Cognitive-Neuromotor Assessment of Substance Abuse: Focus on Issues Related to Cocaine Abuse Treatment

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INTRODUCTION

Choice of the procedures and types of cognitive-neuromotor testing used in assessment of cocaine abusers and their treatment is dependent on a clear definition of the purposes of testing and the characteristics of the individual tests. This chapter will first discuss published studies of testing in cocaine abusers and pharmacodynamic effects of stimulants and withdrawal. The types of tests available and their characteristics will be discussed in terms of the purpose of testing. The case will be made for the value of computerized cognitive-neuromotor testing when repeated assessment is needed in a busy clinical setting.

Questions to be asked regarding the assessment of cognitive-neuromotor testing in substance abuse are: (1) who is to be tested, (2) at what point in the abuse cycle are the tests to be conducted, (3) what pattern and duration of drug abuse is to be tested, and (4) what is the purpose of testing (e.g., for drug abuser evaluation? for change with therapeutic efforts?). Secondary questions include what is the most appropriate test for assessment and whether there is a means of assessing test sensitivity and stability and establishing external validation. Since this monograph is focused on treatment of cocaine abuse, the authors will primarily explore the effects and questions related to stimulant abuse; examples of the effects other types of drugs of abuse have on testing performance will be presented to highlight differences.

REPORTED COGNITIVE-NEUROMOTOR CHANGES IN CHRONIC COCAINE ABUSERS

In assessing cognitive-neuromotor testing (CNT) deficits resulting from chronic stimulant abuse, one must differentiate between effects occurring during the initial 1 to 2 weeks of withdrawal and protracted

deficits occurring following extended abstinence. Since the turn of the century, clinicians have observed diminished intellectual ability in chronic cocaine abusers. More recently, several groups have assessed chronic cocaine abusers during various times after withdrawal with standardized cognitive-neuromotor testing. O'Malley and Gawin (1990) assessed 25 chronic cocaine abusers who had accrued an average of 135 days of abstinence and whose previous use, over a 4-year period, had been approximately 11 g per month. Compared to matched controls, the cocaine abusers performed worse on cognitive motor skills and simple motor skills, as well as in their composite scores. Deficits were reported in spatial relations, grooved pegboard, grip strength, and retaining nonverbal material. In the same report, a greater impairment was observed during the early abstinence period, suggesting that there was a slight improvement with prolonged abstinence. More recently, Berry and colleagues (1993), assessing over a much briefer abstinence period (i.e., at 72 hours and again at 14 to 18 days) found that, in the first test session, cocaine abusers scored significantly worse than the control group on various measures including visuospatial construction (the Rey-Osterrieth figure), Wechsler Adult Intelligence Scale (WAIS) block design, verbal memory, and concentration. Furthermore, when retested 2 weeks later, the cocaine abusers demonstrated less improvement than controls on measures of psychomotor speed and verbal memory. This finding suggests that selective cognitive deficits are identifiable at least 2 weeks beyond withdrawal. Ardila and colleagues (1991) went further to demonstrate that the duration of previous chronic cocaine abuse was correlated with performance, particularly on the digits subtest of the WAIS, memory quotient, and visual memory of the Rey-Osterrieth figure. In contrast, Manschreck and associates (1990) have reported that, in a group of 33 Bahamian cocaine abusers, most of the mental status features such as intelligence, memory, somatic processing, and motor functions did not differ from controls. The only demonstrable impairment was a decrease in short-term recall of auditory material. In contrast to a number of "paper and pencil" studies cited above, the only computerized neuropsychological testing was reported by Herning and colleagues (1990). They found that both auditory and visual rare event monitoring tasks were not different between patients and control; however, the Sternberg Memory Task appeared to worsen over the course of abstinence. An important caveat to the neuropsychological differences cited above is to what extent there is a corresponding difference in the number of affective disorders and/or attentional deficit disorders; those disorders have been reported, to exceed one-third of the patients who have been receiving treatment for cocaine

abuse (see Rounsaville et al. 1991). Differences in the incidence of affective and/or attentional status certainly could complicate interpretation of cognitive-neuromotor performance results. Moreover, these underlying conditions may require treatment before improvement in CNT performance is observed.

