Individual Differences in the Biobehavioral Etiology of Drug Abuse

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Introduction: Individual Differences in the Biobehavioral Etiology of Drug Abuse

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STATEMENT OF THE PROBLEM

Research into substance abuse tends to be divided into two general conceptual approaches to understanding the etiology and nature of drug abuse. One major direction focuses on psychological/behavioral and social/environmental variables and their interactions leading to the abuse of psychoactive substances. The second approach focuses on the neurobiological mechanisms affecting, or affected by, the chemical action of drugs. Studies following the psychological/environmental approach are commonly descriptive, have a strong behavioral orientation, and typically attempt to understand individual behaviors or the behavior of specified subgroups. Individuals are compared and contrasted on such characteristics as psychopathology, self-esteem, and attitudes in order to explicate the nature and development of drug abuse in terms of the individual differences in these variables. In a variation of this approach, culturally, ethnically, and often demographically defined groups are assumed to be homogenous and studied in terms of their experiences within differing family environments, peer group interactions, cultural influences, and community settings. More sophisticated versions of this psychological/environmental approach embed the study of intra-individual characteristics within the context of extra-individual influences. For example, personality and attitudes are assessed in relation to peer group influences and cultural standards. The most comprehensive and successful studies have incorporated a longitudinal or developmental strategy that allows for more powerful causal inferences. These trajectory models are not only becoming more widely accepted, but also produce valuable data as the quality of the assessment and sophistication of the studies increase (see Glantz and Pickens 1992 for a comprehensive review).

These psychological/behavioral and social/environmental variables and the models that emerged from the studies have significantly contributed to the understanding of individual differences in resistance to, and risk for, drug involvement. They have not only illuminated the critical contributions of behavioral and environmental

factors; they also have demonstrated both the complexity and multifactorial nature of the drug-taking behavior. The research has also been valuable because significant studies are conducted with a more systemic and developmental approach. The focus of behavioral/environmental studies can be characterized as an attempt to address the questions: "What characteristics of people and their environments account for the enormous variability in individuals' involvement with drugs?" and "What is the behavioral nature of drug abuse?"

On the other hand, these studies have been incomplete. For example, it may be asserted that drug abusers with psychopathologies and/or low self-esteem are self-medicating their condition. Conclusions based on behavioral characteristics hint at, but virtually ignore, the biological aspects of drug use by failing to incorporate these factors into the person environment models.

Studies following the biological, and especially the neurobiological, approach include those that measure the heritability of drug involvement, identify drug receptor sites, determine the effects of psychoactive drugs on neurotransmitter systems, or attempt to identify the areas of the brain where activity is changed by an action of the drug. Major accomplish-ments in the study of neurobiological systems have facilitated under-standing of the neurochemical mechanisms underlying the action of drugs of abuse, provided insight to the mechanisms associated with drug taking, and contributed to the conceptualization of what determines a drug's abuse liability. Neurobiological studies have provided critical informa-tion about the short-term biological, and long-term medical, effects of drug abuse, laying the foundation for the development of chemical agents that may be effective in the treatment (and perhaps even the prevention) of drug addiction and craving.

While these studies have been taken to the molecular level, the neurobiological approach has given little consideration to individual differences; to the contributions of developmental, behavioral and environmental resistance and disposition factors; to the systemic interactions of these determinative factors; to the heterogeneity of drug abuse patterns and factors; and to the ways in which the neurochemical mechanisms associated with drug involvement translate into or manifest in the larger context of behavior. In summary, neurobiological studies focus on the questions: "What are the biological influences which are determinative of drug abuse?" and, in

particular, "What are the effects of abusable drugs on the neurological systems of the user?"

Development of drug abuse, addiction, or dependency as a result of genetic and biological determinants alone or in interaction with behavioral and environmental factors is in its infancy of study. It is important to focus on the ways in which the neurochemical mechanisms associated with drug involvement translate into or manifest in the larger context of drug-taking behavior. In order for research to continue to make the progress necessary for a thorough understanding of drug abuse, as well as a means for its prevention and treatment, greater concentration is needed on studies of individual differences in neurobiological factors and on studies that focus on the integration of neurobiological systems with behavioral and environmental factors. It is with this perspective that the National Institute on Drug Abuse (NIDA) is supporting research initiatives in this area. As part of this effort, NIDA sponsored a workshop in 1993 on "Individual Differences in the Biobehavioral Etiology of Drug Abuse." The chapters presented in this monograph are updated versions of those originally developed for that meeting.

PURPOSE OF THIS MONOGRAPH

The primary purpose of this monograph is to provide a platform of ideas from which new directions for research in the biobehavioral etiology of substance abuse can be developed. Researchers from a variety of neurobiological disciplines were invited to develop innovative approaches to the study and understanding of individual differences in neurobiological risk and resistance factors for drug abuse. While the researchers were encouraged to be creative and speculative, they were also asked to tie their ideas to available data and to translate their hypotheses into concrete methodology suitable for empirical investigations.

To facilitate the immediate application of these innovative research ideas to pragmatic research projects, the researchers were asked to make presentations as if they were writing a proposal for a research grant. This approach required that the presenters not only propose a creative idea, but that they also show its relation to the extant relevant research and findings, translate it into a feasible project, and demonstrate the worth and utility of the expected results. At the meeting, each proposal was presented, commented upon by a designated referee and then discussed by audience participants.

Revised and updated versions of these proposals and commentary were submitted for inclusion in this monograph. Both the commentary and audience participation were edited and are also included. Some of these proposals have been formally submitted and funded; others are still being developed. All are designed to stimulate further thought and implementation.

TOPIC AREAS

In organizing the workshop and this monograph, the editors selected three research areas on which to focus: genetic bases, neurophysiological correlates, and neurochemical factors underlying drug-abuse risk or resistance. These areas were selected for their importance and research potential as established by innovative and promising research that was already being developed in drug-abuse and nondrug-abuse fields (e.g.,mental health). The researchers who contributed to this monograph have generously agreed to share their ideas at early stages of their work in order to stimulate further research and to communicate their enthusiasm for the potential of integrative biobehavioral research on drug abuse.

Behavioral Genetic Factors

Several years of family, adoptee, and twin studies have demonstrated the likelihood of a genetic contribution underlying drug-abuse risk behaviors including, but not limited to, drug abuse itself. For example, substance abuse in a biological parent has been shown to be associated with drug abuse in adopted-away offspring even when environmental factors are controlled by statistical analysis. This observation suggests that at least one of the determinative variables for drug abuse is related to genetically coded traits. One of the concepts regarding the genetic aspect of drug abuse is emergenesis, which posits that substance abuse as an outcome (behavior) variable is not determined by one specific gene or gene set, but is a behavioral consequence of any of a number of genetically influenced but nonspecific maladaptive functions of the individual (Lykken et al. 1992). From this perspective, substance abuse may be one of many possible behaviors in a dysfunctional system and related in different individuals to differing configurations of genetic variations. Available research does not point to a single drug abuse gene; this gives credence to the emergenesis hypothesis.

One implication of the emergenesis concept is that if a variety of genetically influenced maladaptive functions may lead to substance abuse, then the identification of these gene patterns and maladaptive functions must distinguish their involvement from environmental influences. Twin studies provide one of the best means to separate environmental and genetic contributions to an outcome behavior. For example, monozygotic (MZ) nonabusing cotwins of substance abusers (i.e.,abuse disconcordant) should have high biological risk factors not present in nonabusing cotwins of nonsubstance abusers (i.e., nonabuse concordant). Discovery of these factors will aid in selecting the genetic, and possibly the biological, basis leading to drug-taking risk or, alternatively, resistance. While consideration of nongenetic (familial/ environmental) factors should continue to be incorporated in genetic research, the focus of research should shift to allelic variations analyzed within the context of these nongenetic factors that contribute to individual differences in risk behaviors. Although environmental factors serve to modify the expression of gene differences, discovery of underlying gene variations and their respective functions in context will dramatically increase the power of models tracing the etiology of drug abuse.

Another approach to studying the genetic contribution to drug abuse propounds the possibility that a single gene or a small number of genes do not code specifically for drug abuse per se, but rather code for a particular behavior or characteristic (e.g., stress)which is a risk factor for, or an intermediating determinant of, substance abuse instead. Research following this approach must focus on identifying these mediators and their underlying genetic components. Such behaviors and characteristics include those accompanying (comorbid with) drug abuse or those that likely underlie an abuse liability.

Historically, a serious obstacle has been to define the drug-abuse phenotype, or even an at-risk phenotype. Without a good definition of the phenotype, the search for the associated genes is near impossible. But based on the broad assumption that some of the risk behaviors are derived from genetically controlled mechanisms, the task has been to employ association studies where candidate gene polymorphisms are compared across groups of individuals who have, in common, patterns of the putative risk behaviors. One expectation is that genes will be discovered that increase the manifestations of certain behaviors or psychological states which, in turn, increase or decrease the propensity to take and abuse psychoactive substances.

The chapter by McGue, Lykken, and Iacono follows the emergenesis approach and seeks to outline traditional behavioral genetic methodology to determine the interaction of genetically influenced psychological characteristics and experiential factors leading to a path of drug abuse. The challenge is to separate the biological/environmental contributions, on the one hand, and to determine the incremental effect of their interaction, on the other. Using a twin-family approach, the authors propose to determine the relative degree of genetic or environmental influences that lead to drug abuse, determine the degree to which individual differences are affected by exposure to an adverse environ-ment, and show how these differences are enhanced or potentiated by interaction with the environment. The sample will include a number of families in which there is high drug-abuse risk for the child due to the drug-use pattern of the parents. This powerful design, coupled with well-validated assessment instruments, is the model offered for behavioral genetic research.

Tsuang and Lyons also plan to use twins, but theirs are to be selected from a registry of Vietnam veterans. Given their large sample, they will be able to compare concordant and discordant (for drug use and abuse) MZ pairs for a variety of biological and behavioral variables. For example, variables present in the nonabusing cotwin of a discordant pair, and not present in a cotwin of a concordant nonabusing pair, would be indicative of vulnerability variables. This powerful design allows one to explore whether the presence of the variable is due to drug use or rather to the genetic connection to the abusing twin. Again, with such a large sample, subjects may be segregated into specific drug abuse patterns. Additionally, this design can potentially distinguish variables that may be associated with, for example, opiate addiction as compared to barbiturate addiction.

Comings' proposal employs the mediator approach and directly explores the genotype of the drug-abusing individual. The best candidate genes, it is hypothesized, are related to the reward system in the brain. Specifically, these would be genes associated with dopamine receptors. Therefore, the search for candidate genes will look for particular allele(s) more prevalent in severe drug abusers. It is assumed that it is not likely that such mutations or variations would be direct causes for drug abuse, but rather might be responsible for modifying behavior that increases the vulnerability to either seek drugs in the first place and/or continue and escalate use once there has been initial exposure. Therefore, the proposed study will attempt to not only determine the association of the polymorphic genes among

drug abusers, but try to tease out the personality or behavioral characteristics that may more closely result from action of the gene itself.

Neurophysiological Factors in Behavioral Etiologies

Postulating that drug abusers have a biological predisposition to continue from use to abuse of psychoactive substances, and to dependence and addiction, implies that there must be measurable premorbid individual differences in neurophysiological variables. Examples would include differences in regional brain responsiveness, metabolism, or activation patterns that are associated with vulnerability to drug abuse itself or with risk behaviors leading to drug abuse. Substantial basic (animal) research has already identified many of the important neurotransmitter systems affected by various licit and illicit psychoactive substances. Missing, however, is information about the differentiating features among human abusers that make their critical brain systems particularly more vulnerable in a way that leads some individuals to abusive drug involvement. From what has been learned, it seems logical that among the possible differences would be cerebral distribution of function, metabolic efficiency, or neural activity associated with those putative systems that underlie abuse liability.

Several newly developed techniques have been successful in displaying the effects of drugs on addicts' brains. Cerebral metabolism and activation can be measured by positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), cortical evoked potentials, and several other modern advances in technology. These techniques can predictively differentiate among certain performances on neuropsychological tests, some of which have predictive value for drug abuse liability. Individual differences in brain function may also be distinguished for other related risk or intermediary behaviors including anxiety, stress, and aggression. Differentiating cerebral functioning for these behaviors in people without behavioral pathologies as well as in individuals who exhibit clinical psychopathology may point to underlying neurobiological contributions for behavior leading to drug abuse.

For example, in research at the Addiction Research Center (the NIDA Intramural Program), aggressive delinquent males showed delays in auditory cortical evoked potentials as well as a decreased slow wave amplitude of cognitive event-related potentials (ERPs) during mental processing (Herning et al. 1989). This suggests that there are

individual premorbid differences in brain organization for nonabusing at-risk adolescents. In rhesus monkeys, there was greater activation of the left frontal lobe in response to diazepam (Davidson et al. 1992) and the magnitude of the asymmetry was highly correlated (r= 0.82) with a measure of anxiety (Davidson et al. 1993). Finally, several studies in humans have shown localized (regional) changes in blood flow as measured by single photon emission computerized tomography (SPECT) (Miller et al. 1992; Pearlson et al. 1993) cerebral metabolism following chronic use (Volkow et al. 1992) or withdrawal (Holman et al. 1993; Volkow et al. 1992) from psychoactive drugs such as cocaine. Research using these types of approaches could be strengthened by the utilization of more sophisticated neurotransmitter tracers, and by behavioral conceptualizations and assessments. For example, it has been shown that the number of dopamine type 2 (D2) receptors are reduced in cocaine abusers compared with controls (Volkow et al. 1993), suggesting that the dopamine dysregulation caused by chronic use may be related to some of the behavioral changes in these individuals. Application of these technologies to research on the biobehavioral etiology of drug abuse may yield critical information.

Iacono, Lykken, and McGue propose that psychophysiological vulnerabilities could be assessed to the degree to which these traits are inherited and relate to substance abuse. They hypothesize that the traits would be associated with behavioral undercontrol or disinhibition exhibited in externalizing disorders. Furthermore, they assert that these traits may be found in, and predictive of, affected individuals and their families, and would be stable over time. It is proposed that these traits can be assessed by electrocortical potentials, either evoked (e.g., P300) or resting electroencephalogram (EEG). Both have been modestly shown to be associated with substance abuse severity or with risk behavior symptomatology leading to substance abuse. Other prime physiological measures that would potentially point to disinhibition are those that assess reactivity to aversive stimuli. Such studies would focus on habituation, or conditioning to distraction.

Similarly, the Herning proposal will use ERPs to study children at risk for substance abuse due to specific personality or diagnostic characteristics including attention deficit disorder, aggressive-ness, and/or depression. Children will be studied before and during a methylphenidate challenge, and retested after 3 years. Since these children, at first assessment, will likely be too young to have engaged in a drug-abuse experience, the ideal result will be an electrocortical

or neuropsychological profile obtained at the first testing that will be predictive of later substance abuse.

Moss's proposal is based on the same general hypothesis that physiological measures can be associated with behavioral risk factors, but this proposed study is more specific. In particular, it is hypothesized that the risk behaviors observed in children of substance abusers are related to dysfunction of the frontal lobes. Accordingly, children of substance- abusing fathers with and without conduct disorder will be compared on prefrontal phospholipid metabolism as measured by 31P magnetic resonance spectroscopy. This methodology is relatively new; it takes advantage of the fact that specific phosphorus-containing molecules can be detected, which, in turn, can be used to assess the degree of metabolism. The ratio of phosphocreatine to inorganic phosphates may be indicative of the synthesis of adenosine triphosphate, an important energy-transporting molecule. While this technique has its limitations in terms of cortical localization, it is a relatively inexpensive, noninvasive assessment that potentially can identify at-risk children.

Neurochemical Factors in Behavioral Etiologies

Identification of individual differences by electrocortical and imaging techniques (which are related to systematic and variable findings in measurements hypothesized to be related to specific behaviors) implies there are differences in underlying neurohumoral substances that give rise to the neurophysiological measurements. While potentially very informative, these neurochemical system factors are impossible to directly assess in humans because current techniques would require assays of live human brain tissue to evaluate the concentrations of neurotransmitter systems. Examination of postmortem tissue in humans is possible and may give indications of consequences of certain drug-related effects and perhaps even etiological factors leading to substance abuse. For example, nicotinic receptors can be quantified with [3H]cytisine, a nicotinic receptor ligand in smokers, according to smoking history (Hall et al. 1993). Nevertheless, there are limitations to the possibilities of this approach. In the past, the extensive development of animal models has defined each of the neurochemical systems critical for maintenance of a drug-taking behavior. However, in the final analysis, human neurosystems are the principal concern because animal models can never represent the psychological aspects of abusive drug taking. Given the difficulty of such research in humans, progress has been limited to date.

Fortunately, human models for behaviors associated with drug abuse as well as new neurochemical assay techniques are leading the way for study in this area. Individual differences in neurotransmitter levels can now be detected and related to behavioral function. This has been accomplished methodologically by observing individuals with behaviors at risk for substance abuse and obtaining appropriate samples from plasma or cerebrospinal fluid that are indicative of central nervous system metabolic activity. For example, low levels of cortisol are correlated with increased aggression in animals (Politch and Leshner 1977) and hypo-mania in nondrug-abusing humans (Ballenger et al. 1983). Also, since the reward system of the brain is largely dependent on the neuro-transmitter dopamine, individual differences in the efficiency of this system in the reward areas of the brain may underlie abuse liability for certain psychoactive substances. Use of these types of indirect indicators may lead to critical new information.

King and Flowers, in their proposal, intend to examine the relationship between neurochemical and behavioral factors in order to predict vulnera-bility to drug abuse. To do this, they propose to assay for dopamine metabolites in cerebrospinal fluid and relate these measures to cocaine craving in addicts after long-term abstinence. A behavioral check of this same relationship will be made with motor activity that is believed to be related to central nervous system (CNS) dopamine activity. Illuminating the nature of craving is a key element in these studies, because if a reliable correlation can be established between craving and a neuro-chemical substance, progress can be made toward treatment and prevention.

The dopaminergic neurotransmitter system has dominated research and theory on the involvement of neurotransmitters in drug abuse. However, the serotonergic neurotransmitter system may also be implicated in psychological behaviors at risk for substance abuse. Similar to dopamine's association with certain behavior, reduced serotonergic activity appears to correlate with aggression and inability to control impulse behavior (Coccaro 1992) while increased activity is associated with inhibition (Spoont 1992). The interaction of serotonin and dopamine is evident in studies of habituation to environmental stimuli where higher serotonin levels result in reduced startle activity in animals (Geyer and Tapson 1988). In spite of the well-established connection of dopamine to pleasurable experiences, research relating the serotonergic, dopaminergic, or other endogenous systems to vulnerability to drug abuse has been very limited. This is

largely due to the complexity of the issue and lack of unifying theory, and is compounded by methodological difficulties.

As proposed by Kaye and Wisniewski, one solution to this dilemma for drug abuse may lie in drawing on research models of eating disorders. Patients diagnosed with bulimia nervosa (BN) are more likely to develop drug abuse and have many more substance abusers in their families compared with patients with restricting type anorexia nervosa (RAN). One current model of these related disorders is a faulty serotonergic system in each group—in one case acting to potentiate impulse control; in the other, to overcontrol or restrict actions. The authors' proposal addresses this observation and related hypotheses, first exploring whether behavioral factors of control, novelty seeking, and emotionality (unstable mood states) are associated with eating-disordered women (normal weight bulimics (NWB) and those with RAN). Then, once the relation-ships of these characteristics are established, the contribution of the serotonergic system to these behaviors and to substance abuse or avoidance can be studied.

Another approach to studying the neurochemical aspects of vulnerability to substance abuse is reflected in the proposal by Volkow, Fowler, Hitzemenan, and Wang which investigates individual differences in dopamine reactivity to psychostimulants. It is hypothesized that these differences in reactivity will reflect differences in brain biochemistry and predisposition for drug abuse. The basis for this hypothesis is the assumption that behavioral responses to a drug as well as one's personality characteristics and disposition reflect the neurochemistry of the individual. The study design includes assessment of the subjects' behavioral response symptomatology after methylphenidate (or placebo) exposure, and the use of PET to determine the relationship of these symptoms to dopamine activity. The dependent variable is 11C-raclopride binding, which is a measure of D2 receptor activity.

PUBLIC HEALTH SIGNIFICANCE

It seems likely that there are multiple pathways leading to an individual’s first trying and then, in a limited number of cases, escalating the use of psychoactive drugs to abuse, dependence, and/or addiction. The majority of theories and research on humans about the etiology and nature of drug involvement have omitted extensive consideration of individual differences underlying biological or

physiological components of these pathways. The result of this omission is that psychological/environmental research and models have been incomplete.

Conversely, neurobiological components of drug effects and abuse liability have been studied extensively in animal models where psycho-logical and environmental factors are either controlled or irrelevant. Human neurobiological research has been largely confined to verifying the animal work, largely omitting consideration of psychological and environmental factors. In humans, as in animals, individual differences were considered "noise" in this research approach, to be controlled or minimized so as to provide clear answers about neurochemical mechanisms underlying the neurosystems involved with psychoactive drugs. Accordingly, this approach has failed to explain the variability of human drug involvement not only as a result of individual differences in these neurobiological systems, but also as these systems co-occur and interact in varying environmental contexts.

It is believed that drug abuse is not only a heterogeneous phenomenon but also a multiply determined one involving the interaction of biological, psychological, and environmental determinants; research and theory must incorporate this multiplicity. Inclusive consideration of these deter-minants is already being initiated by some researchers, but the field in general has not embraced a multidimensional approach to drug abuse research. The concepts and studies presented in this monograph focus on biological factors underlying vulnerability to (and by implication, variability in) human substance abuse. Most incorporate, either explicitly or implicitly, a more integrated consideration of biological and behavioral factors than is generally found in the drug abuse field. Similarly, the power of most of these studies is enhanced by their recognition of the importance of individual differences in biological and behavioral factors and by their consideration of biological mechanisms within this larger context.

The hypothesis of a genetic contribution to substance abuse behaviors has been gaining acceptance for some time, but only now, with rapidly evolving methodology, can researchers hope to corner the derelict genes. It will be a challenge to determine how these genes modify human behavior to increase drug abuse risk, but neurophysiological measures that differentiate such individuals will provide clues. As imaging (especially) and neurochemical models of human behavior are studied, the all-important breakthrough to associate drug abuse

vulnerability to neurochemical mechanisms will be differentiated. Such discoveries will inevitably open currently unavailable avenues for treatment and prevention. The time is ripe for these researchers to broaden their scope and include drug abuse as the disease focus. It is certainly fair to argue that the best methodology and design are essential to success of such speculative research, but it is also essential that such work be started. While many may argue that more basic research in animal models is needed, such as finding better candidate genes of substance abuse, it is argued there is never a guarantee of recognizing the "right time." Researchers must seize the moment, taking advantage of advances in technology that make the task less formidable. Even if there is argument that some studies are "fishing expeditions," good fishermen know where to fish.

NIDA would like to thank the researchers who have been both generous and courageous enough to share, through the original conference and in this monograph, their speculations and their research in such early forms. The Institute joins with these innovative researcher leaders in encourag-ing others to adopt a biobehavioral approach to the study of drug abuse.

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Genetic Factors in Drug Abuse and Dependence

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STATEMENT OF THE PROBLEM

The etiology of drug abuse/dependence is a complex interplay of psychosocial and biological factors. These factors include socioeconomic status, education, drug availability, peer pressure, childhood and adult comorbid psychiatric disorders, and specific mutant genes. The emphasis of this chapter is on the role that genetic factors play in an individual's vulnerability to drug abuse/dependence, henceforth simply referred to as drug abuse. One major point is that there are no genes unique to causing drug abuse. Instead there are genes that alter the normal function of the central nervous system as manifested by a wide range of interrelated impulsive, compulsive, addictive, affective, and anxiety behaviors. One of the outcomes or associated behaviors of attempting to cope with these disorders is substance abuse. In this light, the genetics of any one of these interrelated behaviors has relevance to drug abuse. Drug abuse is not an island unto itself.

One of the major neurophysiological players in vulnerability to drug abuse in humans is the reward system. Pathways of this system are composed of dopaminergic neurons; the administration of addicting drugs results in its stimulation. A reasonable hypothesis for the neurochemical basis of drug abuse is that vulnerable individuals self-medicate to compensate for defects in this dopamine (DA) reward system. To investigate the possibility that variations in the prevalence of different forms of the dopamine type 2 (D2) receptor (DRD2) gene in drug addicts may be involved in the vulnerability to drug addiction, the frequency of the DRD2 variants was determined in several hundred substance abusers. There was a high correlation between the frequency of the Taq I A1 variant and multisubstance abuse, based upon the number of drugs on which more than $25 per week was spent ($p < 0.006$). Using the Defense Style Questionnaire (Andrews et al. 1989), drug addicts carrying the 1haplotype, which is in linkage disequilibrium with the D2A1 variant, showed much greater use of immature defenses than non-1 haplotype carriers.

These preliminary studies support the concept that differences in the prevalence of DA receptor variants play an important role in fundamental personality traits that affect a person's vulnerability to drug abuse as well as to other impulsive, compulsive, and addictive behaviors. To verify this association, the proposed specific aims are to study 200 male substance abusers from the addictions treatment ward of a Veterans' Administration (VA) hospital, and 200 sex, age, race, and ethnically matched controls. This study will include: genetic testing of the D2A1 and haplotype variants of the DRD2 gene; genetic testing for variants of the remaining four dopamine receptor genes, D1, D3, D4, and D5; testing of all subjects with the Diagnostic Interview Schedule, Minnesota Multiphasic Personality Inventory (MMPI), Addiction Severity Index (ASI), Defense Style Questionnaire, and Axis II Personality Index; and statistical analyses to test for possible correlations between the indepen-dent genetic variables, personality variables, and drug abuse.

BACKGROUND AND SIGNIFICANCE

Family, Twin, and Adoption Studies

Family, twin, and adoption studies are the classic techniques for examining the role that genetic factors play in a given disorder. The greatest source of information on family studies in drug abuse comes from reports that have also examined alcoholism. Since genetic factors appear to play a significant role in risk factors for alcoholism (Cloninger 1987; Goodwin 1981; Stabenau 1990), it is a reasonable assumption that genetic factors also play a role in drug abuse. There is a high rate of comorbidity between alcoholism and drug abuse; between 30 and 51percent of drug abusers have concomitant alcohol abuse or depen-dence, and relatives of alcoholics often have problems with drug abuse, and vice versa (Dinwiddie and Reich 1991; Mirin et al. 1991; Weiss et al. 1986, 1988). In a study by Miller and colleagues (Miller et al. 1989a, 1989b), 50 percent of drug abusers had at least a first- or second-degree relative with a diagnosis of alcohol dependence. O'Donnell (1969) reported that 57 percent of fathers and 12 percent of brothers of opiate addicts were alcoholics. Ellinwood and colleagues (1966) reported that 25 percent of fathers and 15 percent of brothers of opiate addicts were alcoholics.

Two other studies (Luthar et al. 1992; Mesonero et al. 1991) examined 476 siblings of 201 opiate addicts using a structured interview. They found a marked increase in the frequency of

antisocial personality (ASP), depression, drug addiction, and alcoholism among the relatives of opiate addicts. Relevant to the theme of the interrelationship between drug abuse and other disorders, they found a variety of psychiatric disorders in the siblings even when the drug addict proband did not have the same, suggesting segregation for a genetic spectrum disorder. Some, however, have suggested that the frequency of drug addiction in the relatives of drug addicts is higher than in the relatives of alcoholics (Hill et al. 1977; Kosten et al. 1991; Meller et al. 1988), suggesting that drug addiction is the behavioral outcome more closely associated with the modified genetic substrate. In a study of relatives of probands with alcoholism and depression, Merikangas and colleagues (1985) observed a significant increase in frequency of both alcoholism and depression compared to controls.

Childhood conduct disorder and adult antisocial personality disorder have frequently been implicated as risk factors in substance abuse (Cadoret et al. 1986; Croughan 1985; Jaffe et al. 1988; Rounsaville et al. 1982, 1991; Schubert et al. 1988; Stabenau 1984). Since genetic factors have been implicated in both conduct disorder (Comings and Comings 1987) and antisocial personality disorder (Bohman et al. 1982; Cloninger et al. 1982; Crowe 1974; Mednick et al. 1984; Sigvardsson et al. 1982), it is reasonable to suggest that these same genes can play a role in susceptibility to drug abuse.

Cadoret and colleagues (1986) reported a study of 242 male and 201-female adoptees separated at birth from their biological parents. Drug abuse was highly correlated with ASP, which in turn was predicted from antisocial behaviors in the biological parents. In addition, a biological background of alcohol problems predicted increased drug abuse in the adoptees who did not have antisocial personalities. Environmental factors such as divorce or psychiatric disturbance in the adoptive family were also associated with increased drug abuse. They concluded there were two genetic pathways to drug abuse: one through biological parents with antisocial personality, and the second from biological parents with alcohol problems who themselves were not antisocial.

While designed as a twin study of alcoholism, Pickens and colleagues (1991) also examined drug abuse. They found a concordance rate among 114 male monozygotic twins of 63.4 percent versus 43.8 percent for dizygotic twins ($p = 0.05$). They found that in males the genetic influence on drug abuse was comparable to that of alcohol abuse.

Grove and colleagues (1990) utilized the powerful approach of identical twins raised apart. This study found a high degree of heritability for drug abuse and childhood or adult antisocial behavior and a much more modest heritability for alcohol abuse. There were significant genetic correlations between drug and alcohol abuse scores ($r = 0.78$), drug abuse and childhood antisocial behavior scores ($r = 0.87$), drug abuse and adult antisocial behavior scores ($r = 0.53$), alcohol abuse and childhood antisocial scores ($r = 0.54$), and alcohol abuse and adult antisocial scores ($r = 0.75$). These correlations supported the idea that there was a common core set of genes for all these reported behaviors.

Genetic Loading Studies

While family, twin, and adoption studies provide evidence for the role of genes in drug abuse and related disorders, one of the disadvantages is that they provide no clues as to which genes are involved. An approach that does supply such clues was found in a well-defined genetic impulse disorder, Tourette syndrome (TS) (Comings et al. 1984; Pauls and Leckman 1986), and used to examine genetic factors in both alcoholism (Comings 1994b) and drug abuse (Comings 1994a). The drug use/abuse histories of 217 TS probands, 79 of their relatives who also had TS (nonproband TS), 249 relatives without TS (non-TS relatives), and 50controls were examined. Regardless of the mechanism of inheritance of TS, probands would have the highest number or genetic loading for TS (Gts) genes, nonproband TS relatives would have the next most loading, non-TS relatives would have still less loading, and controls the fewest Gts genes or least Gts gene loading. It was assumed that if there were a significant correlation between the degree of genetic loading for Gts genes and symptoms of drug abuse, then the Gts genes would be playing a role in drug abuse. This proved to be the case.

The correlation between the endorsement of eight of the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (Robins et al. 1981) symptoms, criteria for drug abuse/dependence as defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed., rev. (DSM-III-R), and the genetic loading for the Gts gene(s) was significant at $p < 0.00000001$ (Comings 1994a). The correlation with alcohol abuse/dependence was also significant (Comings 1994b) but, as in the twin study of Grove and colleagues (1990), less so than for drug abuse. Of a number of comorbid disorders examined, the greatest predictor of drug abuse was

concomitant alcohol abuse, and the greatest predictor of alcohol abuse was concomitant drug abuse. This finding, plus the fact that the same genetic disorder was examined in both studies, suggests that the behavioral outcomes of alcoholism and drug abuse are related to similar genotypes.

Genetic loading studies were also performed with a smaller number of probands and relatives with attention deficit-hyperactivity disorder (ADHD), a disorder with strong genetic links (Faraone et al. 1991, 1992). Again, there was a significant correlation with genetic loading for the ADHD genes. Except for the presence of tics, TS and ADHD are virtually identical disorders with similar clinical symptoms, comorbid disorders in probands and their relatives, genetics, and treatment (Comings and Comings 1993). Previous studies had already suggested that children with either ADHD (Cloninger et al. 1988; Gittelman et al. 1985; Goodwin et al. 1975; Hechtman and Weiss 1986; Loney et al. 1981, 1983; Mannuzza et al. 1991; Mendelson et al. 1971; Tarter et al. 1977) or TS (Comings 1989, 1990a; Comings and Comings 1990) are at significant risk to develop substance abuse disorders as adults.

The DRD2 Gene in Substance Abuse and Related Impulse Disorders

Blum and colleagues (1990) reported that the Taq I A1 variant of the DRD2 gene was present in 69 percent of severe alcoholics compared to 20 percent of controls. Subsequent studies have been mixed, with some supporting (Arinami et al. 1993; Blum et al. 1991; Comings et al. 1991a; Cook et al. 1992; Parsian et al. 1991) and some not supporting (Bolos et al. 1990; Gelernter et al. 1991; Schwab et al. 1991; Turner et al. 1992) this association. One avenue of research is to determine if the D2A1 allele might correlate better with impulsive, compulsive disorders than with alcoholism per se for the following reasons: One of the major theories of TS is that it involved defects in DA metabolism; haloperidol, a DRD2 agonist, is one of the more effective medications for treating TS; and there is an increase in the prevalence of alcoholism among TS probands and relatives (Comings 1990a; Comings and Comings 1990).

A significant increase was found in the prevalence of the D2A1 allele in subjects with ADHD, TS, conduct disorder, and posttraumatic stress disorder (PTSD) (Comings et al. 1991a), all of which have significant associations with drug abuse (Comings 1990a; Comings and Comings 1990; Gittelman et al. 1985; Kulka et al. 1990). In these association studies, intragroup comparisons were used and the subjects and

controls were restricted to a single racial group to help eliminate gene frequency as a confounding variable. Fifty-nine percent of non-Hispanic caucasian, "battle-hardened" Vietnam veterans with PTSD carried the D2A1 allele, while only 5percent of those without carried the D2A1 allele ($p < 0.001$) (Comings et al. 1994). Within the group of TS probands, the prevalence of the D2A1 allele was 29 percent in 763 controls (Comings et al. 1994), 35.0percent for 20 mild cases, 40.4 percent for 146 moderate cases, and 55.5percent for 54 severe cases (Comings 1992).

These observations suggest that the D2A1 allele is in linkage disequilibrium with physiologically important variants of the DRD2 gene. Since drugs such as cocaine and dextroamphetamine produce a greater perturbation of the dopaminergic reward pathways than alcohol (DiChiara and Imperato 1988), it is hypothesized that the D2A1 allele would correlate more strongly with drug addiction than alcohol per se. To test this, 200 caucasian subjects on a VA inpatient addiction treatment unit were examined. Compared with controls, this group showed a significant increase in the prevalence of the D2A1 allele in individuals with polysubstance abuse (42 percent) ($p < 0.006$), but not in individuals with alcohol abuse only (21 percent) or alcohol dependence only (32percent) (Comings et al. 1994). Of those who spent more than $25 a week on two or more drugs, 57 percent carried the D2A1 allele versus 28.2 percent of those abusing only a single drug ($p < 0.0005$). Smith and colleagues (1992) have also reported a significant increase in the prevalence of the Taq I B1 allele of the DRD2 locus in drug addicts; Noble and colleagues (1993) reported a significant increase in the prevalence of the Taq I A1 allele in cocaine addicts.

Additional within-group comparisons were also informative. For those on the addiction treatment ward who had been jailed for nonviolent crimes only, such as driving under the influence (DUI), 29 percent of 111subjects carried the D2A1 allele. By comparison, 53 percent of 32subjects who had been jailed for violent crimes (e.g., assault, armed robbery), carried the D2A1 allele. In a subset of 13 subjects who had been arrested for violent crime and been expelled from school as children for fighting, 69 percent ($N = 9$) carried the D2A1 allele.

Pathological gambling is a disorder that combines the elements of impulsive, compulsive, and addictive behaviors. In preliminary studies of 96 pathological gamblers, approximately half carried the D2A1 allele (Comings et al., unpublished results). This study and others

reviewed above suggest that drug abuse, alcoholism, ADHD, TS, conduct disorder, antisocial personality disorder, PTSD, and pathological gambling have genetic substrates in common, and that the DRD2 gene is one of the genes involved.

Oligogenetic Disorders in Psychiatry

Even though the D2A1 allele was significantly more prevalent in a number of impulsive, compulsive, and addictive behaviors, most affected individuals did not carry the allele, and the relative increase in carrier rate compared with controls was only modest. These and other observations (Comings, in press; Comings and Comings 1992) led to the suspicion that, unlike single gene disorders such as Huntington's disease and cystic fibrosis, psychiatric disorders are oligogenetic in nature (i.e.,caused by a clustering of several major and modifying genes). The disorders are common because the mutant alleles themselves are common, as are the chances of acquiring a sufficient number of genetic variations that modify behavior to clinically diagnostic levels. These considerations led to the speculation that each of the DA receptor genes might possess functional allelomorphic variants and thus play a role in psychopathology.

The DRD3 Gene in Impulse Disorders

The DA type 3 (D3) receptor is described (Lannfelt et al. 1992) as a polymorphism that alters the coding sequence in the first exon resulting in the substitution of a glycine for serine and producing a Msc I polymorphism. In 139 TS probands, there was a significant decrease in the presence of D3A1A2 heterozygotes and an increase in D3A1A1 homozygotes and, to a lesser extent, D3A2A2 homozygotes (Comings et al. 1993). Crocq and colleagues (1992) reported virtually identical results in 141 schizophrenic patients versus controls in samples from England and France. But the results in TS were not confirmed in a small number (N= 19) of TS cases all from the same large pedigree (Brett et al. 1993). However, this was not a suitable test; only a single proband was examined and all subjects were mildly affected individuals from a single pedigree (Comings et al. 1993; Hebebrand et al. 1993).

Hebebrand and colleagues (1993) examined a larger number of probands (N= 66) from Germany and found no decrease in D3A1A2 heterozygotes compared with 100 controls. This prompted the examination of additional cases. Of 350 TS probands, 38.3 percent were D3A1A2 heterozygotes versus 49.7 percent D3A1A2

heterozygotes in a total of 358 caucasian controls ($p < 0.002$). In addition, structured interviews were available on a subset of these, allowing stratification by severity. There was a progressive decrease in heterozygosity, from 48.3 percent for 29 mildly affected TS subjects, to 39.5 percent for 119 moderately affected TS subjects, to 31.3 percent for 48 severe TS patients ($p < 0.005$, Cochran-Armitage linear rank test). It was suggested that the D3 receptors in D3A1A1 homozygotes were relatively hypofunctional, since previous studies in a series of Hispanic females showed that D3A1A1 homozygotes had higher prolactin levels than D3A1A2 homozygotes; hypothalamic DA neurons inhibit prolactin secretion. Ongoing studies have found a significant deficiency of D3A1A2 heterozygotes in pathological gamblers. These findings concerning the DRD3 receptor support those with the D2A1 allele, in that there was an increasing prevalence in TS patients with increasing severity.

The Dopamine Transporter

The DA transporter is responsible for the reuptake of DA at the synapse. It plays a critical role in the regulation of synaptosomal DA levels and is the pharmacological site of action of cocaine (Usdin et al. 1991). The cloning and sequencing of the DA transporter gene (Carroll et al. 1992; Kilty et al. 1991; Usdin et al. 1991; Vandenbergh et al. 1992) and demonstration of a polymorphism at the 3' end of the gene due to a variable length tandem repeat provided the potential for uncovering an exciting gene effect in cocaine and other forms of substance abuse. Studies are underway in a number of laboratories to determine if there is an association between this polymorphism and susceptibility to substance abuse.

Serotonin in Psychiatric Disorders

Defects in serotonin metabolism have been implicated in a wide variety of psychiatric disorders including alcoholism, drug addiction, depression, suicide, aggressive behaviors, antisocial borderline personality disorder, phobias, panic attacks, eating disorders, ADHD, and TS (Brown and van Praag 1990; Comings 1990a; Murphy 1991; Whitaker-Azmitia and Peroutka 1990). Because a similar spectrum of disorders was present in TS probands and their relatives (Comings 1990a), the blood serotonin and tryptophan levels were examined in 1,440 TS probands, their relatives, and controls (Comings 1990b). There was a significant decrease in both platelet serotonin and blood tryptophan in TS patients and their parents. A likely candidate gene responsible for this combination of defects would affect the synthesis

of tryptophan 2,3 dioxygenase (TDO2). If a mutation resulted in the constitutive hyper-induction of this enzyme, it would result in a relative deficiency of both tryptophan and serotonin.

To test this association, the human TDO2 gene was cloned and sequenced for over 8,400 base pairs of exon, intron, and regulatory deoxyribonucleic acid (DNA). Since many restriction endonucleases failed to produce any polymorphisms, large regions of the gene were sequenced in TS patients and controls. This procedure resulted in the detection of three intron polymorphisms. Two are testable by allele-specific polymerase chain reaction (PCR), and to date only one is detectable by denaturing gradient gel electrophoresis (DGGE) of a PCR product. Preliminary results with these polymorphisms suggest that this gene may play a role in impulsive, compulsive, and addictive behaviors.

Conclusions

1. Genetic factors play an important role in the vulnerability to drug abuse; the more severe the abuse, the greater the role of genetic factors.

2. Drug abuse is the result of a complex interplay of environmental, social, comorbid psychiatric, biochemical, and genetic factors.

3. Childhood impulsive disorders such as ADHD, conduct disorder, and TS are associated with vulnerability to drug and alcohol abuse.

4. Adults with drug abuse have a high frequency of other comorbid psychiatric diagnoses including alcoholism, ADHD, TS, antisocial personality disorder, depression, panic attacks, anxiety disorders, and others.

5. There are no genes unique to drug abuse. The genes involved are likely responsible for modification of the neurotransmitter balance resulting in a life-long spectrum of impulsive, compulsive, addictive, affective, and anxiety disorders.

6. There is no single gene responsible for this spectrum of disorders; rather, a small number of major genes and a larger number of modifying genes play a role. Genes affecting the serotonin-DA balance in the brain are particularly important. Since a number of genes are involved, the effect of each one is modest and is best identified by comparison of a large number of probands stratified by

severity against a large number of racially (and if possible, ethnically) matched controls.

7. The allelomorphic variants at the DRD2 locus play a role in a wide range of impulsive, compulsive, and addictive behaviors.

8. Other candidate genes for a role in this spectrum of behaviors are the DA D1, D3, D4, and D5 genes; the DA transporter gene; DA ß-hydroxylase; TDO2; serotonin; and other receptor genes.

9. The identification of an important role of genetic factors and comorbid disorders in drug abuse has important implications for treatment. While abstinence from street drugs is the goal in treatment, abstinence from all drugs may be counterproductive. The potential role of the serotonergic and dopaminergic agonists or reuptake blockers as adjuncts in the treatment of the biochemical defects underlying substance abuse needs attention and continued study.

EXPERIMENTAL METHODS

Clinical Studies

In the proposed study, two major groups of subjects will be evaluated: 200 adult male caucasian substance abusers, and 200 adult caucasian male healthy controls who do not meet criteria for lifetime drug abuse, but may have had minor to moderate degrees of drug use. In addition, to prepare for future studies of drug abuse in females and in other races, 25to 50 male blacks, 25 to 50 male Hispanics, and 25 to 50 female caucasians will be examined.

Setting

The clinical section of the study will be undertaken on the addiction treatment unit (ATU) of a VA medical center. The ATU contains a 30-bed inpatient program and a large outpatient program (1,600 patient visits per month). The patient population is made up of 65 percent polysubstance abusers, 20 percent alcohol-dependent patients, and 15percent single-drug abusers. The majority are considered chronic and severe in their addictive patterns, with lengthy treatment histories at numerous other facilities. Additionally, roughly 40 percent of the treatment population has a second psychiatric diagnosis (in order of frequency: unipolar depression, PTSD, and bipolar affective disorder). The multidisciplinary treatment team includes a

full medical staff (psychiatrist, internist, psychiatry resident) as well as psychologists, social workers, addictions therapists, and nurses.

Sample Acquisition

The principal component of the proposed investigation will study 200adult white male admissions to the 28-day ATU inpatient program who meet DSM-III-R criteria for diagnosis of psychoactive substance abuse disorders. All subjects will be between the ages of 25 and 55. Fourteen days after the hospital admission (to ensure clearance of ethanol and drug neurotoxicity), subjects will be asked to participate and their written informed consent obtained. Randomly chosen subjects in the ATU are routinely given, at admission, a urine drug screen for the commonly abused substances. This information will be used to verify statements concerning drug use reported by research subjects.

Ethnicity

The ethnic origin of all four grandparents of the test subjects and controls will be determined. This will allow stratification of the subjects and controls by major ethnic groups to determine if this factor plays a role in accounting for differences between subjects and controls.

Psychiatric-Psychological Testing

DIS-III-R. A trained interviewer will administer the Diagnostic Interview Schedule, Version III Revised (DIS-III-R) to obtain lifetime DSM-III-R diagnoses. The computerized version will be employed. However, since subjects are able to learn the branching system of the DIS and develop shortcuts, the interviewer will read the contents of the screen to the subject and input the responses, thereby increasing the validity. All interviews will be reviewed by a staff psychiatrist to verify and finalize the diagnosis.

Drug Use Survey. The Drug Use Survey, developed by the Addiction Research Center (ARC) of the National Institute on Drug Abuse (NIDA), indexes both the quantity and frequency of use of all major psychoactive drugs including cigarettes and alcohol. Trained interviewers will assess the amount, frequency, and/or dollar cost of the time of lifetime peak use for drug classes used more than five times. Blinded ratings of lifetime peak use of each individual substance will subsequently be made on a four-point scale: 0 = absent, 1 = minimal,

2 = moderate, or 3 = heavy use. The Drug Use Survey was chosen for two reasons: it is a standardized test used by the ARC of NIDA; and information on all aspects of substance abuse is needed for this study, since variants of different DA receptors may also be related to cigarette smoking.

Minnesota Multiphasic Personality Inventory (MMPI-2). The computer-administered version of the MMPI-2 will be used to assess personality dimensions. The MMPI was chosen for two reasons: it gives quantitative scores of various clinically relevant variables, such as depression, while the DIS gives only dichotomous diagnostic results; and it is a well-standardized, reproducible, and validated test.

Addiction Severity Index (Hodgins and Guebaly 1992). The ASI is a semistructured interview that collects data from substance abusers in seven problem areas: medical, employment, legal, alcohol, other drug use, family-social functioning, and psychological status. In each area, the subjects provide an estimate of the seriousness of the problem and their need for treatment. This test was chosen because it is a standardized test for estimating addiction severity.

Defense Style Questionnaire (Andrews et al. 1989). This 188-item, paper-and-pencil test allows assessment of the degree of reliance upon mature, neurotic, and immature ego-defensive operations. This test was chosen because it provides information concerning basic defense styles, and because preliminary studies indicate that carriers of haplotype 1 of the DRD2 gene use significantly more immature defense styles than noncarriers.

Axis II Personality Inventory. To further access the role of axis II personality disorders on the distribution of the various genetic variants, the Computerized Personality Disorder Interview (C-PDI) will be self-administered.

Controls

The study will recruit 200 controls matched by age, sex, and race from the staff of the VA hospital (physicians, nurses, medical students, secretaries, janitors, others) and from those attending routine screening clinics for diabetes, hypertension, cholesterol, and blood lipid testing. The ratio of hospital personnel to screening clinic controls is expected to be 1 to 3.

Genetic Studies: Genotyping of the DRD2 Gene

The details of the method for testing the Taq A1 allele of the DRD2 gene have been presented elsewhere (Comings et al. 1991b). The allele-specific oligomers and haplotyping procedure for the DRD2 gene are described by Sarkar and Sommer (1991).

Other Dopamine Receptor Gene Polymorphisms

The necessary probes are available and synthesized, and the necessary DNA primers for genotyping all the other DRD1, DRD2, DRD3, DRD4, and DRD5 polymorphisms have been tested. The molecular biology of these additional genes was described above.

Statistics: Sample Size Calculation

One of the specific aims is to determine if the subjects with multi-substance abuse will show a higher prevalence of the genotype and haplotype 1 variants of the DRD2 gene than those with single substance abuse or alcoholism alone. Based on preliminary studies, the prevalence rates of D2A1 alleles were 27.8 percent in single drug abusers (usually alcohol) and 55.9 percent in multiple substance abusers. A power analysis indicates that a sample size of 200 drug abusers and 200 controls will be sufficient for all the polymorphisms to be studied.

Statistical Analysis

Data analyses will be done with the use of Statistical Packages for the Social Sciences (SPSS), Statistical Analysis Software (SAS), Biomedical Data Processing Program (BMDP), or Fortran language programs. The significance of association between two categorical variables (e.g., the relation between DA receptor alleles and haplotypes and a specific diagnostic category) will be assessed by the chi-square test, and the magnitude of association will be measured by

the odds ratio. Significance test of the association between categorical and continuous variables (e.g., the association of DRD2 alleles and haplotypes and various clinical scores) will be done with the t-test, analysis of variance, or nonparametric tests such as Wilcoxon tests and Kruskal-Wallis tests.

In addition to the perspective represented by univariate analyses, the study will explore the extent to which the combination of several variables could explain the characteristics by using multivariate analyses. Possible confounding effects of ethnic, epidemiologic, psychological, and psychiatric risk factors will be assessed using multivariate analyses. Standard general linear models (GLM) will be used to study interrelations among variables. Specifically, multiple regression analyses can be used when outcomes are continuously measured, and multiple logistic regression analyses can be used when outcomes are dichotomous or categorical in nature.

STRENGTHS AND WEAKNESSES

The strengths of this proposal are that all the power of the explosive field of molecular genetics can now be brought to bear to provide an under-standing of the risk factors in drug abuse at the most fundamental level available—human genes. In addition, sufficient preliminary data are already available to indicate that many of the most important genes involved have probably already been identified, cloned, and sequenced; the method of determining if these genes play a role in a specific behavior is clear-cut. This determination involves identifying genetic variants at the candidate genes of interest followed by studies of sufficient numbers of subjects and racially matched controls to determine if the alleles of these polymorphisms are present at a significantly different frequency in drug abusers than in controls. These are called association studies.

A further strength of this approach is that it is not necessary to identify the mutations that affect the function of the candidate gene in question. Since such mutations can occur anywhere in the thousands of base pairs 5' and 3' to the gene or in introns, exons, or transcribed portions of the gene, their identification can be very difficult. However, the presence of a phenomenon called linkage disequilibrium allows almost any polymor-phism in the region of the gene to provide some genetic information about the role of that gene in a specific behavioral disorder. Because of the relatively small distances between the polymorphism of interest and the putative real mutation affecting

the function of the gene, the alleles of the polymorphism and the alleles of the real mutation segregate nonran-domly. Thus, any difference in frequency of the real mutation in drug abusers will be at least partially reflected by differences in the frequency of most of the more numerous polymorphisms at or near the candidate gene.

While this approach uses association studies, many investigators in the genetic community still assume that linkage studies are the only reliable method of identifying the genes involved in hereditary disorders. However, this assumption is rapidly changing within the psychiatric community. A major impetus for the change is that despite massive efforts to find genetic linkages for many psychiatric disorders including TS (95 percent of the genome excluded), schizophrenia, manic-depressive disorder, alcoholism, dyslexia, panic attacks, and others, no confirmed linkages have been identified. The perception is growing that this failure is due to the fact that these disorders are polygenic rather than due to single, rare autosomal dominant genes with reduced penetrance. One argument favoring association studies of polygenic disorders over linkage studies followed from a computer simulation that showed the power of linkage analysis deteriorates so severely for a disorder caused by more than 4 to 6 genes that a negative lod score will be obtained immediately over loci that in fact do have an effect on the phenotype (Popping et al. 1993). Thus for complex, multifactorial, polygenic disorders such as drug abuse, association studies provide the most appropriate and powerful tool.

The major problem with association studies is the potentially con-founding variable of racial and ethnic variations in the frequency of the alleles being studied. If the racial and ethnic mix of the test individuals and controls is different, spurious results may be obtained. This problem can be circumvented in three ways: limiting the studies to homogeneous racial and ethnic groups, using large numbers of subjects and controls to avoid spurious results due to chance variations in small sample sizes, and using within-group comparisons. An example of the latter would be to compare gene frequencies within the total group of drug addicts stratified by severity measures such as the number of drugs abused or frequency of use. Such a comparison would lessen the degree to which geographical or socioeconomic differences between the subjects and the controls would confound the results. All of these precautions have been taken in this proposal.

PUBLIC HEALTH SIGNIFICANCE

In an article entitled "Medicalizing the Drug War," Fishbein (1991) reviewed the numerous studies that have shown that the majority of the violence and crime perpetrated upon society by drug addicts can be traced to a relatively small number of individuals who commit a large number of criminal acts and have a very high recidivism rate. These individuals tend to have a history of ADHD and aggressive, undersocialized conduct disorder dating back to early childhood. These observations, as well as numerous twin and adoption studies (Bohman et al. 1982; Cadoret and Stewart 1991; Cloninger and Gottesman 1987; Cloninger et al. 1982; Crowe 1972, 1974; Hutchings and Mednick 1975; Zur Nieden 1951), indicate that genetic factors play a significant role in the behavior of such individuals. Since genetic factors are not expected to be specific to drug abuse, identification of these factors will simultaneously identify genetic factors involved in other behavioral difficulties such as ADHD and conduct disorder. If such behavior can be understood and treated, then researchers will have come a long way toward alleviating major burdens in society.

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DISCUSSION

Audience and Panel Participants: Harold Gordon, George Uhl, David Comings, Howard Moss, Ming Tsuang, Jag Khalsa, EricHollander, Ellen Witt, and EricDevor

Dr. Gordon: Thank you very much for the commentary and the ideas. We'll start a discussion on the genetic approach to biobehavioral etiology of drug abuse. I would like to give the first opportunity to those presenters especially involved in genetics research to comment, ask questions, and what-have-you and basically discuss the issues.

Dr. Comings: For a long time I've been intrigued with chaos theory as one explanation for why one can have similar input and get a wide variety of outputs on a particular set of variables. One could imagine, for example, that there's now a norepinephrine transport available and that it might be more related to anxiety disorders than it would be to drug abuse. So, if we find that there's a higher association between that transporter gene and panic attacks, then perhaps chaos is not as important as different genes going into the mix.

On the other hand, if we find again that there is no significant difference in the frequency in the transporter genes—assuming it's increased—of variance of the norepinephrine transporter in these different disorders (drug abuse and anxiety), then it would be another piece of evidence that the same set of genes can result in a wide spectrum of disorders. So, I think it's just going to take more work to sort these out.

Dr. Gordon: Any comments or questions now, especially from the folks at the table here who might be involved in this research who would like to raise issues?

Dr. King: I have a question. Are there any published data on preliminary results on the nature of association between the DRD2 allele variant in the control sample? Is it related to personality differences or to other aspects of behavioral impulsivity?

Dr. Comings: It's a good point. Dr. Jim McMurray, a member of our group, in fact looked at a group of controls in Loma Linda to stratify them according to the DRD2 polymorphism. He gave a questionnaire assessing defense style and found that those within the normal group

who carried haplotype I had more immature defenses than those that did not carry it.

Dr. Uhl: Do some of the people with more classic genetics background want to comment on the ways in which the genetics for a number of these disorders might, in fact, represent a unitary genetic predisposition, or to what extent fragmentary data exist in the literature that there might be genetic specificity (e.g., attention deficit disorder compared to substance abuse or Tourette's syndrome compared to ADHD)? I think the silence is probably because there haven't been many studies of these things in these groups of disorders yet.

Dr. Khalsa: You're showing the direction of the genes and the drug abuse in that direction. Can you comment on the other direction where drug abuse results in changes in genetic makeup?

Dr. Comings: I don't think it would result in changes of genetic makeup, per se, but it could certainly cause change to the neurophysiology. I would agree that, at least at a phenotypic level, there are some consequences of abusing drugs suggesting some arrows go in the other direction as well.

Dr. Uhl: But, I think it is important to stress that in some sense the idea of the genetic changes as a consequence of drug use is worth thinking about. The mutations that have made the RFLPs that are being studied were fairly specific because of the ability to trace them in races, actually, in the sort of population genetics sense. One can show that many of them predate the separation of—for example, African and European—races as they're currently recognized. So, these are not randomly occurring with high frequency series of point mutations; these are actually remarkably stable. But, because of the evidence for so-called founder effects in these populations these are tens of thousands, or more, years old.

Dr. Khalsa: That may be true, but I ask this because I have not come across any literature—really convincing literature—suggesting the genetic effects of cocaine or marijuana. If those mutagenic effects are there at all, they must be at very, very high dosages. As you well know, caffeine, for example, is known to be a chromosomal-breaking agent at extremely high dosages.

Dr. Raleigh: My question concerns gender differences. You've seemed to have identified a nice relationship between serotonergic and

dopami-nergic factors in terms of predisposing use and maybe accounting for severity. Are those data largely from males? And, if so, do you expect to generalize to females?

Dr. Comings: Well, it's interesting that you brought up the question of gender differences because that's an area of intense interest in our laboratory right now. We've actually used a technique called haplotyping, which is a different way of looking at yet another polymorphism of the D2 allele, and we find significant differences in haplotypes both by age and by gender.

You would expect that an autosomal trait would not have significant differences by gender. So, we think that this has an effect on some other aspects of human behavior, perhaps child rearing, who gets married and who doesn't, and so forth. But, depending on the disease we looked at, the controls tend to be equal in males and females. For Tourette's, of course, there were more males. The drug abusers in the addiction ward were all males. But, yes, that's why I put sex in there. I think sex and age are going to play a very important role in these things.

Dr. Moss: I'm somewhat cautious when I see these tables with 15 and 20 different studies displayed as indicative of an effect in substance use disorders. There's a wide variety of approaches that have been utilized to characterize the same phenotype of interest. For example, on some of Dr.Comings' slides he noted drug abuse as alcoholism. On other slides, substance dependence disorders would be contrasted with substance use disorders. Right now we're in another state of flux in that DSM-IV is being implemented and that really establishes a whole new set of criteria, diagnostic clinical criteria, for psychoactive substance use disorders. How are we going to handle this degree of heterogeneity in the pheno-types that are of interest to us for genetic etiology?

Dr. Comings: This problem is one of the reasons, in our Tourette's syndrome study, that we didn't use the DSM-III diagnosis. We used, in fact, the variables that go into the DSM-III diagnoses independent of criteria because the criteria keep changing on us all the time. Every one of those variables was highly significant; so, I think that transcends the temporal changes in the criteria somewhat.

Dr. Moss: Physical dependence was as salient as the psychosocial dysfunction domains?

Dr. Comings: Well, to partly answer your previous question, in the study we've most recently done, we've used classic DSM-III-R criteria for alcohol abuse, alcohol dependence, drug abuse, drug dependence, and the combination of the two. So, in that study we did use the DSM-III-R criteria. In the Tourette's syndrome study, I simply took the DIS questions and looked at each question individually. The answer to every one of those questions was significantly greater with greater genetic loading for the Tourette's syndrome gene.

Dr. Moss: Let me sort of give an example of the way this can be problematic. The way DSM-III-R is structured, the psychological dependence and physical dependence are subsumed under the rubric of the dependence disorder. Abuse conditions, for example alcohol abuse where somebody who drinks alcohol on weekends and repeatedly drives their car to get home from the bar, would get a DSM-III-R diagnosis for alcohol abuse. It's a distinctly lower severity kind of syndrome than the dependence categorization. I'm not sure that it's completely legitimate to lump together individuals who have that residual abuse diagnosis, which may be a much milder variant of the condition, with the people who have the full-blown syndrome of dysphoria that we consider dependence.

Dr. Comings: I agree with you completely. I know the data were presented quickly, but we differentiated between alcohol abuse and alcohol dependence. The alcohol abuse category, if anything, showed a lower D2A1 prevalence than the general population, and alcohol dependence jumped up 12 percentage points. So, I think you're right, these are relative.

We've also looked at, with either just a quantity frequency—how much substance has been consumed over what period of time—or with quasi-DSM criteria, and they both give the same answer in terms of the gene association, which is a modest but noisy effect. It's certainly likely that if one had the right behavioral questions to address then one could get a stronger effect. We hope to be able to, in some sense, perhaps parse out the effect of specific genes that can help make the DSM revisions more specific. They're not, as far as I know, informed with a whole lot of genetic information; they're fairly set up to make clinical diagnoses. And perhaps also, as more specific genetic influences become available, that will allow the environmental features to be put into sharper focus individually and distinctly.

Dr. Hollander: Dr. Comings, you draw an association between Tourette's syndrome and substance abuse and a very wide range of

impulsive and compulsive spectrum disorders. It may be that you may be able to look at certain kinds of subgroups within the impulsive and compulsive spectrum and find that they may not all be associated with the same risk of substance abuse. For example, pathological gamblers, or Tourette's syndrome, or certain other disorders that have high impulsive and aggressive features may differ somewhat from, let's say, certain subgroups of OCD patients or, for example, anorexics who may have a lower likelihood than the general population of engaging in substance abuse. So, you might want to look at certain kinds of subgroups within that whole impulsive/compulsive spectrum.

Dr. Comings: As a matter of fact, we did that, and I didn't present those data here. But, just to give an example, we've been impressed for many years by the compulsive eating in many of our Tourette's syndrome families. But, when we used compulsive eating as a variable relating to the diagnosis of Tourette's syndrome and Tourette's syndrome nonprobands, it was barely significant.

But, when we looked at it as a subclassification of those who had OCD of the Tourette's syndrome, it was overwhelmingly significant—10-9. So, if you looked at the whole group, it was barely significant, and, if you looked at a subgroup, it was highly significant. So, we call this "association by association." It's clear that the Tourette's syndrome gene plays a role in OCD, and we looked at just that group of Tourette's syndrome patients. Their frequency of compulsive eating disorders was off the scale. So, I agree with you. Yes.

Dr. Gordon: Dr. Uhl, you brought up the potential problem with the gene variants in several populations, several studies, around the world. I noticed France was low, or somebody else was high. This might be a problem, but what is the implication? How does one get around it, and can we still learn anything about substance abuse and the relationship to these genes? I just picked that particular difference, but there are others. What's the implication?

Dr. Uhl: In terms of study design, I think it has very important implications. Clearly, the controls are as important as the probands, the individuals that are accessed, and that's, you know, substantially more true for association than just about any other study. If one had an ideal strategy and could go into a population-based sample and identify both a substance abuser subset and a control subset in a population-based fashion, that would be ideal. The second best is to try to make sure that the control group studied is as closely representative—in terms of all the demographic features that you

could imagine—of the, for example, substance abusers, as possible. Within caucasian ethnicity, variation exists. It's tempting to combine controls from all over the world, but that may not, in fact, produce a mix that's representative of your local Tourette's, substance abuse, attention deficit—whatever population. Control is key.

The history of the allelic association studies is hugely flawed based on inadequate control comparison groups and a number, even in alcoholism, with A/B/O blood group comparisons, and so on. A number of asso-ciations thought in the past to exist have subsequently been invalidated. So, I think this is one of the things that raises cautions about these results, as well as the increasing optimism. Because of replication in a number of different centers some of this association may, in fact, be real.

Dr. Comings: I'd like to comment on that, too. In our studies in California we generally find somewhere between 8-12 different national groups among the four grandparents, so it's really quite a heterogeneous mix. I think when we do these studies in the United States, we hope that some countries like Germany, France, England, and Japan will then pick them up and look at them within not only racial groups but within single ethnic groups, and that has been done. In fact, the most recent study—it just came out of France—was the most positive of almost all the studies that I've seen. The A1 allele was, I think, 22 percent in controls and 43percent in alcoholics, which is overwhelming. And even in Japan, where the frequency of the allele is very high—around 60 percent in controls—they found a highly significant association with severity.

The other issue about controls is that the Gelernter group used relatives of patients with Tourette's syndrome in their control group. Now, when we studied relatives of patients with Tourette's syndrome, the prevalence of the D2A1 allele runs around 40 percent. You have to be careful what control group you take. Jim McMurray and I have been interested in controls. He looked at a group of physicians and PhDs in Loma Linda compared to non-physicians and non-PhDs, and there was a significant difference in these alleles between these two groups. In fact, when he did the psychological tests, he found that the physicians and the PhDs tended to have a history of some fairly aggressive behaviors in childhood which then, as they grew up, channeled it into competitiveness. Maybe that's why they're doing what they're doing. So, even among the controls you have to be careful within one racial group.

