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Opioid withdrawal results in an increased local and remote functional connectivity at EEG alpha and beta frequency bands

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Abstract

Withdrawal may be a natural model to study craving and compulsive drug seeking, since craving can be viewed as a conditioned dysphoric state. It has been suggested that functional connectivity between brain areas may be of major value in explaining excessive craving and compulsive drug seeking by providing essential link between psychological and biological processes. Considering that withdrawal initiates a widespread activation of cortical regions responsible for compulsive drug seeking and desire for the drug, we predict that withdrawal would result in a significant increase in functional cortical connectivity. We applied the novel operational architectonics approach that enables us to estimate both local and remote functional cortical connectivity by means of EEG structural synchrony measure. In 13 withdrawal opioid-dependent patients we found the evidence that local and remote cortical functional connectivity was indeed significantly enhanced (for both alpha and beta frequency oscillations). Additionally, statistical relationship between functional connectivity and the severity of opioid withdrawal has been found.

Keywords: Addiction; Brain interactions; Cortex; Metastable states; Opiate; Opioid dependence; Structural synchrony; Synchronization

1. Introduction

It is well established that craving (the intense desire to take a drug) is a central aspect of drug dependence and a contributing factor in relapse after a period of abstinence (McKay, 1999). Thus, opioid withdrawal may be considered as a natural model to study craving and compulsive drug seeking, since craving can be viewed as a conditioned dysphoric state (i.e. 'conditioned withdrawal' hypothesis; Wikler, 1973). This condition results in the desire for drugs to alleviate this negative affective state (for the review, see Drummond, 2001).

The modern concept of brain and mind disorders considers disease to be a process with a change in the balance of autonomy and connectedness of different brain systems that sustains health (for review, see Fingelkurts et al., 2005b; see also Kelso, 1995; Friston, 2001; Freeman, 2003). Functional connectivity, which is defined as the temporal correlation between spatially remote neurophysiological events (Friston et al., 1993), is believed to serve as the mechanism for such a balance, leading to the coordination (or discoordination) of activity between different neural systems (dynamic cell assemblies across the cortex) (for review, see Friston, 2001; Breakspear and Terry, 2002; Stam et al., 2003; Fingelkurts et al., 2005a). Thus, functional connectivity between brain areas may be of major value in explaining excessive craving and compulsive drug seeking by providing essential link between psychological and biological processes (Fingelkurts et al., 2005a).

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From the clinical and cognitive psychology it is known that when addicts crave for drug, the anxiety, nervousness, lack of inhibitory control, positive drug related expectancies, and intrusive thoughts related to drugs are simultaneously active (De Vries and Shippenberg, 2002; Franken, 2003). Consistent with the Coordination Dynamics (Kelso, 1995; Bressler and Kelso, 2001) and Operational Architectonics (Fingelkurts and Fingelkurts, 2001, 2006) frameworks, these complex cognitive functions are critically based on the dynamical interactions between and within many cortical neuronal assemblies (see also Bressler, 2002; Edelman and Tononi, 2000; Varela et al., 2001; Freeman and Holmes, 2005). Furthermore, if the neural level alteration involves changes in the communication between different functional modules in the brain, then they should be associated with changes in the underlying EEG activity (synchrony between different brain areas, see recent synthesis and review Fingelkurts and Fingelkurts, 2006). Thus, by focusing on the functional connectivity locally and among remote cortical areas in the addicted brain during such negative affective state as withdrawal condition, we aimed to better understand the mechanisms which are responsible for the desire for drugs as a reward-producing behavior and a way to alleviate this dysphoric psychophysiological state.

However, research on functional connectivity in abnormal appetitive states is restricted only to two studies on coherence of the EEG signal in abstinent heroin users (Franken et al., 2004) and in abstinent polysubstance abusers (Roemer et al., 1995). Therefore, the functional connectivity during withdrawal has not been studied intensively. Furthermore, coherence measure (used in these two studies) describes some similarities between continuous time-series, rather than the temporal correlation between spatially remote neurophysiological events (for a detail review, see Fingelkurts et al., 2005a), as the functional connectivity definition has required (Friston et al., 1993).

Structural EEG synchrony analysis (Kaplan et al., 2005) offers a more direct measure to study both local and remote cortex functional connectivity. Compared to coherence and other synchronicity measures, the advantage of structural EEG synchrony measure is that it is sensitive to EEG nonstationarity, and utilizes explicitly the notion of neurophysiological events, as well as local and large-scale levels of description (Fingelkurts et al., 2005a). EEG nonstationarity (Kaplan, 1998; Kaplan and Shishkin, 2000) implies that the EEG signal consists of quasi-stationary segments that reflect the changes in local metastable states of the brain on different time scales (for the recent review, see Fingelkurts and Fingelkurts, 2004). Within the period of such segments neurons participating in the neuronal assembly are functionally synchronized (Lehmann, 1990; Fell et al., 2000; Nunez, 2000). Therefore, the analysis of EEG segmental characteristics enables to study the *local* functional cortex connectivity (Fingelkurts et al., 2004).

The *remote* functional connectivity among distinct neuronal assemblies is reflected at the EEG level in the temporal synchronization of inter-segmentary rapid transitions between different EEG electrode sites (brain regions) in specific frequency bands (Kaplan et al., 1997, 2005; Fingelkurts et al., 2005a). As a result of such synchrony the periods of short-term metastable brain states originate (for the reviews, see Kaplan, 1998; Fingelkurts and Fingelkurts, 2001, 2004). In the metastable regime of brain functioning, the individual parts of the brain exhibit tendencies of functioning autonomously at the same time as they exhibit tendencies of coordinated activity (Kelso, 1995).