In addition to affective attentional disorders, other medical history of the patient needs to be considered. For example, a history of seizures, strokes, hypertensive crisis, etc., also needs assessment for possible contribution to impairment (Kaye and Fainstat 1987; Levine et al. 1987; Rowbotham 1988; Stein and Ellinwood 1990; Tuchman et al. 1987). Furthermore, the fact that nonspecific cognitive deficits are found in many types of chronic drug abusers, whether due to drug effects, infections, or other medical complications including chronic malnutrition (Bruhn et al. 1981; Carlin 1986; Parsons and Farr 1981), needs consideration. A final caveat is that clinicians report loss of mental energy, incentive, and motivation in the intermediate withdrawal period (see Gawin and Ellinwood 1988 for review), which is difficult to factor out of neuropsychological testing.

Acute Pharmacodynamic Effects of Cocaine and Withdrawal

Most assessments of the direct pharmacodynamic effects of stimulants on cognitive-neuromotor skills have been performed with amphetamine or methylphenidate at moderate doses. Stimulants improve WAIS performance including spatial relations, form constancy, visual scanning, visual memory, and short-term recall for learned paired associates (Hurst et al. 1969; Mohs et al. 1978; Rapaport et al. 1978; Weingartner et al. 1980). However, stimulant-induced improvement in performance is specific for moderate doses. Cocaine in moderate doses has also been found to improve vigilance and motor functions in fatigued individuals (Fischman and Schuster 1980). At high doses, stimulants are not effective, especially with complex tasks (MacWorth 1950; Smith and Beecher 1959). High-dose stimulant use can lead to either hyperactive distractibility or highly stereotyped focused attention to details. Although these are opposite effects, both can preclude flexibility in directed attention needed in complex tasks. High-dose use is also associated with more marked withdrawal changes. In addition, because cocaine has a short-effect half-life, an abuser using late into the night or to a point of stimulated exhaustion is also at risk of precipitous withdrawal impairment as the excitatory effects of the cocaine suddenly wear off. Rapid withdrawal may be especially important to vehicle traffic accidents late at night. Prevalence of recent cocaine use in fatal

accident drivers (age 16 through 45) was above 15 percent between 1984 and 1987 in New York City (Marzuk et al. 1990). Thirteen percent of drivers stopped for reckless driving in Memphis in 1993 had urines positive for cocaine (Brookoff et al. 1994). A model representation of the relationship of stimulant dosing level as well as withdrawal on performance is shown in figure 1, indicating that both high dosing and withdrawal effects impair performance and judgment. The "crash" withdrawal performance is also further deteriorated by use of alcohol and sedatives to come down from the high (Gawin and Ellinwood 1988).

COGNITIVE-NEUROMOTOR TESTING FOR THERAPEUTIC DRUG TRIALS

Germane to the theme of this monograph is the consideration that knowledge of stimulant-associated residual impairment is important to the identification and effective treatment in chronic cocaine abusers. In addition, therapeutic drug effects need consideration from two view-points: (1) the therapeutic drug may either improve or impair perfor-mance, and (2) the interactive effects of the therapeutic drug with subsequent cocaine use may impair performance. Both need consider-ation for acute and chronic administration of the therapeutic drug.

For Phase I and Phase II studies, initial pharmacological assessment of new central nervous system (CNS) active drugs testing is needed to ensure that it either induces no impairment or that the effect concentration (EC) curve or the 50 percent impairment concentration (EC_{50}) is well above the EC_{50} for the therapeutic effect. To accomplish this type of testing the cognitive-neuromotor tests used need to have: (1) a reasonable linear scale of impairment, and (2) the capacity to establish a stable baseline across drug dosing sessions. Tests that assess attentional capacities, psychomotor speed, and coordination most often fit these criteria whereas verbal learning performance does not. The ability to establish a baseline plateau is also important in assessment of actual cocaine abusers undergoing treatment over time, where they can act as their own controls. More difficult to assess is the interactive impairment or even toxic consideration of the treatment drug with subsequent abuse of cocaine. Examples might be catechol-enhancing drugs or drugs with local anesthetic properties (e.g., the tricyclic antidepressants that could potentiate cocaine's potential for toxicity).

