Psychomotor and Electroencephalographic Sequelae of Cocaine Dependence

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INTRODUCTION

Cocaine is abused because it affects brain function. It would therefore not be surprising to discover that functional brain impairments figure prominently as a consequence, and perhaps an antecedent (Bauer and Hesselbrock 1993; Bauer et al. 1994; O'Connor et al. 1994), of chronic abuse. It would also not be surprising to discover that these impairments persist after the chronic cocaine abuse has ended. Yet, there are relatively few studies published in the human research literature that either support or refute these assumptions. Much of what is hypothesized about the consequences of chronic cocaine abuse in human patients is based on clinical impressions, case reports (Cardoso and Jankovic 1993; Choy-Kwong and Lipton 1989; Farrell and Diehl 1991; Merab 1988; Mesulam 1986; Pascual-Leone and Dhuna 1990; Satel and Swann 1993), or extrapolations from studies of cocaine's acute effects (Fischman and Schuster 1980; Herning et al. 1985; Morgan et al. 1993; Sherer 1988). As a consequence, some disagreements have arisen in the clinical literature, and there is little consensus (Cottler et al. 1993; Gawin and Kleber 1986; Satel et al. 1991; Weddington et al. 1990) regarding the nature, severity, and/or duration of the postcocaine abuse syndrome.

One factor confounding discussions over the residua of cocaine abuse is the nature of the data. Studies focusing on subjective symptoms and mood (Satel et al. 1991; Weddington et al. 1990) have typically described the postcocaine abuse syndrome as mild in severity and approximately 3to 4 weeks in duration. In contrast, studies focusing on objective signs of functional brain impairment (Alper et al. 1990; Bauer 1993a, 1993b, 1994a, 1994b, 1994c; Herning et al., this volume; O'Malley et al. 1992; Roberts and Bauer 1993; Roemer et al., unpublished data; Volkow et al. 1992) point to a syndrome that is significantly more severe and persistent. These different conclusions are likely the result of method-related differ-ences in measurement sensitivity and/or error. Yet, one should not con-clude that the postcocaine abuse syndrome is therefore a statistically significant but clinically trivial entity. Several studies have associated poor clinical

outcomes, such as relapse to alcohol (Bauer 1994a; Rohsenow et al. 1994) or nicotine (Niaura et al. 1989) dependence, with subtle neurophysiological deficits that are not always expressed in a symptom or mood disturbance. Relapse to cocaine abuse represents another clinically significant psychiatric outcome that may be related to subtle cocaine-induced neurophysiological deficits (Carroll et al. 1993). Thus, there must be important, measurable sequelae of cocaine abuse, which have been largely underestimated or missed in the extant studies of psychiatric symptomatology (Satel et al. 1991; Weddington et al. 1990).

The goal of the present chapter is to review objective neurophysiological evidence for a postcocaine abuse syndrome. The focus is on the author's studies of psychomotor function and electroencephalographic (EEG) activity, or evoked EEG responses. Many of these studies were described in journals published during 1993 and 1994. Since that time, more sub-jects have been added to the data set and one can now report a replication of the original findings in an expanded sample.

METHODOLOGICAL CONSIDERATIONS

Before reviewing the specific details of these studies, it may be valuable to offer several general comments concerning the methodological problems attendant to conducting research with this population. Similar comments have been offered (Reed and Grant 1990) regarding neuro-psychological studies of substance abusers. These comments are also germane to studies of resting EEG activity, event-related potentials (ERPs), and most other clinical and basic science studies of recovering cocaine abusers.

Table 1 provides a list of disorders or conditions that often co-occur with cocaine dependence. It is by no means a complete list. Some would add attention deficit-hyperactivity disorder (ADHD) to the list of premorbid risk factors (Barkley et al. 1990; Gittleman et al. 1985). However, the association of childhood ADHD and adult drug abuse is controversial (Halikas et al. 1990; Kaminer 1992). Nonetheless, all of the cited varia-bles have been shown to affect psychomotor function or EEG activity (Bauer and Hesselbrock 1993; Bauer et al. 1994; Jabbari et al. 1993; Pollock and Schneider 1990; Smiley 1987). They therefore represent potential confounds in any study that professes to examine the sequelae of cocaine dependence and must be considered.

TABLE 1. Potential threats to causal inference.

Premorbid factors
Antisocial personality/conduct disorder
Aggression
Family history
Medical factors
Head injury
Seizures (including drug-related seizures)
HIV/AIDS
Other major medical disorders
Psychoactive medications
Psychiatric factors
Polysubstance abuse
Depression (including moderate depression)
Other DSM-III-R Axis I disorders

Although the variables listed in table 1 do represent confounds in deter-mining the specific effects of chronic cocaine abuse, they are also impor-tant variables for study because they may amplify, moderate, or entirely explain cocaine's purported effects. Indeed, one goal of the University of Connecticut research program is to add such variables incrementally to the existing, uncomplicated sample of cocaine abusers so that additive or interactive relationships can be studied. A popular alternative method for accomplishing the same goal involves the recruitment of a heterogenous subject sample and the post hoc "removal" of unwanted variance through analysis of covariance or regression. But these statistical methods rest on tenuous assumptions (Adams et al. 1985; Cronbach et al. 1977) which are frequently violated in clinical research. Furthermore, the level of control that can be achieved through post hoc statistical methods will always fall short of what can be achieved through a priori means (i.e., by construc-ting narrow inclusion criteria).

This desire for strict experimental control and narrow inclusion criteria challenges the clinical reality and speaks to a common controversy in drug abuse research. The result of using highly restrictive inclusion criteria can be a finding that does not generalize to the larger cocaine-dependent population. However, the findings are less ambiguous in origin. Furthermore, through the use of such criteria, it becomes possible to define and validate homogenous subtypes of cocaine abusers (Ball et al. 1995) and develop hypotheses regarding subtype-specific inter-ventions (Kosten 1989).

For example, antisocial personality disorder (ASPD) and a family history of alcoholism have recently been found to be associated with different patterns of EEG and neuropsychological impairment (Bauer and Hesselbrock 1993; Bauer et al. 1994; Gillen and Hesselbrock 1992; O'Connor et al. 1994). ASPD and a family history of alcoholism are both risk factors for the development of cocaine dependence (Bauer and Kranzler 1994; Miller et al. 1989; Rounsaville et al. 1991). Yet, if each is associated with a different neurophysiological path toward the same endpoint, then a different type of preventive intervention may be required.