Dr. Tsuang: I would like to rephrase the question that Dr. Uhl emphasized in terms of specificity. And I want to ask Dr. Comings about his current impression, and also in response to DSM-III and DSM-IV, how to characterize phenotype? I think, here, commonsense of doing clinical genetics will tell us traditionally that the manifestations of the different symptoms and signs are actually phenotypic heterogeneity. You mentioned about the common or predisposition leading to various mani-festations of symptoms or signs. This may be one way of looking at it.

The other way is to look at the genetic heterogeneity. If there has not been molecular genetic research in this area, I'll bet all this is phenotypic hetero-geneity. Look at the case with Alzheimer's disease. Before the discovery of chromosomes 21, 14, and 19, no one would stick out their necks to say that is the single gene. They were always talking about the polygenic and the genome manifestation—and in the case of Alzheimer's may manifest these clinical symptoms, may manifest obsessive-compulsive symptoms, may manifest all kinds of symptoms—and that is what we call phenotypic heterogeneity.

Yet, recent advances in molecular genetics have led me to think that even though it looks like phenotypic heterogeneity, it may be part of that syndrome—may be due to genetic heterogeneity. So, how to compromise between DSM-IV and whatever the Chinese cooking style of the diagnoses is that we shouldn't forget that the phenotypic manifestations are so variable and so unstable, and from the longitudinal followup of what we have done it's changing. Schizophrenia, the same thing, from paranoid schizophrenia you cannot rely on them. So, one factor that should be included is what geneticists call endophenotype, which essentially is not observable but with the biological or neurochemical with imaging and neuroanatomical studies. You may be able to get a grasp on what are the phenotypes; what is the specific phenotype we use. So that this spectrum concept of the genotypes manifesting typical cases of drug abuse or dependence, then within the family you have to look into what are the subforms of the aggregate of the dependence, even not meeting DSM-III criteria. So, family data are very important. Biological data are important. Then, if we can identify specific genetic predisposition in subforms of those, we may be able to identify those carriers, gene carriers, who may not have any symptoms at all. This is a very complex issue.

So, I'd like to ask both of you, what's your bet? Are we really looking at the phenotypic heterogeneity, or genetic heterogeneity, of drug abuse?

Dr. Uhl: Dr. Comings mentioned something I think that is worth stressing again: The reason why a linkage study might be negative, even when an association strategy would work, actually relates to this concept of genetic heterogeneity. The linkage method is a lot more susceptible to genetic heterogeneity than association methods. If one starts with a few families and if there are heterogeneous genetics in the different families, then that's going to reduce the power of a linkage approach much more than genetic heterogeneity reduces the power of an association strategy. I'm not sure that there's no reason—and I would argue that there's some fragmentary evidence to suggest both—why there couldn't be both genetic hetero-geneity and phenotypic heterogeneity. I think that's the likely scenario, in fact, unfortunately to account for the clinical phenomena of substance abusers.

Dr. Comings: There's several issues you brought up. One was the phenotypic heterogeneity. We think, I think, of Tourette's syndrome as a tridimensional spectrum disorder. Patients themselves have a wide range of phenotypes; their family members have a wide range of phenotypes. Over time, the natural history of Tourette's syndrome is not to start with tics but to start with attention deficit disorder. Then, a couple of years later, they start developing tics. Those tend to go away in adolescence, and then they have trouble with alcohol and drug abuse and conduct disorder. Later, in their 20s, they're having problems with panic attacks and anxiety. Later in life, they're having trouble with chronic depression. So, depending on what age you look at, they can have completely different phenotypic expression. Yet, the genetic underpinnings are fairly similar regardless of what age you get them or look at them.

The other issue about linkage studies, the reason I think they are failing, is just this issue of genetic heterogeneity. Linkage studies can pick up a gene that is genetically heterogeneous, but it's predicated on the assumption that there's going to be only 2 to 3 genes involved. However, in fact, 5 to 20genes may be involved. As a result, the power of linkage study is just drastically reduced. But this does not happen with association studies. All you need to do is look at a large number of probands and stratify them properly by race. I think you can pick up a 1 to 10 percent effect with association studies that you could never pick up with linkage studies.

Dr. Witt: I'd like to know what is the state of the statistics geneticists use to deal with genetic heterogeneity?

Dr. Uhl: My impression is that people have done models looking at various assumed genetic heterogeneities and looked at—for example—reductions in power in the work of Dr. Gershon—reductions in power and association linkage studies and so on. Is that your question?

Dr. Witt: Are there models to account for multiple genetic disorders looking at cause rather than the correlation among multiple genes? Or is that just something that needs to be developed?

Dr. Uhl: The quantitation?

Dr. Witt: Yes. The quantitation.

Dr. Uhl: You can make these assumptions, I guess. And you can look at the effect on different genetic parameters. But that doesn't seem to address your question.

Dr. Comings: One of the approaches is to use a thing called sib-pair analysis or the haplotype relative risk approach. These require parent/child sets. The idea with the haplotype relative risk technique is to take parents with an affected child and put the two genes that that child has inherited in one group and the other two genes in another group that serves as your control group, then determine if they are significantly different.

The beauty of that approach is that it's totally independent of racial and ethnic differences, so you would think, "Gee, this is an ideal way to look at these issues." But the drawback of that is that, where you had 100cases with the association study, you now need 300 samples for the haplotype relative risk procedure. You have to get all their parents together, which can be very difficult in older people. Finally, about half of those cases are going to give you no information because both parents have the same allelic makeup. So, now you need 600 samples to get the same thing that you could get with 100 probands in the association study. These issues of heterogeneity and how to get at them with linkage studies have been intensively investigated, but they all have problems.

Dr. Devor: I just wanted to make a couple of comments—methodologic comments—bearing on what Drs. Comings and Uhl

have said. The implicit recognition that I hope comes out of this, that dealing with a complex heterogeneous developmental phenomenon is a mistake that went over the heads of a lot of people working in alcoholism. There was the implicit recognition that there was a complex developmental phenomenon going on, and then everybody jumped on linkage studies, which are inappropriate to that kind of disorder.

The model that I hope can be used as an overall heuristic model is one in which things like incomplete penetrance—which is also just as deadly to a linkage study as is genetic and etiologic heterogeneity—can be accounted for by the fact that there may be genes (for example in a dopaminergic system) that give you an underlying risk to illness through a complex of illnesses and through the environmental and subsequent genetic gene-gene/gene-environment interactions that channel into the phenotypes that we see at the endpoint. But, the phenotypes at the endpoint do not necessarily have to be one-for-one specificity with a particular allelic variant or particular quantitative trait.

One case in point, and one that I've been fairly close to for awhile, is the situation with MAO-B. The criticism of MAO-B is that it seems to be lowered in everything. However, when you start properly stratifying within either a family or an association study for severity and concomitant psychiatric illness, what you find is that you have overlapping decreasing quantitative distributions of MAO-B activity that correspond to increasing levels of severity of the illness—say, for example, alcoholism—and increasing levels of secondary psychopathology in the unaffected family members. It's this that is leading me to believe that there are these under-lying genotypes—the primary genotypes—that lead to a general risk, giving a context on which other genes and environmental effects then take hold and channel the individual—it may be an improper way to put that—but channel it into what we now look at as the end phenotype. Comment if you will.

Dr. Comings: That's exactly the same effect we were seeing with the dopamine genes. Thank you.

Genotype-Environment Correlations and Interactions in the Etiology of Substance Abuse and Related Behaviors

Matt McGue, David T. Lykken, and William G. Iacono

STATEMENT OF THE PROBLEM

Although the relevant behavioral genetic literature on substance abuse is limited, findings from this research, as well as from other behavioral genetic studies, strongly suggest that genetic factors exert some influence on substance abuse behavior. Consequently, although there is a need to carefully document the existence and strength of genetic influences, behavioral genetic research in this area needs to address how, rather than just whether, genetic factors influence substance abuse behavior.

Efforts at characterizing the mechanisms of genetic influence may proceed at multiple, complementary levels ranging from the molecular to the psychological. The approach described here focuses on traditional behavioral genetic methods to explicate what might be considered the ultimate step in the gene-to-behavior pathway: the transaction between genetically influenced psychological characteristics and experiential factors. It is argued that two behavioral genetic processes, genotype-environment correlation and interaction, may help in understanding how a complex and clearly experientially sensitive behavior like substance abuse might nonetheless be influenced by inherited factors. A behavioral genetic methodology relevant to identifying genotype-environment interactions and correlations is outlined.

BACKGROUND AND SIGNIFICANCE

The approach outlined in this proposal is based on two empirical conclusions derived from the research literature. Given the limited availability of empirical research in this area, these conclusions should be considered tentative and subject to further empirical confirmation. These conclusions are offered as premises that motivate this approach, rather than as empirically established truths.

Premise #1

Although the currently available evidence is limited, substance use and abuse, like most behavioral characteristics, are likely to be partially, albeit not entirely, genetically inherited.

In the past 20 years, as behavioral geneticists have turned their research efforts away from intellectual ability (the original focus of the nature-nurture debate) to other behavioral traits, they have been drawn towards a remarkable conclusion: Genetic factors appear to exert a pervasive influence on individual differences in virtually every aspect of behavior. Although the magnitude of the genetic effect certainly varies from one behavioral characteristic to the next, psychological characteristics ranging from brain waves and evoked potentials to personality self-ratings and social attitudes all appear to evidence some degree of genetic influence.

A direct and simple demonstration of the pervasive influence of genetic factors on human behavior is provided by Bouchard and colleagues' widely publicized study of twins reared apart (Bouchard et al. 1990). Since the study began in 1979, Bouchard and the research staff have located and assessed more than 120 twin pairs whose members had been separated at or near birth (average age at separation less than 6 months), and reared separately, for the most part without knowledge of one another's existence, until adulthood (average age at reunion approximately 30 years). Figure 1 summarizes findings from the Bouchard study for four separate domains of psychological functioning: cognitive ability, personality, interests, and social attitudes. The figure reports correlations, averaged across separate measures within each of the domains, among reared-apart identical twins (MZA) and reared-together identical twins (MZT), as well as the average reliability of the measures used. (For a discussion of methodology and description of findings in other domains, the reader is referred to Bouchard et al. 1990.) In this proposal, the authors focus only on the findings summarized in figure 1.

The substantial correlation in psychological functioning between the genetically identical yet separately reared MZA twins implicates the importance of genetic factors. Significantly, the findings from the Bouchard and colleagues' (1990) study replicate or have been replicated by other studies of separately reared twins (Pedersen et al. 1992) as well as by a large number of adoption studies and studies of reared-together twins (Plomin et al. 1990). The figure also demonstrates the importance

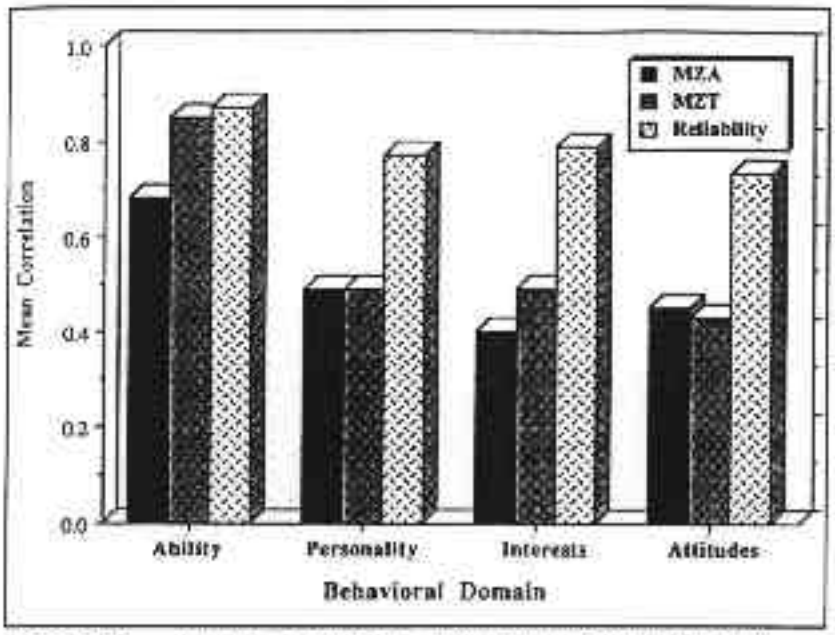

FIGURE 1. *Average correlation among reared-apart identical twins (MZA) and reared-together identical twins (MZT) and the average test-retest reliability in four behavioral domains.*

SOURCE: Adapted from Bouchard et al. 1990.

KEY: MZA = monozygotic reared apart; MZT = monozygotic reared together.

of environmental factors; the average MZA correlation is substantially less than the average test reliability in each of the four domains. However, as the average MZA and MZT correlations are approximately equal in at least three of the four domains, it appears that the relevant environmental factors are those that are not shared by reared-together relatives. This finding has also been replicated in a large number of studies of reared-together and reared-apart relatives (Plomin and Daniels 1987).

Given that the vast majority of psychological traits bear some relationship to intellectual ability, personality, or interests, the Bouchard study findings establish a strong a priori expectation that psychological traits in general, and substance use/abuse in particular, are at least partially inherited. This expectation has been repeatedly confirmed in the behavioral genetic literature, where virtually every

behavioral trait investigated appears to evidence some degree of genetic influence, and even finds support in the limited number of behavioral genetic studies on substance abuse. Pickens and colleagues (1991) reported monozygotic (MZ) twin concordance for drug abuse and/or dependence (other than alcohol or tobacco) as defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed. (DSM-III) to be significantly higher among male MZ than male dizygotic (DZ) twins (concordance of 0.63 on N = 41 MZ pairs versus 0.44 on N=32 DZ pairs) and higher, but not significantly so, among female MZ as compared to female DZ twins (concordance of 0.22 on N = 19 MZ pairs versus 0.15 on N = 13 DZ pairs). Moreover, Cadoret and colleagues (1986) reported significantly higher rates of drug abuse in adulthood among the adopted-away biological offspring of parents with alcohol problems than among the adopted-away biological offspring of parents with no evidence of alcohol problems.

Implications of Premise #1. While the primary focus of much behavioral genetic research over the past 20 years has been to establish the existence of genetic influences on behavior, the accumulated weight of affirmative evidence has served to render most tests of the null hypothesis of no genetic influence relatively uninteresting. Thus, while it will be necessary, given the limited number of relevant studies in this area, to carefully document the existence and magnitude of genetic influences on drug use and abuse behavior, researchers can anticipate the likely result of such efforts: Substance use behavior, like virtually all other behavioral traits, will be shown to be partially, but not entirely, inherited. The chal-lenge to the present generation of behavioral genetics researchers is not so much in establishing whether genetic factors influence behavior, but rather how. As discussed below, two behavioral genetic processes, genotype-environment correlation and genotype-environment interaction, may prove particularly useful for moving beyond simple demonstrations of genetic effects to characterizing the nature of those effects and how those effects relate to the environmental factors known to influence substance abuse etiology.

Premise #2

Substance abuse exists within the context of a broad array of behaviors that include other indicators of undersocialization (e.g., delinquency), psychiatric disturbance (e.g., antisocial personality disorder (ASPD)), and temperamental/personality deviations (e.g., aggression).

In clinical settings, the polysubstance abuser is the norm rather than the exception; most substance abusers have also abused alcohol sometime in their lifetime, and cessation of one form of substance abuse is often followed rapidly by initiation of abuse of a different substance (Tarter and Mezzich 1992). The lack of substance abuse specificity also applies to other indicators of poor socialization. For example, precocious sexuality, gambling, delinquency in adolescence, and antisocial behavior in adulthood (Orford 1985) all occur more frequently among substance abusers than nonabusers. Substance abuse also coaggregates with a wide array of psychiatric illness, including depression and ASPD, both within individuals (Weiss 1992) as well as between individuals within the same family (Merikangas et al. 1992), suggesting that these disorders may share a common familial etiology.

There is also an extensive research literature relating substance abuse to specific personality characteristics (Sher 1991). Deviations along two broad dimensions of personality appear to be particularly relevant. The first dimension has been variously termed behavioral control, constraint, or behavioral dysregulation, and roughly corresponds to an individual's ability or willingness to inhibit behavior (Tarter and Mezzich 1992). Indicators of this first dimension include hyperactivity, impulsivity, and conduct disorder. The second robust personality correlate of substance abuse is negative emotionality (Pandina et al. 1992), or the tendency to experience negative mood states, indicators of which include neuroticism, anxiety, and alienation.

Figure 2 illustrates the association between substance use and personality factors using preliminary observations from an ongoing study of male adolescent twins. Self-reported substance use behavior of 17-year-old twins is classified as either light/abstinent (comprising the 51 percent of the total sample of 172 who reported no use of illicit substances over the past year), moderate (comprising the 38percent of the sample who reported limited use of one or two substances over the past year), or heavy (comprising the 11 percent of the sample who reported regular use of one or more illicit substances over the past year). In this study, personality is assessed through maternal and teacher report, and is thus not confounded with the self-reports used in making the substance use classification. Figure 2 gives the standardized effect sizes (i.e., mean difference in standard deviation units) comparing the light/abstinent and heavy groups for those personality ratings on which the groups differed significantly. As can be seen, the heavy substance-using twins were rated as more delinquent, more aggressive, higher on thrill seeking and

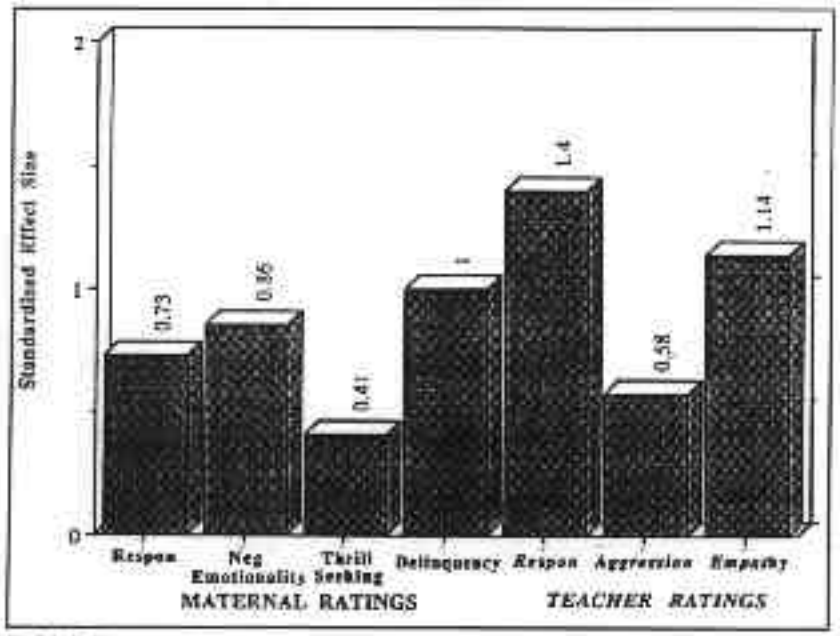

FIGURE 2. *Standardized effect sizes comparing heavy and abstinent/light substance-using male 17-year-old twins.*

NOTE: Effects sizes computed as mean difference divided by the standard deviation of the abstinent/light group. For responsibility (rated by mother and by teacher) and empathy dimensions, the heavy group scored lower on average than the abstinent/light group; for other dimensions, the heavy group scored higher. Effect sizes are reported only for dimensions for which there were significant group differences.

negative emotionality, and lower on empathy and responsibility, as compared to their nonsubstance-using peers (measures of positive emotionality failed to significantly differentiate the groups). The consistency and magnitude of the effects suggest that personality factors may play a fundamental role in the etiology of substance abuse.

Implications of Premise #2. The various correlates of substance abuse may help resolve the substantial clinical heterogeneity that characterizes this disorder. For example, alcohol researchers have long distinguished between two idealized pathways to alcoholism (Knight 1937; Sher 1991), and the correlations summarized above suggest that the same pathways may operate with substance abuse.

Included in the first group are those whose alcohol abuse appears to be a means of coping with psychological distress (i.e., the neurotic "self-medicators"). Included in the second group are those for whom alcohol abuse appears to be a manifestation of an underlying personality disorder (i.e., antisocial, thrill-seeking alcoholics). Cloninger (1987) has argued further that different biological pathways may underlie the expression of the two forms of alcoholism, with genetic factors playing a greater role among the antisocial as compared with the neurotic type. The Cloninger model provides a valuable conceptual framework for exploring genetic heterogeneity in other substance use disorders.

Findings from behavioral genetic research on other undersocialized conditions, and especially alcohol abuse, criminality, and delinquency, may help provide an important foundation for exploring the etiology of substance abuse. In particular, as reviewed below, behavioral genetic research indicates that the nature of environmental influence in sociali-zation disorders differs fundamentally from the nature of environmental influence with other psychological conditions.

Conceptual Framework

In considering the etiology of a complex behavioral characteristic like substance abuse, it is useful to distinguish proximal and distal determinants. The most powerful and immediate determinants of drug use behavior involve the context in which it occurs—substance availability, peer group pressure, prior reinforcement history, and so on. Genetic factors, to the extent they are relevant, would necessarily exert a remote and probabilistic influence on drug use behavior. The challenge to behavioral geneticists is to demonstrate how knowledge of a distal influence such as genetic factors can help researchers identify and understand the relevant proximal determinants of behavior.

Figure 3 (adapted from McClearn 1993) provides a useful heuristic model for conceptualizing the nature of genetic influence on behavior. The figure emphasizes two features of behavior that need to be considered in designing approaches aimed at identifying genetic etiology. First, the figure emphasizes the multiple levels of mediation, ranging from the molecular to the social, between primary gene product and an observed behavioral phenotype. Characterizing the gene-to-behavior pathway will

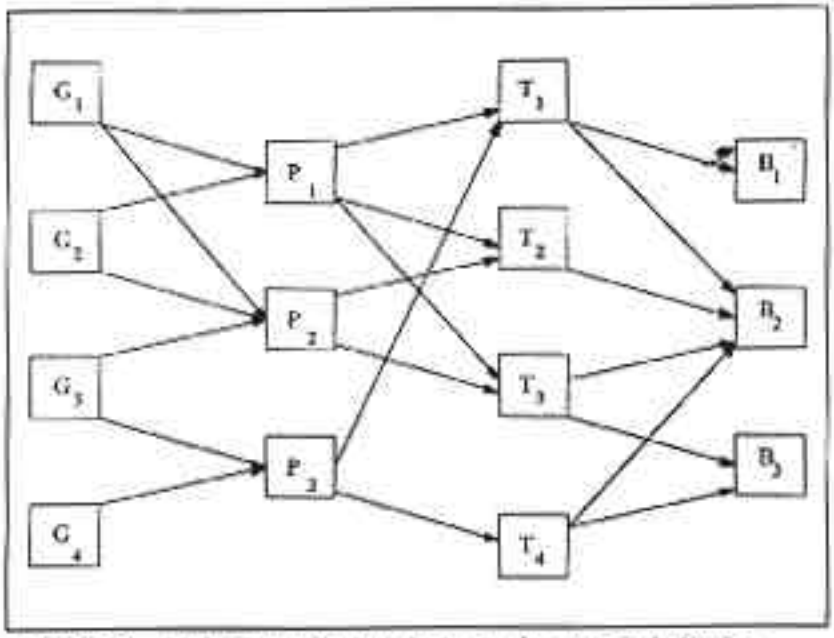

FIGURE 3. *Multiple mediating chains in the gene-to-behavior pathway.*

SOURCE: Adapted from McClearn 1993.

KEY: G = single gene effects; P = the effects of physiological systems; T = the effects of psychological traits; B = observable behaviors.

require multiple levels of analysis. Thus, although the association of single gene products with behavioral conditions is likely to provide major insight into the heterogeneity and etiology of behavioral disorders, it is highly unlikely that behavior will ever be reduced effectively and entirely to interactions among proteins. Alternatively, those who seek to characterize inherited behavior disorders through mediating, genetically influenced psychological and psychiatric conditions need to be aware of, and take into account, the molecular and neurochemical basis of these conditions.

The figure also serves to emphasize the fundamental influence of the environment on behavior. The further removed the phenotype is from the primary gene product, the greater the opportunity and thus the greater the likelihood for environmental effects. A comprehensive evaluation of environmental influence on substance abuse behavior

might parallel the multiple levels of genetic analysis: How do environmental factors moderate gene expression, neurochemical processes, and behavioral tendencies? Moreover, the existence of substantial environmental influence is likely to obscure attempts at identifying the molecular basis of behavior. One need only consider the general failure to find single gene effects on behavioral disorders such as schizophrenia (Sherrington et al. 1988), manic-depressive illness (Egeland et al. 1987), and alcoholism (Gelernter et al. 1993) to realize that application of molecular genetic methods to human behavior research is likely to proceed much more slowly than society has grown accustomed to after witnessing the remarkable discoveries made when this new method was used on classical genetic disorders such as cystic fibrosis and Huntington's disease. Indeed, without knowledge of the environmental mechanisms that produce incomplete penetrance and the resultant false negatives that vex genetic linkage studies, effective progress in identifying the genes that underlie behavior disorders may be altogether precluded.

The interest in this proposed study is in what might be considered the ultimate step in the gene-to-behavior pathway, that involving the trans-action between underlying, inherited psychological characteristics and the experiential determinants of substance abuse behavior. If contextual factors exert a strong proximal influence on substance abuse behavior, then distal genetic influences might usefully be characterized by how they increase an individual's chance of experiencing provocative situations (apossibility behavioral geneticists term "genotype-environment correlation"), how genetic factors cause different individuals to experience the same situation differently (a possibility behavioral geneticists term "genotype-environment interaction"), or both. Both possibilities can be explored using traditional behavioral genetic methods such as twin, adoption, and family studies.

The conceptual orientation and placement of substance abuse behavior within the broader context of undersocialized behaviors and conditions has led to the following three hypotheses about the behavioral genetics of substance abuse.

1. As there is increased opportunity for environmental influence in phenotypes far removed from the primary gene product, the strength of environmental influence is expected to be greater on socialization disorders such as drug abuse than on other behavioral characteristics more directly linked to physiological processes.

2. One mechanism of genetic influence involves the mediation of experiential risk factors by genetically inherited psychological conditions (i.e., genotype-environment correlation).

3. A second mechanism of genetic influence involves the inheritance of differential sensitivity to environmental influence (i.e., genotype-environment interaction).

GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO PHENOTYPIC VARIATION

Biometrical genetics is founded on the assumption that the variance (V) in a quantitative trait or phenotype, P, can be decomposed into components associated with genetic factors, G, shared environmental factors, C (environmental factors shared by and potentially contributing to the similarity among reared-together relatives, including socio-economic status of the rearing home, parental child-rearing strategies, etc.), and unshared environmental factors, E (i.e., environmental factors not shared and thus potentially contributing to the dissimilarity among, reared together relatives). That is,

$$VP = VG + VS + VE ,$$

where VP represents the total phenotypic variability, and VG, VS, and VE represent, respectively, the components of total phenotypic variance attributable to genetic, shared environmental, and unshared environ-mental factors. Alternatively, by dividing both sides of the equation by VP, one can decompose the phenotypic variance into proportions associated with genetic factors (h2 = VG/VP) (heritability)), shared environmental factors (c2=VS/VP), and unshared environmental factors (e2=VE/VP). Observations of twins and other reared-together and reared-apart relatives can be used to estimate the three relevant variance ratios and thus provide information on the relative contribution of genetic, shared, and unshared environmental factors to total phenotypic variability (Neale and Cardon 1992).

One of the more remarkable and provocative findings to emerge from recent behavioral genetic research is the observation that, while environmental factors exert a substantial influence on individual differences in virtually every psychological characteristic, the relevant environmental factors appear to be those that create differences rather than similarities among reared-together relatives (Plomin and Daniels

1987). That is, there exists a substantial body of research suggesting that the psychological similarity between two related individuals is largely independent of whether or not those individuals were reared in the same home by the same parents. However, there are two notable exceptions to this otherwise general conclusion on the absence of shared environmental effects on behavior. The first is intellectual ability and achievement (Thompson et al. 1991), and the second involves outcomes of the socialization process. With respect to the latter, for example, Mednick and colleagues (1984) reported that an adoptive parent background of criminality predicted likelihood of criminal registration in a sample of Danish adoptees. Cloninger and colleagues (1981) found rearing socioeconomic status to be related to alcohol abuse among Swedish adoptees. Of direct relevance to the present topic, Cadoret (1992) reported that adoptive parent divorce, sibling drug problem, or antisocial behavior among adoptive relatives were all related to drug abuse in a sample of Iowa adoptees.

The magnitude of shared environmental effects can be estimated from observations made in a classical twin study (i.e., the study of reared-together MZ and DZ twins). This can be illustrated from preliminary observations made in an ongoing study of male adolescent twins. Table 1 reports twin correlations derived from teacher ratings of 11-year-old male twins on three personality dimensions (aggression, responsibility, and extraversion), and three behavioral dimensions (inattention, hyperactivity, and conduct disorder). Under the standard biometrical model, the correlation (r) between MZ twins is rMZ = h2 + c2 while the correlation between DZ twins is rDZ = 1/2h2 + c2. Consequently, the parameters h2, c2, and e2 can be estimated from the observed twin variances and covariances using maximum likelihood methods described in Neale and Cardon (1992). These estimates (along with their standard errors) are also given in table 1.

Of greatest interest to the present discussion is the consistently substantial estimate associated with shared environmental effects. Extraversion, the dimension that is least related to socialization processes and thus of least relevance to substance abuse, is the dimension that evidences the highest degree of heritability and lowest degree of shared environmental effects, while conduct disorder (in this case specifically related to the rule-breaking behavior at school that can be rated by teachers) is the dimension that evidences the lowest degree of heritability and highest

TABLE 1. Twin intraclass correlations and variance components estimates for teacher ratings of 11-year-old male twins.

	Twin Correlation		Variance Component Estimate		
	MZ (N=111)	DZ (N=74)	h2	c2	e2
Behavioral Dimensions					
Inattention	0.74	0.56	0.38±0.15	0.37±0.15	0.25±0.04
Hyperactivity	0.72	0.48	0.20±0.17	0.49±0.17	0.31±0.04
Conduct Disorder	0.61	0.65	0b	0.63±0.05	0.37±0.05
Personality Dimensions					
Aggression	0.69	0.37	0.42±0.22	0.25±0.22	0.33±0.05
Responsibility	0.74	0.48	0.50±0.18	0.24±0.17	0.26±0.04
Extraversion	0.76	0.39	0.79±0.03	0b	0.21±0.03

KEY: h2 = heritability; c2 = proportion of variance due to shared environmental effects; e2=proportion of variance due to nonshared environmental effects; b = boundary solution, standard error is not estimable.

degree of shared environmental effects. In fact, the estimated heritability of the conduct disorder measure is 0.0, in apparent contradiction to the earlier claim that all behavioral traits evidence at least some degree of heritability. It is possible that this estimate may reflect a chance sampling fluctuation from a modest population value; other studies have reported significant but modest genetic influences on delinquency (Cadoret et al. 1983).

Although there is a clear need to replicate these preliminary observations in larger samples, the results summarized in table 1, as well as earlier twin adoption research, suggest that socialization behaviors may be less heritable and more environmentally influenced than other psychological characteristics. This is not an altogether unexpected result; much more is known about the environmental basis of rule-breaking behavior than about the conditions that promote extraversion among adolescents (Loeber and Dishion 1983). In any case, as the authors follow these 11year olds into early adulthood and the onset, in many cases, of drug use and abuse, they expect to find greater evidence of shared environ-mental effects than has been found in behavioral genetic studies of other behavioral characteristics and disorders.

Genotype-Environment Correlation

While individual differences in some behavioral traits may be traced relatively directly to nervous system processes, the behavioral complexity of the vast majority of psychological traits would seem to preclude easy reduction to basic neurophysiological processes. The size of an indi-vidual's vocabulary (Pedersen et al. 1992), one's interest in specific occupational pursuits (Moloney et al. 1991), and one's attitudes toward political ideologies (Martin et al. 1986) are all traits for which there is substantial evidence of heritability, yet none of these traits could be considered "hardwired." In each case, environmental factors—be they exposure to a rich assortment of words, specific political philosophies, or occupational models—appear to be the proximal determinants of behavior. The apparent contradiction of distal genetic with proximal environmental influence may find resolution in the proposition that genetic factors can influence complex psychological traits like interests and attitudes (or sub-stance abuse) by affecting the range of individual experience, a phenom-enon behavioral geneticists term "genotype-environment correlation" (Plomin et al. 1977; Scarr and McCartney 1983). In particular, individuals with different talents, temperaments, and physical characteristics (all traits that are, in part, genetically influenced) tend to evoke different reactions from parents, teachers, and peers (aprocess Scarr and McCartney call "evocative genotype-environment correlation"). When given a choice, these individuals may select experiences that are consistent with and reinforce their underlying genetically influenced abilities and interests (a process Scarr and McCartney call "active genotype-environment cor-relation"). In short, in a permissive society, the nature of individual experience is likely to reflect, in part, inherited behavioral tendencies and thus, perhaps ironically, represent a potential pathway for genetic influence.

To illustrate the mechanism of genotype-environment correlation and suggest how it might be applied to the etiology of substance use and abuse, consider what certainly is one of the strongest and most robust correlates of drug use behavior—peer group affiliation (Kandel and Andrews 1987). For the 11-year-old twins in the authors' study, teachers were asked to rate characteristics of the twins' peer groups in addition to rating the behavioral and personality dimensions mentioned above. When factor analyzed, these peer group ratings yielded two relatively distinct but correlated dimensions, positive peer group models (e.g., good students, involved in school activ-ities) and negative peer group models (e.g., rebellious, dangerous to be with).

Table 2 shows the twin correlations and the estimated variance components for these two dimensions of experience based on a preliminary sample of the 11-year-old twins. Although, as expected, there are sub-stantial shared environmental effects, there are also small (not estimated to be statistically significant) genetic influences on both peer group factors.

TABLE 2. Twin intraclass correlations and variance components estimates for teacher peer group ratings of 11-year-old male twins.

	Twin Correlation		Variance Component Estimate		
	MZ (N=93)	DZ (N=62)	h2	c2	e2
Positive peer models	0.75	0.62	0.17±0.15	0.57±0.15	0.26±0.04
Negative peer models	0.73	0.53	0.24±0.18	0.46±0.17	0.29±0.05

KEY: h2 = heritability; c2 = proportion of variance due to shared environmental effects; e2=proportion of variance due to nonshared environmental effects.

Insight into the process by which genetic factors might influence peer group affiliation is obtained by considering other correlates of peer group affiliation. As might be expected, there is a strong correlation between rated level of responsibility and exposure to negative peer group models ($r = -0.617$, $N = 310$, $p < 0.001$)—individuals rated as untrustworthy tend also to have friends who were rated as being problematic. Unlike standard cross-sectional research, however, research with twins provides additional information on the nature of phenotypic associations through analysis of cross-twin correlations (i.e., twin A's rated responsibility with twin B's negative peer models). The MZ twin cross-twin correlation between responsibility and negative peer group models ($r = -0.615$, $N=93$ pairs, $p< 0.001$) is substantially greater than the DZ cross-twin correlation ($r=-0.390$, $N = 62$ pairs, $p < 0.01$), implicating genetic mediation. Indeed, the MZ twin cross-twin correlation approximates the within-person correlation, indicating that MZ co-twin level of responsibility is as accurate a predictor of peer group affiliation as an individual's own level of responsibility. A genetic influence on peer group affiliation may reflect the effect of inherited psychological and behavioral characteristics on peer group choice.

An additional example from Lytton's (1990) recent analysis of parent and child effects in childhood conduct disorder illustrates how genotype-environment correlations can influence developmental processes. In reviewing the available evidence, Lytton makes a strong case for the proposition that much of the destructive and ineffectual parental behavior one sees associated with childhood conduct disorder may actually reflect the reactions of parents to the aggressive and defiant actions of their children. That is, child defiance is apt to be met, initially, with physical punishment and, if punishment proves ineffective, ultimately with neglect. In fact, both parental conflict and neglect are factors that characterize parent-child relationships in conduct-disordered families (Loeber and Stouthamer-Loeber 1986). Granting that ineffective parenting may represent reactions to offspring behavior, however, is not to conclude that these parental behaviors do not contribute to the etiology of childhood conduct disorder. In a series of investigations, Patterson (1982) has shown how evocative offspring behaviors can help establish "coercive cycles" that lead to an escalation of behavioral disturbance. Given the similarities between substance abuse and conduct disorder, the extensive literature relating experiential factors to substance abuse (Brook et al. 1992), and the likelihood that these critical experiences reflect individual choice to some extent, it will be important to determine the extent to which genetic influence on substance use and abuse is ultimately mediated by experiential factors.

Genotype-Environment Interactions

Most behavioral geneticists believe that inherited differences in sensitivity to environmental influence, a phenomenon they term genotype-environment interaction, represents a basic mechanism by which genes can influence behavior. Indeed, the dominant conceptual model of psychopathology is the diathesis-stress model, which emphasizes the integral and synergistic nature of genetic and environmental influences (Rende and Plomin 1992). That is, inherited factors (the diathesis) are hypothesized to establish individual levels of vulnerability that alone are not sufficient for the expression of behavioral pathology but rather depend in their expression upon the degree of environmental exposure (stress). In particular, the diathesis-stress model posits that environmental factors will be most critical among the biologically vulnerable, while those with low levels of biological vulnerability carry a low risk for the development of a behavioral disorder even when exposed to high levels of environmental provocation.

The most consistent support in the behavioral genetic literature for the existence of genotype-environment interactions has come from investigating socialization-related disorders (Cloninger et al. 1981 (alcoholism); Cadoret et al. 1983 (adolescent conduct disorder); and Mednick et al. 1984 (adult criminality)), which again motivates concern for the phenomenon in exploring the etiology of substance abuse. For example, not every child is swayed by negative peer group pressure, nor is every child likely to use drugs even when they are widely available. Inherited vulnerability may involve pharmacological responses that influence drug sensitivity as well as psychological characteristics that influence the likelihood of being affected by negative peer models.

DESIGN AND EXPERIMENTAL METHODS

The position and research from which this proposal is designed is that behavioral genetic research is appropriately directed not only at identi-fying specific gene products and characterizing the mediating role of inherited neurophysiological systems, but also at understanding how inherited factors combine with environmental effects to influence the development of complex behavioral characteristics such as substance abuse. In order to explore the joint influence of inherited and environ-mental factors in the etiology of substance abuse, the Minnesota Twin Family Study (MTFS) was initiated 5 years ago as a prospective behavioral genetic study of substance abuse. Details of this study are provided elsewhere (Iacono et al., this volume). This chapter focuses on those features of this ongoing study that are directly relevant to under-standing the relationship between genetic and environmental risk factors in the etiology of substance abuse.

Research Aims

The conceptual orientation motivated three testable hypotheses about the relationship between genetic and environmental influences, which are now specific research objectives.

1. Determine, using a twin-family study design, the relative contribution of genetic and environmental factors to the etiology of substance abuse and test the proposition that environmental factors exert a stronger influence (and genetic factors exert a weaker influence) on the development of substance abuse than on the

psychological and physiological factors that mediate the expression of this disorder.

2. Determine whether exposure to the environmental factors that increase the risk for substance abuse is associated, in part, with genetic factors (i.e., genotype-environment correlation).

3. Determine whether individual differences in susceptibility to the influence of the environmental risk are associated with inherited factors (i.e., genotype-environment interaction).

Sample Ascertainment and Structure

Ultimately the MTFS sample will be composed of 1,300 twin families. Families are selected such that: the twins in the family are either 11 or 17years old at time of assessment; approximately equal numbers of MZ, like-sex DZ, male and female twin pairs are included; and approximately 40 percent of the sample is designated as "high-risk" by virtue of having a biological parent who is alcoholic.

Each of these design features deserves comment. The cross-sectional composition of the sample is meant to capture adolescents at two key transition points in the etiology of substance abuse. At age 11, most individuals will have had limited or no direct experience with alcohol or prohibited substances. Consequently, the age 11 assessment will help to identify predictors of substance abuse initiation unconfounded by the consequences of substance use. Rates of substance use and antisocial behavior peak in late adolescence and then decline markedly in early adulthood. The purpose of the age 17 assessment is to identify factors that differentiate adolescent substance users who go on to have persistent adult problems from those whose substance use is transitory and primarily exploratory.

The study of a relatively large sample of identical and nonidentical twins and their parents represents one of the most powerful designs in behavioral genetics for resolving the separate influence of genetic and environmental factors. Because of the availability of national twin, adoption, and medical registers, most behavioral genetic research has been undertaken in the Scandinavian countries. Recently, however, MTFS researchers as well as others have shown how representative twin registers can be established in the United States (Lykken et al. 1990). In the present study, twin pairs are identified from records of twin births (birth records are public records in Minnesota) and the current status and location of the twins were determined using various

public sources (e.g.,telephone and reverse directories, school records). In the case of the adolescent twins in the MTFS, 92 percent of surviving twins have been located and approximately 80 percent of the twin families have been recruited to participate in a 1-day assessment. Consequently, this sample of 1,300 twin families is broadly representative of the population of Minnesota and includes twins who are being reared in especially challenging circumstances (e.g., single-parented, inner-city, on government assistance) as well as those from privileged backgrounds (e.g., intact family, low-crime community, high-income family).

The MTFS sample is selected to overrepresent families with alcoholic biological parents. Because most behavioral disorders, including substance abuse (Merikangas et al. 1992), aggregate in families, the offspring of affected parents constitute a group at relatively high risk for developing the disorder. Specifically, there is an extensive literature documenting that the offspring of alcoholics are more likely to suffer alcoholism, drug abuse, and psychiatric disorders and score higher on measures of delinquency and personality risk as compared with the general population (Sher 1991). Moreover, the strong phenotypic association between alcoholism and other substance abuse suggests that the offspring of alcoholics are a group that is at relatively high risk for developing substance abuse disorders.

Assessment

MTFS participants complete a day-long assessment protocol. An overview of the major components of this 8-hour assessment follows.

Systematic Assessment of Environmental Risk Factors. The assessment of environmental influences is organized around two broad categories that roughly correspond to the behavioral genetic decomposition of environmental variance into shared and unshared components. Familial environmental measures are those that aim to characterize the rearing home environment of adolescent participants and include assessment of family climate (e.g., Family Environment Scales, Moos and Moos 1981), specific parent-offspring relationships (e.g., that between rearing father and son), material resources of the home (e.g.,socioeconomic status, parental income), and parental attitudes about and models of substance abuse. Extrafamilial environmental measures are those that aim to identify formative experiences the adolescent twins have outside their rearing homes including peer group characteristics, life events, and nonfamilial social support.

Behavioral geneticists have been legitimately criticized for the simplicity of their approach to environmental assessment (Wachs 1992). Although some recent behavioral genetic research has begun to address this limitation (Plomin et al. 1994), all too often in behavioral genetic investigations the environment is conceptualized as nothing more than a residual, that which is left over after genetic effects have been partialled out. Comprehensive assessment of environmental risk is, however, critical to the general aim of understanding the relationship between inherited risk and environmental provocation. The assessment of environmental risk used in this study is based upon the substantial body of substance use/abuse research demon-strating, for example, that substance abusers are more likely to have poor relations with their parents than nonabusers (Coombs and Landsverk 1988), to come from families where behavioral control systems are incon-sistent and lax (Reich et al. 1988), and to be associated with peer groups where deviance is valued and reinforced (Kandel and Andrews 1987).

Multidimensional Assessment. Participants in the MTFS complete a comprehensive substance use and abuse assessment. The subjects are administered a structured psychiatric interview to assess comorbid diagnoses including depression and antisocial personality disorder (ASPD); undergo a comprehensive assessment of personality that includes multiple indicators of the two broad dimensions hypothesized to be most directly relevant to the etiology of substance abuse (i.e., negative emotionality and behavioral constraint) by self-report as well as by ratings by significant others (e.g., parents and teachers); complete an extensive psychophysio-logical battery (Iacono et al., this volume); and complete an assessment of academic achievement, aptitude, and commitment.

The need for a multidimensional approach to assessment is justified both by the oft-replicated observation that substance abuse characteristically exists within the context of other antisocial behaviors, and the need to move beyond the simple demonstration of genetic effects to a characterization of the nature of those effects.

Followup

There is a growing realization among behavioral scientists that many adult behavioral disorders are developmental; that is, while the disorder may be expressed primarily in adulthood, early signs may be manifest in adolescence or even preadolescence. For example, there is a strong association between adult drug use disorders and hyperactivity in child-hood (e.g., hyperactive boys are 10 times more likely than nonhyper-active boys to have a drug use disorder in early adulthood (Mannuzza et al. 1991)). Apart from the increased risk of adult behavioral disorder these early signs signal, they also implicate specific developmental pathways in the etiology of the disorder.

Mannuzza and colleagues (1991) showed that the association between childhood hyperactivity and adult substance abuse is mediated entirely by antisocial behavior, suggesting that the mechanism underlying the association may involve the relative difficulty of socializing hyperactive boys rather than, say, some untoward effect of early pharmacological treatment on later pill-taking behavior.

Adolescent participants will be followed into early adulthood in order to identify those twins who develop a chronic pattern of substance abuse. Participants are assessed annually with telephone interviews and through teacher ratings, and every 3 years complete an in-person assessment designed to coincide with major life transitions (e.g., from elementary to junior high, from high school to college or the job market).

Analytical Approaches

It is far beyond the scope of this document to comprehensively review developments in biometric genetics relevant to the aims of the MTFS. These developments (summarized in Neale and Cardon 1992) have provided behavioral genetic researchers with powerful analytical tools for exploring both univariate and multivariate hypotheses with twin and family data. Of relevance here is the development of methods to fit general univariate models to twin and family data, estimate the genetic and environmental components of phenotypic variance in those models, and test the goodness-of-fit of those models to the observed data.

Multivariate extensions of univariate models have been developed that allow investigation of genetic and environmental contributions to longitudinal stability and change and the covariances among a set of

measures. Most significantly, methods to explore the existence of both genotype-environment correlation and interaction with twin data are now available (Neale and Cardon 1992).

PUBLIC HEALTH SIGNIFICANCE

The consistent finding of genetic influences on most psychological characteristics suggests that, once the basic behavioral genetic studies are completed, substance abuse will also be shown to be affected by genetic factors. The likelihood of this result spurs consideration not only of whether genetic factors influence complex behavioral characters like substance abuse, but also of the mechanisms underlying that influence. Explicating these mechanisms may proceed along many levels of analysis; the approach proposed here is focused upon the transaction between inherited psychological traits and experience. In particular, it is argued that it will be difficult to understand the nature of inherited influence without simultaneously considering the nature of environmental influence. Genetic and environmental effects are likely to be synergistic (i.e., a genotype-environment interaction) and mutually interdependent (i.e., a genotype-environment correlation). This program of research is aimed at addressing these issues empirically.

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DISCUSSION

Audience and Panel Participants: Meyer Glantz, David-Comings, David Lykken, Remi Cadoret, George Uhl, Howard Moss, and Ralph Tarter

Dr. Comings: I was somewhat surprised, as I see you were also, about the negative heritability, zero heritability, for conduct disorder. Then I was pleased to hear you say—if I heard you right—that this tends to come from a lower socioeconomic group of individuals.

There's a beautiful study by Satterfield, probably 20 years old now, where he looked at respective scores, ADHD children grown up and stratified by socioeconomic status. And those in the higher and middle status had a twentyfold increase in the respective controls, and the lower socio-economic status only had a fourfold increase. So, obviously the people where you get the group from can make an enormous difference in that.

Dr. Lykken: Yes. I think that's right. My primary interest is in psychopathy and general socialization problems. And I've always thought that the best way to get a pure psychopathic group is to begin with a group with intact parents, middle-class parents, where you can attribute the problems to environmental effects. Psychopaths occur also in the underclass, but there it's more complicated and it's harder to tell them apart.

I may make a couple of slight responses to the comments. I'm not really that apologetic about the question of the gene effects on substance abuse. My colleague Matt McGue, who wrote this paper, is much more conservative than I, and there is an interaction between us such that my presence tends to make him all the more conservative. So, knowing that I was going to talk about this he was very careful, trying to curb my behavior.

And, I should explain that you're quite right; we don't want to study substance abusers or twins—only twins whose parents are alcoholic because that gives us the problem of coaggregation and special classifi-cations. So, we merely enriched our sample with parents who are alco-holic, and we intend—fully intend—to study the two groups separately.

Dr. Cadoret: [Editor's note: The following is a minipresentation from the floor]:

I think that the twin studies and the adoption studies are good ways to come up with models as to how people get to be substance abusers. I'd like to

demonstrate this with some of our adoption data, starting with a model that I developed back in 1985 and then giving you results of a study I just finished for National Institute on Drug Abuse of about 200adoptees separated at birth.

If we look at the first figure, we see adoptees who are adopted away at birth by nonrelatives. We use a kind of case-control method. I match an adoptee who has a know biologic background of psychopathology with a control adoptee. We match the adoptees with another adoptee from the same agency, same sex, same age, as a control. This figure shows a model that was developed for males back in 1985 for alcohol dependence. We found that there were several pathways to alcohol dependence. One was a direct pathway from a biologic parent who was alcoholic to adoptee alcohol abuse/dependence (figure 1, relationship 2). These are adult adoptees, and we determine their psychiatric condition by giving them a

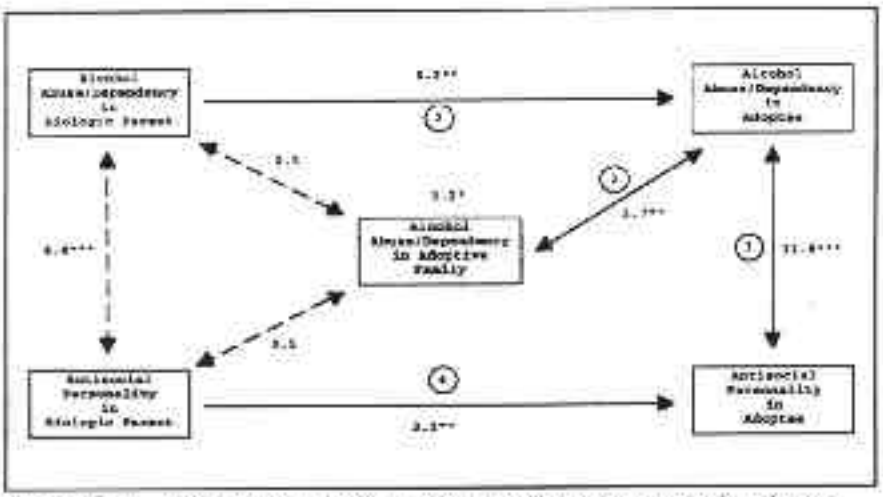

FIGURE 1. *Interaction diagram of etiologic factors for male adoptee alcohol abuse/dependence and antisocial personality.*

KEY: * = odds ratio significant at 5% level; ** = odds ratio significant at 1% level; *** = odds ratio significant at 0.1% level;
→ = relationship found in data; - -➤ = relationship forced into model to control for selective placement. Circled numbers refer to relationships.

SOURCE: Modified from Cadoret et al., *Arch Gen Psychiatry* 42:161-167, 1985. Copyright 1985, American Medical Association. Used with permission.

DIS. It's given to them blindly by our research assistant who doesn't know anything about the biologic background. So that is one pathway.

The other pathway seems to come from biologic parents who are antisocial, increasing the chance that the adoptee will be an antisocial as an adult (figure 1, relationship 4). I think that the direction of effect goes from antisocial personality to alcohol abuse/dependence as the second pathway (figure 1, relationship 1). There's a third pathway: An adoptive family that had someone in the family who was an alcohol abuser or dependent increases the probability of an adoptee's becoming an alcohol abuser as an adult (figure 1, relationship 3). So, these are three independent pathways to alcohol abuse/dependence.

This is a log-linear model, and all pathways are independent of the others. We control for selective placements by forcing relationships into the model as shown by the dotted arrow in figure 1.

Figure 2 shows what we found with a model with 95 male subjects [Cadoret et al., "Adoption Studies Demonstrating Two Genetic Pathways to Drug Abuse." Arch Gen Psychiatry 52:42-52, 1995]. In this study, we start out with a biologic parent who has alcohol abuse or dependence and you can see there is a direct effect to adoptee drug abuse and dependence (figure 2, relationship 2). There is also an effect to antisocial personality, which is mediated by adoptee aggression (figure 2, relationships 3 and 4). Biologic parent antisocial personality increases the chance of aggression (figure 2, relationship 3), which in turn leads to adoptee antisocial personality and thence to drug abuse/dependence. Of course, there is a high correlation between abuse and dependence and alcohol abuse and dependence (figure 2, relationship 6). Here again is a model that shows that there might be a direct pathway and an indirect pathway, both leading to adoptee drug abuse/dependence. This implies that these may be different genes, and I think it would be very interesting to see if some of the allelic studies that we heard about earlier this morning would be more characteristic of the induced pathway than of the direct pathway.

Figure 3 shows what happens when we add to that model environmental factors. As an environmental factor we selected variables that indicated disturbed adoptive parents such as psychiatric or behavior problems, marital separations, and divorce. These factors were added together to form a disturbed adoptive parent variable that, when added to the model just shown inn figure 2, increases the chance of an antisocial personality diagnosis in the adult adoptee (figure 3, relationship 3). This augmented

[--- Unable To Translate Text Box ---]
model is shown in figure 3. Here again are three independent pathways to substance abuse. These findings are relevant to the question that we have been struggling with today of how do you determine genetic and clinical heterogeneity in your sample. Adoption studies like this could indicate how much effect these different environmental factors have in producing what you see clinically, and help distinguish genetic from environmental effects.

Dr.Uhl: I was just going to comment that in a group of incarcerated individuals, virtually all of whom were substance abusers and roughly half of whom had psychopathy diagnoses, Dr. Steven Smith found no difference in our hands between the dopamine receptor gene frequency in

[--- Unable To Translate Text Box ---]
the psychopathic drug abusers compared to the nonpsychopathic drug abusers (Biological Psychiatry 1993).

Dr. Cadoret: That may be a very extreme sample. Once your dopamine is so off that you end up in prison, it may not matter much whether you're on drugs or not.

Now, I think one of the advantages of twin and adoption studies is that you're dealing less with a clinical sample than with population samples, and, for instance, our correlations that we get between adult antisocial personality and adult drug abuse or alcohol abuse are very similar to what the ECA reports in population samples. The sample is picked out because they're adoptees, not because they're coming for help. As a matter of fact, most of the abusers in these samples have

never sought help. The usual tip of the iceberg sort of thing. But, I've always thought that information from this type of study could be used to improve the prediction of what phenotype really represents a genotype, if you see what I mean. If you know an environment has caused a phenocopy, then I think you're in much better shape, and I don't see how you can do it from other types of studies.

Dr. Moss: A question for Dr. Cadoret about the study you reviewed with us. Can you tell me whether or not there was spousal resemblance among the biological parents for substance use disorder, or was only one parent affected?

Dr. Cadoret: It's usually one parent. We made the diagnoses on the parents from actual hospital or prison records, so we're pretty sure of their diagnoses. Unfortunately, you don't have the same amount of information available on their mate.

Dr. Moss: So, the effects that you see could not be ascribed to social homogamy—well in this case not—among the parents, or assortmentive mating?

Dr. Cadoret: Well, I think there probably is some kind of assortitive mating. I think the old song about "birds of a feather flocking together" is very true here.

Dr. Moss: Would that increase, though, the liability value in the offspring in the adopted offspring?

Dr. Cadoret: I think it would, and that's one factor that's not too easy to measure in adoption studies because we go back anywhere from 20 to 40years to get records. But, you know, when you look at the social circumstances under which a lot of these children are created, it's a drinking dad and he meets a mom who is also in the bar.

Dr. Moss: You didn't show a pattern of alcoholism in parents to alcoholism in offspring, but presumably that exists in both those cases?

Dr. Cadoret: In these log linear models, we just put in all of the variables and this is what comes out. This is the best fitting model. None of the pathways went directly, in this case, to alcohol abuse, just indirectly through drug abuse.

Dr. Glantz: It's kind of a shame that one of the variables that cannot be considered because of historical reasons is whether or not the parents would have used drugs if drugs had been more widely available. In other words, there were certain periods of time where, if you chose to use an abusable substance, pretty much you were limited to alcohol in most strata of society. Not that one would wish that more people had been affected by drug abuse, but it certainly, for control purposes, would have been interesting to see who would have gravitated toward which type of abusable substance in all of these lineage studies. In the future, parents will become available who had more choices. Then, we can perhaps determine what choice means.

Dr. Cadoret: We already see that. Starting about 20 to 25 years ago, there are a lot more notations in hospital records of polysubstance abuse by these biological parents. When we put a drug abuse factor in bio-logical parents in the model, it's close but it doesn't go into the model. If you look at the drug abusers, the biological factor tends to go to drug abuse, but it's not significant. We don't have a large enough sample, but, as you say, given another 5 or 10 years there will be a lot of those people.

Dr. Tarter: I have a speculative question both for Dr. Cadoret and Dr.Lykken. In light of those very elegant papers in the current [1993] issue of "American Psychologist and Sociobiology" with respect to the question of parental investment in these offspring, the parental investment in your own biological offspring, and the increased risk for that offspring to experience abuse and even death and the extent to which there can be increasing—well, equal—parental investment where you have two twins—I think that was even commented on in the paper—is there a heuristic basis for research with respect to substance abuse on this, on developmental pathways, from this perspective using these paradigms?

Dr. Lykken: Well, I'm not sure I have a bright idea, but it is clear to me that there is a big difference between the substance abuser, if he exists, who has good nurturing, intelligent, competent, providing parents with whom he has a good relationship and the substance abuser who has a more typical parental background. I think it would be fascinating to get a group of substance abusers, or a group of delinquents, or criminals who come from what we would think of as being ideal family backgrounds so that we can rule out that kind of influence and compare them to the general run of abusers. But, I'm in hopes that the study we're doing at Minnesota, because these Minnesota parents are pretty good by and large and dedicated, that we

will have an opportunity to look at that in a preliminary way, but I can't guarantee it.

Dr. Cadoret: Dr. Tarter, I'm sorry I didn't read that article, but I've always been intrigued by the sociobiology of the spread of antisocial genes, and wondering where things like altruism come in—behaviors that you don't usually associate with antisocials. But, I think that there is a possibility that for antisocials who drink, there's something about that situation that might lead to more sexual behavior and more spread of the genes under those conditions. An awful lot of women who give up children for adoption report that they were drinking when they got pregnant or they were drinking during pregnancy, so that the combination of antisocial genes plus sexual interaction promoted by drinking may even facilitate the spread and the maintenance of the antisocial genes in the population.

Dr. Glantz: I'd just like to say briefly that although it probably isn't all that likely, there is always the possibility that the effect is teratogenic and congenital, rather than traditionally genetic, at least in some cases.

Dr. Cadoret: Yes. I'm glad you brought that up, because 21 of our biologic moms were drinking during their pregnancy. Now, because the records are not the world's greatest, you don't know how much they drank, how much they smoked, how poor their diet was, and all those other environmental factors that are probably important. But, even when you put fetal alcohol syndrome into the equation you still get these direct genetic factors. What the fetal alcohol exposure does seem to increase is the number of adult personality disorder symptoms that people have in Group A and Group C and, of course, in Group B. And that's only in the offspring of the drinking moms, which is quite interesting. I just wish that our records were a little better, but fetal alcohol exposure is certainly a factor. However, you don't know whether it's a gene-environment interaction because we don't know how many of the moms who weren't alcoholic were also tippling during their pregnancy. You just don't get that kind of fine grain information.

An Identical Twin High-Risk Study of Biobehavioral Vulnerability

Ming T. Tsuang and Michael J. Lyons

STATEMENT OF THE PROBLEM

The proposed study begins with the assumption that individuals differ in their vulnerability to develop drug abuse. Therefore, a crucial step in developing prevention and treatment programs for drug abuse is the identification of the biobehavioral basis of the vulnerability. The proposed study is a type of high-risk study using only identical (monozygotic, MZ) twins, rather than a conventional twin approach with both MZ and dizygotic (DZ) twins. The examination of MZ twins discordant for abuse offers the unique opportunity to use genetically identical individuals to look for potential biological and psychological markers or correlates of vulnerability unconfounded by the effects of drugs; it is a method for disentangling the cause and effect of drug usage, albeit in a high-stress, atypical group.

To identify groups of individuals with differing levels of drug abuse vulnerability, a large data set of approximately 2,000 MZ twin pairs will be recruited from the Department of Veterans Affairs' Vietnam Era Twin (VET) Registry. Using data collected by a National Institute on Drug Abuse (NIDA)-supported Harvard Twin Study of Drug Abuse and Dependence, MZ twin pairs will be selected in which the twin siblings are concordant for no drug abuse, concordant for drug abuse, and discordant for drug abuse. The presumed low-vulnerability group is composed of nondrug-abusing twins from nondrug-abusing MZ twin pairs, while the presumed high-vulnerability group is composed of nondrug-abusing twins from abuse-discordant MZ pairs.

Informative concordant and discordant pairs will be recruited and brought to a research center for the assessment of the putative vulnerability indicators. Indicators have been selected on the basis of relevant empirical findings, clinical observation, and theory. The advantage of this design is that the nondrug-abusing twin from an abuse-discordant pair has identical genetic vulnerability and similar environmental experiential vulnerability to drug abuse as the drug-abusing twin, but hasnever been exposed to the potentially confounding consequences of drug abuse.

The proposed project has two specific aims: identification of biological and psychological vulnerability indicators, and evaluation of the drug specificity versus generalizability of the vulnerability indicators.

Specific Aim 1

Identification of biological and psychological vulnerability indicators addresses the question: Are there biological and psychological differences between individuals at high risk for drug abuse by virtue of being genetically identical to a drug abuser versus those at low risk? High- and low-vulnerability groups (nonabusers from abuse-discordant pairs and nonabuse-concordant pairs, respectively) will be compared on relevant measures identified by previous research. Specifically, it is hypothesized that high-risk subjects will have lower blood platelet monoamine oxidase (MAO) activity; have reduced amplitude and more rapid habituation in event-related potentials (ERPs) in certain paradigms; have neuropsychological deficits in sustained attention, linguistic ability, executive cognitive functions, problemsolving, and abstraction; score higher in the personality traits of novelty seeking and neuroticism and lower on harm avoidance and conscientiousness; and have higher rates of antisocial personality disorder and antisocial traits.

Specific Aim 2

The evaluation of the drug specificity versus generalizability of the vulnerability indicators addresses the question: Is a given vulnerability indicator associated with risk of abuse for one, several, or all psycho-active substances? This aim is more exploratory than Specific Aim 1. It will be determined if the identified vulnerability factors are associated with only one specific drug (e.g., cocaine), with one class of drugs (e.g.,stimulants), or with abuse of numerous illicit drugs and alcohol. An associated question is: Are there differences in vulnerability indicator status associated with different levels of drug usage? The authors will apply biometrical modeling approaches to data from the Harvard Twin Study to define patterns of drug abuse that are most heritable, then conduct analyses of vulnerability indicators using groups defined by the results of biometrical modeling.

A byproduct of the design and measures used to identify vulnerability indicators is the opportunity to address several subsidiary goals: to

identify psychosocial risk and protective factors for drug abuse by comparing both twins from abuse-discordant pairs for psychosocial variables predating their onset of drug usage; to investigate potential heterogeneity in biological and psychological vulnerability to drug abuse by comparing familial and sporadic drug abusers; and to identify biological, psychological, and psychosocial consequences of drug abuse by comparing outcomes for MZ abuse-discordant cotwins.

BACKGROUND AND SIGNIFICANCE

Rationale for Proposed Study

The proposed study rests on the assumption that there are individual differences that determine, at least in part, the risk of developing drug abuse, and that these differences are present and detectable before the onset of drug abuse. Glantz (1992) described two contrasting models of the etiology of drug abuse: the social-pharmacogenic and the clinical-psychiatric models. According to the social-pharmacogenic model, the progression from the initiation of drug use to drug abuse is along a single continuum, changing quantitatively but not qualitatively. Little attention is paid to individual differences in risk of developing abuse problems once use has been initiated. Emphasis is placed on the neuropharma-cological properties of the drugs as the reason for progression in patterns of usage, rather than on vulnerability characteristics of the individual. The most important factors for escalation of use are considered to be social pressures and the drug-related effects. Factors that reduce the influence of deviant drug-abusing peers are viewed as protective. This model has been very influential in the formulation of policies, especially those that emphasize the critical importance of preventing any use of alcohol or illicit drugs.