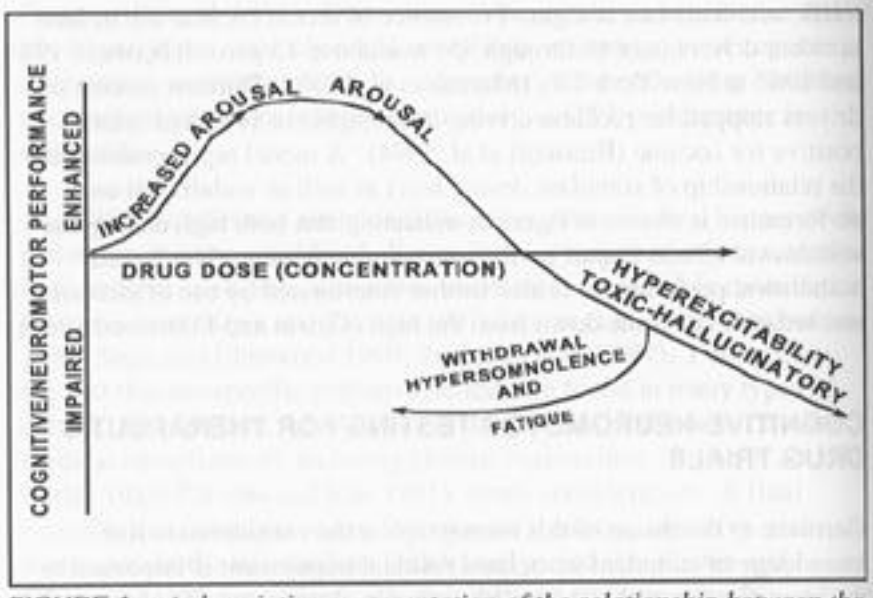

FIGURE 1. *A descriptive representation of the relationship between the drug concentration and the behavioral effects of stimulants. An initial improvement in performance at lower doses is followed by performance impairment at higher doses and during drug withdrawal.*

SOURCE: Adapted from Ellinwood and Nikaido (1987*b*).

MERITS OF COMPUTERIZED COGNITIVE-NEUROMOTOR TESTING

In assessment of treatment over time, the neuropharmacologist's task is not unlike that of the industrial environmental toxicologist, i.e., to detect modest changes under conditions where contributions to variance have multiple sources. Thus, using the individual as his or her own control and repeated testing over the period of extended cocaine abstinence (i.e., longitudinal assessment) is important in establishing reliable indices of therapeutic efficacy. A single impaired score flanked by stable baseline scores is likely to indicate a temporary change (e.g., potential recidivism). Usually testing over time involves the use of a battery of tests administered at intervals between testing with one or two reliable performance tasks given more frequently as indicators of changes in the clinical picture (e.g., recidivism). Computer-driven performance batteries, with their

capacity to maintain a running profile of the individual's scores over time, certainly facilitate this process and reduce personnel costs dramatically. In addition, computerized batteries of tasks can be presented in a consistent objective manner and can provide ready databases for multisubject and multicenter studies.

Additional merits of computerized batteries need mention. Most paper-and-pencil tests provide summary scores. For example, the powerful component of the WAIS test: digit symbol substitution (DSS), is typically scored as the number of correct answers in a given time period. The version used in the computerized CNT requires the subject to key in the correct number on a telephone keypad as one of the symbols is presented at the bottom of a digital screen; at the screen top the corresponding number-to-symbol code pairs are displayed. Importantly, with computers, the same type of test can provide the reaction time and its profile over the testing period (i.e., learning curve): the number of correct answers, and the composite power score, as well as fluctuations in performance indicating attentional variance. Since DSS is one of the tests with high "*G*," i.e., tests requiring multiple capacities, these can be fractionated into components. Although DSS provides a powerful screening tool, with additional parallel testing a more definitive breakdown of component capacities is possible. For example, the psychomotor speed component can be obtained by reducing the task to keying in a number that is presented on the screen. When this simple keypad task reaction time is subtracted from the DSS reaction time, an estimate of the central processing speed of the DSS can be obtained. Other versions of the DSS test for posttest memory retrieval of the code by erasing the code from the screen and asking the subject to recall the code pairs from memory.

With appropriate simple transducers and manipulandi, computer testing can assess many neuromotor and sensory components in addition to cognitive function. Extremely sensitive testing of postural stability, eye tracking and saccades, dynamic visual acuity, and hand tremor are some of the tasks available in the task battery in the authors' CNT laboratories. Attentional components are easily tested, including sustained, selective, and divided attention. Other cognitive tasks sensitive to drug effects and easily performed by computers include: Trails A&B various complex or choice reaction time tasks as well as pattern recognition, hidden figure, and memory tests (Ellinwood and Nikaido 1987*a*). Detailed descriptions of many computerized testing systems can be found in the review by Kane and Kay (1992).

