Published in final edited form as:

Clin EEG Neurosci. 2009 April ; 40(2): 122–128.

Recent EEG and ERP Findings in Substance Abusers

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Abstract

Research on electroencephalographic (EEG) correlates of substance use has a long history. The present paper provides a review of recent studies – 2001 to the present – with a focus on EEG findings in human participants characterized by a history of chronic substance use, abuse or dependence. In some areas (e.g., alcohol and cocaine dependence), the field has attempted to build upon earlier work by incorporating different methodologies or pursuing research questions of a transdisciplinary nature. New areas of inquiry, such as the investigation of EEG differences among users of ecstasy (MDMA) and methamphetamine, have emerged, primarily as a result of an alarming rise in popularity of these drugs.

Keywords

Alcohol; Cannabis; Cocaine; Ecstasy; Electroencephalography; Event-related Potential; Heroin; Nicotine

INTRODUCTION

Summarizing the literature on the topic of electroencephalography (EEG) and event-related potential (ERP) studies of substance abuse is a formidable undertaking. In 2001, one of us¹ reviewed the literature in book chapter format. The chapter was an integration and summary of 231 articles published between 1931 and 2001. Dozens of additional articles were also listed within a separate bibliography section.

Our decisions about the format and content of the present article were guided by this history. In our opinion, readers of the present review would not be well served if we now provided a cursory review of old information that has been more thoroughly reviewed elsewhere and is still available. We also did not wish to perform a disservice to article authors by being too selective in the present review and focus only on those articles that interest us and/or confirm our own hypotheses. Instead, the approach adopted here was to provide a comprehensive review of articles published after the 2001 book chapter. Using this approach, we hope to

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DISCLOSURE AND CONFLICT OF INTEREST

N. A. Ceballos, L. O. Bauer and R. J. Houston have no conflicts of interest in relation to this article.

provide readers with a sense of the questions and methods that various investigators now consider to be at the cutting, if not leading, edge of substance abuse research.

This review is organized into sections that focus on EEG/ERP findings in the categories of alcohol, stimulant, nicotine, hallucinogen, and heroin abuse.

ALCOHOL

The current family of studies of EEG responses recorded from alcohol-abusing patients is a mixed marriage of theoretical and methodological approaches. One category of studies derives from an old tradition in which differences between patient and control groups are ascribed to their different levels of alcohol exposure and neurotoxic effects. The studies have also adhered to a tradition within clinical neurology in which the latencies of early sensory components of the ERP are of primary interest.

An example of the traditional approach is the work of Smith and Riechelmann.² They recorded brainstem auditory evoked responses from 38 male patients, of whom 19 were awaiting surgical treatment of a head or neck tumor and 19 were candidates for elective plastic surgery. The investigation did not compare groups of alcoholic and nonalcoholic patients. Instead, a continuous measure of alcohol exposure, the lifetime number of grams of ethanol consumed, was derived from a questionnaire. It was then correlated with the absolute and inter-peak latencies of the lower (Wave I), middle (Wave III), and upper (Wave V) brainstem components of the auditory evoked response.

From this analysis, the authors reported a finding consistent with similar investigations reported decades earlier: the latency difference between the lower and upper brainstem components was positively related to the level of alcohol exposure. The authors interpreted their finding as evidence of an adverse effect, presumably mediated by loss of white matter.

Nazliel and colleagues³ adopted a similar approach in their study of pattern shift visual evoked potentials (VEP) among 24 alcohol-dependent patients abstinent for less than 30 days, 16 patients abstinent for 30-76 days, and a normal control group of unspecified number and character. Analyses focused on group comparisons of P100 latency, as well as the percentage of patients within each group with clinically abnormal responses (i.e., a P100 latency 3 standard deviations greater than the control group mean, or absent unilateral or bilateral responses). The analyses revealed minor but statistically significant delays in P100, and an increased number of clinical VEP abnormalities, among alcoholic patients in comparison to the subjects forming the control group. The differences were no greater in the alcoholic subgroup characterized by the shorter period of abstinence than in the subgroup with a longer abstinence history.

