Cognitive and neuropsychopharmacological processes in human drug craving
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Electroencephalographic Power and Coherence Analysis Suggests Altered Brain Function in Abstinent Male Heroin Dependent Patients

Previous studies have shown that drug abuse is associated with altered brain function. However, studies on heroin use related brain dysfunctions are scarce. Electroencephalogram (EEG) power and coherence analysis are two important tools for examining the effects of drugs on brain function. In the present study, we compared EEG power and coherence measures of 18 abstinent heroin dependent subjects with 12 healthy control subjects. Furthermore, within the heroin group, associations between heroin use in the past, heroin craving and these EEG measures were studied. The results show that heroin dependent subjects have increased relative beta2 power and increased left intrahemispheric gamma coherence compared to control subjects. Furthermore, coherence measures showed correlations with clinical variables. These EEG abnormalities may reflect underlying changes in brain function due to long-term drug use.


Introduction
The EEG can be used to study brain dysfunction in subjects with chronic drug and alcohol abuse. The most frequently observed abnormality in substance dependent subjects is an increased activity (power) in the 13-25 Hz or beta frequency range\(^{4,15,28,31}\). However, the significance of this increased beta power is not known. In most studies, beta power was not associated with substance abuse variables such as length of exposure to drugs, time since last use of drugs, age of drug use or frequency of drug use\(^{14}\). Furthermore, EEG power has not been found to be related to clinical symptoms such as the severity of craving. These results indicate that EEG power is not related to the use of substances itself, but may be related to other factors such as pre-morbid individual differences.

EEG coherence analysis is a technique that focuses on the pairwise correlations of power spectra obtained from different electrode leads. It measures the functional interactions between brain areas in different frequency bands. High levels of coherence between two EEG signals indicate the existence of coactive neuronal populations. Although it does not provide information on the source of the synchronization\(^{19}\), it does provide information on the interdependency between brain regions due to functional coupling between these areas.

Several disorders such as multiple sclerosis\(^{27}\), dementia\(^{7}\), depression\(^{18}\), that have been associated with brain dysfunction are accompanied by abnormalities in EEG coherence. In addition, coherence analysis may be a powerful tool for detecting neurological consequences of drug abuse. For example, in a sample of poly-substance abusers, Roemer et al.\(^{31}\) found reduced interhemispheric coherence in delta and theta bands and frontally in the beta band. Dafers and colleagues\(^{5}\) found a negative correlation between EEG coherence and MDMA (ecstasy) use.

Coherence analysis has not been applied to EEGs of heroin dependent subjects before. In the present study, power and coherence of the EEG signal in a population of abstinent heroin users were compared with a healthy control group. In addition, associations between history of substance abuse variables (age of onset, total years of use) and clinical state (heroin related thoughts, heroin craving) were studied among the heroin dependent group.


Table 1. Drug use characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of first heroin use (≥ 3 times a week) (n=18)</td>
<td>23.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Age of first cocaine use (≥ 3 times a week) (n=16)</td>
<td>21.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Age of first methadone use (≥ 3 times a week) (n=10)</td>
<td>24.7</td>
<td>5.3</td>
</tr>
<tr>
<td>Total years of heroin use (n=18)</td>
<td>9.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Total years of cocaine use (n=16)</td>
<td>10.6</td>
<td>6.5</td>
</tr>
<tr>
<td>Total years of methadone use (n=10)</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Number of days of heroin use in month before detoxification (n=18)</td>
<td>25.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Number of days of cocaine use in month before detoxification (n=16)</td>
<td>26.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Number of days of methadone use in month before detoxification (n=10)</td>
<td>13.5</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Methods And Materials