In summary, testing with computers is being increasingly used clinically because repeated testing at fairly frequent intervals is a sensitive means of comparing treatment and underlying illness interactions. The specific strengths of computerized procedures include: (1) standardized presentation of stimuli and recording of responses; (2) use of everyday manipulandi (e.g., telephone keypad, car steering wheel), which are familiar to subjects; (3) efficient, accurate, and rapid collection of detailed data components by computer; (4) collection of more precise detailed data or sensory visuomotor and neuromotor function than is usually assessed by qualitative neurological exam; (5) immediate onsite analysis of data and availability to the clinician; and (6) the ease of compiling and analyzing data across subjects and centers.

EFFORTS TOWARD EXTERNAL VALIDATION OF TESTING

External validation in neuropsychological testing has always presented problems: do tests predict real-world situations (e.g., activities of daily life)? For example, IQ tests in fact have predictiveness for academic performance and job success. Unfortunately, academic and job success data are not readily available from the substance abuser on the "street," whose academic career may have been truncated in early adolescence. In fact, poor school attendance by drug abusers may preclude use of tests such as verbal learning, which are education-level sensitive. Therefore the discussions of the relation of testing to the real world will rely on the driving accident yardstick since even drug abusers are motivated to maintain a driver's license.

Well-documented alcohol studies provide a transitional framework to relate other drugs of abuse induced impairment to: (1) automobile accidents, and indeed (2) the legal limits for blood alcohol concentrations (BACs) while driving are defined. The alcohol accident rate is based on a number of different studies of blood alcohol levels in drivers of both fatal accidents or accidents in general, compared with BACs of drivers in the vicinity who were not involved in the accident (Hurst 1973). By far, the largest study ever accomplished was that of the Grand Rapids, Michigan, analysis where approximately 6,000 blood alcohol determinations from drivers involved in automobile crashes were compared with traffic scene-matched controls. Whereas these data have been analyzed and reanalyzed for potential biases (Hurst 1973), the curves (see figure

2A) indicate that the relative probability of alcohol-related crash is minimal below 0.04 mg/mL BAC, but rapidly increases with higher blood level concentrations. In figure 2B, the laboratory testing with the sensitive digit substitution task shows similar impairment as a function of BAC (i.e., there is a linear relationship between BAC and impairment similar to that of the relative probability of the crash data). Illustrated in figure 2B from a study of eight young, eight middle-aged, and eight elderly subjects (Tupler et al. 1995) are the average change in performance score related to alcohol concentrations. The slope of the curve (figure 2B) is not only very similar to that of figure 2A, but intersects the placebo range at 0.04 BAC, the point in figure 2A in which accident rates begin to rise. At the top of the impairment scale it can be noted that the elderly sample baseline (from which the changed scores are calculated) is very much higher than the alcohol-dosed impairment effects for the young subjects. This indicates the absolute necessity of age-matched controls in any study. Thus, laboratory testing with the "gold standard," alcohol, indicates that the shape of the concentration effect (impairment) curve is similar to what would be predicted from accident rates. Similar results were obtained from several other tasks.

As discussed earlier, the published studies on abused stimulants are sparse. Moderate doses of stimulants actually improve most cognitive- neuromotor performance. Only at the higher stimulant doses or during withdrawal from the higher doses is the marked impairment reported to occur. Obviously, experimental studies with higher doses and chronic stimulant administration present hazards that laboratory researchers cannot risk. Thus, results from safer drugs (e.g., sedative/anxiolytic) studies can serve as examples of potential drugs of abuse to compare with alcohol for relative impairment.