Method

For the past 5 to 6 years, a group based at the University of Connecticut School of Medicine has been conducting research funded by the National Institute on Drug Abuse (NIDA) to examine EEG activity and psycho-motor functioning among cocaine-dependent patients during their initial 3months of abstinence. One concern that arose early in formulating the study design was the specification of an appropriate control group. As table 2 indicates, two separate control groups were included. One group consisted of alcohol-dependent patients who were matched to the cocaine-dependent group on a variety of premorbid variables such as the number of ASPD characteristics and the prevalence of a family history of alcoholism. The groups were also matched on a number of symptom measures such as the Beck Depression Inventory (BDI) and Spielberger State-Trait Anxiety Inventory (STAI). All of the groups were screened to exclude individuals with other drug dependence; other Axis I diagnoses; seizures (including drug-related seizures); head injury; intravenous (IV) drug use; current medication use; and neurological, cardiovascular, or liver disease. The cocaine abusers were no more dependent or medically complicated than the alcoholics, as measured by their number of previous hospitalizations. The cocaine abusers and alcoholics were also recruited from the same treatment facilities. While these two groups of patients differed significantly from an age- and socioeconomic status (SES)-matched nondrug-dependent control group, they were quite similar in many other respects, thereby making it easier to attribute any psycho-motor or EEG differences between them to the effects of either cocaine or alcohol.

TABLE 2. Demographic and clinical features of study groups.

Variable	Cocaine dependence	Alcohol dependence	Control
Age (SD)	31.3 (1.8)	31.0 (1.7)	32.1 (1.2)
Gender (M/F)	24/4	19/3	26/2
# ASP criteria**			
before age 15	2.3 (1.1)*	2.0 (1.3)*	0.2 (0.5)
after age 15	3.7 (0.7)*	3.1 (0.5)*	0.3 (0.1)
Proportion FHA+	0.3 (0.2)*	0.4 (0.1)*	0.1 (0.2)
BDI Score	9.3 (8.2)*	8.9 (8.4)*	2.6 (5.2)
STAI Score			
State anxiety	42.3 (12.4)*	40.8 (13.1)*	31.3 (9.3)
Trait anxiety	38.8 (8.7)*	37.0 (11.3)*	32.7 (9.1)
# Prev. detox.	0.9 (0.2)*	1.3 (0.3)*	0.0 (0)
Avg. # days/week last 6 months			
used cocaine	3.0 (0.5)*	0.3 (1.5)	0.0 (0.1)
used alcohol	4.0 (2.6)	6.2 (0.7)*	3.2 (2.4)
used opiates	0.0 (0)	0.0 (0)	0.0 (0)
Avg. amount/occasion			
cocaine (g)	0.9 (0.3)*	0.1 (0.4)	0.1 (0.2)
alcohol (# drinks)	4.0 (1.8)	16 (2.4)*	2.3 (1.6)

KEY: * = $p < 0.05$ versus control group; ** = excluding substance abuse related items; BDI = Beck Depression Inventory; STAI=State-Trait Anxiety Inventory; FHA+ = family history of alcoholism; ASP = antisocial personality.

The cocaine-dependent group consisted of individuals who primarily used cocaine in its freebase form. None were IV users. Only six met criteria for alcohol abuse; none met lifetime criteria for alcohol dependence. Cocaine use during the month preceding treatment exceeded 5 grams. The alcohol-dependent group was likewise uncomplicated.

The study design was longitudinal. Patients were evaluated repeatedly: 7to 10 days (session 1), 16 to 21 days (session 2), and 94 to 100 days (session 3) after their last use of cocaine or alcohol. Abstinence was verified through frequent and irregularly scheduled urine screens. Limiting the variability in abstinence was important since, at least among alcohol-dependent patients, there are electrophysiological data (Begleiter and Porjesz 1979; Begleiter et al. 1974) suggesting a transition in the early phases of abstinence from central nervous system (CNS) hyper- to hypoexcitability. Among cocaine abusers, CNS excitability is hypothe-sized (Gawin and Kleber 1986) to change in the opposite direction. Accordingly, assessments that were imprecisely timed relative to the initiation of either alcohol or cocaine abstinence would result in contradictory findings or, on average, no findings at all. The normal control group was also repeatedly tested to control for the effects of practice or familiarization.

Each subject participated in a 2-hour evaluation that included assessments of motor system functioning and EEG reactivity, among others. A particu-lar emphasis was placed on the assessment of motor system functioning. This emphasis was inspired by an early report (Volkow et al. 1988) of altered blood flow in the frontal brain of human cocaine abusers, as well as numerous reports of locomotor hyperactivity, sterotypy, and altered nigro-striatal dopamine turnover among cocaine-exposed animals (for a review see Johanson and Fischman 1989). Indeed, of all the tests included in the present battery, tests of motor system functioning have proven to be the most robust and persistent discriminators of cocaine-dependent patients.

A description of the test battery follows. The description of each test includes a verbal summary of the major findings resulting from an analysis of the expanded sample. For a detailed description of previous findings, data analysis techniques, and test parameters, the reader should consult recent publications (Bauer 1993a, 1993b, 1993c, 1994b, 1994c; Roberts and Bauer 1993).

Psychomotor Sequelae

Hand Tremor and Body Sway. Hand tremor was the simplest test in the battery to administer. It was transduced using an accelerometer taped to the subject's forefinger (Bauer 1993a). Other techniques could have been used; however, many of these techniques (e.g.,-electromyography, infrared or magnetic position sensors, and touch-activated electric circuits) are difficult to engineer or provide unwanted feedback cues to the patient.

Hand tremor is actually a complex phenomenon. Because it possesses an inherent rhythmicity, tremor can be objectively analyzed in the frequency domain using quantitative techniques such as Fourier analysis and the fast Fourier transform. The output of this transformation is a power spectral density function that provides estimates of tremor amplitude (power) as a function of the underlying frequency.