The clinical-psychiatric model is predicated on the concept that the individual's vulnerability to the development of drug abuse is primarily a function of endogenous characteristics. This model assumes that the vulnerability or diathesis exists within the individual before any experience with the drug occurs, deemphasizing environmental factors. This vulnerability may be biological, psychological, or psychiatric. If the vulnerable individual does not abuse one type of drug, he or she may abuse some other drug or alcohol, or may manifest the vulnerability in the form of another type of problematic behavior. The model emphasizes the centrality of the desired effect (e.g., anxiety reduction) rather than a specific drug as

the motivation for the user's behavior. When the drug of choice is unavailable, the user is likely to substitute an alternative substance or behavior in an effort to achieve the desired effect. Drug abuse is seen as being a distinct psychopathological state, not just a quantitative increment starting from nonabusive use.

The proposed study, with its emphasis on individual differences, is motivated by the clinical-psychiatric model described above. The primary goal is to identify biological, psychological, and/or psychiatric characteristics of the individual that enhance vulnerability for abusing psychoactive substances. Individual differences will be examined from a number of domains that seem likely to be related to the risk for drug use problems. Several different criteria are used to identify promising variables for study. One criterion for inclusion is evidence that suggests that drug abusers differ from controls on the characteristic. Another criterion for potential relevance is evidence that the characteristic may be a vulnerability indicator for either alcohol abuse or antisocial personality disorder because these are risk factors for drug abuse.

There is compelling evidence for the potential relevance of genetically determined individual differences in reaction to various drugs from animal research in psychopharmacogenetics. An extensive animal research literature supports the importance of genetically determined individual differences that influence many aspects of drug-related behaviors, including preference for drugs and reactions to drugs. The use of animal models allows for much more invasive (and for some purposes, informative) methods than may be applied to human subjects. The following section is not intended to be a review of the very extensive findings concerning genetically determined aspects of drug action in various species, but rather to support the meaningfulness of investigating the role of heritable and other individual differences.

Researchers using animal models have demonstrated that genetic differences account for observed differences between different strains in a number of different responses to opioid drugs (Belknap and O'Toole 1991). Effects of a single gene have been shown to have a pronounced effect on reaction to opiates; a single genetic locus that determines coat color also influences physiological and behavioral responses to morphine. Nichols and Hsiao (1967) conducted a selective breeding study for addictive morphine drinking. By selecting and breeding offspring for either high or low preference for drinking a morphine solution, within three generations they were able

to produce rats with a fourfold difference in their rates of voluntary consumption of morphine. The morphine- preferring rats also demonstrated a strong preference for alcohol relative to the rats that did not prefer morphine, suggesting a genetic commonality shared by both morphine and alcohol.

Seale (1991) reviewed the findings regarding variation in reactions to amphetamines and cocaine among genetically different strains. Differences among strains in response to amphetamines were noted for arousal state, sleep pattern, motor activity, reverse tolerance, exploratory rearing, stereotyped behavior, learning, rewarding effects, seizure susceptibility, and lethality; these findings clearly implicate polymorphic genetic factors (polymorphic traits are those on which there is significant individual variation within a population) as very important for explaining individual variation in response to amphetamines. Seale concluded that genetic studies of amphetamines using animal strains demonstrate large, genetically based differences in amphetamine responsiveness that in some cases are due to polygenic mechanisms and in others due to mutations in one or a small number of genes. Seale also reported that genetic differences predispose strains of mice and rats to differ substantially in their cocaine-seeking behavior. There are comparable findings for other classes of drugs.

Specificity versus Generalizability of Vulnerability

An important issue in the investigation of vulnerability to drug abuse is whether there is a specific vulnerability for one drug, such as cocaine, or for a class of drugs, such as stimulants (Maddux and Desmond 1989; Solomon and Corbit 1974; Steele and Josephs 1990; Wise 1988; Wise and Bozarth 1987). The alternative possibility is that there is a vulnerability to the abuse of psychoactive substances in general. Glantz (1992) suggested that, at least for some abusers, the particular drug abused is almost incidental; it is the effect rather than the drug itself that motivates the individual. The abuser may use different drugs in different fashions to try to obtain the desired effect. To the extent this is true, drug users would be more likely to be polydrug users.

In criticizing disease models of substance abuse because they imply that each type of addiction has a specific etiology, Tarter and Mezzich (1992, p. 171) concluded from several findings that "There is no definitive evidence indicating that individuals who habitually and preferentially use one substance are fundamentally different from

those who use another." Therefore, there may be a generalized behavioral disposition or risk for the following reasons: individuals who terminate abuse of one substance often initiate use of another substance; no vulnerability factors in humans have been identified that indicate risk for one particular substance; and the lack of evidence that abuse of any drug, such as marijuana, cocaine, heroin, or alcohol, breeds true—what seems to be transmitted is a liability to substance abuse in general. Generalized risk was implied by a family study of drug abuse in which there was "Little evidence of specificity of drug preference between drug abusers and their siblings" (Merikangas et al. 1992, p. 94).

Significance of Putative Vulnerability Indicators

Personality. There are a number of reasons to include the assessment of personality in a study to determine vulnerability indicators for drug abuse. King and colleagues (1992) suggested a neurochemical trait model of risk for drug abuse. According to their model, differences in personality traits that predispose to drug usage have their basis in certain neuromodulatory systems. Drug consumption is a response to tempera-mental factors and is motivated by self-medication for these traits. They suggested that neuromodulatory systems influence the likelihood of drug usage, which then may affect these systems in a type of feedback loop. King and colleagues (1990) found significant differences between 53 drug abusers and 20 controls on sociability, impulsivity, and neuroticism as assessed by the Eysenck Personality Inventory (Eysenck and Eysenck 1968). Aggressiveness may also be related to vulnerability for drug abuse (Stattin and Magnussun 1989) as well as impulsivity, hyperactivity, and poor self-regulation (Block et al. 1988; Cloninger et al. 1988; Gittelman et al. 1985; Tarter and Edwards 1988). Drug abuse may sometimes occur in response to trauma (Hendin and Pollinger-Haas 1984; Rohsenow et al. 1988).

Neuropsychological Functioning. Tarter and Mezzich (1992) suggested that neuropsychological functions associated with behavioral self-regulation are likely candidates for vulnerability indicators for substance abuse. Specifically, they suggested executive cognitive functions associated with the anterior region of the frontal lobes as potentially relevant to drug abuse risk. The specific abilities include the ability to plan strategies in goal-directed behavior, to sustain and monitor behavior, and to respond flexibly as the demands of a situation change.

Biochemical Characteristics. There has been a growing interest in identifying biochemical vulnerability indicators for drug abuse. In research on psychopathology, platelet MAO is among the most widely studied biochemical substances. MAO is an enzyme that metabolically degrades monoamine neurotransmitters such as dopamine (DA), norepinephrine, and serotonin (Snyder 1985). Both MAO-A and MAO-B are found in the human brain, but only MAO-B is found in blood platelets. Platelet MAO activity is genetically controlled and there is some evidence that it correlates with central nervous system (CNS) monoamine turnover (Oreland et al. 1981; Zuckerman 1984), and thus may offer a relatively noninvasive probe for neurotransmitter activity in the CNS.

There are several lines of research that lend support to the potential significance of platelet MAO as an indicator of vulnerability to drug abuse. In a series of papers, von Knorring and colleagues (1984, 1985, 1987) reported results of an investigation of 18-year-old males selected from the general population. They found that 18-year-old men who smoked cigarettes were more extraverted, sensation seeking, easily bored, and monotony avoidant than nonsmokers. The smokers were also more likely to abuse glue, alcohol, cannabis, amphetamine, and morphine. As a group, the smokers not only had significantly lower platelet MAO activity, but also there was more drug abuse (as well as alcohol and tobacco use) among subjects with low platelet MAO activity compared with subjects with higher MAO activity (von Knorring et al. 1984). Subjects with mixed substance abuse had significantly lower platelet MAO activity, while subjects with only alcohol abuse did not have low platelet MAO activity.

Pandy and colleagues (1988) studied a sample of alcoholics admitted for detoxification. Subjects were excluded from their sample if they had an episode of drug abuse or dependence that preceded their first episode of alcoholism. These authors reported significantly lower platelet MAO activity among the alcoholic sample compared with controls. They then used admixture analysis and identified two different distributions of MAO activity among the alcoholics: 64 alcoholics were in the low MAO activity group and 11 were in the normal MAO activity level group. The low MAO activity alcoholics did not differ from the normal MAO activity alcoholics in terms of their rate of drug abuse or dependence. However, the low MAO activity alcoholics reported significantly more drugs used and significantly higher frequency of drug use, although the power of such comparisons was not high due to there being only 11subjects in one group.

Yehuda and colleagues (1987) investigated a group of college students screened with the psychosis proneness scales (Chapman and Chapman 1980). Among high scorers on one of the psychosis proneness scales, one-third were identified as chronic marijuana users and their platelet MAO activity was in the lower range of subjects. Stillman and colleagues (1978) also found lower platelet MAO activity among male marijuana smokers compared with controls. Although no immediate effect of smoking a marijuana cigarette on MAO activity was observed, the level of reported marijuana use had a significant negative correlation with MAO activity.

Lowered MAO activity is not always associated with psychopathological or drug abuse diagnoses. In a sample of male patients with borderline personality disorder, Yehuda and colleagues (1989) did not find an association between platelet MAO activity and recent substance abuse. However, 4 of their 7 "non-recent" substance abusers had met the "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. rev. (DSM-III-R) criteria for drug dependence within the preceding 5 years. Dolinsky and colleagues (1985) studied MAO activity in a sample of hospitalized male alcoholics. While they found lower MAO activity in the alcoholics compared with normal and psychiatric controls, MAO activity was not associated with use of additional drugs in the alcoholics.

Makusa and colleagues (1990) compared small groups of control subjects, subjects with alcohol dependence, and subjects with meth-amphetamine dependence. Platelet MAO activity was lower in the alcoholic subjects than in controls or the methamphetamine subjects; methamphetamine subjects did not differ from controls on MAO activity. The authors speculated that the platelet MAO activity observed in their methamphetamine subjects might reflect the prolonged use of metham-phetamine or treatment with neuroleptics.

Electrophysiological Measures. ERPs are changes in the electroen-cephalogram (EEG) elicited by sensory stimulation or synchronized with a behavioral output. ERPs, specifically P3 latency prolongation, have been reported to distinguish alcoholic siblings from their nonalcoholic siblings (Hill et al. 1990; Steinhauer et al. 1987). Patterson and colleagues (1987) and Pfefferbaum and colleagues (1991) found that family history of alcoholism, rather than alcohol abuse per se, best correlated with reduced P3 amplitude in alcoholic men. P3 latency abnormalities are typically associated with cognitive dysfunction, while amplitude reduction has been associated with a

variety of psychiatric disorders including hyperactivity, depression, and schizophrenia (McCarley et al. 1993; O'Donnell et al. 1992b; Pfefferbaum et al. 1989). A correlation between P3 latency and perceptual motor deficits in alcoholics has been reported (Parsons et al. 1990; Pfefferbaum et al. 1991).

ERPs have rarely been studied in drug abusers. Auditory P3 latency has been reported to be prolonged in adolescents with a history of drug use and antisocial behavior (Pickworth et al. 1990). P3 amplitude has been reported to be reduced in adolescents with a history of drug use (Herning et al. 1989).

Psychiatric Comorbidity. Substance abuse is found to be comorbid with virtually every major psychiatric disorder at a rate higher than that found in the general population (Tarter and Mezzich 1992), most commonly with affective disorder and antisocial personality disorder (Alterman et al. 1985; Block et al. 1988; Cadoret et al. 1980, 1986; Deykin et al. 1987; Hesselbrock et al. 1985). Antisocial personality disorder, affective disorder, and criminal or delinquent behavior tend to co-occur with drug abuse in families (Hesselbrock 1985; Kosten et al. 1985). Antisocial personality disorder is more likely to predispose to drug abuse, while depression is more likely to be a consequence of drug abuse (Merikangas et al. 1992).

Supporting the relevance of personality disorders in addition to antisocial personality disorder, King and colleagues (1992) observed a correlation between drug abuse and a schizoid-histrionic dimension of personality disorder. Drug-abusing subjects who were histrionic had a longer history of use of cocaine; the authors suggested that this might reflect a deficit in mesolimbic DA activity. However, the authors acknowledged that their design could not distinguish cause from effect. Longtime cocaine usage may lead to a more histrionic personality. This type of ambiguity in the interpretation of the association between drug abuse and comorbidity will be eliminated by the design of the proposed study.

Attention deficit-hyperactivity disorder (ADHD) is another psychiatric disorder that may have relevance to vulnerability for drug abuse. Although 50 percent of ADHD children will no longer meet criteria for the disorder by adolescence, the persistence of the disorder in other children significantly increases their risk for antisocial and substance use disorders (Gittelman et al. 1985; Mannuzza et al. 1991; Weiss et al. 1985). Current research strongly indicates that ADHD is

associated with high levels of alcohol and drug abuse and dependence in adolescence and adulthood.

There also appears to be a familial, and perhaps genetic, link between ADHD and drug abuse. Several family studies found high rates of drug abuse among the biological relatives of ADHD children (Stewart et al. 1980). For example, Biederman and colleagues (1992) documented drug dependence in 13 percent of the relatives of ADHD children compared with 6 percent of control relatives. Faraone and colleagues (1991a) found substance abuse in 7.2 percent of the relatives of ADHD girls compared with 0 percent of control relatives. Consistent with data from followup studies, Faraone and colleagues (1991b) also found that the familial link between ADHD and drug abuse is strongest for children with conduct disorder, the childhood precursor to antisocial personality. Further evidence for a link between ADHD and drug abuse comes from studies of adults retrospectively diagnosed as having had childhood-onset ADHD. For example, Biederman and colleagues (1993) found that 18percent of clinically referred adults with ADHD had a history of drug abuse compared with only 6 percent of normal control adults.

Relevance of MZ Twins to Investigating Vulnerability

Two types of influences serve to make MZ twins similar to each other—genetic factors, on which they are identical, and those features of the environment common to both twins such as the family's shared experiences, socioeconomic status, and parental substance abuse. Twins differ from each other due to unique environmental influences. The unique or unshared environment refers to any features of the environment that are different for the two twins; for example, one twin falls off a bicycle and breaks a leg while the other twin does not. The comparison of nonabusing cotwins of drug abusers to nonabusers from nonabuse-concordant pairs is a powerful approach for identifying familial vulnerability indicators. For example, if the nonabuser cotwins of abusers were to perform more poorly on a neuropsychological measure of sustained attention than the nonabusers from nonabuse-concordant pairs, it would indicate clearly that relative decrements in the ability to sustain attention reflect a vulnerability to drug abuse, and more specifically, it would demonstrate that such a decrement is a familial vulnerability factor. Such a finding by itself could not distinguish between vulnerability caused by genetic or shared environmental factors. The distinction between genetic and family environmental sources of the vulnerability will await the application of the relevant measures to a representative sample of MZ and DZ twins.

History of the Development of the VET Registry

The VET Registry was originally developed to investigate the influence of Vietnam service and combat exposure on the health of veterans. The registry consists of pairs of male twins, both of whom served in the military during the Vietnam Era (May 1965-August 1975). Methods of assembling the registry have been detailed elsewhere (Eisen et al. 1987). Zygosity was evaluated by using a series of questions on twin similarity and limited blood group typing obtained from the military records (Eisen et al. 1987). Of the total VET Registry of 4,774 twin pairs, 2,092 twin pairs (43.8 percent) were identified as DZ, 2,556 (53.5 percent) as MZ, and 126 (2.7 percent) could not be identified as to zygosity and were excluded from further analysis. The relative overrepresentation of MZ pairs is due to the absence of opposite-sex DZ pairs. The first data collection on this registry was conducted in 1987 with the Survey of Health, a mailed survey supported by the Department of Veterans Affairs that assessed military service characteristics, preliminary health status self-reports, alcohol and tobacco use profiles, traumatic stress symptom-atology, and mental health status.

Harvard Twin Study

An interview was designed, based upon segments of the Diagnostic Interview Schedule assessing drug, alcohol, and tobacco use and pertinent comorbid psychiatric disorders to evaluate the extent and nature of drug use in this population. Further information was solicited about duration and frequency of drug use and the presence of other psychiatric disorders. As of June 1993, a total of 8,071 interviews had been completed.

RESEARCH DESIGN AND METHODS

Design

The following section describes the design that will be used for the proposed study. The twins will be divided into the following groups: twins 1A and 1B are MZ twins concordant for being affected. Twin 2B is the affected member of discordant MZ pairs. Twin 2A is the unaffected member of discordant MZ pairs. Twins 3A and 3B are MZ twins concordant for being unaffected. The study will include all discordant pairs (twins 2A and 2B) and one twin randomly selected from abuse-concordant pairs and nonabuse-concordant pairs.

Comparisons. Table 1 graphically displays the informative comparisons between the various groups that will be carried out. The cells of the table indicate the types of inferences that can be drawn from each of the relevant two-group comparisons.

TABLE 1. *Comparisons between various twin groups.*

	Twin 2B (Discordant abuser)	Twins 3A/3B (Concordant nonabuser)
Twins 1A/1B (Concordant abuser)	Test generalizability of findings from discordant pairs (A) Assess "familial" vs. "sporadic" distinction	(B)
Twin 2A (Discordant nonabuser)	Assess environmental risk/protective factors for drug abuse (C) Assess biological and psychosocial consequences of drug abuse	Assess biological and psychological vulnerability indicators (D)

Discordant Nonabuser (2A) versus Concordant Nonabusers (3A/3B) (CellD). This is the crucial comparison for the identification of vulnerability indicators. Twin 2A represents an individual who is putatively at risk by being genetically identical to a drug abuser, but, by virtue of being free of abuse, allows for inferences to be drawn about vulnerability rather than sequelae. With a different design, differences found between drug abusers and nonabusers could reflect either a predisposition or a consequence of drug abuse. The present study includes subjects who share the same genetic vulnerability with a drug abuser but who are free of serious drug abuse. These subjects can be compared to matched subjects who are less likely to have a genetic vulnerability to drug abuse by virtue of being members of a pair who are both free of drug abuse.

Differences observed between these groups might also reflect protective factors. For example, if the nonabusers from discordant pairs (2A) were found to be higher in religiosity than nonabusers from concordant pairs (3A/3B) this could be interpreted to indicate that religiosity is associated with a vulnerability for drug abuse. However, a more plausible hypothesis would be that for an individual with a high vulnerability to drug abuse to remain a nonabuser, more protective factors such as religiosity are required to buffer the vulnerability. To sustain the hypothesis that some characteristic of the nonabuser in a discordant pair is protective, the nonabuser should differ on the characteristic from the drug-abusing cotwin (2B)(cell C).

Concordant Abusers (1A/1B) versus Discordant Abusers (2B) (CellA). These subjects will be compared on biochemical, electrophysiological, neuropsychological, and personality measures; number and types of drug symptoms; subjective effects of drugs; and psychiatric comor-bidity. These comparisons test whether affected members of discordant pairs differ from affected members of concordant pairs. If these tests indicate differences, it may suggest that affected members of discordant pairs are sporadic or nongenetic cases who differ from familial cases. If this is supported, it may help identify "more genetic" and "less genetic" types of drug abuse for study. This comparison also has important implications for the generalizability of results from the comparison of nonabusers from nonabuse discordant pairs to nonabusers from nonabuse-concordant pairs. If the abusers from concordant and discordant pairs differ, the vulnerability indicators identified in nonabusers from discordant pairs may not apply to all abusers.

Discordant Nonabuser (2A) versus Discordant Abuser (2B) (CellC). Twins 2A and 2B are genetically identical; therefore, differences in drug use outcomes must be due to environmental factors. Twins will be compared on combat experiences and other trauma, educational background, physical and sexual abuse, marital status and adjustment, and other relevant factors that predate problematic drug usage. This is the critical test of psychosocial risk and protective factors. This twin comparison will also allow examination of the biological, psychological, and psychosocial sequelae of drug usage.

Models. Figures 1 through 4 indicate the various informative patterns of results that may be obtained for the putative vulnerability indicators. Figure 1 illustrates the vulnerability model in which a lower frequency of concordant nonabusers (the low-risk subjects) perform high on the vulnerability indicator compared with a high

frequency of nonabusers from discordant pairs (the high-risk subjects) who score high on the indicator. A hypothetical example of this might be false hits on a measure of sustained attention. If the nonabusers from discordant pairs have significantly higher rates of false hits than the nonabusers from concordant pairs, this would be evidence that deficits in sustained attention represent a vulnerability indicator for drug abuse. The results from abusers are not as informative in identification of vulnerability indicators because results from such individuals may reflect vulnerability to drug abuse or consequences of drug abuse. However, if some characteristic is a vulnerability indicator, it should be higher in abusers.

Figure 2 illustrates hypothetical results that fit the consequence model. For example, if the indicator under consideration were the prevalence of depression, figure 2 would indicate that more abusers from both concordant and discordant pairs score high on depression compared with

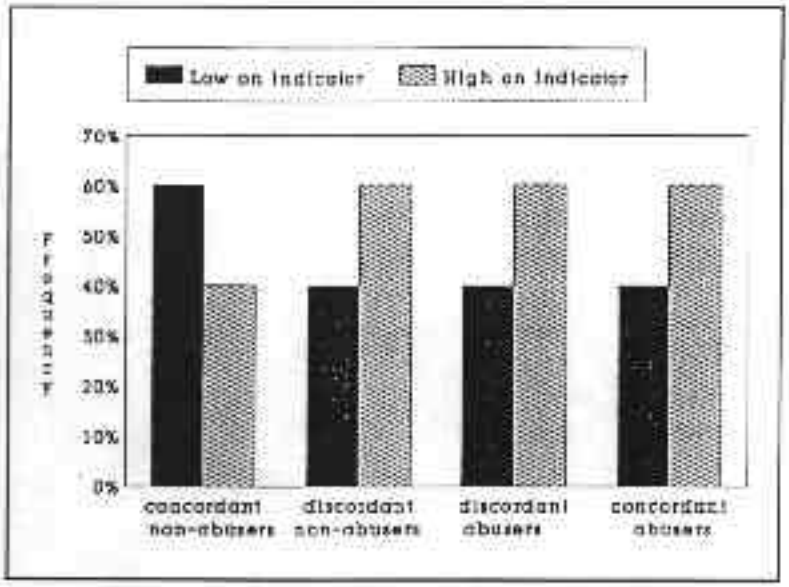

FIGURE 1. *Vulnerability model.*

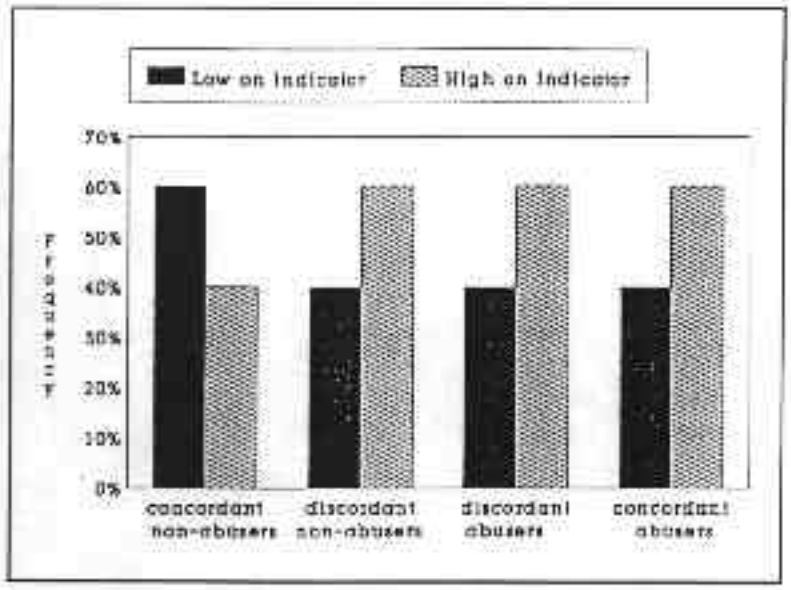

FIGURE 1. *Vulnerability model.*

the frequent high depression scores observed in nonabusers from both concordant and discordant pairs. Such a pattern of results would be most parsimoniously interpreted as demonstrating that the indicator reflects the effect that drug abuse has on the probability of developing depression.

Figure 3 illustrates hypothetical results that fit the familial versus sporadic model. For example, if the indicator under consideration were number of adult symptoms of antisocial personality disorder, figure 3 would indicate that abusers from discordant pairs are more likely to have high levels of these symptoms. Given that all individuals in both groups are drug abusers, the difference in antisocial behavior could not reasonably be attributed to the effects of drugs. Such a result would suggest the presence of psychological differences between the groups that reflects different characteristics in the familial abusers (those from concordant pairs) versus the sporadic abusers (those from discordant pairs). This difference might be one that predates drug abuse and would have distinguished the groups before the onset of drug abuse, or it might reflect differences in the effects of drugs related to familial versus sporadic status. That is, in the current hypothetical example, the two groups might not have differed in antisocial symptoms before initiating drug abuse, but behavior in the familial group was more adversely affected by drug usage.

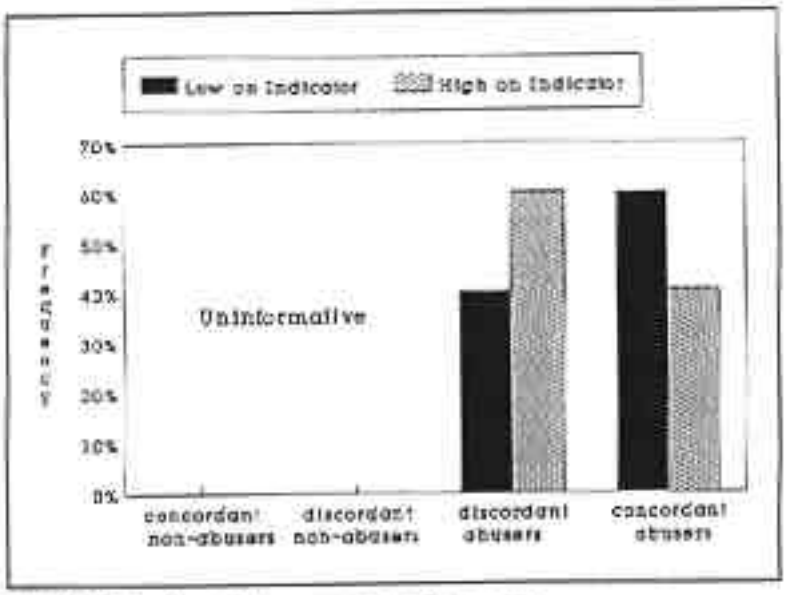

FIGURE 3. *Familial versus sporadic model.*

Figure 4 illustrates hypothetical results that fit the protective factor model. For example, if the variable being examined were religiosity, the hypothetical results in figure 4 would indicate that most subjects in both groups of drug abusers have low scores in religiosity, the same number of nonabusers from concordant pairs score high or low on religiosity, and more nonabusers from discordant pairs are high on religiosity. If religiosity is a protective factor, one would expect the abusers to score relatively low. Because the concordant nonabusers are assumed to have low levels of putative vulnerability and therefore to be at low risk for drug abuse, the presence or absence of the protective factor, religiosity, has little bearing on their status as nonabusers. Because the nonabuser from a discordant pair is assumed to be vulnerable, the abscence of abuse suggests the presence of a protective factor.

Measures

Rationale for Measures. Several measures have been selected to serve as noninvasive probes of the subject's CNS. Measures from domains such as neurophysiology, neurochemistry, neuropsychology, and personality are intended to tap functions presumed to reflect aspects of the CNS related to drug use. Unlike research using animal models

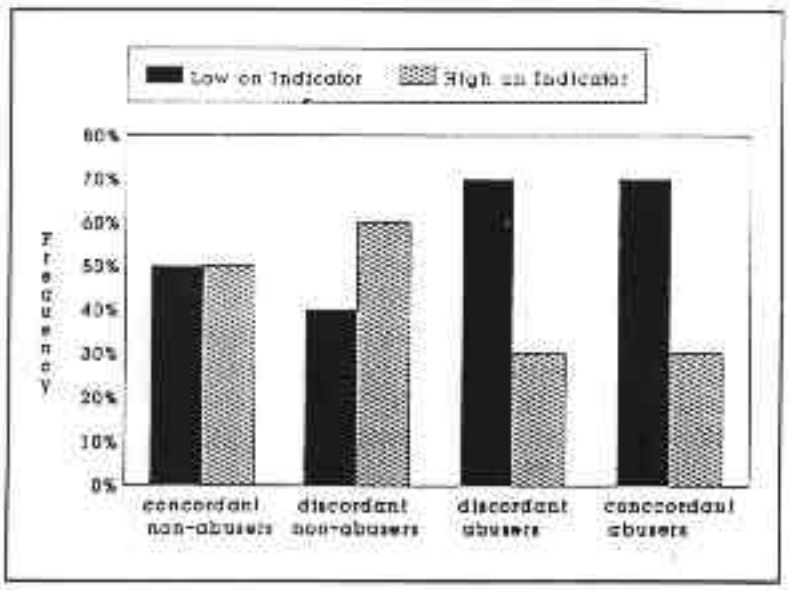

FIGURE 4. *Protective factor model.*

described above, there is constraint in the invasiveness of the measures. However, the work proposed here is a valuable and necessary complement to the informative research on other species; the probes applied in the twin sample that prove to be vulnerability indicators are then very strong candidates for further study.

Data Already Collected from the Twins. As part of the Harvard Twin Study of Drug Abuse and Dependence, data are being collected on exposure to illicit drugs, initiation and continuation of use, quantity and frequency measures, all symptoms of substance abuse and dependence, routes of administration, and reports of subjective reactions. The substances include marijuana, barbiturates, stimulants, cocaine, opiates, psychedelics, alcohol, and nicotine. Data are also collected on a range of diagnoses using a modified version of the Diagnostic Interview Schedule (DIS) (Robins et al. 1981). The diagnoses included are generalized anxiety disorder, phobias, panic disorder, posttraumatic stress disorder, major depression, bipolar disorder, dysthymia, antisocial personality disorder, and pathological gambling disorder. The authors also have data on combat experience, type of discharge, treatment at Veterans' Admini-stration (VA) medical facilities, self-reported physical symptomatology, education, marital status, offspring, sexual orientation, promiscuity, and family history of parental and sibling alcohol and drug problems.

Data To Be Collected in the Proposed Study. Three ERP paradigms will be used, two using auditory stimuli, and one using visual stimuli. The first auditory paradigm is the Brockton Veterans Affairs Medical Center (VAMC) Brain Imaging Laboratory's standard auditory oddball protocol (McCarley et al. 1993). This will allow comparison of results in twins with a large body of data collected and published over the past 5years establishing the reliability, topography, clinical correlates, and anatomic correlates of this P3 component in control subjects and psychiatric populations. The second auditory paradigm uses novel, nontarget tones to elicit an automatic P3 component without task demands (Knight et al. 1989). This paradigm was included because it provides an electrophysiological measure of orienting (passive attentional activation). A visual task will be included to complement the ERP assessment of auditory processing. This task requires that a subject sit at a monitor that displays a line either at a central location or displaced 10degrees to the right or left of midline. In three blocks the central stimuli will be targets, and in three other blocks the peripheral stimuli will be targets. In all cases, the subject will be required to respond to the target with a keypress.

The Structured Interview for DSM-III-R Personality Disorders (SIDP) (Pfohl et al. 1983) was the first structured interview designed to assess the diagnostic criteria for all of the DSM-III-R personality disorders. The interview includes 160 questions in 16 sections reflecting areas of functioning relevant to assessing personality disorder. Stangl and colleagues (1985) reported reasonably good levels of interrater reliability. This interview will be administered to all subjects.

Assessment of ADHD. To assess ADHD in adults, the ADHD module from the children's version of the Schedule for Affective Disorders and Schizophrenia (Kiddie SADS-E (epidemiologic version)) (Orvaschel and Puig-Antich 1987) will be administered. This is a widely used, semi-structured, DSM-III-R-based psychiatric diagnostic interview with established psychometric properties. It was designed for use in clinical and epidemiological research to obtain a past and current history of psychiatric disorders in children and adolescents aged 6 to 17. Adult assessment instruments do not include ADHD; the authors' previous work has shown that modules from the Kiddie-SADS can be used to make retrospective diagnoses in a reliable and valid manner (Biederman et al. 1990, 1993).

The NEO Five Factor Inventory (NEO-FFI) (Costa and McCrae 1985) is an abbreviated version of the NEO Personality Inventory. It is

designed to assess the 5-factor or "big five" model of normal personality. The dimensions included are neuroticism, extraversion, openness, conscien-tiousness, and agreeableness. The NEO-FFI is a relatively short (60 item) self-report questionnaire that correlates well with more time-consuming measures of the 5-factor model, and will be administered to all subjects.

The Tridimensional Personality Questionnaire (TPQ) (Cloninger 1987) measures three personality dimensions (novelty seeking, harm avoidance, and reward dependence) as defined by Cloninger's unified biosocial personality theory (Cloninger 1987). The questionnaire itself contains 100 items, takes about 15 minutes to complete, and will be administered to all subjects. The basis of the instrument is found in Cloninger's integration of the neuroanatomical and neurophysiological foundations of behavioral tendencies, styles of learning, and the adaptive interaction of the three dimensions. The TPQ is intended to correspond more closely than alternative approaches to the underlying genetic structure of personality (Cloninger 1987).

The available research data, summarized by Tarter and Mezzich (1992), tentatively suggest that a core feature of vulnerability may involve a dysfunction of neural systems lying along the frontal-midbrain neuroaxis (Tarter et al. 1989). This is reflected behaviorally in deficits of behavioral regulation (Tarter and Mezzich 1992). From the neuropsycho-logical perspective, self-regulation is subserved by executive cognitive functions that are thought to be disrupted by disorders of frontal system (frontal-subcortical) function (Goldberg and Seidman 1991). Executive functions include the ability to plan strategies of goal-directed behavior, sustain goal persistence, and to flexibly respond to changing demands through the use of feedback. Deficits in abstract reasoning have long been thought to reflect frontal lobe dysfunction (Luria 1980).

This battery of tests will emphasize those functions shown to be impaired on an empirical basis (problem solving, abstraction, linguistic ability) and theoretical basis (behavioral self-regulation, impolarity, shift of set, sustained effort, and attention). Table 2 contains the names of the neuropsychological instruments that will be used and the functions that each assesses.

The following psychosocial variables will be assessed through interview and questionnaire: peer group drug usage, stressful life events and

TABLE 2. Test battery function.

Test	Function	Reference
WAIS-R Vocabulary, Comprehension, Information	Verbal knowledge and reasoning	Wechsler 1981
WAIS-R Digit Span and Arithmetic	Auditory attention and working memory	Wechsler 1981
WAIS-R Block Design	To be used with vocabulary for IQ estimate	Wechsler 1981
WRAT Reading, Spelling and Arithmetic	Academic achievement, language, and calculations	Jastak and Wilkinson 1984
Visual Continuous Performance Test (CPT) (degraded stimuli)	Sustained visual attention (signal detection indices— perceptual sensitivity and response bias)	Mirsky Sunrise System— Nuechterlein 1991
Dichotic Listening (digits)	Sustained auditory attention and cerebral lateralization of function	Kimura 1967
Auditory Consonant Trigram	Verbal memory under condition of interference	Peterson and Peterson 1959
Stroop	Attention and impulsivity	Golden 1978
Wisconsin Card Sorting Test	Abstraction, shift of set	Heaton 1981
Booklet Category Test	Concept formation and reasoning	DeFilippis and McCampbell 1979

trauma, religiosity, adult role functioning, childhood physical and sexual abuse, nature of the relationship between twins, and peer relationships during childhood and adolescence.

Sample

The VET Registry was assembled from a computer file of discharges from the military maintained by the Department of Defense.

An algorithm was used that matched database entries for the same last name, different first name, same date of birth, and similar Social Security numbers. From a list of approximately 5.5 million veterans, 15,711 potential twin pairs were identified. Military records were then searched to evaluate twinship. Twinship was confirmed for 7,369 pairs (46.9percent). A pilot study demonstrated that, by comparison with a wide variety of sociodemographic and other variables, these twins were representative of all twins who served in the military during

the Vietnam War (Goldberg et al. 1987). A complete description of registry construction has been published (Eisen et al. 1987).

The starting point for subject selection will be discordant pairs because they are the least common type of pair and therefore the "rate-limiting step." One twin in the discordant pair must be unaffected. The reason for selecting discordant pairs is to have an individual who is genetically identical to an abuser but who is free of the biological, psychological, and psychosocial sequelae of substance use. It is not necessary that the unaffected twin never used illicit drugs, but it is necessary that illicit drugs were not used to an extent that could lead to biological, psycho-logical, or psychosocial consequences. Specifically, unaffected twins will be selected on the basis of never having used any of the drugs more than fivetimes, having no symptoms of alcohol abuse or dependence, and having no preexisting condition that could compromise neurophysio-logical or neuropsychological assessment or other biological measures (e.g., history of severe head trauma).

To achieve the goals of this study it is imperative that affected status be defined in a manner that results in a sample with clinically meaningful drug usage. Therefore, affected individuals will be defined as individuals who were at some time regular users of marijuana, barbiturates, stimu-lants, cocaine, opiates, or psychedelics for at least 1 year. A regular user is defined by an affirmative response to the question, "Have you ever used (drug name) regularly, that is, once per week or more?" Affected subjects may have used more than one substance regularly and may have comorbid alcohol problems.

Both twins in pairs designated as concordant for nonabuse will meet the above definition of unaffected. Both twins in pairs that are designated abuse-concordant will meet the definition of affected. One twin from the selected concordant pairs will be randomly selected for inclusion in the proposed study. Two twins within a pair might both fit the definition of affected, but differ substantially in their severity of abuse. Because the goal of this project is to identify indicators of vulnerability to abuse rather than severity of abuse, such a pair would be classified as concordant for abuse.

Procedure

Subjects will be identified from the data collected in the Harvard Twin Study of Drug Abuse and Dependence. Twins will be sent a letter

introducing the study, which will be followed with a telephone call soliciting their participation. For twins who agree to participate, arrangements will be made to provide them with transportation to one of the research centers. When twins arrive at the center, the study will once again be explained and their informed consent will be obtained. Subjects will then be administered the interviews and questionnaires described above. Blood will be drawn for the assessment of platelet MAO activity. Subjects will be administered the ERP protocol and neuropsychological assessment.

Data Analysis

The identification of vulnerability indicators will be addressed by comparing nonabusers from discordant pairs to nonabusers from nonabuse-concordant pairs on platelet MAO activity, electrophysiological charac-teristics, neuropsychological functioning, personality, and psychiatric comorbidity. Both vulnerability indicators and protective factors are expected to differ between nonabusers from concordant versus discordant pairs. In part, the distinction between the two will be made on rational grounds. For example, if nonabusers from discordant pairs are found to have had higher rates of conduct disorder symptomatology, it is unlikely that this served as a protective factor. For characteristics that are vulnerability indicators, the nonabuser from a discordant pair should resemble the abusing cotwin. If the characteristic is a protective factor, the nonabusing twin should differ from the abusing cotwin. In the initial analyses, continuous measures will be compared using analysis of variance (ANOVA) and dichotomous variables will be tested using the chi-square statistic (c2). The interrelationships among the identified vulnerability indicators will be determined through examination of correlations and the application of factor analysis. Finally, multivariate procedures such as discriminant function and logistic regression analyses will be used to examine the joint influence of the identified vulnerability indicators.

Evaluation of specificity versus generalizability of vulnerability indicators will be addressed by subdividing the abusers from discordant pairs according to the type(s) of substance used. The unaffected cotwins of drug abusers from the discordant pairs will be subdivided according to the class of drug abused by the drug-abusing twin. Because the authors do not expect to have enough subjects who abuse only a single drug other than marijuana, subjects will be grouped by drug use as follows:

1) marijuana only;

2) amphetamines (may also abuse marijuana), or cocaine (may also abuse marijuana), or cocaine and amphetamines (may also abuse marijuana);

3) barbiturates (may also abuse marijuana), opiates (may also abuse marijuana), or barbiturates and opiates (may also abuse marijuana);

4) psychedelics (may also abuse marijuana); and

5) polydrug usage—falls into more than one of groups 2 through 4.

The analyses described for the identification of vulnerability indicators will be repeated using each of the subdivided groups separately. For example, do the high-risk nonabusing cotwins of twins who abuse cocaine/amphetamine differ from low-risk nonabusing twins, and do they differ from high-risk twins related to opiate/barbiturate abusers? Analyses will also be carried out in which drug abusers with concomitant alcohol abuse or dependence are separated from drug abusers without concomitant alcohol abuse or dependence.

An alternative approach to subgrouping patterns of drug abuse is to apply the biometrical methods of quantitative genetics to identify "more" and "less" genetic patterns of drug abuse. Using these methods with the entire sample of over 8,000 twins, the most heritable drug abuse phenotypes can be identified, and it can be determined if the nonabusing cotwins of these abusers prove more informative with regard to vulnerability indicators.

The effects of psychosocial variables predating the onset of drug abuse (e.g., religiosity) on the outcome of affected versus unaffected will be assessed. A one-way, four-group ANOVA will be used for continuous variables. Categorical variables will be tested using log-linear models. If the groups do differ significantly, the authors will test for the pattern-protective factors illustrated in figure 4. The predicted pattern is: nonabusers from discordant pairs > nonabusers from concordant pairs > abusers from discordant pairs = abusers from concordant pairs. Planned contrasts will be used to assess the differences between groups.

The issue of a distinction between familial and sporadic drug abuse will be addressed by comparing the drug abusers from discordant

pairs to one of the drug-abusing twins from abuse-concordant pairs. Variables that are measured on continuous scales will be compared using t-tests and dichotomous variables will be tested using the chi-square statistic.

The consequences of drug abuse will be assessed by comparing the abusers to the nonabusers from discordant pairs on the biological and psychosocial variables that may reflect the consequences of drug abuse. The authors will also examine consequences using ANOVA or c2 with subjects from all 4 groups as illustrated in figure 2. The pattern predicted is nonabusers from concordant pairs = nonabusers from discordant pairs < abusers from discordant pairs = abusers from concordant pairs. These differences will be assessed using planned contrasts.

The problem of controlling the type I error rate, given that separate statistical tests will be conducted for each of the putative vulnerability indicators, will be addressed by using a more stringent 0.01 level of significance. Using the 0.01 level will mean that a larger effect size is necessary to obtain significance. The goal is not to conduct as many tests as possible, but to treat a set of complex phenomena in a systematic and comprehensive manner.

Limitations

One potential limitation of the proposed study is the possibility that twins may differ from singletons with regard to drug abuse. There are no known data that suggest that this might be the case, but the findings of rates and patterns of drug usage will be compared with comparable published findings to determine if any differences seem to exist. If meaningful differences are found, it would weaken the generalizability to nontwins.

In general, this population of veterans might be expected to be slightly higher in IQ than the general population because individuals with mental retardation were excluded. Perhaps reflecting this, the average level of educational attainment of the veterans in the sample is slightly above the mean for the general population. Veterans were also selected for physical and psychiatric health at the time of induction, which might reduce psychiatric or physical morbidity at least from conditions with an early onset. Preliminary analyses show that combat exposure has only a slight influence on drug usage, with the exception of heroin use. Because only about one-third of the sample actually served in Vietnam and the authors have detailed

information about combat, any effects that military experience may have on drug usage can be examined and controlled. The National Vietnam Veterans Readjustment Study (Jordan et al. 1991) found no differences between male veterans of the Vietnam era and their civilian counterparts in the lifetime prevalence of drug abuse/dependence, which suggests that results of the proposed study might be generalized to nonveteran males.

Another potential limitation of the proposed study is the fact that the putative vulnerability factors are being assessed some years after the subjects have passed through the period of peak risk for the development of drug use problems. Only the vulnerability indicators that endure from late adolescence/early adulthood until middle adulthood may be detected. It is possible that this will result in a failure to identify some indicators that change over the lifespan. However, it is likely that there are vulnera-bility indicators that are stable enough to be detectable in middle life.

PUBLIC HEALTH SIGNIFICANCE

Traditionally, programs to prevent drug abuse are aimed at the general population, not reflecting the reality that only a minority of users will go on to develop significant drug abuse (Tarter and Mezzich 1992). The clinical-psychiatric or individual difference model on which this study is predicated implies that there are preexisting vulnerabilities that lead to differential risk for different individuals, independent of their social situation. The practical benefit of discovering vulnerability indicators would be twofold: it will allow the early identification of high-risk individuals who can then be targeted for intensive preventative inter-vention, and it will inform the development of preventive interventions and treatments that are tailored to specifically address and remediate the vulnerability.

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DISCUSSION

Audience and Panel Participants: Ming Tsuang, Michael Lyons, Roy Pickens, George Uhl, HowardChilcoat, Meyer Glantz, SethEisen, Roy King, AlMirsky, and Howard Moss

Dr. Uhl: Can you speak any more to the drug class specificity issues?

Dr. Tsuang: We actually are starting to analyze the more recent data, and we hope to be able to talk about that issue later. But, I'd like to stress what you have just said in your commentary, that we never claimed that this is a representative sample. I hope that we can do a stratified random sample among the general population. If NIDA would like to really make some dent in this area of research, as a psychiatric epidemiologist I'd like to recommend that a stratified random sample in a well-defined population is very, very important to do. What we have in terms of twins is that we have this unique twin sample that God sent to us, and we are trying to capitalize on that. So we are very aware that this is not a general population representative sample, but yet it's a unique population of twins.

I was very impressed that in such a short period of time, you can really go into the gist of what we are trying to do and come up with the area of interest in this diagram. Today, I intentionally tried not to talk about the significance because the data are coming in and it may change and I don't like to give the P value, so to give the false assurance that something is there. With the experience of teaching medical students or school of public health students, I don't like to put the P there. Once a P of 0.05 is there, they always say, "That's it," and never think about the implication of the false error and so on. And I think Dr. Lyons has more to say in terms of the current new data. We are getting more pairs. What I presented is actually based on the June 1993 data, and we have already updated some of them.

Dr. Lyons: Well, we are only beginning analysis on the data set with over 8,000 pairs. Some of the other things that we're looking at with the twins that were not included in the presentation is the subjective effects of drug, as was mentioned earlier. For example, we found that feeling paranoid after smoking marijuana has a strong genetic component to it, whereas reporting feeling creative after smoking marijuana seems to have more of a common, shared environmental component to it. So, in terms of what was said about the heterogeneity of the phenotypes of drug abuse, we're hoping that the

data we've collected already will help us to home in on some endophenoptypes. The proposed high-risk paradigm really is a way to try and get at these endophenotypes that may be more clearly related to genetic and/or environmental factors than we've previously been able to determine.

Dr. Glantz: Just a quick question for clarification. Dr. Tsuang, did you say that your sample included twins who were comorbid for alcohol?

Dr. Tsuang: Actually, in terms of affected, we exclude alcoholism from the new study, but in what we currently have we didn't exclude it. For the new proposal, we'd like to have a very well-defined affected/nonaffected sample. But, for the current study we have all kinds of studies.

Dr. Glantz: So, the data you showed just a minute ago included twins who were comorbid for alcohol?

Dr. Tsuang: Yes.

Dr. Glantz: This is a problem, as I'm sure you're aware. Because alcohol use is associated with drug use, or because drug use is often associated with alcohol use, what you might be seeing here is drug use that's riding on the back of alcoholism that's going on in your sample. So, what would appear to be higher MZ than DZ concordance for drug abuse may reflect nothing more than higher MZ than DZ concordance for alcoholism. It's good to hear that your new sample will be such that you could exclude the alcoholics from it and see what is happening. I heard you say you had a sample that would potentially look at the shared genes between alcoholism and substance abuse and a sample that would not look at those.

Dr. Lyons: Right. In the data we've already collected, one can model those various things. But, even with a sample of 8,100 people, when you start subdividing into heroin users who are not alcohol abusers, who are not serious abusers of marijuana, the cell size gets very small. So, for some models I think we're going to be able to distinguish shared contributions of alcohol to given drugs, but for others the models won't resolve even with this large a sample.

Dr. Glantz: How about the same question related to comorbid psychiatric disorders?

Dr. Lyons: I think it's basically the same answer. Again, the modeling procedures allow you to factor those in. For example, one can look at using cross-sectional twin data and make some inferences. For example, where there is a co-occurrence between substance dependence and major depression, one can look at whether the causal arrows go from the sub-stance dependence to depression, from depression to substance depen-dence, and whether it's reciprocal. We can consider to what extent they share common genetic influences on both, and so we'll be looking at it that way. Again, the power to address specific questions will depend on the frequency of the given outcomes in the sample, but that certainly is to be included.

Dr. Glantz: You have to wonder, once you've factored out all of the different possible comorbid conditions, how representative the resultant group will be in drug abusers.

Dr. Lyons: Well, it's not stratified, per se. With the biometrical modeling procedure, everything is in the equation at the same time. So, they're statistically handled rather than having one group who has X and Y, one group with X, one group with Y, and crossing your fingers that you have enough N in each cell.

Dr. Glantz: Then you do have to make a decision where the variance is to be attributed. I understand what you're saying, but at the same time the decisions you make may still lead to some conclusions that are…

Dr. Lyons: Well, for example, in the high-risk paradigm that we're proposing here, we're suggesting that high-risk twins—that is the nonabuser cotwin of an abuser—will be at elevated risk for antisocial personality disorder, which would suggest that that's a vulnerability indicator. We're suggesting they won't be at elevated risk for depression because we're suggesting that that's a consequence. That is, we're suggesting the abusers will have elevated rates of depression versus the nonabusers. So, there's a sort of more intuitively straightforward way to address some of those issues too.

Dr. Glantz: And the power is going to come from addressing specific hypotheses rather than general exploration?

Dr. Lyons: I think we'll do both. But, I think it is more powerful to be able to state one's hypotheses a priori, and then go about testing them.

Dr. Chilcoat: I just had a question about the role of time in genetic studies, in twin studies, in terms of the natural history of drug abuse. That's one of the things I was looking at—not just lifetime prevalence of either disorders or use, but changes over time. One thing in relation to Vietnam vets that comes into mind is Robins' studies of people who used heroin or opiates in Vietnam but stopped once they came here, and I don't know if your sample size may limit any analysis of that time. You may be breaking it down into too small numbers. But, it would be interesting to look at those people who were exposed and continued versus those who stopped when the environmental context changed over time. And also another role of time, I think, to keep in mind is the importance of cohort effects, that over time we have cohorts of twins, or individuals, who are exposed to different… As you say, you've got to have the drug. It has to be present for the dependence to occur. Pre-Vietnam there was little exposure to a wide variety of drugs, and even now we see some changes, at least in terms of younger individuals' initiating drug use. Even though the drugs are probably out there, attitudes have changed somewhat in terms of initiating use. One question to consider is what's the impact of these different sorts of variable exposures on genetic estimates to the contribution of genetic factors and drug dependence?

Dr. Eisen: It's certainly true that we would have loved to begin collecting data on our twins at the time they were in military service. One of the advantages of this dataset of twins is that we did originally abstract a considerable amount of data from military service records, so we do have a fair amount of data.

Dr. Chilcoat: Do you have a retrospective report?

Dr. Eisen: Yes. And we have collected that data in our current dataset. We're always very concerned about the retrospective collection of data. There have been three data collections: one by us in 1987, a second by NHLBI in 1990-1991, and now ours. So, we are beginning to collect a large set of data over time. Unfortunately, of course, we would have liked to have collected data between, let's say, 1970 and 1987.

Dr. Lyons: I think also, to address your question about changes in the environment, that the estimates of how heritable, how much the environ-ment contributes, are very relativistic. I once heard it suggested that asking whether it's nature or nurture that determines the outcome is like asking whether it's the length or width of a rectangle

that determines its area. You can't have a rectangle without length and width; you can't have an organism without genes and the environment.

As an example, under the kinds of methods that we're using here, if you did a twin study of PKU you would determine that it was 100-percent heritable. But, if phenylalanine was not ubiquitous in the environment, if only 10 percent of people were exposed to phenylalanine, it would be maybe 50 percent heritable and 50 percent from the environment. If everyone had the PKU gene and 10 percent of people were exposed to phenylalanine, it would be 100 percent environmental, zero percent heritable, even though the mechanism would not have changed at all. So, the kind of estimates that we get here of heritability in a common environment really are very relativistic and, as the environment changes, those estimates change.

In some ways the study we're proposing is to extend this a step further and try and use what we're already learning to leverage information about the mechanisms that are going into the phenomena that we're observing here.

Dr. Tsuang: Of course, from an epidemiological point of view, the prospective controlled study will be the best. But, it's time consuming and you have to wait for the result. And it's expensive. Particularly now Congress would like you to have immediate results. So, what we are actually doing is capitalizing on what we have. The beauty about our sample, now that I've reviewed the dataset, is that we are not just asking the past history; we are still asking the longitudinal picture, although it's retrospective. We ask when did you start it, and are you still using it, and how many times you use what sort of drugs. So, essentially there is an abundance of information there. The issue is that because of the polydrug abuse, if we start to tease apart each drug, you may not have the abuser with just one drug and the N is going to become smaller. So, we are very cognizant of the limitation of this. What you mention is very important, the longitudinal aspects of it, and we are trying to do it.

For the new proposal, we are trying to essentially answer that in part—that the non-drug abusers and actually the cotwins of the drug abusers are carrying the genetics for predisposition. We should be able to tease apart what areas are actually a comorbidity prior to the drug abuse that is actually the consequence of that.

Now, I'd like to ask a question for our research proposal. We tried to get into this endophenotype business and, as you say, in terms of drug

abuse we reviewed all the literature under the sun to try to see if any neurochemical aspects had actually been confirmed; the literature is actually very soft. Could you, or anyone here in the neurobiology area, advise us if with this sample, this strategy, what sort of an exploratory measurement can we do? As you said very clearly, we actually trans-formed our schizophrenia research paradigm into drug abuse, and you rightly pointed out even that, in drug abuse, is still very preliminary. But, we'd like to look for any innovative area of measurement that can serve the purpose of capitalizing on this very unique sample size.

Dr. Uhl: This is clearly a limitation of the drug abuse field in general. I think that the data that you saw this morning on dopamine receptor geno-types are as replicated and as robust as any other physiologic concomitant of substance abuse of which I'm aware. That's a fairly radical statement. My impression is that certainly looking at a number of different candidate genes in such a sample would be of interest and would fit with the genetics.

Having said that, I think that later on in the meeting other individuals will. Dr. Herning will talk more about the evoked responses. We'll hear some about the fancy and maybe not generally applicable, but maybe doable in a small part of the sample, the functional cortical changes in response to drugs and so on.

Dr. King: I just wanted to add that you might consider looking at measures of arousal, particularly the hypothalamic-pituitary-adrenal axis. Dr. Moss' group and my group have found correlates with impulsivity and conduct disorder in these types of samples, so that might be worthwhile I think.

Dr. Comings: I have two comments. First of all, when we looked at our drug patients and compared the different drugs used by relatives with drugs versus those without, we got the identical sequence that you did, a most severe genetic loading for psychotropics, then heroin, then sedatives, then cocaine, and marijuana the least. One might argue that this is not neces-sarily an indication that there is anything unique genetically about, say, heroin, but about a combination of factors such as availability of the drug and other factors.

The other thing is in this modern molecular biological era—and I understand that most of your interviews were done by telephone, is that correct—you can now send out a little set and you can get blood smears in the mail. We've gone out to some of our patients, and we

were able to get 100 different DNA tests out of one of those little samples. So, this would be something where you could take the higher end of your twins with the most loading, or drug use, and the lower end. Just pick 50 of each and do a very nice study, depending on what you want to look at.

Dr. Tsuang: The twin registry usage of this sample has a specific instruction. Each time you are going to add one thing you have to go to the committee to ask for special permission. Currently, we are doing a very intensive telephone interview. One subject may last for 2 hours, 3hours, and sometimes they just finish the first phase and then on the following day to do another telephone interview. For this new proposal, I am trying to really warn NIDA to carry out this research, to really go into the field, to do all kinds of measurements—you can immediately think about the astronomical budget. So, I'm thinking from this conference we can actually zero in, phase-by-phase to determine which phase should be primarily for which measurement and to really divide into Phase I, Phase II, Phase III to carry out. Otherwise, as we know, there is a restricted amount of money to really carry all this out. So, this is just a theoretical issue that we are talking about. By reviewing the literature is this mono-amine oxidase really real, or is it really something we don't jump into? Could I get some sense of it? I'm not a specialist in this area.

Dr. Moss: One of the confounds with using MAO-B from platelet is that Tabikoff and colleagues have shown that the consumption of ethanol, in itself, lowers platelet MAO activities. It's an enzyme that's exquisitely sensitive to having alcohol in its milieu. So, some of the early studies on alcoholics linking low MAO activities with alcoholism may have been really due to that particular confound where they did not allow for an adequate sober interval to have taken place before a sample was drawn.

We recently looked—Dr. Tarter actually—at MAO-B concentrations in adolescent substance abusers, and we do not find them to be lower than control levels.

Dr. Mirsky: The largest N I was ever associated with was something like 435, so I'm stupified at these Ns, and my hat goes off to you folks for this sample. But, just a couple of questions about what we might call the premorbid functioning of these people.

In some studies on World War II, and I think Korean vets, an important variable was, in some neuropsychological investigations, the

premorbid intellectual level as assessed by the Armed Forces Qualification Test, or something like that. It turned out when the data were examined, it helped explain certain things that otherwise might not have been interpretable.

I also wonder about the effect of SES, socioeconomic status. I would guess that you have a fairly restricted sample as people served in Vietnam if they couldn't get out of it some way. But, I wonder if you folks—you probably are—are looking at that variable as well?

And one last thing. It is clear that you are going to try to compare the—I think I'm using the right word—the prevalence of drug abuse in this sample in comparison to some other sample to see whether or not you have more drug abuse here or less, or is that just an unsolvable conundrum?

Dr. Eisen: Well, in terms of that, one of the kinds of data we've abstracted from military service records is the Armed Forces Intelligence Test data. One of our concerns is that there is some variation in the tests that were administered by military service. Secondly, we have some concerns about the quality of those data. So, as of yet, we've not utilized the data in any of our analyses, but we're always aware of it and may return to it at some later time, certainly as we get into our analyses of substance abuse.

We do have data, of course, on educational attainment. Perhaps a little surprising to some people is the high degree of educational status of veterans. Over 90 percent of registry members are high school graduates. These are data that were abstracted actually not only from their self-reported statements but also from military service records. So, those who participated who are subjects are unusual, I think, in having a higher educational level.

The question was the prevalence of substance abuse in relation to the general population. We certainly plan on examining the prevalence of substance abuse in our group in relation to probably the ECA data and other population-based data.

Dr. Lyons: The reason for that is just to ensure that there is not a twin effect for drug abuse. For example, twins may be at higher risk for autism, so using twins to study the etiology of autism may be misleading. As opposed to in schizophrenia, twins have a similar risk as singletons, so one probably can generalize in findings with twins and we would like to do the same thing with this sample. We're

hoping that it will demonstrate that twins don't differ in terms of drug outcomes from nontwin populations.

Dr. Eisen: The prevalence of drug abuse in our population is probably lower than the prevalence of drug abuse in the general population because there really is a screening process in entering military service. We have in our data looked at MZ twins and have demonstrated, for example, that military service has not had an effect on alcohol consumption, current alcohol consumption, by an analysis of MZ twin pairs. On the other hand, military service, and combat in particular, does seem to have an effect on cigarette consumption. Obviously, we'd be looking at using these same approaches to look at reported drug abuse.

Dr. Tsuang: One other thing with regards to the personality is that combat experience surprisingly is related to personality trait of novelty seeking. We happened to publish, or are in the process of publishing this.

Dr. Lyons: There is a genetic influence on whether or not someone went to Vietnam, given they were in the service, with how much combat they saw and self-report but also how many medals they won in combat, which is abstracted from military records. There is a significantly higher concordance among identical twins than among fraternal twins. I told that finding at the outset to a colleague of mine whose wife was a personality psychologist. He came back the next day and she said, "How the hell can that be? That doesn't make any sense." I then mentioned it to a good friend of mine who had won a number of medals in Vietnam, who is not a psychologist or psychiatrist, and he said it made perfect sense to him. He said, "Every day you made decisions that would influence the likelihood of being in a fire fight, of being wounded." He said, "Some guys like to volunteer to walk point, and almost every day they'd walk 200 yards ahead of the rest of the platoon through the jungle. Other guys stayed there a year without ever doing that." So, in fact individual differences, in part genetically influenced individual differences, may be related to those outcomes. As Dr. Lykken said, what's more surprising these days is to find outcomes that don't have at least some influence from genetic characteristics.

Dr. Moss: I was sort of curious about the analytic end of things and what sorts of models would ultimately be tested. For example, is the plan to test a liability threshold model and, if so, how? Will you

model severity and diversity of drugs used as well as individual kinds of drugs that people consume?

Dr. Lyons: Well, I think there will be a hierarchy of complexity. The main questions that we addressed today will really be addressed with t-tests and chi-squares. That is, here is the high-risk group; here is the low-risk group. Does P300 amplitude differ between the two groups? Following that, there will be increasing levels of complexity. We would like to tease out, for example, subjects who have concomitant alcohol problems versus those without concomitant alcohol problems and test the specificity versus generalizability. We probably will end up grouping substances. For example, amphetamine, cocaine, and marijuana might be one group and heroin, barbiturates, and marijuana in another group. It would be nice to get down to the single drug, but I think the reality, again, even starting with quite a large sample, to just get people who are dependent on heroin and never abused another substance I'm afraid we're not going to be able to address that.

Dr. Mirsky: You mentioned P300 again. Just logistically, how are you going to manage that? Are you going to bring 8,000 subjects to MacCauley's lab? Is that going to be a stratified sample?

Dr. Lyons: He's planning on expanding his lab. (Laughter.) No. Actually we haven't finalized the N. The rate-limiting step is likely to be the number of discordant pairs. Right now, it looks like, using a fairly strict definition of dysphorias, there are 228 pairs where one member was an abuser and the other member did not use any drug more than five times. Then, we will probably pick out a similar number, let's say 228, of people randomly selected from within a pair of concordant nonabusers for com-parison and 228, one from each pair, of pairs where both were abusers. So, we'd be talking about an N in that case of around 700 people. We plan to have a center in Boston, St. Louis, and Chicago to minimize the distance that people have to travel to come in.

Dr. Tsuang: Again, probably it's because of our presentation in talking about the current study and then, based on this, to indicate the future study that gives some confusion. The current one is a huge N, as you say, but it's the questionnaire type of telephone interview. Then, the one that we are proposing is actually talking about the discordant cotwin versus the nonabuser or concordant twin. So, the pairs become smaller. So, I hope it is manageable.

Commentary: Three Approaches to Drug Abuse Genetics

George R. Uhl

Several different lines of evidence now suggest substantial genetic influences on inter-individual differences in vulnerability to drug abuse (Uhl et al. 1994). The three proposed studies described by Comings, by Tsuang and Lyons, and by McGue, Lykken, and Iacono each approach issues relating to genetics of drug abuse vulnerability in ways that are distinctive and interesting. Moreover they appear to represent several of the major perspectives in this emerging and exciting area of human genetics.

OVERVIEW

Each of these groups of researchers, at least implicitly, agrees that current evidence suggesting genetic influences on interindividual differences in vulnerability to drug abuse is reasonably strong, although McGue and colleagues are the most circumspect about accepting such evidence. Nevertheless, they conclude that "The challenge to the present generation of behavioral genetics researchers is not so much in establishing whether genetic factors influence behavior, but rather how" (McGue et al., this volume). The behavioral emphases of these groups are evident in their focus on mechanisms by which gene and environment might interact to produce a coherent picture of drug abuse vulnerability.

Tsuang and Lyons use their own Vietnam Era Twin Study data to provide one of the principal supports for accepting the notion of substantial genetic influences in drug abuse vulnerability. They seek biological and psychological vulnerability indices reflecting possible differences in genetic and environmental factors contributing to individual vulnerability to abuse of different classes of psychoactive substances. This approach is consonant with the background of these workers in assessing the genetic and biological marker status of other major psychiatric disorders.

Comings has included consideration of substance abuse in broader thinking about impulsive disorders, defense-style personality, and other behavioral components that largely originate from extensive studies in the genetics of Tourette syndrome (TS) and attention

deficit-hyperactivity disorders (ADHD). Comings' laboratory has also applied single, candidate gene marker association studies to samples of substance abusers; the work proposed here reflects and extends this approach.