There is extensive experimental literature on benzodiazepine impairment detailing both dose response effects as well as plasma concentration profiles (Gupta and Ellinwood 1995). Figure 3A and 3B compare the effects of the popular benzodiazepines, triazolam and alprazolam, in young and elderly subjects (Nikaido et al. 1990) with alcohol (Tupler et al. 1995). As can be noted, the concentration effect curves for alcohol are marked (see arrow, figure 3) by significant impairment at the legal intoxication concentrations of 0.08 mg/mL and above in both young and elderly subjects. The concentration effect curves for triazolam and alprazolam illustrate that in single doses used clinically (the lower dose for both drugs), there is an impairment equal to or greater than that produced by alcohol at the legal intoxication limit. The other concentration

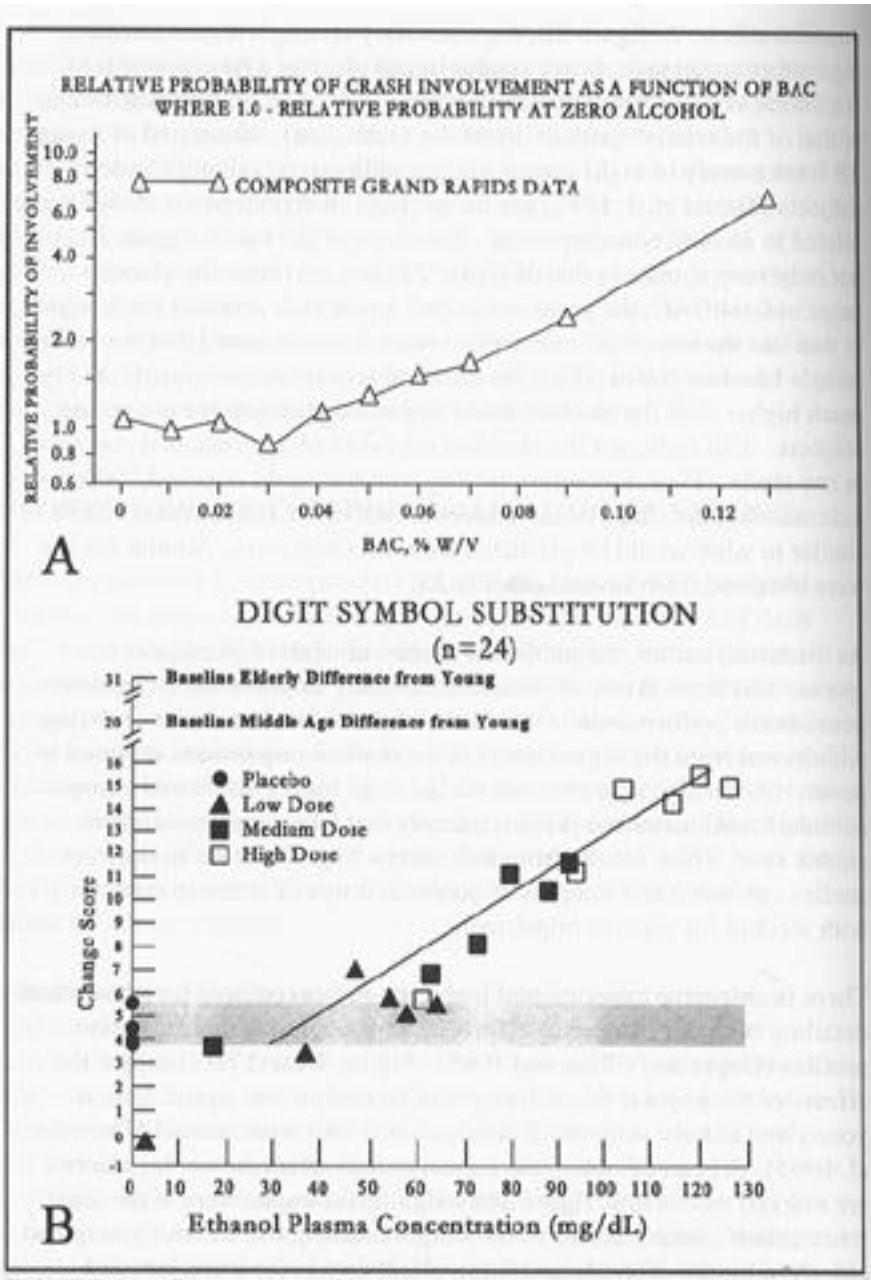

FIGURE 2. *Comparison of DSS impairment to accident probability as a function of BAC.*