In our previous work (Fingelkurts et al., 2006a) it was shown that opioid dependence may be conceptualized as a new metastable state around altered homeostatic levels in the brain. Based on the study of 22 opioid-dependent patients under acute opioid influence, our analysis has shown that longitudinal opioid exposure impairs cortical local and remote functional connectivity, which characterizes brain pathology as altered metastable brain state (Fingelkurts et al., 2005b). Precisely, we found that local connectivity increased, whereas the remote one decreased. Both these findings were interpreted as specific signs of independent processing in the cortex of chronic opioid addicts. It has been suggested, that such independent processes may constitute the candidate mechanism for a well documented pattern of impairment in addicts that expresses the lack of integration of different cognitive functions for effective problem solving, deficits in abstract concept formation, behavioral control, and problems in the regulation of affect and behavior (see Fingelkurts et al., 2006a).

The present study was designed as a second part of the longitudinal research program and was aimed to explore the role of local and remote functional cortical connectivity in the opioid addicts during short-term withdrawal period. Considering that withdrawal initiates a widespread parallel activation of cortical regions responsible for compulsive drug seeking, poor inhibitory control, and desire for the drug (De Vries and Shippenberg, 2002), together with positive drug related expectancies and intrusive thoughts (Franken, 2003), we predict that such condition would result in a significant increase of local and remote functional cortical connectivity. This increased functional connectivity would then suggest a strong motivation for the excessive drug craving, where the dynamics of local brain operations (functions) would be restrained by the large-scale context (removal of the aversive state) of mutually connected cortical areas.

2. Materials and methods

The study was approved by the Ethics Committee of the Helsinki University Central Hospital in accordance with national and international standards.

2.1. Subjects

The study included a total of 13 right-handed, opioid-dependent patients, 8 men and 5 women aged between 21 and 41 years of age (32 ± 5 years) and 14 controls, 6 men and 8 women aged 33 ± 5 years. These patients were hospitalized for 2 weeks in a drug-withdrawal unit before starting methadone maintenance therapy. Criteria for such therapy at Helsinki University Central Hospital included minimum age of 20 years, 4 years of documented i.v. opioid abuse, and failure of institutional or long-lasting out-patient withdrawal therapy, which also served as criteria for the present study inclusion. Exclusion criteria for methadone maintenance therapy were uncontrolled polysubstance abuse, physical or psychiatric illness that made routine therapy impossible, and alcohol

dependence. In the present study, additional exclusion criteria for both patients and controls were major head trauma and neurologic illness.

All patients had abused opioids for 4–26 years (10 ± 5 years). Self-reported daily dose was 0.05–1.2 g for i.v. street heroin and 2–16 mg for i.v. street buprenorphine. Almost all patients reported irregular (episodic) use of cannabis, amphetamine, and alcohol for short periods earlier in their lives. Some patients reported use of benzodiazepines (8 patients), cannabis (5 patients), and amphetamine (5 patients) when heroin was not available. However, street buprenorphine and heroin was the only drugs used by the patients regularly (daily) for several years (at least 4).

Psychiatric diagnoses of patients and controls were explored using Structured Clinical Interviews I and II (SCID I and II) (First et al., 1994a,b) that afford detailed information according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994). All patients met DSM-IV criteria for opioid dependence, while eight patients met also DSM-IV criteria for benzodiazepine dependence. Patients fulfilled no other DSM-IV criteria aside from substance abuse on axis I; all met DSM-IV criteria of axis II diagnosis for personality disorders. The most common was antisocial personality disorder, diagnosed in all except three patients, who nonetheless had some features of antisocial personality disorder. Patients also fulfilled criteria of other personality disorders, such as obsessive–compulsive, paranoid, borderline, narcissistic, schizoid, passive–aggressive, dependent, and depressive personality disorders. Controls were volunteers from the staff of the Institution, and no control had any experience with illegal drugs but all had drunk alcohol on social occasions. However, none met criteria of abuse of or dependence on alcohol. Controls did not fulfill any criteria for DSM-IV disorders on SCID I or II. The study was accepted by the Ethics Committee of Helsinki University Central Hospital and all the subjects studied gave informed written consent before enrolling in the study.

2.2. Trial design

At the time of the EEG assessment, patients had been abstinent for 12–15 days. As a usual practice of the Helsinki University Central Hospital, for the management of withdrawal symptoms in patients, lofexidine was used three times per day (0.2–0.4 mg). It is not reduce cravings (what was important for our study), but it 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 anti-adrenoergic drug; it does not give rise to withdrawal symptoms of its own (Strang et al., 1999). Smoking and alcohol use were not allowed during the abstinent period.

The severity of withdrawal syndrome was also verified by Gossop test (Gossop, 1990). Following electrode placement and instruments calibration, a subject (patient or healthy control) was seated in a comfortable chair in a dimmed registration room and the experimental procedure was explained. The EEG recording was started at Noon. To reduce muscle artifacts in the EEG signal, a subject was instructed to assume a comfortable position and to avoid movement. A subject was instructed also to look straight in front of him/her (even though the eyes were closed). The behavior of a subject was observed on a TV monitor throughout the experiment. Each subject underwent five minutes EEG registration with eyes closed.