COMMENTARY AND ALTERNATE IDEAS

A major feature of the clinical nosology of substance abuse is the frequent comorbidity observed between substance abuse and psychiatric diagnoses, including antisocial personality disorder (ASPD) and depression. Each of these three genetics proposals includes assessment of this feature in substance abusers in search of a common or defining mechanism. However, each stops short of asking more sharply defined questions that may now be appropriate to pose. Can substance abusers in general be considered to display these comorbidities, or do those with ASPD represent a more homogeneous subgroup of substance abusers than would be obtained by mixing them with those without this comorbid condition? If so, is explicit analysis of substance abuser subtypes, defined by these comorbidities, likely to improve the power of other genetic assessments? Are there other means of defining, a priori, better approaches to constructing and evaluating substance abuser subtypes that may provide better clinical and experimental focuses for analyses? Segregation of such comorbid conditions with substance abuse in multigenerational pedigrees would provide an improved rationale for such subtypes. Unfortunately, the drugs that are available and fashionable in most communities change with time. These striking secular trends in abusing illegal substances make such analyses difficult.

Many of the suppositions and perspectives revealed by the three distinctive lines of approach reveal more particular research directions, however. McGue, Lykken, and Iacono describe one such conceptual framework when they suggest that genetic factors "necessarily exert a remote. . . influence," while behavioral influences are "more proximal determinants of behavior." One could easily argue the converse. Many genetic influences on behavior are present continually, so that their impact is likely to be felt much less remotely than the environmental influences, and may largely have been laid down at much more distant times. Genetics may be also more readily controlled in human studies. Twin studies, including the work of Tsuang's group, emphasize the importance of nonshared environment as dominant among the environ-mental determinants of interindividual differences in substance abuse vulnerability. Twin, sib-

pair, and other genetic methods may also make it much easier to control for genetics in many human studies than to control for many of these sorts of environmental influences.

McGue, Lykken, and Iacono focus on the distinction between genotype-environment correlation and genotype-environment interaction as well as the above-mentioned substance abuse-related comorbidities. They note that certain genetic influences may be manifest because individuals of a specific genotype are more likely to experience a unique kind of environ-ment. If the genotype elicits the environment in question, the term "evocative genotype-environment correlation" is used. When the individual seeks a different environment due to the genotype, "active genotype-environment correlation" is manifest. The work on peer group affiliation described by McGue and colleagues provides a direct example of the possibility that genotype could lead to differential acquisition of environmentally derived stimuli. Since abused substances are environ-mental in nature, this sort of pathway could plausibly provide major influences on drug abuse vulnerability. Genotype-environment inter-actions, in which individuals of specific genotypes are more vulnerable to environmental factors, could also play a substantial role in substance abuse vulnerability.

STRENGTHS AND WEAKNESSES OF THE PROPOSED STUDIES

McGue, Lykken, and Iacono propose to study drug abusers to test the idea that environmental factors will be more influential in development of substance abuse and that genetic factors will affect "the psychological and physiologic factors that mediate the expression of this disorder." They then propose to separate genotype-environment correlations from genotype-environment interactions. The strength of such an approach appears to depend on the robustness of assumptions about the primacy of environ-mental factors in the development of substance abuse. Currently, available evidence of strong genetic influences on, for example, age of onset of initiation of alcoholism suggests that key features of the "establishment" of at least some addictive disorders are likely to be genetic. Were this the case for drug abuse, the rationale for seeking genetic influences chiefly in later-developing features of substance abuse would be less compelling.

Tsuang and Lyons propose to evaluate whether differences in event-related evoked electroencephalogram (EEG) potentials, specific

neuro-psychological deficits, specific personality traits, and higher rates for ASPD will mark individuals at higher risk for abuse of one or many psychoactive substances. They propose to use the powerful genetic twin method and to employ the relatively robust findings concerning ASPD-drug abuse comorbidity. However, these investigators are in some sense compelled by the state of development of the field, to use other much less well-established or less-robustly established biologic paradigms to seek correlation with monozygotic/dizygotic twin differences. One conclusion might be that the robust and substantial power of the twin method that Tsuang's group has so carefully used may dwarf the more modest extent to which robust biobehavioral markers for drug abuse are now available.

Tsuang and Lyons also propose to utilize the power of their twin sample to separately examine genetic influences in abusers of different substances. Abusers of only a single drug class may not represent the modal form of substance abuse; the polydrug abusers clinical phenotype is exceedingly common. Moreover, neurobiologic studies suggest that many abused substances, while working at different primary receptors in the brain, nevertheless share abilities to activate common brain reward circuits. From both of these perspectives, it is possible that many genetic influences on abuse of different drug classes might be similar. However, the ability to test this idea would be of substantial utility in exploring the drug-class specificity of genetic and environmental influences on vulnerability.

Comings proposes a more descriptive correlation study, testing whether variants at the dopamine (D) types 1, 2, 3, 4, or 5 (D1, D2, D3, D4, or D5) gene loci will correlate with results from items found in several diag-nostic and behavioral assessment instruments, including the Diagnostic Interview Schedule (DIS), Addiction Severity Index (ASI), the Minnesota Multiphasic Personality Inventory (MMPI), a defense-style questionnaire, and other personality indices. Comings' perspective is broad, with a working hypothesis that variant forms of specific major and modifying genes contribute to groups of symptoms characterizing a number of impulsive disorders. Comings postulates that a small number of major genes and a large number of modifying genes may play a role in a lifelong spectrum of "impulsive, compulsive, addictive, affective and anxiety disorders."

These broad and interesting ideas need to be balanced by studies that emphasize precision in identification of genetically driven syndromes, precision in application of linkage disequilibrium/association methods so that ethnic factors and other confounding features do not provide

false positive or false negative results, precision in separating working hypotheses from well-supported data (e.g., concerning the numbers of "major and modifying genes"), and precision in suggesting whether the genes involved in antisocial personality "can play a role in susceptibility to drug abuse," generally, or if antisocial personality/substance abuse comorbidity defines the substance abuse subtype with, perhaps, its own discrete genetics. Attention to each of these features (and many more) is essential to make sense of what is likely to be complex, non-Mendelian genetics of drug abuse vulnerability. Controls for multiple statistical tests and clean separation of hypothesis-generating from hypothesis-testing research are other important features. It is likely that the kind of broad searches that Comings' group is pursuing will yield positive correlations between gene markers, drug use, and/or other personality factors. However, it is important to be able to state a priori the hypotheses that are being tested and to define the rest of the work as hypothesis generating.

CONCLUSION

The three proposals presented here thus provide an interesting snapshot of the genetics of substance abuse vulnerability. This field is in transition from its initial stage of identification of the presence of genetic influences in drug abuse vulnerability to the beginning of an era in which identifi-cation of the particular genes involved and particular genetically driven substance abuse nosologic subtypes should allow increasingly precise identification of the nature of the genetics and genetic/environment interactions that produce vulnerability to this widespread, common, and debilitating condition.

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Psychophysiological Prediction of Substance Abuse

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STATEMENT OF THE PROBLEM

A decade of large-scale, cross-sectional, and longitudinal research on adolescents has provided a wealth of information concerning the personality and psychosocial correlates of adolescent drug abuse. However, relatively little is known about psychophysiological factors related to drug abuse. This chapter outlines a rationale for the psycho-physiological investigation of psychoactive substance use disorders and introduces several experimental paradigms likely to identify psycho-physiological characteristics underlying the vulnerability for substance abuse (SA).

First, it is hypothesized that there exists an inherited vulnerability to SA that is expressed through personality, externalizing behaviors, and dis-orders indicative of undersocialization (see McGue et al., this volume, for a brief review of the pertinent literature). Second, it is hypothesized that there are psychophysiological deviations associated with this inherited vulnerability that are present early in life (i.e., during late child-hood or adolescence), before an individual begins to use or abuse sub-stances. The etiology of SA is assumed to be multifactorial, reflecting both genetic and environmental heterogeneity. One of the challenges facing those researching SA is how to carve SA into etiologically meaningful subgroups. Psychophysiology may provide a tool for doing this. Psychophysiological differences among substance abusers or those at high risk for SA may identify subtypes and provide clues to the nature of the underlying etiology.

The focus here is on one form of SA that is believed to be determined in part by genes that influence a collection of personality traits and disorders characterized by behavioral disinhibition. These traits and disorders include, but are not limited to, aggressive and impulsive behavior, low fearfulness or harm avoidance, sensation seeking, juvenile delinquency, criminal acts, antisocial or psychopathic personality, excessive use of alcohol, and externalizing disorders of childhood such as conduct disorder (CD) and attention deficit-hyperactivity disorder (ADHD). Although the psychophysiology of

SA has received little study per se, the psychophysiology of this family of traits and disorders has been investigated and provides a useful starting point for developing a strategy to study SA from a psychophysiological perspective.

The strategy advanced in this proposal derives from the following hypotheses in a search for psychophysiological deviations associated with SA. These deviations are related to characteristics indicative of behavioral undercontrol; are, like the associated behavioral predisposition, under partial genetic control; have the potential to identify vulnerable individuals at risk for SA; and are both assessable and present in children.

In consideration of what types of psychophysiological paradigms might be best suited for this kind of investigation, two reasonable alternatives are possible. One is to develop experimental protocols that derive logically from theoretical notions of the psychophysiological substrate underlying behavioral disinhibition. The other is to select procedures derived from well-established paradigms that yield robust results when applied to the study of externalizing disorders. The latter approach has largely been adopted for the proposed study.

BACKGROUND AND SIGNIFICANCE

To evaluate the utility of different psychophysiological approaches to the study of SA, guidelines based on empirical findings would be expected given the hypotheses posited above. There are no measures associated with paradigms that have demonstrated all of the expected empirical relationships. Further evaluation and refinement of the chosen paradigms will determine whether they satisfy the criteria outlined below. The paradigm is expected to identify a replicable psychophysiological deviation that:

- is found in "affected" individuals. By affected, the authors mean that the individual possesses a characteristic feature associated with behavioral undercontrol (e.g., has SA or antisocial personality disorder, is impulsive, has been alcohol dependent). Because drug or alcohol abuse may alter an individual's physiology, caution is required when interpreting the results of investigations of those who are acutely intoxicated, are experiencing withdrawal, or have chronically abused a psychoactive substance. Psychophysiological deviations found in these individuals are

likely to be state related, and therefore do not necessarily reflect a trait predisposition for SA. Deviations of special interest would be those present in abstinent chemical abusers with a recent onset of dependence.

- is stable over time. Because there is interest in traits associated with SA, the deviation is expected to be stable over time at least in adults. Stability might not hold in young children because their nervous systems and character are constantly developing. Unfortunately, littleis known about developmental effects on psychophysiological measures, so these must be evaluated for each measure and age group.

- is heritable. It is hypothesized that the deviation is under partial genetic control, suggesting that it could be expected to run in families. Of special interest are twin studies demonstrating that a deviation shows higher concordance in monozygotic (MZ) than in dizygotic (DZ) twins.

- identifies at-risk persons. The deviation should be present in a substantial percentage of the first-degree relatives of affected individuals, including those who have SA or traits and disorders related to SA. Because not everyone who carries the genetic diathesis for what underlies SA and related disorders can be expected to manifest signs of behavioral disinhibition, psychologically healthy relatives can also be expected to possess the deviation. The study of adult and child relatives may generate different results because, as noted above, there is a paucity of knowledge regarding age and developmental effects on psychophysiological characteristics. The ultimate at-risk test involves longitudinal study of those at risk to demonstrate that psychophysiological measures obtained prior to the appearance of SA ultimately predict its development.

Four types of psychophysiological paradigms have been identified that are believed to have special potential to yield information predictive of SA. In subsequent sections, the literature for each type of paradigm is reviewed with special attention to the criteria presented above.

Event-Related Potentials and Cognitive Processing

A late positive component of the cerebral event-related potential (ERP), called P3 or P300 because it is usually the third ERP wave producing a positive voltage deviation and it has a latency of about

300 milliseconds (ms), has been advanced as a possible indicator of risk for one type of behavioral undercontrol—alcoholism. The first report to raise interest in this possibility was that of Begleiter and colleagues (1984). Boys (average age about 12 years), half of whom were the offspring of alcoholic men and all of whom had never been exposed to alcohol or other substances of abuse, engaged in a "rotating heads task." Subjects watched a computer screen that displayed an oval (neutral condition) or one of two types of target stimuli: an oval, representing a top view of a human head, with a "nose" pointing up and an "ear" on either the left or right side (easy target condition), or an oval with a "nose" pointing down and an "ear" on one side (difficult target condition). The subject's task was to decide whether the ear presented on a target trial was on the left or right side of the head. Because the target stimuli were presented infrequently compared with the neutral stimuli and involved a cognitive load, they elicited a P3 wave. The sons of alcoholics produced smaller P3 amplitudes to the target stimuli than sons of nonalcoholic men. This P3 finding, coupled with earlier work carried out by these investigators showing that abstinent alcoholics evidence a similar P3 deviation, led Begleiter and colleagues (1984) to suggest that this response pattern was an electrophysiological antecedent of alcoholism, possibly indicating a working memory deficit.

Various investigators, including those from the Begleiter group, have replicated this finding using a variety of P3 eliciting tasks (Korman and Guglielmi, unpublished data; Polich et al. 1994). This literature has also been extended by investigators who have shown that the latency of the P3 wave is delayed in high-risk children (e.g., Whipple et al. 1991). However, some investigators (Polich and Bloom 1986, 1987, 1988) have failed to replicate the basic P3 finding.

In their analysis of this literature, Korman and Guglielmi (unpublished data) demonstrated that P3 findings were more consistent across labora-tories if studies were grouped according to whether investigators studied young or adult children of alcoholics. The five reports Korman and Guglielmi reviewed that examined children from 7 to 15 years old all found diminished P3 amplitude to be associated with risk for alcoholism. Those studies focused on children 18 or older had mixed results, with three obtaining the effect and six failing to do so. This analysis raises the possi-bility that younger high-risk children are demonstrating an effect indicative of developmental delay, a delay many may overcome by the time they reach adulthood. A similar conclusion was reached by Polich and colleagues (1994) following their meta-analysis of this literature.

Unfortunately, it is not possible to convincingly address this possibility with the existing cross-sectional research. It would be necessary to employ a longitudinal approach or a single study that includes both younger and older children. Itis also possible that the different outcomes stem from the fact that studiesof adult children tend to use college students as subjects, sometimes screening them for alcoholism, a procedure that may actually lower subject risk. These individuals may be less likely than children from the popu-lation at large to have the type of cerebral deficit that is indexed by diminished P3.

Further evidence that P3 has potential as an electrophysiological marker comes from twin studies that show, in general, that features of ERPs are heritable (Buchsbaum 1974; Dustman and Beck 1965; Lewis et al. 1972; Osborne 1970; Rust 1975; Surwillo 1980). Of special interest is a report by Polich and Burns (1987) that demonstrates that P3 amplitude and latency are highly similar in MZ twins but essentially unrelated in matched pairs of singletons.

Electroencephalographic (EEG) Activity at Rest

Compared with the alcohol/P3 literature, relatively little is known about the likelihood that EEG can be used to predict the development of SA. However, if an investigator is already measuring the ERP, resting EEG can be easily recorded, adding nothing to subject preparation time and only a few minutes to the length of an experimental session. Moreover, what literature there is suggests that there is good reason to believe that a particular EEG pattern may be related to the predisposition for SA.

Resting EEG can be simply recorded by having subjects relax with their eyes closed for several minutes. Lund and colleagues (1995) have shown that as little as 2 minutes of resting EEG is sufficient to derive highly reliable estimates of the amount of electrical activity in EEG spectral bands covering the standard delta (0 to 3 hertz (Hz)), theta (3.1 to 8.0Hz), alpha (8.1 to 13.0 Hz), and beta (13.1 to 30 Hz) frequencies. Although resting EEG is dynamic and indicative of an individual's current state of cerebral arousal, EEG spectral parameters are temporally stable if individuals are evaluated under similar psychological circum-stances at different points in time. This conclusion is supported in part by twin studies which show that MZ twins have remarkably similar EEG spectra when tested under the same experimental conditions (Lykken et al. 1974, 1982; Stassen et al. 1987, 1988). Indeed, when assessed under similar circumstances,

identical twin pairs are more like each other than a given twin is like him- or herself with repeated testing under dissimilar circum-stances (Lykken et al. 1982). Other investigators have also shown that EEG patterns are genetically influenced (Vogel 1970; Propping 1977).

Deviations in resting EEG have been associated with the prediction of two different types of SA-related behavior, criminality and alcoholism. It has been hypothesized that a psychophysiological predisposition to criminality manifests itself through autonomic and central nervous system (CNS) underarousal (Raine et al. 1990b). In support of this notion, Raine and colleagues (1990b) showed, in a longitudinal study of an unselected sample of male schoolchildren, that the resting EEG assessed at age 15 predicted those who became criminals at age 25. In particular, those who became criminals had disproportionately more slow-frequency EEG—significantly more theta and a strong trend toward more delta and alpha. Volavka (1987) also demonstrated that childhood EEG could predict adult criminal behavior. Volavka monitored the alpha rhythm in 11- to 13-year-old children at high risk for delinquency and found that a slower average alpha frequency predicted thievery in adulthood.

Several investigators have examined how risk for alcoholism might be related to resting EEG. Propping and colleagues (1981) divided alcoholic women into two extreme groups: one characterized by synchronized EEGs displaying a great amount of alpha, and the other by little synchro-nized activity characterized by more beta and indicative of greater cerebral arousal. Propping and colleagues (1981) found that the nonalcohol-abusing first-degree relatives of individuals in these two groups showed the same EEG patterns as their alcoholic relatives. Although this study raised the possibility that these EEG patterns reflect a predisposition for alco-holism, it is not possible to determine whether this is so from this design. The similarity in EEG across relatives may be a product only of their genetic relatedness.

Gabrielli and colleagues (1982) extended this line of research by examining the sons and daughters of male alcoholics when the children were about 12 years old. Sons, but not daughters, were found to exhibit excessive beta activity compared with control children. Using a somewhat similar design, Pollock and colleagues (1983) failed to replicate this finding in a study of the sons of alcoholic fathers when the sons were approxi-mately 19 years old. However, this research team did report hemispheric differences in EEG, indicating that the sons of alcoholics showed more bilateral beta

and theta and less bilateral delta symmetry in their EEGs compared with controls.

Although the data are hardly overwhelming, when the EEG studies of children at risk for criminality and alcoholism are taken in the aggregate, they clearly point to the desirability of evaluating resting EEG as a psychophysiological predictor of SA. Interestingly, the differences in the Gabrielli and colleagues and Pollock and colleagues studies may be attributable to the possible effects of maturation on the EEG, like the results of the alcohol/P3 investigations reviewed above.

Autonomic Reactivity in Anticipation of Aversive Stimuli

Psychopaths have been characterized as fearless, unable to learn to avoid punishment, and in high need of stimulation—all features suggesting a characteristic lack of anticipatory arousal. Earlier research by Lykken (1957) and Hare (1965) demonstrated that psychopaths show relatively attenuated electrodermal reactivity to the threat of noxious stimulation. In following up these results, Hare developed a "countdown" paradigm to assess reactivity in anticipation of an aversive event (see Hare 1978 for a review). In this procedure, electrodermal and cardiac activity are assessed while subjects anticipate a strong, unpleasant event. The stimulus can be made predictable by having the subject listen to a countdown from 9 to 1, recited slowly, with the knowledge that the noxious event (an electric shock or very loud noise) will be presented after a specified number is heard.

Compared with nonpsychopaths, psychopaths have consistently shown smaller anticipatory skin conductance but larger anticipatory heart rate increases preceding the aversive stimulus (Hare and Craigen 1974; Hare et al. 1978; Tharp et al. 1980). A similar cardiac response pattern in antici-pation of painful shocks has been observed by Lykken and colleagues (1972) in university undergraduates selected to be low in fearfulness, an attribute that Lykken (1957) has argued may be fundamental to the development of psychopathy. The cardiac acceleration evident in psycho-paths has been hypothesized to reflect an active coping response to reduce the aversiveness of the stimulus (Hare 1978; Fowles 1980). By contrast, the electrodermal activity preceding the stimulus is viewed as indicative of the success of this strategy and the degree to which anticipatory fear is experienced.

Ogloff and Wong (1990), motivated by these theoretical speculations, extended the countdown paradigm in a way that enables further

differentiation of psychopaths from nonpsychopaths. Their study included a countdown task in which subjects could escape a 120 decibel (dB) tone by pressing a button during the last second of the countdown. Although psychopaths were less electrodermally responsive during the countdown, their heart rates were elevated preceding the aversive stimulus only when the tone was unavoidable. By comparison, the nonpsychopaths displayed high and equally elevated heart rates during both types of countdown.

All of these countdown studies were carried out using the Cleckley-Hare definition of what constitutes psychopathy (Cleckley 1976; Hare et al. 1991) using prison inmates as subjects. Although criminal psychopaths also satisfy criteria defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed. rev. (DSM-III-R) for antisocial personality disorder (ASPD), they represent only a subset of prisoners with this diagnosis. For these reasons, it remains to be determined whether the countdown procedure would yield the same results in noncriminal subjects or the broader class of criminals with DSM-III-R antisocial personality disorder.

Electrodermal Reactivity, Habituation, and Conditioning

The most common technique for studying electrodermal activity involves measuring palmar skin conductance response to the repeated presentation of a stimulus such as is typically done in studies of habituation. Common dependent variables include both tonic (skin conductance level) and phasic (spontaneous and elicited skin conductance responses) measures and estimates of habituation rate. These types of variables have been shown to be stable over time and heritable. Iacono and colleagues (1984) have shown that various electrodermal indices derived from a habituation assessment are stable over a 1-year time interval in normal adults. Twin studies of skin conductance have demonstrated that tonic level, response frequency, and habituation rate are all under partial genetic control (Bell et al. 1977; Hume 1973; Lader and Wing 1966; Lykken et al. 1988; Zahn 1977). In the only electrodermal study of twins reared apart, Lykken and colleagues (1988) showed that most of the stable variance in habituation rate was genetically determined and that electrodermal activity was strongly influenced by genes.

Finn and colleagues have shown that the relatives of alcohol-dependent men show electrodermal deviations characterized by either hyper- or hyporesponsivity. Finn and Pihl (Finn et al. 1990b; Pihl et al. 1989) have examined electrodermal responding in the offspring of

alcoholics using a habituation paradigm in which subjects were repeatedly exposed to 70 dB tones. In a study by Finn and colleagues (1990b), the sons of alcoholics had larger skin conductance responses, shorter response latencies, and slower habituation rates than the sons of nonalcoholics. These findings were replicated in a subsequent study of the daughters of alcoholic and nonalcoholic men. In these and other studies (e.g.,Finn and Pihl 1987), Finn and colleagues found similar over-responsiveness when recording cardiovascular measures during exposure to a Hare countdown that ter-minated with a painful shock (see Pihl et al. 1989 for a review). Exposing the high-risk subjects to alcohol tended to normalize their excessive electro-dermal and cardiovascular responding. These results were used to argue that the observed hyperactivity creates an unpleasant state that leads to an increased likelihood of chemical abuse. Given the appropriate milieu, these autonomically overaroused individuals might find the use of a depressant drug like alcohol negatively reinforcing because it reduces their exaggerated responding, thus increasing their propensity for SA.

Although Finn and colleagues found autonomic hyperactivity in these investigations (all of which were carried out in Quebec), more recent studies conducted in Indiana (Finn et al. 1994) have found the progeny of alcoholics to be hypoactive. Finn and colleagues (1990a) reported nonsig-nificant trends indicating that the sons of alcoholics were less electro-dermally responsive than the sons of nonalcoholics in a habituation task that required subjects to push a button when target tones differing in frequency from nontarget tones were presented. Further evidence that the male children of alcoholics are electrodermally nonres-ponsive was subse-quently provided by Finn and colleagues (1994). These investigators used an aversive classical conditioning paradigm to show that only the sons of alcoholics generated small skin conductance responses to a conditioned stimulus, both during acquisition and during assessment of the spontaneous recovery of the conditioned response. The high-risk subjects also failed to show electrodermal differentiation between stimuli signaling an impending punishment (shock) and those signaling nonpunishment. The electrodermal data were paralleled by those associated with peripheral vasoconstriction.

These findings, indicating autonomic underarousal in high-risk subjects plus the failure of these individuals to differentiate stimuli associated with aversive events from those that are not, lead to speculation that the off-spring of alcoholics may be at increased risk for SA because they are insensitive to the negative, punishing

consequences of their behavior. The results for the high-risk subjects are similar to the pattern of electro-dermal activity observed in conditioning studies of psychopaths (Lykken 1957; Hare 1965) and are thus consistent with the present hypothesis that a common diathesis might underlie a variant of undersocialization that includes proneness to SA and antisocial behavior. Further evidence supporting this notion derives from Raine and colleagues (1990a, 1990b), who have shown that adolescents who later become criminals have electrodermal and cardiovascular reactions similar to the high-risk subjects studied by Finn and colleagues (1990a, 1994).

Summary

Both these cerebral and autonomic psychophysiological paradigms have yielded findings that have been shown to be replicable, stable over time, and related to risk for behavioral disinhibition, especially alcoholism, psychopathy, and criminality. Both of the cerebral measures, P3 and resting EEG, may be influenced by maturational effects, a possibility best resolved through longitudinal study. Two measures, resting EEG and electrodermal reactivity, have been associated with psychophysiological signs of both under- and overarousal. It is not possible to determine from the existing literature why this state of affairs exists. One possibility is that these findings reflect etiologic or psychophysiological heterogeneity in the risk for SA and related characteristics that is attributable to sampling differences across sites. Samples are often unrepresentative (e.g., at-risk offspring of alcoholics are selected from treatment programs or all subjects are college students) and typically small (e.g., the Finn and colleagues studies have 12 subjects per group). Larger samples, ideally epidemiologically based, are needed to help clarify the relationship between these measures and risk for SA.

DESIGN AND EXPERIMENTAL METHODS

There are many obstacles to resolving the inconsistency evident in previous studies and to advancing firm conclusions regarding the psychophysiological prediction of SA. These obstacles include using small, unrepresentative samples, studying only one member of a family, not using behavioral genetic designs, studying at-risk individuals after they have already reached the age of risk, focusing only on male relatives or the offspring of affected men, using cross-sectional designs, employing only one type of psychophysiological paradigm in isolation, and relating a psychophysiological deviation to

only one manifestation of behavioral disinhibition. To circumvent these obstacles, the authors have launched the Minnesota Twin Family Study (MTFS), a longitudinal investigation of twin children designed to identify genetic and environmental influence on the development of SA and associated disorders.

Overview

The MTFS is based on an epidemiologically derived sample of 1,300 adolescent and preadolescent same-sex twin pairs, equally divided between males and females, and their parents. Subjects undergo a comprehensive 1-day assessment that includes mental health, substance use and abuse history, psychophysiological indicators of risk, personality, interests and abilities, social adjustment, and environmental moderators of risk. Twins are first assessed either when they are in the sixth grade (usually 11 years old), just prior to their possible initial experimentation with drugs and alcohol, or as high school seniors (at about age 17), prior to the establishment of adult drug use and drinking patterns or the onset of adult psychopathology. The sample is selected so that approximately 40 percent of the twins have at least one substance-dependent parent. The twins are studied prospectively for 9 years, thus providing an opportunity to map out the development of SA and related disorders over an 11- to 26-year age range.

Recruitment and Sampling

Beginning with Minnesota State birth records, the authors are able to locate approximately 90 percent of the families of the roughly 400 same-sex twin pairs born in the State during a given calendar year and enter them into the authors' twin registry. Once located, families are sent a brief biographical questionnaire, usually completed by the mother, that provides preliminary information used to determine risk status. Because the registry contains many more twins than the authors can assess, twins are selected in a manner that enriches the sample with those who are at high risk for SA by using responses to the biographical questionnaire plus driver's license checks for drunk driving arrests to identify parents with SA (nonnicotine) related problems. Although this preliminary method for identifying high-risk families has limited sensitivity, it has great specificity and designates about 15 percent of the registry sample as high risk. All designated high-risk families are asked to participate in the study along with a random sample of all remaining registry families so that about 40percent of the twin pairs have a SA-affected parent. Twins

and their parents are asked to visit the psychology laboratory for a 1-day comprehensive assessment.

Psychophysiological Assessment

The psychophysiological assessment is derived from the cerebral and autonomic paradigms reviewed above. These paradigms were used to develop experimental protocols that were simple, that could reasonably be expected to be associated with psychophysiological deviations of interest given the extant empirical literature, and that had already been successfully used in the authors' laboratory.

Event-Related Potentials. The ERP assessment was very closely modeled on the rotating heads task used by Begleiter and colleagues (1984). Subjects are presented with 240 computer-generated stimuli with a variable interstimulus interval ranging from 3 to 5 seconds. One hundred and eighty of the stimuli are ovals. The remaining presentations consist of 80 heads with a nose pointing up or down and one ear on either side of the head, with the stimuli evenly split between easy and difficult targets. EEG is recorded from parietal, central, and frontal sites. The electro-oculogram is used to record blinks and control for blink artifacts from one eye. The physiological channels are sampled at 256 Hz for 2seconds per stimulus presentation using a quarter-second prestimulus baseline. For the easy and difficult trials, the subject's decision regarding whether the ear is on the left or right side of the head is recorded from microswitches attached to both armrests of the subject's chair. After the data are collected, the ERPs are digitally filtered, corrected for blink artifact, and averaged separately for each of the three types of trial. The amplitude and latency of the P3 wave is then determined.

Resting EEG. Five minutes of resting EEG is recorded while subjects sit quietly with their eyes closed (Lykken et al. 1982). EEG is recorded from occipital, temporal, frontal, and central sites and digitized at a rate of 128 Hz. To minimize the contamination of the EEG by biopotential noise, bipolar recording leads are used. The electro-oculogram is also recorded and subtracted from the EEG to eliminate eye movement artifact. The processed EEG signals are then subjected to a Fourier analysis and the parameters of the resulting EEG spectra are determined.

Anticipation of Aversive Stimuli. In the "cooltest" procedure—so named because the purpose is to determine if the subjects can remain calm in the face of pending unpleasant stimulation—a computerized

clock face with a sweep second hand is used to indicate when a loud blast of static (2 seconds of 107 dB white noise) might occur. On three trials, the occurrence of the stimulus is predictable just as in the Hare countdown procedure. For two trials, the stimulus display is the same except that there is no mark on the clock face indicating when the aversive stimulus is due to be presented. On these trials, the blast of noise is unpredictable. This variant of the count-down task allows examination of the effects of stimulus predictability and "preception," the ability to attenuate the impact of aversive stimuli made predictable in time (Lykken et al. 1972). The final trial is modeled after Ogloff and Wong's (1990) demonstration that ability to block the aversive stimulus produces a unique autonomic response pattern in psychopaths. For this trial, if subjects press a button during the second that precedes the static blast, they prevent its occurrence. Bilateral skin conductance, heart rate, finger pulse volume, and respiration are recorded and digitized at 128Hz for later offline analysis.

Habituation. Habituation is examined following procedures very similar to those of Lykken and colleagues (1988). Subjects are presented with 17half-second, 105 dB tones every 30 to 90 seconds while they watch a video movie presented with closed captions rather than an audio track. Subjects are told to focus their attention on the movie and to ignore the meaningless, distracting tones. All the tones are 1,000 Hz except the sixteenth, which has a frequency of 600 Hz. This novel tone is included as a test of dishabituation. The same autonomic variables recorded during cooltest are measured during the 20 seconds following each tone presentation. Habituation is quantified by counting the number of trials preceding two consecutive failures to respond. Habituation is also estimated by fitting a straight line habituation curve to the skin conduc-tance amplitude versus log of trial number data and determining the x-intercept.

Clinical/Personality Assessment

Although this assessment of psychopathology and personality is intended to be comprehensive, the primary focus is on disorders and characteristics related to behavioral disinhibition. Structured interviews, standardized personality scales, and behavioral ratings by parents and teachers are used to assess undercontrolled behavior. Because reports from multiple informants increases the reliability of assessments, family members are interviewed about each other, medical and school records are obtained, and teachers are asked to

provide information about the twins' behavioral adjustment and personality.

The younger twins are interviewed with a modified version of the Diagnostic Interview for Children and Adolescents-Revised (DICA-R) (Welner et al. 1987). This interview covers selected internalizing and externalizing disorders of childhood including CD, oppositional defiant disorder (ODD), ADHD, and drug/alcohol use disorders. Part of the interview involves asking the twins about their cotwin's use of sub-stances. Because 11 year olds are not necessarily reliable informants for symptoms related to these disorders, mothers are interviewed about each child using the parent version of the DICA. The twins also complete a computerized substance use and abuse questionnaire. The personalities of the younger twins are assessed using rating scales completed by their mothers and teachers.

The older twins receive an assessment of childhood disorders identical to that used with the younger twins. To cover adult disorders, the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al. 1987) and the Substance Abuse Module (Robins et al. 1987) of the World Health Organization's Composite International Diagnostic Interview (Robins et al. 1988) are used. In addition, a structured interview to assess ASPD was developed (Iacono et al., unpublished data). The older twins also complete the computerized substance use and abuse assessment and a personality inventory (Tellegen et al. 1988) that taps positive and negative emotionality as well as a behavioral constraint dimension (impulsivity, harm-avoidance, and other indicators of undersocialized behavior). The California Psychological Inventory Socialization Scale (Gough 1964) is also administered.

The parents receive an assessment identical to that of the 17 year olds, except that the DICA-R interview is not used to assess childhood psycho-pathology in the parent. Each parent also completes a family history interview on the twins' other biological parent and the first-degree relatives of each parent.

Once the interviews are completed, blinded case conferences are held for each study participant. At these meetings, audiotapes of interviews and coded interview instruments from all informants are reviewed to determine if the symptoms of the various disorders are present. Then DSM-III-R (American Psychiatric Association 1987) and other diagnostic system algorithms are used to assign diagnoses.

Followup Assessment

The psychophysiological and clinical assessments, with some variations, are repeated every 3 years. Because the mother is interviewed at length about the twins as well as about herself and her family during her intake assessment, she cannot be tested in the psychophysiological laboratory until she accompanies the twins on a return assessment visit. In addition to these triennial in-person assessments, the twins and their mothers are contacted annually for a phone interview that covers substance use and important life circumstances over the preceding year.

Analysis and Anticipated Results

A large, complex set of data will be gathered using a multivariate approach that seems justified given the developmental complexity of the SA phenotype. Only a general approach to data analysis is outlined here. The primary hypothesis is that individuals inherit a general vulnerability to SA and other forms of rule-breaking behavior that is manifest early in life in psychophysiological deviations which predict the future likelihood of SA.

Hence, a strong correlation is expected among SA, other indicators of undersocialized behavior, and psychophysiological deviations. This pattern is expected in affected individuals, but the children of affected individuals are expected to show the psychophysiological deviations even though the children themselves show no signs of disorder. It is antici-pated that the deviations, as well as behavioral indices of SA risk, will be heritable, showing higher similarity in MZ than DZ twins. Compared with DZ twins, MZ twins are expected to show more cross-twin resem-blance for these characteristics; thus SA-related characteristics in one twin will predict psychophysiological findings in the other.

By carrying out cross-sectional comparisons of 11 and 17 year olds and their parents, the authors will be able to determine whether age influences the expression of the psychophysiological deviations as well as their heritability. By taking repeated measures on the same children as they age, cross-sectional findings can be extended by examining how matura-tion affects psychophysiological measures. This prospective design enables determination of whether psychophysiological deviations developmentally predate the onset of SA and related disorders and ultimately whether they will predict their development.

Little is known about the risk for SA in women or whether psychophysio-logical deviations have predictive potential with females. Almost all of the psychophysiological research reviewed in this chapter used male subjects and paternal offspring. A major strength of the MTFS rests in the inclusion of twins of both sexes. Through separate analyses of male and female twins, it will be possible to determine if similar processes underlie the development of SA in the two sexes. Analyses comparing outcomes for the offspring of affected mothers versus the offspring of affected fathers will further contribute to the understanding of the role of gender in the psychophysiology of SA.

PUBLIC HEALTH SIGNIFICANCE

It is hypothesized that a characterological predisposition for SA is marked by undersocialized behavior. The psychophysiological measures chosen are hypothesized to be indicators of the underlying vulnerability to this predisposition. As noted elsewhere (McGue et al., this volume), there is considerable evidence to suggest that there is a second important pathway to the development of SA, one characterized by internalizing disorders (mood and anxiety disorders) and negative emotionality (neuroticism, general maladjustment). This predisposition for psychological distress, which may be more common in women prone to SA, is apt to have different genetic and psychophysiological underpinnings. For this reason, different psychophysiological paradigms may be needed to identify this vulnerability.

Unfortunately, there are few psychophysiological paradigms associated with internalized behavior disorders that yield replicable results, thus rendering the psychophysiological study of this possible pathway to SA difficult. An exception involves the study of electrodermal and cardio-vascular habituation in mood disorders, especially major depression. Individuals with mood disorders have been found to be electrodermally nonresponsive, even when they are euthymic (e.g., Iacono et al. 1983, 1984). Bernstein and colleagues (1988) have shown that electrodermally nonresponsive depressives nevertheless have normal cardiovascular responses. The combination of electrodermal hypoactivity and normal cardiovascular reactivity appears to distinguish major depression from other forms of psychopathology.

Another paradigm that holds the promise of identifying psychophysio-logical deviations associated with negative emotionality is the startle procedure of Lang and colleagues (1990). Subjects are presented with affectively laden slides that elicit strong positive and negative emotional reactions. During the slide viewing, a startle stimulus is presented and the electromyogram is recorded to quantify the magnitude of the eyeblink startle response. In normal individuals, the amplitude of the startle eye-blink is potentiated during negative emotional states and attenuated during positive states. One could expect anxious or depressed individuals to show excessive startle response, especially to negative stimuli. Interestingly, Patrick and colleagues (1993) have shown that psychopaths do not show startle potentiation to negative stimuli, thus raising the possibility that the startle paradigm can be used to differentiate the neurotic from the charac-terological predisposition for SA.

The potential findings from this project may have public health significance. This research will contribute to the understanding of how biological, genetic, and environmental factors combine to determine the development of SA. It should enable more accurate identification of risk for SA and prediction of who is especially likely to develop substance use disorders. For these reasons, the findings stand to provide important direction for the development of intervention strategies designed to prevent the occurrence of SA.

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Commentary on "Psychophysiological Prediction of Substance Abuse" by Iacono, Lykken, and McGue

Scott E. Lukas

SUMMARY

A large-scale multivariate study including both cross-sectional and longitudinal designs is proposed to identify factors that contribute to an adolescent's vulnerability to substance abuse. The design calls for the use of a large number of adolescent twins who are scheduled to enter the sixth grade, and it proposes to study these individuals until they are age 26. The protocol is designed to compare male and female preadolescents and adolescents who are designated as high or low risk on the basis of parental drug self-administration with respect to personality character-istics, rates of externalizing and internalizing behaviors, mental health, familial and extrafamilial environments, aptitudes and scholastic perfor-mance, psychophysiological markers, and substance use and abuse history. Additional features of the cross-sectional design include bio-metrical analyses of the twin data to determine the extent to which variance is a predictor and outcome measures are associated with genetic, shared, and nonshared environmental factors. This design also will allow the investigators to determine whether estimates in variance components increase, decrease, or remain stable over development from age 11 to 26.

The aims of a longitudinal design are to characterize the diverse develop-mental pathways that result in substance abuse by measuring a number of psychophysiological indices, including event-related potentials (ERPs), electroencephalographic (EEG) activity, and electrodermal reactivity. In addition, the project is designed to shed light onto whether issues such as peer group membership or educational abilities are, in fact, guided by genetic factors.

Since there is a great deal of cross-sectional and longitudinal research on adolescence concerning personality and psychosocial correlates of adoles-cent drug use, the proposed research should fill a gap in the literature by identifying the factors of adolescent deviance that exist prior to any exposure to illicit substances. The proposed research

focuses on inherited vulnerability to substance abuse that is expressed early in life in personality deviations, behavioral or adjustment difficulties, parent-offspring conflict, inadequate or destructive peer relationships, and a variety of externalizing behaviors. The investigators hypothesize that an individual's inherent general antisocial and rulebreaking behaviors will be correlated with measurable psychophysiological indices and the pressure of these markers may predict future drug abuse.

STRENGTHS OF THE PROPOSED RESEARCH

One of the major strengths of the proposed program is the use of the multivariate strategy to achieve specific aims. The use of highly sophis-ticated bivariate and multivariate biometrical analyses of the twin-family data should determine the extent to which genetic and environmental factors mediate the relation between putative risk markers and outcome status. Given the large number of variables proposed, such a strategy is necessary to ensure that observed relationships are real and not due to chance.

Another significant strength of the proposed research plan is the scope of the longitudinal design. Such designs are rarely implemented because they are inherently expensive and very difficult to complete. The proposed research plan will start off with enough subjects to result in a final sample size of 675 20-year-old and 530 26-year-old subjects. Since the researchers plan to study the subjects for 9 years, the consistency and quality of the data obtained are vastly improved over other designs. The inclusion of female twin pairs will further understanding of whether there are gender-related differences in sensitivity to developing drug abuse. Far too many prior studies have omitted females; the inclusion of women, especially twins, will help delineate the differences in markers and propensity for drug abuse between male and female adolescents.

By including an extensive assessment of specific biological and environ-mental factors, the researchers will be able to go beyond abstract variance components estimation and begin to identify underlying mechanisms of action. The researchers are aware that the breadth of the proposed assess-ments might be too great for an individual project. However, the investi-gators' rationale for being overinclusive, at least in the early phase of the research, is convincing. Indeed, it would be a shame to find out 10years from now that a very critical environmental or behavioral variable was not recorded. Thus,

the research team is attempting to include as many variables as possible without weakening the statistical strength of the design.

The time points for assessing the adolescents (ages 11 and 17) were carefully selected to coincide with the ages at which most adolescents are about to experiment with drugs and when they are just about to reach their peak time of substance abuse, respectively. An additional strength of the proposal is that the dependent variables will be obtained via personal interviews conducted by trained researchers instead of relying on self-report questionnaires. Such a strategy significantly strengthens the study design, especially as it encompasses such a long time period. The research protocol calls for frequent contacts with the subjects during the year either by phone or by mail; these are strategies that have been shown to be successful in prior longitudinal studies. Such a design also is more likely to be successful than other studies in which the subjects are contacted only once during the long intervals between the assessments.

Another strength of the research plan is the inclusion of a number of procedures for minimizing attrition. Subjects are paid for their expenses and are provided with feedback on information learned up to the present time. The inclusion of a semiannual project newsletter and birthday cards for the subjects is a clever ploy to increase the subject's interest in the study. Items such as a T-shirt with the university's logo are also given to the subjects. As twins consider themselves relatively special and different and often desire to learn more about their unique biology, it is likely that the subjects' interest will be maintained.

Another major strength of the research relates to the selection of the various psychophysiological tasks. The use of ERPs, especially the rotating heads procedure designed by Begleiter's group (Begleiter et al. 1984), has been shown to be sensitive to identifying differences between young boys who are at risk for developing alcohol abuse. Since other researchers have found that a similar relationship may not exist in adult populations, it is likely that the proposed investigation will uncover electrophysiological changes due to a maturation of the central nervous system (CNS). The proposed use of a longitudinal study will directly measure this possibility. Although few studies have identified a resting EEG pattern as a specific marker for substance abuse, there is abundant evidence suggesting that resting EEG activity is under genetic control (Propping et al. 1980). In addition, acute drug-induced intoxication parallels transient increases in EEG alpha activity (Lukas and Mendelson 1988; Lukas et al. 1986, 1989), while

chronic marijuana smokers display much more resting alpha activity than individuals who did not smoke marijuana (Struve et al. 1989). These findings, coupled with the relative ease of acquiring EEG data, makes this dependent variable a good candidate for further study in the program. In addition, resting EEG and electrodermal activity (the other electrophysiological measure to be obtained in the present study) have both been associated with signs of under- and overarousal of the CNS. Thus, it is likely that several differences between the twins in high- versus low-risk families will be discernible using these fairly sensitive psychophysiological techniques.

WEAKNESSES OF THE PROPOSED RESEARCH

As with all twin studies, the issue of whether the subjects are identical or fraternal twins needs to be addressed. The proposed study does not seem to make that distinction; this could have a major impact on the outcome of the study.

One potential weakness of the proposed research is inherent in the recruiting procedure. The researcher makes a point of emphasizing that interviews will be done in person by trained researchers, yet all of the information obtained during the early phase of the research will be obtained by self-report questionnaires. Self-reports, without corroboration, are often inaccurate for some measures. This is particularly important to the study because the initial classification of the twin-family unit as to whether it has a high, medium, or low risk of substance abuse is done on the basis of these self-reports. Because degree of risk is one of the factors in the research plan, it is important that this information be accurately coded. It is, however, recognized that such a biographical questionnaire would be difficult to give in person during the initial recruiting phase because of the number of subjects who would have to be screened. In addition, questions dealing with the difficulty of the birth should be included because fetal distress, low birth weight, prolonged labor, and other factors can all influence oxygen delivered to the babies during parturition. Thus, without knowledge of these facts, the results may be confounded because factors relating to fetal distress could interfere with later develop-mental and maturation processes.

Another potential weakness of the proposed research is that either one or both biological parents could have a diagnosis of substance dependence as defined in the "Diagnostic and Statistical Manual of Mental Disorders" (3d. ed. rev.) (DSM-III-R). The inclusion of a

biological mother who may have had a positive diagnosis of substance abuse or alcohol abuse raises the question of whether the in utero exposure to drugs or alcohol may have contributed to the subject's behavior or responses to the questionnaires. It is highly recommended that subjects whose biological mothers were substance abusers or alcoholics be excluded or, at the very least, be separated into a different group for analysis. In addition, a recent trend in alcohol research has been to explore the utility of genetic density as a means of reducing the variability in the subject population. It is suspected that individuals who have three or more family members who meet DSM-III-R criteria for alcohol abuse/dependence may have a greater density or likelihood of developing the problem than someone who has only a single relative with this diagnosis. Finally, the recruit-ment procedure needs to be more explicit in the family tree evaluations. For example, would individuals who have an uncle who meets DSM-III-R criteria for substance abuse be considered to have a positive family history? In essence, the preconceived notion that inherited vulnerability to substance abuse can only be detected in the individual's parents may limit the generalizability of the conclusions.

Even though the researchers noted that substance abuse problems are most likely to be genetically influenced in males as opposed to females, the critical comparisons of the positive correlation (in the males) with pre-sumably a negative correlation in young women would be a very important and strong finding. However, it is recognized that the inclusion of women in these studies would reduce the number of males who can be studied (thus decreasing the subject size by one-half). Unless the number of sub-jects were doubled, the power of the proposed research plan would be adversely affected. Since it would not be feasible to double the initial sample size, statistical power would need to be recalculated on the basis of half as many subjects.

While it is important to include women in these studies, there must be a control for differential responding during various phases of the menstrual cycle. There is ample evidence in the literature suggesting that women are likely to self-administer more drugs during the premenstrual phase of the menstrual cycle as opposed to other phases (Mello 1986; Mello et al. 1990). Furthermore, it is likely that some of the subjects in the older groups (ages 17 to 26) will begin to take oral contraceptives. The study protocol should be designed to accommodate these variables and be able to identify menstrual cycle phase and oral contraceptive use as possible sources of variance in the

data set. The difficulties associated with tracking different phases of the menstrual cycle have kept researchers from studying women for some time. Now that there are protocols and controls for conducting such studies, the procedures should be implemented.

ALTERNATE IDEAS

One area of future research would be to compare the data from children who were raised by nonbiological parents. The conduct of this parallel study (of the twin studies done in Europe) would be a major strength to the research protocol and would significantly delineate the factors that are inherited from those that are under environmental control.

Familial resemblance may be a result of genetic and/or shared environ-mental factors, and the separate influence of these factors cannot be determined from family data alone. The researchers state that twin and adoption studies are needed in this field. However, it is well known that siblings do not always maintain the same peer groups. An observed difference in outcome in a particular twin pair may erroneously be assumed to be due to a genetic factor when, in fact, the two individuals were exposed to very different levels of peer pressure. It is not entirely clear how this potential confounding factor will be controlled in future studies but it is certainly worth the effort. An alternate idea would be to provide some additional metric of environmental conditions that are shared within twin pairs. Furthermore, it may be important to segregate the data of individual twin pairs who share many common environmental conditions from twin pairs who diverge from one another.

Finally, a methodological suggestion. Because of the controversy over whether the P3 of adults is different in those with a positive family history of alcoholism, it may be advisable to include an auditory P3 paradigm as well. Such a comparison might provide insights in the differential maturation rate of auditory versus visual cognitive processing pathways.

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DISCUSSION

Audience and Panel Members: William Iacono, George Uhl, David Comings, Ralph Tarter, and Dan Hummer

Dr. Iacono: I'd like to make a few comments. One is that Dr. Lukas was talking about the cooltest paradigm that we're using in this research, and it's actually a variant of Hare's countdown procedure. We have a slightly different type of presentation, but we tell the children in the study that it's a test of their cool, how well they can handle the anticipation of an aversive stimulus.

Also, Dr. Lukas mentioned that the use of psychophysiological measures tends to eliminate some problems with subjective responsiveness inherent to other kinds of measures. Although that's true, it's also the case that these techniques involve psychology as well as physiology. It's very important to pay attention to the relevant psychological methodological issues that might affect the outcome of this research, just as it is important to pay attention to the quality of physiological recording.

A lot of effort goes into this type of research to refine a paradigm and to get it to the point where you can generate reproducible results. That's difficult to do in psychophysiology just as it is in many other areas of research.

Let me say a little about the actual study that we're doing. It's a study of twins who are at risk for developing substance use disorders. Dr. Lykken talked a little bit about it this morning, as did Dr. Lukas. It's an epidemio-logical investigation in which twins are identified from birth records. These are the twins born in the State of Minnesota. We're very effective at finding the twins. We find over 90 percent of them at age 11 and age 17. We send them questionnaires that include questions about the drug and alcohol use of family members as well as other questions about mental health and criminal activity. We make sure we overselect families who belong to risk groups defined by parental antisocial behavior and drug and alcohol use. Because there are more twins in any given year than we can possibly bring in, we randomly select from the remaining twins. We bring the twins and their parents who come from all over Minnesota into our laboratory for a full day's assessment, putting them up in a hotel if neces-sary. We have a large number of assessments and diagnostic interviews, some of which are repeated annually through phone and mail

contacts, and an extensive reassessment is carried out every 3 years in our lab. The project includes over 1,000 pairs of twins and their families, studied for about 10 years.

Dr. Uhl: This is a bit of a naive question. You have access to the birth records and so on. So, do you have any sense that perinatal issues that can lead to these changes (I think long-lasting changes) in things like evoked responses, and so on, are contributing to some of the concordances in the genetic studies with physiologic measures basically? It seems like that's an area that could covary again in the correlational substitutions with such measures as small for gestational age, prematurity, and so on. These may link directly to the perinatal issues that can have subsequent evoked response reflections that will last 6 months.

Dr. Iacono: Yes, it's an interesting question. As it turns out, the records we have are the birth certificates. We don't have hospital records, but we do interview the mother about the twins' births. That's as close as we get to covering this issue.

Dr. Comings: I think you mentioned this morning that there have been two studies now. One in our lab and one in Opel's lab that showed that the latency in the P300 is highly correlated to the D2/A1 allele pool. To me, it would be a shame for you to do all this work and then not, some-where down the line, do some genetic correlates with it.

Dr. Iacono: Well, I was wondering, since your talk this morning, how hard would it be for us to add something like that?

Dr. Comings: All you have to do is draw blood and find somebody that will do it for you.

Dr. Iacono: We've already got the blood.

Dr. Comings: We'd be happy to talk about it.

Dr. Tarter: I was surprised that you didn't mention anything about the use of visual tracking and eye-movement measurements, particularly since we've had a lot of discussion today about attention deficit disorder as a potential risk factor and some discussion centered around ERPs. Can you comment on the potential value—and I'm speaking again naively to this group—of looking at those kinds of variables as markers of frontal lobe development or functional

maturation, those processes that are supposed to be subserved by the frontal lobes such as eye movement, visual tracking studies?

Dr. Iacono: Yes. In the first place, I do schizophrenia research that includes eye-tracking studies. We have looked at schizophrenics' smooth pursuit eye-tracking and related it to performance on neuropsychological tasks, and we get a fairly strong correlation between the inability to generate smooth pursuit eye movements and various indices of frontal lobe dysfunction in adult schizophrenics. That particular finding has also been reported in other labs using less extensive neuropsychological assessments than the one we use. So, it does seem to be the case that the inability to do pursuit tracking might be related to some kind of frontal lobe problem.

In the twin study we're talking about here, we are assessing smooth pursuit eye tracking. I was a little timid about including that in my presentation because I'm less certain what the relationship of pursuit eye-tracking dysfunction might be to substance use disorders. And we've also found a strong developmental effect in our assessment of smooth tracking. For example, the 11-year-old twins in this study are about as good at smooth tracking as the typical person with schizophrenia. On the other hand, the 17-year-olds are among the best trackers that I've ever assessed. And I've assessed, up until now, over 500 people ranging in age up to about 70. If you plot eye-tracking proficiency versus age, the 11-year-olds are at about the same level as people who are 70 in terms of eye-tracking proficiency. There's a peak in proficiency—maybe at ages 16, 17, or 18—and then a gradual dropoff toward around age 40 or 50; the dropoff then starts to accelerate. So, there's something developmental going on with pursuit eye tracking, at least early in life, in these kids that we need to get a better handle on before we look at this as a way of assessing frontal lobe functioning.

People aren't born with the ability to produce smooth pursuit eye move-ments, and children mature at different rates. It could be the case that some individuals never get to the point of having full frontal lobe maturation and never really develop the ability to produce smooth eye movements, whereas others mature and eventually reach a point where they can produce them. In a study like this in which we carry out multiple assessments over time, I hope we'll be able to get an answer to this question of how development relates to smooth eye-tracking performance.

Dr. Tarter: Do you have any preliminary data around correlations with noncognitive variables such as impulse control and hyperactivity?

Dr. Iacono: It would be wonderful if I did, but I don't.

Dr. Hummer: I'd just like to say that we've seen the same kind of correlations in children and smooth pursuit eye tracking that you're reporting, with adult levels reaching around 15-17. And the other thing we've seen is children with ADHD, on and off Ritalin, using the delayed response task. This is a task in which a person has to inhibit eye move-ments until the target actually disappears, so it's a way of looking at ability to inhibit responses. This task has been extensively studied in nonhuman primates to understand the prefrontal cortex. What we find is that the kids with ADHD are normal in all other aspects of their eye movements, including smooth pursuit, but they have difficulty inhibiting premature responses during—only during—a delayed response task, which I think gets to your question about some of the frontal lobe kinds of deficits. We're preparing to look at that in children of alcoholics and other risk groups.

Cognitive Event-Related Potentials in Populations at Risk for Substance Abuse

Ronald I. Herning

STATEMENT OF THE PROBLEM

Cognitive information processing alterations are observed in populations at risk for drug abuse and in patients whose psychiatric disorders are often comorbid with drug abuse and dependence. A common early information processing deficit in these at-risk populations is hypothesized. The hypo-thesis is that the severity of this deficit or changes in this deficit produced by stimulants will be related to the individual's specific vulnerability to drug abuse and will predict subsequent substance abuse.

Specifically, this proposal is to study cognitive processing of 8- to 10-year-old children with attention deficit-hyperactivity disorder (ADHD), overt aggression, and depression. Appropriately matched control subjects and their parents will also be evaluated. Each child will be studied before and after a dose of methylphenidate and placebo in a double-blind, cross-over design. The biological parents of the child will also be tested at baseline. The children will be followed to 12 to 15 years of age with a battery of psychometric, drug history, and demographic questionnaires.

The study employs a cognitive event-related potential (ERP) testing battery sensitive to psychiatric disorders, overt aggression, and the effects of stimulant drugs. The experimental design assesses group differences both at baseline and after a stimulant challenge. Substance abuse detected at 12 to 15 years of age will be predicted from cognitive deficits observed at 8years of age. Comparisons between the cognitive ERPs of the at-risk child and drug-free parent will test for transgenerational mechanisms. Complete demographic, drug history, and psychometric information will be obtained and used to aid in the interpretation of the neurophysiological and outcome data.

BACKGROUND AND SIGNIFICANCE

Cognitive information processing alterations have been described in a number of psychiatric populations. High rates for the diagnosis of depression are observed in substance abusers (Harin and Grant 1987). Substance abusers in treatment who have major depression do more poorly than those with attention deficits (Rounsaville et al. 1987). Depression is often comorbid with substance abuse disorders in adolescents (Lewinsohn et al. 1993). Childhood depression may be a risk factor for substance abuse in both males and females. Neurophysiological measures of cognitive information processing are altered in adult depression. Cognitive ERP components (see below) are reduced in unmedicated depressed patients (Knott and Lapierre 1987; Pfefferbaum, et al. 1984). There are no studies that investigate neurocognitive status of depressed children and the relation of these indices to later substance abuse.

ERP research in populations at risk for substance abuse has been promising, but the effort has been focused on the sons of alcoholics. However, children with ADHD, aggressive boys, sons of drug abusers, and children with intrauterine exposure to abused drugs reportedly have altered sensory and cognitive ERPs (Brigham et al. 1993; Guo et al. 1994; Herning et al. 1989; Satterfield et al. 1987, 1988, 1990). These children are also at risk for substance abuse (Davis and Templer 1988; Kofoed and MacMillian 1986; Mannuzza et al. 1993; Weiss et al. 1985). The sensory and cognitive ERPs of these at-risk children are reviewed in an attempt to determine a common underlying deficit. Whether infor-mation processing deficits are associated with or predict a greater risk for drug abuse is not known.

Information processing can be evaluated in children as well as adults by noninvasive electrophysiological methods. Brain potentials or ERPs reflecting neural events related to sensory transmission of the stimuli or endogenous processing of task-related stimuli can be extracted from scalp recorded electroencephalogram (EEG). The brain potentials that are time-locked to sensory or endogenous events in the brain are extracted by signal-averaging techniques (Johnson 1993). The resulting waveforms have a sequence of peaks (positive activity) and valleys (negative activity) repre-senting the different stages of information processing. The peaks or valleys (ERP components) are named for their polarity (P for positive components, N for negative components) and the peak or valley number or latency. Thus, P3 would be the third positive component in the ERP waveform.

Family History of Alcoholism

Alcoholism research has focused on a reduced P3 as a marker of increased vulnerability to substance abuse. P3 is an endogenous component elicited by task-relevant auditory, visual, and somatosensory stimuli. It is thought to represent the updating of recent memory (Donchin and Coles 1988; Johnson 1993). A reduced P3 component would suggest limited evaluation of the task-relevant stimulus. Elmasian and colleagues (1982) were first to note a reduced P3 component in the auditory ERP of 18- to 26-year-old men who had a family history of alcoholism. The P3 component of the ERP in a visual discrimination task was reduced in 7- to 10-year-old boys who had alcoholic fathers as compared with boys with normal fathers (Begleiter et al. 1984).

Many attempts have been made to replicate these findings, but the results have been mixed. Polich and colleagues (1994) have performed a meta-analysis on data from the 30 studies evaluating the P3 in sons of alcoholics and found that the P3 is more often reduced when a complex visual task is used. In a prospective study, the sons of alcoholics with smaller P3 ampli-tudes at age 13 had a greater risk of becoming a substance abuser at age 16 (Berman et al. 1993).

Reduced P3 amplitude was also observed in schizophrenia, depression, Parkinsonism, dementia, ADHD, persons with excellent pitch discrimination, and children with learning disorders (Ebmeier et al. 1992; Holcomb et al. 1986; Morstyn et al. 1983; Pfefferbaum et al. 1984; Polich 1991; Satterfield et al. 1990). Whether individuals with reduced P3 amplitude who are not sons of alcoholic fathers are at increased risk for alcohol and drug abuse is not known. The focus on P3 may preclude the study of other aspects of sensory and cognitive processing in sons of alcoholics. Table 1 summarizes ERP studies of children of alcoholic fathers wherein com-ponents other than P3 were analyzed. N1, P2, N2, and late waves are also altered in these children.

ADHD and Learning Disorders

Children with ADHD and learning disorders have increased risk for substance abuse (Mannuzza et al. 1993; Weiss et al. 1985). Cognitive ERP deficits were found in children with reading disorders (Conners

TABLE 1. Cognitive ERPs in individuals at risk for alcoholism: Studies investigating brain components other than the P300.

Population	Task: ERP	Results	Study
7-15 year olds, FHA+, FHA-	Oddball (a): N1, P2, N2	P2 in FHA+	Begleiter et al. 1987
11-12 year olds, FHA+, FHA-	Discr(v): N2	Trend toward smaller N2 in FHA+	Sponheim and Ficken 1990
8-14 year olds, FHA+, FHA-	Oddball(a): N1, P2, N2	Trend toward smaller N1 in FHA+ N2 at Fz in FHA+	Hill et al. 1990
8-18 year olds, FHA+, FHA-	Discr(v): N1, P2, N2	N1 latency in FHA+	Hill and Steinhauer 1993
7-11 year olds, FHA+, FHDA+, controls	Oddball(a): LW	LW latency for FHA+ and FHDA+	Brigham et al. 1993

KEY: LW = Late waves; Discr = discrimination task; a = auditory;
v = visual; FHA = family history of alcoholism; FHDA = family history of drug abuse.

1970; Holcomb et al. 1986; Preston et al. 1974), dyslexia (Taylor and Keenan 1990), and ADHD (Halliday et al. 1976; Prichep et al. 1976; Satterfield et al. 1987, 1988, 1990). Table 2 lists studies comparing the ERPs of these children to those of controls. Various ERP components were reduced in amplitude or increased in latency in these disorders.

Methylphenidate reverses these alterations of ERP in children with ADHD. Table 3 lists studies evaluating the acute or chronic effects of methylphenidate on cognitive information processing and clinical out-come in ADHD children. The stimulus intensity/ERP amplitude slope was reduced in children with ADHD who clinically responded to amphetamine or methylphenidate (Buchsbaum and Wender 1973; Klorman et al. 1983; Saletu et al. 1975). Prichep and colleagues (1976) observed that the P2 component was depressed in ADHD children, and that methylphenidate normalized the reduced P2.

TABLE 2. Cognitive ERPs in ADHD, dyslexia, and reading disorders: Comparisons with matched controls.

Population	Task: ERP	Results	Study
Good and poor readers	Discr: N1, P2	N1 in poor readers	Conners 1970
Reading disorder (RD)	Discr: N1, P2	N1 in RD	Preston et al. 1974
Dyslexia (D)	Discr: N1, P2	N1-P2 in D RT in D	Sobotka and May 1977
ADHD 12-14 years	Selective attention task: N1, P2	N1 in ADHD	Zambelli et al. 1977
ADHD 12-14 years	Selective attention task: N1, P3	N1 and P3	Loiselle et al. 1980
ADHD and reading disorder (RD)	Complex oddball: N2, P3, SW, Pc, Nc	P3 in ADHD P3 latency in ADHD and RD P3 latency over blocks	Holcomb et al. 1986
ADHD, ADHD and aggression	Passive task: N1, P2, N2	N2 in ADHD with aggression	Satterfield et al. 1987
ADHD	Attention task: P2, N2, ND	N2 & ND in ADHD	Satterfield et al. 1988
ADHD	Selective attention task: PN, P3	P3b in ADHD PN in ADHD	Satterfield et al. 1990
Dyslexia (D)	3 Reading-related tasks: N2, P3	N2 and P3 latency P3 in D	Taylor and Keenan 1990

KEY: Discr = visual flash sensory discrimination task.

TABLE 3. Cognitive ERPs in ADHD and stimulant challenges.

