Long-term abstinence syndrome in heroin addicts: indices of P300 alterations associated with a short memory task

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Abstract

Attentional deficits have been implicated in the pathophysiology of opioid addicts. The P300 component of event-related potentials (ERPs) is considered as a manifestation of attentional operations. The authors’ goal was the comparison of P300 elicited during a short memory test between subjects with prolonged heroin abstinence and current heroin users as well as healthy controls. The P300 component was evaluated during the anticipatory period of a short memory task in 20 patients characterized by a past history of opioid dependence (6 months abstinence), in 18 current heroin users and in 20 healthy comparison subjects, matched for age, sex and educational level. Abstinent heroin addicts exhibited significant reduction of P300 amplitude at central frontal region, relative to the other two groups. The findings are discussed in connection to the aim of identifying psychophysiological indices, addressing issues in opioid use disorders, and suggest that knowledge about cognitive operations, such as those reflected by P300 component, could provide further insight into psychophysiological mechanisms underlying the long-term abstinence state of heroin addicts.

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1. Introduction

Recent clinical, neuropsychological and experimental evidence have emphasized the role of attentional deficits in modulating the development and maintenance of drug dependence, as well as the relapse phase. For example, Sjogren et al. (2000) reported that chronic nonmalignant pain patients receiving long-term oral opioid therapy performed significantly poorer than controls in a continuous reaction time (CRT) test measuring vigilance/attention. Similarly, neurophysiological studies indicate the involvement of opioids in the modulation of attention-related responses. Finally, neuropsychological studies support the idea that attentional bias for a drug-related stimulus occurs in opiate dependence (Lubman et al., 2000). In parallel to this context, Robinson and Berridge (1993) put forward the theory that drug-related stimuli capture attention, and the neural mechanisms underlying this attentional bias play a key role in the development and maintenance of drug dependence, as well as in the relapse phase. Although these new findings provide valuable insight on the association between attentional operations and drug dependence, such as heroin dependence, knowledge on...
the subject remains scarce (Selby and Azrin, 1998; Self and Nestler, 1998; Darke et al., 2000).

Event-related potentials (ERPs) provide a valuable means for studying brain–behavior relations (Fabiani et al., 2000). The auditory P300 is a late cognitive ERP component generated in response to a target detection task, which occurs about 300 ms after a warning stimulus. One of the most prominent assumptions regarding the cognitive basis of this component is that it indexes attentional operations (Polich, 1998; Kok, 2001).

Very few studies have examined the effects of opioids on P300 measures of cognitive functioning. For example, Kouri et al. (1996), using an oddball paradigm, reported that chronic heroin- and cocaine-dependent individuals demonstrated normal P300 amplitudes under the influence of heroin or heroin and cocaine, while they manifested reduced P300 amplitudes during detoxification, when ERP data were obtained after 6 days of complete abstinence and when ERPs were recorded on the 15th day of treatment with buprenorphine. On this basis, they suggested that P300 component could be conceived as a “more sensitive measure of withdrawal and protracted abstinence than some physiological or behavioral measures.” In addition, the fact that drug-dependent individuals exhibited normal P300 amplitudes under the influence of heroin or heroin and cocaine, while they manifested reduced P300 amplitudes during detoxification, when ERP data were obtained after 6 days of complete abstinence and when ERPs were recorded on the 15th day of treatment with buprenorphine. On this basis, they suggested that P300 component could be conceived as a “more sensitive measure of withdrawal and protracted abstinence than some physiological or behavioral measures.” In addition, the fact that drug-dependent individuals exhibited normal P300 amplitudes under the influence of heroin or heroin and cocaine might be tentatively linked to the “self-medication” hypothesis, suggesting that heroin is a self-medicating tool used to control innate psychic sensitivity (Khantzian, 1985; Drummond, 2001; McCusker, 2001).

Bauer (2001), using visual ERP recordings, reported that opioid-dependent patients, having an abstinence period from 1 to 5 months, exhibited decreased P300 amplitudes, suggesting that “P300 is a useful measure of the central nervous system (CNS) recovery.” In this study opioid, cocaine- and alcohol-abstinent patients were compared with normal controls, but not with current users.