2.3. EEG registration

All recordings were performed in a magnetically and electrically shielded room (Euroshield, Eura, Finland) in the BioMag Laboratory, Helsinki University Central Hospital. Electric spontaneous brain activity was recorded with a 60-channel EEG data acquisition system (Neuromag Vectorview, Helsinki, Finland) with a frequency band of 0.06–86 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 corrected by means of Independent Component Analysis (ICA) procedure (Hyvärinen et al., 2001). After removing artifact-related components, the back projection of remaining components originating from the brain was performed (Joyce et al., 2004). By the same procedure we can filter off a wide range of artifacts, improving the relative amount of any types of useful information in the signal (Cichocki et al., 2005). It is implemented as "The FastICA package for MATLAB" freely available online http://www.cis.hut.fi/projects/ica/fastica/.

A full EEG streams free from artifacts contained 5-min continuous signal (eyes closed) for each patient and control subject. EEG data were split into 2 distinct groups: "withdrawal" and "control." Further data processing was performed separately for each 1-min portion of the signal. Due to the technical requirements of the tools which were later used to process the data, EEGs from 20 electrodes ($F_{7/8}$, F_z, $F_{3/4}$, $T_{3/4}$, $C_{5/6}$, C_z, $C_{3/4}$, $T_{5/6}$, P_z, $P_{3/4}$, O_z, $O_{1/2}$) were analyzed with a converted sampling rate of 128 Hz.

After resampling and prior to the nonparametric adaptive segmentation procedure, each EEG signal was bandpass filtered (Butterworth filter of sixth order) in the alpha (8–13 Hz) and beta (15–21 Hz) frequency bands. Phase shifts were eliminated by forward and backward filtering. These frequency bands were chosen because it has been well documented that the most consistent changes in EEG during opioid abstinence were observed in alpha and beta ranges (for the review, see Polunina and Davydov, 2004).

2.5. Estimation of the local functional interrelations

Local functional interrelations were estimated in two stages. At the *first stage*, the adaptive level segmentation of local EEGs was performed. Each 1-min EEG was segmented using method of identification of rapid transition processes (RTP) in the EEG amplitude (*RTPseg* tool). For the details see (Fingelkurts et al., 2006b). RTPs are the markers of boundaries between quasi-stationary segments in EEG. This method is based on the automatic selection of level-conditions in accordance with a given level of the probability of "false alerts" and carrying out simultaneous screening of all EEG channels (for details, see Fingelkurts et al., 2003a,b; Kaplan et al., 2005).

The following steps are taken to estimate RTPs: (1) Comparisons are made between ongoing EEG amplitude absolute values averaged in two windows (first window $\ll$ second window), both starting from the first data point. (2) If the absolute maximum of the averaged amplitude values in the small window exceeds the averaged amplitude values in the large window, according to the threshold of "false alerts" (the Student criteria)—its time instant becomes the preliminary estimate of the RTP. (3) Using additional statistical analysis the preliminary RTP is verified and assumed to be actual. (4) Then, each of the windows shifts by one data point from the actual RTP, and the procedure is repeated. With this technique, the sequence of RTPs with statistically proven ($P < 0.05$, Student t-test) time coordinates has been determined for each channel of each 1-min EEG. The theoretical concepts behind this analysis are described elsewhere (Kaplan, 1998; Kaplan and Shishkin, 2000; Fingelkurts et al., 2005a).

At the *second stage*, after quasi-stationary segments (indexed by RTPs) were obtained, several characteristics (attributes) of segments (Kaplan and Borisov, 2003) were calculated. These attributes reflect different aspects of local processes in the cortex and thus permit assessing the mesolevel description of cortex interactions (interactions within transient neuronal assemblies) through large-scale EEG estimates (Fingelkurts et al., 2004). The attributes are:

(1) *Average amplitude* (A) within each segment (μV)—as generally agreed, indicates mainly the volume or size of neuronal population: indeed, the more neurons recruited into assembly through local synchronization of their activity, the higher will be the amplitude of corresponding to this assembly oscillations in the EEG (Nunez, 2000; Klimesch et al., 2005).
(2) *Average length* (L) of segments (ms)—illustrates the functional life span of neuronal population or the duration of operations produced by this population: since the transient neuronal assembly functions during a particular time interval, this period is reflected in EEG as a stabilized interval of quasi-stationary activity (Fell et al., 2000; Fingelkurts et al., 2004).

(3) *Coefficient of amplitude variability* (*V*) within segments (%)—shows the stability of local neuronal synchronization within neuronal population or assembly (Truccolo et al., 2002).
(4) *Average amplitude relation* (AR) among adjacent segments (%)—indicates the neuronal assembly behavior: growth (recruiting of new neurons) or distraction (functional elimination of neurons) (Kaplan and Borisov, 2003).
(5) *Average steepness* (*S*) among adjacent segments (estimated in the close area of RTP) (%)—shows the speed of neuronal population growth or distraction (Kaplan and Borisov, 2003).