The advantage of applying Fourier analysis to tremor rests on the assumption that tremor frequency bears an important relationship to the underlying generator. This position was most strongly advocated by Holmes (1904) and more recently by Findley and colleagues (1981). A more conservative view is probably appropriate, however. The reason for conservatism derives from the fact that there is usually more than one type of tremor associated with a given neurological disease. These multiple tremors may be a direct effect of the disease process itself, or may reflect the gradual recruitment of multiple tremor generators due to chronic inflammation, edema, or tumor growth.

In the case of Parkinson's disease, for example, there is evidence of a characteristic hand tremor (Findley et al. 1981) occurring at rest at a stable frequency of 4 to 5 hertz (Hz). Postural and kinetic tremors have also been observed in Parkinson's-diseased patients, although at a different predominant frequency and with a lower prevalence than rest tremor. These latter tremors may therefore reflect a secondary process of the disease.

There is an additional type of tremor that can be detected in some disease states and in normal individuals with no significant neuropathology. This normal physiologic tremor (Young 1984) has a peak frequency of approxi-mately 9 Hz and is not significantly altered by intention or action. Normal physiologic tremor is

exaggerated by anxiety states or other factors that arouse peripheral adrenergic systems.

An analysis of hand tremor (figure 1) in substance abusers revealed significantly more hand tremor among the two patient groups relative to the normal controls. However, the types of tremor exhibited by the two patient groups were different. In both cases, the predominant frequency of tremor was in a slower, abnormal range (i.e., < 9 Hz). Therefore, it is unlikely that their hand tremors were a consequence of enhanced adrenergic outflow, anxiety, fatigue, or the other benign processes that 9Hz tremor is believed to index.

Alcohol-dependent patients exhibited significantly more low frequency (<4 Hz) tremor than the other two groups, but only during the first laboratory session (i.e., after 7 to 10 days of abstinence). The eliciting stimulus for this tremor was a task that required rapid ballistic pointing movements toward a moving visual target, alternating with periods of sustained posture. Thus, the amount of tremor recorded during the task was actually a combination of true action tremor with tremor of the postural type. Both types of tremor have previously been reported in

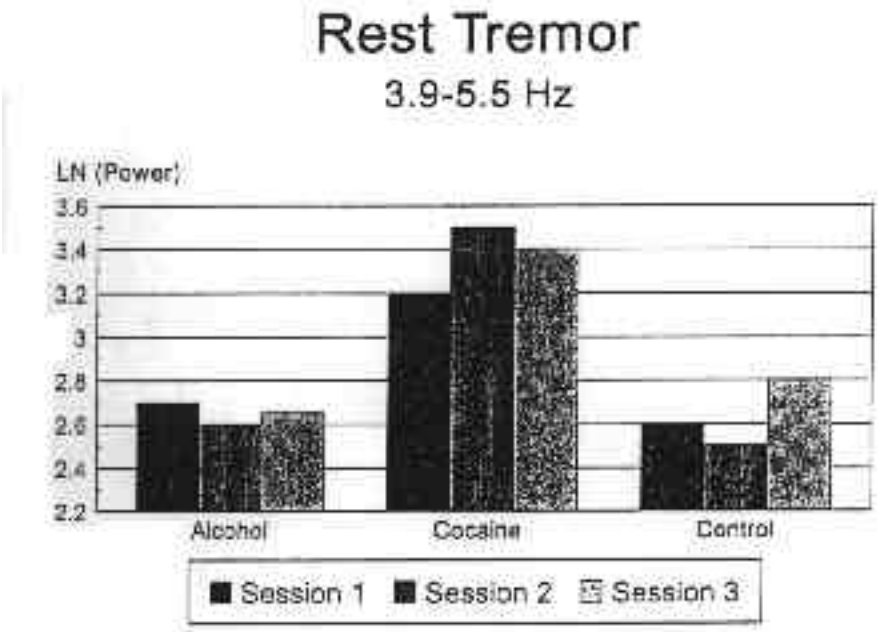

FIGURE 1. *Hand tremor as a function of subject group and session. Differences greater than 0.38 units are significant (Tukey critical difference, $p < 0.05$).*

alcohol-dependent patients (Neiman et al. 1990; York and Biederman 1991) and in patients with known cerebellar pathology (Victor et al. 1959).

The hypothesis of cerebellar dysfunction as the source of postural/action tremor among 1-week abstinent alcohol-dependent patients was further supported by the demonstration of enhanced body sway among these same patients, also during the first week of abstinence. Of course, enhanced body sway can be produced by other alcohol abuse-related factors, including peripheral neuropathy (Scholz et al. 1986) and some premorbid factors (Bauer and Hesselbrock 1993). But the young age and relatively excellent health of study patients, and the careful matching of the two patient groups on the prevalence of ASPD and family history of alcoholism, argue against these alcohol-related factors as significant contributors.

Cocaine-dependent patients exhibited a 4 to 6 Hz tremor that appeared while the hand rested in a supine position. The hand tremor was not accompanied by signs of cerebellar dysfunction, such as the enhanced body sway found in alcoholic patients, or nystagmus (Bauer 1993b). It was also not present during posture or movement. Most importantly, the exaggerated resting hand tremor of the cocaine-dependent patients did not diminish in amplitude, even after 94 to 100 days of verified cocaine abstinence (figure 1).

It is tempting (but still premature) to draw an analogy between the resting hand tremor observed in the present study and the characteristic resting hand tremor of Parkinson's disease. As noted above, numerous case reports have suggested an association between the effects of chronic cocaine abuse and the effects of Parkinsonism. These reports imply that cocaine can exacerbate preexisting extrapyramidal movement disorders or produce a Parkinsonian-like extrapyramidal disorder where none existed previously (Cordoso and Jankovic 1993; Choy-Kwong and Lipton 1989; Farrell and Diehl 1991; Merab 1988; Mesulam 1986; Pascual-Leone and Dhuna 1990; Satel and Swann 1993). Controlled studies demonstrating altered basal ganglia glucose metabolism in cocaine-exposed brain (Volkow et al. 1991) and altered cocaine receptor binding in Parkinson's-diseased striatal tissue (Kaufman and Madras 1991) reinforce the cocaine abuse-Parkinsonism analogy.

