Composition of EEG Oscillations and their Temporal Characteristics: Methadone Treatment

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Abstract
In this study, we examine the composition of electroencephalographic (EEG) oscillations within a broad frequency band (0.5-30 Hz) for opioid abuse (22 patients), during withdrawal (13 patients), and after 6 months of methadone treatment (6 patients) and in 14 healthy subjects during a resting condition (closed eyes). The exact compositions of EEG oscillations and their temporal behaviour were assessed using the probability-classification analysis of short-term EEG spectral patterns. The study reveals the dynamics of particular EEG oscillations throughout the conditions of opioid dependency, withdrawal and methadone-based treatment. It was shown that methadone maintenance treatment normalized considerably the composition of EEG oscillations and their percentage ratio and restored the temporal structure of patients' EEG comparable with healthy subjects. The importance of the methadone's ability to restore a normal temporal structure of the brain's activity is discussed.

Keywords: Opioid dependence; Opioid withdrawal; Methadone maintenance treatment; Electroencephalogram (EEG); Multiple EEG oscillations; Short-term spectral patterns; Probability-classification analysis; EEG temporal structure.

1. Introduction

This study is the third part of a longitudinal research program which aims to explore the composition of electroencephalographic (EEG) oscillations and their temporal behaviour in

opioid addicts who entered the hospital unit for withdrawal and evaluation for methadone treatment. In our previous studies (Fingelkurts et al., 2006d, and Fingelkurts et al., submitted for publication) we have demonstrated that the EEG of patients during opioid abuse and withdrawal is characterized by a significant reorganization of EEG oscillations and their temporal behaviour. These effects were widely distributed across the cortex. The results supported also the concept of an allostatic state of addiction (Koob and Le Moal, 2001) which is defined as an adaptive stability through change, a stability that is not within the normal homeostatic range (McEwen, 1998).

The actual composition of EEG oscillations, their percentage ratio and temporal behaviour within a broad frequency band (0.5-30 Hz) were examined using a probability-classification analysis of short-term EEG spectral patterns (SP) (suggested by Kaplan et al., 1999; for more details, see Fingelkurts et al., 2003a): Short-term power spectra were calculated from a long EEG time series; the individual power spectra were then classified using a set of reference spectra; the relative occurrence of each class was subsequently determined, giving a probability classification profile (PCP) and the temporal dynamics of SPs for each electrode and subject.

Differences between this method and conventional methods are as follows: conventional EEG analysis has a serious limitation in that spectral analysis is based on averaging the EEG parameters across extended periods of time and/or across broad fixed frequency bands. It has been shown that the total power spectrum does not characterize each of the individual power-spectra for each EEG segment (Fingelkurts et al., 2003a, 2004) and does not reflect the sequence of spectral patterns. As such, a power spectrum averaged in the conventional way may not only mask the temporal dynamics of EEG characteristics, but may also lead to ambiguous interpretation of data (Fingelkurts et al., 2002, 2004). Therefore, when examining the average brain electromagnetic parameters, it is not clear whether the phenomenon observed is real (not the "virtual" result of the averaging procedure) and typical for the whole analyzed signal. Moreover, according to Dumermuth and Molinari (1987), the total EEG power may be affected by polyrhythmic disorganized activity (a mixture of activity of small neuronal subpopulations each with its own mode (Tirsch et al., 2000)). In this case different EEG indices and parameters may suffer from the influences of this type of activity instead of reflecting the actual rhythmic activity. In addition in all studies related to EEG spectral analysis in opioid abusers, the frequency bands were predefined and taken in isolation from each other. This does not allow researchers to examine the behaviour of the

actual/natural composition of the EEG oscillations involved. At the same time, brain functions are indeed represented by multiple oscillations (Basar et al., 2000).

The advantages of the probability-classification analysis of short-term EEG SPs are the following: it (a) is a robust and model-independent approach, (b) considers the non-stationarity of the EEG, (c) does not need prior knowledge about the underlying dynamics, and (d) produces results which are easy to interpret in terms of their neurophysiological correlates. It was shown that PCP is highly stable over time (Fingelkurts et al., 2006a) and provides an adequate and detailed description of electromagnetic brain activity for healthy (Kaplan et al., 1999; Fingelkurts et al., 2002, 2003a,b) and pathological brain conditions (Fingelkurts et al., 2000; 2006b,c). Additionally, the index is sensitive to, for example, the effects of drugs on the activity of the brain (Fingelkurts et al., 2004, 2006d).

In the present study we (a) reviewed the dynamics of reorganization of the composition of EEG oscillations throughout the conditions of opioid dependency, withdrawal and methadone-based treatment and (b) examined whether methadone treatment normalizes the actual composition of EEG oscillations and their temporal behaviour in opioid-dependent patients.

Due to the fact that many studies have proved the efficacy of methadone maintenance (MM) treatment in reducing the use of opioids (Simpson and Sells, 1982; Ball and Ross, 1991), MM treatment has become standard practice in many countries (Maremmani and Reisinger, 1995). Nevertheless, several problems remain. By acting on the same opioid receptors as opioids, methadone prevents withdrawal symptoms which occur when the administration of opioids is stopped. Methadone is associated with fewer problems of psychological dependency as it does not give the same sense of euphoria which comes from, for example, heroin, however, methadone does cause physical dependency. Thus, several studies have shown that MM treatment is associated with a number of altered brain and cognitive functioning when compared to healthy subjects: (a) Silveri et al. (2004) reported changes in cerebral phospholipid metabolite levels for MM, (b) methadone subjects performed significantly poorer in a number of tests of learning and immediate recall when compared to abstinent subjects (Gritz et al., 1975), (c) one year of methadone maintenance treatment significantly increased serum leptin levels (Wilczek et al., 2004), (d) Zajicova et al. (2004) reported a significantly higher production of interleukins (IL-6) in MM patients, (e) MM patients usually demonstrate impairment in psychomotor speed and attention tests (Darke et al., 2000; Specka et al., 2001).