An intriguing divergence from the traditional approach is the recent work of Mochizuki and colleagues.⁴ They investigated a factor hypothesized to amplify or mediate the adverse effects of alcohol on sensory ERP components. More specifically, they focused on a genetic mutation seen primarily among individuals of Oriental ancestry – a mutation which impairs the enzymatic (ALDH) metabolism of alcohol and fosters excess accumulation of an intermediate metabolite, acetaldehyde. Acetaldehyde was hypothesized to be the neurotoxic agent mediating the effects of alcohol on sensory transmission.

To this end, the investigators genotyped a large group of alcoholic patients and assigned them to either of two subgroups. Twenty-seven patients were characterized by a gene polymorphism associated with hypoactive ALDH2. An additional 43 patients possessed the normal, fully-active variant. The intriguing result was the demonstration of significant delays in sensory transmission time, reflected in the inter-peak latency difference between two somatosensory

evoked potential components, among patients with the gene polymorphism conferring hypoactive ALDH2 activity.

It would be erroneous to conclude from the Mochizuki et al. study⁴ that hypoactive ALDH2 activity and excess acetaldehyde accounts for all of the neurotoxic effects of chronic alcohol consumption. Indeed, the gene mutations which impair ALDH2 are rarely seen in people of European American or African ancestry. Yet, these people also experience brain damage from chronic alcoholism. However, the study highlights an important point and a new opportunity. Genetic heterogeneity may influence other aspects of alcohol metabolism and/or its effects on the brain. A relevant target for future investigations might be polymorphisms of genes which regulate ADH and its initial role in forming acetaldehyde from alcohol. Dysfunctional ADH gene polymorphisms are not as exclusive to a specific racial/ethnic group as are ALDH2 variants, and may therefore play a more powerful and prevalent role in mediating alcohol-associated brain damage. To our knowledge, ADH genes have not been examined in this context.

In contrast to the interpretations applied within studies of the sensory components, many studies of the later, cognitive ERP components have adopted a different theoretical approach. These studies recognize that many alcoholic patients are not only characterized by a long history of alcohol abuse but are also characterized by genetic, personality, and psychiatric differences that motivate abuse. Accordingly, it is not correct to view all EEG or ERP differences as reflections of a pharmacologic effect. Predisposing characteristics may be just as, if not more, important.⁵⁻⁸

Several recent studies of the P300 ERP have not directly examined predisposing characteristics but have produced findings which support their role. Two notable examples are recent reports work by Ehlers et al.⁹ and Suresh et al.¹⁰ In the former report, an association between genetic risk for alcoholism and a P300 amplitude reduction was implied in that the alcohol-abusing adolescents had a period of alcohol exposure which appeared too brief to cause neural damage. Instead, the amplitude reduction was related to the fact that these adolescents were from families in which many members became alcoholic. In the report by Suresh and colleagues,¹⁰ an association between P300 amplitude reduction and genetic risk was inferred from the demonstration that the amplitude reduction persisted long after the drinking had ended and might therefore reflect an abnormality which preceded the drinking career.

Several studies of other late ERP components have either not considered predisposing factors or dismissed their contribution. For example, Fein, Whitlow and Finn¹¹ examined the Mismatch Negativity (MMN) in alcoholic patients and suggested that, unlike P300, it is not related to alcoholism risk. They defended their hypothesis from the failure to find differences in MMN amplitude or latency between a control group and alcoholics who had maintained abstinence for a minimum of 6 months. In addition, they failed to find an association between the MMN and various measures of risk, including family history, disinhibited personality traits, and antisocial behavior. Admittedly, their hypothesis rests on the weak foundation of accepting the null hypothesis. However, in the context of other studies which did find an association between MMN abnormalities and recent alcohol abuse, the hypothesis is defensible. Unlike P300, the MMN may be more powerfully determined by state factors, such as recent alcohol abuse, and less determined by factors which would persist throughout long term recovery.

ILLICIT STIMULANTS: COCAINE AND METHAMPHETAMINE

Cocaine

The literature on stimulants has focused primarily on crack/cocaine. It includes manuscripts addressing a variety of topics, including EEG or ERP correlates of length of stay in treatment, responses to drug-related cues, and psychiatric comorbidity.