Despite the superficial similarity of tremors associated with cocaine abuse and Parkinsonism, it is important to recognize that the resting hand tremor exhibited by cocaine-dependent patients in the present study was far more subtle than described in the aforementioned case reports of cocaine abusers or in Parkinson's disease patients. In fact, the hand tremor detected in the present study was not visually obvious and would not have been detected without sensitive recording devices. Therefore, it is probably not significant in their daily lives, except for a subset of patients whose occupations require fine motor control and/or rapid motor responses.

Yet, it would be clinically and scientifically valuable to follow a group of cocaine-dependent patients as they enter middle age or senescence and determine if the subclinical tremor evolves into a significant clinical entity. For the same reason, it would also be valuable to follow a group of cocaine-dependent patients receiving neuroleptics for the management of schizophrenic symptoms and determine if they are more likely to develop clinically significant dystonic reactions or tardive dyskinesias. Kumor and colleagues (1986) have already reported data supportive of this hypothesis.

Reaction Time Performance. The very mild hand tremor exhibited by abstinent cocaine-dependent patients appears to bear a relationship to the slower-than-normal reaction times (RT) exhibited by these same patients. In fact, within this group, there is a significant correlation ($r = 0.43$, $p<0.05$) between rest tremor and simple reaction time.

The reaction times shown in figures 2a and 2b (Roberts and Bauer 1993) were measured during visual and auditory divided attention tasks. The tasks are similar to those used in the Reitan-Klove Sensory Perceptual Exam (Golden et al. 1981). During each task, a 20-millisecond (ms) stimulus (light flash or tone) is presented in either the right or left sensory field or in both sensory fields simultaneously. The stimulus location is varied randomly from trial to trial. Trials occur at the rate of one every second. Subjects are instructed to press one of two horizontally aligned response keys to indicate the spatial location of the stimulus, or both keys simultaneously when stimuli occur bilaterally. Reaction time and errors are calculated.

In clinical applications of this or similar variants of the Reitan-Klove Sensory Perceptual Exam in brain-damaged patients, neuropsychologists have focused on a particular type of performance error, an inability to detect simultaneous bilateral stimulation. Errors of this type are most often associated with posterior parietal lobe disease (i.e., the sensory neglect syndrome). Neither cocaine- nor alcohol-dependent patients

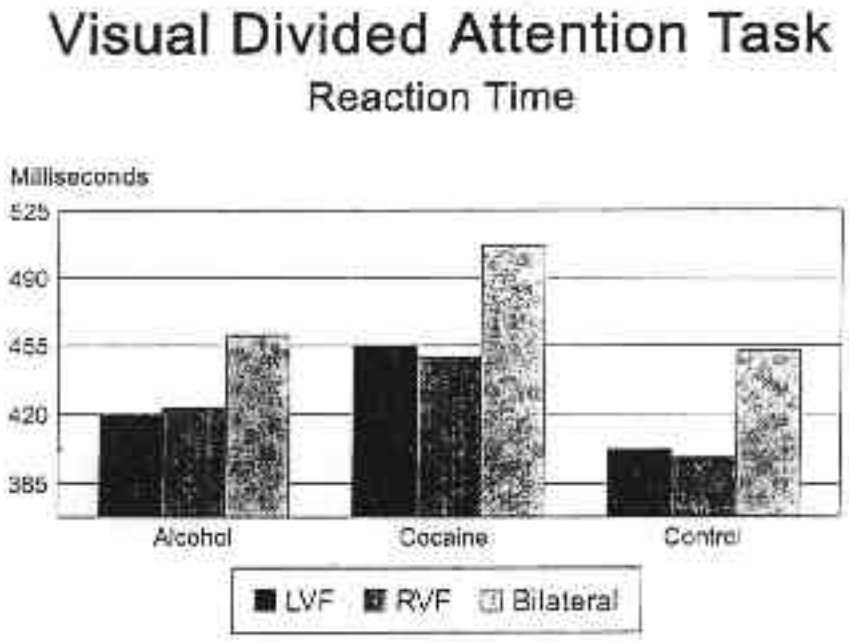

FIGURE 2a *Reaction time (in ms) during the visual divided attention task plotted as a function of subject group and stimulus location (visual field). The session effect was not significant and the data are accordingly collapsed over sessions. Differences greater than 27 ms are significant.*

exhibited a pattern of errors consistent with this clinical syndrome. Rather, cocaine-dependent patients were just slower than the other two groups during all three laboratory sessions. The magnitude of the slowing did not change as a function of the complexity of the discrimination (uni-lateral versus bilateral) or as a function of the sensory modality of the task (visual or auditory). Thus, the slowing appeared limited to the motor side of the reflex arc.

In a different experiment (Bauer 1994c) employing the same subjects, reaction time, performance errors, and EEG activity were examined during a vigilance task 30 minutes in duration. The justification for evaluating vigilance derived from clinical observations of disordered arousal (e.g.,the postcocaine use "crash," alcohol withdrawal insomnia)

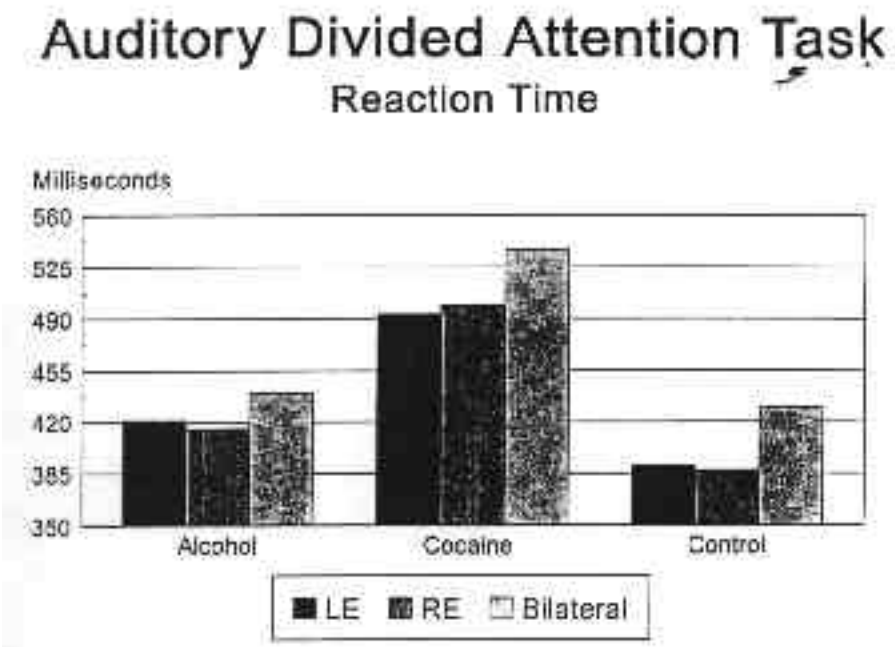

FIGURE 2b. *Reaction time (in ms) during the auditory divided attention task plotted as a function of subject group and stimulus location (ear). The session effect was not significant. Differences greater than 22 ms are significant.*