2.6. Estimation of the remote functional connectivity

Remote functional connectivity was estimated by calculation of the index of EEG structural synchrony. The index of structural synchrony (ISS) was estimated through synchronization of rapid transition processes (RTP) between different EEG channels (*RTPsyn* tool). Details can be found in (Fingelkurts et al., 2006b). This measure reveals functional (operational) interrelationships between cortical sites different from those measured by correlation, coherence and phase analysis (Kaplan et al., 2005; Fingelkurts et al., 2005a). As the details of this technique are beyond the scope of this paper, we will only concentrate on some essential aspects. In brief, each RTP in the reference EEG channel (the channel with the minimal number of RTPs from any pair of EEG channels) was surrounded by a short "window" (ms). Any RTP from another (test) channel was considered to coincide if it fell within this window. The ISS for pairs of EEG channels can be estimated using this procedure and particular mathematical formalism (for details, see Kaplan et al., 2005; Fingelkurts et al., 2003a,b). The ISS tends towards zero where there is no synchronization between the EEG segments and has positive or negative values where such synchronization exists. Positive values indicate "active" coupling of EEG segments (synchronization of EEG segments are observed significantly more often than expected by chance; $P < 0.05$, random shuffling, computer simulation), whereas negative values mark "active" decoupling of segments (synchronization of EEG segments are observed significantly less than expected by chance; $P < 0.05$, random shuffling, computer simulation). From a qualitative perspective, the coupling of EEG segments corresponds to the phenomenon of synchronization of brain operations or operational synchrony—OS (Kaplan et al., 1997; Fingelkurts and Fingelkurts, 2001, 2004, 2006).

Using pair-wise analysis, structural synchrony (SS) was identified in several channels (more than two). These are described as operational modules—OM (Fingelkurts and Fingelkurts, 2001, 2005, 2006). OM means that the set of the cortical areas participated in the same functional act during the analyzed period. The criterion for defining an OM was a set of EEG channels in which each channel forms a paired combination (with high values of ISS) with all other EEG channels in the same set; meaning that all pairs of channels in an OM have to have significant index of structural synchrony (Fingelkurts and Fingelkurts, 2005). The number of cortical areas recruited in OM is described as "the order of areas recruitment."

2.7. Statistics

(1) For each condition ("withdrawal" vs. "control" groups), group-EEG-segment-attributes averages and respective standard deviations were calculated in the following manner: (a) At first and for each segment attribute, per-subject individual averages were calculated from the 5 epochs of 1-min EEG registrations (separately for each channel); (b) For all subjects of the group-condition, the previously calculated per-subject average parameters were again averaged together, now aiming to characterize the group. The initial per-subject averaging prevents the error induction in the group statistics that would happen if the statistics would be calculated to the whole group subject pool directly. The per-subject averages permit to check if the results between the subjects are consistent for each group-condition, and only then if the consistency exists, it would be correct to average the group. All subjects in our study have very similar changes in the EEG segment attributes, what was reflected in very small values of standard deviations; these justify the pulling of all data of the group-condition together in order to characterize the group. As in the previous work (Kaplan et al., 2002; Kaplan and Borisov, 2003; Fingelkurts et al., 2004, 2006a), the comparison of the same segment attributes between different group-conditions was performed using Wilcoxon *t*-test.
(2) The differences in the number and strength of structurally synchronized (SS) EEG patterns between patients and controls were assessed using the Wilcoxon *t*-test as in the majority of the functional connectivity studies (for overview, see Rappelsberger, 1998; Weiss and Rappelsberger, 2000). All SS pair EEG patterns were divided into nine categories ($short_{left/right}$, $short_{anterior/posterior}$, $long_{left/right}$, $long_{anterior/posterior}$, $long_{interhemispheric}$) separately for alpha and beta frequency bands. Pairs of EEG electrodes which have one or more electrodes between the "members" of the pair were classified as long-range connections (according to Weiss and Rappelsberger, 2000). Since the absolute number of possible SS EEG pairs within each category was different, the percentage of the number of SS EEG pairs was calculated.
(3) Separate computer maps of the ISS values were created for each subject and for each 1-min EEG. The problem of multiple comparisons between maps cannot easily be overcome due to the large number of electrode pairs (Rappelsberger and Petsche, 1988) in the SS maps. This problem is common to all studies which require multiple comparisons between maps (Razoumnikova, 2000; Weiss and Rappelsberger, 2000). The comparisons that have been made should therefore be considered descriptive rather than confirmatory (Stein et al., 1999). However, as we have done in our previous work (Fingelkurts et al., 2003a,b, 2004), to have valid results and to overcome the problem of multiple comparisons (for justification, see Appendix E in Fingelkurts et al., 2006b), all pair combinations of EEG channels exhibiting statistically proven SS ($P < 0.05$) were ranged in accordance with their rate of occurrence within all analyzed 1-min EEG epochs in each subject and across all subjects. Only the most frequently found combinations (not less than 85% occurrence in all epochs and all subjects) for the same experimental group ("withdrawal" versus "control") were analyzed further.
(4) Although it is often claimed that volume conduction is the main obstacle in interpreting EEG data in terms brain connectivity, we have shown through modeling experiments that the values of the ISS are sensitive to the morpho-functional organization of the cortex rather than to the volume conduction and reference electrode (for relevant details, we address the reader to Kaplan et al., 2005; for further discussion, see also Appendix A in Fingelkurts et al., 2006b).

3. Results

3.1. Local functional connectivity

3.1.1. EEG segment attributes

Fig. 1 presents the maps of withdrawal-induced changes in EEG segment attributes for alpha and beta activity (data averaged across all subjects). Corresponding data presented separately for five segment attributes (A, L, V, AR, and S, see Section 2).

Average amplitude (*A*) of EEG segments was significantly larger in patients during withdrawal ($P < 0.05$–0.001 for different locations) when compared with healthy controls in all EEG locations (Fig. 1). This was the case for both alpha and beta frequency bands. Average length (*L*) of EEG segments was longer also in patients ($P < 0.05$–0.001). However, six locations in the anterior section of the cortex for the alpha activity and right parietal area for the beta activity have not been affected (Fig. 1).