Population	Task: ERP	Results	Study
MBD	Aug/Red: P1, N1, P2	VEP in MBD. A slope in nonresponders and in responders	Buchsbaum and Wender 1973
ADHD 6-13 years	Visual flash: 12 peaks	A latency and amplitude	Saletu et al. 1975
ADHD 6-11 years	Aug/Red: P1, N1, P2	Failed to replicate Buchsbaum	Hall et al. 1976
ADHD X = 9.3 years	Mixed oddball: N1, P2	N1 and P2 in ADHD Normalized in responders with M	Halliday et al. 1976
ADHD 8-11 years	Click guess: N1, P2, N2, P3	P2 and N2 in ADHD M P2 P3 in ADHD	Prichep et al. 1976
ADHD X = 9.5 years	CPT: P3	P3 with M in ADHD M errors	Klorman et al. 1979
ADHD X = 8 years	Aug/Red: CPT: P3b Oddball: P3b (visual) Oddball: P3b (auditory)	M P2 slope M P3b and reduced errors M reaction time	Klorman et al. 1983
ADHD X = 10.6 years	Mixed oddball: N1, P2	N1-P2 with M in clinical responders	Halliday et al. 1984b
ADHD 6-12 years	Attention task: PN, N1	M PN and N1	Klorman et al. 1990
ADHD	CPT	M P2/N2 and P3	Overtoom et al. 1993

KEY: CPT = Continuous performance task; Aug/Red = augmenting reducing task; A = amphetamine; M = methylphenidate; X=mean; MBD = minimal brain dysfunction; VEP = visual evoked potential.

Halliday and colleagues (1976) also found reduced N1 and P2 components in ADHD children; methylphenidate normalized these components in children who responded clinically to methylphenidate. Overtoom and colleagues (1993) found a P2 deficit in ADHD; methylphenidate reversed it. Methylphenidate increased the amplitude of two ERP components specifically linked to attention in children with ADHD (Klorman et al. 1990). Methylphenidate normalized P3 amplitude and latency in ADHD children (Klorman et al. 1979, 1983; Overtoom et al. 1993).

The effect of methylphenidate on ERPs of normal subjects is less clear (seetable 4). Peloquin and Klorman (1986) observed a small increase in P2 and P3b at one electrode site following methylphenidate administration in normal children. In normal adults, task fatigue is sufficient to lower P3 amplitude and increase its latency, but methylphenidate normalizes these alterations. Methylphenidate affects the ERPs of ADHD children who clinically respond to it, but does not have clear effect on the ERPs of normal children or ADHD children who do not respond clinically. Methyl-phenidate also produces a mixed response on the ERP of normal adults, which may reflect the variable clinical response. The basis for this differential response to methylphenidate is not known.

It is important to note that cognitive processing components of the ERP occurring before the P3 are altered in children with ADHD are consistent with the altered sensory processing observed in this population. For example, Camp and colleagues (1983) reported the brainstem auditory evoked response (BAER) components were delayed in children with ADHD, but this effect was reversed by methylphenidate. Mason and Mellor (1984) found BAER, middle latency, and cognitive ERP components altered in children with speech and language disorders.

Antisocial Personality Disorder (ASP) and Aggression

The relationship between antisocial behavior and substance abuse has been known for some time. Impulsive, aggressive, and shy-aggressive individuals have been shown to be at risk for drug abuse (Kellam et al. 1980; Kofoed and MacMillan 1986; Lewis 1984; Sutker 1984). Most ERP research with antisocial and aggressive individuals has been with adults in passive tasks and with warning rather than target stimuli (Jutai

TABLE 4. Cognitive ERPs in normal subjects given stimulants: Placebo-controlled design.

Population	Task: ERP	Results	Study
Young adults	SAT: N1, P3	No change in any measure with M	Hink et al. 1978
Young adults	CPT: P3 Choice RT Task: P3, CNV	M P3 amplitude late in the session. M RT No change in P3 with M M RT	Coons et al. 1981
Adults	SE/RS: P3	M RT	Callaway et al. 1983
Young adults	Vigilance: P2, P3 P-A: P3	M blocked the in P3 amplitude and in P3 latency seen with placebo. M RT No change in P3 with M	Strauss et al. 1984
Children 8-14 years	CPT: P2, P3b Sternberg: P3b	M P2. M P3b M RT and errors M errors	Peloquin and Klorman 1986
Young adults	Sternberg: P3b Sternberg: P3b	M RT and error M P3b latency and RT	Brumaghim et al. 1987
Old adults	SE/RS: P3	A RT	Halliday et al. 1984a
Young adults	Sternberg: P3	M RT	Fitzpatrick et al. 1980
Young adults	SE/RS: P3	A RT	Halliday et al. 1984a

KEY: A = Amphetamine; CNV = contingent negative variation; CPT = continuous performance task-visual; M = methyl-phenidate; RT= reaction time; SE/RS = stimulus evaluation/response selection task-visual; SAT = selective attention task-auditory; P-A = paired-associate learning task.

and Hare 1983; Raine and Venables 1987; Satterfield et al. 1988; Syndalko 1979; Syndalko et al. 1975). The findings are summarized in table 5. The P3 evoked by a warning tone was larger in noninstitutionalized delinquent adolescents than in controls, but the P3 to the target tone was not measured (Raine and Venables 1987). However, the P3 to a target was similar to that of control boys in the author's sample of overtly aggressive adolescents (Herning et al. 1989). When Raine and Venables (1990) compared crimi-nality in this sample 10 years later with the earlier brain potentials, N1, not P3, predicted incarceration. N1 amplitude is related to changes in attention.

ERPs at various stages in the auditory information processing system differed significantly between the more delinquent, overtly aggressive adolescents compared with neighborhood-matched control boys (Herning et al. 1989). The latency of wave V of the BAER was longer, N1 was earlier during high background noise, and frontally the slow wave was abnormal in the aggressive boys. These differences were not due to psychiatric disorders other than conduct disorder (CD) as measured by a computerized version of the "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. (DSM-III). These ERP differences were also not the result of drug use since the limited drug use in the sample had been statis-tically removed. These patterns of ERP alterations are similar to those observed in children with ADHD.

A second study compared the EEG and BAERs of 125 adult drug abusers who entered the Addiction Research Center's (ARC's) Inpatient Research Unit for variety of different drug studies (Fishbein et al. 1989). Electro-physiological and psychometric data were collected when the subjects were drug free. An extensive psychometric evaluation included a computerized DSM-III interview, Addiction Severity Inventory, Buss-Durkee Hostility Inventory (Buss and Durkee 1985), and delinquent behavior questionnaire developed by Dunford and Elliott (1984). After statistically correcting for drug use and age, greater aggression scores were associated with longer latency BAER peaks. Thus, aggressive adults, like aggressive adolescents, have longer latency BAER peaks.

ERP alternations in aggressive individuals also occur at many stages of information processing system starting as early as 3 to 5 milliseconds (ms). Although few studies have looked at aggressive children, the ERP alterations are similar to those observed in children with ADHD.

TABLE 5. Cognitive ERPs in ASP and aggression: Comparisons with matched controls.

Population	Task: ERPs	Results	Study
Adult psychopaths	Warned RT: CNV	CNV	McCallum 1973
Adult psychopaths	Warned RT: CNV	CNV equal controls	Syndalko et al. 1975
Adult psychopaths	Oddball: P3	P3 equal controls	Syndalko et al. 1979
Adult psychopaths	Passive: N1, P2	N1	Jutai and Hare 1983
Adult: ASP	Warned RT: CNV	CNV	Howard et al. 1984
Adult: ASP	BAER: I-V	II-IV latency	Josef et al. 1983
15 year olds	Warned RT: P3, N1, CNV	P3 for warning stimulus	Raine and Venables 1987
15 year olds	Warned RT: P3, N1, CNV	N1 amplitude predicts criminality at 24	Raine and Venables 1990
Adult psychopaths	CPT: P3	P3 latency	Raine and Venables 1988
11 to 18 year olds aggressive	BAER: I-V Oddball: N1, P2, P3, SW	V latency N1 latency SW	Herning et al. 1989
Adult substance abusers	BAER: I-V	III latency ASP and aggression	Fishbein et al. 1989

KEY: RT = Reaction time; BAER = brainstem auditory evoked response; CRT = continuous performance task; Aug/Red=augmenting reducing task; ASP = antisocial personality disorder.

Aggressive children may have an information processing system that is more sensitive to stimulants than nonaggressive children, and thus may differentially respond to methylphenidate. The neurophysiological response to methylphenidate may predict subsequent drug abuse, other factors notwithstanding.

Intrauterine Drug Exposure

Children with intrauterine exposure to illicit drugs are at risk for substance abuse. School-aged children with intrauterine heroin exposure were impulsive, had poor self-control, paid poor attention, and were hyperactive (Bauman and Levine 1986; Kaltenbach and Finnegan 1989; Lifschitz et al. 1985; Wilson 1989; Wilson et al. 1979, 1981). It has been reported that in utero exposure to marijuana produced attention deficits (Fried et al. 1992) and that both in utero and environmental factors place these children at risk for drug abuse (Chasnoff et al. 1986; Davis and Templer 1988). A similar argument could be made for intrauterine exposure to licit drugs, but further research is required.

Few studies have used ERP methodology or task performance only to investigate cognitive processing in school-aged children with intrauterine drug exposure. Table 6 lists studies measuring cognitive processing by in utero drug-exposed children. Two prospective studies investigating the in utero effects of marijuana (Fried, in press) and methadone (Hans 1989, in press) found altered attention processing on a continuous performance task (CPT). These CPT findings are consistent with the author's retrospective ERP study of boys born to opiate-using mothers.

Cognitive ERP components and task performance were altered in 7- to 12-year-old sons of opiate-abusing mothers (Guo et al. 1994). The P2 component of auditory ERP, as well as P2 and N2 components of the visual ERP, were smaller in sons of opiate-using mothers as compared with the same components in boys from similar socioeconomic status (SES). The sons of opiate-using mothers made more errors than the control boys. The boys who had no in utero opiate exposure but lived with an opiate-using mother were impaired on P2 and N2 components on the oddball task and the Sternberg tasks. This pattern of deficits suggests the involvement of environmental factors or poor mother-child inter-actions (Bauman and Levine 1986). Here again, the ERP deficit was similar to that found by others in ADHD children.

TABLE 6. Cognitive processing in children exposed to drugs in utero: Comparison to matched controls.

Population/Drug	Task: ERP	Results	Study
7-10 year olds/ Marijuana	CPT	Exposed made more errors	Fried, in press
7-10 year olds/ Methadone	CPT	Exposed made more errors	Hans 1989,in press
7-11 year olds/ Opiates	Oddball (a): N1, P2, N2, P3 Sternberg (v): N1, P2, N2, P3	P2 P2 and N2 Exposed made more errors	Guo et al. 1994

KEY: CPT = continuous performance task; a = auditory; v = visual.

Children of Drug Abusers

Transgenerational and environmental factors place children of drug abusers at greater risk for substance abuse. The ERPs as well as event-related EEG alpha synchronization and desynchronization (stimulus-induced changes in the ongoing EEG) of young sons of substance abusers and alcoholics in the auditory oddball task were studied by Brigham and colleagues (1993; in press). N1 was delayed in the sons of substance abusers, but not sons of alcoholics, when compared with the control boys. Boys with a family history of substance abuse had smaller N2 amplitudes than control boys, but a longer latency. Event-related EEG alpha synchronization and synchronization measured in the auditory oddball task differed between the risk groups and the control group at various times after the stimuli. As with the other at-risk populations, the sons of substance abusers have neurocognitive alterations at a number of information-processing stages.

Implications of ERP Research

The focus of ERP research in populations at risk for drug abuse differs greatly from that in populations at risk for alcoholism. ERP research in alcoholism attempted to understand why young sons of alcoholics have smaller P3 amplitudes. By contrast, the ERP research in populations at risk for drug abuse tried to characterize sensory and cognitive processing at different levels in the different at-risk populations per se. This latter research was not focused on the P3

component. Individuals at risk for drug abuse have alterations in sensory and cognitive ERP components that occur throughout the poststimulus period.

Findings from diverse research groups point to a common deficit in stimulus processing in individuals at risk for drug abuse. A deficit in early sensory processing and attention was observed in children with ADHD, aggressive children, intrauterine drug-exposed children, and children of substance abusers. Stimulants have reversed these ERP alterations in children with ADHD and may reverse them in the other populations at risk for drug abuse. The mechanism by which the early sensory and cognitive alterations may lead to subsequent drug abuse is not known. Drugs such as methylphenidate may be useful as probes to assess individual differences in vulnerability of these children. A prospective study relating deficits in information-processing components or stimulant-induced changes in these components to subsequent drug abuse is needed.

DESIGN AND EXPERIMENTAL METHODS

The proposed study would examine sensory and cognitive processing in three groups of children exhibiting behaviors that often lead to substance abuse: overt aggression, ADHD, and current depression. Both ERPs andtask performance will be assessed at baseline and after stimulant (methylphenidate) challenge when the children are in the age range of 8to 10. Drug use will be determined after a 4-year interval. This proposed research will clarify and extend what is known about early sensory processing and attention in children with ADHD and aggressive children of both sexes, as well as explore the possibility of childhood depression as a risk factor for substance abuse in a prospective study. Appropriate control children and parents of both index and control children will be evaluated to tease apart transgenerational factors. The goal will be to determine whether the altered ERP components in the at-risk populations will predict future drug use.

Experimental Design

Children with at-risk behavior disorders and their parents will be assessed on neurophysiological variables and task performance. The children will be tested a second time during a challenge session with methylphenidate. At the time of testing, extensive demographic and family data will be collected. Four years later, demographic and family data will again be collected along with drug use history and psychometric data from both the child and the parents.

Five groups of children will be recruited: overtly aggressive (N = 100), ADHD without aggression (N = 100), ADHD with aggression (N = 100), depressed (N = 100), and matched control children (N = 100). Each group will be racially balanced and composed of equal numbers of females and males. The children with ADHD and depressed children will be tested on a neurophysiological battery when medication free. ADHD children are likely to be already on medication. This methodological problem may be circumvented in two ways: The subjects can be tested after a fixed washout period, or newly identified ADHD children can be tested before they are placed on medication. The overtly aggressive children will meet the criteria of "high" delinquency, reporting 25 or more lifetime self-reported delinquent acts on the Dunford and Elliott (1984) questionnaire. The control children will be obtained from the same neighborhoods or schools as the at-risk children. Social, economic, legal, educational, psychometric, medical, drug history, and family interaction information will be obtained from all subjects.

Neurophysiological Assessment

After the demographic, psychiatric, and psychometric screen, appropriate children and their parents will undergo a 2-day neurophysiological testing. Methylphenidate (0.3 milligrams per kilogram (mg/kg)) or placebo will be administered to the child in a double-blind crossover design. The parents will be expected to abstain from alcohol and illicit drugs for 24hours before a baseline testing. Compliance will be determined by urine toxicologies and breath alcohol monitoring. It is recognized that complete neurophysiological data may not be obtained from all parents because of positive urine toxicologies. In previous outpatient work, about 10 to 15 percent of the subjects failed to comply with similar restrictions. These patients will be dropped from the study. Thus, the sample size to test the similarity of ERPs of the parent to those of the child will be slightly less than the comparisons between groups of children.

The battery of neurophysiological tests (table 7) will be administered before the oral ingestion of placebo or methylphenidate and at 1 and 2hours postingestion. The tasks in this battery have previously been used successfully with adults and 7- to 11-year-old children. Both ERPs and performance will be obtained on these tasks. Heart rate and blood pressure will be measured, and the visual-analog drug effects scale and Profile of Mood State questionnaire will be administered before and at 45, 90, 150, and 210 minutes after the drug administration.

TABLE 7. Neurophysiological Performance Assessment Battery.

Sensory evaluation1
- Brainstem auditory evoked response procedure
- Pattern reversal visual evoked response procedure

Cognitive evaluation2
- Auditory rare event monitoring task (oddball task)
- Auditory selective attention task
- Continuous performance tasks (visual)
  - Single target letter task
  - Paired letter task
- Sternberg memory tasks (visual)
  - Short memory set (2 letters for child, 3 for adult)
  - Long memory set (4 letters for child, 6 for adult)

KEY: 1American Electroencephalographic Society (1984) guidelines will be followed for these clinical tests.
2Military guidelines will be followed for these tests (Reeves et al. 1991).

ERP Recording and Measurement

The ERPs will be recorded from 13 locations (Fz, Cz, Pz, F3, F4, C3, C4, T3, T4, P3, P4, O1, and O2) based 10-20 International System. An electro-oculogram (EOG) will be recorded from the side of the left eye and from above the left eye and referred to the left eartip in order to monitor eye movement artifacts. Silver/silver chloride electrodes will be used at all locations. Testing will be performed in a sound-attenuated, electrically shielded chamber. Each EEG or EOG channel will sample at 2.0 ms intervals using software developed inhouse for this purpose. Faster sampling rates will be used with the sensory procedures. The inter-channel sampling time was 40.0

microseconds (μs). The raw EEG and EOG data will be saved on magnetic media for subsequent analysis.

The EEG and EOG will be processed for artifact. Artifact-free single trials will be averaged according to stimulus type after the test session. ERPs will be measured by an individual who is blind to the subject's group. The auditory ERP peaks will be measured in the following latency ranges for N1 (50 to 180 ms), P2 (100 to 250 ms), N2 (181 to 400 ms), and P3 (250 to 700 ms). The visual ERP peaks will be measured in latency ranges for P1 (80 to 120), N1 (50 to 180 ms), P2 (100 to 250 ms), N2 (181 to 400 ms), and P3 (250 to 700 ms). BAER and pattern reversal evoked responses will be measured in accordance with American Electroencephalographic Society guidelines (1984). In addition, the cognitive ERP components will be extracted by principal component analysis (Herning et al. 1989).

Analysis and Expected Results

The first major hypothesis to be tested is whether the three at-risk groups have similar sensory and cognitive ERP alterations and performance levels and whether these neurocognitive alterations differ from those of controls at baseline and after methylphenidate challenge. The three at-risk groups at baseline are expected to have delayed BAER waves, delayed P1 in the pattern-reversal evoked response task, and reduced or delayed N1, P2, and P3 components of the auditory and visual cognitive ERPs when compared with control children.

Not all children in the risk groups will respond to the methylphenidate challenge in a similar manner. For some children, no ERP components would change with the drug challenge; for ADHD children, some of the baseline ERP alterations would be reversed; and for still other children, the drug challenge would produce greater ERP alterations than in the baseline condition. Which particular pattern is related to subsequent substance abuse is the focus of this research. These three patterns will be observed in the three risk groups. Little or no change is expected in control children.

These predictions are based on ADHD research findings that some ADHD children respond clinically to methylphenidate and some do not (Buchsbaum and Wender 1973; Klorman et al. 1983; Saletu et al. 1975). The ERPs of those who respond are also normalized by methylphenidate. The other risk groups have similar ERP alterations and may also respond to methylphenidate in a similar fashion. The

intent is to determine which children are at greater risk for drug abuse: those with altered ERPs that are normalized, those with altered ERPs that are not affected, or those with altered ERPs that are further modified by the methylphenidate challenge.

The hypothesis that the ERPs of child and parent are similar will be tested. Some similarities are expected in the deficits observed in the at-risk children and their parents. Both aggressive boys and aggressive men have some similar BAER deficits (Fishbein et al. 1989; Herning et al. 1989). Children with intrauterine heroin exposure as well as their mothers were impulsive, had poor self-control, paid poor attention, and were hyperactive (Bauman and Levine 1986). The transgenerational transmission of ADHD has been suggested. The evaluation of ERPs of child and parents will aid in understanding the nature of the trans-generational mechanism.

When the 4-year assessments are complete, a stepwise discriminant analysis will be used to determine which ERP measures collected at 8-years of age predict substance abuse at age 12 for each group separately and for all the children pooled together. The significant ERP predictor measures will also be combined with identical ERP measures from the parent to determine whether prediction can be improved. If, indeed, genetic or other transgenerational factors are operating, the addition of the parent's neurophysiological data would enhance the prediction. Models and theory in this area are rather sparse. However, there is reason to believe ERP measures will be useful in predicting substance abuse. An ERP component, N1, measured in childhood, successfully predicted criminality as a young adult (Raine and Venables 1990). The amplitude of P3 in sons of alcoholics predicted substance abuse 4 years later (Berman et al. 1993).

One possible outcome would be that the children who had the largest neurocognitive change (specific changes are noted below) to the methylphenidate challenge at an early age would be substance abusers at the time of followup. On the other hand, the at-risk children who have the largest neurocognitive deficits as compared with control children in baseline recording may be substance abusers at followup. The strength of the study is that both predictions are tested. It is possible that a combination of baseline and drug challenge neurocognitive measures may best predict drug and alcohol use. Although it is hypothesized that the neurocognitive deficits in the four at-risk groups are similar, different neurocognitive deficits may exist in each of the groups that may predict subsequent drug use for that

group. Little is known about the ERPs of depressed children and their response to methylphenidate. Likewise, it is not known whether the ERP alterations observed in aggressive children will normalize with methylphenidate. This study is intended to clarify these points. The study is designed with a sufficient sample size in each group to separately predict substance abuse from baseline or methyl-phenidate challenge neurocognitive measures for each group.

While it is difficult to foretell whether baseline or drug challenge measures would predict subsequent drug use, some predictions can be made as to which ERP components may predict subsequent drug use. The neurocognitive alterations currently observed in at-risk populations occur at a number of ERP components starting as early as 3 to 5 ms after the onset of the stimulus. Alterations at earlier stages of information processing may produce deficits in later stages. Alterations in ERP components up to 250 ms were found in populations at risk for substance abuse and were sensitive to the effects of stimulants. Alterations in these components which reflect early sensory processing and attention, are most likely to predict subsequent drug abuse.

Many outcomes are possible, and all outcomes will provide useful information about neurocognitive factors that place an individual at risk for substance abuse. The design of the study is based on the hypothesis that certain underlying cognitive deficits are common to populations at risk for substance abuse and that specific changes in these neurocognitive alterations after a stimulant challenge will predict subsequent drug abuse.

STRENGTHS AND WEAKNESSES

Populations at risk for substance abuse to be tested in this prospective study have been clearly identified in many epidemiological studies and carefully characterized in terms of their sensory and cognitive ERPs in numerous neurophysiological studies. Alterations in information processing are clearly defined in these populations, and patterns of processing appear to be similar across different samples. Stimulants normalize these alterations in some individuals. What remains is to understand why there is a differential response to stimulants and its relationship to subsequent drug use.

An additional strength is that the study attempts to identify a neuro-physiological mechanism common to different at-risk populations,

which makes these individuals vulnerable to drug abuse. While information processing deficits common to individuals in an at-risk group may not by themselves place an individual at risk, they may be linked at the neural substrate level and be responsible for this vulnerability.

There are some methodological weaknesses. First, only a single dose of a single challenge drug, methylphenidate, is administered, and this drug affects more that one transmitter system. Unfortunately, only a limited number of drugs may be given to children. Methylphenidate is one such drug and its effects on ADHD are well known.

A second weakness is that only stimulant abuse may be predicted from a challenge with a stimulant. However, this was not the case in the study by Berman and colleagues (1993), where the sons of alcoholics with smaller P3 amplitudes at age 13 were found to have a greater risk of becoming substance abusers rather than just alcohol abusers.

PUBLIC HEALTH SIGNIFICANCE

This study identifies neurocognitive deficits in grade school children which predict subsequent drug and alcohol use. The early identification and treatment of these neurocognitive deficits may both enrich the educational and cognitive development and reduce the risk of substance abuse in these children.

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Commentary on "Cognitive Event-Related Potentials in Populations at Risk for Substance Abuse" by-Herning

Scott E. Lukas

SUMMARY

Herning has proposed a finely circumscribed study to evaluate the cognitive processing abilities of 8- to 10-year-old children who either have attention deficit-hyperactivity disorder (ADHD), are overtly aggressive, or are depressed. The children will be studied before and after a dose of methylphenidate or placebo using a double-blind cross-over design. To complete the assessment, the child's biological parents will be tested and challenged with the pharmacological agents. A followup of the experiments will be done when the children reach ages 12to 14 years.

The experimental design employs a battery of cognitive event-related potentials (ERPs) that have been found to be sensitive to psychiatric disorders. The premise is that drugs of abuse alter sensory and cognitive processing abilities, and it is hypothesized that individuals at risk for substance abuse may be more or less sensitive to these effects on sensory and cognitive processing. Attention is focused on the P300 ERP since its amplitude has been found to be reduced in patients with depression, schizophrenia, Parkinson's disease, dementia, ADHD, aggressive disorder, and in children with learning disorders. It is also known that children with ADHD and learning disorders have a greater risk for substance abuse. Taken together, these facts suggest that this area of research should provide promising new information into the neurophysiological profiles of individuals who are at risk for developing substance abuse.

STRENGTHS OF THE PROPOSED RESEARCH

One of the major strengths of the proposed study is the sample population to be studied. The proposed study begins with children 8 to 10 years of age who presumably have not been exposed to any drugs so that the effects observed are not likely to be attributable to

prior history of substance use. In addition, four individual groups of children will be studied: overtly aggressive, ADHD-diagnosed, depressed, and matched controls. A further strength of the application is that all subject groups will be racially balanced and contain an equal number of males and females.

Another major strength of the application is the selection of the neurophysiological performance assessment battery. This particular battery chosen by the investigator evaluates both sensory and cognitive components. These procedures rely heavily on neurophysiological responses to external stimuli, a tactic that has yielded highly reproducible results and is fairly sensitive to subtle behavioral and pharmacological changes. As a further assurance that the data analysis will be conducted appropriately, the investigator plans to save individual sweeps of the ERPs. In this manner, simple averaging will not inappropriately induce ERP amplitude decreases that are due to slight changes in P3 latency.

Since the subjects will be retested a number of years later, a stepwise discriminant analysis can be used to determine which of the ERPs obtained at 8 to 10 years of age are useful to predict substance abuse 4years later. This analysis can be done separately for each group as well as for all the children pooled together. The resultant equation would permit the investigator to factor in demographic and psychometric measures to determine whether a better prediction equation can be constructed.

Independent assessments of males and females represent a major strength since there are few or no data available on adolescent females. Thus, this study will contribute greatly to the area, but at the same time it will also provide comparative data with age-matched male subjects.

WEAKNESSES OF THE PROPOSED RESEARCH

One weakness of the study is that, even though the subjects are carefully selected, the child's family history of alcohol or substance abuse is not used as an independent variable. In addition, the psychiatric status of the parents is not used as a covariant in these studies. This second factor is particularly important since the biological parents will also be tested in the protocol. There is reason to believe that a positive family history of alcoholism can be detected in ERP data (Begleiter et al. 1984); thus, it would seem that the study

would be strengthened if the test groups were separated on this basis. At the very least, family history should be included as a covariant in the statistical analysis component.

It appears as though some of the parents will be dependent on alcohol or opiates, yet this variable does not seem to be counterbalanced in the population selected. It is noted that the individuals who are dependent on drugs will only be tested during the baseline period and will not receive the methylphenidate challenge. While this decision has an obvious ethical rationale, it is unclear how these data will be integrated with those obtained from the other parents.

Details regarding the specific tasks that will be used to elicit the ERPs should be more clearly delineated to permit other labs the opportunity to replicate the proposed study. There is a great deal of controversy over whether the tasks need to be elicited by auditory, visual, or somato-sensory stimuli. Both auditory and visual ERPs will be used, but the actual method of eliciting them was not specified. As with other studies attempting to correlate changes in a dependent variable with an individual's use of drugs, the proposal was not clear in how the adults' drug use will be verified. Verbal reports of abstinence from drugs prior to an electrophysiological study are usually not sufficient. Instead, the individuals should undergo urine screens to verify abstinence from licit and illicit drugs.

Another weakness of the protocol is the very long time period between the initial assessment and the followup (4 years). This type of longitudinal study suffers from large attrition rates mostly because there is little or no contact with the subjects in between evaluations. The protocol should include some intermediate assessments in order to maintain contact. The contact does not necessarily have to involve electrophysiological assessments; simply bringing the subjects into the lab to fill out questionnaires and to verify drug status would be enough to keep their interest and to maintain contact. Without such procedures, the sample size of 100 could become so small by the fourth year that all power would be lost.

Another weakness is the decision to study only a single dose of methylphenidate. If the alterations in sensitivity to these neurophysiological test batteries are important, then the use of a standard single dose of methylphenidate may not adequately test the investigator's hypothesis; a dose-response comparison may be needed.

ALTERNATE IDEAS

One procedure that might strengthen the proposed study is to segregate the individual subjects on the basis of their family history of alcoholism and/or psychiatric disorders as proposed in the twin study by Iacono and colleagues. The inclusion of a separate high-risk group would produce a significantly stronger research proposal. Further, the proposal may be further strengthened by using the subjects' siblings as controls for environmental conditions. Thus, the variability of the study could be reduced by obtaining subjects from a narrower pool.

The study might also be strengthened by adding novel ways of eliciting a P3 wave that has some significance to the individual groups. For example, visual P3s might be elicited by slides of scenes depicting various themes relating to aggression, depression, or hyperactivity. These tasks should be additions to the proposed tasks and not substitutions because their validity has not been demonstrated. However, the investigator has the extensive database and laboratory resources to conduct such studies.

Finally, it may be of interest to include analyses of spontaneous electroencephalographic (EEG) activity. As noted in the twin program, the data are easily obtained if ERP data is being collected. Given that there is evidence suggesting that specific EEG patterns are associated with introversion and extroversion (Gale et al. 1969), the inclusion of these data might help define the differences among the subject population.

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DISCUSSION

Audience and Panel Participants: Ron Herning and Lance Bauer

Dr. Herning: The bottom line, I think, that I've tried to make very hastily by looking at a lot of studies is that we should not necessarily fall into the trap that happened in alcoholism with the focus on the P300 component. The message I'd like to leave with you is when you collect evoked responses, you get these other components. In the 30 studies I looked at in sons of alcoholics, only 5 of them really looked at the other components. Some of these deficits were before the P300, which suggests that perhaps whatever P300 process represents, it's getting faulty information from an earlier stage and that stage of cognitive processing needs to be considered also.

The second point is that there is some commonality in these populations at risk. I don't mean to suggest that the sensory and cognitive deficits are precisely similar in each, but there appears to be early sensory and cognitive deficits that are reflected in event-related potential components in these populations at risk for drug abuse.

Dr. Bauer: Dr. Herning, you just mentioned there may be some commonality in findings. Focusing specifically on the P300 literature, that's not always true; it depends greatly on the nature of the task. I'm thinking specifically of the literature on P300 effects of psychopathy or antisocial personality (ASP) disorder. You have reported data in the past showing reduced P300s in delinquents.

Dr. Herning: We found, in that study, reduced latency N1s and altered slow wave, but not P300 changes.

Dr. Bauer: In any case, there is a small body of findings suggesting reduced P300 amplitudes in individuals with ASP disorder or with psychopathy. There is also another perhaps equally small body of literature focusing mainly on prisoners that has found enhanced P300s. There are, I think, a number of possible explanations for these disparate results. These explanations have to do with whether or not drug abuse was assessed, what type of ASP one is studying, and whether it's maybe an aggressive or nonaggressive type that can all alter the P300 outcome.

But, given the fact that ASP disorder either increases or decreases P300 relative to normal, I think it does suggest that if one wants to look at the P300 effects of a family history of drug abuse, let's say, or a family history of alcoholism, careful attention must be given to ASP or psychopathy since that may mediate, or even moderate, the effects one is trying to demonstrate. That's the only point I wanted to make.

Dr. Herning: I think you're right in looking at it in that particular fashion. Just in looking at the early prisoner studies I'm not sure there was a good drug history obtained in those studies and that may explain the divergent results. There is a debate in the literature over whether the P300 increased or decreased, but certainly it was measured and it was affected.

^{31}P Magnetic Resonance Spectroscopy in Children at Risk for Substance Abuse

Howard B. Moss

STATEMENT OF THE PROBLEM

Evidence strongly indicates that the risk for developing a substance abuse (SA) disorder is not randomly distributed in the population. However, the mechanisms underlying this risk are largely unknown. Particularly, little is known about neurobiological mechanisms involved in SA vulnerability. Increased risk for SA has been linked to behavioral disorders such as attention deficit-hyperactivity disorder (ADHD) across the lifespan, conduct disorder (CD) during childhood and adolescence, and adult antisocial personality disorder (ASPD). Previous research has suggested that these latter disorders may be associated with frontal lobe dysfunction. Consequently, it is postulated that a component of the liability to SA is associated with a variant of frontal cortical physiology. Furthermore, it is hypothesized that this physiologic variation will be manifested by abnormalities of brain energy and membrane phospholipid metabolism detectable by in vivo phosphorus 31 (31P) magnetic resonance spectroscopy (MRS).

Specific Aim 1

The first goal of the proposed study is to determine whether boys and girls with a conduct problem (CD+), oppositional defiant disorder (ODD), or CD as defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. rev. (DSM-III-R), and a father with history of psychoactive substance dependence (SA+) can be differentiated from sons and daughters of SA+ fathers who are CD-, and from age-matched normal controls with respect to variations in dorsal prefrontal cerebral energy metabolism measured by in vivo 31P MRS.

Specific Aim 2

The second goal of the proposed study is to determine whether SA+/CD+ children can be differentiated from SA+/CD- boys and girls and from age-matched normal controls on dorsal prefrontal phospholipid metabolism measured by in vivo 31P MRS.

Specific Aim 3

The third goal of the proposed study is to determine the associations in SA+ (both CD+ and CD-) youth between measures of dorsal prefrontal cerebral energy and membrane phospholipid metabolic activity with dimensional measures of aggression, inattention, impulsivity, and hyperactivity. These behaviors are thought to be important components of SA vulnerability.

BACKGROUND AND SIGNIFICANCE

Several lines of evidence converge upon the heuristic value of research directed at clarifying the neurobiological basis of SA vulnerability. The following discussion is a summary of the existing evidence implicating a neurobiological basis of SA vulnerability that is particularly manifest in the anterior cerebral regions. A brief description of MRS and its potential to elucidate aspects of this neurobiologic substrate is also included.

Evidence Suggestive of Anterior Cerebral Disorder in SA Based on Neuropsychologic Studies of ASPD and Its Antecedents

The most prevalent adult psychiatric disorder occurring comorbidly with psychoactive substance abuse is ASPD (Regier et al. 1990). Antisocial individuals demonstrate impulsive, aggressive, and disinhibited behavior similar to that seen among humans and primates with lesions in the anterior cortical region (Pribram 1973). These same features of dysregulated behavior have been frequently shown to predispose to psychoactive substance use disorders (Gorenstein and Newman 1980).

Although similarity in behavior does not necessarily imply commonality in underlying mechanisms, it is important to point out that individuals at high risk for alcoholism and those with CD/ASPD show impairment on neuropsychologic tests of executive functioning (Moffitt 1993). A host of neuropsychological investigations have

suggested that ADHD both in childhood and as a residual disorder in adulthood, CD in adolescence, and ASPD in adulthood are associated with dysfunction of the frontal lobes (Kandel and Freed 1989). ASPD adults have been shown to perform as poorly on neuropsychological tests sensitive to frontal lobe functioning as patients with actual frontal lesions (Gorenstein 1982). However, a replication that studied ASPD and non-ASPD psychoactive substance abusers failed to confirm this finding (Hoffman et al. 1987).

Since SA per se can produce neuropsychological deficits (Grant et al. 1978), and since SA is almost invariably present in ASPD, it is critical to differentiate any central nervous system (CNS) effects of SA from an underlying neurobiological diathesis. This proposed investigation of frontal cerebral high-energy phosphate and membrane phospholipid metabolism in children at high risk for SA affords a unique opportunity to evaluate this putative predisposition for SA disorder without the confounding effects of prior exposure to drugs.

Obviously, not all adults with prefrontal abnormalities have ASPD or SA, and dedicated positron emission tomography (PET) studies of ASPD individuals have yet to be reported. Thus, it is premature to draw con-clusions concerning the relationship between prefrontal anomalies on PET and the syndromal diagnosis of ASPD. In that most psychiatric syndromes are multifactorial, prefrontal dysfunction may be concep-tualized as one aspect of the total liability for ASPD and/or for SA.

Evidence Suggestive of Anterior Cerebral Disorder in SA Based on Neuroimaging Research

Attentional and cognitive impairments have been implicated as risk factors for SA disorders (Tarter et al. 1985). To date, neuroimaging investigations has been conducted on youth with ADHD; this group of individuals has syndromal attentional deficits and have been frequently documented in longitudinal investigations as being at increased risk for SA. Youth with ADHD, particularly those who have comorbid CD or ODD, are at signi-ficant risk for developing SA disorders, as well as ASPD in adulthood (Biederman et al. 1990; Cantwell and Baker 1988; Gittelman et al. 1985). Furthermore, among adult substance abusers, up to 40 percent meet diagnostic criteria for ADHD-residual type (Wood et al. 1983).

An early neuroanatomical investigation of ADHD used computerized axial tomography (CAT), but was hampered by the inclusion of a

large number of subjects who already had an SA disorder, thereby confounding the interpretation (Nasrallah et al. 1986). Nonetheless, investigators observed a significant degree of anterior cerebral atrophy. However, another study that also used CAT technology to evaluate neuroanatomic features reported no significant structural differences between ADHD cases and controls (Shaywitz et al. 1983).

Regional cerebral blood flow (rCBF) studies provided a significant methodologic improvement over static neuroanatomic examination of the brain because they inform about cerebral metabolic activity in specific brain regions and neural structures. In the normal brain, cerebral blood flow and cerebral glucose metabolism correlate in an almost 1:1 ratio, and both are closely related to brain function (Mathew et al. 1985; Raichle et al. 1976). Early rCBF studies of ADHD children using the xenon-133 inhalation method revealed hypoperfusion and low metabolic activity in the white matter of the frontal lobes and the caudate nuclei (Lou et al. 1984). However, a practical drawback to this method is the exposure of prepubertal children to a significant dose of ionizing radiation, which has the potential for long-term adverse sequelae.

Recently, Zametkin and colleagues (1990), cognizant of the problems inherent in exposing children to ionizing radiation, reported results of a PET study of regional cerebral glucose metabolism in adults who had ADHD since childhood but no history of SA or CD in adolescence. Significant reductions in cerebral glucose metabolism were demonstrated in the premotor cortex (control of motor activity) and the superior prefrontal cortex (regulation of attention), consistent with deficits in neuropsychologic tests of children with ADHD. This study supports the notion that reduced anterior cerebral metabolism may be an important indicator for the risk of ADHD and, by implication, for the risk of SA.

Evidence Suggestive of Anterior Cerebral Disorder in SA Based on Dispositional Behavior

Several specific dispositional propensities have been linked to heightened risk for SA. These include negative mood states, sensation-seeking behavior (Zuckerman 1972), and impulsivity (Jones 1968; McCord et al. 1960). Each of these propensities has been linked to anterior cerebral function.

The experience of negative mood states may be mediated through dys-function of the prefrontal cortex. For example, Grafman and

colleagues (1986) investigated the effects of lateralized orbitofrontal and dorsolateral prefrontal injuries on mood regulation. Lesions of the right orbitofrontal region were associated with increased irritability, anxiety, and depression, while left dorsolateral lesions were associated with greater anger and hostility. These affective characteristics have been implicated to presage SA (Jaffe et al. 1988; Kandel et al. 1986; Kellam et al. 1982). Sensation-seeking or risk-taking behavior has been linked to reduced behavioral inhibitory capacity. Associated with this behavioral characteristic is impulsivity. This propensity, like sensation seeking, has been frequently related to SA (Cadoret et al. 1986) and is manifest following an anterior cerebral injury (Mattson and Levin 1990). Nonalcoholic offspring of alcoholics not only exhibit these latter behavioral propensities but also demonstrate a pattern of evoked potential abnormalities, which have been interpreted to reflect maturational retardation in the anterior cerebral region (Hill et al. 1990).

Actions of Drugs of Abuse on Anterior Cortical Structures

Several drugs of abuse exert actions on the anterior structures of cerebral cortex. High doses of alcohol (Volkow et al. 1988) appear to increase cerebral blood flow, while low doses of benzodiazepines (Mathew et al. 1985) decrease cerebral blood flow to this area. Both drugs produce effects that are more pronounced in the right frontal cortex. Amphet-amines have been reported to bilaterally reduce cerebral metabolic rates in the frontal regions (Wolkin et al. 1987). Cocaine has been found to reduce glucose metabolism in most brain regions, including the frontal lobes (London et al. 1990).

Individual differences in the subjective and objective responses to drugs of abuse may account for the variability in outcomes for those adolescents who experiment with drugs. One possible mechanism for these individual differences is an interaction between the premorbid neurobiologic substrate of the adolescent with the actions of the drug. It is reasonable to hypothe-size that the frontal cortex is the site of this interaction. Drug-induced reductions in the already diminished frontal activity of individuals at heightened risk for SA may further disinhibit these individuals, thereby augmenting affective and behavioral dysregulation and increasing the propensity for continued drug use.

Description and Utility of In Vivo 31P Magnetic Resonance Spectroscopy

Although nuclear MRS was discovered more than 30 years ago, the technique has only recently been applied to the study of metabolic functions of the living human brain (Bottomley et al. 1984; Welch 1989). Subsequently, this noninvasive technique has been used to study a variety of clinical conditions affecting human brain functioning (Pettegrew 1991). Simply stated, MRS takes advantage of the fact that many specific atomic nuclei align in a particular direction under the influence of an external magnetic field. In order to detect this alignment, the magnetic moment of these nuclei must first be disturbed by a brief pulse of radiowaves at a specific and unique frequency that causes the nuclei to precess. After the pulse is switched off, the precessing nuclei briefly induce an alternating voltage at a fixed frequency in a receiving coil until the precession decays. In complex biological materials, the particular nuclei of interest produce characteristic shifts in signal resonance frequency (called chemical shifts) due to slight differences in the chemical structures of the associated molecules. The voltage changes from these shifts are detected and amplified so that the signals can be digitized and stored in computer memory. The frequencies associated with the chemical shifts can be analyzed by Fourier transforms, making possible the identification of specific molecules of interest.

Phosphorus is present in molecules of living tissue and is critically important for transformation and use of energy by neurons and glia and synthesis and degradation of phospholipids that comprise neuronal and glial membranes. 31P MRS brain spectra are sensitive to the presence of these phosphorus-containing molecules in which concentrations are 0.1-millimole and above. As seen in figure 1, these spectra manifest as resonance signal peaks that quantify the presence of phosphocreatine (PCr), inorganic phosphates (Pi), phosphomonoesters (PME), phospho-diesters (PDE), and the g, a, and ß phosphates of adenosine triphosphate (ATP). Biochemical inferences are made based upon the contribution of each resonance signal to the total phosphate resonance signal and the changes in their areas under the curve (Welch 1989).

ATP is a critically important energy-transporting molecule that links energy sources such as nutrients (e.g., glucose) to energy-requiring cellular processes such as biosynthesis and membrane transport. In mammalian brain, the ß and gATP 31P MRS signals reflect additive contributions by the major energy-carrying compounds ATP, adenosine diphosphate (ADP), and adenosine monophosphate (AMP) (Pettegrew et al. 1986). The a-ATP signal is less specific since it also contains contributions from dinucleotides. The PCr signal reflects the concen-tration of a high-energy phosphate compound catalyzed by creatine kinase, which functions as a buffer to keep brain levels of ATP constant.

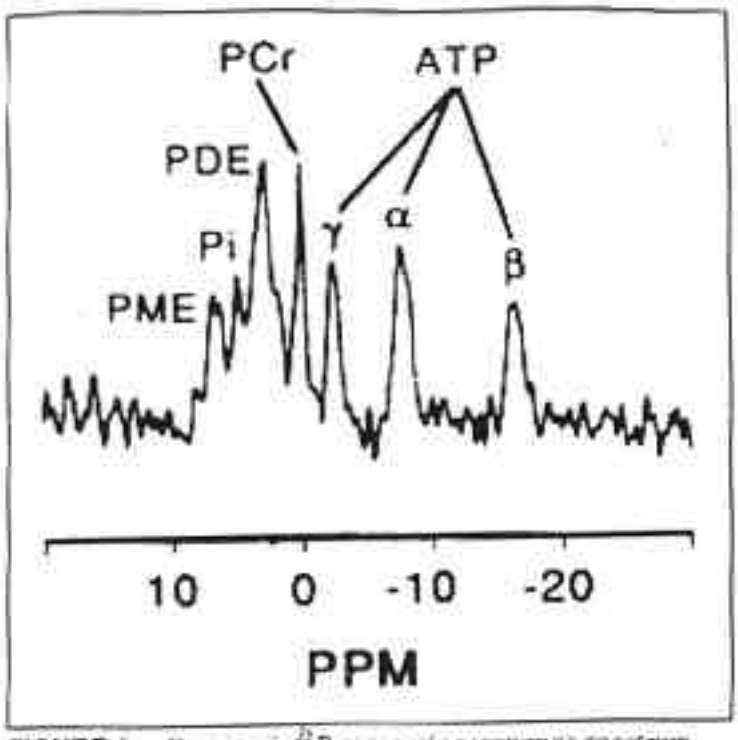

FIGURE 1. *Prototypic ^{31}P magnetic resonance spectrum.*

The Pi signal reflects concentrations of one of the catabolic breakdown products of ATP metabolism. Thus, the PCr/Pi ratio may indicate ATP synthesis relative to catabolism.

The PME signal reflects the presence of precursors of membrane phospholipids primarily including phosphocholine, phosphoethanolamine, and alpha-glycerophosphate. The PDE signal reflects concentrations of degradative products after membrane phospholipid breakdown. The PDE region includes glycerophosphodiesters, phosphorylated glycolipids, and glycoproteins (Pettegrew et al. 1986, 1987). Thus, the PME/PDE ratio may reflect membrane phospholipid synthesis relative to catabolism. Importantly, preclinical and clinical studies have demonstrated that 31P MRS can provide valuable heuristic insights into both the bioenergetic status of the brain and the dynamic biologic membrane synthetic processes occurring within the brain during development and maturation (Hida et al. 1992; Holtzman et al. 1991; Minshew et al. 1992; Pettegrew et al. 1987, 1990). For example, it has been established that the frontal cerebral cortex undergoes a maturational decline in synaptic density (sometimes

called synaptic pruning) between ages 2 to 16 years (Huttenlocher 1979). Preliminary research suggests that this synaptic pruning is reflected in a decrease in synthesis of membrane phospholipids and an increase in their degradation, which can be monitored using 31P MRS (Minshew et al. 1992). Although speculative, this technology may ultimately be useful in testing hypotheses concerning the presence of a putative delay (or dys-function) in the chronological attainment of stages of cerebral maturation among youth at high risk for psychoactive substance abuse disorders (Hudspeth and Pribram 1992).

Significance

This initial investigation will be used to determine if 31P MRS of the frontal brain region is a heuristic strategy able to delineate the neuro-biologic substrate of the risk for a SA disorder, which can present prior to a child's actual exposure to drugs of abuse. 31P MRS provides a unique picture of in vivo brain energy metabolism and the metabolic status of neural membranes' structural constituents without the drawbacks associated with more invasive techniques involving exposure to ionizing radiation. The elucidation of a neurobiologic risk factor for the develop-ment of SA can lead to novel biopsychosocial models for SA etiology with significant ramifications for prevention and treatment. To the author's knowledge, this technology has yet to be applied to either cross-sectional or longitudinal research on SA vulnerability.

Preliminary Evidence for Disturbances in Executive Functions in the Proposed Study Population

Table 1 summarizes some selective findings to date from a preliminary study on a sample of prepubertal boys comparing SA+/CD+, SA+/CD-, and control boys (as previously defined) on measures of behavioral deviation implicative of disturbances in executive functions that are associated with the prefrontal cortical regions. Elevations on these same neuropsychological dimensions have been implicated in the liability for later SA in several longitudinal studies (Kandel et al. 1986; Kellam et al. 1982; McCord et al. 1960). On the majority of measures the SA+/CD+ group differs significantly from the other two groups. This observation supports a gradient of SA risk such that SA+/CD+ boys > SA+/CD- boys > SA-/CD- boys. The study sample from which these data were collected will constitute the males in this proposed study; females will be recruited from a similar population.

TABLE 1. Evidence for disturbances in executive functioning postulated to be localized to prefrontal cortex.

Measure	Group I: SA+/CD+ (N = 27)	Group II: SA+/CD- (N = 64)	Group III: Normal (N = 69)	F-ratio; 2-tailed probability
Behavioral Dysregulation Scales (Martin et al. 1994)	mean±SD	mean±SD	mean±SD	
Aggression	0.71±0.5	-0.11±0.6	-0.80±0.6	F = 24.5, p< 0.00001
Inattention	0.57±0.6	-0.01±0.7	-0.20±0.6	F = 14.4, p< 0.00001
Hyperactivity	0.19±0.4	-0.03±0.4	-0.05±0.4	F = 3.9, p < 0.02
Impulsivity	0.42±0.7	0.06±0.6	-0.20±0.6	F = 7.5, p < 0.0008
Distraction episodes observed during written arithmetic test	5.20±4.4	2.40±3.2	2.58±3.4	F = 5.6, p < 0.0047
Response bias (impulsivity) during computerized vigilance task	0.01±0.01	0.01±0.01	0.006±0.0	F = 4.7, p < 0.01

NOTE: In post-hoc comparisons, group I differs from group II and group III for all measures except impulsivity, where group I differs from group III only.

DESIGN AND EXPERIMENTAL METHODS

Overview of Design

This study will use a case-control design in which the two risk groups will consist of 10- to 12-year-old boys and girls who are the offspring of fathers who meet DSM-III-R criteria for a psychoactive substance dependence disorder (above and beyond nicotine dependence) and either have a conduct problem (SA+/CD+) (defined as meeting DSM-III-R criteria for ODD or CD) or do not have a conduct problem or any other psychiatric disorder (SA+/CD-). The subjects will be matched and contrasted with medically and psychiatrically normal sons and daughters of fathers who do not meet DSM-III-R criteria for any disorder (SA-/CD-). Fathers with psychoactive substance dependence will be selected for sampling in order to ensure an adequate severity of SA to confer significant risk to their offspring. The groups will be compared on magnetic resonance spectra derived from 31P MRS scans of the dorsal prefrontal cortex.

Hypotheses

Based upon the results of prior investigations in subjects with disruptive behavior and using technologies such as rCBF studies (Lou et al. 1984) or PET (Zametkin et al. 1990), and based on PET studies of normal CNS maturation (Chugani et al. 1987), it is hypothesized that SA+/CD+ children will show evidence of reduced dorsal prefrontal metabolism and increases in CNS biomembrane breakdown (possibly reflecting greater synaptic decline) in comparison with matched SA+/CD- subjects and normal control children. Specifically, the following hypotheses will be tested.

1. Ten- to 12-year-old SA+/CD+ children will be differentiated from age, sex, and socioeconomic status (SES) matched SA+/CD- children and psychiatrically and medically normal children of psychiatrically normal parents (SA-/CD-) on the basis of reduced dorsal prefrontal bioenenergetic metabolic activity as indicated by increased 31P MRS signal for ATP (suggesting reduced ATP utilization) and a greater PCr/Pi ratio (suggested reduced catabolism relative to synthesis).

2. SA+/CD+ children will be differentiated from age, sex, and SES-matched SA+/CD- and SA-/CD- subjects on the basis of reduced dorsal prefrontal PME/PDE ratios (suggestive of increased membrane catabolism).

3. Within the SA risk groups (SA+/CD+ and SA+/CD-), subject scores on composite measures of impulsivity, aggression, hyperactivity, and inattention will directly predict dorsal prefrontal 31P MRS signals for ATP and the PCr/Pi ratio (indicative of reduced dorsal prefrontal metabolism) and inversely predict with the PME/PDE ratio recorded over the dorsal prefrontal region (indicative of increased membrane catabolism).

Subjects

Inclusionary Criteria. The highest risk group (SA+/CD+) will include 16 boys and 16 girls (ages 10 to 12 years) who meet DSM-III-R criteria for either ODD or CD and whose fathers meet lifetime DSM-III-R criteria for psychoactive substance dependence disorder (in addition to nicotine dependence, if present). The moderate risk group (SA+/CD-) will comprise 16 boys and 16 girls whose fathers are SA+ but the subjects do not meet any DSM-III-R diagnostic criteria. Normal daughters and sons of control fathers who met no DSM-III-R criteria will be studied as a normal control group (SA-/CD-). The groups will be matched on age, sex, race, physical maturation (Tanner stage), intelligence, and family SES. The sample will be drawn from a community population (rather than treatment programs) using advertising and reverse telephone book solicitation in order to maximize representativeness of the sample.

Exclusionary Criteria, Children. Children will be excluded for the following criteria:

1. Any current diagnosis or history of a DSM-III-R psychoactive substance abuse disorder or any significant history of experimentation with alcohol or drugs. To further rule out drug use, quantity/frequency indices will be obtained from the Substance Use Questionnaire (Tarter, unpublished data). The validity of self-reports of drug use are enhanced through the implementation of a "bogus pipeline" procedure (Evans et al. 1977) using hair samples. Specifically, subjects are told that self-reports of drug use will be reconciled with results obtained from the analysis of a hair sample. However, no such hair analysis actually takes place. Urine drug screens utilizing standard immunoassay methods are also used to provide collaborative evidence of abstinence from recent drug use both during subject ascertainment and on the day of the scan.

2. Any current or lifetime diagnosis of autistic disorder or psychosis.

3. Prior history of open or closed head injury with or without loss of consciousness (e.g., concussion).

4. The presence of a seizure disorder or any other neurologic illness or neurodevelopmental disability.

5. Current administration of any neurologically active drugs (e.g.,-tran-quilizers, antidepressants, neuroleptics, or anticonvulsants).

6. Cigarette smoking or other habitual use of nicotine products.

7. Intelligence quotient (IQ) below 90 as determined by the Weschler Intelligence Scale for Children (WISC-III) (Weschler 1991) or Weschler Adult Intelligence Scale, revised (WAIS-R) (Weschler 1981) to eliminate confounding effects of mental deficiency.

8. The presence of metallic plates or pins anywhere in the body.

In addition, all subjects must be abstinent from caffeine for at least 12hours and over-the-counter cold medicine or any other medications that possess a psychoactive effect for 24 hours prior to MRS scanning.

Exclusionary Criteria, Parents. Subjects will be assigned to high-risk or low-risk SA group status based upon the presence or absence of a psychoactive substance dependence disorder (besides nicotine dependence) in the father. However, subjects will be excluded if:

1. Substance-abusing fathers have (a) a life-threatening medical illness, (b) a chronic neurologic disorder, or (c) a psychotic illness;

2. If nonabusing fathers have (a) any past or current DSM-III-R axis I or II disorder, (b) a life-threatening medical illness, or (c) a chronic neurologic disorder; or

3. Any of the mothers have (a) any past or current DSM-III-R axis I disorder, (b) a life-threatening medical illness, (c) a history of alcohol and/or drug use during the research subject's gestation, and (d) a chronic neurologic disorder.

Mothers of high-risk subjects who themselves have a DSM-III-R psychoactive substance use disorder would be included in order to allow for an exploratory analysis of the effects of bilineal versus unilineal familial substance abuse on their offspring. However, if mothers of high- risk subjects report that drugs were used during the index pregnancy, they would be excluded.

Sample Size and Power Requirements

In order to test hypotheses 1 and 2 (i.e., the SA+/CD+, SA+/CD-, and SA-/CD- comparisons), the proposed sample size of 32 per group (16-boys and 16 girls) would be sufficient to achieve benchmark statistical power= 0.8 at a one-tailed a = 0.05, for a moderate effect size= 0.32.

In order to test hypothesis 3, the combined SA+/CD+ and SA+/CD- groups sample size of 64 would be sufficient for a benchmark statistical power = 0.8 at a one-tailed a = 0.05, assuming a moderate correlational effect size of 0.32.

Independent Variables: Psychiatric and Substance Abuse Diagnoses of Father and Child

At the time of ascertainment, substance-abusing and nonabusing fathers will be administered an expanded version of the Structured Clinical Interview for Diagnoses (SCID). Best-estimate DSM-III-R diagnoses are generated using data obtained from the SCID, confirmatory information from the spouse, and any available clinical records. This diagnostic approach is in accordance with the method described by Leckman and colleagues (1982), and was recently validated by Kosten and Rounsaville (1992). Index boys and girls (10 to 12 years of age) will be assessed using an expanded version of the Children's Schedule for Affective Disorders and Schizophrenia (K-SADS) administered to both the child and mother (reporting on child). The expanded K-SADS contains a detailed inquiry about deviant, aggressive, and illegal behavior. DSM-III-R diagnostic formulations for index children will be based chiefly upon maternal reports of the child's behavior with confirmation through the child's self-report and any available clinical records. Both adult and child best-estimate diagnoses will be compiled and ultimately finalized after case presentations at a diagnostic consensus conference. At such conferences only numerical identifiers are used so that psychiatric diagnoses of children are made blind with respect to the psychiatric status of their parents.

Composite Measures of Dysregulated Behaviors

Numerous measures from multiple data sources will be used to construct indices of aggression, inattention, hyperactivity, and impulsivity (Martin et al. 1994). Data sources include mother's report on child, child's self-reports, teacher's reports on child, and child laboratory test measures. "Mother reports on child" data use item

endorsements from the disruptive behavior disorder symptoms on the K-SADS-E (Orvaschel et al. 1982), the Child Behavior Checklist (Achenback and Edelbrock 1983), and a minimal brain dysfunction questionnaire (Tarter et al. 1977). Child self-report data will be primarily taken from symptoms endorsed on the K-SADS-E (Orvaschel et al. 1982). Teacher reports will be taken from responses on the Child Behavior Checklist-Teacher Version (Achenback and Edelbrock 1983), the Disruptive Behavior Disorders Rating Scale (Pelham and Murphy, unpublished data), and the Connors Behavior Rating Scale (Connors 1969).

Laboratory test data on the child will be obtained from a computerized provocation-to-aggression task (Pelham et al. 1991), objective measure of motor activity during specific tasks (Tryon 1991), a computerized vigilance task (Schneider and Detweiler 1987), and subtests of the WISC-III (Weschler 1991). Summary score indicators and their covariances will be examined on the basis of data type and data source in a systematic fashion. Indicators will first be evaluated on measures from specific informants; indicators that show good convergent validity (e.g.,high Cronbach's alpha) will be retained. Then, the convergence of summary scores from different data sources will be evaluated. Next, factor and construct scores derived from this procedure will be subjected to concurrent validity analysis using variables that are not used in the data reduction procedure.

This structural approach to data reduction will minimize the possibility that a particular instrument or a particular data source wields an undue degree of influence on resultant construct scores. The convergent validity of the resultant constructs and the estimation of method variance parameters were tested using a latent variable approach (Jöreskog and Sörbom 1989) in a multitrait, multimethod model (Campbell and Fiske 1959). The results indicated that the covariance between these indicators is best represented by the four specified traits and four specified methods. The majority of significant factor loadings stemmed from the underlying traits rather than the method factors, providing further evidence for the validity of these measures.

Dependent Measure: 31P Magnetic Resonance Spectra

This procedure will involve first generating a morphologic image using standard longitudinal relaxation time (T1)-weighted spin-lattice proton magnetic resonance imaging (MRI) scans in order to define the anatomic region of the dorsal prefrontal cortex and its volume that

are the desired signal sources (volumes of interest) for 31P MRS. The magnetic field strength will be 1.5 Tesla tuned to a phosphorus nuclear magnetic resonance frequency of 25.895 megahertz (MHz) and a proton frequency of 63.970 MHz. The 31P nuclear magnetic spectra will be obtained utilizing a magnetic field strength (B1) field gradient as described by Bendall (1990), but without phase cycling.

The 31P spectra will be acquired using the same set of surface coils used to obtain the morphologic image, and will be reconciled with this image using the image-processing capabilities of the scanning system in order to ensure an accurate determination of the spectral signal source. The imaging and spectroscopy scans will be obtained using the surface coil technique with coils mounted over the frontal region of the head of the supine subject. For 31P MRS, surface coils are used to transmit the radio frequency impulse and receive the resulting voltage oscillations. To maximize the signal-to-noise ratio in the shortest time possible from a well-defined spatial focus, which in this case is the prefrontal cortex, surface coils will be dual-tuned to detect both the proton and 31P frequencies. Specifically, a 20-centimeter (cm) 31P surface coil and a coplanar 7.5 cm surface coil will be used. Hydrogen (proton) images for spectral localization will be obtained by transmitting with the Helmholtz surface body coil and receiving with the 7.5 cm coplanar surface coil. This will permit a uniform excitation of the head, but with a receptivity profile based on the 7.5 cm coil. The 31P spectra will be acquired by transmitting with the 20 cm coil and receiving with 7.5cm coil. The 20cm coil is sufficiently large (compared with the 7.5cm coil) to produce the same radio frequency homogeneity in the area of interest as that of the body coil used for the proton images of the brain. Conse-quently, the acquired 31P spectra can be directly related to the localized proton image. Other acquisition parameters will be the same as described by Pettegrew and colleagues (1991).

Identification and Calculation of Peak Areas for ATP, PME, PDE, and the PCr/Pi Ratios

All spectra will be processed on a data station with a 5 hertz (Hz) exponential multiplication, first- and second-order phase correction to bring all peaks into absorption mode, and with baseline correction by means of linear tilts known as baseline points. Integrated areas would then be calculated using a program that fits the spectrum with a series of Lorentzian lines. Known doublets, such as the ionized ends regions, will be fitted with two Lorentzian lines, and known triplets, such as the middle region, will be fitted with three Lorentzian lines.

The PME and PDE peaks will then be fitted with one, two, or three Lorentzian lines to obtain the most accurate fit.

The accuracy of fit will be assessed by determining if the difference between experimentally observed and simulated spectra yield a flat line. For each spectrum, the integrated areas of the PME, Pi, PCr, ionized ends (g-ATP), and esterified ends (a-ATP) and middles (ß-ATP) will be determined. From these integrated areas, the mole percents of PME, Pi, PDE, PCr, and ATP will be measured. The signals will be expressed as mole percentages of the total 31P MRS signal, thereby giving relative amounts of these molecules in the brain region.

Analysis and Expected Results

Following a graphic display of the raw data, assessment for normality (with appropriate transformation of data to induce normality, when appropriate), and testing for outliers, descriptive statistics will be generated for all independent and dependent variables. Dependent variables will also be assessed for homogeneity of variance and significant intercorrelation. Between-group tests of matching variables will be conducted to assure group comparability. Should between-group differences in matching variables be found, analyses of covariance (ANCOVA) will be employed using the differentiating variable as covariate. Should there be significant correlations between dependent MRS measures, a multivariate analysis of variance (MANOVA) procedure will be used instead of the analysis of variance (ANOVA) approach to test hypotheses 1 and 2. If multi-collinearity is found in multiple regression analyses, then ridge regression procedures will be utilized.

The general linear model ANOVA will be employed to test research hypotheses 1 through 3. This approach was chosen because it permits an evaluation of the extent to which variation in one or more of the quanti-tative or qualitative independent variables is associated with variation in a quantitative dependent variable.

To test hypothesis 1 (proposing group differences in dorsal prefrontal bioenergetic metabolic activity), a one-way ANOVA or MANOVA will be performed across three groups with the high-energy phosphate metab-olites and ratios (PCr/Pi and ATP) as dependent variables. The null hypothesis of no between-group differences will be rejected if the variance ratio (F) is significant at the 5 percent level. Post-hoc comparisons will be conducted using the Sheffé test.

Similarly, to test hypothesis 2 (proposing group differences in membrane catabolism), a one-way ANOVA or MANOVA will be performed across the three groups, and the membrane phospholipid metabolites PDE and PME will be treated as dependent variables. The null hypothesis of no between-group differences will be rejected if F is significant at the 5per-cent level. Post-hoc comparisons will be conducted using the Sheffé test.

In order to test hypothesis 3 (proposing that personality and behavior variables predict prefrontal metabolism and membrane catabolism), separate multiple regression analyses will be employed for bioenergetic and membrane metabolite effects. If high-energy phosphate metabolites or membrane phospholipid metabolites, as dependent variables, are highly intercorrelated, then multivariate multiple regression will be used. The following linear model will be used:

MRS variables = ß0 + ß1Impulsivity + ß2Hyperactivity
+ ß3Inattention + ß4Aggression + error

All variables will be entered simultaneously. Should multicollinearity beobserved, redge regression will be used. If significant effects of impulsivity, hyperactivity, inattention, or aggression are found at the 5percent level or better, then the null hypothesis of no association will be rejected. The sign(s) of the significant unstandardized regression coefficient(s) will be indicative of a direct or inverse association.

Expected Results

The author anticipates that the analysis will reveal that the CD+/SA+ children have the lowest frontal energy metabolism, as well as the greatest frontal phospholipid metabolism, as measured by 31P MRS.