and more systematic demonstrations (Gawin and Kleber 1986; Gillin et al. 1990) of disrupted sleep among patients in the early phases of cocaine or alcohol withdrawal. Therefore, it was logically of interest to determine if these disruptions were reflected in patients' daytime alertness and if altered alertness persisted into the later phases of the withdrawal and recovery period.

The vigilance task was a conventional signal detection paradigm (Davies and Parasuraman 1982) in which subjects listened to 100 ms duration of pure tones occurring at a rate of 30 per minute. On one-third of the trials, a 1,000 Hz tone was substituted for the 500 Hz standard tone. Subjects were instructed to press a response key upon detecting the rare 1,000 Hz tone and to ignore the other. EEG activity and performance were monitored continuously and summarized separately for each 10-minute period during the 30-minute vigil.

As expected, omission errors increased with time on task, as did reaction time and EEG alpha (7 to 13 Hz) power. However, there were no differences among the cocaine-dependent, alcohol-dependent, and control groups with respect to the magnitude or rate of these time-related changes. At the risk of interpreting the null hypothesis, these null findings suggest that recovering cocaine- or alcohol-dependent subjects are no more vulner-able to the effects of mental fatigue, at least in the present task setting, than are controls. Indeed, available data indicate that acute doses of cocaine and alcohol also have little (Fischman and Schuster 1980) or no effect (Erwin et al. 1978) on time-related reductions in vigilance. Rather, acute cocaine and alcohol primarily affect the average level of performance.

The only variable to differentiate groups was reaction time averaged across the 30-minute vigil. As in the divided attention task (see above), the reaction times of the cocaine-dependent patients were 50 to 75 ms slower than the other groups. The magnitude of the reaction time slowing, also as above, did not change as a function of duration of abstinence (figure 3).

ERP Correlates of Motor Function. In a new study in which subjects are tested after 3 and 9 months of verified abstinence, the author is examining P300 ERPs during various information-processing tasks. In one such task (after Knight 1984), subjects hear a 5-minute train of discrete 50-ms duration tones (presentation rate 40 per minute). The tones are mostly uniform in pitch. However, in 10 percent of the trials, the filtered and shaped sound of a dog bark is substituted for the tone. The subject is instructed to ignore this change. In another 10 percent of the trials, a higher pitched tone is substituted for the standard tone. The subject is instructed to press a key when this event occurs.

Thus, there are two types of rare events during the task: a rare nontarget (the dog bark) and a rare target (the higher pitched tone). Figure 4 shows averaged ERPs for the two patient groups for these two events. Prelim-inary analyses of the P300 evoked by the rare nontarget revealed it to be similar in the cocaine-dependent and alcohol-dependent groups and only slightly reduced relative to the normal control group (not shown). The P300 evoked by this rare nontarget event consisted of only one wave with a peak latency of approximately 300 ms.

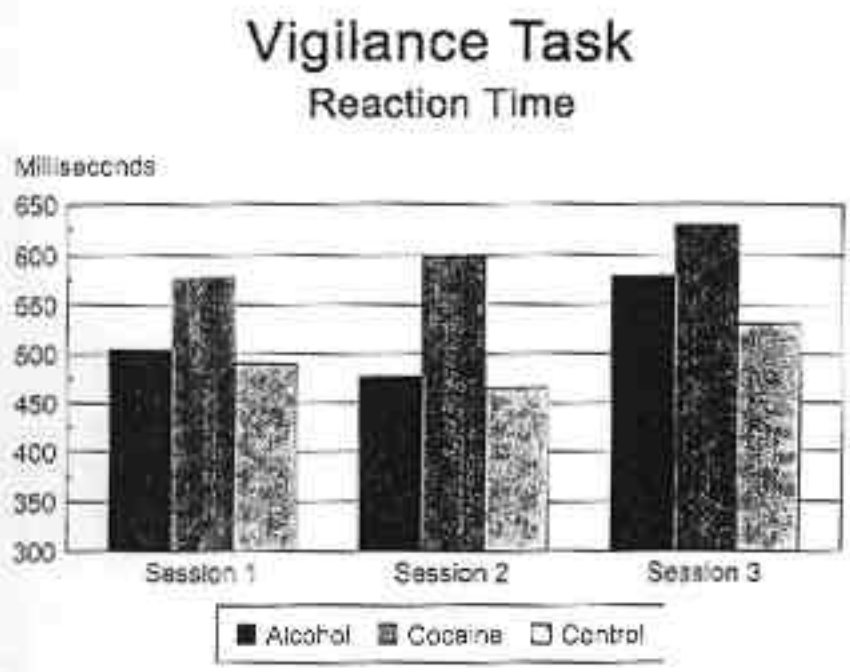

FIGURE 3. *Reaction time (in ms) during the auditory vigilance task. Differences greater than 43 ms are significant.*

In contrast, the rare target event evoked a complex of two positive waves, hereafter called P300a and P300b, among both alcohol-dependent patients and normal controls. But, among the cocaine-dependent patients, the P300b wave was significantly reduced in amplitude. In other words, when a motor response was required, cocaine abusers showed a reduced P300. This decrement was present after 3 months of verified abstinence. Later phases of the study will examine whether the P300 decrement is detectable after 9 months of cocaine abstinence.