Length of Stay in Treatment—In a series of investigations, Reid, Pritchep, and colleagues have asked a practical and significant question: can EEG features predict length of stay in treatment and thereby potentially inform treatment plans? One recent study in the series extended a prior study¹² which had identified two clusters of EEG features that were associated with different lengths of stay. In the follow-up,¹³ QEEG features were examined in a larger sample of cocaine-dependent males (n=57). Consistent with the previous finding, two major subtypes emerged: an alpha cluster characterized by significant deficits of low frequency activity, significant excess of alpha activity and relatively more normal levels of beta activity; and a beta cluster characterized by deficits of delta, normal amounts of theta and anterior excess of alpha and beta activity. Individuals exhibiting the alpha cluster pattern remained in treatment longer than those who exhibited the beta cluster. In the follow-up study, an additional subtype was described. This subtype appeared to be similar to the beta cluster: it was also characterized by a short length of stay in treatment. The authors concluded that these outcome-related subtypes are likely related to a trait which could predispose individuals to cocaine addiction.

Responses to Drug-Related Cues—Two recent investigations have examined EEG responses evoked by cocaine-relevant and cocaine-irrelevant stimuli in cocaine-dependent patients. In one study,¹⁴ patients abstinent for an average of 7 months and nondependent controls were exposed to neutral and cocaine-related pictures and asked to rate the valence of the pictures as either positive or negative. Patients exhibited larger N300, late slow positive wave (LSPW), and sustained slow positive wave (SSPW) amplitudes following the cocaine-related pictures relative to the neutral pictures. These components did not vary by picture type in the control group. The authors interpreted the findings as further support for the supposition that drug-dependent individuals attribute more salience to drug-related stimuli.

Another study examined visual ERP and auditory startle eyeblink responses in abstinent cocaine-dependent patients (mean abstinence = 9 weeks) during the presentation of cocaine-related, positive, negative, and neutral pictures.¹⁵ The startle stimulus, a white noise burst, was presented after stimulus onset on 75% of the picture trials. Patients were divided into high and low craving groups based on self-reported ratings. The major finding was a larger positive slow wave in the high craving group compared to the low craving group following the presentation of cocaine-related pictures. In addition, the slow wave was larger in high “cravers” for all picture categories compared to the neutral category.

Psychiatric Comorbidity—A number of studies have examined ERP correlates of paranoia and antisocial or impulsive personality features in cocaine-dependent patients. Boutros and colleagues¹⁶ examined the P50 ERP in relation to the level of cocaine-induced paranoia. Cocaine-dependent patients who reported high levels of paranoia exhibited impaired sensory gating of the P50 response during a paired-click paradigm in comparison to subjects reporting less paranoia. Another study¹⁷ examined additional mid-latency evoked potentials during the same sensory gating paradigm. The authors reported smaller N100 and P200 amplitudes, and impaired gating of N100 and P200, among patients compared to healthy controls. Prolonged latencies of N100, P200, and P50 components were associated with cocaine-induced paranoia.

Antisocial and impulsive personality features have also been linked to ERPs. Bauer¹⁸ demonstrated that cocaine-dependent patients with comorbid Antisocial Personality Disorder

(ASPD) were less able to inhibit premature responding during a time estimation task and accordingly exhibited larger Contingent Negative Variation (CNV) amplitudes during the time estimation interval. Findings reported by Moeller and colleagues¹⁹ suggest that impulsive features – independent of ASPD – might also relate to impaired attention, for they detected a negative correlation between P300 amplitude and self-reported impulsivity while statistically controlling for the number of childhood conduct disorder symptoms.

Deficits in error monitoring are likely related to both ASPD and impulsivity. Franken and colleagues²⁰ have reported the only study to date of error processing in cocaine-dependent patients. Cocaine-dependent patients exhibited smaller and error positivity (Pe) amplitudes in comparison to nonpatient controls.

Methamphetamine

Methamphetamine abuse has increased at an alarming rate over the past several years.²¹ Studies of its EEG/ERP correlates are only now beginning to appear. In one QEEG study,²² methamphetamine dependent subjects exhibited more slow wave activity (delta and theta) than nondrug using controls. In addition, a larger percentage of their EEGs were considered abnormal (64% vs. 18%). In a second, related study,²³ QEEG activity was examined in relation to performance on reaction time and working memory tasks. In general, theta activity was significantly correlated with slower and/or poorer performance on neuropsychological tasks, but only in the methamphetamine-dependent group.