Subjects

Twenty-three male heroin dependent subjects were recruited from a detoxification unit of a substance abuse program (Parnassia Mental Health Care). All participants had been abstaining from drug use (including heroin, cocaine, methadone) for a minimum of 2 weeks. At the time of testing none of the subjects was taking prescribed or non-prescribed medications. The persons recruited from the alcohol treatment program were detoxified for at least one week and free of withdrawal symptoms. None of the subjects were positive on urine drug tests, which are employed routinely in the detoxification unit. Fourteen healthy control subjects who never used opiates were recruited from treatment staff. Data from two control subjects and three heroin dependent subjects were excluded from the analyses because of excessive artifacts in the EEG-signal, resulting in a final group of 18 heroin dependent subjects and 12 healthy control subjects. Candidates were excluded from the study if one of the following conditions was present: withdrawal symptoms, lifetime use of neuroleptic medication, schizophrenia, affective disorder, mental retardation, significant somatic disorders such as Parkinson disease (or symptoms). All subjects were male in order to rule out gender effects.

The heroin dependent group consisted of 8 subjects with lower education, 8 subjects with middle education and 2 subjects with higher education (according to the Dutch educational system). For the control group these numbers were 2, 4, and 6, respectively. Chi-square analysis showed that the educational level was different for both groups ($\chi^2=5.9, p=.05$). The mean age of the heroin dependent group was 32.4 years ($SD=5.9$) and of the control group 32.6 years ($SD=9.5$), [t(28)]=.08, $p=ns$.

Drug use characteristics of the heroin dependent group are summarized in table 1. Most heroin dependent subjects (n=16) had a history of additional cocaine use and ten subjects had ever been in methadone maintenance treatment. The study was approved by the Ethical Committee of the institution in which the work was performed. All subjects provided written informed consent.

Procedure

Subjects were asked to participate in a study concerning the measurement of brain function. They were informed that participation involved EEG measurements. Both the patients and control subjects received a remuneration of 20 euro. All subjects provided written informed consent. The experiment started with a short explanation of the procedure and informed consent was obtained. Personal data and history of drug use were recorded by the experimenter. Then the subject completed the questionnaires. After completion the subject was seated in the EEG chair and electrodes were attached. Instructions were to sit relaxed and still and keeping the eyes closed. After EEG measurements, electrodes were removed and subjects received their financial compensation.
**Self-report measures**
Demographic data were self-reported (age, education, and length of treatment). Chronic craving (in the past week) was measured by the 13-item Obsessive Compulsive Drug Use Scale (OCDUS)\(^6\). The OCDUS is a 13 item self-rating questionnaire (5 ordinal response categories) and consists of three subscales. The first scale is the "heroin thoughts and interference scale". This scale refers to thoughts, e.g. "How much of your time when you are not using is occupied by ideas, thoughts, impulses, or images related to heroin use and interference, e.g. "How much does the urge to use heroin interfere with your social life or occupational activities?". The second scale consists of items that deal with "chronic desire", e.g. "How strong was the drive to use heroin in the past week?". The third scale is "resistance to thoughts and intention" and consists of two items that refer to resisting heroin thoughts and resistance to the intention to use heroin. From the validation study it was found that OCDUS has satisfactory psychometric properties\(^6\).

Drug use severity was assessed by means of the Drug Use scale of the Addiction Severity Index (ASI)\(^7\). Questions in this scale refer to the age of onset of drug use, the numbers of days used in the month before detoxification, and total years of of drug use. The ASI has appropriate psychometric properties\(^7\).

**EEG recording**
EEG was measured with a digital Schwartzert amplifier using Electrocap Ag/AgCl electrodes at the 21 scalp sites according to the International 10 / 20 System, right and left mastoid locations (mean of last two served as reference channel). The vertical electro-oculogram (VEOG) was recorded with an Ag/AgCl electrode located above the right eye, using the same reference channel. The horizontal electro-oculogram (HEOG) was recorded bipolarly with two Ag/AgCl electrodes located at the outer canthus of each eye. Ground was placed between Fz and Cz. All signals were digitized without filtering on a PC with Brainlab (OSG, Belgium) software with a sample rate of 500 Hz and 16-bit A/D conversion. Off-line, an average reference channel was computed (all channels except A1/A2), and used for all analysis. Furthermore, frequencies were cut-off below 1 Hz and above 50 Hz (both phase shift-free Butterworth filters; 24dB/octave slope). For all electrodes, impedance was kept under 10 Kohm. With modern high input-impedance amplifiers such as used in the present study, and accurate digital filters for power line noise, high-quality EEG can be recorded with impedance below 40 Kohm\(^5\). One epoch of 160 seconds was recorded. All physiological signals were analyzed using BrainVision software (Brain Products, Germany).