It has been suggested that brain oscillatory systems act as possible communication networks with functional relationships to the integrative brain functions (Basar et al., 2001a). It is assumed that EEG oscillations are of fundamental importance for mediating and distributing "higher-level" processes in the human brain (Klimesch, 1999; Basar et al., 2001b).

All these aspects demonstrate the importance of carrying out further studies into the effects of MM treatment on the ongoing brain oscillatory activity in opioid-dependent patients. To this end, the EEG provides a satisfactory measure of the large-scale dynamics of brain activity (with a temporal resolution in the order of milliseconds) and reflects the integrative brain and cognitive functions associated with health and pathology (Livanov, 1977; Nunez, 2000).

Hence, the aim of this study is to investigate the actual composition of EEG oscillations and their temporal behaviour within a broad frequency band (0.5-30 Hz) for opioid-dependent patients after receiving six months of methadone treatment. Additionally, the dynamics of the composition of EEG oscillations throughout healthy state and the conditions of opioid dependency, withdrawal and methadone-based treatment was examined. Considering that (a) long (at least three months) abstinence results in considerable or even complete normalization of EEG (Shufman et al., 1996; Costa and Bauer, 1997; Bauer, 2001; Gekht et al., 2003) and (b) MM treatment leads to a slowing down of the EEG in comparison with healthy subjects (Gritz et al., 1975), we predict that after MM treatment, the EEG will be characterized by a normalization of the composition of EEG oscillations (with a slight EEG slowing) and by a recovering of the temporal structure of EEG oscillations.

2. Materials and methods

2.1. Subjects

This longitudinal study included a total of 22 opioid-dependent patients (aged 33 ± 5 years, 14 males) (*current opioid-dependent group*) (Table 1). Of these, 13 patients (aged 32 ± 5 years, 5 males) agreed to undergo a withdrawal (*opioid withdrawal group*) and of these, 6 patients (aged 33 ± 5 years, 3 males) managed to complete at least six-months (11 ± 6 months) of MM treatment (*MM group*). Fourteen healthy subjects (aged 33 ± 5 years, 6 males) served as control. Patients were hospitalized for two weeks in a drug-withdrawal unit before starting methadone maintenance therapy. The criteria for this therapy which took

place at Helsinki University Central Hospital were, inter alia, a minimum age of 20 years, 4 years of documented i.v. opioid abuse, and a failure of institutional or long-lasting out-patient withdrawal therapy which also served as a criterion for inclusion in this study. The criteria for exclusion from the methadone maintenance therapy were uncontrolled polysubstance abuse, physical or psychiatric illness that made routine therapy impossible, and alcohol dependency. In this study, additional criteria for exclusion for both patients and controls were major head trauma and neurological illness. Each participant was evaluated by brain MRI, and participants showing lesions indicating vascular pathology or brain injury were excluded.

Table 1. Patients demographics.

Subject ID	Subject Hand	Age	Education (years)	Years of abuse	Dayley dose of heroin (g)	Dayley dose of buprenorfine (mg)	DSM axis I Diagnosese	DSM axis II Diagnosese
1	R	36	11	6	1	0	Opioid dependence	Antisocial, borderline, features of paranoid, schizoid, obsessive-compulsive
2	R	41	9	26	1	16	Opioid & benzodiazepin dependence	Antisocial, borderline, features of obsessive-compulsive, avoidant
3	R	25	12	8	0.5	14	Opioid & benzodiazepin dependence	Antisocial, borderline, features of obsessive-compulsive
4	R	35	12	5	1	4	Opioid dependence	Antisocial, borderline
5	R	34	12	9	0	4	Opioid dependence	Antisocial, features of passive-aggressive, paranoid
6	R	29	12	12	1	0	Opioid & benzodiazepin dependence	Antisocial, features of borderline, obsessive-compulsive
7	R	33	14	12	1	8	Opioid dependence	Antisocial, features of obsessive-compulsive
8	R	28	10	8	1	16	Opioid & benzodiazepin dependence	Antisocial
9	R	21	12	4	0.2	16	Opioid dependence	Antisocial
10	R	36	9	8	1	0	Opioid & benzodiazepin dependence	Borderline, features of paranoid, obsessive-compulsive
11	R	36	12	7	0.5	2	Opioid & benzodiazepin dependence	Antisocial
12	R	35	10	20	0.2	8	Opioid & benzodiazepin dependence	Antisocial, borderline, features of paranoid, schizotypal
13	R	25	12	8	1.2	8	Opioid & benzodiazepin dependence	Antisocial, features of obsessive-compulsive
14	R	30	13	10	1.5	10	Opioid & benzodiazepin dependence	Antisocial, borderline, features of paranoid, schizotypal, obsessive-compulsive
15	R	38	8	20	1.5	8	Opioid & benzodiazepin dependence	Antisocial
16	R	46	10	10	0.1	0	Opioid dependence	Antisocial, features of obsessive-compulsive, avoidant, depressive
17	R	32	11	5	0.4	8	Opioid dependence	Antisocial, features of obsessive-compulsive, paranoid
18	L	34	13	7	0.2	8	Opioid & benzodiazepin dependence	Antisocial
19	R	24	10	7	1	4	Opioid & benzodiazepin dependence	Borderline
20	R	43	9	26	0.1	0	Opioid & benzodiazepin dependence	Features of borderline, antisocial, and narcissistic
21	R	29	12	10	0	4	Opioid & benzodiazepin dependence	Antisocial, borderline
22	L	30	10	8	2	48	Opioid & benzodiazepin dependence	Antisocial

Subjects 1–6: MM group. Subjects 1–13: Opioid withdrawal group. Subjects 1–22: Current opioid dependent group.

L - Left, R - Right, MM - methadone maintenance

Almost all patients in the *current opioid-dependent group* reported irregular (episodic) use of cannabis, amphetamines, and alcohol for short periods earlier in their lives. Some patients reported use of benzodiazepines (15 patients), cannabis (5 patients), and amphetamines (5 patients) when heroin was not available. However, street buprenorphine and heroin were the only drugs used regularly (daily) by the patients for the past few years (at least 4).