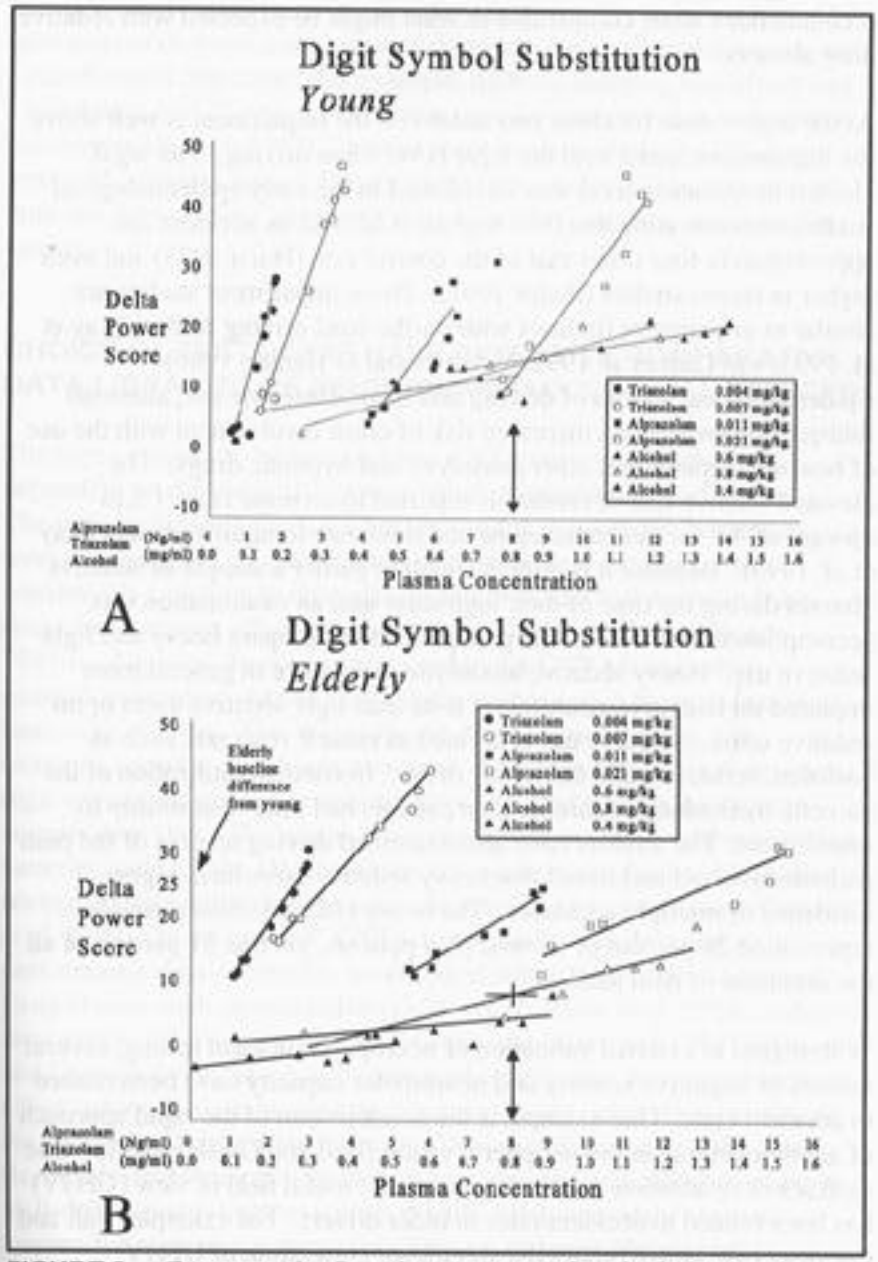

FIGURE 3. *Concentration/impairment curves for alcohol, triazolam, and alprazolam in young and elderly.*

effect curve for alprazolam and triazolam is at twice the highest recommended dose, comparable to what might be expected with sedative drug abusers.

At the higher dose for these two sedatives, the impairment is well above the impairment found with the legal BAC when driving. The legal alcohol intoxication level was established in the early epidemiological studies demonstrating that 0.10 mg/mL BAC had an accident rate approximately four times that of the control rate (Hurst 1973) and even higher in recent studies (Zador 1991). These impairment studies are similar to impairment findings with on-the-road driving studies (Ray et al. 1993; van Laar et al. 1992; Volkerts and O'Hanlon 1986). Epidemiological studies of driving and benzodiazepine use, although limited, demonstrate an increased risk of crash involvement with the use of benzodiazepines and other anxiolytic and hypnotic drugs. The elevated relative risk of crashes is reported to increase from 1.5 to upward of 4.9 for benzodiazepine and moderate tranquilizer users (Ray et al. 1993). Because it is quite difficult to garner a sample of sedative abusers during the time of their high-dose use, an examination was accomplished with 68 chronic pain patients to compare heavy and light sedative use. Heavy sedative/anxiolytic users were in general more impaired on cognitive-neuromotor tests than light sedative users or no sedative users. Sedative use is defined as muscle relaxants such as baclofen, sedatives, and anxiolytic drugs. In contrast, utilization of the narcotic methadone in chronic pain patients had little relationship to impairment. The authors have also examined driving records of the pain patients involved and found that heavy sedative users have higher incidence of multiple accidents. The heavy sedative abuser sample represented 28 percent of chronic pain patients, yet had 51 percent of all the accidents of pain patients.