**Spectral power analysis**
For each subject a relatively artifact free continuous epoch of 60 seconds was selected by visual inspection. Subsequently, epochs of 1 second were detrended by the method of Hennighausen et al.\(^1\). After removing all segments with an EEG activity above 100 µV or a gradient above 50 µV (more than 50 µV step / sampling point), the remaining epochs were corrected for horizontal and vertical eye movement\(^1\). A Fast Fourier Transform (FFT) was applied to calculate the power (µV\(^2\)) within the delta (1-4 Hz), theta (4-8 Hz), alpha1 (8-10 Hz), alpha2 (10-13 Hz), beta1 (13-20 Hz), beta2 (20-35 Hz), and gamma (35-45 Hz) frequency bands. A 10 % Hanning window was applied. Both relative and absolute power was calculated. Relative power was calculated for the particular band in the total spectrum. All power scores were log-transformed to correct for the typical skewed distribution of EEG power data. In order to reduce multiple testing, the overall power in each frequency band was calculated by taking the grand mean of all electrode positions. MANOVA analysis with Bonferroni correction with group as independent and overall power within each frequency band as dependent variables was conducted in order to test for differences. Furthermore, only frequency bands with significant group differences in overall power were analyzed further on electrode
level (MANOVA with Bonferroni correction). Spearman’s rho correlations were calculated in order to examine the associations between EEG power, history of heroin use and heroin craving (drug history and craving were not normally distributed).

Coherence analysis
In order to reduce the number of statistical tests, pre-defined inter-hemispheric and intra-hemispheric coherence was calculated for each frequency band. Pair-wise coherence was calculated by the cross-spectrum/auto-spectrum for intra-hemispheric connections between anterior and posterior sites, the so-called Fascicle coherence (Fp1-O1, Fp2-O2) and inter-hemispheric (Transcallosal) channels (F7-F8, T3-T4, T5-T6). For every frequency and every channel, the result is a value between (almost) 0 and 1 which is calculated in accordance with the formula:

\[ \text{Coh}(c, c')(f) = \frac{|\text{Cov}(c, c')(f)|^2}{\text{Var}(c, f) \cdot \text{Var}(c', f)} \]

In conjunction with \( \text{Cov}(c, c')(f) = \sum (c_c(f) - \text{avg}(c_c(f))) (c'_{c'}(f) - \text{avg}(c'_{c'}(f))) \). In the second formula, \( i \) is totaled via the segment number. Formation of the average also relates to segments with a fixed frequency \( f \) and a fixed channel \( c \). Z-transformation was applied to the coherence data for adaptation to parametric statistical tests. MANOVA analysis with Bonferroni correction with group as independent and coherence within each frequency band as dependent variables was conducted in order to test for differences. Spearman’s rho correlation coefficients between EEG coherence and craving, heroin use were calculated.

Results

Absolute EEG power
The MANOVA did not reveal any significant group effect on overall absolute power, Wilks’ Lambda = .629, \( F(7,24)=2.0, p=.094 \). Correlation analysis showed that absolute power in none of the frequency bands was significantly related to any of the drug history nor to any of the craving variables (p’s >.05).