LICIT STIMULANTS: NICOTINE

Many studies of ERPs in substance dependence have ignored the contribution of tobacco use. Recent work suggests that it may be an important complicating or confounding factor. In addition, its effects may persist long after the cessation of use. This section of the review will focus on the tobacco literature, as well as a number of methodological issues relevant to tobacco research.

Recency of Use

Recent use is a methodological issue that is relatively unique in tobacco research. For this reason, EEG and ERP studies of tobacco users cannot easily distinguish between nicotine's acute activating effects²⁴ and those that accompany nicotine withdrawal²⁵ or long-term abstinence. The problem is less commonly encountered in EEG or ERP studies of other drug abusing populations wherein longer periods of abstinence and recovery are more practical for the researchers and are typically mandated.

To address the issue of recency of use, a variety of experimental designs have been employed. In studies of chronic smokers, investigators have contrasted three groups: active smokers, former-smokers, and never-smokers. In addition, some investigations add an acute administration component (after Pritchard, Sokhadze, Houlihan²⁶) wherein active smokers are given nicotine, via cigarette or nicotine patch, within the laboratory and evaluated before and after the administration. This acute administration component confronts the problem more directly because it allows one to identify patterns associated with, for example, the current versus previous cigarette.

Chronic Tobacco Use

The literature assessing the chronic effects of nicotine on ERPs remains sparse and contentious. For instance, Anokhin and colleagues²⁷ reported decreased P300 amplitude among active and former smokers in comparison to never-smokers. However, work by Aşçioglu and colleagues did not replicate these differences. In their study, 10 smokers were compared to 10 non-

smokers. Participants were medical students with a mean age of 23 years (± 2.8). Within the smoking group, participants reported at least 1 year of smoking at the rate of approximately 14 cigarettes per day (± 4.2). Non-smokers were matched on parental socioeconomic status and intelligence level; both were likely to be quite high given that medical students were the research participants. The level of previous tobacco experience was not given for the non-smoking group; therefore, it is unclear whether or not this group was composed of ex-smokers, occasional smokers or never-smokers. Standard auditory oddball paradigms were used, and N1, P2, N2 and P300 ERPs were examined. Results indicated no significant differences in amplitude or latency of these ERPs among smokers versus non-smokers.

It is important to note that the study protocol did not require participants to abstain prior to the evaluation: they were told to maintain their usual amount of nicotine consumption. As a control measure, the smoking participants were asked to smoke a cigarette 15 minutes before the testing session. Because each individual's smoking pattern is unique, it is possible that the resulting noise and variability in recent nicotine exposure, coupled with the small N, diminished power for detecting group differences. The analysis did not include potential covariates such as the number of cigarettes consumed per day, length of smoking career or, the number of cigarettes consumed within the previous 24-hours. Further, although the use of a restricted sample of relatively young participants with higher than average socio-economic status (SES) and intelligence (i.e., medical students) may impose a level of control in the quasi-experimental design of this study, it is important to note that the technique may also negatively impact the generalizability of the findings. In addition, premorbid factors were not examined or controlled.

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Smokers vs. Ex-Smokers vs. Never-smokers

A recent study by Littel and Franken³⁰ focused on the effects of prolonged nicotine abstinence on smoking-related processing bias. Three groups were compared: smokers, ex-smokers and never-smokers. The smoking group reported consuming approximately 10 to 30 cigarettes per day. The ex-smoking group reported similar characteristics during their smoking careers, with a mean quit duration of approximately 1.4 years (± 1.8). Importantly, smokers and ex-smokers did not differ on a variety of variables including smoking duration and level of nicotine dependence. Never-smokers reported using fewer than 3 cigarettes in their lifetime.

Another study focused on the N300, P300 and slow positive wave (SPW) components of an ERP elicited with a visual cue.³¹ N300 and P300 amplitudes were identified using peak-detection; whereas, the SPW was measured using area under the curve techniques between 400-750ms following stimulus presentation. Results indicated that both the P300 and SPW amplitudes elicited by smoking-related pictures were *enhanced* at frontal and central sites for smokers, as compared to ex-smokers and never-smokers. ERPs elicited by tobacco-irrelevant control stimuli (e.g., individuals holding pens) did not differ across groups. With regard to the P300 and subsequent late positive waveforms, these findings are quite standard, as heightened P300 response to drug-related stimuli has been noted for a variety of abstinent substance-abusing subgroups, including alcohol dependent populations.³² Late positive enhancement has also been shown in previous work by Bartholow, Henry and Lust.³³ Such findings support the idea that P300 and SPW amplitudes may reflect the motivational significance of substance-related cues.³³