The coefficient of amplitude variability (*V*) within EEG segments decreased significantly in patients during withdrawal

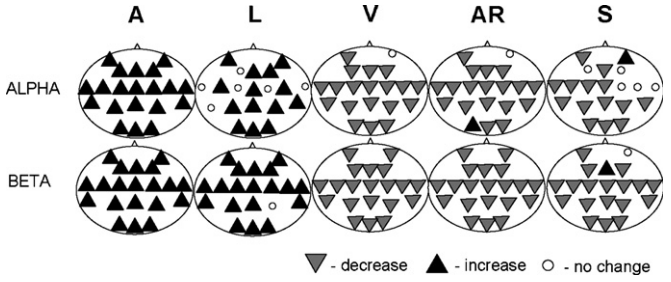

Fig. 1. The maps of withdrawal-induced changes (after the Wilcoxon filtering; $P < 0.05$) in alpha and beta activity segment attributes for the chronic opioid-dependent patients. Corresponding data presented separately for five EEG segment attributes, comparing the "withdrawal" patients with healthy "controls." EEG labels: first level of electrodes from the top—F_7, F_8; second—F_3, F_Z, F_4; third—T_3, C_5, C_3, C_Z, C_4, C_6, T_4; fourth—T_5, P_3, P_Z, P_4, T_6; fifth—O_1, O_Z, O_2. *A*, average amplitude within segments (μV); *L*, average length of segments (ms); *V*, coefficient of amplitude variability within segments (%); AR, average amplitude relation among adjacent segments (%); *S*, average steepness among adjacent segments (estimated in the close area of RTP) (%).

($P < 0.05$–0.01) in all cortical areas (besides right prefrontal area for the alpha frequency band) for both alpha and beta oscillations. Average amplitude relation (AR) among adjacent EEG segments decreased significantly in patients ($P < 0.05$) in all EEG locations for beta frequency band and in vast majority of locations for the alpha frequency band. However, right prefrontal area was not affected, while left occipital area exhibited increase in patients for alpha oscillations (Fig. 1).

Average steepness (*S*) among adjacent EEG segments decreased significantly in patients during withdrawal ($P < 0.05$) in majority of cortical areas for alpha and beta activities (Fig. 1). Exceptions were right fronto-central cortex areas, where right prefrontal area (for alpha frequency band) and central area (for the beta frequency band) exhibited significant increase of this index during withdrawal.

3.2. EEG structural synchrony—remote functional connectivity

3.2.1. The number of structurally synchronized EEG pairs

Fig. 2 (top row) illustrates the number of structurally synchronized (SS) EEGs registered from different cortical areas (estimated by an index of structural synchrony, ISS) in patients during withdrawal and healthy control subjects. The number of SS EEG pairs was significantly higher ($P < 0.05$–0.001 for different categories) in patients during withdrawal than in healthy controls for most categories of functional connections. Generally, this was the case for both alpha and beta frequency bands. However, the significant increase in the number of functional connections for the alpha activity was observed in $\text{short}_{\text{left/right/anterior}}$ and $\text{long}_{\text{anterior}}$ categories, whereas for the beta activity all categories of functional connections exhibited the significant increase, besides the $\text{short}_{\text{posterior}}$ category.

3.2.2. The strength of the structurally synchronized EEG pairs

The strength of the structurally synchronized EEG pairs can be estimated by the values of the index of structural synchrony (ISS): the higher is this value the lager is the strength. One important finding was the absence of negative values of index of structural synchrony (ISS) in all obtained combinations of EEG channels for both alpha and beta frequency bands.

Fig. 2 (bottom row) illustrates the mean values of ISS for the nine SS EEG pair categories in patients during withdrawal and healthy controls separately for alpha and beta EEG frequency bands. There were no differences in ISS values for the majority of categories in alpha frequency band between patients and controls. Only in $\text{short}_{\text{right}}$ and $\text{long}_{\text{left/interhemisphere}}$ categories the ISS values were significantly lower in patients during withdrawal than in control subjects ($P < 0.05$–0.01 for different categories). On the contrary, in beta frequency band ISS values were higher in patients than in healthy controls in majority of categories. The significant increase in the ISS values was found for the $\text{short}_{\text{left/anterior}}$ and $\text{long}_{\text{right/interhemisphere}}$ categories of functional connections (Fig. 2, bottom row).

3.2.3. Relationships between severity of withdrawal symptoms and the number/strength of SS EEG pairs

The severity of withdrawal symptoms was measured by Gossop index (26). Patients were assigned to the Strong- and Mild-symptoms group if they had Gossop scores in the range 10–25 and 1–9 correspondently. It has been shown that number and strength of SS EEG pairs were higher in the Strong-symptoms group than in the Mild-symptoms group of patients for both alpha and beta frequency oscillations. However, this dependence has not reached statistical significance for the strength of functional connections in the alpha frequency band (Table 1).

3.2.4. Topology of EEG structural synchrony

Fig. 3 presents the reliable statistically significant ($P < 0.05$) ISS values mapped onto brain schemata as connecting lines between corresponding EEG sites in patients during withdrawal and control subjects for alpha and beta frequency bands.