Relative EEG power
The MANOVA did reveal a significant group effect on overall relative power, Wilks’ Lambda = .567, \( F(7,24)=2.65, p=.035 \). Further analysis showed that beta2 was the only frequency band with significant differences between heroin dependent subjects and control subjects, with heroin dependent subjects having more relative power in the beta2 frequency band than control subjects, \( F(1,30)=5.93, p=.021 \). By analyzing the beta2 band on the electrode level, MANOVA showed that relative power in the heroin dependent group was increased at all sites (all p’s < .05) except at Fp1, Fp2, O1, O2, F7, T3, T5 sites (p’s>.05). However, none of the frequency bands was found to be significantly related to any of the drug history nor to any of the craving variables (p’s>.05).

Intrahemispheric Coherence
The left intrahemispheric Fascicle gamma coherence was found to be significantly enhanced in the heroin dependent group compared to the control group, \( F(1,30)=4.99, p=.023 \). Within the heroin dependent group, no significant correlations were found between intrahemispheric coherence values, history of drug use variables, and craving.

Interhemispheric Coherence
No significant group differences on interhemispheric coherence was found. However, within the heroin group, chronic heroin craving scale of the OCDUS was positively associated with frontal interhemispheric alpha1 coherence, \( r=.61, p=.007 \) and temporal interhemispheric delta coherence, \( r=.52, p=.026 \). The obsessive heroin related thoughts scale of the OCDUS was positively associated with temporal interhemispheric beta2 coherence, \( r=.61, p=.007 \) and temporal interhemispheric delta coherence, \( r=.52, p=.006 \).

Of the history of drug use variables, age of first heroin use was positively associated with frontal interhemispheric beta1 coherence, \( r=.52, p=.028 \), and frontal interhemispheric theta coherence, \( r=.72, p=.001 \). Total years of heroin use was nega-
tively associated with frontal interhemispheric beta1 coherence, \( r = -0.42, p = 0.038 \), and frontal interhemispheric theta coherence, \( r = 0.75, p < 0.001 \), see figure 1.

![Graph showing correlation between total years of heroin use and frontal interhemispheric theta coherence (Spearman's \( r = -0.75 \)).](attachment:figure_1.png)

**Figure 1.** Correlation between total years of heroin use and frontal interhemispheric theta coherence (Spearman’s \( r = -0.75 \)).

### Conclusions

The current study shows that abstinent heroin dependent subjects have an enhanced relative beta2 power compared to healthy control subjects. This finding is in line with other EEG frequency studies on alcohol and cocaine.\(^{27,28,31}\) Previous studies indicated that beta power is a predictor of relapse among drug dependent patients.\(^{1,2,42}\) However, as expected from these previous studies, frequency power indicators did not correlate with clinical variables such as previous drug use and craving symptoms. It has been suggested that increased beta power is associated with premorbid differences\(^{4}\) and cognitive or emotional activation\(^{29}\) rather than with an altered brain functions due to drug use. Furthermore, Porjesz et al.\(^{27}\) found that beta frequencies in the human EEG reflect a state of central nervous system activation, with GABA (typeA) receptor action as pacemaker. This beta activity is linked to genetic differences in GABA receptor genes\(^{27}\). The current findings also corroborate the conclusion of a large EEG study in alcoholics that elevated beta power does not suggest a direct drug effect but rather a predisposition to substance use\(^{28}\). This EEG power has been found to be heritable to a high degree.\(^{36}\)