With regard to external validation of neuropsychological testing, several indices of cognitive sensory and neuromotor capacity have been related to accident rates. One example is the nondetection of the rapid approach of another vehicle in the peripheral vision (Ball and Owsley 1991). One such selective attention measure known as the useful field of view (UFOV) has been related to accident rates in older drivers. For example, Ball and Owsley (1991) have reported a significant correlation of UFOV impairment with previously reported accidents, especially if the accidents were at an intersection.

Another laboratory measure associated with accidents is selective attention, which requires the ability to both focus as well as shift

attention on stimulus locations or salient features. It can be evaluated by such tests as dichotic listening, visual search (e.g., trail-making test), and a cue-directed detection. For example, dichotic listening task errors had a correlation of 0.37 with accident rates over a 1-year period in professional bus drivers (Weiner 1984). A major problem of correlating laboratory tests with accident rates is that accident rates are low-frequency events; thus, the data-relating laboratory tests to driving accident rates remains sparse.

CHOICE OF TESTS THAT HAVE EXTENSIVE COMPARATIVE DATA LIBRARIES OF NEUROPHARMACOLOGICAL EFFECTS

The types of tasks to be included in a CNT battery obviously are dependent on the particular experimental questions being addressed. The tests included in the CNT battery used at the authors' laboratory were derived from an examination of the literature for tasks most consistently sensitive to drug effects and ones that had the most linear drug concentration effect relationships (see Ellinwood and Nikaido 1987*a*). Actually, the type of test used in the CNT lab and other neuropharmacology labs is very similar to those used by environmental neurotoxicologists. The World Health Organization battery, for example, includes simple reaction time, digit span, digit visual retention, digit symbol, an aiming or coordination task, and a Santa Ana motor coordination task. The reason for using these tests from well-recognized batteries includes the fact that there is a much larger database including normative data with which to relate findings in any given study (Cassitto et al. 1989). In the authors' CNT lab, normative and drug-induced performance data on literally hundreds of subjects have been acquired. Drug classes such as anticholinergic drugs (Nikaido et al. 1990), sedative anxiolytics (Ellinwood et al. 1990; Gupta and Ellinwood 1995; Johnson and Chernik 1982), alcohol (Tupler et al. 1995), etc., have concentration effect curves that can be generated across studies, increasing the size of the background comparison groups. Thus the EC_{50}s for new drugs in their early developmental phase can be compared with libraries of other well-documented drugs in young, middle-aged, or elderly men and women for comparison purposes. The use of larger libraries of background data helps considerably when analyzing and interpreting data from a given sample of subjects since age, sex, and genetics all contribute to both the pharmacokinetic and pharmacodynamic variance.

CONCLUSION

In conclusion, cognitive-neuromotor testing can be utilized in several areas of assessment in cocaine abusers, including: (1) evaluation of residual withdrawal effects of chronic abuse, (2) timecourse of these effects, (3) testing of the acute effects of cocaine and subsequent withdrawal, (4) evaluation of novel early-phase therapeutic drugs for treatment of stimulant abuse, and (5) evaluation of baseline withdrawal impairment profiles of cocaine abusers for the relation to treatment outcome. The choice of the specific cognitive-neuromotor tests to be used in assessments should be made after consideration of pharmacological sensitivity, linearity to dose or plasma concentration, and capacity to establish a stable baseline performance. External validation specific to a drug abuser population will be difficult. In contrast to paper-and-pencil testing, computerized testing allows for the needed reliability and ease of testing in a busy treatment setting as well as facilitating data collection across individuals and treatment sites. Several computerized tasks have current data libraries on drug effects that would provide background information for new studies.

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