Maps of synchronized cortical areas (indexed by ISS) differed in withdrawal and control groups. Indeed, the SS EEG pairs in control subjects were mostly symmetrical for both alpha and beta frequency bands. In contrast, SS EEG pairs in patients were asymmetric: they concentrated mostly along frontal brain areas for the alpha and beta activity, and within

Table 1
Relationships between severity of withdrawal symptoms and the number/strength of functional connections

Functional connections	Strong	Mild	*P*
Number (alpha band)	37.4 (17.3)	30.1 (15.9)	<0.05
Strength (alpha band)	4.8 (0.7)	4.6 (0.7)	n.s.
Number (beta band)	50.8 (14.8)	47.6 (15)	<0.05
Strength (beta band)	5 (0.7)	4.6 (0.6)	<0.05

Strong, strong-symptoms withdrawal group of patients (Gossop scores, 10–25); mild, mild-symptoms withdrawal group of patients (Gossop scores, 1–9). Values: mean (±S.D.).

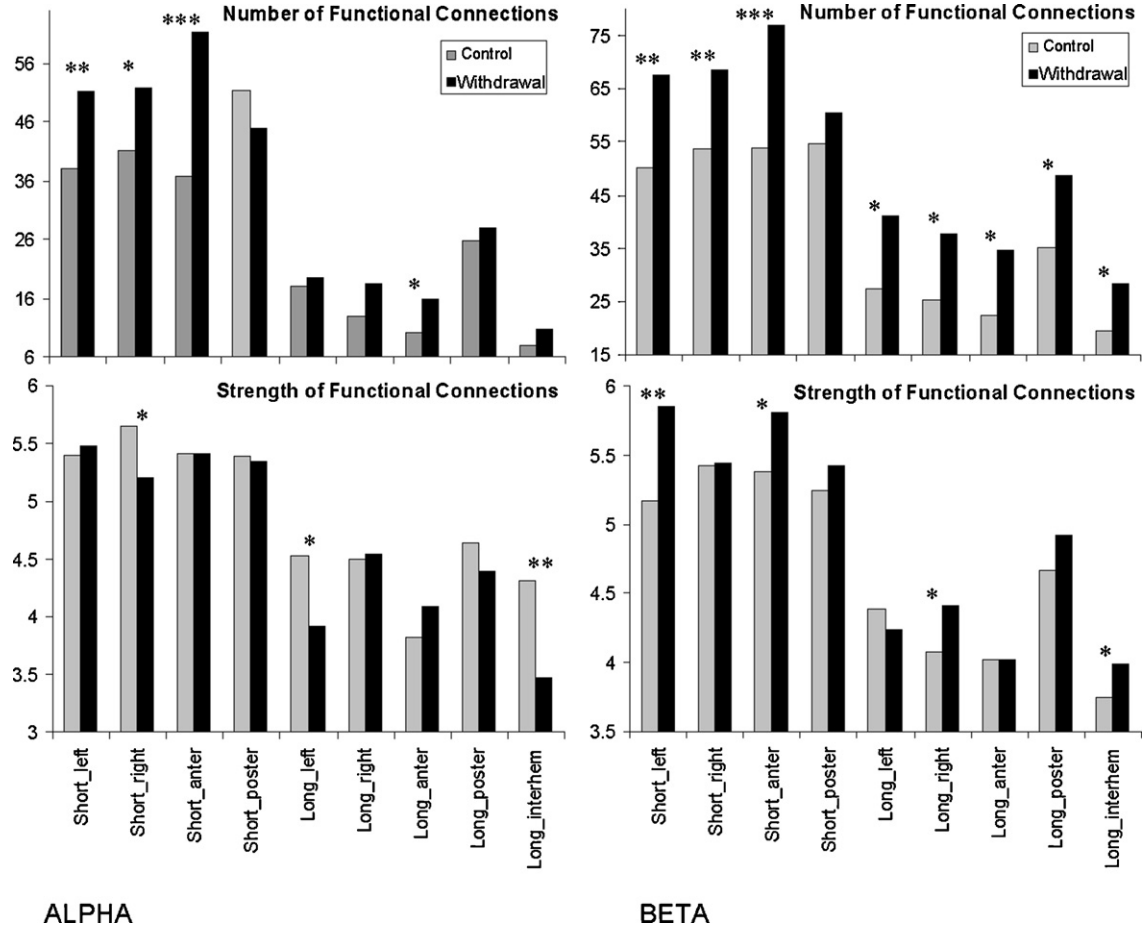

Fig. 2. The number (top row) and strength (bottom row) of structurally synchronized (SS) EEG pairs (indexed by the Index of Structural Synchrony) in withdrawal opioid-dependent patients and healthy subjects separately for alpha and beta frequency bands. The *X*-axis displays the labels of the categories for EEG pair connections. The *Y*-axis displays either the percentage from the maximum number of the EEG pair connections within each category (top row) or the average values of ISS for EEG pair connections within each category (bottom row). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$: control, group of healthy subjects; withdrawal, group of withdrawal opioid-dependent patients.