The psychiatric diagnoses of patients and control subjects were explored using Structured Clinical Interviews I and II (SCID I and II) (First et al., 1994a,b) which elicit detailed information based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994). All the patients met DSM-IV criteria for opioid dependency, whilst several patients met also DSM-IV criteria for benzodiazepine

dependency (Table 1). Patients fulfilled no other DSM-IV criteria other than substance abuse on axis I; all met DSM-IV criteria of axis II diagnosis (American Psychiatric Association, 1994) for personality disorders. Patients had no neurological complaints. Controls were volunteers from the Institution's staff, and no control had any experience of illegal drugs but all had drunk alcohol on social occasions. However, none met the criteria of abuse of or dependency on alcohol. Controls did not fulfill any criteria for DSM-IV disorders on SCID I or II. Even though the patient group had on average fewer years of education than the control group, the difference was not significant. The study was accepted by the Ethics Committees of Helsinki University Central Hospital and all the subjects studied gave their written consent before enrolling in the study.

2.2. Trial Design

Current opioid-dependent group. Prior to the start of the study patients gave urine samples twice a week for a minimum of six weeks so as to be able to exclude substance abuse other than opioids. The patients were investigated on the day of admission and all had abused opiods within a period of twelve hours before the EEG recording; the dosages were the patients' usual dosages (Table 1). This allowed us to investigate patients abusing opioids without the influence of withdrawal symptoms. None of the patients had a withdrawal syndrome at the time of the EEG recording, as verified by the Gossop test (Gossop, 1990).

Opioid withdrawal group. At the time of the EEG assessment, patients had been abstinent for 12-15 days. During the withdrawal period, patients were visited frequently (i.e. twice per week) and at unspecified times in order to detect relapses or continued withdrawal via urine and breath screening. 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, diarrhea, muscle pain, runny nose and eyes (Washton et al., 1983). Lofexidine is an adrenoreceptor antagonist; it does not give rise to withdrawal symptoms of its own (Strang et al., 1999). All patients underwent a blood test to detect traces of the opioids on the day that the EEG was recorded and all had negative results. The severity of the withdrawal syndrome was also verified by using the Gossop test (Gossop, 1990).

MM group. At the time of the EEG assessment, patients had been on MM treatment for at least six months (11 ± 6 months). During this period, patients were visited frequently (i.e.

twice per week) and at unspecified times in order to detect relapses or continued abstinence via urine and breath screening. For the management of withdrawal symptoms in patients, methadone was used once in the morning in dosages of 95-150 mg (depending on the patient). All patients underwent a blood test to identify traces of the opioids on the day that the EEG was recorded and all had negative results. The withdrawal syndrome was also verified by using the Gossop test (Gossop, 1990).

After the electrodes were put in place and instruments calibrated, the subject (patient or healthy control) was seated in a comfortable chair in a dimmed recording room and the experimental procedure was explained. The EEG recording was started at noon. To reduce muscle artifacts in the EEG signal, the subject was instructed to assume a comfortable position and to avoid movement. The subject was also instructed to look straight in front of him/her (even though the eyes were closed). The behavior of a subject was observed on a TV monitor throughout the experiment. Each subject underwent five minutes of EEG recording with their eyes closed.

2.3. EEG Registration

All recordings were performed in a magnetically and electrically shielded room (Euroshield, Eura, Finland) in the BioMag Laboratory of the 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.

2.4. Data Processing

EEG components containing artifacts due to eye blinks, significant muscle activity, and movements were automatically removed by means of the ICA (Independent Component Analysis) procedure (Hyvärinen et al., 2001). After removing artefact-related components,

the back projection of the remaining components originating from the brain was performed (Joyce et al., 2004). It is implemented using "The FastICA package for MATLAB" freely available online at http://www.cis.hut.fi/projects/ica/fastica/.

EEG streams, fully corrected from the influence of artifacts, contained a continuous 5-min signal (with eyes closed) for each patient and control subject. The EEG data were split into 4 distinct groups: "C – control subjects", "O – current opioid dependency", "W – withdrawal", M –methadone maintenance treatment". Further data processing was then performed separately for each 1-min portion of the signal. This increases the effective number of degrees of freedom and improves the statistical confidence in the results. Due to the technical requirements of the tools which were later used to process the data, EEGs from 20 electrodes ($F_{7/8}$, F_z, $F_{3/4}$, $T_{3/4}$, $C_{5/6}$, C_z, $C_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, O_z, $O_{1/2}$) were analyzed with a converted sampling rate of 128 Hz.

After re-sampling and prior to the spectral analysis, each EEG signal was bandpass-filtered within the 0.5-30-Hz frequency range. This frequency range was chosen because approximately 98% of spectral power lies within it (Thatcher, 2001). Since EEG is widely referred to as a non-stationary signal with varying characteristics (for the review, see Fingelkurts and Fingelkurts, 2001), EEG oscillations are expected to be dynamic in nature. In order to capture these changing dynamics and to compare the results of this study with our previous studies (Fingelkurts et al., 2006d), the data series were divided into overlapping windows. Thus, individual power spectra were calculated in the range of 0.5–30 Hz with a 0.5-Hz resolution (61 values), using FFT with a 2-sec Hanning window shifted by 50 samples (0.39-sec) for each channel of 1-min EEG. Based on the findings of previous studies (Levy, 1987; Kaplan, 1998; for details, see Fingelkurts et al., 2006b), these values proved the most effective for revealing oscillatory patterns from the signal. A sliding spectral analysis (a) compensated for the effects of windowing, meaning that we did not lose information from residual activity and (b) improved statistical confidence of the results. Additionally, a shift in 50 samples enabled us to obtain a relatively high resolution (0.39-sec) of the boundaries of the EEG segments with temporally stabilized oscillatory activity.

