronic heroin length at C4 [Davydov & Polunina, 2004]. 5. Significantly higher amplitudes of slow positive waves in left central lead (C3) compared with right central lead (C4) at showing of heroin-cued pictures. The elevated amplitude of slow potentials at C3 and Cz significantly correlated with desire to use heroin, and at C3 and C4 with need to relieve negative states [Franken et al., 2003].
<p>Other clinically significant abnormalities and correlates of brain electric activity in heroin addicts</p> <ol style="list-style-type: none"> 1. Residual changes in elicited brain potentials in heroin addicts 6 months after complete withdrawal of opioids [Papageorgiou et al., 2001; Papageorgiou et al., 2004]. 2. Correlation between decreased P300 amplitude and number of DSM-III-R childhood conduct disorder criterion behaviours [Bauer, 2001]. 3. Correlation between increased temporal (T3/T4) interhemispheric delta coherence and chronic heroin craving/obsessive heroin-related thoughts [Franken et al., 2004]. Correlation between increased alpha1 coherence at frontal (F7/F8) and beta2 at temporal derivations and chronic heroin craving/obsessive heroin-related thoughts, respectively [Franken et al., 2004].

Table 2. Neurological and psychophysiological correlates of brain electric activity in heroin addicts

Normal EEG parameters in chronic heroin abusers, and EEG parameters, which rapidly recover after heroin withdrawal

1. Normal absolute power several weeks after complete opioid withdrawal [Costa & Bauer, 1997; Franken et al., 2004].
2. Normal relative power 2-3 months after complete opioid withdrawal [Shufman et al., 1996; Costa & Bauer, 1997].
3. Intrahemispheric and interhemispheric coherence in eight (except gamma) frequency bands [Franken et al., 2004].
4. Normal amplitude of visual elicited potentials [Bauer, 1998; Franken et al., 2003] and slow potentials (between 500 - 950 ms) [Bauer, 2002] several weeks after opioid withdrawal.
5. Normal latency of elicited brainstem auditory potentials [Arzumanov, 2001], visual potentials [Bauer, 1998] and P300 component of cognitive elicited potentials several months after heroin withdrawal [Bauer, 2001; Papageorgiou et al., 2004].
6. Recovery of deficit of absolute or relative spectral power in alpha2 frequency band during first weeks of abstinence [Shufman et al., 1996; Polunina & Davydov, 2004].
7. Recovery of excessive beta power during first weeks of heroin withdrawal [Polunina & Davydov, 2004].

between craving magnitude and increased coherence between frontal/temporal derivations in several frequency bands^[17].

Thus, persistent brain electric abnormalities in chronic heroin addicts predominate in frontal/central regions, with a consistent trend towards a more marked right hemisphere involvement. Electric activity in the left central region correlated with prominent psychopathological symptoms in two studies, but not with heroin abuse duration.

Discussion

The data in the EEG studies cited above on the predominant dysfunction of frontal/central regions in chronic heroin abusers are consistent with functional neuroimaging findings in heroin addict cohorts. Five studies reported a decrease in blood flow or metabolism changes in frontal lobes and/or the anterior cingulate cortex in methadone-maintained or abstinent (up to several years) heroin-dependent subjects^[18, 21-23, 28]. Two studies showed a trend towards more severe blood flow changes in the right frontal lobe of heroin addicts^[21, 28]. So, the sensitivity of computer EEGs to heroin-induced brain alterations seems to be at least comparable with other functional neuroimaging techniques (SPECT, PET, fMRI et al.), which are much more expensive than EEGs and are only rarely available in regular clinical practice. Given the importance of frontal and right hemisphere structures in behaviour regulation and emotional processing, the cited EEG and other neuroimaging technique data offer a plausible explanation for marked psychopathological changes contrasting with intact general intelligence in

chronic heroin users.