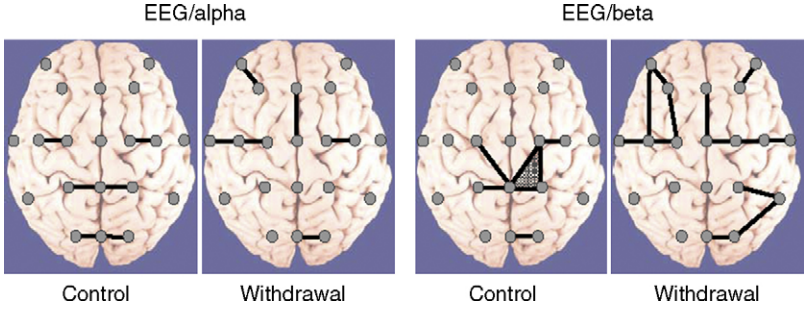

Fig. 3. The specific patterns of synchronized cortical areas (indexed by the Index of Structural Synchrony, ISS) in withdrawal opioid-dependent patients and healthy subjects for the alpha and beta frequency bands. The ISS values which occur more than in 85% of repetitions across all subjects are mapped onto schematic brain maps as connecting lines between the EEG channels involved. Grey areas indicate the operational module (OM). EEG labels: first level of electrodes from the top—F_7, F_8; second—F_3, F_Z, F_4; third—T_3, C_5, C_3, C_Z, C_4, C_6, T_4; fourth—T_5, P_3, P_Z, P_4, T_6; fifth—O_1, O_Z, O_2. Control, group of healthy subjects; withdrawal, group of withdrawal opioid-dependent patients.

right occipito-parietal section of the cortex for beta frequency band (Fig. 3).

There was one operational module (OM) with ''third order of recruitment'' in the right hemisphere of control subjects in the beta frequency band (Fig. 3). This OM was absent in patients.

4. Discussion

Findings of the present study fully support our prediction that there should be an increased brain functional connectivity in withdrawal opioid addicts. Patients during withdrawal indeed exhibited increase in local and remote cortex functional

connectivity in both alpha and beta frequency ranges when compared with healthy controls.

4.1. Local functional connectivity

We found in the present study the significant increase in local functional cortical connectivity during the withdrawal state (Fig. 1). For both alpha- and beta-generated neuronal assemblies, the total increase in size (*A*), functional life span (*L*), and stability (*V*) of these assemblies was observed in the patients during withdrawal when compared with healthy subjects. Stability of these assemblies was reflected also in the low speed (*S*) with which new neurons were excluded (AR) from the neuronal assemblies, probably indicating the process of compensation for the large size of neuronal assemblies which was characteristic for the withdrawal state (Fig. 1).

In numerous experimental conditions, the distribution of large neuronal assemblies in the cortex synchronized within alpha broad band typically reflects the activation of some nonspecific selective attention, semantic memory processes (Klimesch et al., 1998; Knyazev et al., 2003; Basar et al., 2004), and anxiety (Reid et al., 2006; Knyazev et al., 2005), whereas the neuronal assemblies synchronized within beta frequency band usually represent a general state of arousal and alertness (Krause, 2002; Porjesz et al., 2002). In previous studies these same cognitive processes were reported more present also in short-term withdrawal patients than in healthy controls (Franken et al., 2004). It has been suggested that such attentional enchantment, anxiety, and semantic arousal in patients during withdrawal may activate the feeling of craving and may trigger more explicit cognitive processes such as positive drug related expectancies and intrusive thoughts related to drugs (Franken, 2003). The stability of these enlarged alpha- and beta-generated neuronal assemblies (attribute V) obtained in the present study may be one of the neurobiological underpinnings of notable persistence of addiction and compulsive desire to take a drug (Fingelkurts et al., 2006a).

Considering the correlation between life-span of neuronal assemblies (indexed as the length of EEG segments; attribute L) and reaction times (Fingelkurts et al., 2004), one may expect that prolonged life-span of neuronal assemblies in patients during withdrawal, obtained in the present study, would represent the slowing of selected cognitive processes. Previous studies indeed indicated that opioid-dependent patients during withdrawal exhibit slowing of reaction times independently on the task (Bauer, 1996) together with impairment in some cognitive functions (Davis et al., 2002). These findings, thus corroborate the conclusion that brain of addicted individuals is less able to cope with the demands of a constantly changing environment and is rigidly engaged in the stereotypical drug-reward-producing behavior (Fingelkurts et al., 2006a), where drug priming, drug cues, and acute stressors acquire even more power to elicit drug-seeking motivation (Koob and Le Moal, 2005).

In our previous study (Fingelkurts et al., 2006a) in the same patient sub-sample under the acute opioid influence very similar findings were registered: increase in the size, functional life span, and stability of neuronal assemblies in both alpha and beta frequency bands. However, majority of these values (especially for the beta frequency band) during the withdrawal state became closer to the values of healthy controls, thus indicating some level of normalization of the metastable brain state.

4.2. Remote functional connectivity

Findings of the present study indicated an increase in remote functional connectivity of brain processes in distributed neuronal networks in the opioid-dependent patients during withdrawal as compared to healthy controls. Specifically, we found that the number and strength of remote functional connections among different cortical areas (estimated by the index of EEG structural synchrony, ISS) was significantly higher in patients than in healthy controls for most categories of functional connections (Fig. 2). Although this result was observed in the alpha as well as in the beta frequency bands, it was most prominent for the beta range. The latter finding might be interpreted as evidence that beta oscillations might be important for a large-scale integration of information across brain areas distributed over temporal, fronto-parietal, and occipital regions, a mechanism suitable for the cortex activation and retrieval of episodic information (Rolls, 1996; Basar et al., 2004), in the present context related to drug craving. Indeed, it has been shown that drug addicted individuals have selected memory and attention, when more attentional and memory resources are directed towards drug cues compared to neutral cues (Franken et al., 2000).