The outcome of this was that the total number of individual spectral patterns (SP) for each channel of 1-min EEG was 149 (Fig. 1). These SPs were those selected for further classification procedure. The compositions of EEG oscillations (in terms of EEG SPs) were estimated using a probability-classification analysis of the short-term EEG SPs (SPclass tool, see Fingelkurts et al., 2006d). In view of the fact that a detailed description of this analysis

has already been published elsewhere (Fingelkurts et al., 2003a), we are highlighting here only the most important stages. In short, this analysis was undertaken in two stages (Fig. 1).
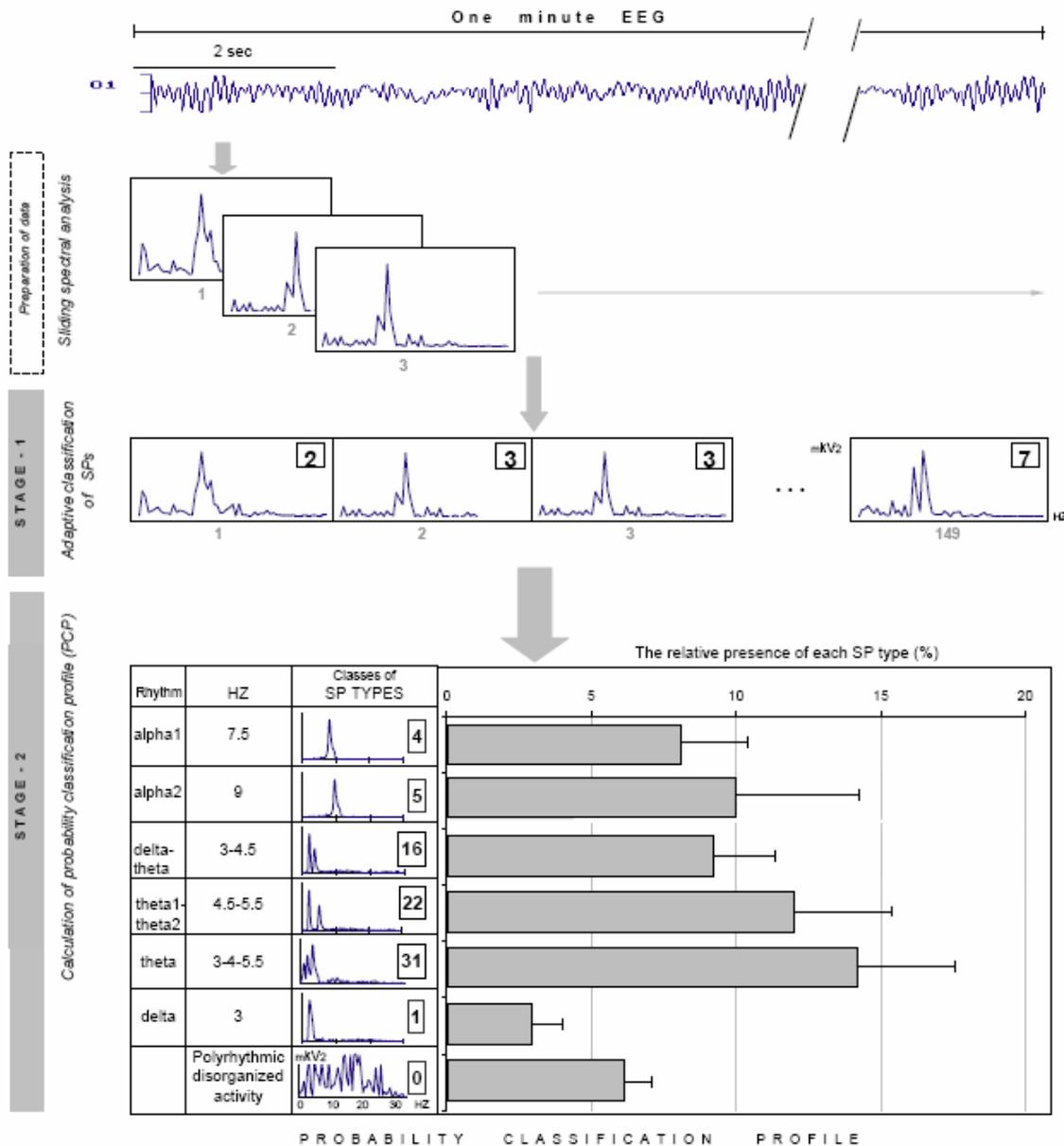
Figure 1. The scheme of the data processing. Sliding spectral analysis, adaptive classification of spectral patterns (SP) and calculation of the probability-classification profiles (PCP) were done separately for each subject and each channel of 1-min EEG. Modified from Fingelkurts et al., 2006a, Int J Psychophysiol. The grey 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. The PCP illustrates the composition and percentage ratio of EEG oscillations in O_1 EEG for the control subject with closed eyes.

During the first stage, sequential single EEG SPs were adaptively classified in each channel of 1-min EEGs using a set of standard SPs (which were generated from the data

itself) (Fingelkurts et al., 2003a). Using this adaptive classification technique, each current SP was labelled according to the index of the class to which it belonged. Hence, each EEG signal was reduced to a sequence of individually classified SPs (Fig. 1).

In 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 number of all SPs within each EEG channel – presented as the histogram of the relative presence of each SP type. PCPs were averaged across 110 (for opioid-dependent patients), 65 (for withdrawal patients), 30 (for MM patients), and 70 (for healthy control) 1-min EEGs separately for each EEG channel. It was expected that these PCPs would show in detail (in SP description) the composition of EEG oscillations and their percentage 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 spectral patterns. A polyrhythmic spectral pattern constitutes a pattern where peaks occupy a majority of the frequencies within the studied range. This type of spectral patterns indicates a mixture of activity of small neuronal subpopulations, each with its own mode (Tirsch et al., 2000).

b) The 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) The index of *non-stability of classification profile* (NSCP) is a percentage value that reflects how the set of distinct SP types changes across the three EEG sub-segments of 20-sec 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-sec EEG segment i; n_s is the number of SP types found in all three 20-sec EEG segments. The range of this index is 0–67.