The correlations of EEG abnormalities with heroin history that were reported in three studies seem to reflect different stages of heroin-related brain damage and disintegration rather than the same neuromorphological phenomenon. The patients in our study^[30] were young and healthy. Many of them were involved in heroin abuse during the ‘heroin epidemic’ in Russia between 1995 and 2000, when heroin was cheap and contained few contaminants. The EEG parameter in our patients – alpha2 mean frequency – that was correlated with chronic heroin duration differed significantly from that of controls. The patients of Franken et al.^[17] were older and had used heroin for about 9 years. Even so, only patients with a longer duration of heroin history in that cohort demonstrated decreased beta1- and theta-coherence in lateral frontal regions. Lastly, in the study of Bauer^[6], a similar patient population with chronic heroin intake averaging 10.6 years showed no deviations from controls in the latency of visual potentials. Only patients with heroin abuse lasting 17-24 years showed this evidence of diffuse brain damage affecting visual pathways in occipital regions. Thus, further research is needed in order to determine the clinical significance of reported neurophysiological correlates of chronic heroin duration. At present, the elevation of the mean frequency of alpha2-activity in frontal/central regions (especially, at C4) seems to be the earliest and most reliable EEG sign of adverse chronic heroin effects.

Two studies consistently showed a prominent association between abnormal electric activity at the left central lead and psychological deviations in heroin addicts. Franken et al.^[16] found marked involvement of this region in the craving processes. Whereas, we observed a highly abnormal frequency of alpha2-activity at C3, which significantly interfered with patients’ performance on the Tower of London Test. Importantly, this last association did not correlate with chronic heroin effects.

Neuroimaging studies of opiate craving on viewing heroin cues also recorded the predominant activity of the left hemisphere midline neural network, which consisted of the left anterior cingulate cortex, the left insula and/or the left frontal/temporal cortex^[12, 33]. Interestingly, that effective performance on TLT is predominantly supported by left frontal structures and the left anterior cingulate cortex, too^[1, 15, 34]. It seems probable that a neural functional network in this region is excessively involved in craving processes in heroin addicts and is no longer able to subserve a set of goal-directed (planning) cognitive operations such as TLT tasks. The absence of any direct relationship between neurophysiological abnormality in this region and chronic heroin duration provide evidence that a subpopulation of heroin addicts is especially likely to decompensate soon after involvement in drug abuse. These subjects probably suffer from psychiatric comorbidity (e.g. disturbances in left hemisphere alpha oscillating networks were also displayed in attention-deficit/hyperactivity disorder^[4] or antisocial personality disorder^[14]).

The present review supports the case for further extensive research into the clinical significance of brain electric activity abnormalities in heroin addicts. Contemporary methods of computer analysis of EEG recordings offer good opportunities to objectively and quantitatively evaluate deviations in brain functioning in this problematic

patient population. The sensitivity of computer EEGs to heroin-induced brain alterations is comparable with other functional neuroimaging techniques, which have the disadvantage of being much more expensive and cannot be used regularly in the assessment of heroin addicts. Resting EEG band mean frequency (especially, alpha2 mean frequency in frontal/central regions) or coherence seem to be the most valuable parameters, and are easy to obtain. Even so, precise recommendations for using EEGs in the clinical management of heroin addicts will become feasible only after further thorough research in this field.