In view of the above observations, the present study explored the differential patterns of P300 elicited during a short memory test in (a) patients with prolonged heroin abstinence, (b) current heroin addicts and (c) healthy controls matched for age, sex and educational level. By examining the differences in P300, in a study designed in this way, we aimed at identifying plausible psychophysiological indices, addressing certain issues in opioid use disorders, such as the hypotheses that the P300 is a “measure” of the CNS recovery during long-term opioid abstinence (Bauer, 2001) and the “self-medication” hypothesis (Khantzian, 1985; Rauch, 2000).

2. Methods

2.1. Patients

It is well known that substance abusers constitute a heterogeneous group and addicts using primarily one class of drugs may probably have used drugs of other classes. Therefore, the subjects selected for the study met the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for drug abuse/dependence, mainly for heroin abuse or dependence (American Psychiatric Association, 1994). The addicts studied were not characterized by double dependence or prolonged use of drugs other than heroin. Previous consumption of other drugs of abuse, use of psychotropic agents and excessive alcohol intake were criteria for exclusion. Participants were volunteers who sought treatment for substance dependency from the Drug-Free Outpatient Clinic of the Psychiatric Department of the Athens University Medical School. Furthermore, subjects were excluded if there was a DSM-IV Axis I diagnosis (excluding substance abuse and dependence), provided a history of mental retardation, or major neurological/medical disorders (e.g., epilepsy, AIDS, etc.) or demonstrated electroencephalogram (EEG) abnormalities. Information for the latter exclusion was obtained from the subject’s medical record, which included general medical, neurological, psychiatric and psychological evaluations.

The first patient group, i.e., the current users, initially comprised 20 right-handed current heroin abusers. Two subjects were excluded from the evaluation due to eye movements during the test (see below). The final sample comprised 15 males and 3 females, with mean age 29.57 ± 6.23 years, mean educational level 10.52 ± 2.65 years and mean duration of heroin abuse 9.25 ± 6.29 years.

The second patient group, i.e., the abstainers, included 20 right-handed heroin addicts, 16 males and 4 females, with mean age 31.05 ± 5.3 years, mean educational level 11.35 ± 3.45 years and mean duration of heroin abuse 4.74 ± 2.90 years. After detoxification, patients were admitted to a long-term residential psychological rehabilitation program. Since the validity of the self-report data is a continual subject of debate, the subjects had undergone a urine examination, in order to establish a possible presence of any substance of abuse. The patients were eligible for inclusion in the study only when twice-weekly analyses for urine metabolites of the main substances of abuse excluded their consumption in the first 6 months after admission. It is interesting to note that withdrawal signs, such as restlessness, insomnia, dysphoria and depression, fearfulness and hostility, increased blood pressure, diarrhea, etc., were not detected in this group at the time of assessment.

2.2. Normal comparison subjects

A total of 20 right-handed healthy volunteers, 15 males and 5 females, matched to the addicts on age (30.7 ± 4.82 years) and educational level (12.15 ± 3.43 years), were recruited from the hospital staff and local volunteer groups. They were free of psychiatric and physical illness. All participants were right handed as assessed by the Edinburgh inventory (Oldfield, 1971) and had no history of any
neurological or hearing problems. The study protocol had been approved by the ethics committee of the university hospital, and written informed consent was obtained from both patients and control subjects.

2.3. Stimuli and procedure

Patients and controls were evaluated by a computerized version of the digit span Wechsler test (Wechsler, 1955; Papageorgiou et al., 2003). The subjects sat in an anatomical chair placed inside an electromagnetically shielded room. An outline of the procedure is provided in Fig. 1. A single sound of either high (3000 Hz) or low (500 Hz) frequency was presented to the subjects, who were asked to memorize the numbers that followed. The warning stimulus lasted 100 ms. A 1-s interval followed, and then the numbers to be memorized were presented. At the end of the number sequence presentation, the signal tone was repeated, and subjects were asked to recall the administered numbers as quickly as possible. The numbers were recalled by the subject in the same (low frequency tone) or in the opposite order (high frequency tone) than that presented to him/her.