2.5. Statistics

We studied the behaviour of each type of spectral patterns separately and did not make any conclusions *per se* about any differences between PCPs. In order to reveal any statistically significant differences in the relative presence of each SP type in PCPs between MM patients and control subjects the Wilcoxon test was used separately for each type of SPs presented in the PCP. Statistical significance was assumed to be where $P < 0.05$ (only statistically significant values are displayed). Since we intended to assess each variable in its own right, no Bonferroni correction was applied (for the problems associated with Bonferroni adjustments, see Perneger, 1998). The decision not to make adjustments for multiple comparisons will lead to fewer errors of interpretation when the data under evaluation is not random numbers but actual observations of nature (Rothman, 1990).

However, where we (a) compare four conditions (healthy state, current opioid dependency, early abstinence, and one-year MM treatment) and (b) examined the spatial distribution of significant differences, a Bonferroni correction was made in order to control for repeated observations of the same measures. $P_{corrected}$ is the value required to keep the number of false positives at $P = 5\%$.

Surrogate data was used to control for the neural origin of the temporal dynamics of SPs, a technique which is commonly applied to directly probe for a signal of a non-random temporal structure (Ivanov et al., 1996). Surrogate signals have identical parameters to 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 this 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".

3. Results

3.1. The dynamics of EEG change throughout healthy state and the conditions of opioid dependency, withdrawal, and methadone-based treatment

A comparative analysis of PCPs (averaged across all subjects and all EEG channels) for healthy subjects, for opioid-dependent patients, during their abstinence, and after MM treatment illustrates the dynamics of EEG oscillations present in the EEG of opioid-dependent patients, from those currently with an opioid dependency, through withdrawal to the end of methadone treatment (Fig. 2).

EEG activity	C	O	W	M
Polyrhythmic				
Pure Delta				
Delta-Theta				
Pure Theta				
Theta-Alpha				
Pure Alpha				
Theta-Beta				
Pure Beta				
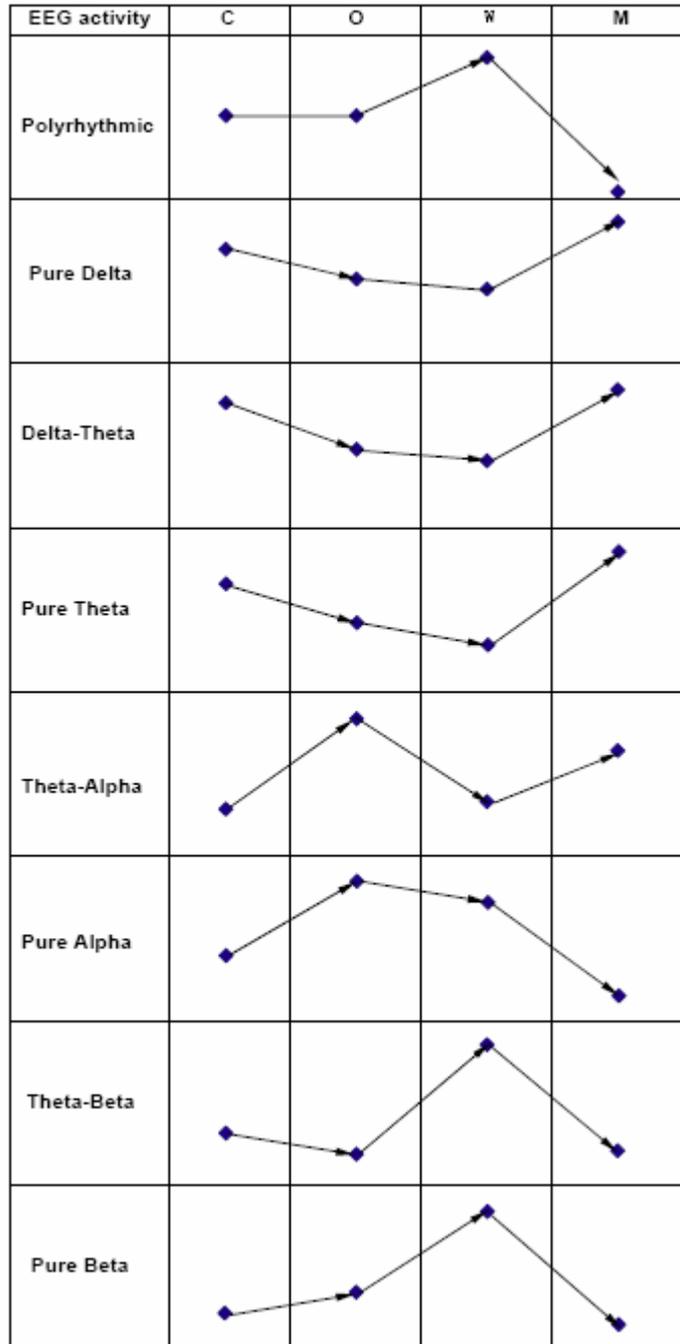
Figure 2. The scheme of the changes of the probability of particular EEG oscillations occurring (measured as the sum of percentages of all SP types which belong to one type of EEG oscillation). The scheme scale is proportional to the real data. Data averaged across all subjects and all EEG channels. On the left side of the scheme the EEG oscillation' types are presented. At the top of the scheme the conditions are labelled, which are presented in chronological sequence: C – control subjects, O – current opioid dependency, W – withdrawal, M –methadone maintenance treatment. Solid arrows indicate significant ($p_{corrected}$ < 0.001-$p_{corrected}$ < 0.00000001) changes and solid lines mark insignificant changes.

As can be seen in figure 2, the probability of SP types occurring with pure delta, delta-theta, pure theta, and theta-beta activity decreased for those with opioid dependency when compared with healthy subjects ($p_{corrected}$ < 0.001-$p_{corrected}$ < 0.0000001). This decrease

continued until the withdrawal condition (from nonsignificant to $p_{corrected} < 0.0000001$). Then, after MM treatment, the probability of SP types with these EEG oscillations occurring significantly increased and reached the level of the healthy subjects (but still higher than in healthy subjects, $p_{corrected} < 0.0001$-$p_{corrected} < 0.0000001$, Fig. 2). SP types with pure beta and polyrhythmic activities showed the opposite behavior ($p_{corrected} < 0.00001$-$p_{corrected} < 0.00000001$) whereas the probability of SP types with pure alpha activity occurring increased ($p_{corrected} < 0.0000001$) for subjects with opioid dependency when compared with healthy subjects. This index then decreased ($p_{corrected} < 0.00001$) during withdrawal and continued to decrease ($p_{corrected} < 0.00000001$) in probability after MM treatment (Fig. 2). The main finding of this analysis is that MM treatment (M) restored the probability of SP types with these EEG oscillations occurring independently of the dynamics of particular EEG oscillations for those currently with opioid dependency (O) and undergoing withdrawal (W) (Fig. 2). However, this probability index still differed significantly ($p_{corrected} < 0.0001$-$p_{corrected} < 0.000001$) in healthy subjects and patients after MM treatment.