References

1. ANDREASEN N.C., REZAI K., ALLIGER R., SWAYZE V.W. 2ND, FLAUM M., KIRCHNER P., COHEN G., O'LEARY D.S. (1992). Hypofrontality in Neuroleptic-Naive Patient and in Patients with Chronic Schizophrenia. *Arch Gen Psychiatry* 49: 943-958.
2. ARZUMANOV YU.L. (2001). Psychophysiological aspects of alcoholism and drug addiction. Izdatel Gainullin, Moscow.
3. ARZUMANOV YU.L., DUDKO T.N., ABAKUMOVA A.A., TVERITSKAYA I.N., TRUDOLYUBOVA M.G., USMANOVA N.N., KAMENSKAYA A.I. (2003). Perception of significant information by patients with heroinomania. *Voprosi narkologii*. N°5: 55-62.
4. BARRY R.J., CLARKE A.R., MCCARTHY R., SELIKOWITZ M. (2002). EEG coherence in attention-deficit/hyperactivity disorder: a comparative study of two DSM-IV types. *Clin Neurophysiol* 113: 579-85.
5. BAŞAR E., BAŞAR-EROGLU C., KARAKAŞ S., SCHÜRMAN M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. *Int. J. Psychophysiol.* 39: 241-248.
6. BAUER L.O. (1998). Effects of chronic opioid dependence and HIV-1 infection on pattern shift visual evoked potentials. *Drug Alcohol Depend.* 50(2): 147-55.
7. BAUER L.O. (2001). CNS recovery from cocaine, cocaine and alcohol, or opioid dependence: a P300 study. *Clin Neurophysiol.* 112: 1508-15.
8. BAUER L.O. (2002). Differential effects of alcohol, cocaine, and opioid abuse on event-related potentials recorded during a response competition task. *Drug Alcohol Depend.* 66: 137-45.
9. BENOS J., KAPINAS K. (1980). EEG-Untersuchungen bei Heroinisten in der Entwöhnungsphase. *MedWelt Bd.31/Heft 39*: 1395 – 1399.
10. BÜTTNER A., MALL G., PENNING R., WEIS S. (2000). The neuropathology of heroin abuse. *Forensic Science International.* 113: 435-442.
11. COSTA L., BAUER L. (1997). Quantitative electroencephalographic differences associated with alcohol, cocaine, heroin and dual-substance dependence. *Drug Alcohol Depend.* 46 (1-2): 87-93.
12. DAGLISH M.R., WEINSTEIN A., MALIZIA A.L., WILSON S., MELICHAR J.K., LINGFORD-HUGHES A., MYLES J.S., GRASBY P., NUTT D.J. (2003). Functional connectivity

- analysis of the neural circuits of opiate craving: “more” rather than “different”? *Neuroimage*. 20(4):1964-70.
13. DAVYDOV D.M., POLUNINA A.G. (2004). Heroin abusers' performance on the Tower of London Test relates to the baseline EEG alpha2 mean frequency shifts. *Progress in neuropsychopharmacology and biological psychiatry*. V.28 (7): 1143-1152.
 14. DECKEL A.W., HESSELBROCK V., BAUER L. (1996). Antisocial personality disorder, childhood delinquency, and frontal brain functioning: EEG and neuropsychological findings. *J. of Clinical Psychology*. 52: 639-50.
 15. ELLIOTT R., BAKER S.C., ROGERS R.D., O'LEARY D.A., PAYKEL E.S., FRITH C.D., DOLAN R.J., SAHAKIAN B.J. (1997). Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography, *Psychological Medicine*. 27: 931-942.
 16. FRANKEN I.H.A., STAM C.J., HENDRIKS V.M., VAN DEN BRIK W. (2003). Neurophysiological evidence for abnormal cognitive processing of drug cues in heroin dependence. *Psychopharmacology*. 170: 205-212.
 17. FRANKEN I.H.A., STAM C.J., HENDRIKS V.M., VAN DEN BRINK W. (2004). Electroencephalographic power and coherence analyses suggest altered brain function in abstinent male heroin-dependent patients. *Neuropsychobiology*. 49: 105-110.
 18. GALYNKER I.I., WATRAS-GANZ S., MINER C., ROSENTHAL R.N., DES JARLAIS D.C., RICHMAN B.L., LONDON E. (2000). Cerebral metabolism in opiate-dependent subjects: effects of methadone maintenance. *The Mount Sinai Journal of Medicine*. 67: 381-387.
 19. GARCIA-SEVILLA J.A., VENTAYOL P., BUSQUETS X., LA HARPE R., WALZER C., GUIMON J. (1997). Marked decrease of immunolabelled 68 kDa neurofilament (NF-L) proteins in brains of opiate addicts. *Neuroreport*. 8: 1561-1570.
 20. GEKHT A.B., POLUNINA A.G., BRIUN E.A., DAVYDOV D.M. (2003). Brain bioelectrical activities in heroin addicts during early abstinence period. *Zh Nevrol Psikhiatr Im S. S. Korsakova*. 103(5): 53-59.
 21. GERRA G., CALBIANI B., ZAIMOVIC A., SARTORI R., UGOLOTTI G., IPPOLITO L., DELSIGNORE R., RUSTICHELLI P., FONTANESI B. (1998). Regional cerebral blood flow and comorbid diagnosis in abstinent opioid addicts. *Psychiatry Research: Neuroimaging Section*. 83: 117-126.
 22. HASELHORST R., DÜRSTELER-MACFARLAND K.M., SCHEFFLER K., LADEWIG D., MÜLLER-SPAHN F., STOHLER R., SEELIG J., SEIFRITZ E. (2002). Frontocortical N-acetylaspartate reduction associated with long-term IV heroin use. *Neurology*. 58: 305-307.
 23. KRISTAL J.H., WOODS S.W., SEIBYL J.P. (1995). Opiate dependence and withdrawal: preliminary assessment using single photon emission computerized tomography (SPECT). *Am J. Drug Alcohol Abuse*. 21(1): 47-6.
 24. MOROZOV G.V., BOGOLEPOV N.N. (1984). *Morphinism*. Medicina Publishers. Moscow.