Impulsivity and inattention are expected to predict both the MRS bio-energetic and phospholipid metabolic variables in a negative direction. That is, the lower the frontal energy metabolism and the greater the phospholipid metabolism, the more impulsive and inattentive behaviors will be manifest. Aggression and hyperactivity will not predict any of the MRS variables; these behaviors are less salient to frontal executive functioning.

PUBLIC HEALTH SIGNIFICANCE

The results from this investigation will clearly demonstrate the presence of a neurobiological diathesis associated with the liability for an SA disorder. It will thereby confirm the extant data from neuropsychologic and neuro-physiologic studies of populations at risk for SA. The results will provide molecular geneticists with a narrower field in which to search for candidate genes that influence SA liability. However, the most important ramifi-cations will be in the realm of SA prevention. Few prevention efforts, if any, have attempted to identify high-risk individuals based upon neurobio-logical profiles and employ interventions directed towards neurocognitive remediation. In other contexts, such programs have been quite effective in improving aggressive and impulsive behavior, attention, and memory. Furthermore, both EEG and event-related potentials (ERPs) can be modified through the processes of classical and operant conditioning (Begleiter and Platz 1969; Kamiya 1969; Rosenfeld et al. 1984). Research has also shown that it is possible to normalize ERPs through pharmaco-logical intervention (Brumaghim et al. 1987).

Behaviorally dysregulated and antisocial substance abusers, as a group, exact a significant social cost. There is a clear need to develop identifi-cation and intervention strategies that are specific to the characteristics of this dysregulated population at substantial risk for SA. Neurobiologic risk factors may be an important component of their liability. The elucidation of a neurobiologic risk factor for the development of SA can lead to novel biopsychosocial models for SA etiology with significant ramifications for prevention and treatment. The characterization of a putative neurobiologic diathesis would ultimately lead to the development of novel prevention approaches that are specific, efficient, and efficacious.

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Commentary on "^{31}P Magnetic Resonance Spectroscopy in Children at Risk for Substance Abuse" by Moss

Scott E. Lukas

SUMMARY

Moss proposes to use a relatively new and technically advanced neuro-imaging technique that can measure cerebral energy metabolism in vivo. In essence, magnetic resonance spectroscopy (MRS) takes advantage of the fact that certain atomic nuclei align in a particular direction under the influence of an external magnetic field. By disturbing the nuclei with pulses of radio waves and then recording the emitted waves as the nuclei realign, it is possible to detect chemicals that reflect changes in energy and metabolism in almost any organ. The investigator proposes to use MRS brain spectra to measure the presence of phosphorous-containing compounds that are critically important in transformation in the use of energy by neurons and glia cells.

Phosphorous 31 (31P) MRS provides a unique picture of in vivo brain imaging metabolism as well as the metabolic status of structural components of neural membranes. This noninvasive method may be useful in detecting subtle differences in the biochemical makeup of subjects from different populations. By comparing these values, the techniques may help elucidate the nature of neurobiological risk factors for the development of substance abuse. The proposed protocol is probably one of the first to attempt to use this technology in either cross-sectional or longitudinal research on vulnerability to substance abuse.

STRENGTHS OF THE PROPOSED RESEARCH

One of the major strengths of this procedure is that the technique is not invasive and does not use ionizing radiation. The noninvasive nature of this procedure readily allows it to be used in populations (e.g., children) that are typically protected from relatively new and unproven techniques. The lack of the need for ionizing radiation is

another important strength because it allows for repeated assessments over a relatively short period of time, if necessary. This approach permits a repeated measure design to be used and subjects can easily serve as their own controls. There are restrictions on the amount of ionizing radiation that can be given to an individual subject; without such restrictions, MRS offers the researcher an opportunity to be more creative with the experimental designs.

The subject population and selection criteria to be used are carefully considered such that the populations are relatively homogeneous. This attention to the composition of the subject population will markedly reduce the variability. Ten- to 12-year-old boys and girls (offspring of fathers who meet "Diagnostic and Statistical Manual of Mental Disorders" (3d. ed. rev.) (DSM-III-R) criteria for psychoactive substance dependence disorder and who themselves have a conduct problem) will be compared with other groups of children who have an array of positive family histories for substance dependence and psychiatric disorders. The inclusion of girls in the research proposal is an added strength in that there are very little data on any aspect of substance abuse liability in women. It is likely that the age of the girls in the present study (10 to 12) will avoid the confounding effects of the onset of puberty. If some of the girls begin to menstruate during the study, the investigator may need to take this into account in the data analysis component.

Another strength of the proposal is that the researcher plans to use urine screens as an objective assessment of whether the children or their parents have been exposed to illicit drugs in the recent past. This adherence to a rigorous recruiting procedure is strengthened by the assistance of an ongoing project at the University of Pittsburgh.

Another strength of the proposed research is the extensive measures of dysregulated behaviors that will be collected. The study will include assessments of aggression, inattention, hyperactivity, and impulsivity. A further strength is the procedure for relating the acquired 31P spectra to the localized individual image. Identification and calculations of the peak areas for adenosine triphosphate (ATP), phosphomonoesters (PME), phosphodiesters (PDE), and the phosphocreatine/inorganic phosphate (Pcr/Pi) ratios will be performed under the supervision of experts in the field. These state-of-the-art procedures should result in extremely accurate measures of these substances. A separate validation procedure utilizing the difference in chemical shifts between the gamma ATP and the alpha ATP and using

the method described by Pettegrew and colleagues (1991) represents another significant strength of the application.

WEAKNESSES OF THE PROPOSED RESEARCH

This entire technology is so new that it is easy to find weaknesses in the proposal; basic questions regarding sensitivity, specificity, and validity still remain unanswered. As with any newly emerging technology, there are critics who claim that findings are not confirmed until reproduced in another lab. The difficulty here is that this is an expensive technology, and the likelihood that individual studies will be directly replicated is low. Thus, the major criticism of this study is that it prematurely employs extremely expensive technology. For example, have traditional methods of measuring other biological measures been exhausted before this study is run? Have all of the baseline parameters been adequately defined and measured so that real differences will be discernible?

Overall, the consensus is that this technology should be used in the proposed studies since the scientific questions about central nervous system function can only be answered with MRS. However, there is always the danger of using an overly sophisticated instrument when a pencil and paper task would have sufficed.

The high cost of these studies does, however, impact somewhat on the experimental design of the project. In particular, the proposed sample size is relatively small for a project of this scope. Only 16 boys and 16girls will be used in the proposed studies. The use of relatively small sample sizes puts the research at risk for type II errors, especially because of the multifaceted nature of the proposed work. Furthermore, there is little room for attrition in these studies. The range of demographic variables in each group (even though they will be matched to a control group) will be very wide. For example, matchings will be done on race, intelligence quotient (IQ), physical maturation, and family socioeconomic status. If each of these variables were to become highly significant (Schuckit 1987), the power of the study that initially started with 16 boys and 16 girls would drop dramatically.

Another potential weakness is the researcher's calculation of a power function. Because the proposal includes comparisons between males and females, it is inappropriate to define the sample size as 32 per group since 16 will be boys and 16 will be girls.

One significant weakness relates to identification of individuals at high or low risk for substance abuse. The protocol calls for evaluating only the individual's father as an indicator of high or low risk for substance abuse. The alcohol literature suggests that this is not an appropriate method-ological procedure and, in fact, may underestimate the degree of risk (Schuckit 1987). The high-risk/low-risk subgroups are a major area of interest, so this factor is particularly important.

Although not technically considered a weakness, the plan to use analyses of hair samples as evidence of past drug use (Baumgartner et al. 1989) is questionable mostly because the validity of this technique has not been demonstrated in other laboratories (Magura et al. 1992; Sauls 1990). Although it is likely that the hair sample technique could be perfected to provide accurate and sensitive data, until this has been demonstrated, this information should be used with caution and compliance data should be collected using conventional means (Cone 1990).

ALTERNATE IDEAS

The investigator has focused attention on a very narrow voxel of interest for evaluating changes in brain chemistry. Once this area is documented, it might be interesting to evaluate other brain regions as well to determine if there are differences in various brain regions. For example, procedures for determining family alcohol history pedigrees in the subject population should be employed. With this information, a better delineation of high-risk and low-risk substance abuse groups will be attained and will reduce the variability due to whatever inheritable factors are present in this population.

Functional MRI is a rapidly growing field and represents a significant merger of two independent technologies (Kim et al. 1993). Nevertheless, this in vivo study of 31P magnetic resonance spectroscopy in children at risk for substance abuse could be expanded by including some behavioral measures while the children are in the magnet. For example, the investi-gators might be able to develop versions of their behavioral dysregulation assessments that could be administered during acquisition of the spectra. Computerized vigilance tasks are particularly adaptable to this type of measure. Even though the strong magnetic fields are hostile to most other equipment, nonferrous instrumental devices have been

developed to measure behavioral responses while subjects are in the whole-body imager (Lukas et al. 1993).

An additional area of interest would be to obtain extensive morphological measurements on these children. For example, some psychiatric popu-lations are known to have different ventricle sizes; it would be interesting to see if a similar phenomenon existed in the study population. Very little is known about this area, and an initial attempt to document ventricular size as well as the ratios of gray and white matter to water in the brains may provide some insights into individual differences in response and may contribute significantly to the identification of individual populations.

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DISCUSSION

Audience and Panel Participants: David Comings, Scott Lukas, Howard Moss, Meyer Glantz, RonHerning, Remi Cadoret, EricDevor, Dan Hummer, RitaLiu, and Jag Khalsav

Dr. Comings: I was very impressed by the studies published a number of years ago using the Wisconsin Card Sort during a PET scan in schizophrenia. Dr. Lukas talked about functional studies. Can you do that kind of testing with your little air puff machine?

Dr. Lukas: There's a mirror in the magnet itself and we're testing that ability right now. The key will be to get a nonferrous screen that can be placed near the magnet and won't get sucked into the magnet. We're working with small LCDs and on a unit that projects it on the back with a magnifier that then brings the image right in so that the child can actually see the task at a distance.

Dr. Moss: We're using video projection as a way of getting the image.

Dr. Comings: Do you get a video screen far enough from the magnet so that it doesn't destroy it?

Dr. Moss: We have it all the way across the room.

Dr. Glantz: But you also have to have some kind of control for things like kids, who otherwise would perform normally, that have claustrophobic responses.

Dr. Lukas: Sure. That's a good point. We've actually played around with vanilla extract to try to allay some of the fears. It's a funny thing that straight olfactory stimulation tends to reduce some of the claustro-phobia, and those of you who are working with a magnet may want to try it. It doesn't work for everybody, but it's a very good issue, not a trivial matter. How many of you have ever been in one of these things? It's a tight squeeze and you do get a feeling of being blocked in. I think the mirror does help a lot, and so does good subject preparation. We actually spend a lot of time on our informed consent. We have this fully detailed procedure that explains exactly the types of sounds in layman's terms. For example, some of the sounds sound like a backfire of a car; others sound like you've lost

your drive train or something like that—things that people can identify with.

Dr. Moss: We also go through a procedure in which we pick up a metal wastepaper basket and we bang on it a few times and you say to the kid, "This is what the scanner sounds like." We also permit the parent to come in and talk to the child while the child is in the scanner and that seems to allay a lot of fears as well. And, of course, at any point that the child wants to terminate the procedure, that's what happens.

Dr. Lukas: Do you let the parent touch the child?

Dr. Moss: No. But the parent can be there and talk to the child over the course of the procedure. I might add that as this technology improves, and with the use of larger magnets, acquisition time is much, much faster. In fact, echoplanar acquisition time is something like 100 milliseconds. So, you can do a procedure that now may take half an hour in the scanner within a matter of minutes, and that may make it much more useful for children.

Dr. Lukas: That's a very good point, Dr. Moss. That's the way to go, I think.

Dr. Comings: Both of you talked about cost. What is the cost of an hour in one of these?

Dr. Moss: It depends on the center. It's about $650 a scan in Pittsburgh, and then we have to pay for the time we spend on the data processing unit in addition. So, it's $650 just for the procedure itself, and then for the postscan analysis also the price can be very high.

Dr. Lukas: It's similar at McLean Hospital. We charge $750 for the hour in the scanner, but then there's no charge for time on a computer. Some small grants—like Digital for example—will provide a lot of the hardware for you. We were able to get one of those small grants to put up a couple of computer workstations. So, right now we're not charging for that. We may as more people use it.

Dr. Herning: One question comes to mind. We've seen—in terms of brain potentials, particularly sensory brain potentials—the auditory ones that are delayed in some of these populations. There’s always been a question as to whether it's a delay in myelination that causes

the delay in the potentials. Will this technique tell us something about myelination?

Dr. Moss: Yes. Because the process of myelination is the process of laying down biological membrane, we should be able to see that reflected in decreases in the precursors, the PMEs, and possibly static levels of the breakdown products.

Dr. Herning: In this population, then, it might be interesting to look at, in addition to the longer latency brain potentials that you are collecting, perhaps the earlier ones in which you see clear delays that can be directly linked to myelination.

Dr. Moss: Absolutely. Dr. Brigham and I talked quite early about trying to find ways that we could incorporate her ERP data with our P31 data because we all share the same subject population.

Dr. Cadoret: This goes back to more of the clinical issue. At your school I think that Dr. Tarter has been interested in looking at develop-ment of different types of convert disorder—the overt and the covert. Do you have access to that sample, and do you plan to use it?

Dr. Moss: Dr. Tarter has the Pittsburgh Longitudinal Study sample, he's a member of our center, and he collaborates quite closely with us. But we are accessing a different sample. We do utilize Dr.Tarter's expertise, of course, in helping us with taxonomic issues as far as conduct disorder goes.

Dr. Cadoret: I think it would be very interesting to see if this correlates with some taxonomic variety of conduct disorder that may be very relevant to the substance abuse issue.

Dr. Moss: Absolutely.

Dr. Hummer: That's very exciting methodology, Dr. Moss, and I congratulate you on it. I had two questions. One is what is the actual spatial resolution of the scanner in this situation? The reason I'm asking is if you want to look at white matter versus gray matter in terms of the phosphoesters, you'd like to be able to say, "Well, this is clearly from white matter and this region is clearly from gray matter." Can you do that now given the technology?

Dr. Moss: For other atoms of interest—like protons for example—you have much better spatial resolution. You have much less so with phos-phorus and that's a problem. You're getting crude regions, rather than highly specific anatomic areas, which is why quantitative metabolic mapping may ultimately be a more satisfying technology where the anatomy is revealed by the proton MRI and then the metabolite concentrations laid out on the anatomic map. I think that will be very nice, and we are working on that. But, at this juncture, even saying that we're scanning prefrontal cortex, per se, is fraught with a degree of imprecision. We know where the surface coils are being placed. We're very careful about that. But we're unable, for example, to pick out specific regions within the frontal cortex that might be of particular interest, like you can with PET.

Dr. Hummer: The other question: Has there been any animal work done with nonhuman primates looking at development? It seems that one of the hypotheses is that you'll be able to track the ratio of the monoesters over the diesters as a function of age and development. It would seem to me that it would be critically important to look in an animal model for development to see how those change, and it seems like that could be done.

Dr. Moss: Absolutely. It hasn't been done in our center on nonhuman primates; its been done on the rat model and on humans.

Dr. Hummer: But in humans you can't get brain biopsies or postmortem tissue to actually measure the ratio. I mean that would seem to be critical for calibrating.

Dr. Khalsa: A quick question. A couple of questions actually. What about the process of myelination on maturation affected by multiple exposures to the magnetic field?

Dr. Moss: There is none.

Dr. Khalsa: The second and third questions are related to your technique once again. Some of these radio-opaque dyes tend to be allergenic, and I don't know whether you're going to test the children for hypersensitivity.

Dr. Moss: This technique, really, at this stage of the game, does not involve employing a contrast medium. There is no contrast medium. However, I know you're interested in consequences of drug abuse, and I did have a slide. I think I mentioned to you that in last week's

"Biological Psychiatry" there is an article by a group in San Francisco, I think McKay and colleagues, that shows significant differences in PME and PDE in white matter among chronic cocaine abusers versus normal controls I think it may actually have some utility in some studies that want to look at the brain effects of chronic substance use.

Dr. Devor: Dr. Moss, from the perspective of a molecular biologist who is not obsessed with dopamine receptors, can you see the metabolic mapping techniques as potentially generating candidate genes in the future?

Dr. Moss: Well, as we know more and more about the genetic regulation of the process of maturation, and if we find a dismaturity in one select population that we are studying, then I see some very interesting candidate genes emerging on the horizon. But, I think we're at least 5-10 years away from that point. I guess there's all that work on homeoboxes and matura-tion, and that may be one place to begin looking, but first I'd like to be able to see some demonstration that dismaturation is involved in some of these dysregulated behaviors that are precursors to substance abuse.

Dr. Liu: I'm really intrigued with your synapto--(inaudible)--and how do you translate--(inaudible)--with such densities of synapses?

Dr. Moss: This procedure is very, very new and it involves, instead of using phosphorus as our atom of interest, sodium, sodium 23. The way the procedure is done involves taking advantage of the fact that extracellular fluid is rich in sodium and intracellular fluid is relatively poor in sodium. Through a process of imaging sodium and then a subtractive process, you basically subtract away the water, or the cerebrospinal fluid, in the blood. What you're left with is intracellular synaptic density. And then there are some mathematical ways to convert that information into something a little bit more meaningful in terms of density measures.

Neurochemical Predictors and Correlates of Vulnerability to Cocaine Use

Roy J. King, Jr., and Christopher Flowers

STATEMENT OF THE PROBLEM

The ultimate goal of the proposed research is to examine the neuro-chemical and behavioral factors that may predict vulnerability to cocaine craving, which is believed to be associated with relapse among abstinent cocaine abusers. In general, the proposed studies are linked through an overarching postulate that cocaine craving results from heightened mesocorticolimbic dopamine (DA) activity.

This hypothesis is explored through between-subject as well as within-subject designs. In between-subject designs, it is hypothesized that individuals prone to cocaine craving will exhibit elevated measures of dopaminergic functioning. In within-subject designs, increased craving is believed to be associated with increased dopamine activity within an individual over time. Since direct assessments of DA activity in humans are relatively limited, several indirect measures of DA function are proposed. These measures are based on animal models derived from the literature on incentive motivation and on previous studies in human sub-jects. They include cerebrospinal fluid (CSF) concentrations of homo-vanillic acid (HVA), the major metabolite of DA; CSF dopamine sulfate (DASO4) levels, reflecting central nervous system (CNS) DA activity; and real-time measurement of motor activity associated with increased DA activity. Specifically, the plan is to accomplish four specific aims.

Specific Aim 1

This project will assess the relationship between cocaine craving and variations in DA-related measures between individuals after long-term cocaine abstinence. In particular, the proposed research will test whether CSF-HVA and CSF-DASO4 levels correlate with cocaine craving. A confirmation of this hypothesis will offer more precise CNS correlates of

the subjective measures of cocaine craving, which will be useful in testing the "priming" models of craving and relapse using these biological indices.

Specific Aim 2

The project will also study the utility of using motor activity as a peripheral monitor of individual differences in CNS DA activity. Motor activity will be correlated with CSF-HVA and CSF-DASO4 in the sample of cocaine abusers. This aim will quantify the practicality of using motor activity as a reflection of CNS DA metabolism.

Specific Aim 3

In addition, the project will examine the relationships between motor activity and cocaine craving both between individuals and within individuals. In within-subject studies, the relationship between craving episodes and increased motor activity will be traced in the naturalistic setting among long-term hospitalized cocaine abusers. In addition, mean daily levels of activity and automated behavioral self-recordings of craving will be determined across subjects. The studies under the pur-view of this aim will provide information on the dynamics of cocaine craving and, in conformance with the incentive motivational model of craving, test whether heightened locomotor activity occurs with spon-taneous attacks of craving in these subjects. Findings from this work may reveal noninvasive means to identify the acute onset of cocaine craving and surrogate markers for identifying individuals at increased risk of craving cocaine.

Specific Aim 4

Finally, the project will study the relationship between Axis II personality disorder traits (as defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed., rev. (DSM-III-R)) and cocaine craving. Preliminary data indicate that histrionic personality traits may predict long-term use of cocaine. Under this specific aim, it is postulated that histrionic personality disorder traits will be associated with heightened cocaine craving in long-term abstinent cocaine abusers. Moreover, using multiple regression of the Axis II personality disorder traits as indepen-dent predictors of cocaine craving, it is proposed that this association will be found to be distinctive and, thus, contribute the predominance of covariation between personality disorder and cocaine craving. A clear corollary

of this finding would be that histrionic individuals show increased craving and, thus, may be at increased risk for relapse.

BACKGROUND AND SIGNIFICANCE

Cocaine use is a major public health concern in America. In spite of numerous attempts to reduce the prevalence of cocaine abuse and dependence, long-term treatment remains a virtually intractable social problem. Even after successful detoxification, relapse remains a recurrent difficulty (Wallace 1989). One factor related to relapse into cocaine use is the continued craving that individuals experience even after long-term abstinence. Studies by Kozlowski and Wilkinson (1987) and Extein and Dackis (1987), and treatment strategies espoused by Washton and colleagues (1986) and Wesson and Smith (1985), point to craving as a substantial factor in cocaine abusers' relapse into drug use.

Treatment of stimulant abuse is typically divided into two phases: initiation of abstinence and prevention of relapse. Intense cocaine craving arises during the period of anhedonia 12 to 96 hours after the last use of cocaine, and craving can reemerge episodically months or years after its last occur-rence (Gawin and Ellinwood 1988). Thus, management of cocaine craving is crucial for prevention of relapse during detoxification and long-term treatment.

To date, several pharmacological and behavior interventions have been investigated for treating cocaine craving. Behavioral intervention strategies have focused on deconditioning or reconditioning stimuli (e.g.,environmental cues, recall of euphoria, and mood) that patients associate with craving attacks (Childress et al. 1988a, 1988b; Wallace 1989; Weddington et al. 1990). Most pharmacological interventions have been based upon the DA depletion hypothesis (Dackis and Gold 1990; Dackis et al. 1985), that proposes that withdrawal from cocaine use involves a hypodopaminergic state introducing anhedonia, which provokes craving and subsequent drug use. Proponents of this model have employed DA agonists such as apomorphine (Hollander et al. 1990), bromocriptine (Dackis et al. 1985, 1987), pergolide mesylate (Malcolm et al. 1991), amantadine (Gawin et al. 1989b), flupenthixol (Gawin et al. 1989a), and desipramine (Gawin et al. 1989b) without clear indications of therapeutic efficacy.

Although a dysphoric component possibly related to hypodopaminergia probably exists as a component of craving, human and animal evidence (Stewart 1984; Wise and Bozarth 1987) have directed recent research to focus on the relationship between the craving experience and the rewarding and reinforcing effects of cocaine. Some studies suggest that the rewarding effects of cocaine are mediated by an enhancement of mesolimbic/ meso-cortical DA function (Pettit et al. 1984; Ritzetal. 1987). As a result, behavioral and pharmacological therapies based on alleviating the effects of the positive reinforcement associated with cocaine-induced hyperdopa-minergic functioning seem a more plausible means of extinguishing cocaine craving and preventing relapse. However, before such inter-ventions can be developed, the relationships between cocaine craving and neurochemical and behavioral factors known to be involved in cocaine abuse must be carefully examined. Clarification of the relationships between dopaminergic functioning, motor activity, mood states, personality features, and cocaine craving will serve as a foundation upon which to build a comprehensive and efficacious treatment strategy. Thus, the proposed research is of particular clinical significance for developing treatments to prevent relapse among cocaine abusers.

Individual Differences in Cocaine Craving and Dopaminergic Activity (Specific Aim 1)

Cocaine craving as a medical phenomenon has yet to be distinguished as an event arising from a fundamental set of conditions. Moreover, the use of craving as a medical construct has been confounded by its connota-tions in common language. In most connotations, craving refers to a strong desire or intense longing. Typically, craving is used to describe two distinct states that often are not carefully distinguished: aversive craving associated with the anhedonic effects of drug withdrawal and appetitive craving, a desire to reinstate the euphoric effects of the drug. Although some inconsistent findings exist in the literature on cocaine craving, the research discussed here focuses on craving as a motivational state associated with the positive reinforcing qualities of cocaine. The behavioral, psychopharmacological, and neurochemical evidence supporting this model of cocaine craving is presented.

Individual differences in vulnerability to cocaine craving have been suggested by animal models of cocaine self-administration and human studies, but they have yet to be demonstrated directly. The conditions in which cocaine craving arises and the time course for

development of craving also remain unmeasured. Several means have been proposed to measure cocaine craving at a single point in time, but few have charac-terized changes in craving intensity over a period of time. Methods to assess cocaine craving include a 29-item self-administered test (Gawin and Kleber 1986), a 13-item withdrawal symptom scale (Tennant and Sagherian 1987), a 20-point analog scale (Kosten et al. 1987), the Brief Psychiatric Rating Scale (Giannini and Billet 1987), the Addiction Severity Index (ASI) (McLellan et al. 1980), and the Beck Depression Inventory (O'Brien et al. 1988).

More recently, Voris and colleagues (1991) and Halikas and colleagues (1991) have focused on describing the craving episode, and they have demonstrated the reliability and validity of measurements of cocaine craving. Employing a 20-point visual scale, Voris and colleagues (1991) found statistical reliability among 25 patients' self-assessments of intensity of craving, mood, energy, and general health measured on successive days. This evidence suggests that the experience of craving and related variables can be reliably measured by self-assessment techniques. Halikas and colleagues (1991) described cocaine craving in terms of three dimensions: intensity, frequency, and duration. Data gathered from 234 questionnaires completed by 35 subjects indicate cocaine craving to be infrequent (< 2 times per day), of short duration (<20 minutes), and of variable intensity. A test of internal consistency revealed that the three measurements described the same construct, a=0.826. Also, the intensity, frequency, and duration of craving components each correlated positively with cocaine-use dreams. These data suggest that craving is a robust construct related to individual psychological and cortical functioning; they pave the way for more detailed descriptions of cocaine craving and the associated behavioral and psychosocial variables. These scales and inventories serve as a foun-dation upon which an automated assessment of cocaine craving was constructed to measure mood covariants and the time course of cocaine craving. This information will be useful to construct a dynamic model of cocaine craving that can be readily incorporated into the corpus of neurochemical and psychiatric knowledge concerning cocaine abuse.

Most neurochemical models of cocaine craving have focused on fluc-tuations in dopaminergic functioning as the underlying mechanism to account for variations in craving. Until recently, theoretical investigation of the postacute period of cocaine administration has been influenced primarily by the dopamine depletion hypothesis, which asserts that a hypodopaminergic state underlies the dysphoric aspects of abstinence leading to anhedonia, craving, and subsequent

drug use (Dackis and Gold 1985; Gawin and Kleber 1986). This postulate has been supported by empirical work in animal models (Karoum et al. 1990; Robertson et al. 1991) and studies of human subjects measuring glucose metabolism (Volkow et al. 1991) and DA receptor activity (Volkow et al. 1990), but it has yet to be demonstrated directly. However, this hypothesis is contra-dicted by research in which cocaine craving appears to be accompanied by a rise in dopaminergic functioning (Martin et al. 1989), and by findings that craving is induced by elevated DA (Jaffe et al. 1989).

Psychostimulants such as cocaine generate a relatively weak withdrawal syndrome and elicit responses in animals that suggest these agents serve as positive reinforcers (Stewart 1984; Wise and Bozarth 1987). Therefore, alternative hypotheses explaining the presence of craving have been proposed. One interesting interpretation is that craving states are mediated by the incentive motivational properties of both external and internal events (Marlatt 1987). Marlatt dissociates craving from the dysphoric effects of withdrawal and conceptualizes drug craving following abstinence as a motivational state that seeks to reproduce the primary appetitive quality of the original state induced by cocaine use. Marlatt specified the realm of craving to be a desire to experience primary and secondary reinforcers. Even though this model of craving as "a motivational state associated with a strong desire for an expected positive outcome" (Marlatt 1987, p. 43) is still speculative, such a scheme fits readily into the corpus of basic research in the psychopharmacology of cocaine.

Evidence establishing the dopaminergic system as integral to incentive motivation and reward-dependent conditioning (LeMoal and Simon 1991) suggests enhanced dopaminergic activity may mediate the positive reinforcement associated with cocaine use. In animals, dopaminergic activity in the nucleus accumbens (NACC) increases when subjects are presented with a conditioned stimulus previously associated with cocaine (Blackburn et al. 1989). Increases in dopamine have also been shown to potentiate responding for other reward-related stimuli (Cador et al. 1991), presumably by enhancing the animal's motivation for weak cues (Kelley and Delfs 1991; Robbins et al. 1989). While some disparate opinions exist (Ettenberg et al. 1982; Pettit et al. 1984), the preponderance of evidence from studies exhibiting the reduction or elimination of the reinforcing effects of psychostimulants through 6-hydroxydopamine lesions of the ventral tegmental area (VTA) and NACC (Roberts et al. 1980) or pharmacological blockade of the dopaminergic system (Bozarth and Wise 1981; De Wit and Wise 1977; Roberts and Koob 1982; Spyraki

et al. 1982) also emphasize the dopaminergic pathway as fundamental to the positive reinforcing effect of cocaine.

Recently, the association between mesolimbic DA activity and incentive motivation processes has been extended to individual differences in psychostimulant reactivity in rats. In a series of studies, Hooks and colleagues (1991a, 1991b) have investigated individual differences in rats divided into high responders (HR) and low responders (LR) based on their locomotor response to a novel environment. Studies of these subtypes of rats show neurochemical differences between these two groups, including elevated baseline and cocaine-induced mesolimbic DA levels in the HR group. For instance, following exposure to a novel environment, HR and LR rats show differences in NACC and prefrontal 3,4-dihydroxyphenylacetic acid (DOPAC)/DA ratios (Piazza et al. 1991) and corticosterone elevations (Piazza et al. 1990).

In other studies, reactivity in the mesolimbic DA system predicted individual responsiveness to both the initial effects of amphetamine as well as the more prolonged sensitization to this psychostimulant (Piazza et al. 1989, 1991). There was also a significant correlation between rats' locomotor responses to novelty and to cocaine administration (10 mg/kg dose, $r = 0.65$, $p < 0.005$; 15.0 mg/kg dose, $r = 0.92$, $p < 0.0001$) (Hooks et al. 1991a).

Following 15.0 mg/kg cocaine administration, HR rats experienced a larger NACC DA response and a greater increase in locomotor activity than LR rats. Correlations were demonstrated between rats' locomotor responses to novel environment and dopaminergic response to cocaine. However, HR and LR rats did not express detectable differences in their basal concentrations of DA, suggesting that differences in dopaminergic responsiveness to cocaine is unlikely to be mediated by baseline-dependent effects. Nevertheless, changes in both pre- and postsynaptic dopaminergic mechanisms are believed to be involved. Both DA type 1(D1) and type 2 (D2) receptor sites undergo priming, which could provide a mechanism for the strong enhancement of the effectiveness of an agonist (supersensitivity) and for making otherwise ineffective doses effective at causing a response (Criswell et al. 1989; Morelli et al. 1989). Individual differences in D1 or D2 DA receptor functioning may sustain individual differences in the priming of incentive motivational states or the quality of reinforcement, which would influence the induction and maintenance of cocaine craving.

Studies of human subjects suggest that individual differences in mesocorticolimbic DA functioning exist in humans as well, as reflected by variations in the observable manifestations mentioned above. In humans, the CNS dopaminergic system seems to be a crucial mediating element for motivational excitement (Wise 1988). CSF-HVA levels of cocaine-dependent subjects were not significantly different from those of control subjects, although cocaine abusers with heightened craving had higher HVA levels (Knoblich et al. 1992). This evidence, combined with the data from animal subjects discussed above, suggests that abusers experiencing heightened craving may be a subtype of cocaine abusers who have heightened dopaminergic responsiveness and increased susceptibility to cocaine.

It is not the intention of this proposed study to uncover the mechanisms underlying individual differences in responsiveness to psychostimulants, but rather to examine the behavioral concomitants (differences in motor activity and histrionic features) associated with these underlying mechanisms. Measurement of CSF-HVA and DASO4 levels in larger samples of cocaine-abusing and control subjects is necessary to confirm or refute the model supported by previous findings (Knoblich et al. 1992) and by animal studies (Hooks et al. 1991b). Comparison of baseline CSF-HVA and DASO4 levels in cocaine-abusing and control subjects could reveal whether differences in mesocorticolimbic DA system activity exist in humans and whether these differences reflect individual differences in dopaminergic activity, DA-mediated cocaine craving, or both.

Motor Activity as Potential Indicator of DA Metabolism (Specific Aim 2)

Since the sum of the evidence from animal and human studies suggests that individual differences in motor activity mediated by the mesocorti-colimbic DA system may predict individual differences in vulnerability to psychomotor stimulants, the second specific aim of this research focuses on the relationships between a noninvasive real-time measure of DA activity and a measure of motor activity that is sensitive enough to distinguish individual differences. Much evidence exists from animal studies to support the viability of this measure. For instance, under baseline conditions, Pradhan and colleagues (1990) have shown that variations in spontaneous locomotor motility correlate highly with DA and its metabolite levels in the striatum. Moreover, cocaine adminis-tration is known to elicit locomotor activity (Post and Contel 1983) and to increase extracellular DA in the NACC (Kalivas and Duffy 1990; Pettit et al. 1990).

As discussed above (Specific Aim 1), studies in animal models suggest that dopaminergic systems mediate individual differences in locomotor activity related to psychostimulant administration. Specifically, findings by Hooks and colleagues (1991a,b) and Piazza and colleagues (1989, 1990) propose that individual differences in locomotor response are mediated by the mesocorticolimbic DA system. In an experiment examining the role of NACC DA in individual differences, HR rats exhibited a 250 percent higher basal DA concentration (6.45±1.01nM, n= 6) than LR rats (2.58±0.16 nM, n = 7) (Hooks et al. 1992). Following intraperitoneal (IP) cocaine administration, HR rats had both a greater locomotor response and increase in absolute DA concentration compared to LR rats. Together these findings suggest that measures of motor activity potentially may be used as surrogate markers for CNS dopaminergic activity in humans.

In support of this concept, there have been several studies demonstrating a correlation between motor activity and CSF-HVA levels in human subjects. For example, Banki (1977) showed a significant correlation between CSF-HVA and nurse-rated motor activity in a large sample of patients. In general, manic or hypomanic patients who have higher motor activity than depressed patients also have higher levels of CSF-HVA (Post et al. 1973). Evidence indicates that measurement of motor activity may offer a noninvasive, real-time reflection of DA output. In the present proposal, a measurement of wrist motor activity (described below) will be tested as a potential marker for CNS dopaminergic activity. If significant correlations are found between cocaine abusers' CSF-HVA and/or CSF-DASO4 levels and wrist activity measures, this method may provide a peripheral noninvasive measure reflecting CNS dopaminergic activity.

Conditioned Locomotor Activity and Cocaine Craving (Specific Aim-3)

Since cocaine craving appears to be associated with heightened dopaminergic functioning (as discussed above in Specific Aim 2), it seems reasonable that the onset of a craving episode would be associated with a real-time measure of a change in dopaminergic functioning (i.e.,motor activity). As suggested above, animal studies have shown that locomotor activity is correlated with a propensity to self-administer psychostimulants. In human studies as well, changes in DA-related mood states might be expected to be associated with motor activity. Wolff and colleagues (1985) observed decreased daytime

motor activity levels in 27depressed patients in their depressed states as compared with their manic or euthymic states. Affectively ill subjects exhibited lower mean daytime motor activity levels during their euthymic periods (measured by a self-contained wrist apparatus) than a group of volunteer normals housed in the same ward. These results suggest that motor activity may reflect interpersonal and intrapersonal variation across mood continua. Measures of wrist motor activity may prove to be a reflection of acute variations in dopaminergic functioning and a source for objective studies of craving within and between individuals that could advance the understanding of the temporal relationships between craving and dopaminergic activity. More signifi-cantly, activity monitoring may provide a noninvasive means for diagnosis and prognosis in the treatment of cocaine abuse.

Relationship Between Personality Disorder and Cocaine Craving (Specific Aim4)

Recent models of personality broadly propose relationships between DSM-III-R Axis II personality disorders and patterns of drug use (Cloninger 1987; King 1986). In general, studies indicate a relationship between the impulsive personality disorder cluster including antisocial, borderline, narcissistic, and histrionic disorders, and both alcohol and drug abuse. For example, Kosten and colleagues (1982) showed that opiate addicts had higher frequencies of antisocial, borderline, and histrionic personality disorders.

Recent evidence demonstrated significant relationships between histrionic traits and cocaine use (King et al. 1991). In a sample of 70 male poly-substance abusers in a long-term drug rehabilitation program, histrionic personality disorder traits were uniquely associated with measures of lifetime abuse by the ASI ($r = -0.52$, $p < 0.0001$). Post hoc correlation with individual traits also suggested that histrionic individuals had used cocaine longer ($r = 0.41$, $p < 0.0004$). In separate studies, significant correlations have been shown between CSF-HVA and indices of cocaine craving (Knoblich et al. 1992) and histrionic ($r = 0.35$, $p < 0.05$) and antisocial ($r = 0.36$, $p < 0.05$) personality disorder features (unpublished data). Similarly, in a study of long-term abstinent cocaine abusers (Knoblich et al. 1992), CSF-HVA was positively correlated with a composite craving score ($rs = 0.61$, $p < 0.05$).

These observations are in accordance with the proposed model of the interaction of abused drugs with personality and neurochemistry.

That is, individual differences in mesolimbic DA activity, which may be temperamentally based, could lead to differences in histrionic, prosocial, and emotionally expressive behavior. Those who are readily excited by social cues (i.e., histrionic individuals) might be more sensitive to the rewarding aspects of cocaine consumption, specifically the dopaminer-gically mediated activating effects as manifested by increased activity, talkativeness, and emotionality. Because of this increased sensitivity, such individuals might be more likely to crave cocaine and continue long-term use even after treatment. Furthermore, because the acute effect of cocaine appears to be a blockade of DA reuptake at the nerve terminal, frequent or prolonged use might lead to enhanced histrionic behavior under the influence of the drug, thereby exaggerating those very personality traits presumed to be risk factors for cocaine use. Thus, individuals might, over a period of time, begin to acquire the self-concept of being social or histrionic under chronic use. Also, one may find the self-administration of cocaine rewarding enough to overcome the anticipated dysphoric effects after the drug has worn off. As a result of this motivation, such a person would be particularly prone to developing cocaine craving as a result of appetitive desires.

By seeking specific associations between cocaine craving and personality disorder traits, the proposed study expects to clarify the relationships between histrionic personality traits and propensity to crave cocaine. Figure 1 shows the hypothesized relationships between the biological indices associated with dopaminergic functioning and measures of cocaine craving. Mean hourly activity, CSF-DASO4, and CSF-HVA are believed to be measures reflecting individual variations in CNS dopa-minergic functioning. Findings from animal and human studies suggest that these measures are related to individual differences in susceptibility to cocaine craving. In the present studies, this susceptibility is measured by a variety of craving indices.

PRELIMINARY DATA SUPPORTING THE SPECIFIC AIMS

Automated Craving Measures: Behavioral Studies (SpecificAim 1)

In order to determine craving changes within individuals, procedures have been developed to track and record these variations over time. For 5consecutive days male cocaine-abusing subjects carried a pocket computer and responded to questions each time they heard a programmed

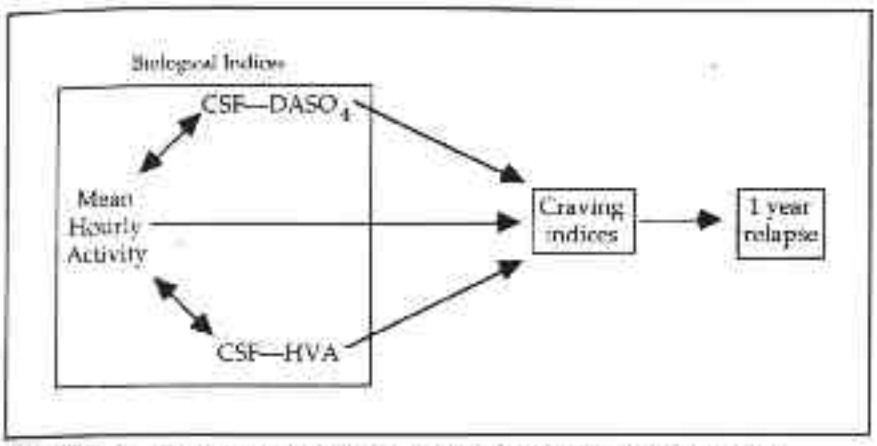

FIGURE 1. *Relationship between biological indices and cocaine craving.*

signal. Seven times during the course of each day each subject was asked if he experienced craving since his last report. If so, the subject was instructed to rate his urge to use cocaine (1 to 10), subjective of cause for the urge, degree of control over the urge (none to extreme), and means of resisting the urge. Using 10-point scales, the subject was asked to describe three aspects of mood: sad to happy, anxious to relaxed, and excited to calm. Finally, the subject was asked to rate the chance of craving in the next 3 hours. To ascertain whether cocaine craving arises with a circadian or ultradian rhythm, the total number of craving attacks occurring within each hour interval was tabulated. A Kolmogorov-Smirnov goodness-of-fit test of the distribution of craving attacks (N=48) over a 24-hour period demonstrated craving to be nonuniformly distributed over time ($p = 0.007$). A histogram of the distribution of craving attacks over time shows that craving occurred more often after 10:00 (figure 2). Table 1 shows the frequency of self-reported attributions of craving attacks to various causes. Most commonly, subjects attributed these craving attacks to the experience of bad mood and physical feelings.

The relationships between fluctuations in mood and onset of craving also were explored. Time course changes of mood in periods of craving versus periods of no craving were tabulated and graphed on a 10-point ordinal scale. Figure 3 compares changes in mood before, during, and after periods of craving versus periods of no craving and demonstrates

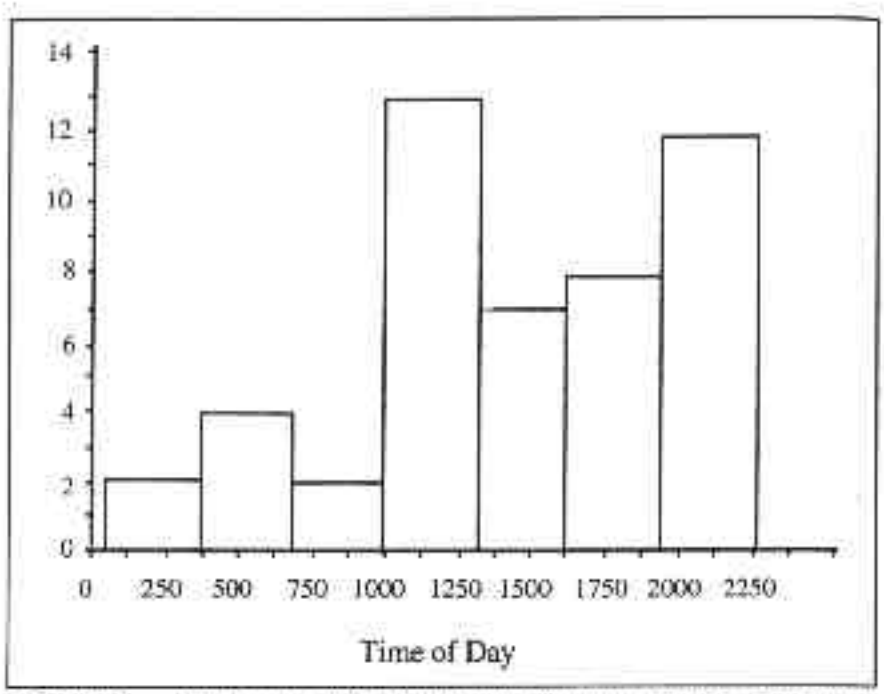

FIGURE 2. *Histogram of the distribution of craving attacks by the time of day.*

TABLE 1. Frequency of attributed causes of cocaine-craving attacks.

Attribution	Percentage of Attacks
Bad mood	43
Physical feelings	38
Flashbacks	35
Stressful interactions	27
Memories	19
Bad news	13
Sensory reminders	6

that subjects tend to be happier and more relaxed before craving attacks, sadder and more excited and anxious during craving periods, and tend to feel likely to crave again in the next 3 hours after craving episodes.

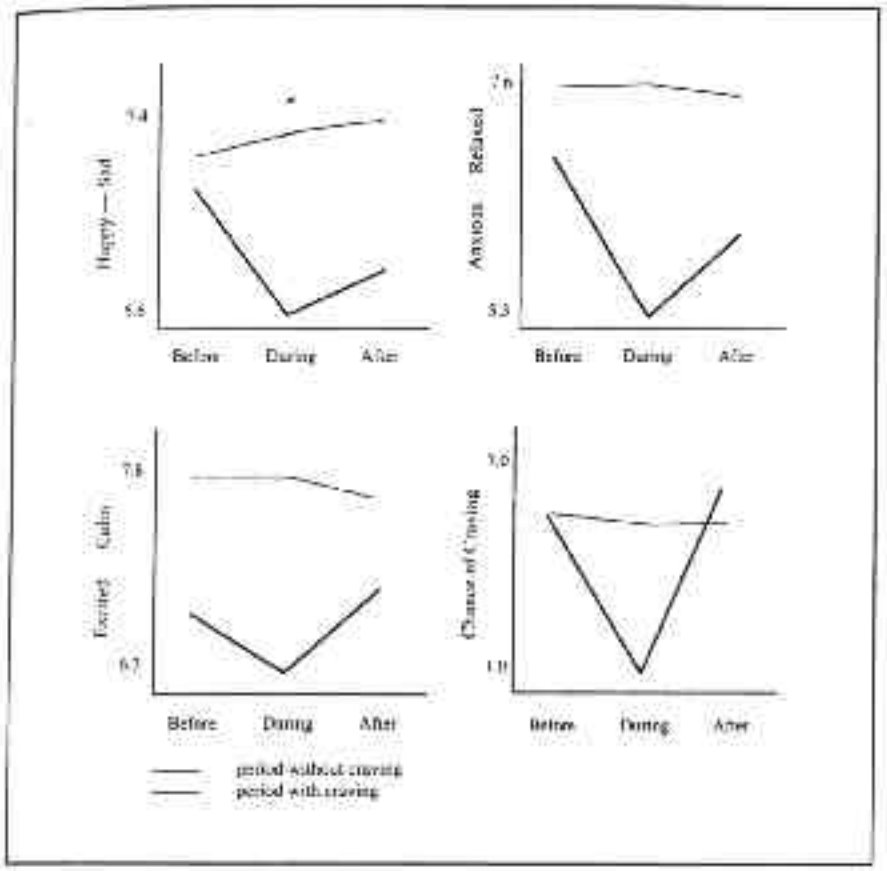

FIGURE 3. *Comparison of the changes in mood before, during, and after periods of craving versus periods of no craving.*

To determine which of the mood variables assessed before or during a craving attack could predict craving, multiple stepwise regression analyses were performed. Regression analysis to predict craving using the mood variables and chance of craving before the episode yielded the excited-calm scale as the only variable that entered significantly (multiple R= 0.23; F(1,115) = 6.2; p = 0.014). Using the mood variables happy-sad, excited-calm, and anxious-relaxed and the chance-of-craving scale during the craving event to predict craving revealed that only anxious-relaxed and chance of craving entered significantly (multiple R = 0.69; F(2,114)= 52.4; p< 0.0001; ß chance of craving = -0.52; ßanxious-relaxed = -0.38).

Individual Differences in Craving Related to Dopamine Function (Specific Aim 2)

Strong preliminary data show a relationship between cocaine craving in long-term abstinent cocaine addicts and CSF levels of HVA. In this study (Knoblich et al. 1992), nine cocaine-dependent males from a long-term inpatient drug treatment program and nine community controls underwent diagnostic interviews followed by the Personality Diagnosis Examination (PDE) (Loranger et al. 1987) and lumbar puncture. On the day of the lumbar puncture, all subjects were rated using the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1967).

In order to test the hypothesis that craving would be positively associated with HVA, three craving indices were a priori selected. These were frequency of pleasant thoughts of cocaine during the past month, frequency of craving episodes during the past month, and intensity of desire for cocaine during the past week. To minimize the possibility of type I error due to multiple tests, a composite craving score was computed adding the three ranged-normalized craving indices. A one-tailed Spearman rank correlation was used to demonstrate a positive association between the composite craving score and HVA; a Mann-Whitney nonparametric test of means compared HVA levels between the cocaine-dependent and control subjects.

Results demonstrated that patients diagnosed with cocaine dependence did not differ significantly in levels of CSF-HVA from normal controls, with the mean CSF-HVA levels being 267 (±66) picomolars (pmol)/ml and 267 (±85) pmol/ml respectively. Within the group of abusers, however, the dopamine metabolite was positively correlated with the composite craving score ($rs = 0.61$, $p < 0.05$). Post hoc, the association was seen in questions referring to frequency of pleasant thoughts of cocaine ($rs = 0.70$, $p < 0.02$) (see figure 4) and approached significance with frequency of craving episodes ($rs = 0.59$, $p = 0.051$) in the past month. CSF-HVA was associated neither with other measures of cocaine use nor with depression (see table 2).

Motor Activity, CSF Dopamine, and Craving (Specific Aim 3)

Much of the animal data predict that various forms of locomotor activity measures may be important reflections of the underlying status of activity in the DA system. Since locomotor activity may be more readily

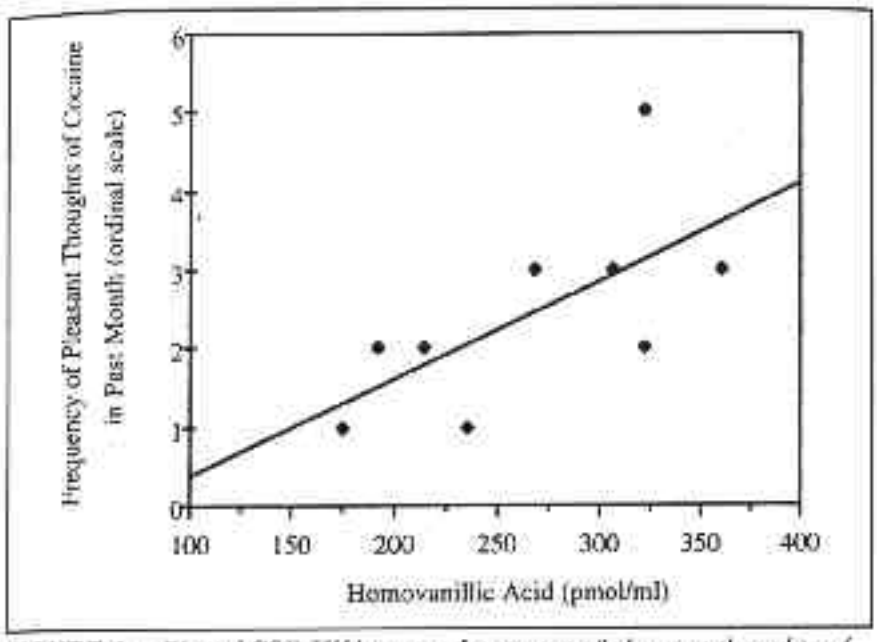

FIGURE 4. *Plot of CSF HVA versus frequency of pleasant thoughts of cocaine in the past month.*

monitored than the dynamics of the DA system, measuring associated motor activity in humans might be quite useful in testing the hypotheses outlined in this proposal. In previous work, theoretical models of DA activity have been sought that mathematically predict chaotic instability over time in manifest behavior (King et al. 1981, 1984). These are nonlinear, dynamic models of DA activity that predicted the appearance of both oscillations and chaos in variables coupled to the DA system. Natural extensions of these models would also predict oscillation and chaos in motor activity under certain conditions.

Motivated by these models, empirical studies were designed to analyze tonic individual differences in motor activity (King et al. 1988). On the basis of the model of histrionic traits as expressions of a heightened dopaminergic responsiveness, it is hypothesized that histrionic traits would be correlated with locomotor activity. Indeed, in a study of individuals who presented with a diagnosis of panic disorder and were recruited to undergo a clinical trial for reduction of panic attacks, histrionic traits were found to be significantly correlated with average

TABLE 2. *Correlations of cocaine use, craving, and depression indices with CSF-HVA in male cocaine abusers.*

Item	Mean±SD	Range	Corr with CSF-HVA
Frequency of pleasant thoughts of cocaine in the past month	2.4±1.2	1-5	0.70**
Frequency of craving episodes in the past month	1.9±1.2	1-4	0.58*
Intensity of desire for cocaine in the past week	3.3±5.1	0-15	0.50
Typical daily consumption (gms)	1.9±2.1	0.25-7.0	0.31
HRSD score	3.4±4.1	0-10	0.20
Total years of cocaine use	6.2±5.8	1-20	-0.02

KEY: CSF-HVA = cerebrospinal fluid homovanillic acid; HRSD = Hamilton Rating Scale for Depression; * = $p = 0.051$; ** = $p < 0.02$.

daily locomotor activity ($r = 0.35$, $p < 0.025$, one-tailed Pearson's, N-=33). Subsidiary findings from that study also showed high 8-week retest reliability in motor activity ($r = 0.73$). This indicates that locomotor activity in the sample is stable over time and, therefore, is a good variable to assess individual differences.

Locomotor activity was measured using a solid state microcomputer monitor worn on the belt; the associated motion sensor consists of six liquid mercury switches attached to the lateral thigh. Preliminary studies used an updated technique with watch-size wrist monitors with activity sensed by transducers, digitized, and counted in 15-second epoch bins. In a pilot study of a small sample of eight volunteers, the bipolar mood measure happy/sad correlated with locomotor activity averaged during the 30-minute period surrounding the mood recording. In this group of subjects the intraindividual correlations between happy/sad and activity ranged from -0.37 to 0.96. A nonparametric sign test demonstrated that these correlations were significantly greater than 0 ($p < 0.035$). This pilot work shows the

feasibility of monitoring mood states and locomotor activity on a real-time scale.

Axis II Personality Traits and Cocaine Use (Specific Aim 4)

The overlap between the key Axis II traits related to incentive motivation and cocaine use has been investigated in a series of studies using the PDE to assess Axis II traits. The PDE rates each of 11 Axis II personality disorders according to an ordinal scale of severity through a semistructured interview. To show construct validity for the proposed models, it was necessary to assess the reliability of the PDE. Table 3 shows the internal consistency (Chronbach alpha), the interrater reliability (interclass r), and the 6-month retest reliability for each of the Axis II scores from the PDE in the subject pool. As can be seen, each of the cluster B Axis II traits demonstrates high reliability and temporal stability.

TABLE 3. Personality Disorders Examination reliability data.

Diagnostic Category	Chronbach a	F interclass	Interclass r	6-mo. retest reliability
	(N = 289)	(N = 229)	(N = 22)	(N = 48)
Paranoid	0.71	40	0.95	0.74
Dependent	0.74	96	0.98	0.80
Avoidant	0.74	191	0.99	0.65
Antisocial	0.87	188	0.99	0.95
Schizoid	0.50	12	0.85	0.54
Schizotypal	0.68	25	0.92	0.72
Compulsive	0.62	92	0.98	0.71
Histrionic	0.73	38	0.95	0.75
Narcissistic	0.68	46	0.96	0.47
Borderline	0.80	117	0.98	0.76
Passive-aggressive	0.67	69	0.97	0.55

Recent work has shown relationships between histrionic traits and cocaine use (King et al. 1991). Using the structured interview for assessing personality disorder traits according to the DSM-III-R, a group of 200 male subjects (40 community controls, 70 patients in a long-term drug rehabilitation program, and approximately 90 other male psychiatric controls) were rated according to the severity of their Axis II disorder traits using the PDE. A principal component of analysis was performed on these 11 dimensions of Axis II traits, which demonstrated the presence of two unrotated components with eigenvalues greater than 1. Table 4 shows the factor loadings for each of the Axis II personality traits on these two factors.

Clearly, factor 1 is a general psychopathology factor involving a multitude of interpersonal and affective problems. It is highly loaded for borderline, paranoid, and narcissistic personality disorder traits. Factor 2 is bipolar, loaded at one extreme on histrionic personality traits and in the other direction on schizoid personality traits. In a subset of this group

TABLE 4. Personality Disorders Examination principal components analysis (N = 200).

Diagnosis Category	Factor 1	Factor 2
Paranoid	0.86	0.10
Dependent	0.69	-0.26
Avoidant	0.79	0.27
Antisocial	0.67	-0.13
Schizoid	0.46	0.80
Schizotypal	0.79	0.37
Compulsive	0.66	0.11
Histrionic	0.65	-0.50
Narcissistic	0.83	-0.32
Borderline	0.89	-0.05
Passive-aggressive	0.70	-0.20

(N= 72) who completed the ASI (McLellan et al. 1980), these two factor scores were correlated with measures of lifetime abuse of drugs. Lifetime abuse of cocaine was strongly associated with the second bipolar (his-trionic versus schizoid) factor ($r = -0.52$, $p < 0.0001$). Neither of the factors correlated with any of the other drugs of abuse, including opiates, amphetamines, marijuana, or ethanol.

On the basis of post hoc correlations with individual traits, those who are histrionic appear to have a longer use of cocaine ($r = 0.41$, $p < 0.0004$). Another demonstration of the interrelation among incentive motivation, DA activity, and personality was performed using community control subjects. In this preliminary study, 26 volunteers who were screened using the DSM-III-R Structured Clinical Interview (SCID), found to be free of Research Diagnostic Criteria (RDC) diagnoses, and were screened with the PDE to rule out Axis II personality disorder diagnoses, underwent a lumbar puncture. Log CSF levels of HVA were then correlated with the cluster B personality disorder traits as measured by the PDE. As shown in table 5, log HVA was significantly correlated with histrionic and antisocial per-sonality disorder features in this sample of control subjects. As hypothe-sized, histrionic traits were related to putative measure of incentive motivation. Moreover, mild antisocial traits also appeared to aggregate with heightened DA activity. Given the family studies data showing that antisocial and histrionic personality traits may overlap in familial trans-mission (Cloninger 1987), this study demonstrates that those traits may also overlap in this biological measure. It was concluded that these observations are in accordance with the proposed model of the interaction of abused drugs with personality and neurochemistry.

TABLE 5. HVA correlations with cluster B personality traits in normal subjects (N = 26).

Personality Trait	Correlation with log HVA
Histrionic	0.35*
Antisocial	0.36*
Narcissistic	0.19
Borderline	0.30

KEY: * = $p < 0.05$, one-tailed Pearson's.

DESIGN AND EXPERIMENTAL METHODS

Hypotheses Restated

The basic hypothesis for this proposal is that individual differences in the degree of vulnerability to cocaine craving are mediated by individual differences in the mesocorticolimbic DA system. As a result, individual differences in cocaine craving should be predictable by differences in measures of the mesocorticolimbic DA system, namely CSF-DASO4 and CSF-HVA. Moreover, it is hypothesized that individual differences in craving also are observable in other personality and behavioral measures known to be associated with the mesocorticolimbic DA system, specifi-cally histrionic features and motor activity. These measures may serve as noninvasive markers for susceptibility to cocaine craving and relapse after treatment. The findings from the proposed research could provide clinical measures that would help define patient subpopulations at increased risk of cocaine craving during abstinence. The assessment of covariance in motor activity and automated self-report measures of cocaine craving within individuals also could offer means to predict when an individual is at increased risk to crave. Such measures could help maintain patient abstinence from cocaine use and help prevent relapse after treatment.

General Design and Methods

Subject Selection. A total of 70 subjects for the proposed studies will be drawn from the patient population of a long-term, inpatient, drug rehabili-tation unit. All subjects are to be screened on the basis of two exclusionary principles: Subjects cannot have been diagnosed with AxisI disorders other than drug and alcohol dependence, and they cannot have any major medical problems, including a positive human immunodeficiency virus (HIV) status that would influence their participation in the study.

Fifty experimental subjects will be selected on the basis of a history of cocaine dependence taken from the history on admission. Twenty controls will be drawn from members of the patient population who are abusers of drugs other than cocaine. These patients are to be free of psychotropic medications, including cocaine, during the course of the study as verified by random breath and urine analysis. All subjects will have been inpatients on the ward and abstinent from drug use for a minimum of 6 weeks. Data from previous studies of patients on the same ward (Knoblich et al. 1992) demonstrated that nine

subjects who volunteered to receive a lumbar puncture were free of psychotropic medications, including cocaine, for an average of 28 weeks (ranging from 12 to 60 weeks).

Patients and controls will be age-matched since it is possible that dopaminergic functioning decreases with age (Gerner et al. 1984). Potential subjects will be informed of the nature of the research and their responsibilities, and they will be encouraged to inquire about the project. All selected subjects will certify their compliance with the proposed research guidelines by reading and signing consent forms.

Measurement of Dopaminergic Functioning. Twenty-five cocaine-dependent and 10 control subjects selected according to the criteria stated above will undergo lumbar puncture to measure CSF-HVA and CSF-DASO4 as assessments of dopaminergic functioning. These subjects will fast and remain in bed overnight before undergoing a lumbar puncture performed in the lateral decubitus position at 8:00. A 25 cc aliquot of CSF will be collected, immediately frozen, and stored at -80°C until the time of analysis. HVA will be measured using amperometric detection as previously described (Bankiewicz et al. 1990). Samples will be thawed and vortexed, and 300 micromolars (μM) of each sample will be mixed with 50 pmol of internal standard 3-ethoxy, 4-hydroxyphenylglycol (EHPG). Samples will be analyzed in a single run if possible. In previous studies, the intra-assay coefficient of variation (CV) was approximately 5 percent for each of the compounds of interest (Knoblich et al. 1992). In general, the interassay CV is approximately 10 percent. Measurement of DASO4 will be performed using a modification of high-performance liquid chromatography (HPLC) with the electrochemical detection procedure described by Mefford and colleagues (1983).

Measurement of Craving and Mood. Subjects will characterize their cocaine craving episode by self-assessments of their craving experiences using written questionnaires and a palmtop computer. Previous studies have demonstrated both reliability (Voris et al. 1991) and validity (Halikas et al. 1991) of these self-assessment procedures. Since craving appears to be relatively infrequent and of short duration (Halikas et al. 1991), patients will respond to questions administered by a pocket computer at 35 time points over a consecutive 5-day period. The computer will be programmed to beep seven times during the course of each day at times selected to coordinate with free times in the patients' therapy schedules.

At each interval, the subject will be asked about craving experience since the last report. If craving is reported, ratings are requested for the urge to use cocaine (1 to 10), subjective cause for the urge, degree of control over the urge (none to extreme), and means of resisting the urge. Next the subjects will be asked to rate four mood variables (10-point scale): happy-sad, anxious-relaxed, excited-calm, and agreeable-angry. These bipolar mood states were included in those found by Lorr and Wunderlich (1988) in studies of 210 high school boys that confirmed the presence of five mood factors in semantic space: cheerful-depressed, energetic-tired, good natured-grouchy, confident-unsure, and relaxed-anxious. Finally, the subject will also be asked to rate the chance of craving in the next 3 hours.

Answers to each question are registered by touching responses listed on the computer screen. Data will then be compiled and prepared for statis-tical analysis. Subjects will also complete an instrument to measure lifetime cocaine use (Gawin and Kleber 1986) and the ASI (McLellan et al. 1980) to assess drug use patterns.

Measurement of Personality, Psychiatric Diagnosis, and Drug Use. Each subject will be administered the PDE to determine diagnoses and symptoms assessment (Loranger et al. 1987), the SCID to screen for AxisI personality disorders (Endicott and Spitzer 1978), and the Eysenck Personality Inventory (EPI) (Eysenck and Eysenck 1964) to assess personality traits such as sociability, impulsivity, and neuroticism. On the day of the lumbar puncture subjects will be rated by one interviewer using the HRSD (Hamilton 1967). The results will be compiled for later statistical analysis.

Measurement of Activity. For the duration of the study each subject will wear an activity monitor on the wrist of the nondominant hand (Redmond and Hegge 1985). This device weighs about as much as a digital wristwatch, and poses about as much hazard to subjects. The activity monitor contains a piezoelectric accelerometer to measure wrist motion in three axes. This transducer provides a linear transformation of physical movement into an electronic signal that lends itself to analog processing, filtration, calibration, and adjustment using standard linear circuitry.