Before any ERPs’ recording, a pre-process was performed so that the two sounds were differentiated by the subjects. According to this process, various trials have taken place until each subject understood both the different frequencies and the requirements of the test, concerning the storage and retrieval of presented numbers. After the completion of the above-mentioned process, a rest period of 5 min followed, before the recording of ERPs.

ERPs were recorded during the 1.1-s interval between the start of the warning stimulus and the first administered number. The electrophysiological signals were recorded with Ag/AgCl electrodes. Electrode resistance was kept constantly below 5 kΩ. Electroencephalographic (EEG) activity was recorded from 15 scalp electrodes based on the International 10–20 system of electroencephalography (Jasper, 1958), referred to both earlobes. An electrode placed on the subject’s forehead served as ground. The bandwidth of the amplifiers was set at 0.05–35 Hz. During the administration of stimuli, the subjects had their eyes closed in order to minimize eye movements and blinks. Eye movements were recorded through electro-oculogram (EOG), and recordings with EOG higher than 75 μV were rejected.

Warning stimuli, as well as learning material, i.e., the numbers to recall, were presented binaurally via earphones at an intensity of 65 dB sound pressure level. The evoked biopotential signal was submitted to an analog-to-digital conversion, at a sampling rate of 500 Hz, and was averaged by a computerized system. Each recording session consisted of 26 repetitions of the trial. Eye movements corresponding to EOG higher than 75 μV, resulting in rejection of the recording, ranged from 1 to 2 per recording session. Thus, the minimum number of artifact-free trials that were averaged to produce an ERP was 24.

Since the warning stimuli were of two different frequencies, one high and one low, it was not clear whether they could generate the same P300, although P300 component is included in the array of late-endogenous ERPs’ components, which, normally, are not modality specific (Fabiani et al., 2000). In order to ensure that there were no differences in P300 waveforms caused by the two frequencies, a series of t-test comparisons was conducted between P300 waveforms (amplitudes and latencies) evoked by the two frequencies (13 high and 13 low frequencies) in

<table>
<thead>
<tr>
<th>Time period</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB (100 ms)</td>
<td>Administration of warning stimulus (500 or 3000 Hz, 65 dB).</td>
</tr>
<tr>
<td>AC (1.1 s)</td>
<td>Recording of ERPs.</td>
</tr>
<tr>
<td>CD (varies)</td>
<td>Computerized administration of the set of numbers of Wechsler Direct Auditory Memory Test. The duration of this period varies depending upon the numbers of digits to be recalled in each trial (from 2 to 9 digits across trials). However, between administered digits, time interval is 1 s.</td>
</tr>
<tr>
<td>DE (100 ms)</td>
<td>Repetition of warning stimulus.</td>
</tr>
<tr>
<td>EF (varies between 15 and 30 s)</td>
<td>Recording of memory recall performance, according to the accuracy of responses.</td>
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</table>

Fig. 1. Outline of experimental procedure.
all subjects. No differences were found in P300 waveforms, by frequency, in each subject. Consequently, the pooled P300 waveforms for each lead were used in the analysis. The following parameters were calculated:

(a) ERPs were recorded for each subject at leads Fp1, Fp2, F3, F4, C3, C4, C3-T5/2, C4-T6/2, P3, P4, O1, O2, Pz, Cz and Fz for each of the 26-test repetition. In this context, it should be noted that the positions C3-T5/2 and C4-T6/2 are used as electrode leads, because these positions correspond to brain areas serving verbal memory and language (Binder, 1997). Recordings with acceptable EOG level were averaged, for each lead, by a computerized system. An algorithm was used, which identified the P300 as the most positive peak, in each averaged lead curve, between 240 and 500 ms, after the warning stimulus. Peak amplitudes were measured relative to the mean amplitude of the 100-ms pre-stimulus baseline period, and latency measurements were computed relative to stimulus onset.

(b) The behavioral performance concerning recalled digits.