An interesting feature of the cue reactivity study is that the ex-smokers exhibited ERPs that were similar to that of non-smokers, suggesting (as in the Aşcioglu study) that chronic nicotine use does not have a long-term effect on ERPs. The authors³⁰ also liken their results to those of Munafò et al.,³⁴ who found a significant difference in attentional bias between smokers and ex-smokers but no difference between ex-smokers and never-smokers.

Effects of Prolonged Abstinence

In a study by Neuhaus and colleagues,³⁵ former smokers (mean abstinence = 11.9 years, $\pm$ 9.9) were compared with current smokers (mean cigarettes per day = 15.2, $\pm$ 9.9) and never-smokers. Criteria for recruitment of never-smokers were not given; therefore, it is unclear whether some degree of previous tobacco use was allowed. Current smokers were not restricted from smoking before the onset of the experimental procedure; however, participants were prevented from smoking for approximately 1 hour during the preparation period.

The authors examined potential correlations between P300 amplitude and daily cigarette consumption as well as lifetime exposure to cigarette smoke (e.g., pack-years). P300 waveforms were elicited using an auditory oddball procedure. Results indicated that both current and former smokers exhibited significantly diminished P300 amplitudes. Neuroelectric source analysis [LORETA^{36,37}] revealed hypoactivation of the anterior cingulate, orbitofrontal cortex and prefrontal cortex of smokers and former smokers, as compared to never-smokers.

HALLUCINOGENS

The extant literature on electrocortical activity in participants with a history of abuse of or dependence on hallucinogen drugs includes a diverse and varied group of studies. This is due, in part, to the wide range of frequency and intensity of use for these substances as well as the high levels of polydrug use in these populations. Furthermore, the notion of dependence for these substances is a controversial issue.^{38,39} Due to a rise in popularity and social concern, two substances in this category have emerged as primary targets for investigation: cannabis/marijuana and ecstasy (MDMA).

Research aimed at understanding the electrocortical effects of marijuana abuse/dependence has been somewhat inconsistent in the past.⁴⁰ A recent study of resting EEG in a fairly large sample of marijuana abusers (n=75) and nondrug using controls (n=33) reported an association between duration of use and reductions in alpha and beta power at posterior electrode sites.⁴¹ These findings provide support for previous studies, which indicated a relation between abnormal EEG patterns and chronic marijuana use.⁴²

Rather than focusing on marijuana dependent populations, per se, two recent studies have examined early to mid-latency evoked potentials in marijuana “users.” Methodologically, these studies differ in terms of the criteria for being classified as a marijuana user; however, both studies reported some type of deficit associated with regular marijuana use (at least once a week). Namely, the studies have noted a reduction in N160 amplitude in response to visual photic stimulation⁴³ and shorter N200 (and N300) latencies during an auditory selective attention task.⁴⁴ The Kempel et al. study⁴⁵ also reported a reduction in target P300 amplitude in marijuana users, a finding in contrast to earlier reports of no significant decrements among marijuana users. Further research using consistent group characterization, task manipulation, and rigorous pharmacokinetic approaches are needed to better identify which of these attentional/sensory processing components may be most useful in extending our understanding of the effects of marijuana use and dependence.

In the only study⁴⁶ to examine emotional processing in marijuana-dependent individuals, a facial discrimination task was used in a sample of Southwest California Indian participants divided into 3 groups: 1) those meeting criteria for marijuana dependence, 2) those meeting criteria for marijuana dependence and other drug dependence, and 3) those with no drug dependence disorders. Analyses controlling for age, gender, and a lifetime diagnosis of alcohol dependence indicated latency increases for the P350 and P450 components associated with marijuana dependence (both groups). In addition, women exhibited larger latency increases compared to men. These findings suggest that marijuana dependence may have specific effects

on the evaluation of emotional stimuli. A notable and novel aspect of this study is the fact that comorbid drug dependence was taken into consideration when recruiting the participant groups.