In the present study, coherence differences between heroin users and control subjects were found to be present on left fronto-occipital intrahemispheric gamma coherence; abstinent heroin dependent subjects displayed more gamma coherence than control subjects. Although a decrease of high frequency coherence is considered to be the expression of decreased functional cortico-cortical connections, increased coherence is not yet understood.\(^{27,30,37}\) Excessive coherence may indicate that two areas of the brain are overly functional connected. This may be an attempt to compensate for local malfunctioning. Alternatively, enhanced gamma coherence may represent a general state of arousal\(^{38}\), which is presumably more present in recently abstinent drug users than healthy controls. Although only coherence in the gamma-band reached a statistical difference between the heroin and control group, coherence measures in several frequency bands were significantly correlated with previous drug use and clinical symptoms. Enhanced heroin exposure (larger total years of use and earlier age of onset) was correlated with a decreased frontal interhemispheric theta and beta1 coherence. It is possible that these EEG abnormalities are the results of underlying changes in brain structure and/or function due to long-term drug use. Reduced interhemispheric theta coherence has been associated with subcortical MRI lesion load\(^{22}\) in multiple sclerosis patients. Furthermore, theta and beta coherence is reduced in dementia of Alzheimer type.\(^{34,33,35}\) Reduced theta and beta coherence is also associated with non-neurological disorders such as depression.\(^{38}\) Generally speaking, interhemispheric coherence is shown to represent the degree of connectivity between brain hemispheres.\(^{20,26}\) This connectivity represents functional interactions and coupling between different brain areas. This does not imply that the anatomical connections (association fibers) have to be damaged. Anatomical connections are a necessary but not sufficient condition for this connectivity. Possibly the altered connectivity is the result of changes in the neuromodulators on synaptic level,
such as changes in the dopaminergic or GABA (type A) transmission. It is known that the chronic drug abuse, including heroin, acts upon the dopamine system. For example, chronic heroin exposure produces a reduction in dopaminergic activity\(^{16,19}\). In addition, it is known that abnormalities in the dopaminergic system can cause changes in interhemispheric coherence\(^{21-24}\). The current neurophysiological findings are in line with neuropsychological studies that focus on cognitive impairments in opiate users. Studies of Mintzer & Stitzer\(^{27}\) and Darke et al.\(^{19}\) found a wide range of impaired cognitive functions in active methadone maintenance patients. In contrast, Davis and colleagues did not find any differences between ex-users and a healthy control group. The present study shows that long-term opiate use is related to alterations in brain functioning in ex-users. Possibly, EEG-coherence may be a more sensitive measure of brain functioning than cognitive neuropsychological tests. In contrast to the power findings, the observed association between coherence and drug use variables suggest that coherence reflects the direct drug effects rather than a predisposition to substance use (which is reflected in elevated beta power).

In addition to the association between EEG coherence and previous drug use, coherence measures were also found to be associated with clinical symptoms. Chronic heroin related thoughts were associated with temporal interhemispheric beta2 coherence, and temporal interhemispheric delta coherence, and chronic heroin craving was found to be associated with frontal interhemispheric alpha1 coherence, and temporal interhemispheric delta coherence. These findings suggest that the daily experience of craving drug use history is associated with altered interhemispheric connectivity. Previous studies show that heroin craving is associated with abnormal cortical processing\(^{21-46}\). Although to exact meanings of the coherence of the different frequency bands is not known, the present study shows that frontal interhemispheric communication may be one of the neurological underpinnings of these biased cognitive processes in drug dependence. Event-related coherence analysis shows that frontal theta and theta frequencies are the result of memory processes. For example, during the retention phase of a working memory task the coupling in theta band frequencies between frontal and post-rolandic association cortex increases\(^{17}\). In addition, 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)\(^{46}\). It may be that the current findings represent internal mental activities such as memories, mental images or thoughts.

The findings of the present study may be attributable to other factors beside heroin induced brain dysfunction. First, most subjects in the present study were poly-drug users. It may be that other substances that were used in the past may also be a relevant factor. Second, it may be that the rest EEG was influenced by ongoing cognitive processes such as memory processes. It is known that EEG synchronization in theta and beta bands are modulated by memory processes\(^{46}\).

The present study indicates that, in addition to power analysis, coherence analysis may be a useful tool for studying substance-induced abnormalities of the functioning of the brain. The findings suggest that coherence measures, in contrast to power measures, are associated with drug use variables and clinical variables suggest that coherence measures reflect state related conditions and power measures reflect premorbid traits. This hypothesis should be examined in future research. Furthermore, research is needed that address the usefulness of EEG coherence measures as indicators of drug craving.

References


29. Ray W, Cole H. EEG alpha activity reflects attentional demands and beta activity re-
Chapter 8