Relationship Between CSF Dopamine Metabolites and Cocaine Craving (Specific Aim 1)

Protocol. The clearest demonstration in humans of a relationship between CNS DA neurochemistry and cocaine craving would be the concurrent measurement of craving and DA activity. Twenty-five subjects who meet the exclusionary criteria, who also meet the SCID inclusionary criteria for cocaine dependence, and who have spent a minimum of 6 weeks off psychotropic or abused medications will be recruited. A separate sample of 10 control subjects who have never used cocaine and meet the other selection criteria will be recruited to form a contrast group of nonabusers of cocaine.

One week before the lumbar puncture all subjects will undergo an assessment of cocaine craving using the ASI to measure lifetime use and the QCH to record the indices of recent cocaine craving. They will also undergo an independent assessment of cocaine craving with the auto-mated behavioral questionnaire on the palmtop computer. The computer data will be used to create a sum score of number of cocaine craving attacks per day for each cocaine-abusing subject or, for those in the control group, the number of craving attacks for that individual's dominant substance of abuse.

Data Analysis. To demonstrate reliability of the measure for craving attacks, the number of attacks per day for the first 2 days of recording will be correlated across the 25 individuals with the number of attacks noted during the last 3 days of recording. Furthermore, the average number of craving attacks per day will be correlated with the composite craving score from the QCH to determine convergent validity.

The specific hypotheses to be tested are that CSF-HVA and CSF-DASO4 correlate with subjective measures of cocaine craving. Thus, the Ztrans-form of the three individual dimensions of the quantitative cocaine history that assess craving (current desire, imaginations of pleasant thoughts during the past month, and level of craving during the past month) will be added together and correlated with both CSF-HVA and CSF-DASO4. For the purpose of power calculation, a minimal correla-tional coefficient of 0.55 is assumed; this is compatible with published pilot data. For a power of 85 percent chance of detecting such a difference, a sample size of 25 subjects is required.

After testing the first-order correlation coefficients between craving and DA metabolite measures, multiple regressions will be performed using CSF-HVA and CSF-DA as dependent measures to be predicted by the self-report craving score and the frequency of craving recorded during the computerized behavioral assessment. This information will yield an estimate of the comparative utility of the two independent measures in predicting neurochemical differences.

Central DA Associations of Wrist Motor Activity

Protocol. A total of 25 cocaine abusers who participated in the lumbar puncture study (specific aim1) will be monitored for wrist motor activity before the tap. For the activity monitoring, the volunteers will wear the wrist actimeter on the nondominant arm. They will wear the monitor from 7:30 a.m. to 7:30 p.m. for a period of 5 consecutive days in order to ensure homogeneity of counting time. The actimeter will collect activity counts in 15-second epochs.

Data Analysis. For these 25 subjects, the stability of activity over time will be estimated by correlating the first 2 days of recording with the last 3days of recording in total mean hourly activity. CSF measures relevant to DA turnover, namely CSF-HVA and CSF-DASO4, will be used as esti-mates of CNS-DA activity. A multiple regression will be performed correlating these two metabolites with mean hourly wrist activity, indi-cating both the raw correlation coefficients and the relative contribution of CSF-HVA and CSF-DASO4 levels to variations in wrist motor activity. This study should indicate whether or not mean hourly wrist reflects variations in CNS DA functioning across individuals. Although the CSF-HVA and CSF-DASO4 measures are taken at a single time point (8:00), because of the slow clearance of these metabolites through the CSF the measures may in fact reflect a temporal integration of DA activity. Thus, it is plausible that the hourly averages in wrist motor activity may mirror CSF-DA metabolite levels.

Within-Subject Associations Between Motor Activity and Craving Attacks (Specific Aim3)

Protocol. The purpose of this aim is to investigate whether changes in motor activity occur within a person during naturally occurring craving attacks while under the conditions of long-term abstinence. For this study, the full sample of 50 recruited cocaine addicts (specific aim2) will wear the wrist monitor and use the palmtop computer to assess craving frequency and intensity. All 50 subjects will be

instructed to press the event marker on the monitor at the time the individual is first aware of a craving attack. The data will be recorded for 5 consecutive days.

Data Analysis. In this within-subject design, locomotor activity will be averaged over the 15-second bins for a 30-minute interval preceding a reported craving episode and over the 30-minute interval following a craving episode. These two measures will be compared with motor activity before and after a neutral period, at the same time on a different day, randomized to either the previous day or the day following the craving event. Thirty-minute intervals have been chosen to serve as a preliminary measure of the mean motor activity for the periods imme-diately preceding and following craving. Since the protocol measures motor activity every 15 seconds, this interval may be adjusted in future studies to provide better approximations of motor activity surrounding the onset of craving.

A repeated-measures analysis of variance (ANOVA) will be performed to test whether there is an increase in activity during a craving attack compared with two consecutive 30-minute periods at the same time on a nonevent day. It is hypothesized that there will be an increase in motor activity during a craving attack that may reflect a CNS release in DA during naturalistic craving events.

Studies Testing the Relationship Between Cocaine Craving and Axis II Personality Disorder Traits (Specific Aim 4)

Protocol. In this section, the full cohort of 50 cocaine-abusing subjects will be used. These experiments will refine the relationship between cluster B personality disorder traits that have been linked to enhanced DA turnover (histrionic personality disorder traits) and cocaine craving. The inclusion and exclusion criteria are the same as those outlined in the general methods section. The 50 subjects will be long-term cocaine abstinent (> 6 weeks). All of them will be given the PDE to assess AxisII personality disorder traits; the Eysenck Personality Inventory to measure personality traits such as sociability, impulsivity, and neuroti-cism; the ASI; the QCH for recording patterns of drug use; and the SCID for formal psychiatric diagnoses. In addition, all subjects will wear the wrist activity monitor and carry the palmtop computer to rate the temporal occurrence of a cocaine craving attack.

Data Analysis. Because of the large sample size, data analyses in this section will be optimally used to reduce the number of cocaine

craving variables studied. In particular, a principal component analysis with varimax rotation will be performed on the three craving variables from the QCH, the average number of daily craving attacks, and the average reported intensity of urge of craving for the craving attacks. The resulting factors with eigenvalues > 1 will be correlated with histrionic traits with the expectation that there will be a positive association between the factor scores and histrionic traits. A multiple regression will also be performed tofind the best predictors for histrionic personality traits among the craving factors. For these experiments, a minimal correlation coefficient of 0.40 isexpected to correlate histrionic traits with the craving factors. At 85per-cent power of detecting such difference, a sample size of 53 is required.

Expected Results

Each of the specific aims and hypotheses of the proposed research has been designed to examine the neurochemical and behavioral factors that influence cocaine craving. Previous findings, literature on animal models of incentive motivation, and some findings in human subjects by other researchers suggest that heightened corticomesolimbic DA activity mediates cocaine craving. Between subjects, individuals prone to cocaine craving are expected to demonstrate elevated measures of dopaminergic functioning. Baseline levels of CSF-HVA and DASO4 measured in cocaine-abusing subjects should correlate with the frequency of craving recorded using the palmtop computer and a composite score of the three individual dimensions of cocaine craving (current desire for cocaine, imaginations and pleasant thoughts of cocaine during the past month, and level of cocaine craving during the past month) assessed on the QCH.

Such findings would support previous work that has shown that, within a group of nine long-term abstinent cocaine abusers, CSF-HVA was positively correlated with the composite craving score from the QCH ($r_s=0.61$, $p < 0.05$), but was not associated with other measures of cocaine use or with depression (Knoblich et al. 1992). The multiple regression using CSF-HVA and CSF-DA as dependent measures may also demonstrate the ability of levels of CSF-DA metabolites to predict the likelihood that individuals will crave cocaine, which may prove a useful tool for prognosis and treatment.

Personality features shown to be associated with CSF-HVA and cocaine use may also correlate with the frequency and degree of cocaine craving. Previous findings that histrionic individuals appear to have a longer use of cocaine ($r = 0.41$, $p < 0.0004$) (King et al.

1991) and that log HVA was significantly correlated with histrionic and antisocial personality disorder features in a sample of control subjects suggest that factor scores derived from a principal component analysis and the three craving variables from the QCH will correlate positively with histrionic traits from the PDE. These observations would be in accordance with the proposed model of the interaction of abused drugs with personality and neurochemistry.

This study also proposes to assess the ability of a noninvasive, readily accessible measure, peripheral motor activity, to reflect CNS-DA activity both between individuals and within a subject over time and to investi-gate whether changes in motor activity occur within a person during naturally occurring craving attacks. Substantial evidence in the literature on animal models of incentive motivation indicates that locomotor activity is associated with CNS dopaminergic activity. Thus, it is expected that CSF-HVA and CSF-DASO4, as estimates of CNS-DA activity, will correlate average wrist activity in human subjects. Within subjects wrist motor activity is expected to be elevated during periods when subjects experience craving compared with periods when they do not. Such findings would be of particular significance for the design and implementation of noninvasive means for performing prognostic assess-ments of cocaine abusers experiencing craving, which could reduce relapse among abstinent individuals.

PUBLIC HEALTH SIGNIFICANCE

The treatment of cocaine abuse remains an important but difficult task for this socially devastating condition. In recovering abstinent individuals, cocaine craving has been associated with relapse. An important inroad into discovering novel methods of treatment is the investigation of biological factors that predict differences between individuals in cocaine craving. Results from animal research indicate the importance of the corticomesolimbic DA system in the reward/reinforcing effects of cocaine self-administration.

This proposed study will apply these concepts from animal studies to investigate the relationship between DA function and cocaine craving in long-term abstinent cocaine abusers. As previously discussed, research in human subjects, in concert with the data from animal models, suggest a cluster of interrelationships between motor activity, CNS dopaminergic functioning, personality features, and cocaine craving. The present research focuses on elucidating these

relationships in both between-individual and intra-individual paradigms. It is hoped that this work will generate potential measures such as motor activity and CSF DA metabolite levels that can be used as baseline measures in longitudinal studies of high-risk individuals prior to substance abuse. Furthermore, the findings may reveal motor activity to be an acute noninvasive measure of CNS dopaminergic activity, a reflection of individual propensity to experience craving, or both. Such findings could lead to the development of a useful tool for the prevention of relapse among abusers of cocaine and other substances.

However, there remain some specific concerns about the measures to be tested as correlates of cocaine craving. First, lumbar CSF-HVA and CSF-DASO4 may not strongly reflect DA activity in the regions of interest, the corticomesolimbic system. To the extent that large sample sizes allow for some component of CSF-DA measures to reflect variations in incentive motivation, this problem can be partially overcome. Imaging studies utilizing specific markers of DA activity in localized regions may be the method of choice for reducing such problems. However, CSF measures and the monitoring of motor activity may offer insight into the optimal craving measures to be used in future studies.

An additional conceptual limitation arises from the multiple systems per-spective of neurobiological functioning. As with models from depression (Potter et al. 1991), monoamine systems can be perturbed in a variety of ways to produce similar effects. Interactions between DA and serotonin may be important in the regulation of cocaine self-administration. Furthermore, interactions with opiate systems (Mello 1991) may also be relevant to cocaine use in animal models. Although the methodology is not sufficient to address opiate interactions, other monoamine metabolites such as 5-hydroxyindoleacetic acid (the major metabolite of serotonin) will be measured through HPLC analysis. Thus, these studies will offer additional pilot data potentially exploring the relationships among serotonergic and dopaminergic functioning and cocaine craving.

Early theoretical investigation of cocaine craving has been influenced primarily by the DA depletion hypothesis, which asserts that a hypo-dopaminergic state underlies the dysphoric aspects of abstinence leading to anhedonia, craving, and subsequent drug use (Dackis and Gold 1985; Gawin and Kleber 1986). Another model of cocaine craving (Marlatt 1987) dissociates craving from the dysphoric effects of withdrawal, and conceptualizes it as a motivational state initiated by

external or internal events that reproduces the primary appetitive quality of the state induced by drug self-administration. Much contention and confusion exists concerning these two models of cocaine craving.

The proposed study builds on previous research in human subjects and animal models and could clarify the importance of appetitive and aversive components in cocaine craving. The relationships between personality features, mood, motor activity, and cocaine craving will help distinguish these components of craving within individuals during periods of craving compared to periods without craving and/or expose individual differences that predict the likelihood to crave.

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Commentary on "Neurochemical Predictors and Correlates of Vulnerability to Cocaine Use" by-King and Flowers

Eric Hollander, Lisa Cohen, and Don Stein

SUMMARY

This proposed study concerns the neurochemical and behavioral factors that influence cocaine craving. The researchers hypothesize that heightened mesolimbic dopamine (DA) activity leads to cocaine craving and is associated with both histrionic behavior and increased sensitivity to the rewarding aspects of cocaine use. Finally, they hypothesize that heightened DA activity is reflected in increased motor activity. These points may be summarized as follows: Increased mesolimbic dopamine function is associated with increased cocaine craving, histrionic behavior, increased reward, and increased motor activity. Cocaine craving is associated with increased DA and homovanillic acid (HVA) in cerebro-spinal fluid (CSF), histrionic behavior, and increased motor activity. Increased DA and HVA in CSF is associated with increased motor activity.

The investigators therefore plan to determine whether levels of DA and HVA in CSF correlate with cocaine craving, whether histrionic traits as defined in the "Diagnostic and Statistical Manual of Mental Disorders" (3ded. rev.) (DSM-III-R) correlate with cocaine craving, whether increased motor activity correlates with cocaine craving, and whether CSF DA and HVA levels correlate with increased motor activity.

STRENGTHS OF THE PROPOSED RESEARCH

The authors of this proposal have made a series of bold hypotheses, and they are to be commended for the originality and novelty of their thinking, as well as for the thorough and logical way in which they support their arguments. The overarching idea—that individual differences in dopaminergic function are reflected not only in cocaine craving but also in personality traits and physiological measures—

integrates current thought on the neurobiology of reward, cocaine abuse, and personality. The strengths can be summarized as follows:

1. Individual differences in DA function are associated with assessment of cocaine craving, personality traits, and physiological measures.

2. Theoretical framework integrates thoughts on the neurobiology of reward, cocaine abuse, and personality.

3. Promising preliminary data are presented.

4. Methodology includes study of long-term inpatient substance abusers, which yields a better control of variables such as CSF measures.

The appeal of integrative biologically based approaches to psychiatric phenomena is readily understood. Several biological psychiatrists have criticized their field for its often limited approaches. The authors of this proposal, on the other hand, offer their hypotheses within a systematic and ambitious framework. They cite the work of Cloninger and Siever, both of whom have also made pioneering attempts to construct inte-grative approaches to the psychobiology of Axis I and II disorders.

WEAKNESSES OF THE PROPOSED RESEARCH

The appeal of the systematic and integrative biologically based approaches should be balanced by an acknowledgment of the difficulties faced. Approaches (such as the one taken in these proposed studies) that empha-size individual differences in a particular neurotransmitter run the risk of being overly reductionistic. Furthermore, approaches that situate unitary biological differences as the basis of a broad range of heterogenous behaviors (e.g., from cocaine use to extroversion) run the risk of ignoring a variety of other factors (biological and psychological) that may account for their expression. Weaknesses and potential difficulties with these studies are summarized as follows:

1. Single neurotransmitter approach is reductionistic.

2. Single biological difference is correlated with heterogeneous behavior (e.g., cocaine use with extroversion) that excludes multiple

factors and interactions, for example, between biological, psychological, and sociological domains.

3. Lumbar CSF levels of DA and HVA are measured, but the meso-limbic DA systems contribute only a small effect in the lumbar tap.

4. There is no indication of comparing ratios of CSF metabolites (e.g.,HVA and 5-hydroxyindole acetic acid (5-HIAA)).

5. Long-term cocaine use may modify DA uptake.

6. Cocaine craving measures need to be reliable.

7. Concept of cocaine craving attacks has not been generally accepted.

8. Sociopathy is not identical to histrionic behavior, but terms are used interchangeably.

9. Motor activity is not solely influenced by DA activity. For example, attention deficit-hyperactivity disorder (ADHD) may influence both motor activity and substance abuse.

10. Motor activity measures need to be valid and standardized (e.g.,-comparison between wrist monitor and nurse ratings).

Despite the difficulties, some of which are common for proposals of this type, it is clear that the authors have a track record of providing empirical validation of their theoretical claims. In particular, they have preliminary data on the correlation of CSF HVA and cocaine craving, of CSF HVA and histrionic traits, and of histrionic traits and motor activity. This lends support to the proposed studies. In fact, the authors acknowledge several methodological limitations to their proposal. First, lumbar CSF DA and HVA may not strongly reflect mesolimbic DA activity. Evidence is needed, therefore, to establish the extent to which the CSF measures reflect the intracerebral ones. CSF studies remain a valuable approach, yet they need to be understood in terms of the context of their total contribution.

The authors also acknowledge the limitations of focusing on a single neurotransmitter system, and they propose to measure monoamine metabolites other than those of DA. This is particularly timely in view of recent work suggesting that measuring patterns of CSF metabolites is more meaningful than focusing on any particular concentration

level (Potter and Manji 1993). It is also important in view of recent work emphasizing the involvement of the serotonin system in cocaine craving.

The effects of long-term cocaine use itself lead to difficulties in studying the DA system. Thus, long-term cocaine use could potentially modify the parameters of DA uptake. The authors plan to use statistical methods to minimize this effect. This is a difficult problem, and it would be helpful to know the extent of the difficulty from preliminary data.

Finally, measurements need to be selected for reliability and validity. In the measurement of cocaine craving, several groups have succeeded, but the reliability should be checked in the authors' laboratory using the same questions. Data on this would be necessary. Further details on cocaine craving attacks are needed. The issue of personality traits also needs clarification. For example, how do histrionic traits compare to antisocial personality disorder and other sociopathy? It is noted in the proposal that the histrionic factor is loaded primarily on histrionic, borderline, and dependent traits. Further, it is noted that CSF HVA is correlated with antisocial features in control samples. These personality and sociopathy connections to biological measures need support.

ALTERNATE STRATEGIES

Because of the theoretical and empirical concerns regarding the correlation between dopaminergic function and motor activity, it might be appropriate to consider the role of hyperactivity in this context. The relationship between attention deficit disorder (ADD) and dopaminergic function should be assessed, perhaps by administering Ward and colleagues' (1993) recent scale that measures childhood ADD in adult subjects. It has been found (Manuzza et al. 1991) that a subgroup of children with ADD become substance abusers. Finally, previous work has used nursing assessments as measures of motor activity; this might be supplementary or an alternative to wrist movement. Some alternate and additional ideas are summarized as follows:

1. Use DA challenges (e.g., apomorphine) to elucidate dopaminergic function instead of CSF levels.

2. Study serotonin function also, using both CSF metabolite measures (5-HIAA) and challenges (e.g., m-chlorophenylpiperazine (mCPP) or fenfluramine).

3. Assess ADD with the Wender scale for childhood ADD (Ward et al. 1993).

4. Obtain functional measures of DA with imaging positron emission tomography (PET).

5. Study homogenous personality-disordered patients such as those with borderline personality disorder or antisocial personality disorder.

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Vulnerability to Substance Abuse in Eating Disorders

Walter H. Kaye and Lucene Wisniewski

STATEMENT OF THE PROBLEM

Two types of eating disorders, bulimia nervosa in normal-weight bulimic (NWB) women and restricting-type anorexia nervosa (RAN), may provide insights into permissive or protective factors contributing to psychoactive substance use disorders (PSUD) in humans. These two eating disorders, while often grouped together, are at opposite extremes for rate of PSUD. Substance abuse is common in NWB patients and their family members, but rare in RAN patients. In addition, NWB and RAN are at opposite extremes in terms of pathologic feeding style and many behavioral traits (table 1). NWB individuals are impulsive, labile, may be overly sensitive to external cues, and have poor control of eating. In contrast, persons with RAN are rigid and perfectionistic, restrict eating, and are insensitive to internal and external cues.

Studies in humans at risk for PSUD have identified factors that may play a contributory role in the pathogenesis of PSUD. These factors include behavioral undercontrol, emotionality, and sensitization and tolerance to the reinforcing effects of drugs. Thus, NWB individuals may have many vulnerability factors for PSUD. It is provocative to speculate that factors that are the opposite of these vulnerabilities may protect RAN individuals from PSUD.

Specific Aim 1

This proposal characterizes factors that may contribute to the high rate of PSUD in NWB women. Specific Aim 1 will assess factors such as behavioral undercontrol; personality characteristics such as novelty seeking; and emotionality, especially unstable mood states. Four groups of women will be studied: NWB with a lifetime diagnosis of PSUD (+PSUD), NWB without a lifetime diagnosis of PSUD (-PSUD), RAN women, and healthy controls. This study hypothesizes that the behavioral factors are exaggerated in the +PSUD NWB women compared with the PSUD NWB women, and that both groups of NWB women have greater behavioral undercontrol and unstable moods than control women,

TABLE 1. Comparison of RAN and NWB women.

Restrictor AN (RAN)	Normal Weight BN (NWB)
Restricted eating	Binge eating
Denial of weight loss	Ashamed of bingeing
4+ fear of fat	1+ fear of fat
4+ exercise	Normal exercise
Rigid, obsessive, perfectionistic	Labile, mood extremes, impulsive
Substance abuse - rare	Substance abuse - common
Increased 5-HT activity	Reduced 5-HT activity

whereas RAN women have rigid and inflexible moods and enhanced self-control compared with control women or NWB women.

Specific Aim 1a. This study proposes to characterize which, of a number of paper-and-pencil self-assessment instruments, best quantifies the risk factors of impulsivity and personality in subgroups of women with eating disorders in terms of vulnerabilities to PSUD.

Specific Aim 1b. It also aims to improve the measurement of the constructs for this patient group by identifying the best items from existing scales in order to develop a revised behavioral under/overcontrol scale more specific for eating-disordered women.

Specific Aim 1c. In addition, this study will determine whether NWB women have disturbances of impulse control as reflected by laboratory assessments such as the Go/No-Go, Continuous Performance Test, and Matching Familiar Figures Test (MFFT). The ability to test behavioral undercontrol would be of much importance in future studies of the behavioral expression of risk factors in humans with PSUD.

Specific Aim 1d. This study also will test the hypothesis that NWB women will show much greater variance of negative and positive affects than RAN patients with respect to hourly ratings over a 2-day period. Unstable emotionality may be a contributory risk factor to PSUD in NWB women.

Specific Aim 2

The hypothesis is that the clinical presentation of disturbances of impulse control and mood stability reflects a more pervasive disturbance of reactivity in RAN and NWB subjects that may shed light on why differences in vulnerabilities to substance abuse occur.

Specific Aim 2a. Since preliminary data suggest that NWB women may become sensitized to the reinforcing effects of food intake. This study will replicate and extend this work, since the sensitization of reinforcing drug effects is central to current addiction theory. In contrast, this study hypothesizes that RAN women will rapidly habituate to food stimuli and thus may be insensitive to the reinforcing effects of food or drugs.

Specific Aim 2b. This study will also test the hypothesis that disturbances found as a response to a food stimulus will generalize to nonfood-related stimuli and NWB subjects will become sensitized (in terms of heart rate and skin conductance response) to nonfood stimuli such as auditory tone, whereas RAN subjects will show increased habituation.

Specific Aim 3

Other factors will be explored that may contribute to extremes of substance abuse in NWB subjects. These factors include NWB women's perception of their motivation, expectancy, and self-efficacy. In addition, the study will determine whether the severity of PSUD symptoms correlates with frequency of bingeing and purging and other eating disorder-related symptoms in NWB subjects.

BACKGROUND AND SIGNIFICANCE

The reasons that people engage in PSUD behaviors remain complex and uncertain. This study will develop the thesis that the eating disorders anorexia nervosa (AN) and bulimia nervosa (BN) may provide models for understanding permissive and protective factors underlying development of PSUD in humans. While AN and BN appear superficially similar, they are actually at opposite extremes in terms of behavioral characteristics. Behaviors in NWB individuals are consistent with some data about how pathophysiology may be related to risk for PSUD. In contrast, the study of behavior in RAN

individuals may generate insight into why some people are resistant to PSUD.

Since PSUD will likely prove to be a heterogeneous disorder, relationships between behavior and psychopathology may be obscured. In contrast, AN and BN are relatively homogeneous psychiatric disorders with stereotypic behaviors and relatively consistent physiologic abnormalities. Thus, the eating disorders may serve as an excellent model with which to understand and contrast a group of risk or protective factors.

Risk Factors for PSUD

While there is limited understanding of risk factors that contribute to the onset of PSUD, certain behaviors that occur in NWB individuals have been theoretically implicated.

Behavioral Undercontrol. Sher (1991) reviewed prospective and archival studies suggesting that traits related to behavioral undercontrol such as impulsivity, rebelliousness, and aggression also appear to characterize the prealcoholic male. These traits appear to be common in NWB women, although it is not certain whether they are associated with only those NWB subjects who develop PSUD or are also present in NWB subjects without PSUD.

Negative Mood States or Emotionality. A tendency to experience negative affective states has been associated with both clinical PSUD and a vulnerability to PSUD (Tarter 1988), particularly for women (Jones 1971). NWB patients commonly have negative mood states and tend to be mood unstable. Exaggerated ingestive behaviors (food, substance abuse) in NWB women may be an attempt to externally control mood states and suppress negative mood extremes that cannot be internally modulated.

Personality. Cloninger (1987a) has postulated that different types of alcoholism are associated with different personality profiles. Type I alcoholism is characterized by low novelty seeking, high harm avoidance, and high reward dependence; it is associated with binge drinking and may be more prevalent in females. Type II alcoholism is characterized by high novelty seeking, low harm avoidance, and low reward dependence; it is associated with antisocial behavior and may be more prevalent in males. Preliminary data from NWB subjects (Bulik et al. 1994) do not correspond to either type of alcoholism,

although NWB subjects with PSUD were higher in novelty seeking than NWB subjects without PSUD.

It is hypothesized that the clinical presentation of impulse control disturbances in NWB women is a reflection of a more pervasive cognitive disturbance that may shed light on why vulnerabilities to PSUD occur. NWB patients may be prone to binge eating and engage in substance abuse for several reasons. For example, they may be overreactive to environ-mental stimuli since they tend to be mood unstable. Exaggerated ingestive behaviors (food, substance abuse) may be an attempt to externally control mood states and suppress negative mood extremes that cannot be internally modulated. While this area is in its infancy and is somewhat controversial, there is evidence (Casper 1990; Casper et al. 1992) that other measures of personality may differentiate RAN from NWB subjects.

Sensitization. Preliminary data suggest that NWB subjects may have increased sensitization to the reinforcing effects of food intake. The intent is to replicate and extend this work since the sensitization of reinforcing drug effects is central to current addiction theory (Stewart et al. 1984; Wise and Bozarth 1987). In contrast, RAN subjects are rigid, perfectionistic, and insensitive to internal cues. It is hypothesized that RAN subjects will rapidly habituate to stimuli and thus may be insen-sitive to the reinforcing effects of food or drugs.

Differences Between Anorexia and Bulimia Nervosa

Patients with eating disorders can be subdivided by eating behavior and psychopathological characteristics (Garner et al. 1985; Halmi and Falk 1982; Herzog and Copeland 1985; Strober et al. 1982). The best known eating disorder is AN, whose most distinguishing characteristic is severe emaciation ("Diagnostic and Statistical Manual of Mental Disorders," 3d edition revised (DSM-III-R)) (American Psychiatric Association 1987). Two types of consummatory behavior are seen in AN. Restrictor anorexics lose weight by pure dieting, with no history of bingeing or purging, and are classified as restrictor anorexics in this proposal. Patients with BN remain at normal weight (i.e., NWB) and never become emaciated. That is, they maintain a body weight above 85 percent of average body weight (ABW) (Fairburn and Cooper 1982; Garner et al. 1985; Pyle et al. 1983). There are at least 10 times as many patients with BN as with AN (Halmi et al. 1981; Pope et al. 1983; Stangler and Printz 1980). These patients periodically binge and purge, usually by vomiting or laxative use. There is also a third group of BN patients with AN who

share attributes of both NWB and RAN, but they will be excluded from this study in order to characterize two most extreme subgroups.

Substance Abuse in Eating Disorders

Several lines of evidence suggest a link between NWB and PSUD (Vandereycken 1990). In contrast, AN appears to be associated with a much lower incidence of PSUD (Brisman and Seigel 1984 ; Hudson et al. 1983a; Laessle et al. 1989; Stern et al. 1985). Studies of NWB women using contemporary diagnostic criteria report a high incidence of PSUD (table 2). Hudson and colleagues (1983b) found a 22 percent incidence of alcohol abuse or dependence and a 31 percent incidence of any sub-stance abuse. Mitchell and colleagues (1985), in a study of 275 NWB women, found that 23 percent had a history of alcohol abuse and 18percent had prior treatment for chemical dependency. In other studies, the incidence of substance abuse has ranged between 23 percent and 49percent of NWB women (Bulik 1987b; Hudson et al. 1987; Laessle et al. 1989). Bulik and colleagues (1992) (table 3) found that NWB patients used significantly more licit (alcohol, cigarettes, laxatives, diuretics) and illicit drugs (amphetamines, cocaine, marijuana) than RAN patients. In comparison, PSUD is uncommon in women with RAN. For example, a 6percent lifetime prevalence of PSUD was found in RAN women, compared with 50 percent in BN ($p < 0.01$) (Bulik et al. 1992).

A number of studies have shown an increased rate of PSUD in relatives of BN or NWB patients. For example, in studies of relatives, Hudson and colleagues (1987) found that 16 percent of the first-degree relatives of BN probands had a history of alcohol abuse or dependence, significantly more than the controls (5 percent). Kassett and colleagues (1989) found alcoholism in 28 percent of first-degree relatives of BN probands, significantly more than the 14 percent incidence found in relatives of control women. In proband studies, most (Bulik 1987b; Mitchell et al. 1988) but not all authors (Stern et al. 1985) have reported that between 33percent and 83 percent of BN women have at least one close relative with alcoholism.

Bulik (1987a) studied 35 BN and 35 control women using a semi-structured family history interview. Significantly more (60 percent) BN patients had one or more first- and second-degree relatives with a history of alcoholism than controls (20 percent). While not as well studied, PSUD appears to be less common in family members of patients with RAN (Hudson et al. 1987).

TABLE 2. Incidence of alcohol abuse or dependency in patients with eating disorders.

STUDY	BN	AN	NC
Hudson et al. 1983a	22%	6%	N/A
Mitchell et al. 1985	23%	N/A	N/A
Hudson et al. 1982	36%	N/A	11%
Bulik 1987a	49%	N/A	9%
Laessle et al. 1989	19%	0%	N/A

KEY: N/A = not applicable (no data reported).

Clinical Phenomenology in NWB—Similarities to Substance Abuse

Clinically, many investigators have noted that NWB patients' thoughts about bingeing and purging resemble addiction-like behavior; such thoughts include craving, preoccupation with obtaining the food, loss of control, adverse social and medical consequences, ambivalence toward treatment, and risk of relapse (Bulik 1987a; Hatsukami et al. 1984;

TABLE 3. Comparison of licit and illicit substances.

	AN	BN	P
Number	27	42	
Age	20	22	NS
Cigarettes	6%	52%	0.002
Alcohol	11%	45%	0.003
Caffeine	74%	86%	NS
Laxatives	18%	62%	0.0001
Diuretics	7%	33%	0.01
Amphetamines	8%	30%	0.03
Cocaine	4%	14%	0.08
Marijuana	15%	45%	0.01

KEY: NS = not significant.

SOURCE: Bulik et al. 1992.

Mitchell et al. 1988). Bingeing behavior produces a brief reduction in stress and tension that is similar to intoxication (Johnson and Larson 1982; Kaye et al. 1986). One study of alcoholics with and without NWB reported that many NWB patients experienced negative emotions after binge eating or vomiting and felt that only drunkenness allowed them to sleep afterward (Suzuki et al. 1993). In another study (Rand et al. 1986), NWB patients reported that they drank alcohol to avoid eating, to blot out reality, and to feel calm and sexually relaxed.

Comorbid Behavior and Personality in Eating Disorder Patients

A considerable number of studies have found a high incidence of concurrent depressed mood in patients with RAN and NWB and a high rate of depression in their family members (Gwirtsman et al. 1983; Hatsukami et al. 1984; Herzog and Copeland 1985; Hudson et al. 1983a; Pope et al. 1983). Such findings have led investigators to hypothesize that eating disorders are a variant of major affective disorders (Hudson et al. 1983a, 1983b). However, it should be noted that other evidence such as clinical phenomenology, antidepressant response, biological correlates, course, and outcome yield limited support for the overarching hypothesis that RAN and NWB are variants of major affective disorders (Rothenberg 1988; Strober and Katz 1988; Swift et al. 1986). It is likely that a considerable number of the depression and anxiety symptoms found in ill RAN and NWB patients is secondary to malnutrition.

Recent data raise the hypothesis that there are certain traits of personality that persist in RAN and NWB (Kaye and Wisniewski, unpublished data). These traits are at opposite extremes. RAN individuals tend to be obses-sional and concerned with perfection, symmetry, and exactness. In com-parison, many NWB individuals tend to be more labile and impulsive. Such symptoms may contribute to different rates of PSUD in these two disorders.

The Anger, Irritability, Assault Questionnaire (AIAQ) (Coccaro et al. 1991), a measure of irritability, mood lability, and assaultive behavior, was administered to 24 NWB women and 10 controls (Weltzin 1993). NWB and control women were of similar ages (24±5 versus 22±4 years) and weights (101 percent versus 99 percent ABW). Bulimics reported higher levels of irritability/mood lability as children ($p < 0.02$), adolescents, and adults ($p < 0.01$), higher levels of assault as adolescents ($p < 0.01$), and a trend toward higher levels of assault as adults ($p < 0.07$) compared with controls. In addition, NWB women

with past suicide attempts (N = 7) showed a trend ($p < 0.06$) toward having higher irritability scores compared with NWB women with no past suicide attempt. Furthermore, the NWB subjects with a clinical diagnosis of borderline personality disorder (N = 5) had a trend toward higher mean scores on irritability/mood lability as adolescents (19±6 versus 12±3, $p=0.07$) and adults (19±5 versus 13±4, $p= 0.09$) than those without borderline personality disorder (N = 4). These data confirm that NWB women have higher ratings of irritability, mood lability, and aggressive behavior compared with controls.

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al. 1989), an interview that rates the severity and type of symptoms in patients with obsessive-compulsive disorder (OCD), was administered to patients with RAN-excluding symptoms (obsession, compulsion) pertaining to core RAN symptoms. In terms of impairment, interference, and intensity of current obsessive and compulsive symptoms, both ill (20±8) and recovered RAN women (9±8) had significant elevations in ratings for severity of OCD symptoms compared with controls (3±4), although recovered RAN women had lower scores than ill RAN women. However, both ill and recovered RAN women tended to have similar target symptoms of OCD that particularly concerned a need for symmetry and ordering/arranging, while these symptoms were rarely endorsed by control subjects. Furthermore, these target symptoms found in RAN are different from those found in patients with OCD or NWB. While NWB women have elevated Y-BOCS scores, those scores are significantly lower than ill RAN women and the patterns of symptoms are different. Whether such measures provide the best discrimination between RAN and NWB in terms of PSUD-related risk factors remains uncertain.

Habituation and Sensitization

One means of assessing an individual's responsiveness to stimuli is to measure the response to repeated stimulus presentations. Repeated exposure to a stimulus may result in one of two response patterns: habituation or sensitization. Habituation involves response decrements to repeated stimulus presentations and has been demonstrated with many types of stimuli and many response systems such as repeated visual stimuli on heart rate (Adkinson and Berg 1976), repeated auditory stimuli on the event-related potential (Lammers and Badia 1989; Megela and Teyler 1979; Polich 1989) and measures of skin conductance response (Kimmel and Bevill 1985), localized head-turning reflex (Zelazo et al. 1984), and heart rate (Chang and Trehub 1977). The response decrement indicative of

habituation can be recovered by the presentation of a novel stimulus (Wagner 1979). The demonstration of dishabituation or response recovery illustrates that the attenuated response over repeated presentations cannot be attributed to neural adaptation or fatigue. Sensitization, or response augmentation resulting from repeated stimu-lation, is also a universal phenomenon (Kalivas and Barnes 1988).

Habituation to food stimuli is consistent with the phenomenon of sensory-specific satiety (Rolls et al. 1988). In sensory-specific satiety, the pleasantness of a particular food decreases as it is eaten, but pleasant-ness remains for other foods having different sensory qualities. Previous research linking sensory-specific satiety and habituation has shown that repeated presentation of a food stimulus reliably results in habituation of both the salivary response and hedonic ratings in normal (control) men (Epstein et al. 1992a; Wisniewski et al. 1992) and women (Epstein et al. 1993a, 1993b). Related neurophysiological research in primates has shown that, in response to repeated presentations of food stimuli, food acceptance decreased. Likewise, neurons in the lateral hypothalamus, substantia innominate, and caudolateral orbitofrontal cortex decrease, and responsiveness of those neurons and food acceptability recover with presentation of a new food (Rolls et al. 1986, 1989). These electro-cortical response patterns are consistent with habituation and response recovery, which cannot be accounted for by sensory adaptation or fatigue.

Limited available data raise the possibility that NWB patients fail to develop habituation to food stimuli. Both Rolls and colleagues (1992) and Rodin and colleagues (1990) have found that NWB women do not experience a normal reduction in the pleasantness of a food after eating a large amount of it. Preliminary data also suggest that NWB women have disturbances in habituation to food stimuli. Control women (N = 15) had a significant decrease in the salivary response to food stimuli over eight trials compared to baseline secretion of saliva. In contrast, the NWB women (N=15) did not show such habituation. In fact, they showed a pattern more consistent with sensitization since saliva levels increased slightly. This difference between groups was significant [$F_{7,196} = 2.97$; $p < 0.006$].

This finding is of much potential interest in understanding why NWB women are vulnerable to PSUD and overeating. Clinically, it is common that NWB women describe losing control and "spacing out" when eating or abusing substances. It may be that they are

physiologically unable to inhibit their behavior because they do not habituate normally. Rather, they may become sensitized to reinforcing stimuli and thus vulnerable to overindulging in food and abusing substances.

There are fewer data examining these relationships in RAN patients. One study found that RAN patients reported a significant decrease in pleasantness after eating a food, but consumed less food than control subjects, suggesting it took less for RAN subjects to become satiated on a specific food relative to normal subjects (Rolls et al. 1992).

The intent is to replicate these preliminary data and extend these findings by determining whether such disturbances of habituation extend to other modalities and whether such disturbances persist after recovery.

Additional Characteristic Behaviors

Comparison of NWB With and Without PSUD. Bulik and colleagues (1994) compared the characteristics of 13 +PSUD NWB women and 19 -PSUD NWB women (table 4). These two groups were similar in terms of age, age at onset of NWB, and current weight. There were no differences between groups on the Eating Disorder Inventory (EDI) or on the Beck Depression Inventory (BDI). On Cloninger's Tridimensional Personality Questionnaire (TPQ), +PSUD NWB individuals scored significantly higher on novelty seeking but had similar scores for harm avoidance and reward dependence. In the NWB subjects, novelty seeking and harm avoidance scores were considerably higher in comparison with general population norms for caucasian women in this country. High novelty seeking is associated with thrill seeking, impulsivity, intolerance for monotony, and a quick temper. These data confirm clinical reports of impaired impulse control in NWB subjects and suggest that this characteristic is even more marked in NWB subjects with comorbid PSUD.

Matching Familiar Figures Test. It is important to determine whether standardized tests might measure perfectionism, exactness, and constraint in RAN, and impulse dyscontrol and lability in NWB. Thus, the MFFT was administered. In this paradigm, subjects are given a target picture of an object and are then asked to determine which of six or eight other pictures is the exact match of the target picture. All the matched pictures resemble the target picture. One picture is exactly the same as the target picture, and the rest have subtle differences. The subjects' time to determine a match (latency) and the number of mistakes (errors) are measured.

TABLE 4. Study design.

	Day A	Est time (min)	Day B	Est time (min)
8-11 a.m.	AIAQ, BDHI, MPS, MPQ, EDI, BDI, STAI	180	I7, AEQ, EDAS, TPQ, SSS, MFFT	180
2-5 p.m.	Habit-auditory	90	Habit-lemon	90
	Habit-yogurt	90	Go/No-Go	30
			CPT	30
q 1 hr	PANAS	3	PANAS	3

Ten RAN and nine NWB subjects were studied. (In this pilot study, control women were not studied.) Compared with NWB, the RAN patients took significantly longer to make a choice and made fewer errors. The differences on the MFFT may reflect increased impulsivity in NWB compared with RAN subjects.

Serotonin and Behavior

Serotonin (5-HT) is one neurotransmitter system of interest in explaining a potential link between risk for PSUD, impulse control, and other behaviors in patients with eating disorders.

Serotonin and Substance Abuse. Studies in animals and humans suggest that the augmentation of 5-HT neurotransmission attenuates alcohol consumption while 5-HT depletion enhances alcohol use (Sellers et al. 1992; Tollefson 1991). Animal studies have shown that agents that increase the synaptic availability of 5-HT reduce alcohol consumption (Hill 1974; Levy et al. 1989; Zabik et al. 1985). Conversely, destruction of 5-HT neurons increases alcohol consumption (Richardson and Novakowski 1978). In humans, a few short-term clinical trials of 5-HT uptake inhibitors in mildly to moderately alcohol-dependent individuals (Sellers et al. 1992) have shown a modest reduction in alcohol consumption. Interestingly, such responses are dose-related and onset is immediate, varying in magni-tude across the patient population. Other preliminary studies have shown that drugs with 5-HT activity decrease alcohol consumption (Bruno 1989; Monti and Alterwain 1991; Sellers et al. 1991). Limited data suggest that cerebrospinal fluid (CSF) measures

of 5-HT are decreased in many alcohol abusers (Borg et al. 1985; Eriksson and Humble 1990).

Regulation of Ingestive Behaviors. 5-HT neuronal systems contribute to the modulation of appetitive behaviors (Blundell 1984; Fernstrom and Wurtman 1971, 1972; Leibowitz and Shor-Posner 1986). Treatments that increase intrasynaptic 5-HT or directly activate 5-HT receptors tend to reduce food consumption. Conversely, interventions that diminish serotonergic neurotransmission or 5-HT receptor activation reportedly increase food consumption and promote weight gain. Theoretically, bingeing behavior is consistent with hyposerotonergic function. Alternatively, restricted eating in AN is consistent with hyperserotonin activity.

Mood and Personality. A disturbance of 5-HT activity has been suggested in a number of behavioral disorders. In this brief space, a comprehensive review of this complicated topic is not possible. Still, it is possible to raise a provocative hypothesis that 5-HT may be implicated in factors such as impulse control or mood modulation, which may cut across traditional diagnostic boundaries. Simplistically, reduced 5-HT activity may correlate with reduced impulse control and aggressive behaviors (Coccaro 1992; Siever and David 1991). In contrast, increased 5-HT activity may be related to obsessionality (Hollander et al. 1991; Zohar et al. 1988), inhibition (Cloninger 1987a, 1987b; Soubrie 1986; Spoont 1992), and/or anxiety and fear (Charney et al. 1990). In addition, there is pharmacological and physiological evidence that 5-HT function is altered in depression (Grahame-Smith 1992; Price et al. 1990; Siever et al. 1984).

Habituation and Sensitization. One potential lab test that may be influenced by 5-HT neuronal processes is habituation and sensitization. Geyer and Tapson (1988) noted that there is an extensive literature suggesting central nervous system (CNS) 5-HT neuronal systems are involved in modulating an organism's behavioral responses to environ-mental stimuli, particularly habituation and reactivity (Aghajanian and Sheard 1968; Davis 1980; Geyer and Tapson 1988). There appears to be an inverse correlation between 5-HT levels and startle reactivity. More-over, 5-HT type 1 (5-HT1) receptors influence reactivity, whereas 5-HT type 2 (5-HT2) receptors influence habituation.

Theoretical Perspective. Monoamine neuronal systems, including 5-HT, have a diffuse, widespread distribution, and can be argued to have

a threshold function for information processing independent of specific behaviors (Spoont 1992). Reviews have consistently postulated that 5-HT activity is inhibitory. Soubrie (1986) described the 5-HT system as enabling the organism to arrange or tolerate delay before acting. Cloninger (1987a, 1987b) described 5-HT as responsible for behavioral inhibition, specifically harm avoidance. Spoont (1992) stated that increased 5-HT activity locks in the system's phase, raising the threshold for perturbation by exogenous influences so that no new input is possible. In contrast, as reviewed above, reduced 5-HT activity is correlated with impulsive, aggressive behaviors.

According to Spoont (1992), 5-HT regulates or stabilizes the flow of information through a neural system. 5-HT neuronal activity prevents overshoot of other neurotransmitter systems and thus attenuates signal amplitude. In addition, it controls the sensitivity of the system to perturba-tions by new stimuli entering the system. Thus, 5-HT protects the brain from interference from nonsalient alternate signal sources and from sensiti-zation to potentially threatening stimuli. Therefore, increased 5-HT would result in regionally restricted cycles of information flow, redundant signal propagation and/or maintenance of prepotent response patterns, and hyper-rigid behaviors. In contrast, decreased 5-HT would impair the neural network's ability to maintain signal flow pattern integrity. This would result in increased switching, unstable and amplified signal passage, and impulsive and exaggerated stimulus reactivity.

Specifically, decreased 5-HT might cause behavioral instability by two mechanisms. First, there would be increased overshoot or magnitude of behavioral response (for example, increased feeding, sexual behavior, aggression, or startle response). There would be a decreased response to negative feedback (for example, insensitivity to satiety signals). There would also be a slower recovery time in response to initiated behavior (for example, increased exploring in response to novel stimuli). Second, the organism would have a decreased threshold for perturbation. It would be more susceptible to exogenous influences and would have compromised ability to maintain self-organization. There would be increased facilitation of switching to alternate signal sources and disruption of ongoing sequen-tial behavior. In other words, with decreased 5-HT, there would be behavioral instability. There would be an increased likelihood that a given response will occur, an increase in the magnitude of behavioral response, a slowing of the response recovery,

and an insensitivity to cues that would attenuate or inhibit the behavioral response.

Summary

There appear to be consistent findings regarding 5-HT, vulnerability to PSUD, and behaviors in women with eating disorders (table 4). That is, NWB patients, who may have reduced 5-HT activity, tend to have labile and impulsive behaviors, poor self-control of ingestive behaviors, and a high incidence of PSUD. In contrast, RAN patients, who may have increased 5-HT activity, tend to have restricted ingestive behaviors, inhibited and overcontrolled behaviors, and a low incidence of PSUD. Are rates of PSUD related to issues of ingestive behaviors, self-control, or negative mood states? These factors have been implicated in the patho-genesis of PSUD. Whether some or all of these factors are contributory and whether they are related to a disturbance of 5-HT activity are questions to be answered by appropriate followup studies.

DESIGN AND EXPERIMENTAL METHODS

Hypotheses

NWB individuals have a high rate of PSUD as do their families. It is hypothesized that this high rate of PSUD in NWB patients is related to the presence of the postulated risk factors contributing to development of PSUD. These factors include behavioral undercontrol, negative/unstable mood states, and sensitization to the reinforcing effects of drugs. In contrast, RAN patients have a low rate of PSUD. It is speculated that this low rate of PSUD is related to RAN patients' having opposite behavioral characteristics (behavioral overcontrol, rigid and inflexible mood states, and perhaps rapid habituation to the reinforcing effects of drugs) that may act as protective factors. Poor impulse control, exaggerated mood reac-tivity, and enhanced sensitization may make NWB patients vulnerable to the hedonic properties of substances of abuse. In contrast, RAN patients, who are serious and ascetic people with little ability to experience pleasure, may be insensitive to hedonic properties of drugs of abuse.

Subjects

NWB Women. Two groups of NWB individuals will be studied: 20NWB women with a lifetime history of PSUD and 20 NWB women without a lifetime history of PSUD. The reason for studying two groups of NWB

individuals is to determine whether -PSUD NWB women have the same risk factors as +PSUD NWB women. Methods of determining the presence or absence of PSUD are included in the description of the Schedule for Affective Disorders and Schizophrenia (SADS) interview below. To avoid any confounding effects on assessments, NWB women must not have used any substances of abuse or be on psychoactive medication for at least 30 days prior to the study. NWB women must have no lifetime history of major affective disorder, also to avoid con-founding influences. The NWB women must be ill for at least 4 years prior to study so as to have some substantial period of risk for developing PSUD. NWB women must be between 90 percent and 110 percent ABW. If NWB or RAN women have normal menses, they will be studied in the early follicular phase.

RAN Women. The proposed study will include 20 RAN patients who have no history of PSUD and who have never binged or purged. RAN women must have no lifetime history of major affective disorder and must not have used any psychoactive medication for at least 30 days prior to the study. RAN women must have been ill for at least 4 years prior to the study so as to have some substantial period of risk for developing PSUD or NWB. RAN women, if underweight and malnourished, must be renourished on an inpatient treatment unit for at least 30 days prior to the study and be above 85 percent ABW at the time of the study.

Control Women. The study will include 20 NC women who have no lifetime Axis I or II diagnoses or serious medical condition. Normal control women must have regular menses and will be studied in the first 10 days of the start of their menstrual cycle (early follicular phase) to control for confounding influences. NC women must be between 90percent and 110 percent ABW.

Study Design

All subjects will participate in an identical 2-day study (table 5). Prior to day 1 of the study, subjects will be psychologically and medically assessed. On the morning of days 1 and 2 (designated days A and B), subjects will complete a battery of self-rating psychological assessments. On the after-noon of days A and B, subjects will engage in a battery of performance studies. Studies on days A and B will be randomly counterbalanced.

Days A and B—Morning—Baseline Psychological Assessments. If the subject meets all the inclusion criteria, none of the exclusion criteria, and agrees to the study, she will enter the Eating Disorders

TABLE 5. Major dependent variables and predictions about response.

Assessment	Main Dept Variable	+PSUD	-PSUD	RAN
Behavioral under/over control				
Eysenck I7	Impulsivity	††	†	
Zuckerman	Sensation seeking	††	†	
AIAQ	Irritability, lability	††	†	
Buss-Durkee	Irritability	††	†	
MPS	Perfectionism	†	†	††
Y-BOCS target	Symmetry, exactness			††
Matching figure	Latency of response	¥¥	¥	†
	Errors	††	†	¥
Go/No-Go	Go signal			
	No-Go signal	††	†	
CPT	False alarms	††	†	¥
	Missed targets	††	†	¥
Personality style				
MPQ	Constraint			†
TPQ	Novelty seeking	††	†	¥
PDE (Axis II)	Cluster B, OC	B		OC

KEY: † = increased; ¥ = decreased compared to controls or other eating disorder patients.

Research Laboratory on the evening before day A. During the morning (8 a.m. to 11 a.m.) of days A and B, subjects will complete a battery of tests to assess behavior, mood, personality, and eating disorder-related symptoms. Because of the number of assessments, these assessments will be done over two 3-hour periods. All subjects will complete assessments in the same order. These data will be used to assess the presence and severity of symptoms in the patient versus the control population and to look at relationships with psychophysiological measures of impulse control and cognitive processes. The assessments to be completed are described as follows.

- Buss-Durkee Hostility Inventory (BDHI) (Buss and Durkee 1957). The BDHI is a 75-item true/false questionnaire related to aggression and hostility. The BDHI scales (irritability and assault) are found to correlate with indices of central 5-HT function, including CSF 5-hydroxyindoleacetic acid (5-HIAA) levels (Brown and Goodwin

1984), prolactin response to fenfluramine (Coccaro et al. 1989), m-chlorophenylpiperazine (mCPP) (Coccaro et al. 1989), and buspirone (Coccaro et al. 1990).

• Anger, Irritability, Assault Questionnaire (AIAQ) (Coccaro et al. 1991). The AIAQ is a 42-item self-report questionnaire that yields an assessment of irritability and assaultiveness with a focus on behaviors potentially related to reduced 5-HT activity. This scale has been empirically derived, in part, from the BDHI (Buss and Durkee 1957) and the Affect Lability Scale (Harvey et al. 1989). The authors have shown that this inventory discriminates between NWB and control women (unpublished data). There are three subscales to the AIAQ: behavioral irritability (readiness to explode with negative affect), three types of physical assaultiveness (direct, indirect, and verbal), and affective lability (impulsive dysregulation of anger). This instrument also rates along specific timeframes (past week, past month, adulthood, adolescence, and childhood).

• Multidimensional Perfectionism Scale (MPS) (Frost et al. 1990). This 35-item self-rating scale identifies 5 dimensions of perfectionism: concern over mistakes; high personal standards; parental expectations; doubt about quality of performance; and organization, order, and pre-cision. MPS measures have shown to be reliable and valid measures of different dimensions of perfectionism (Frost et al. 1993). This scale distinguishes differences in perfectionism between RAN and control women (Bastiani et al., in press; Srinivasagam et al., in press).

• Multidimensional Personality Questionnaire (MPQ) (Tellegen, unpublished data). The MPQ is a 300-item self-report questionnaire whose scales represent 11 primary personality dimensions (well-being, social potency, achievement, social closeness, stress reaction, alienation, aggression, control, harm avoidance, traditionalism, and absorption) and three higher order traits (positive affect, negative affect, and constraint). Casper (1990, Casper et al. 1992) showed that this assessment can distinguish differences in personality traits between RAN and NWB subjects. RAN subjects report greater self-control, lower impulsivity, and greater inhibition of emotionality and conscientiousness than NWB patients.

• Eating Disorder Inventory (EDI) (Garner et al. 1983). This 64-item, self-report, multiscale measure is designed for the assessment of psychological and behavioral traits common in women with eating

disorders. This scale is used extensively in the eating disorder field. Reliability has been established for all subscales.

- Beck Depression Inventory (BDI) (Beck et al. 1961). The BDI is a 21-item self-report inventory that correlates well with other established measures of depression.

- Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1970). The STAI is a widely used instrument that consists of separate self-report scales for measuring two anxiety concepts: state anxiety and trait anxiety.

On day B in the morning, subjects will complete the following tests.

- Eysenck (I7) (Eysenck and Eysenck 1975). The I7—a 90-item yes/no scale designed to assess impulsiveness and venturesome-ness—yields 7 factors: psychoticism, extraversion, neuroticism, lie score, impul-siveness, venturesome, and empathy.

- Alcohol Expectancy Questionnaire (AEQ). This is a 90-item, true/false questionnaire developed to assess subjects' beliefs about alcohol's effects in 6 domains using factors such as tension reduction, increased arousal, and performance impairment. Scores on this questionnaire have been shown to correlate with drinking style and the presence of problem drinking. The expectancies one holds about the effects of using alcohol or drugs may be important in determining future sub-stance use. For example, the expectancy that drinking alcohol will have a positive effect is correlated both with current (Goldman et al. 1987) and future drinking habits (Christiansen et al. 1989).

- Effects of Drinking Alcohol Scale (EDAS) (Leigh 1987). This is a 20-item, Likert-type scale designed to assess individuals' beliefs about the effects that alcohol has on their social behavior. This scale yields five factors: nastiness, cognitive/physical impairment, disinhibition, gregariousness, and depressant effects.

- Situational Confidence Questionnaire for Drugs and Alcohol (SCQD, SCQA) (Annis 1990). These are scales that measure self-efficacy, which refers to personal judgements of how well people can organize and implement patterns of behavior in situations that contain novel, unpredictable, and stressful elements. The alcohol scale has been validated (Miller et al. 1989); reliability and validation studies on the drug scale are in progress (Annis, personal communication,

February 1994). The drug scale contains 50 questions and the alcohol scale contains 39 questions. There are eight subscales: negative emotional states, negative physical states, positive emotional states, testing personal control, urges and temptations from intrapersonal deter-minants, interpersonal conflict, social pressure to use substances, and positive emotional states from interpersonal determinants. These scales are computerized so that each drug scale can be customized for each subject to ask questions about self-efficacy for up to three main drugs of abuse.

- Sensation Seeking Scale (Zuckerman 1971). This is a 40-item forced-choice scale developed to assess individual differences in optimal levels of stimulation and arousal. This scale yields four subscales: thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility. Scores on this measure have been hypothesized to be related to behavioral undercontrol and substance use. Personality characteristics indicative of behavioral undercontrol have been shown to be positively related to alcohol use (Earleywine and Finn 1991; Earleywine et al. 1990; Sher 1991).

- Tridimensional Personality Questionnaire (TPQ) (Cloninger 1987b). Three dimensions of personality (novelty seeking, reward depen-dence, and harm avoidance) have been hypothesized to be associated with brain monoamine systems. Specific patterns of these dimen-sions have been hypothesized to be associated with PSUD. Bulik and colleagues (1994) have found that +PSUD NWB women scored significantly higher on novelty seeking than -PSUD NWB women. While still in the early stages of clinical validation, this scale may be highly applicable to the study population.

- Matching Familiar Figures Test (MFFT). Subjects will be adminis-tered the MFFT. The subject is shown a series of 12 pictures, each containing a standard and 6 to 8 comparison figures. One of the comparison figures is identical to the standard, while each of the remaining figures subtly differs from the standard in some detail. The subject is asked which comparison figure is identical to the standard. Latency to first choice and number of errors (to a maxi-mum of two per item) are recorded. This test assesses impulsivity and reflectivity (Kagan et al. 1964).

Days A and B—Repeated Measures of Mood States and Mood Stability. It is hypothesized that NWB subjects have unstable, fluctuating, and overreactive mood states, whereas RAN subjects have rigid and inflexible mood states that are unresponsive to external

stimuli. To document such mood states, subjects will take the Brief Measure of Positive and Negative Affect Scale (PANAS) (Watson et al. 1988), a 20-item self-report inventory that measures positive affect and negative affect. High positive affect is a state of high energy, full concentration, and pleasurable engagement, whereas low positive affect is characterized by sadness and lethargy. High negative affect is a dimension of sub-jective distress and unpleasurable engagement, including anger, guilt, and fear, while low negative affect is a state of calmness and serenity. These scales have been shown to be highly internally consistent and largely uncorrelated. This scale is sensitive to changing internal or external circumstances and has been shown to be useful in quantifying an indi-vidual's mood fluctuations. Each subject will complete this scale at hourly intervals during the 2 days in the laboratory (except when engaged in other studies). It is hypothesized that variance in mood states in NWB subjects will be much greater than in RAN subjects.

Days A and B—Afternoon—Performance Assessments. These experiments will test several disturbances that have been conceptually implicated in the eating disorders: impulse control, response to stimuli, and habituation. Both performance and psychophysiological dependent measures (heart rate, skin conductance, and salivation) are assessed with this design. The tasks are a Go/No-Go reaction time task, a vigilance task (continuous performance test (CPT)), and several orienting/habituation series. Although all three functions are represented to some degree in all of the tests, the Go/No-Go reaction time serves as the primary impulsivity task and the CPT as the primary stimulus responsivity task. Three types of stimuli will be presented in the habituation task: a yogurt food, a lemon food, and an auditory tone.

- Go/No-Go task. The Go/No-Go task is a standard paradigm for the study of impulsivity (Troemmer et al. 1988) and has been used extensively. The Go/No-Go task requires a subject to respond as rapidly as possible to one set of signals (i.e., Go trials) and to withhold response to a second set (No-Go). A fixed foreperiod is typically used so that the subject develops a high state of readiness. In order to control for individual differences in reaction time, a 25-trial sample version of this task will be administered to subjects during baseline to evaluate subjects' average reaction times to the Go trials. For the experimental session, a reaction time will be calculated that is 70 percent of the subject's average, and subjects will be awarded a 5-cent incentive for each response to the Go trial that is equivalent to, or less than, this rate. This manipulation places an emphasis on speed and

accuracy and makes it more difficult for the subject to inhibit responding to the No-Go trials, thus ensuring that all subjects will have some failures to inhibit responses during No-Go trials.

Persons with disorders of inhibition typically show more inhibition failures to No-Go signals than controls (Patterson and Newman 1993). Psychophysiologically, the foreperiod induces heart rate deceleration and phasic skin conductance responses, as does success-ful inhibition. One hundred trials with 20 No-Go trials will provide sufficient data and require approximately 15 minutes.

Both behavioral and psychophysiological measures of impulsivity will be applied. With respect to the behavioral dependent measure, an elevated number of responses to the No-Go trials, also known as false alarms, are thought to indicate problems with impulsivity. It is expected that the NWB group will have a greater number of false alarms than the RAN or NC groups. RAN and NC will not differ from each other. The psycho-physiological measures are also expected to differentiate the groups. In RAN and NC groups, heart rate and skin conductance responses during the foreperiod will decelerate consistently over trials, indicative of appropriate attentional control of perceptual processing. NWB indi-viduals will show variable heart rate and skin conductance response during the foreperiod, indicative of a loss of appropriate attention.

• Continuous Performance Test. Vigilance requires maintained attention to the detection of a sensory stimulus; it provides a key test of a stimu-lus responsivity, but the test also has elements of performance test. The CPT is a computerized vigilance test that requires the subject to focus on an array of rapidly appearing stimuli and press a button every time a designated target appears (e.g., the number 9). To make the task more demanding, degraded visual stimuli (numbers covered by a cross-hatched grid) are used. Six blocks of trials are conducted and include two easy trials (blocks 1 and 6, stimulus duration of 101 milliseconds (ms)) and two hard trials (blocks 3 and 4, stimulus duration of 17ms). Reaction times to both correct and incorrect responses are recorded on disk. Stimuli are presented over a 9-minute period and subjects are not told about the variation in stimulus presentation rates. For each block, 20 percent of the stimuli are targets and the remainder are nontargets. Median reaction times are recorded for each block. Measures of d', an index of perceptual sensitivity, and beta, an index of response bias, are calculated for each block. Together, these measures provide estimates of vigilance and impulsivity. This task runs on an IBM-compatible

computer, and has been used to evaluate clinical patients having neuropsychological problems (Morrow et al. 1992).

It is expected that the NWB group will show greater heart rate and skin conductance responses to targets than the RAN and NC groups over trials, indicative of a disturbance in habituation. Further, the NWB group will have more false alarms and missed targets than both the NC and RAN groups. Extraversion has also been associated with more labile skin conductance during baseline conditions. If NWB subjects share respon-siveness and impulsivity characteristics with extraverts, then such a relationship might hold for the NWB group as well.

• Orientation/Habituation. Habituation and orienting to novel stimuli are basic processes that relate the stimuli of the external world to current knowledge. Preliminary data in 15 NWB women shows that their salivary response to food sensitizes with repeated presentations, compared to matched controls who show salivary habituation. Epstein and colleagues (1992a, 1992b) developed a basic paradigm to specifically study ingestive behavior. The pace of the habituation task is controlled by the necessity of salivary measurement. Dietary controls are also necessary, and will be standard for both days of testing.

Subjects will participate in two afternoon sessions between the hours of 2p.m. and 5 p.m. on both days. On day A, subjects will receive the auditory stimuli followed by the yogurt stimuli. On day B, subjects will receive the lemon juice stimuli followed by the Go/No-Go and CPT studies. On the days of testing, all subjects will consume a light lunch (approximately 350 kilocalories (kcal) from 11a.m. to 11:30 a.m.) and abstain from food and caffeinated beverages until this study is completed. Subjects must have at least a moderate liking (a rating greater than 50 on a 0 to 100 scale) for the food and taste stimuli used in the study.

Following specific instructions regarding the placement of dental rolls for salivation collection, two 2-minute baseline salivation measures will be taken. After these measures, the subject will rate (using a 100 millimeter (mm) line scale anchored by "very" and "not very") her initial degree of hunger, fullness, perceived pleasantness and intensity of the stimulus, desire to binge, and desire to purge before the study begins. The subject will then sit quietly for 3 minutes, after which she will be asked to insert new dental rolls.

The method of stimulus presentation for all groups is as follows: Immediately after insertion, a small amount of the taste stimulus (0.10milliliters (mL)) will be placed on the center of the tongue using a calibrated micropipette, and the salivary response to this taste will be collected for a 2-minute interval. After the stimulus is applied to the subject's tongue, a portion of the test food will be placed on the table in front of the subject and she will be instructed to look at the test food and to imagine eating it. The subject will be told explicitly that she will be asked to eat the test food after salivation collection, since it has been shown that the salivary response is attenuated when subjects do not expect to eat the presented food (Wooley and Wooley 1973; Wooley et al. 1976). After the 2-minute stimulus presentation, the subject will be instructed to remove the dental rolls from her mouth, place them in a plastic bag, and seal the bag. The plastic bag containing the dental rolls will be weighed within 10 minutes after removal. During each 3-minute intertrial interval, the subject will eat a portion of the test food; fill out self-report measures of hunger, fullness, pleasantness and intensity of the stimulus, desire to binge, and desire to purge; and rinse her mouth with water to remove any excess food debris.