“Ecstasy” or 3,4-methylenedioxymethamphetamine (MDMA) has risen in popularity in recent years. As noted, the notion of dependence for this substance remains controversial; further, it is important to note that polydrug use is common in MDMA users, making it difficult to specify direct effects of MDMA exposure. In a 2005 study conducted by Herning and colleagues,⁴⁷ resting EEG activity was compared across 4 groups: MDMA abusers, marijuana abusers, marijuana/MDMA abusers, and controls. Absolute delta power was higher for the MDMA abusers compared to the other groups. Notably, and in contrast to previously reported results, alpha-2 power was also higher in the marijuana-only group. Findings among MDMA users appear to be consistent with greater slow wave activity, which has been previously associated with a number of other psychiatric conditions (e.g., schizophrenia, aggression).

Because MDMA administration results in a large increase in extracellular serotonin (5-HT), a small collection of studies has examined evoked potentials associated with auditory intensity dependence (AID) in MDMA users. The AID paradigm is used as an indirect tool for measuring 5-HT attenuation of neural responses to auditory stimuli.^{48,49} In a study comparing long-term MDMA users (used 20 times or more), long-term cannabis users (e.g., those who used twice a week for 2 years or more and had only used MDMA occasionally), and drug-naïve controls, the MDMA group exhibited a larger N1/P2 intensity dependence slope compared to other groups.⁵⁰ This finding was also related to the total amount of lifetime MDMA consumption. These results are in contrast to a previous study, which reported AID abnormalities that were unrelated to the extent of MDMA use. These findings support evidence of 5-HT abnormalities among MDMA users and may be independent of other confounding factors (e.g., marijuana use). The AID paradigm has also been used in longitudinal studies. Daumann and colleagues⁵¹ examined evoked potential responses at 2 time points (18 months apart) in MDMA users. Although factors such as MDMA use, frequency of use, and period of abstinence were related to intensity dependence (i.e., changes in evoked potential slopes), the study did not detect significant electrocortical changes associated with drug use between the two time points. However, it is important to note that the attrition rate from time 1 to time 2 in this study was quite high (70% of the participants assessed at time 1 did not return for time 2 for various reasons). Taken together, these studies suggest that the use of the AID paradigm as an indicator of 5-HT dysfunction associated with MDMA abuse/dependence holds promise. However, in order to ultimately determine its value in this area, future studies are needed including larger samples, more rigorous criteria, and a better accounting of comorbid drug use.

Two recent studies of ERPs in MDMA users have examined late components using variations on the traditional visual oddball task.^{52,53} One study of MDMA users vs. controls matched for marijuana use employed pictorial stimuli of faces exhibiting neutral, happy or fearful (target condition, counterbalanced) expressions. Control participants exhibited shorter N200 latencies in response to fearful faces (vs. happy faces); however, MDMA users did not exhibit this pattern. The authors interpreted this effect as evidence of attentional processing deficits resulting from chronic MDMA use. Although the effects of marijuana use were controlled via matched controls, the MDMA group may have been somewhat heterogeneous, as the extent or frequency of MDMA use was not well documented. In another study, the P300 (elicited by visual Continuous Performance Test; CPT) was examined in MDMA polydrug users vs. drug-naïve controls. This paradigm addressed the authors' hypothesis concerning decrements of disinhibition among MDMA users. In general, the MDMA group exhibited smaller P300 amplitudes, although this effect was diluted after controlling for age, education, and marijuana use. In addition, the P300 ERP in response to NoGo stimuli (in which inhibition would be required), was topographically distributed in an anterior fashion among controls, but not

MDMA users. Although this study was unable to totally eliminate potential confounds associated with polydrug use in MDMA users, it is one of the first to demonstrate differences related to MDMA exposure using the later cognitive ERP components.

HEROIN

In contrast to the large number of research reports documenting EEG/ERP abnormalities among patients afflicted with histories of alcohol, stimulant, or hallucinogen abuse, studies of the EEG/ERP features of heroin- or methadone-dependent patients are few in number. Most have appeared in journals during the past 10 years. Five of the published articles focus on late positive components of the ERP. The remaining articles describe group differences in various features of the spontaneous EEG.