A more detailed description of the results of the comparative analysis of the composition of EEG oscillations (healthy subjects *vs* patients currently opioid-dependent and healthy subjects *vs* withdrawal patients) can be found in Fingelkurts et al., (2006d) and in Fingelkurts et al., (submitted for publication) respectively.

The probability of SP types with particular EEG oscillations occurring after MM treatment "returned" to the values for healthy subjects but yet there remained differences with those values. We will therefore describe these differences in detail in the following sections.

3.2. General description of EEG after methadone maintenance treatment

MM treatment brought the relative presence of 72-92% of SP types in PCPs up to the level of that in healthy subjects. However, even after MM treatment, the probability of certain types of SPs occurring in PCPs differed from the values for healthy subjects (Table 2).

A comparative analysis of the PCPs showed that the EEGs after MM treatment had a lower percentage of alpha$_1$- [SP5 (main peak at 9 Hz), SP26 (8.5-10 Hz), and SP27 (9-10 Hz)], alpha$_2$- [SP6 (10.5 Hz) and SP29 (10.5-11.5 Hz)], and beta$_1$- [SP9 (15 Hz)] rhythmic segments, and a larger percentage of delta–theta$_1$- [SP16 (3-4.5 Hz)], theta- [SP2 (4.5 Hz), SP21 (4-6 Hz)], and theta$_2$–alpha$_2$- [SP (5.5-10.5 Hz)] rhythmic segments when compared with the EEG of control subjects ($p < 0.05$–$p < 0.0000001$ for different channels) (Table 2,

Fig. 2). These differences were distributed across the whole cortex and were detected mostly in the majority of EEG channels (Table 2).

Table 2. Spectral pattern types which demonstrated statistically significant (*Pcorrected* < 0.001-*Pcorrected* < 0.0000001) difference between methadone-medicated and control subjects in more than 20% of EEG channels.
Data averaged across 30 EEGs for methadone-medicated subjects and across 70 EEGs for control subjects.

Brain oscillation	SP type	Main peak(s) (Hz)	EEG channels (%)	Topographical distrbution
C > M				
Alpha1	SP5	9	65	distributed across majority of brain lobes except frontal
	SP26	8.5 --10	70	distributed across all brain lobes
	SP27	9--10	55	distributed across all brain lobes
Alpha2	SP6	10.5	45	distributed across all brain lobes
	SP29	10.5--11.5	30	distributed across occipital and temporal brain lobes
Beta1	**SP9**	**15**	**90**	distributed across all brain lobes
C < M				
Delta-Theta1	SP16	3--4.5	25	distributed across temporal and frontal brain lobes
Theta1	SP2	4.5	45	distributed across majority of brain lobes except occipital
Theta1-Theta2	SP21	4--6	70	distributed across all brain lobes
Theta2-Alpha2	SP24	5.5--10.5	35	distributed across all brain lobes

C = Control subjects; M = Methadone-medicated subjects; SP = Spectral patterns; Hz = Frequency; "SP type" column represents the labels of spectral pattern types; "EEG channels" column represents the number (in %) of EEG channels where relative presence of a given SP type demonstrated statisically significant difference between methadone-medicated and control subjects; Bold indicates unique spectral pattern types for control subjects.

In addition, the comparative analysis of PCPs for healthy subjects and MM patients showed that the number of SP types observed in PCPs (indexed by NHCP, Fig. 3A) and non-stability of PCPs (indexed by NSCP, Fig. 3B) were significantly lower ($p < 0.0006$-$p < 0.00004$) in MM patients compared to the control subjects.
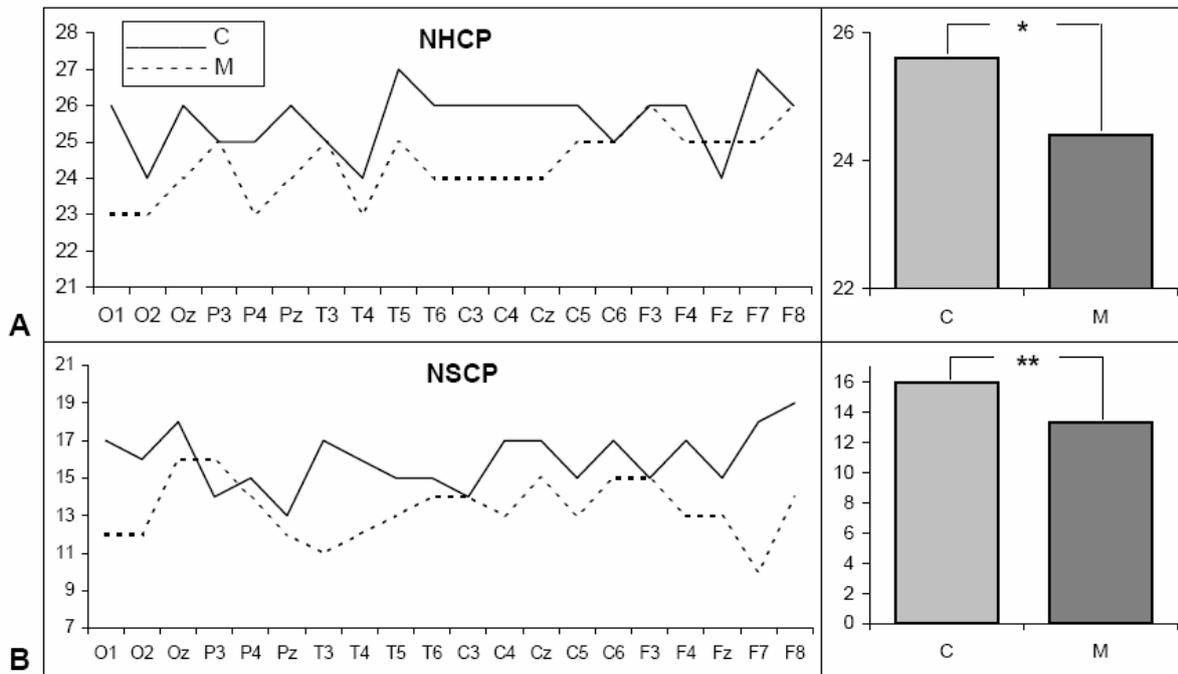
Figure 3. The index of non-homogeneity of classification profile (NHCP) (A), and the index of non-stability of classification profile (NSCP) (B) for each EEG channel separately and averaged across all EEG channels ($n = 20$). Data averaged across 30 EEGs for methadone maintaining patients and 70 EEGs for control subjects. C – control subjects, M - methadone maintaining patients, * – $p < 0.0006$, ** – $p < 0.00004$.