One can plot the scalp topography of the difference between the alcohol-dependent and cocaine-dependent patient groups in the later P300 component. Topographic maps of ERPs are based on several assumptions that may not always hold (Burgess and Gruzelier 1993; Jayakar et al. 1991). Nonetheless, as figure 5 shows, the P300b reduction in abstinent cocaine abusers was greatest at frontal electrode sites. This finding is consistent with the frontal locus of glucose metabolism

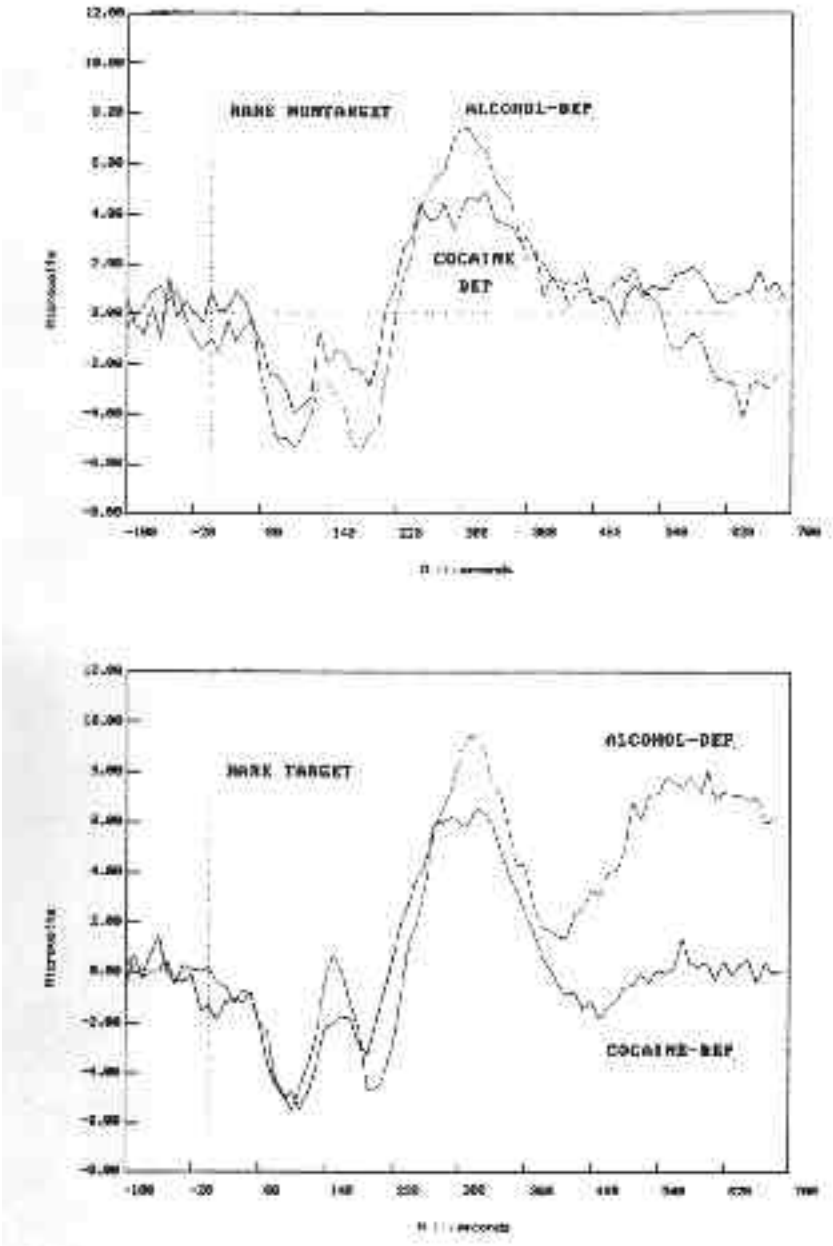

FIGURE 4. *Averaged event-related potentials elicited by rare nontarget (above) and rare target (below) stimuli.*

abnormalities detected among 3- to 4-month abstinent cocaine abusers by Volkow and colleagues (1992).

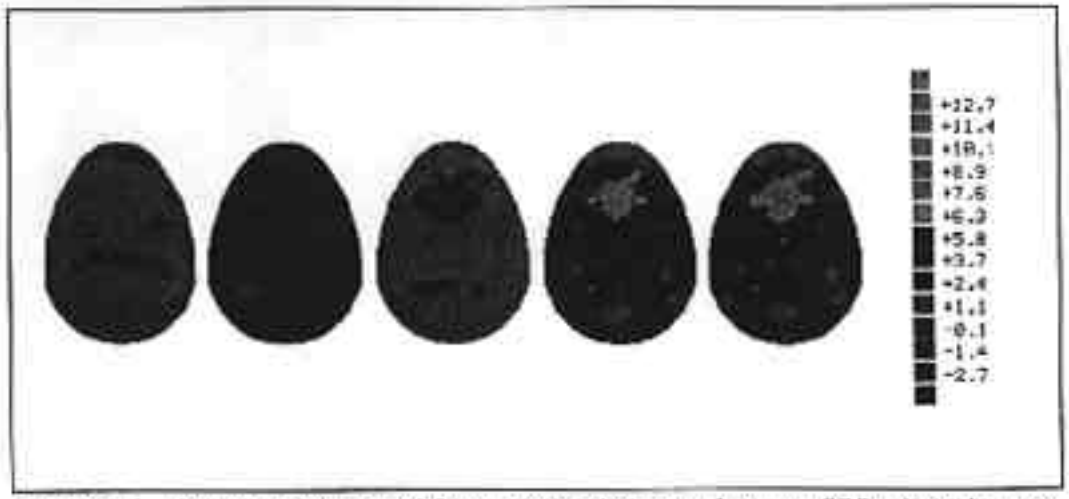

FIGURE 5. *Topographic map of the amplitude difference between ERPs elicited among alcohol-dependent and cocaine-dependent patients in response to rare target stimuli. Note that the maximum difference between the patient groups occurs at frontal electrode sites in a latency range that encompasses the P300b.*

The demonstration of P300 amplitude decrements among abstinent cocaine-dependent patients is not unprecedented in the literature (Amass et al. 1990; Branchey et al. 1993; Herning and colleagues, this volume). However, most previous demonstrations of P300 decrements have used the conventional two-stimulus P300 "oddball" task, which confounds P300a and P300b components as well as the effects of stimulus novelty and motor responding. Another distinguishing feature of the present P300 study (Branchey et al. 1993) was the attempt to control for the effects of ASPD and a family history of alcoholism (Bauer et al. 1994; Polich et al. 1994). Since these two premorbid variables were held constant in the present comparison of cocaine- versus alcohol-dependent patients and the P300 decrement was specific to the cocaine-dependent group, one can more convincingly attribute the decrement to the effects of chronic cocaine dependence. It is important to recognize that the same conclusion cannot be drawn regarding alcohol dependence, where P300 decrements are more reliably related to premorbid variables (Pfefferbaum et al. 1991). Thus, at least with respect to P300, cocaine appears more neurotoxic than alcohol.