25. OLIVENNES A., CHARLES-NICOLAS A., OLIEVENSTEIN C.L. (1983). Altérations de l'électroencéphalogramme de veille dans la grande héroïnomanie. *Ann. Med. Psychol. (Paris)*. 141(4): 458-69.
26. PAPAGEORGIOU C., LIAPPAS I., ASVESTAS P., VASIOS C., MATSOPOULOS G.K., NIKOLAOU C., NIKITA K.S., USUNOGLU N., RABAVILAS A. (2001). Abnormal P600 in heroin addicts with prolonged abstinence elicited during a working memory test. *Neuroreport* 12: 1773-8.
27. PAPAGEORGIOU C.C., LIAPPAS I.A., VENTOURAS E.M., NIKOLAOU C.C., KITSONAS E.N., UZUNOGLU N.K., RABAVILAS A.D. (2004). Long-term abstinence syndrome in heroin addicts: indices of P300 alterations associated with a short memory task. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, in press.
28. PEZAWAS L., FISCHER G., PODREKA I., SCHINDLER S., BRUCKE T., JAGSCH R., THURNHER M., KASPER S. (2002). Opioid addiction changes cerebral blood flow symmetry. *Neuropsychobiology*. 45: 67-73.
29. POLUNINA A.G., DAVYDOV D.M., BRYUN E.A. (2004). Epileptiform activity and heroin dosages in heroin addicts. *Voprosi narkologii*. N°1: 41-46.
30. POLUNINA A.G., DAVYDOV D.M., 2004. EEG spectral power and mean frequencies in early heroin abstinence. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 28: 73-82.
31. ROBINSON, T.E., GORNY, G., SAVAGE, V.R., KOLB, B. (2002). Widespread but regionally specific effects of experimenter- versus self-administered morphine on dendritic spines in the nucleus accumbens, hippocampus, and neocortex of adult rats. *Synapse*. 46: 271-9.
32. SASTRE M., VENTAYOL P., GARCIA-SEVILLA J.A. (1996). Decreased density of I2-imidazoline receptors in the postmortem brains of heroin addicts. *Neuroreport*. 7: 509-512.
33. SELL L.A., MORRIS J.S., BEARN J., FRACKOWIAK R.S., FRISTON K.J., DOLAN R.J. (2000). Neural responses associated with cue evoked emotional states and heroin in opiate addicts. *Drug Alcohol Depend.* 60(2):207-16.
34. SHALLICE T. (1982). Specific impairments of planning. *Phil. Trans. R. Soc. Lond. B*. 298: 199-209.
35. SHUFMAN E., PERL E., COHEN M., DICKMAN M., GANDAKU D., ADLER D., VELER A., BAR-HAMBURGER R., GINATH Y. (1996). Electro-encephalography spectral analysis of heroin addicts compared with abstainers and normal controls. *Isr. J. Psychiatry Relat. Sci.* 33(3): 196-206.
36. SKLAIR-TAVRON L., SHI W.X., LANE S.B., HARRIS H.W., BUNNEY B.S., NESTLER E.J. (1996). Chronic morphine induces visible changes in the morphology of mesolimbic dopamine neurons. *Proc Natl Acad Sci*. 93: 11202-11207.
37. VON STEIN A., SARNTHEIM J. (2000). Different frequencies for different scales of cortical integration. From local gamma to long-range alpha/theta synchronization. *Int. J. Psychophysiol.* 38: 301-313.

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