2.4. Statistical analysis

The significance level was set at 0.05. The Kolmogorov–Smirnov goodness-of-fit test showed that both the amplitudes and the latencies are consistent with a normal distribution, as well as a multivariate normal distribution, while the equality of the covariance matrices was ascertained with Box’s M test. This permitted the use of multivariate tests for the examination of the overall group differences. The multivariate analysis of variance criteria employed are Pillai’s trace and Wilks’ lambda, both yielding an F value with the appropriate degrees of freedom. Furthermore, the value of Wilks’ lambda enables the appreciation of the proportion of the variability of the overall means attributable to group differences. Leads at which group differences were significant were determined by the corresponding univariate statistics. Estimates of effect size were established by the partial eta-squared statistic, which describes the proportion of total variability for each lead attributable to group differences. Leads, at which statistically significant differences between groups were found, were further subjected to twofold post hoc stepdown procedures. The first was the Ryan–Einot–Gabriel–Welsch F procedure (R-E-G-W F procedure), for the classification of the three groups into homogenous subsets for the particular lead (Hochberg and Tamhane, 1987). The purpose of the second procedure was to eliminate those leads, whose apparent significance for group discrimination could be explained by their covariance with other, more significant leads. Comparison of memory performance between groups was performed with classic ANOVA procedure followed by post hoc Bonferroni pairwise comparisons.

Furthermore, in an attempt to elucidate a possible association between P300 differences and duration of heroin abuse, correlations were computed between observed P300 differences and duration of heroin abuse.

3. Results

3.1. Comparison of P300 amplitudes and latencies of the three groups

In Fig. 2, the grand average ERP waveforms for the three groups under investigation are shown, at leads Fz, Cz and Pz. Table 1 displays mean amplitudes, in microvolts, of P300 amplitude waveform for the three groups, at each lead. Pillai’s trace manifested statistically significant difference between overall means of the three groups ($F_{30,84}=2.26$, $p<0.01$). Wilks’ lambda value (0.301) indicated that 69.9% of the variability of amplitude means was attributable to group differences. This is remarkable in view of the fact that...
only at leads Pz and Fz did univariate F-tests showed that between-group variability significantly exceeded the within-group variability (p<0.05). Even more, step-down procedures reduced significance to only one lead, namely, Fz, with a medium-to-strong effect size of 0.135. The R-E-G-W post hoc procedure revealed that mean amplitude values at leads Pz and Fz for abstinent addicts were significantly lower than mean amplitude values for controls and active addicts. The latency waveforms for the three groups did not show any significant dissimilarity.

3.2. Comparison of memory performance (numbers of recalled digits)

Mean values and standard deviation (S.D.) for the three compared groups, i.e., current users, abstinent addicts and normal controls, were 56.4±10.0, 60.9±10.6 and 68.1±8.6, respectively. ANOVA test showed significant group differences (F2,55=6.73, p<0.01). Post hoc tests revealed that this was due to significant differences between current heroin users and normal controls (Bonferroni test, p<0.01). In contrast, mean memory performance of abstinent addicts did not differ significantly from that of the two other groups. However, it was higher than that of current users and lower than that of normal controls.

3.3. Correlations between duration of heroin abuse and P300 differences

P300 amplitude was not significantly correlated with the duration of heroin abuse.

4. Discussion

The aim of the present study was to compare P300, elicited during a short memory test, in patients with prolonged heroin abstinence, with current heroin addicts and healthy controls, matched for age, sex and educational level. Abstinent heroin addicts exhibited significant reduction of P300 amplitude at central frontal region, relative to the other two groups, while current users did not differ from normal controls.