Eye Movements. As the last measure of motor system functioning among recovering cocaine-dependent patients, eye movements were recorded (Bauer 1993b). Eye movement recording is an especially powerful technique for studying brain function. Eye movement control can be disrupted by a wide range of family history (Holzman et al. 1984), neurological (Leigh and Zee 1991), and drug-use variables. The avail-able armamentarium of quantitative eye movement measures is also wide ranging, from assessments of resting nystagmus to reflexive movements elicited by caloric, rotoric, or optokinetic challenges.

For a variety of reasons, both smooth pursuit and saccadic eye movements were examined. The scientific justification was provided by previous studies of acute drug effects in normal controls. In such studies, alcohol has been shown to interfere with both smooth pursuit (Levy et al. 1981) and saccadic (Baloh et al. 1979; Fuster et al. 1985) tracking. Ampheta-mine has the opposite effect (Filip et al. 1978; Tedeschi et al. 1983).

Only two studies have examined eye movements among patients chroni-cally exposed to cocaine. Demer and colleagues (1989) examined a variety of eye movement parameters among cocaine-abusing patients and normal controls. No group differences were found, except for a slight reduction in the gain of the vestibulo-ocular

reflex among the cocaine abusers. Unfortu-nately, only nine patients were tested, and four of the nine patients were receiving antidepressant or antipsychotic medications. The likelihood of detecting eye movement abnormalities was accordingly low.

Rosse and colleagues (1992) contrasted the smooth pursuit eye movements of crack cocaine abusers, schizophrenic patients, and a normal control group. A reduction in smooth pursuit gain and an increase in large ampli-tude saccadic intrusions were detected among both schizophrenic and cocaine-abusing patients. Due to the brevity of the report, it is unclear whether the difference between patients and controls could be explained by some other variable such as a group difference in the prevalence of familial schizophrenia (Holzman et al. 1984). To eliminate this potential confound from the present subject sample, it was important to exclude from the analy-sis any individual with a parent or sibling affected with Axis I schizophrenia, schizophrenia-like disorders, or Axis II Cluster A personality disorders as described in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed. rev. (DSM-III-R) (American Psychiatric Association 1987).

The tasks used to elicit smooth pursuit and saccadic eye movements have been described previously (Bauer 1993b). In brief, the smooth pursuit eye movement task required subjects to visually track a pendulum oscil-lating at 0.4 Hz. Eye movements were recorded electro-oculographically and analyzed in the frequency domain to yield Holzman and colleagues' (1984) log (signal to noise) (LN(S/N)) statistic.

The saccadic eye movement task involved visual tracking of the apparent motion of light emitting diodes briefly illuminated at one of four eccen-tricities (20 or 35 degrees left or right of center) determined randomly. To increase the number of saccadic eye movements, subjects were required to perform a visual discrimination at these locations. Only the initial (i.e., elicited) saccade was measured.

Analyses revealed different types of eye movement dysfunction in the two patient groups. During the step-tracking task, alcohol-dependent patients exhibited longer saccadic reaction times than the other groups. This delay in the ability to establish fixation on a new visual target endured throughout the first 94 to 100 days of abstinence. It may account for the alcohol-dependent patients' longer-than-normal visual search times (Bertera and Parsons 1978) during

neuropsychological tests. Whether it also contributes to reading and comprehension problems is an open question.

In contrast, cocaine-dependent patients exhibited a persistent change in smooth pursuit eye tracking. Somewhat surprisingly, however, the smooth pursuit tracking accuracy of these patients was found to be superior to that of alcohol-dependent patients and normal controls, even after 3 months of abstinence. Since acute amphetamine administration has been shown to improve eye-tracking accuracy (Filip et al. 1978), the supranormal tracking of abstinent cocaine abusers could represent a residual cocaine-like effect. This stands in contrast to cocaine-opposite effects such as their slower-than-normal reaction times (see above). Thus, cocaine appears capable of inducing hyper- or hypoexcitability in different portions of the motor system.

EEG Sequelae

Cocaine's apparent ability to induce simultaneous, directionally opposite changes in neurononal excitability in the motor system also extends into the sensory systems. Figure 6 shows the magnitude of an EEG response to a light flickered at the subject's dominant resting alpha frequency, between 7 and 13 Hz. Photic driving is an old clinical technique still used in clinical EEG assessments. A variety of patient groups, including schizophrenics (Jin et al. 1990) and Alzheimer's disease (Politoff et al. 1990) patients, have been shown to exhibit reduced driving responses; cocaine abusers are no exception. As the intensity of flicker is increased, only normal controls show an increase in response amplitude.

Figure 6 contrasts with the results of another photic driving experiment (figure 7) in which the flicker is produced by means of a sine wave, not a square wave. In many sensory systems, these two types of stimulation are encoded differently and activate different neuronal circuits. In the visual system, for example, high frequency transient events (square waves) and steady states (sine waves) are differentiated at levels as low as retinal ganglion cells and follow different pathways. Thus, as can be seen in the figure, increasing the intensity (modulation depth) of sine wave flicker elicits an exaggerated response in cocaine-dependent patients, while square wave flicker does the opposite (figure 6). These exaggerated and inhibited responses persist even after 3 months of abstinence.