In order to determine whether the impairment in salivary habituation demonstrated in NWB patients is generalizable to nonfood stimuli and other response systems, the subject's heart rate and skin conductance response to repeated presentations of an auditory stimulus will be evaluated. In this particular study, salivation will not be assessed since there will not be a significant salivary response to auditory stimuli. However, the auditory stimuli will be presented in a manner analogous to the salivary habituation paradigm. A sequence of eight stimuli will provide—just as in the food-related version—indices of habituation. Responsivity, via a dishabituating stimulus, causes the reinstatement of orienting; thus, the final stimulus identical to the first eight will also be examined. Rather than food bits, the generalization experiment uses 1,000 hertz (Hz) pure tones for standard stimuli, gated on with a slow rise time and presented for 2 minutes at 65 dB; the dishabituating stimulus is a 600-Hz tone presented for 2 minutes at the same dB.

The methodology for heart rate and skin conductance is common to all tasks. Interpretation of all these measures requires 10-minute resting baselines preceding the task battery and interspersed between the tasks. These measures are derived from surface electrodes, amplified, and then digitized by computer. To evaluate the phasic heart rate and skin con-ductance responses (SCR) to target stimuli in the CPT and Go/No-Go paradigms, the interbeat interval (IBI) and

SCR will be measured for 3seconds before, and 5 seconds after, the motor response to the target stimulus. The mean preresponse value for each measure will be sub-tracted from the mean postresponse value for each measure and for each target stimulus. The IBI and SCR responses to target stimuli will be averaged across subjects and between groups to obtain grand means for each target stimulus presented. In this study, skin conductance responses will be defined as those greater than 0.05 micro-Siemens occurring within 5 seconds after the motor reaction to the target stimulus. IBI will be defined as time between R-waves.

Analysis and Expected Results

The intent is to characterize permissive or protective factors that may contribute to the rates of PSUD in women with eating disorders. Four groups of female subjects will be studied: normal-weight bulimics with substance use disorder (+PSUD NWB); normal-weight bulimics without substance use disorder (-PSUD NWB); subjects with restricting anorexia (RAN); and normal controls (NC). Substance use is not crossed with RAN and NC. Very few individuals with RAN use substances of abuse, making inclusion of RAN subjects with and without PSUD impractical in this preliminary study.

Specific Aim 1. It is hypothesized that there are psychological factors that may permit or enhance the likelihood of developing PSUD, including behavioral undercontrol, personality factors such as novelty seeking; or negative, unstable mood states. Similarly, factors that are the conceptual opposites of these traits may protect against PSUD. These factors include increased self-control and DSM-III-R cluster C personality characteristics, perhaps characterized by perfectionism and obsessive need for symmetry and exactness; increased constraint or inhibition; and rigid, inflexible mood states. Analysis of variance (ANOVA) strategies will be used to test group differences of continuous measures of personality and behavioral traits and for the laboratory performance tests (the Go/No-Go and CPT tests). After multivariate analysis of variance (MANOVA) is conducted to confirm that measures differ from each other, univariate one-way ANOVA comparing the four groups (+PSUD NWB, -PSUD NWB, NC, RAN) will be con-ducted for each measure. Planned contrasts will be used to test the hypotheses that +PSUD NWB will show the greatest impulsivity, mood instability, and novelty seeking and the least perfectionism, inflexibility, and constraint, followed by -PSUD NWB, followed by NC, followed by RAN. For dichotomous variables, such as numbers of subjects who report a need for symmetry, chi-square

and Fisher exact tests will be used. It is likely that the chi-square requirement that at least five observations appear in each cell will not be met. If not, then Fisher exact tests will be used. Fisher exact tests can compare only two groups at a time (e.g., +PSUD NWB and -PSUD NWB); thus, it will be necessary to run multiple tests in order to make all of the comparisons of interest. Standard techniques to limit experiment-wise error will be applied; that is, tests will be conducted according to prior hypotheses and conservative p-values. Expectations are summarized in table 5.

Specific Aim 1a—Measures of Impulse Control and Other Risk Factors— Self-Assessment Paper-and-Pencil Tests. Measures of impulsivity have been developed primarily for aggressive, impulsive men. Such a conceptualization of the construct may not be completely appropriate for women with eating disorders. For example, there is an emphasis on the measurement of assault and, thus, there is less face validity in these measures for young women than is desirable. A major reason for this proposed study is to characterize the assessment tools that best quantify the risk factors for PSUD and discriminate between subgroups of eating disorders.

These tools have been chosen for several reasons. First, some instruments such as the Eysenck I7 or Zuckerman Sensation Seeking Scales (Sher 1991) have been shown to identify potential vulnerabilities in people at risk for developing PSUD. The intent is to determine whether these measures will discriminate NWB and RAN subjects. Second, preliminary studies suggest that some tools (e.g., TPQ, MPQ, MPS, Y-BOCS, and Axis II diagnoses) may discriminate characteristics related to impulse control, mood stability, or personality in patients with eating disorders. The intent is to determine whether these assessments are related to risk of PSUD. Third, certain assessments (BDHI, AIAQ) have been shown to be related to reduced 5-HT activity in studies mainly of aggressive, impulsive men. The intent is to determine whether differences exist between NWB and RAN subjects and how such measures may be related to risk for PSUD.

Specific Aim 1b—Construction of New Measures of Impulsivity From Old Scales. Since multiple measures of impulsivity are being used, it may be possible to improve the measurement for this patient group. As noted, measures of impulsivity have been developed primarily for aggressive, impulsive men, not women with eating disorders. Item-total correlations for each test will be used to ascertain which items best predict impulsivity in this population. Confirmatory factor

analysis will also be conducted. Members of the group will independently choose items across all scales that best characterize impulsiveness as expressed in NWB patients. Factor analysis will then be conducted. Items expected to measure impulsivity in NWB subjects that are shown by the factor analysis to group together will then be constructed into a new, revised scale. The properties of this scale will be tested on the experimental groups. The intent is to apply these techniques across the entire sample of eating-disordered women. However, the distributions across the groups will first be examined to ensure that combining across all four groups is appropriate.

Specific Aim 1c—Comparison of Laboratory Assessments of Impulse Control. Paper-and-pencil self-assessments of impulse control tend to measure how subjects have behaved in the past or how they per-ceive their behavior. Such measures tend not to be useful for assessment of "here and now" impulse control in brief laboratory studies. Traditional paper-and-pencil tests tend not to be designed to characterize short-term changes in impulse control and may be confounded by the artificial setting of the laboratory. Thus, the intent is to develop a lab test to characterize impulse control in women with eating disorders. It will be investigated whether NWB women have disturbances of impulse control as reflected by laboratory assessments such as the Go/No-Go, CPT, and MFFT. The ability to use a lab test of behavioral undercontrol will substantially benefit future studies of the behavioral expression of risk factors in humans with PSUD. For example, researchers could study whether agents that acted on specific neurotransmitter systems, such as 5-HT, altered behavioral undercontrol. Alternatively, the way that drugs of abuse or bingeing behavior altered behavioral undercontrol in NWB women could be studied in a laboratory setting.

Group differences in Go/No-Go, CPT, and MFFT will also be analyzed with ANOVA strategies. For the MFFT, latency of response and errors will serve as the primary dependent variables. For Go/No-Go, responses tothe No-Go signal will serve as the primary dependent variable. For CPT, false alarms and missed targets will serve as the primary dependent variable. Each dependent variable will be analyzed in a one-way ANOVA with four groups (+PSUD NWB, -PSUD NWB, RAN, and NC). As des-cribed above, it is expected that the groups will be ordered, with +PSUD NWB showing the most impulsive responses to each measure and RAN showing the least impulsive responses to each measure. Predictions for the order of the means will be tested with planned contrasts for each measure.

Specific Aim 1d—Negative Mood States and Unstable Mood. It has been suggested that increased negative emotionality may be a contributory risk factor for PSUD (Sher 1991). However, negative mood states in terms of depression and anxiety are of similar magnitudes in NWB and RAN patients. Therefore, negative mood states, per se, do not explain differences in rate of PSUD between NWB and RAN. Clinically, NWB patients have unstable moods and tend to be overreactive to stress and other stimuli. NWB women have a great deal of difficulty control-ling and tolerating extremes of negative affect. They often describe using bingeing or drugs to immediately reduce uncomfortable feelings they cannot otherwise control. Thus, it is hypothesized that a risk factor in NWB may be a vulnerability to unstable, overreactive, poorly modulated negative moods. In contrast, RAN women tend to be insensitive to internal and external cues, tolerate a great deal of physical and emotional distress, and take pride in their self-control and discipline. In fact, a hallmark of RAN is its ego-syntonic nature, with little insight or motiva-tion to change. It is hypothesized that RAN have rigid and inflexible mood modulation, are "stuck" in one mood state, and have little ability to experience or incorporate other perspectives such as pleasure.

This study will assess negative mood states. It is hypothesized that NWB and RAN women will have similar amounts of depression and anxiety in terms of DSM-III-R diagnoses and continuous measures (Beck et al. 1961, Hamilton 1959, Spielberger et al. 1970). The assessment of unstable mood is problematic. It is proposed to use the PANAS, which is a brief self-rating of negative and positive affective states that has been designed to be repeated multiple times during the day. It is hypothesized that NWB subjects will show much variance of negative and positive affects at ratings done hourly over a 2-day period. In contrast, RAN patients will have little change in mood. Group differences in mood stability will be tested by comparing the variance of hourly rated moods on the PANAS using the variance ratio test. Six variance ratio tests will be used to compare the four variances, and a Bonferroni-corrected p-value of 0.0083 will be used to assess significance in the differences of these ratios.

Specific Aim 2. It is hypothesized that the clinical presentation of disturbances of impulse control and mood stability reflect more pervasive characteristics of responsivity or reactivity to the environment in RAN and NWB subjects that may shed light on why differences in vulnerabilities to substance abuse occur. As Braff and colleagues (1992) noted, responses to stimuli and information processing are regulated by a cascade of operations including central

inhibition and selection, habituation, and traditional learning. Failure of some or all of these attentional functions might contri-bute to disturbances of impulse control and mood stability. The authors will test the possibility that people with eating disorders have disturbances in responding to novel stimuli (orienting response) or a disturbance of habituation (the decrement in the magnitude of the response over repeated presentations of the same initially novel stimulus). It is predicted that NWB subjects might fail to adequately habituate to the reinforcing effects of food or drugs of abuse. In comparison, it is hypothesized that hedonic stimuli have little reward value for RAN women because they rapidly habituate.

Specific Aim 2a. Preliminary data suggest that NWB subjects may have reduced habituation to the reinforcing effects of intake of a food such as yogurt. The intent is to replicate these findings using a yogurt stimulus and extend this study in several ways. First, other subjects groups will be investigated (+PSUD NWB versus -PSUD NWB, RAN). Second, a food (yogurt) will be compared with a neutral food stimulus (lemon) that should not elicit strong food associations. Each group of subjects is expected to show similar response patterns to both yogurt and lemon juice stimuli. It is hypothesized that such response is a trait characteristic of subjects and not just related to prior food-related experience or learning. It is predicted that RAN subjects will show the most rapid habituation, NC show intermediate habituation, and bulimic subjects show the slowest habituation. If there are differences between bulimics with and without PSUD, it is expected that bulimics with PSUD will show the slowest habituation of any group.

Specific Aim 2b. The hypothesis will be tested that such response disturbances to food stimuli generalize to nonfood-related stimuli. Thus, it is hypothesized that NWB subjects will have reduced heart rate and skin conductance response habituation to food stimuli (yogurt and lemon juice) and to nonfood stimuli (auditory tone and CPT). Eight trials of food and auditory stimuli will be used; CPT trials will be divided into blocks of eight for the purposes of the analysis. Two types of measures are extracted from the heart rate, skin conductance, and salivary variables.

- The tonic level describes the state of the variable during a baseline or performance of a task. For salivation, the tonic level is the total salivation volume for each trial. For heart rate, the average heart rate during baseline and task periods is calculated. For skin conductance, the average level of skin conductance is calculated and the number of responses within a baseline or task period is counted (a lability

measurement). These measures provide important context for the measures of event-related responsivity, phasic responsivity, which define the primary measures.

• The second type of dependent measure is phasic response. For salivation, the phasic measure is the pre- to posttrial difference in salivary volume. For heart rate, the phasic measure is the cardiac deceleration index formed by the difference between the longest pre- and poststimulus intervals. For skin conductance, the phasic measures are the amplitude of responses after an event compared to that before the event (typically assessed as zero for no response). As events do not elicit responses in all subjects for all stimuli, the probability of a poststimulus response (computed across subjects for a particular event) as a dependent variable will also be used; this will ensure that results are not measure-specific and not due to a small subset of subjects showing large amplitude responses.

The primary dependent phasic measures for salivation, heart rate, and skin conductance will be used. These measures are all predicted to show the same relationship to diagnosis over the eight trials, and thus a MANOVA will be applied first to show the overall result. Following the MANOVA, univariate tests for each of the dependent measures will be conducted. The tonic and phasic measures for heart rate and skin conductance will be subjected to a 4-way ANOVA by diagnosis (+PSUD NWB, -PSUD NWB, NC, and RAN), a 4-way ANOVA by stimulus (yogurt, lemon juice, auditory tone, and CPT), and an 8-way ANOVA by trials (or 8 trial blocks for CPT). Diagnosis will serve as a between-subjects factor, and stimulus and trial will serve as within-subject factors. First, the tonic measures of heart rate and skin conductance will be analyzed; if tonic effects are found, tonic measures will be used as covariates in the analyses of the phasic measures.

In the phasic measures, the expectation is to find main effects for diagnosis with RAN subjects showing the fastest habituation to all stimuli, followed by NC, followed by -PSUD NWB; +PSUD NWB subjects will show the slowest habituation, or perhaps sensitization, to all stimuli. Main effects with no interactions across the different types of measures would provide the strongest evidence that physiological habituation differentiates these groups. However, interactions may be present. It is anticipated that there will be interactions between patient group and trials, indicating differential habituation effects. The presence of interactions with the task factor would obscure the interpretation of the results, and it may be appropriate in this

exploratory grant to pursue a 4-way (+PSUD NWB, -PSUD NWB, NC, and RAN) ANOVA over 8 trials or trial-blocks separately for yogurt, lemon juice, auditory tone, and CPT habituation in order to best illuminate the pattern of results.

Orienting and habituation to novel stimuli are related processes. Clinically, NWB women tend to be overreactive to external stimuli. In contrast, RAN women tend to ignore internal stimuli (hunger) and external stimuli (feedback that they are too thin). It is hypothesized that NWB overrespond and RAN underrespond to stimuli and that this will be reflected in alterations in orienting response (increased in NWB, reduced in RAN). Orienting response will be assessed in the three habituation tasks (yogurt, lemon, and auditory tone) and in the CPT task. For the habituation tasks, there are two opportunities to observe orienting responses and thus test the basic responsivity of the different eating disorder groups: trial 1, initial orientation, and trial 9, the dishabituating stimulus. Relative to their habituated state, NWB subjects are expected to show greater orienting responses than RAN subjects and, to a lesser extent, the controls.

Habituation is only partially dependent on initial orienting. It is also expected that the hyperresponsivity of NWB subjects to be evident in a failure to habituate as well as initial hyperresponsivity. In pilot work, a sensitization over trials was seen in the NWB subjects. Habituation will be evaluated by examining the changes in the size of salivary, heart rate, and skin conductance responses over sequential stimuli. The slope over trials is a precise index of habituation. The slope should be most shallow for NWB, steeper for controls, and most steep for the RAN.

Specific Aim 3—Exploration of Other Factors Related to the Severity of PSUD in NWB. The opportunity provided by this research will be used to test whether substance use in NWB women is associated with some of the factors known to be associated with substance use in noneating-disordered populations. In particular, it is important to study the constructs of motivation, expectancy, and self-efficacy (which will be measured using the Alcohol Expectancy Questionnaire, the Effects of Drinking Alcohol Scale, and the Situational Confidence Questionnaire for Substance Abuse) as they relate to the presence of PSUD and degree of substance use among NWB women. As far as is known, little work has been done investigating such factors in NWB. These studies may shed light on understanding the relationship in NWB women between drug use and stress, tension reduction, interpersonal relationships, and social functioning.

Two types of analyses will be used to explore the relationship of motivation, expectancy, and self-efficacy to PSUD among NWB women. First, t-tests will be conducted for each measure to determine whether they differ between +PSUD NWB and -PSUD NWB women. For the second analysis strategy, presence or absence of substance use will be re-scored to reflect the degree of substance use as a continuous variable. In order to transform the diagnoses of PSUD to a continuous variable, the version of the SADS to be used has 125 summary questions that include DSM-III-R criteria for substance abuse and dependency. These questions quantify a wide range of drug use as well as alcohol use. The number of items endorsed will be a relative approximation of severity of drug and alcohol use for all 40 NWB women. That is, it is expected to find a range of scores of substance use degree within both groups, although the groups will not overlap; some women who do not meet the criteria for lifetime substance abuse or dependency will still have some drug or alcohol experience. It is expected that across the 40 NWB women, the range of scores of substance use will be fairly continuous. It is also expected that the distribution will reflect the genuine distribution within the eating-disordered population fairly accurately, despite the study sample selection of equal numbers of both groups. As far as is known, close to half of bulimic patients are also diagnosed with PSUD.

The correlation among motivation, expectancy, and amount of substance use will be calculated. It is anticipated that Spearman's correlations will be more suitable, as it is expected that substance use will be normally distributed. However, parametric or nonparametric strategies will be used as appropriate. Correlations will be calculated for all 40 NWB women and for +PSUD NWB women alone. Degree of substance use across all subjects may be predicted by different constructs than degree of sub-stance use within substance users alone. While direct tests of differences between the two tests would not be appropriate, methods such as these will be used to generate hypotheses for future work.

It is also important to determine whether extremes of substance abuse correspond with extremes of disordered eating behavior, that is, whether severity of eating disorder as measured by number of binge and purge episodes is associated with severity of substance use. First, it will be tested whether the number of binge and purge episodes differs for bulimics with and without substance use disorder. It is anticipated that the number of binge and purge episodes will not be

normally distributed, and this dif-ference will be tested with the Wilcoxon-Mann-Whitney rank sum test. Next, it will be tested whether binge and purge episodes are correlated with substance use across the two groups (using Spearman correlations for this test). Finally, the association of severity of eating disorder pathology and substance use in the substance use group alone will be examined. This group will be divided into high and low substance use based on a median split and into high and low binge/purgers based on a median split. A chi-square or Fisher exact test (depending on the distribution of frequencies among cells) will be used to test for the association of binge or purge episodes and substance use in this group.

In addition, the relationship of other demographic variables to PSUD in NWB women will be explored. These include current age, age of onset, duration of illness, current and past body weight, the presence of other psychiatric Axis I and II diagnoses, and previous treatment. The factors described in this aim will be correlated with the findings from specific aims 1 and 2 of the proposed study.

PUBLIC HEALTH SIGNIFICANCE

This study is intended to explore and develop a better understanding of risk factors for PSUD in women with eating disorders. First, this proposed study will focus on a better understanding of behaviors related to risk for PSUD in NWB and RAN women. Second, it will determine which psychological and psychophysiological assessments of impulse control may be the best reflection of risk factors for PSUD in NWB subjects. Third, it will attempt to develop a lab test that can be used to assess impulsiveness in the laboratory.

Limited data suggest that augmentation of 5-HT may attenuate alcohol consumption while serotonin depletion enhances alcohol use. NWB patients may have reduced 5-HT activity, whereas RAN patients may have increased 5-HT activity. Reduced 5-HT activity may contribute to impul-sive behaviors in NWB subjects, whereas increased 5-HT activity may contribute to obsessive exactness in RAN subjects. Uncontrolled over-feeding is consistent with reduced 5-HT activity, whereas restricted ingestive behaviors are consistent with increased 5-HT activity. However, a major impediment to understanding the relationship of 5-HT to psycho-logical measures of vulnerabilities is finding an accurate and reliable means of assessing the behavioral expression of risk factors in humans. This pro-posed study is intended to be a building block for future, more intensive, and larger

research studies. The long-term goal is to understand how disturbances of neurotransmitters, such as 5-HT, may play a permissive/ protective role in the development of PSUD in patients with eating disorders.

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Commentary on "Vulnerability to Substance Abuse in Eating Disorders" by Kaye and Wisniewski

Eric Hollander, Lisa Cohen, and Don Stein

SUMMARY

Drs. Kaye and Wisniewski propose an elegant and comprehensive study of serotonergic function in two eating disorder subtypes: anorexia and bulimia nervosa. There is a growing body of literature on the seroto-nergic mediation of behavioral inhibition and affective constriction in both humans and animals. Serotonergic hyperfunction leads to inhibited behavior in animals and anxious and obsessional behavior in humans, while the converse appears to be true with serotonergic hypofunction.

The importance of this work cannot be underestimated both for its inherent heuristic value and for its considerable treatment implications. The numerous common features and high comorbidity in bulimia and alcohol abuse in women (and the lack of this in anorexia) suggest that the study of eating disorders can inform the study of substance abuse. The theoretical bases of the study can be summarized as follows:

1. Decreased serotonin is associated with bingeing, impulsivity, and substance abuse that characterize bulimia nervosa (BN).

2. Increased serotonin is associated with overcontrol, rigidity, restraint, and reduced substance abuse prevalence that characterize anorexia nervosa (AN).

3. Habituation and sensitization to gustatory and other stimulation is reduced in BN.

The proposal has four components comparing AN and BN on:

1. Assessment of mood stability and impulse control using well-known psychiatric instruments.

2. Measures of habituation and startle as assessed by salivary response and galvanic skin response to auditory stimuli, respectively.

3. Feeding behavior and habituation/sensitization to gustatory stimula-tion will be compared using measures of salivation, hunger, fullness, pleasantness, and taste intensity after repeated exposure to foods.

4. Effects of serotonin-affecting drugs by using the acute tryptophan depletion paradigm. The behavioral effects (mood, rigid and overcontrolled behavior, impulse regulation, and feeding behavior) will be assessed following administration (double-blind) of tryptophan-depleting and d-fenfluramine challenges.

Specific methodologies can be summarized as follows:

	Anorexics	Bulimics
Baseline observation	Increased obsession	Decreased obsession
Serotonin metabolite 5-HIAA	Increased	Decreased
Acute tryptophan depletion		Increased impulsivity, substance abuse, bingeing
Augmented serotonin (d-fenfluramine)	Increased obsessions, rigidity, restrictions	

STRENGTHS OF THE PROPOSED RESEARCH

This proposal contains numerous scientific and methodological strengths. Studying serotonergic function in impulsive and impulse-inhibited subtypes of one class of disorders allows both precision and breadth of inquiry. There are considerable implications both for

specific treatment advances and for a general understanding of serotonergic mediation in behavioral and affective pathology. Methodological strengths include:

- comparison of impulsive (BN) and impulse-inhibited (AN) patients on both serotonin depletion and augmentation;

- assessment of the effects of serotonin-depleting (ATD) and serotonin-augmenting (d-fenfluramine) challenges; and

- systematic observation of state/trait naturalistic behaviors in a controlled setting.

WEAKNESSES OF THE PROPOSED RESEARCH

This proposed study is an ambitious and powerful approach to the study of serotonin function in eating disorders. Nevertheless, two major points should be made: The proposed research may be too ambitious for a single study, and there should be more focus on assessment of substance abuse history and substance abuse symptom response to serotonin modulation.

Additional comments and weaknesses have also been noted in an otherwise comprehensive, coherent study with clear focus:

1. More clarification is needed for the specific behaviors affected by serotonin activation.

2. The relationship between eating disorders and substance abuse could be further developed. The suggestion that eating disorders may be a variant of substance abuse may be reductionistic since common features are not equivalent to identity. Nonetheless, the specific commonalities (behavioral, phenomenological, familial, and biological) could be further elaborated. Furthermore, it is not clear if the substance abuse history and family history will be assessed and analyzed. In both the depletion and enhancement study, urge or substance (other than food) craving should be assessed throughout.

3. The relevance of the habituation studies to the serotonin challenge studies is not sufficiently specified. Moreover, habituation to taste seems more a function of sensory-perceptual processes than higher level cognitive functions.

4. Bulimic patients are only assessed after they have recovered from their illness. The authors do not address the question of how their results would vary from a study of acutely ill eating disorder patients.

5. A personal and familial substance abuse history, trauma history, and systematic assessment of Axis II disorders at baseline should be implemented because there is considerable overlap in history of child abuse, personality disorders, and eating disorders.

6. Some of the behavioral ratings appear to rely on visual analog scales that can be easily confounded by poor visual spatial skills.

7. All metabolic blood levels of serotonin probes should be assessed and analyzed because they are important control variables.

8. Side effects to serotonin probes should be systematically assessed to be sure mood changes are not confounded by the side effects.

9. Serotonin challenges are done close together (48 hours), which may cause carryover effects.

10. Baseline differences in mood and behavioral states must be controlled among the subject groups.

11. Multiple analyses pose danger of increased type I error and thus demand data reduction techniques. The use of repeated measures and a discriminant analysis is commendable. However, a multiple regression might be preferable to assess the relative contribution of multiple baseline and independent variables (history and symptom scores) to selected dependent scores (e.g., eating behavior after serotonin depletion). Power analyses need to be done.

ALTERNATE STRATEGIES

The proposal also raises other questions of interest, perhaps to be investigated in later studies.

1. Assess for substance abuse history in subject and family.

2. During acute tryptophan depletion, assess for craving of other substances.

3. Study patients, especially anorexics, in acutely ill phase.

4. Compare anorexics with patients with obsessive-compulsive disorder (OCD) in challenges with mCPP for prolactin response, mood levels, and obsessiveness.

5. Consider the role of other neurotransmitter systems (e.g.,-norepinephrine).

6. Add a treatment component or link with treatment study to see if biological factors can predict outcome.

7. Use serotonin antagonists as a pretreatment agent prior to mCPP administration in anorexia nervosa.

8. Study serotonin and norepinephrine interactions.

9. Consider using mCPP as a serotonin probe to elicit behavioral responses in the anorexic group. The choice of d-fenfluramine over mCPP is worth discussing in more detail.

The similarities and the differences between anorexia and OCD are fascinating. The difference in content between obsessions and compul-sions in anorexics and OCD patients is notable as is the difference in prolactin response to mCPP. While researchers have found blunted pro-lactin response to mCPP in a subgroup of OCD patients, the long-term recovered anorexics show elevated prolactin response in the present proposal. This is an intriguing finding worth further exploration. Furthermore, mood elevation has been found in impulsive but not OCD patients. This proposal reports improved mood and decreased thoughts about body image in anorexics following mCPP; this is surprising as mCPP has produced increased obsessionality in most but not all studies of OCD patients.

The role of noradrenergic regulation is also an important question. Perhaps select noradrenergic challenges with eating disordered patients or use of serotonin antagonists as a pretreatment could be performed at a later date.

Finally, the effect of treatment is an important area to address. If the challenge studies preceded treatment studies, predictors of treatment outcome could be assessed.

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Discussion

Audience and Panel Participants: Walter Kaye, Howard Moss, David Comings, Eric Hollander, Dan Hummer, Rita Liu, and Roy King

Dr. Comings: You said that fluoxetine helped the anorexic. What does it do for the bulimic?

Dr. Kaye: The collaborative study suggested that it reduced bingeing and purging. But, again, the effects are modest as few become abstinent, and most of them have some reduction in bingeing and purging. These are all short-term trials, and it is not clear how effective is the long-term administration of antidepressants. It may actually be a more effective drug in anorexia than it is in bulimia.

Dr. Moss: We did an mCPP challenge study of substance abuse in sociopaths, and the responses that we saw were exactly analogous to Dr.Kaye's responses in the weight-recovered anorexics—a blunted prolactin response, euphoric subjective effects. Is it possible that there is sort of a lack of diagnostic specificity in terms of mCPP responses? How can we explain these similarities to disparate conditions?

Dr. Kaye: Yes. I'd say there are two issues here. One is that the anorexics' prolactin response might have been related to their nutritional or their menstrual state.

Secondly, there's nonspecificity to this agent. This agent works on many different serotonergic receptors, as both an agonist and an antagonist, and has actions on other neurotransmitter systems. It's probably one of the best clinically available tools we have now, but it doesn't allow us the amount of specificity that we would really like to begin to tease apart whether different receptors are abnormal in different psychiatric illnesses. We can't tell that at this point.

Dr. Hollander: But, one of the interesting things about that agent is that it has been given to so many different diagnostic populations, and, to some extent, you could make the claim that it brings out symptoms that are specific to the particular disorder itself. So, for example, there was one study in alcoholic sociopaths in which mCPP seemed to stimulate the symptoms that were similar to what they experienced with alcohol. And there was some kind of cross-reactivity in that respect.

Dr. Moss: Our sociopathic substance abusers thought that they were high on a psychedelic drug.

Dr. Hummer: That study with alcoholics was done at several locations. One of the studies was done here in Bethesda by Dr. Markku Linnoila and some other folks in the NIAAA Intramural Program, and they found a blunted prolactin response, as you found, and also a blunted ACTH response. People said they felt like they were high on alcohol, and people who were experienced with cocaine also said they felt like they were high on cocaine, so there are some nonspecific effects.

But, the other thing that we saw, particularly in the Type 1 alcoholics who at the early onset are more sociopathic type of alcoholic, was that they reported a very strong desire to drink alcohol. I'm struck by the fact that you found, with tryptophan, depletion in the bulimics and a strong desire to binge. So, we're sort of getting it both ways here with trypto-phan augmentation, or serotonin augmentation with serotonin agonists, and also with serotonin depletion. Did you have any thoughts on how we might be able to resolve that, or what that might mean?

Dr. Kaye: Yes. I think it brings up the same issue you were probably focusing on with the fluoxetine: How can the same drug have beneficial effects in very different patient populations? The serotonin system has autoreceptors that inhibit this system from firing as well as postsynaptic receptors that affect other systems. When you give fluoxetine or mCPP, they can both inhibit as well as activate the serotonin system. In people with different illnesses, they may have different balances between their serotonin receptors, and therefore respond differently to the same drugs.

Now, that's theoretical. We don't really know that. That needs to be tested in the next generation of studies. Perhaps looking at various serotonin-related genes may be a better way of assessing the serotonin system.

If serotonin is essentially an inhibitory system and you remove that inhibition, you may get many different kinds of behaviors depending on the context of the different illnesses. For sociopaths, it may be euphoria; for anorexia, there may be a reduction of body image, distortion, and things like that. The actual content of the changes may be more related to the illness.

Dr. Hollander: Another way to look at that is to say that you're dealing with the illnesses that may be on different ends of an extreme. There may be more impulsive-style disorders that are associated with pleasure and gratification and compulsive-style disorders that are associated with an anxiety and sort of ego-dystonic feature. But, there is a common theme really for both types of disorders: People have difficulty inhibiting or delaying repetitive behaviors. So, the common mechanism that serotonergic agents may work on is by helping these people be able to delay or inhibit these kind of repetitive behaviors, whether they are pleasurable, ego-dystonic, or anxious.

Dr. Kaye: Absolutely.

Dr. Liu: I'm just wondering, how much of this disorder goes to disorders related to genetics and gender?

Dr. Kaye: Yes. These are disorders that occur almost exclusively in women; for example, 90-95 percent of the people with eating disorders are women. Why is that? I can only guess. There are animal studies, and some human studies, suggesting that serotonergic activity may be related to gonadal steroid activity.

Dr. Liu: A related question then. How comfortable are you to include both genders?

Dr. Gordon: I was going to ask the same question. If you're going to hypothesize this as a model, for example, that either prevents in the case of anorexics or enhances—I wasn't sure whether it was enhancing and whether it's above average—in bulimics, here is a neurochemical mechanism. You're using this as a model, and let's say you find something. Let's say you find overall it relates to that. Well, there's everything to do with the fact that they're females. And, if it doesn't have anything to do with the fact that they're females, why can't you find the same thing in males? What's going on here?

Dr. Kaye: In another study funded by NIAAA, we're finding a very high incidence of alcoholism in the male relatives of bulimic patients. Perhaps because of cultural or gender reasons women who have this trait may develop bulimia instead of alcoholism. Why is that? Who knows?

In the relatives of anorexics, we're finding that they tend to be constrained and perfectionists, and they're not substance abusers.

That's both men and women. So, in fact, there do seem to be patterns of behavior in their families.

Dr. Moss: In addition, testosterone tends to downregulate serotonin receptors in specific regions of the brain. And then they also have something to do with the gender-specific effects that Dr. Kaye was talking about. In particular, for example, testosterone receptors in the amygdala really reduce the amount of serotonergic inhibitory input to the amygdala, which is one potential anatomic location where aggressive behavior is localized. So, there's less behavioral inhibition due to serotonin then.

Dr. King: I'm very fascinated with your finding that the recovered anorexics showed an increase in tendency to prefer symmetry and order. A few years ago, in research we did in schizophrenia, some of the negative symptom schizophrenics had higher CSF 5-HIAA. The 5-HIAA was correlated with the symptom mannerisms in posture, which we interpreted as kind of stereotype-like behavior that's maybe fostered by serotonin activity. We thought of using some of the schizophrenia methodologies in studying your recovered anorexics in terms of cognitive tasks.

Neurochemical Mechanisms Underlying Responses to Psychostimulants

Nora D. Volkow, Joanna S. Fowler, Robert Hitzemann, and Gene-Jack Wang

STATEMENT OF THE PROBLEM

It is proposed to undertake a study to determine if differences in dopa-minergic reactivity among individuals could explain the variability in response to psychostimulants and to assess the relation of this reactivity to mental state and personality characteristics. Investigation of these relations may provide clues to the association between brain biochemistry and predisposition for drug abuse.

The underlying hypotheses are:

1. Behavioral response to a drug is not only a function of the chemical composition of the drug but also of the unique biochemical characteristics of an individual (Skrinskaya et al. 1992).

2. Personality and mental state of an individual reflect in part his/her unique metabolic and biochemical brain composition (Cloninger 1986).

3. Increased dopaminergic reactivity is associated with increased vulnerability for drug addiction (Deminiere et al. 1989).

Positron emission tomography (PET) (Fowler et al. 1990) in conjunction with 11C-raclopride (Farde et al. 1985), a dopamine (DA) type 2 (D2) receptor ligand that is sensitive to endogenous DA (Inoue et al. 1989; Seeman et al. 1989; Young et al. 1991), will be used to measure DA reactivity. Responsivity of the DA system will be assessed by monitoring changes in 11C-raclopride binding induced by methylphenidate (MP) (Scheel-Kruger 1971). MP increases synaptic DA concentration by inhibiting the DA transporter (Schweri et al. 1985). Changes in DA concentration induced by MP or other drugs that increase synaptic DA concentration interfere with 11C-raclopride binding, and the degree of its inhibition is a measure of

relative changes in DA concentration. This method has been successfully used to measure drug-induced changes in DA concentration in response to pharmacological challenge in the baboon (Dewey et al. 1992, 1993) and in the human brain (Volkow et al. 1994).

BACKGROUND AND SIGNIFICANCE

Cocaine is recognized as one of the more reinforcing and addictive drugs of abuse (Koob and Bloom 1988). The ability of cocaine to enhance dopaminergic activity appears to be critical in its reinforcing properties and is probably also involved in its addictive properties (DeWit and Wise 1977; DiChiara and Imperato 1988; Galloway 1988; Ritz et al. 1987; Roberts et al. 1977; Woolverton and Johnson 1992). It has been postulated that addiction is due to DA depletion resulting from chronic cocaine adminis-tration (Dackis and Gold 1985). However, the mechanisms underlying cocaine addiction are probably more complex, since there are inconsis-tencies in DA brain activity in studies of chronic cocaine use (Post et al. 1987), as well as in effectiveness of DA agonists in long-term treatment of the cocaine addict (Gawin and Ellinwood 1988; Kleber and Gawin 1984). Involvement of the DA system in cocaine addiction is also probably mediated via its regulation of brain regions that subserve addictive behaviors as opposed to these behaviors being encoded in the DA system itself (Le Moal and Simon 1991). Thus, the effects of chronic cocaine on brain DA could lead to addiction through its effects on these regulated brain regions. Alternatively, abnormalities in these brain regions prior to drug exposure could be associated with a higher vulnerability for drug addiction; activity of other neurotransmitters that regulate these regions may facilitate or interfere with addiction.

Cocaine Reinforcement and Addiction: The Role of Dopamine

Research has implicated the mesolimbic DA system as being critical in mediating the reinforcing properties of cocaine and participating in its addiction liability (Goeders and Kuhar 1987; Wise and Bozarth 1984). Furthermore, because most of the drugs abused by humans lead to increased DA concentration in nucleus accumbens (NACC), this has been suggested as being a common mechanism for reinforcement (Koob and Bloom 1988; Wise and Bozarth 1984). Although many investigators have attributed the reinforcing properties to the DA system itself, others have postulated that its role is that of a modulator of regions where the reinforcing and addicting

processes are encoded (Le Moal and Simon 1991). In the latter model, the importance of other neurotransmitters is emphasized since these brain regions are regulated not only by DA but also by other neurotransmitters such as serotonin, opiate peptides, and gamma aminobutyric acid (GABA), among others.

Animal studies investigating dopaminergic changes underlying drug addiction have implicated multiple mechanisms such as changes in DA concentration, dopamine type 1(D1) and D2 receptors, cyclic amethyl-phenidate, and tyrosine hydroxylase (Beitner-Johnson et al. 1992). However, reports on the nature of the changes occurring during chronic cocaine administration are marked by inconsistencies (for review see Post et al. 1987; Woolverton and Johnson 1992). For example, while some studies report decreases in receptor numbers, DA concentration, and DA release in chronically treated animals, others have failed to document such changes. The reasons for these discrepancies are probably multiple and may relate to the dynamic nature of the changes, the interaction of DA with other neurotransmitters also affected by cocaine, and biological variability, among others.

Studies of the DA System in Cocaine Abusers

Various strategies have been used to evaluate the DA system in cocaine abusers. One has been to measure endocrinological parameters that reflect the function of the tuberoinfundibular DA system. Thus, peripheral measurements of prolactin and growth hormone have been used as indirect indices of central nervous system (CNS) DA activity. Although several investigators have reported increased prolactin levels in cocaine abusers (Cocares et al. 1986; Dackis and Gold 1985; Kranzler and Wallington 1989; Mendelson et al. 1988a, 1988b), others have failed to find increased levels (Swartz et al. 1990). Studies measuring plasma growth hormone in cocaine abusers have also yielded similar inconsis-tencies among investigators (Satel et al. 1991). Another strategy has been to evaluate plasma concentration of the DA metabolite homovanillic acid (HVA) in cocaine abusers. Such studies have also been unsuccessful in delineating a consistent pattern of abnormalities (Extein et al. 1989; Martin et al. 1989; Satel et al. 1991).

Postmortem studies have been performed on the brains of known cocaine abusers. Investigators have found decreased brain DA concentration (Wilson et al. 1990; Wyatt et al. 1988), decreases (Staley et al. 1992) and increases (Little 1992) in the number of DA

transporter sites, decreases in messenger ribonucleic acid (mRNA) for D2 receptors (Meador-Woodruff 1992), and decreases in D1 receptors (Toiba et. al. 1992). Pharmaco-logical studies have reported findings suggestive of decreased and/or abnormal function of DA receptors in cocaine abusers, including blunted response to DA agonists (Hitzemann et al., in press; Hollander et al. 1990) and increased sensitivity to DA antagonists (Choy-Kwang and Lipton 1989; Hegarty et al. 1990; Kumor et al. 1987).

Imaging studies evaluating the DA system in chronic cocaine abusers have reported findings that are consistent with decreased activity of the DA system. For example, cocaine abusers have decreases in DA receptor availability (Volkow et al. 1990, 1993a), decreased DA metabolism (Baxter et al. 1988), and decreased metabolism in projection areas of the mesocortical DA system (Volkow et al. 1992). However, because these studies evaluated individuals only after they have become addicted, it could not be determined if these abnormalities were present prior to drug use. It is possible that the abnormalities in DA function preceded drug use and may have contributed to a higher vulnerability for drug addiction. Because prospective studies to evaluate DA function prior to drug abuse would be extremely costly, it is proposed that the association between DA function and response to psychostimulants in normal nonaddicted individuals be investigated.

Genetics and Predisposition to Psychostimulant Abuse

There is increasing evidence that genetic factors contribute to the predisposition to drug abuse (Deminiere et al. 1989). The investigation of the genetic differences in the function of various neurotransmitters and their relationship to drug abuse has found the strongest link to be with the DA system. In animals, heightened responsivity to novel stimuli or to psychostimulants predicts their vulnerability to drug self-administration (Deminiere et al. 1989), and this behavior, in turn, has been associated with dopaminergic activity (Rouge-Pont et al. 1993). Thus, studies on the relation between DA reactivity and behavioral characteristics may be useful in understanding not only the neurochemical correlates of human behavior but also the neurochemical mechanisms underlying vulnerability for drug abuse.

Measuring the Responsivity of the DA System with PET

PET, an imaging technique for mapping neurochemical processes (Fowler et al. 1990), has been used with 11C-raclopride, a D2 PET ligand (Farde et al. 1985) to measure the response of the DA system to pharmacological challenge. 11C-Raclopride has a relatively low affinity for the D2 receptor (Kd = 1.9 nanomolars (nM)), which makes it sensitive to synaptic DA concentration. PET brain imaging studies demonstrating the sensitivity of 11C-raclopride to drug-induced changes in synaptic DA were first done in baboons (Dewey et al. 1992, 1993). Human studies with PET monitoring the response of the DA system to challenge (Volkow et al. 1994) used MP, a psychostimulant drug that increases synaptic DA concentration by inhibiting the DA transporter (Scheel-Kruger 1971). Such studies measured the responsiveness of the DA system to MP by evaluating changes in striatal 11C-raclopride binding. Because uptake of 11C-raclopride in the human brain is highly reproducible (Volkow et al. 1993b), it can be used to probe changes induced by pharmacological interventions.

Addiction: More Than One Behavior

With all the research documenting the relevance of the DA system to the reinforcing and addictive properties of cocaine, one is left to explain why DA-enhancing drugs have not been effective in the long-term treatment of the cocaine abuser. A plausible explanation is the multiplicity of behaviors associated with cocaine addiction. For example, one can distinguish an initial process by which the intake of the drug is experienced as pleasur-able. This process of intrinsic reinforcing drug effects is the one associated with increased DA in NACC and prefrontal cortex (Goeders and Smith 1986; Hurd and Ungerstedt 1989; Ritz et al. 1987). The memory of the drug experience and of the circumstances and behaviors associated with the experience have also been shown to contribute to repeated cocaine intake (Wise 1990). With repeated administration, the ability of this memory to elicit a desire or craving for cocaine becomes more frequent and serves to perpetuate the use of cocaine (Johanson and Fischman 1989).

The neurochemical and neuroanatomical substrates for consolidation of the cocaine experience memory and for eliciting cocaine craving are not well understood, but probably involve the hippocampus among other brain regions. While the memory and intrinsic reinforcing properties of cocaine are important, it is hypothesized that other processes are involved as well. One reason is that compulsive cocaine administration in the addicted individuals occurs despite rapid

tolerance to the subjective effects of cocaine (Fischman et al. 1985) and even in the presence of adverse physical reactions. The drive and loss of control leading to compulsive self-administration of cocaine are probably regulated both by DA and serotonin (Di Chiara et al. 1991; Loh and Roberts 1988) and may involve orbitofrontal, prefrontal, and cingulate cortices. Other processes, such as sensitization, have also been reported to occur with repeated cocaine administration (Post et al. 1987) and may also participate in triggering and/or perpetuating compulsive drug self-administration.

Another contributor invoked in the facilitation of repeated cocaine use is the emotional reaction of the individual to the losses experienced due to cocaine addiction (Johanson and Fischman 1989). In particular, dysphoria during withdrawal has been associated with a higher relapse rate in the cocaine abuser (Johanson and Fischman 1989). One could postulate that because the mesolimbic DA system is involved with reward processes, its dysfunction in the cocaine abuser could intensify depressive symptoms such as anhedonia and loss of drive (Willner et al. 1992). Because of the multiplicity of variables involved in drug addiction, it is highly likely that an individual's unique characteristics, in particular those relating to novelty-seeking behaviors, compulsivity, and impulsivity, may facilitate drug-seeking behaviors.

Preliminary methodological studies support the feasibility of using 11C-raclopride and [18F] fluorodeoxyglucose (FDG) (with and without MPchallenge) to evaluate the function of presynaptic dopamine neurons (PDNs) in humans. Another study provides preliminary data on the correlation between the responsivity to the psychostimulant drug MP and behavioral measures.

Reproducibility of 11C-Raclopride Binding

11C-raclopride has been successfully utilized with PET to assess changes in endogenous DA concentration after pharmacological intervention in the living baboon brain (Dewey et al. 1992, 1993). For similar studies to be feasible in humans, 11C-raclopride measurements need to be reproducible. Reproducibility of 11C-raclopride binding in the human brain was evaluated in five normal controls who were scanned with 11C-raclopride twice, with no intervention, 24 hours apart. After injection of 3.8 to 12.5 millicuries (mCi) of 11C-raclopride (specific activity 0.5 to 1.5 Ci/μM at end of bombardment (EOB); 2 to 24 micrograms (μg) injected dose), a series of20emission scans were obtained from time of injection through 60-minutes. Arterial sampling was used to quantitate total 11C and unchanged

11C-raclopride in plasma. Time-activity (percentage of dose percc) curves for 11C-raclopride in the striatum and cerebellum were highly reproducible with an average difference of 4percent in peak uptake for repeated studies in the same individual. Figure 1 shows the time-activity curves for 11C-raclopride in striatum and in cerebellum for a subject tested twice.

The striatum/cerebellar ratios for the average activity concentration between 30 and 60 minutes showed differences that ranged from -7percent to 8 percent between the repeated studies. Logan plots (graphical analysis for reversible system (Logan et al. 1990)) were used to obtain the ratio of the distribution volume of basal ganglia to cerebellum. These revealed intrasubject values that ranged from -11percent to 5 percent. There were no significant differences between repeated studies in total plasma activity or in percent nonmetabolized 11C-raclopride. Therefore, measurements of 11C-raclopride in the human brain under conditions of no intervention are highly reproducible in the same individual (Volkow et al. 1993b).

Distribution and Pharmacokinetics of 11C-Methylphenidate in Human Brain

In order to determine the time at which MP reached peak concentration in the human brain, brain uptake and pharmacokinetics of 11C-methyl-phenidate were measured. Eight normal healthy male volunteers (20 to 74-years) were scanned twice, 2 hours apart, using 5 to 10 mCi of 11C-methylphenidate. Four subjects had two repeated scans to assess test/retest reproducibility. Four subjects had one scan as baseline and the second scan 10 minutes after intravenous (IV) administration of 0.5milli-grams per kilogram (mg/kg) MP to assess specific to nonspecific binding.

Peak uptake of 11C-methylphenidate in whole brain corresponded to 7 to 10 percent of the injected dose. Binding of MP was heterogeneous, the highest concentration was in basal ganglia, and relatively low levels were detected in cortex and cerebellum. In basal ganglia, MP bound to the DA transporter molecule; binding was inhibited by pretreatment with drugs that inhibit the DA transporter but not by drugs that inhibit the serotonin or the norepinephrine transporter (Ding et al. 1994).

The regional distribution of 11C-methylphenidate in the human brain was almost identical to that of 11C-cocaine (Fowler et al. 1989). The time to reach peak uptake in the brain was 4 to 10 minutes. Peak concentration of 11C-methylphenidate in the brain was maintained for 15 to 20 minutes. In the basal ganglia, the half peak clearance for MP was 90 minutes.

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MP pretreatment significantly decreased 11C-methylphenidate binding in basal ganglia but not in other brain regions. Values for the distribution volumes (Logan et al. 1990) in basal ganglia and cerebellum before and after MP, as well as the ratios for the distribution volume to that in cerebellum, are shown in table 1 along with the values obtained for the test-retest measures.

Effects of Methylphenidate on 11C-Raclopride Binding

The relatively lower affinity of raclopride for the D2 receptor (Kd=-1.1nM) makes it sensitive to competition with endogenous DA (Seeman et al. 1989; Young et al. 1991). Studies in rodents have demonstrated that raclopride binding is increased by pretreatment with drugs that deplete DA and decreased by drugs that increase DA (Ross and Jackson 1989; Inoue et al. 1989). 11C-Raclopride has been used successfully with PET to assess

TABLE 1. Distribution volumes for basal ganglia and cerebellum and for the ratio of the distribution volume of basal ganglia/cerebellum for 11C-methylphenidate.

Test/Retest			
Basal ganglia	Cerebellum	Basal ganglia/ cerebellum	% Change
20.3±1.5	10.5±0.9	1.9±.07	-2.5±4
19.8±1.1	10.2±0.8	1.9±.08	
Methylphenidate Pretreatment			
Basal ganglia	Cerebellum	Basal ganglia/ cerebellum	% Change
16.9±1.6	8.0±0.5	2.12±.10	-37±1
11.7±1.2	8.7±0.7	1.33±.04	

NOTE: Values represent the average for four normal subjects tested twice to assess reproducibility and of four subjects tested with and without pretreatment with MP (0.5 mg/kg IV).

relative changes in DA concentration in the baboon brain (Dewey et al. 1992, 1993). To assess the feasibility of measuring relative changes in DA concentration using 11C-raclopride in humans, the effects of 0.5 mg/kg IV MP in normal human subjects were measured.

Fifteen normal healthy male volunteers (age range 22 to 45) were scanned using a whole-body, high-resolution PET. Description of positioning, preparation, and transmission scans have been published (Volkow et al. 1994). Subjects had two scans done after injection of 4 to 10 mCi of 11C-raclopride. The first scan was done after placebo and the second scan on a different day after 0.5 mg/kg IV MP; the subjects were blind as to which was administered. Either placebo (3 ml saline) or MP was injected 6 to 9 minutes prior to 11C-raclopride. 11C-raclopride binding was quantified using the ratio of the distribution volume in basal ganglia to that in cerebellum, which corresponds to Bmax/Kd-1 (Logan et

al. 1990). Changes in 11C-raclopride binding with MP were quantified as percentage of change from baseline:

(Bmax/Kd (baseline) - Bmax/Kd (MP)/ Bmax (baseline).

Except for one subject, MP consistently and significantly decreased 11C-raclopride binding in excess of the test-retest variability for 11C-raclopride ($F = 44.9$, $p < 0.0001$). Figure 2 shows the time-activity curves for 11C-raclopride after placebo and after MP for one of the subjects. The magnitude of the changes in 11C-raclopride with MP were quite variable, ranging from 10 to 47 percent.

Correlation Studies Between Behavioral Measures and Responsivity to Methylphenidate

Prior to placebo and/or MP administration and every 20 minutes thereafter, subjects recorded their subjective emotional experience for high (defined as euphoria), anxiety, restlessness (defined as the need to

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move), distrust (perception that others are trying to cause harm), and mood (defined as a contrast between being depressed and being happy) using analog scales that were rated from 0 to 10 (Ekman 1967). Baseline behavioral scores were quantified by averaging the measurements obtained during the placebo study.

To quantify the behavioral changes caused by MP, average scores were collected during the MP scan and subtracted from those obtained during placebo. Correlation analyses were performed between the changes in 11C-raclopride binding with MP and the subjective evaluations for mood, anxiety, high, distrust, and restlessness during baseline and MP-induced changes in the behavioral measures. Significant changes in the behavioral measures after MP administration were tested with analysis of variance (ANOVA). To correct for multiple comparisons, the level of significance was set at $p < 0.01$; values smaller than 0.05 are reported as trends.

The behavioral response to MP was quite variable among individuals (table 2). While some subjects reported effects of the drug to be pleasurable and described feelings of high, euphoria, increased sexual desire, and a need to talk, others reported the experience to be unpleasant and described very high levels of anxiety, restlessness, suspicion, and perceptual distortions.

Correlation analyses revealed significant positive correlations with anxiety ($r = 0.82$; $p < 0.0002$) (figure 3) and restlessness ($r = 0.65$; $p < 0.008$) (figure 4). Subjects who reported high levels of anxiety and restlessness during the placebo scan were the ones who showed the largest changes in 11C-raclopride binding with MP.

Similar to previous reports, this study documents a widespread variability in the behavioral response of subjects to the psychostimulant MP. The variability in the response was also observed for MP-induced DA changes. The study documents a correlation between MP-induced DA changes and the baseline mental state of the subjects. The positive correlation observed between response to MP and anxiety and restlessness could be considered analogous to the association observed in animals between sensitivity to psychostimulants, their response to novel stimuli, and their locomotor activity (Hooks et al. 1991; Jones et al. 1990; Piazza et al. 1989; Rouge-Pont et al. 1993). Because the measurement of anxiety was obtained during the placebo scan, it reflects the subject's response to the PET experience. Restlessness was the only measure that could be obtained for motor behavior since subjects are asked to refrain from moving during the PET procedure. In animal studies, behaviors

TABLE 2. Effects of 0.5 mg/kg IV methylphenidate on behavior.

	Placebo	MP	p <
Anxiety	2.5±1.9	2.9±2.7	NS
High	1.4±1.3	4.1±3.9	
Mood	5.4±1.6	6.3±1.8	NS
Restlessness	2.8±1.7	6.1±1.8	
Distrust	0.4±0.7	1.2±2.1	NS

NOTE: Subjects (N = 15) rated the behavioral measures on a scale of 0to 10.

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associated with responsivity to psychostimulant are associated with dopaminergic tone (Deminiere et al. 1989; Le Moal and Simon 1991; Piazza et al. 1991). One could postulate that anxious and restless individuals may have increased dopaminergic reactivity and are more sensitive to stimulant drugs. In animals, these characteristics have been associated with proneness to self-administer psychostimulants; in humans, they may also increase the risk for drug self-administration.

DESIGN AND EXPERIMENTAL METHODS

Subjects

Selection Criteria. This proposed study involves evaluation of normal healthy male and female volunteers with the following inclusion and exclusion criteria:

- Inclusion criteria: right handed, 24 to 50 years of age.

• Exclusion criteria: history of neurological or psychiatric disease; history of alcohol or drug abuse by subject or first-degree relatives; medical illnesses, vascular or metabolic disorders; those requiring medication; history of head trauma or loss of consciousness; and cardiac arrhythmia apart from sinus bradycardia.

Subject Evaluation. Each subject will be evaluated based on the following methods:

1. Diagnostic interview. A diagnostic interview will be performed to ensure absence of psychiatric or neurological disease and to record a mental state examination.

2. Medical examination. All of the subjects will be given a complete physical and a neurological examination. The following laboratory tests will be obtained: cerebellumC, urine analysis, SMA6, LFTs, T3-T4, and urine and plasma tests to identify intoxication.

3. Personality evaluation. To assess personality structure, subjects will be administered the Minnesota Multiphasic Personality Inventory (MMPI). This inventory will be used to extract factor scores for impulsivity, novelty-seeking behavior, and extroversion.

4. The following evaluations will be performed prior to and during the PET procedure.

• Cardiovascular response. MP has been shown to increase blood pressure and heart rate. In rare circumstances it has also been shown to favor the occurrence of extraventricular contraction. To ensure maximal safety during this study, it is proposed to carefully monitor the cardiovascular response to MP by record-ing heart rate, blood pressure, and EKG. For this purpose, subjects are attached to an automatic device that enables continuous monitoring of heart rate and EKG throughout the study. Blood pressure is monitored every 15-minutes starting 30minutes prior to drug administration. Recordings of these measures are obtained at 15-minute intervals until the end of thestudy. At that point measures are only recorded every 30minutes until the subject returns to baseline (values±10percent those recorded prior to MP administration).

• Behavioral measures. Behavioral measures are rated by an outside observer, and subjective evaluation is obtained using analog scales. Measures rated by an outside observer are obtained prior to placebo or MP administration and at 20, 50, and 80 minutes after MP

administration. These measures include the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962). This scale provides a broad overview of symptoms known to be induced by psychostimulants. Scales for the assessment of positive and negative symptoms (SAPS and SANS) will also be administered (Andreasen 1982, 1984). Although these scales are specifically designed for use with schizophrenic patients, psychostimulants can induce some of the same symptoms and have therefore been proposed as models for schizophrenic symptomatology. Measures rated by the individual include subjective analog scales scored from 1to 10 for anxiety, restlessness, high, depression, happiness, mood, suspiciousness, tiredness, desire for more MP, and control over the desire for more MP. The analog scales are obtained prior toadministration of MP or placebo and periodically every 20minutes until the end of the study (100 minutes).

PET Scanning

Each subject will be tested twice with 11C-raclopride: during placebo administration and during MP administration. The order of administration will be randomly assigned for placebo or MP and will be double blind. The studies will be done 1 week apart. Placebo or MP will be administered 6 to 9 minutes prior to 11C-raclopride administration.

The PET studies will be done using a whole-body, high-resolution PET scanner. Subjects will be positioned in the PET camera with the indi-vidual headholder used for magnetic resonance imaging (MRI). The MRI scans are obtained for neuroanatomical coregistration with the PET scans. The fiducial marker that is placed 2 centimeters (cm) above the cantho-meatal (CM) line is used as reference to align the position of the gantry. An external chinstrap device is used in addition to the individual head-holder to minimize head motion during the scan. Before the emission scan, a transmission image will be obtained using gallium-68 to correct for attenuation. In preparation for the initial scans, two catheters are placed into the subject: a venous catheter for tracer injection and an arterial catheter for measurement of total plasma radioactivity concentration. Blood samples are also obtained to measure blood gases and plasma MP concentration.

Emission scans will be performed after injection of 6 to 10 mCi of 11C-raclopride. Scanning is started immediately after injection for a total of 60 minutes. During this period, sequential scans are obtained

at 1-minute intervals for 10 minutes and every 5 minutes thereafter. During scans, lights are dim and noise is kept to a minimum. The only inter-action maintained with patients is the periodic evaluation of their behavioral response to MP or placebo. In order to assess the plasma concentration of MP and metabolites, blood samples will be obtained prior to administration and at 15, 45, 75, 105, and 125 minutes after the injection of the first dose of MP. After completion of the scan, subjects are asked to void to minimize radiation exposure to the bladder.

Magnetic Resonance Imaging

MRI scans will be obtained prior to the PET scans and used for coregis-tration with the PET scans. The patient will be positioned supine on the scanning table with an individually molded headholder that will also be used for the PET scan. A fiducial marker is inserted into the headholder and is placed 2 cm above and parallel to the CM line. This marker will serve as reference to locate the angle of the anterior commissure-posterior commissure (AC-PC) line, which has been found to be a reliable internal indicator of position of structures. Individual determination of the location of the AC-PC angle with respect to the CM line will allow parallel position of the PET gantry using the CM line as a reference. The CM marker is filled with gadolinium and diethylenetriamine-pentaacetic acid (DTPA). Sagittal sections are initially done to locate the angle between the CM (determined with the fiducial marker) and the AC-PC line. Axial planes are then collected parallel to the AC-PC line. Contiguous 5mm thick longitudinal relaxation time (T1)-weighted axial slices (spin echo repetition time (TR) = 60 milliseconds (ms), echo time (TE) = 20 ms) and transverse relaxation time (T2)-weighted axial slices (spin echo TR = 2,500 ms, TE=70ms) will be obtained. The T1 axial MRI images will be used for coregistration with the PET images. For this purpose, an automated computer program has been developed that locates the centroid axis of the volume of the brain for both sets of images (Levy et al. 1989).

Analysis

Image Analysis. Regions of interest (ROIs) will be outlined in the individual's MRI scan. To ensure that the volume of the regions is consistent across subjects, a template has been developed. The template separately identifies regions in the right and the left in the basal ganglia: head of the caudate (2 planes), dorsal striatum (2 planes), and ventral striatum (1 plane). For the cerebellum, only one value is obtained by averaging left and right cerebellar ROIs in 2 contiguous planes The template is adjusted for each individual subject's MRI, and the ROIs are then superimposed on the PET scan.

Statistical Analysis. The primary hypotheses will be rigorously tested. Other analyses will be more exploratory in nature.

- Hypothesis 1: Behavioral response to a drug is not only a function of the chemical composition of the drug but also of the unique bio-chemical characteristics of an individual. It is predicted that indi-viduals with increased dopaminergic reactivity will be more sensitive to MP and vice versa. To test this hypothesis correlation analysis will be performed between the changes in 11C-raclopride binding and the behavioral effects of MP. Significance will be set as per Bonferroni calculations.

- Hypothesis 2: The personality and mental state of an individual reflect in part a unique metabolic and biochemical brain composition. It is predicted that individuals who report high levels of anxiety and restlessness prior to the PET scan will have a larger response to MP than those who do not. It is also predicted that factor scores in the MMPI that relate to novelty seeking will be associated with dopaminergic reactivity.

To investigate possible correlations between personality and mental state variables and the magnitude of the changes in raclopride binding in response to MP, factor analyses techniques will be used to simplify the data into a few vectors that optimize the information and minimize redundancy. Pearson product correlation analyses will be used to assess the significance of these correlations and will be corrected with Bonferroni calculations for the number of tests performed.

- Hypothesis 3: Increased dopaminergic reactivity is associated with increased vulnerability to drug addiction. Because these studies are not longitudinal, it is difficult to test this hypothesis. As an approxi-mate solution, measures of physiological response to MP will be used

to determine whether the behavioral response indicates a reinforcing experience. It is predicted that subjects who show large changes in response to 11C-raclopride will be those who also report desire for more drug as well as loss of control over their desire. Pearson product correlation analyses will be used to assess the significance of these correlations and Bonferroni calculations will correct for the number of tests performed.

Modeling. To quantitate 11C-raclopride, the distribution volume (basal ganglia)and distribution volume (cerebellum) will be calculated using the Logan plot (Logan et al. 1990). The analysis of 11C-raclopride binding in terms of the distribution volume provides a measure of binding that is a linear function of receptor availability as determined by the following:

distribution volume = K1/k2 (1+NS+Bmax /Kd) (equation 1)

for regions containing receptors characterized by an equilibrium dissociation constant Kd and free receptor concentration, Bmax. For non-receptor regions the distribution volume is calculated as follows:

distribution volume = K1/k2 (1+NS) (equation 2)

In both equations, NS represents the ratio of transfer constants for nonspecific binding; K1 and k2 are the plasma-to-tissue and tissue-to-plasma transport constant, respectively. A parameter proportional to Bmax can be obtained from equations 1 and 2 giving

Bmax/Kd (1/1+NS) = [distr vol (basal ganglia)/ distr vol (cerebellum)] -1

(equation 3)

Equations 1 and 2 are based on classical compartmental analysis in which the effects of cerebral blood flow and capillary permeability are implicitly included in the parameters K1 and k2.

PUBLIC HEALTH SIGNIFICANCE

PET studies have documented DA changes in cocaine abusers that appear to be correlated with decreased metabolism in orbitofrontal cortex, cingulate gyrus, and prefrontal cortex. Animal studies have documented a central role of frontal regions (orbitofrontal, cingulate,

and prefrontal cortices) in reinforcing properties of drugs (Dworkin and Smith 1992). It is believed that DA abnormalities in the cocaine abuser lead to dysregulation of these frontal regions, favoring the emergence of behaviors associated with addiction such as impulsivity, compulsion to self-administer cocaine, dysphoria, and inability to refrain from using cocaine. The extent to which these changes represent normal variability that predisposes an individual to drug addiction needs to be investigated in order to better understand mechanisms related to addiction.

Further work is required to determine if the variability in psychostimulant-induced dopaminergic changes represents differences in dopaminergic reactivity, to evaluate if these differences are genetically or environ-mentally controlled, and to assess if they are associated with a higher vulnerability for drug abuse. Future work is required to determine the extent to which specific neurochemical characteristics associated with "liking of psychostimulant drugs" can be generalizable to other drugs of abuse. If they are specific, then future work should also be done to determine if there are specific neurochemical patterns associated with the other abused drugs such as alcohol, tetrahydrocannabinol, or heroin. If patterns can be identified that are associated with proness to addictive behaviors, this knowledge could be used to target therapeutic intervention in the addicted subject.

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