The highest increase in the number of functional connections (short-range) was observed in anterior section of the cortex for both alpha and beta frequency bands (Fig. 2), thus indicating that large neuronal assemblies (see previous subsection) within this part of the cortex temporally synchronize their operations (Fingelkurts and Fingelkurts, 2005, 2006). This enhanced synchronicity within frontal areas may be the neural mechanism underlying activation of attentional, emotional, and other cognitive processes, which may play a key role in the maintenance of chronic opioid related thoughts, memories, and craving urges. Indeed, it has been shown that $alpha_1$ frequency band reflects nonspecific selective attention processes (expectancy) (Klimesch, 1999), whereas $alpha_2$ band reflects specific semantic processes (Klimesch et al., 1998; Basar et al., 2004); and synchronicity between frontal areas within broad alpha band may be responsible for short-term memory processes (Fingelkurts et al., 2003b).

Broad synchronicity among cortical areas (with a dominance of the frontal cortex section) within beta frequency band during short-term withdrawal period is especially interesting in respect with the reward-producing behavior which is characteristic for drug addicts. It has been suggested that the noradrenaline system regulates the balance between exploitation (seeking to maximize utility from a given source of reward) and exploration (seeking new sources) through its influence on mechanisms of learning and attention (Aston-Jones and Cohen, 2005; Yu and Dayan, 2005) and thus, participates in the opiate

withdrawal symptoms (Nutt, 1996; Maldonado, 1997). Noradrenaline, which has been shown in vitro studies to depolarize and excite the cholinergic cells, produced a dose-dependent increase in a high-frequency EEG activity and an increase in arousal (Cape and Jones, 1998). Therefore, the elevated synchrony within beta frequency band obtained in the present study may reflect a state of central nervous system activation toward reward-producing behavior, being a prerequisite of relapse among drug dependent patients (Bauer, 1994, 2001).

In the same patient sub-sample under the acute opioid influence we observed (Fingelkurts et al., 2006a) the changes to opposite direction: significant decrease in the number and strength of remote functional connections, when compared with healthy controls. Thus, the increase (higher than in healthy controls) of remote synchronicity among cortical areas during the short-term withdrawal period, obtained in the present study, may indicate the compensatory reinforcing actions within the cortex by generating learning signals (Montague et al., 1996), and by adaptively updating goal and motivational states together with attentional focus in working memory (Braver and Cohen, 2000) related to drug craving. Generally this can explain a narrowing of the behavioral repertoire for drug in abstinent subjects (Vanderschuren and Everitt, 2004).

4.3. Dependence of withdrawal severity on the number and strength of functional connections

Our data indicated also that the total number and strength of functional connections have had a predictive force towards the severity of withdrawal state. It has been shown that the patients with strong withdrawal symptoms had higher number and strength of cortical functional connections than patients with mild symptoms (Table 1). This finding indicates that the remote functional connectivity between different cortical areas, measured in the present study, is likely to be correlated with opioid withdrawal and follow the expression of severity of this condition. Since (a) the drug withdrawal symptoms include chronic drug related thoughts, memories, and drug craving feeling (Franken, 2003) and since (b) cortical activity that is not driven by external stimuli, such as in the present study, may reflect processing of internal mental context (top down processing) (von Stein and Sarntheim, 2000), we can speculate that the increased synchronicity between different cortical areas during withdrawal may represent increased intensity of the internal mental activities such as memories, mental images or thoughts about drugs of abuse.

4.4. Topological aspects of functional connectivity in withdrawal

The most representative and stable topological combinations of functionally synchronized areas were located in the frontal, central-temporal, and left occipital and parietal cortical poles (Fig. 3). It has been shown that opioid receptors concentrated the most just in the same parts of the brain (Pike, 1993), and drug withdrawal is associated with reduced dopamine and increased noradrenaline transmission in these regions (Nutt, 1996; Maldonado, 1997). Thus, the particular topography of typical functionally connected cortical areas, which we found in the opioid-dependent patients during withdrawal (Fig. 3), may reflect the brain circuits related to craving and compulsive drug seeking and is likely to be responsible for reward-producing and removal-of-the-aversive-state behavior (for the review, see Drummond, 2001).

5. Summary

The present study demonstrated significant increase in local and remote cortical functional connectivity in the opioid-dependent patients during short-term withdrawal period, thus suggesting that increased inter-area communication among cortical areas may be one of the neurobiological underpinnings of the biased motivational and cognitive processes such as attention, emotions, and memories during withdrawal (see Drummond, 2001; Franken, 2003) supporting the removal of the aversive state behavior.

We also found that patients with the strong withdrawal symptoms had denser and stronger synchronicity between cortical areas than patients with the mild withdrawal symptoms. Such significant statistical relationship between functional connectivity and severity of opioid withdrawal gives the ground to suppose that the influence of comorbid psychiatric conditions or some other premorbid brain dysfunctions in the patients participated in the present study, as well as influence of lofexidine treatment on the study results were insignificant.

Altogether results of the present study pointed to the conclusion that withdrawal forms the new behavior of addicts which involves the significant restructuring of established networks of functional connections within and between cortical areas, thus leading to chronic drug related thoughts, memories, and drug craving feeling (Franken, 2003). That restructuring originates in the addicted brain as a new altered metastable state around possible homeostatic brain levels (Fingelkurts et al., 2005b) and is defined as adaptive process of achieving stability through change, a metastability that is not within the normal homeostatic range (Fingelkurts et al., 2006a,c).

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