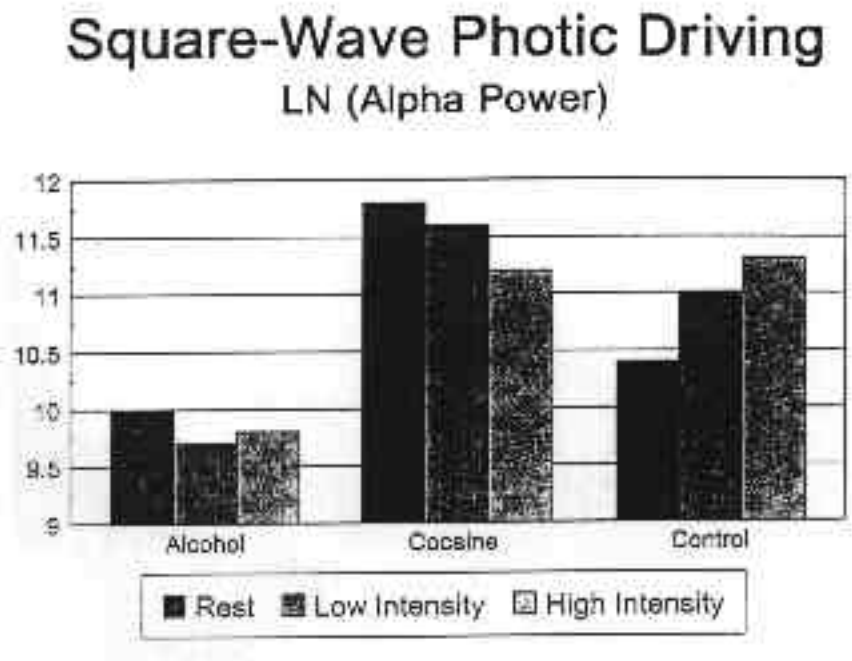

FIGURE 6. *EEG alpha power in the three subject groups as a function of the intensity of a square wave modulated photic stimulus. Differences greater than 0.6 units are significant. The session effect was not significant. The data are accordingly collapsed across the levels of that variable.*

SUMMARY

In conclusion, there appears to be strong evidence from these studies supporting the existence of a postcocaine abuse syndrome. The general hypothesis stated that cocaine-dependent patients would exhibit impaired performance on tests of motor system functioning. It was further hypothe-sized that these impairments would be more severe and persistent than impairments in other areas. These hypotheses were confirmed. Cocaine-dependent patients were found to exhibit a statistically significant resting hand tremor, which did not remit despite 3 months of verified abstinence. In contrast, alcohol-dependent patients exhibited an enhanced action tremor and enhanced body sway that remitted after 1week. Cocaine-dependent, but not alcohol-dependent, patients also exhibited slower reaction times than controls during a protracted vigilance task and during simpler tasks requiring visual or auditory divided attention. The reaction time slowing

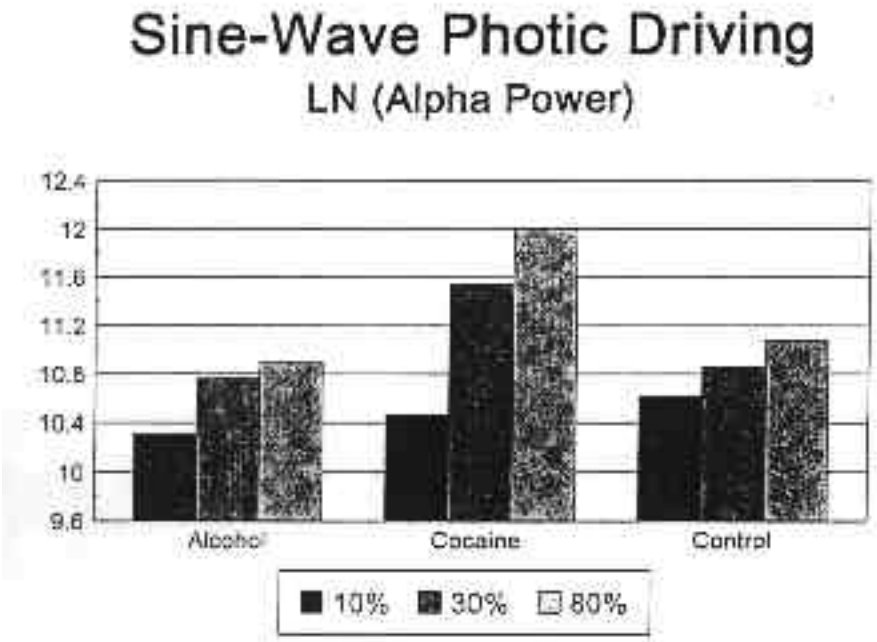

FIGURE 7. *EEG alpha power in the three subject groups as a function of the intensity of a sine wave modulated photic stimulus. Differences greater than 0.9 units are significant. The session effect was not significant. The data are accordingly collapsed across the levels of that variable.*

was substantial (approximately 50 to 75 ms), task independent, and, like resting tremor, did not remit after 3 months of abstinence.

The demonstration of smooth pursuit eye movement irregularities in the cocaine-dependent group further reinforced the motor system hypothesis. During visual tracking of an oscillating pendulum, the tracking accuracy of cocaine-dependent patients was superior to that of controls at all three time points. Studies that have administered acute amphetamine to nor-mal, nondrug-dependent individuals have reported a similar finding. Collectively, these findings suggest that chronic cocaine use may induce a hyperexcitability of the smooth pursuit eye movement control system, which persists into abstinence.

Evidence for EEG abnormalities among recovering cocaine-dependent patients was provided by a variety of experiments. In a new and ongoing experiment, cocaine-dependent patients exhibit

reduced P300b ERPs to rare stimuli, which they must acknowledge with a motor response. Evidence for a nonmotor CNS dysfunction was provided by examining EEG responses to a simple flickering light. However, the nature of the dysfunction was complex. EEG responses to square wave modulated light revealed diminished reactivity among both cocaine-dependent and alcohol-dependent patients at all three time points. In contrast, EEG responses to sine wave modulated light revealed enhanced reactivity among the cocaine-dependent patients only. The coexistence of diminished or enhanced EEG reactivity and diminished or enhanced motor system functioning implies that cocaine dependence can simulta-neously depress and enhance different aspects of brain function in the same individual. The diversity of cocaine's EEG and psychomotor effects may have an analog in demonstrations of the simultaneous development of sensitization and tolerance among animals chronically exposed to cocaine.

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