3.3. Temporal stabilization of EEG spectral patterns after methadone maintenance treatment

The temporal stabilization of SP types was evaluated by calculating 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 between 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 EEG oscillations. The results of this analysis are summarized in Figure 4.
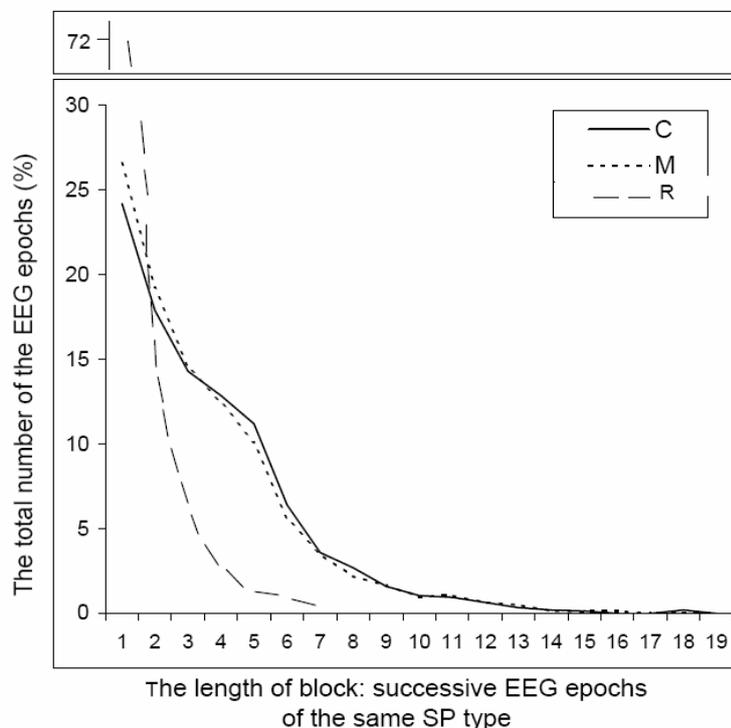
Figure 4. The average number (for all EEG channels, *n* = 20) of successive *m* EEG epochs of the same SP type (including polyrhythmic spectra) (the *y*-axis), where *m* is the range from 1 to 149 (the *x*-axis). The values are presented as a percentage of the total number of epochs in all EEGs, for 6 methadone patients (*n* = 4 768) and 14 control subjects (*n* = 10 728). C – control subjects; M – methadone patients; R – "Random EEG" = EEG where the natural sequence of spectral pattern types has been completely removed in each individual channel.

As can be seen, the temporal stabilization of SPs in both the EEG of MM patients and the EEG of healthy subjects was very similar: differences were not significant (Fig. 4). Moreover, the actual EEG data differed substantially from the "random EEG" (an EEG with a random mix of different SP types separately for each channel) ($p < 0.001$-$p < 0.00001$ for different block lengths).

It should be noted that the analysis presented above did not reveal the potential dependency between the periods of temporal stabilization and the type of SPs. In other words, does a specific type of EEG oscillation (in terms of SPs) maintain a particular period of temporal stabilization? We therefore analyzed the maximum periods of temporal stabilization for all SP types which were found in PCPs for the EEG of MM patients and the EEG of control subjects (Fig. 5).