In three articles published between 2001 and 2006, Papageorgiou and colleagues⁵⁴⁻⁵⁶ evaluated 20 patients with a history of heroin dependence (abstinent > 6 mos) and an equal number of nondrug-using volunteers. The subjects were initially presented with a brief tone whose pitch, low or high, informed them of the difficulty of the task that would follow. One second after the presentation of the tone, subjects were asked to memorize a set of 2-9 digits, and recall the digits in the order (forward or reverse) signaled by the low versus high pitch of an ensuing tone. This tone had the same pitch as the warning tone.

One advantage of the task design used by Papageorgiou and others was the opportunity to contrast ERPs elicited during distinct task conditions: the activation/orienting of attention toward the task versus the retrieval of items from working memory. In their 2003 and 2004 publications,^{55,56} the investigators focused on the former condition. In the 2001 publication,⁵⁴ they focused on the latter.

The results of all three investigations revealed deficient event related potential responses in former heroin abusers. The P300 response to the warning tone was significantly diminished in amplitude and delayed in latency – a result consistent with deficits previously observed in studies of heroin dependent patients abstinent for 6-10 and 30-120 days.⁵⁶ It is unclear whether these P300 deficits can or cannot be eliminated by heroin replacement and might therefore reflect opiate receptor specific changes occurring during acute withdrawal and protracted abstinence. It seems likely that the diminished P300 response to the warning tone, and the delayed P600 response to the recall tone, are also influenced by other factors, including psychopathology that predates and promotes heroin dependence.

In contrast to findings from studies of the ERP, results from studies of the spontaneous EEG have produced variable results. Polunina and Davydov⁵⁷ examined the spectral composition and mean frequency of the EEG in 33 former heroin abusers, abstinent for 6-135 days, and 13 nonusers. The patients were assigned to subgroups based upon the duration of daily heroin use. Absolute power and mean frequency were computed within slow and fast frequency ranges of the 4 conventional spectral bands, i.e., slow delta through fast beta.

Analyses revealed reduced power in the EEGs of heroin dependent patients within the fast theta, and slow and fast alpha frequency bands, coupled with enhanced power in the slow and fast beta frequency bands. Reduced EEG power in the theta and alpha bands was not replicated by Franken and colleagues⁵⁸ in their 2004 analysis of a smaller number of patients abstinent for 14 days. However, the enhancement of beta power did replicate across the two investigations. Enhanced beta power has been linked by other investigators to a number of risk factors for substance dependence, including familial alcoholism,⁵⁹ conduct/antisocial personality disorder, and GABRA2 genotype.⁸

Two other investigations of EEG parameters in heroin dependent patients warrant mention because of their innovative approaches to data analysis. In separate publications describing assessments of the same 22 heroin dependent and 14 non-drug-using volunteers, Fingelkurts and colleagues employed probability classification⁶⁰ and functional connectivity analysis⁶¹ techniques. Probability classification involves determining the relative similarity of an individual EEG epoch to a prototype EEG spectral pattern (e.g., predominantly polymorphic, predominantly 10 Hz, etc). Individual EEG epochs can thereby be segregated by spectral type and tabulated. This technique can be used to derive simple descriptors of the EEG (e.g., number or variance of spectral types, temporal stability of spectral types) that extend beyond conventional measures of power or coherence. From their analysis, Fingelkurts and colleagues reported that the resting EEG of heroin dependent patients could be distinguished by a greater number of epochs containing fast alpha and beta frequencies which are sustained over a longer period of time. The patients also exhibited greater cortical connectivity in the alpha and beta frequency bands in comparison to the members of the control group.

CONCLUSION

Over the years, it has become apparent that EEG/ERP differences in substance abusers reflect the summation or interaction of multiple factors, including the pharmacological effects of the substance, premorbid personality and genetic differences, psychiatric comorbidity, medication use, and medical comorbidities (e.g., hypertension, diabetes, HIV/AIDS, hepatitis, etc). Because of the complexity of the picture, it is unrealistic to propose any single EEG or ERP measure as a diagnostic tool or endpoint for a treatment trial, because it would be arbitrary to attribute the difference to either the substance or treatment unless and until all other relevant factors are controlled. The future of EEG and ERP measures in the area of substance abuse may reside within the context of large clinical investigations wherein all of the factors are measured and parsed. As a result, it may then be possible to interpret the differences using appropriate statistical methods, such as structural equation, cluster, or factor analysis.

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