Recent psychophysiological and neurobiological studies indicate that P300 amplitude represents attentional operations (Holdstock and Rugg, 1995; Knight and Scabini, 1998; Kok, 2001; Polich, 1998). It is suggested that frontal generators of P300 are more involved in automatic orienting, whereas temporoparietal generators are more responsive to evoked stimuli (Halgren et al., 1998; Higashima et al., 1996; Winterer et al., 2001), while reduction in P300 amplitude is thought to reflect gray matter abnormalities (Martin-Loeches et al., 2001; McCarley et al., 1993). In view of the above evidence, it is tempting to assume that the reduction in P300 amplitude found in the heroin-abstinent group in the present study may suggest that long-term heroin abstinence is associated with attentional defects, involving or affecting mechanisms related to automatic orienting, possibly mediated by gray matter abnormalities. In this context, present results support the suggestion that P300 is a “measure” of the CNS recovery during long-term opioid abstinence (Bauer, 2001).

It should be noted that attenuation of P300 amplitude has been also reported for alcoholics (Enoch et al., 2001), schizophrenics (Mathalon et al., 2000), Alzheimer patients (Daffner et al., 2001), as well as Parkinson patients (Robertson and Empson, 1999). These nonspecific abnormalities may indicate that, in addition to disease-specific processes, general disease processes exist, which could represent “an ordered pathway in the brain’s adaptation to many central nervous system insults whether from disease, toxins, deficiencies, accidents or stress” (Tracy, 1995).

The findings of the present study may be tentatively linked to the “self-medication” hypothesis, suggesting that
heroin is a self-medicating tool used to control innate psychic sensitivity (Khnatzian, 1985; Drummond, 2001; McCusker, 2001). Current users did not differ from controls with regard to P300 amplitude, and this may hint at a possible “normalizing” effect of heroin on P300 (Kouri et al., 1996). Nevertheless, in evaluating the present finding that long-term abstinent group exhibited a significant attenuation of P300 amplitude, compared both to current users and to controls, it is important to recognize that differences among groups are not necessarily attributable to the “self-medication” hypothesis. P300 differences can also arise from factors that predispose individuals to become drug dependent (Bauer and Hesselbrock, 1999) or because of many other reasons, such as long-term effects of prolonged drug use, the correlated behavioral and diet habits of long-term users or the recovery related to it. As noted characteristically in Bauer (2001): “P300 obtained from drug-dependent populations is multiply determined. It is influenced by recent events, such as an ongoing process of central nervous system recovery from drug dependence. It is also influenced by a central nervous system deficit, which preceded the onset of drug dependence.”

Another important finding of the present study was that current heroin addicts performed significantly lower as compared to normal controls with respect to the recalled digits of the short memory task. This finding could be discussed in the light of recent neuropsychopharmacological findings, indicating that an increased dose of opioids in chronic heroin addicts produces episodic memory impairments (Curran et al., 2001) and also neurophysiological reports, suggesting that opioid-induced memory impairments may be “partially due to the inhibition of the central cholinergic activity” (Li et al., 2001). On the other hand, the observed trend of better memory performance of abstinent addicts, compared to that of their non-abstaining counterparts, appears to support previous research, which indicated that long-term abstinence may improve neuropsychological functioning in relation to short-term memory performance (Selby and Azrin, 1998).

As far as the observed lack of correlation between P300 amplitude and duration of heroin abuse is concerned, it appears to be in accordance with results by Bauer (2001) reporting that P300 amplitude did not correlate with duration of drug abuse, and this held independently for heroin, cocaine or alcohol abuse.

Certain limitations of the present investigation warrant consideration. Firstly, the post hoc assignment of psychological function to regional activation is somewhat hypothetical, and more experiments are required addressing the specific role of a particular psychological process in the functional anatomy of heroin abstinence. Furthermore, in order to draw general conclusions about auditory P300 elicited during a single short memory test, in heroin addicts and their prolonged abstinence counterparts, future work is required involving different tasks and/or different stimulation modalities.

5. Conclusions

Present findings, employing auditory ERPs on subjects with a standard period of heroin abstinence, as well as on current heroin users and a group of healthy controls, may be linked to a set of hypotheses addressing issues in opioid use disorders. Furthermore, having in mind the limitations that are posed on drawing general conclusions about ERP components, the findings of the present study may also suggest that investigation of cognitive operations, such as those reflected by P300 component, could provide further insight into psychophysiological mechanisms underlying the long-term abstinence state of heroin addicts.

References