Spectral pattern types with the main frequency peaks

- Random diapason
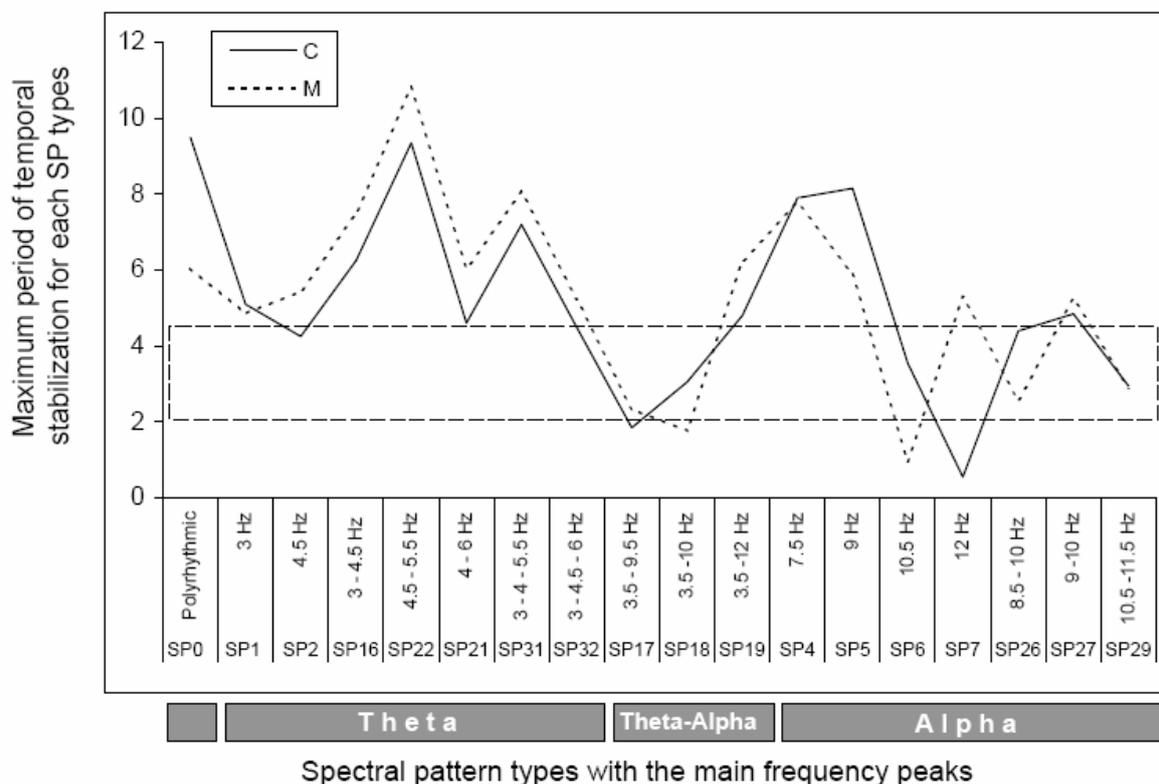
Figure 5. The maximum periods of temporal stabilization for each spectral pattern type, which was found in the EEG probability-classification profiles. The *x*-axis displays the labels (numbers) of the EEG spectral patterns (SP) corresponding to the standard SP set (including polyrhythmic spectra – type "0") and their main frequency peaks. The *y*-axis displays the maximum periods of temporal stabilization for each SP types (in terms of block length – *m* EEG epochs follow in succession without SP type change, where *m* is the range from 1 to 149). Data averaged across all subjects and all EEG channels. Horizontal dotted line bar represents the random range of the maximum periods of temporal stabilization for "Random EEG" (EEG whose natural sequence of SP types has been completely removed in each individual channel). C – control subjects; M – methadone patients.

The maximum periods of temporal stabilization for SP types presented in figure 5 as block length were recalculated in time-scale. This analysis showed that there were no statistically significant differences in the length of the maximum periods of temporal stabilization for each of SP types observed in MM patients and control subjects. The longest maximum period of temporal stabilization was found for $theta_1$-$theta_2$ activity (SP22) in both the EEG of MM patients and the EEG of control subjects (Fig. 5).

4. Discussion

The findings of this study fully support our prediction that the EEG after MM treatment would show normalization in the composition of EEG oscillations (with a slight slowing of the EEG) and recovery in the temporal structure of EEG oscillations.

We found that, in general, the probability of particular EEG oscillations occurring continued to show a dynamic from the current opioid dependency to a withdrawal condition where the probability values reached their peak and then MM treatment "brought" the probability values to the level of healthy subjects (Fig. 2). However, these values still differed from the values for the control subjects after MM treatment (Fig. 2, Table 2). The reason for that may be the long period of treatment (at least 6 months in this study) and/or the dosages of methadone.

Observed in this study the restoration of the probability of particular EEG oscillations occurring reflects a normalization of brain electrical activity when compared with the current opioid dependency and/or withdrawal states. However, MM treatment leads to a slowing of

the EEG compared to healthy subjects (Fig. 2, Table 2). This finding is consistent with the work of Gritz et al. (1975).

The main finding of this study is that methadone restored not only the composition of EEG oscillations and their percentage ration in the overall EEG (Fig. 2) but it also restores the temporal structure of the EEG signal (Fig. 4 and 5). In other words, the temporal stabilization of SPs and the maximum periods of temporal stabilization for particular SP types after MM treatment resembled very closely the values of healthy subjects (Fig. 4 and 5). This finding is of particular interest. It was recently suggested that pathological process is a process where there is a change in the temporal dynamics from what is normal, rather than regularity or irregularity of those dynamics (Glass, 2001). This may suggest the development of an 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. Support for an allostatic view of drug addiction, reward regulation and EEG oscillations has been demonstrated in Fingelkurts et al., (2006d). More and more research (for the review, see Fingelkurts et al., 2005) emphasizes that the majority of brain and psychiatric/mental problems are accompanied by a disruption in the temporal structure of brain activity (Dawson, 2004). Temporal reorganization in the brain dynamics was indeed observed in opioids addiction (Fingelkurts et al., 2006d) and withdrawal (Fingelkurts et al, in submission). It was suggested that this type of temporal reorganization was as a contributing factor to the disorganization syndrome (Haig et al, 2000; Dawson, 2004) in drug addiction and reward regulation (Fingelkurts et al., 2006e). From this perspective, psychotropic drugs, which can *restore the normal* temporal structure of brain activity, are of particular interest (see Fingelkurts et al., 2005). To our knowledge, this is the first study where the capability of methadone to restore a normal temporal structure of the brain's activity was explicitly demonstrated. Further research is needed to establish the optimal dosages of methadone depending on individual brain dynamics and the duration of MM treatment.

At the same time, the data presented in this study is not sufficient to decide whether the reported results were determined by the MM treatment alone or whether the long (at least 6 months) abstinence from opioid consumption were also a contributing factor. Indeed, several reports demonstrated that long (at least three months) abstinence without any specific treatment results in considerable or even complete normalization of the EEG (Shufman et al., 1996; Costa and Bauer, 1997; Bauer, 2001; Gekht et al., 2003) and cognitive functions (Selby and Azrin, 1998). Probably, the combination of both factors may play a role. However, the finding of this study (Fig. 2, Table 2) and literature (Gritz et al., 1975) that MM

treatment leads to a slowing of the EEG compared to healthy subjects suggests that the contribution of MM treatment to changes in the EEG was the main one in our study. An examination of the contribution of each of these factors for a larger sample is the subject of further research.

Conclusions

When considered together, the results of this present study showed that MM treatment normalized considerably the composition of EEG oscillations and their percentage ratio in EEG and restored the temporal structure of patients' EEG comparable with healthy subjects.

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