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, electrophysio-logical, 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
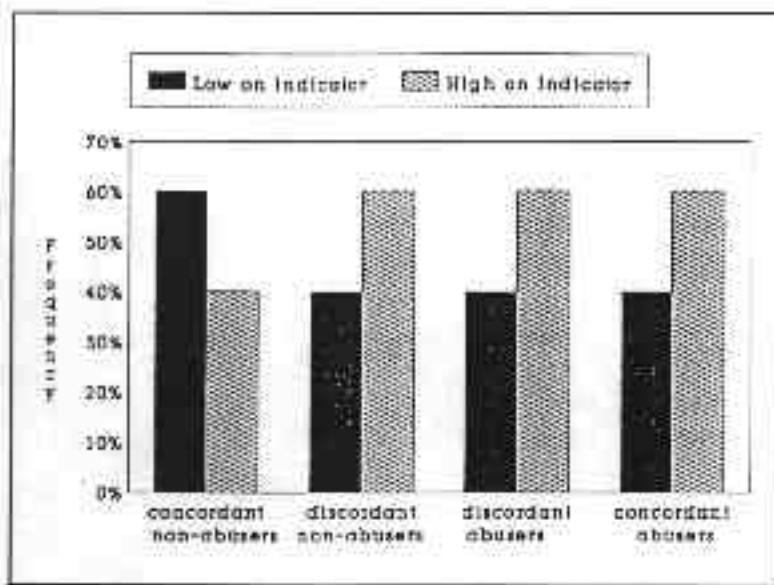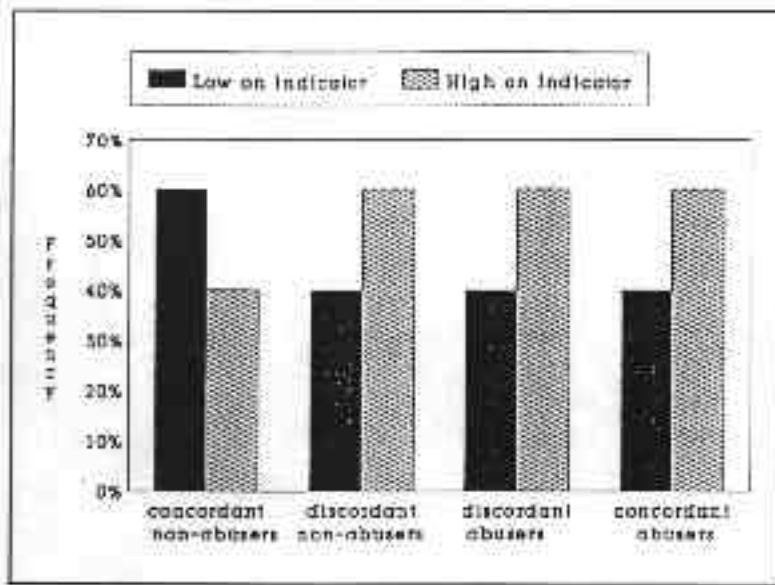

FIGURE 1. *Vulnerability model.*

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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.
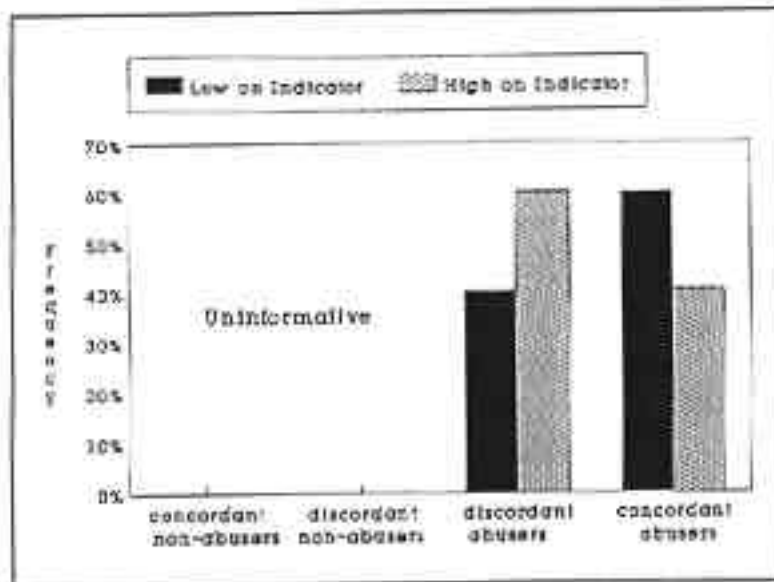
FIGURE 3. *Familial versus sporadic model.*

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
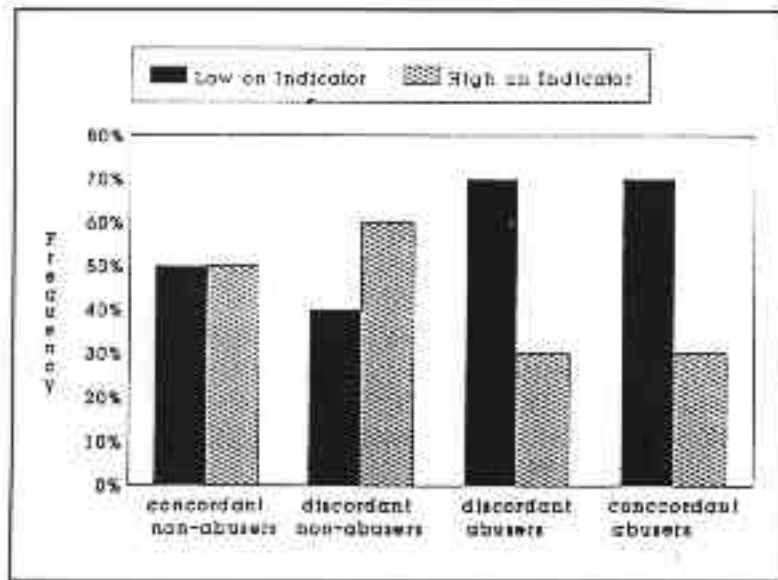
FIGURE 4. *Protective factor model.*

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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ACKNOWLEDGMENTS

AUTHORS

Ming T. Tsuang, M.D., Ph.D., Sc.D.
Stanley Cobb Professor of Psychiatry and Director
Harvard Institute of Psychiatric Epidemiology and Genetics
Harvard Departments of Psychiatry and Epidemiology

and

Head
Department of Psychiatry
Harvard Medical School at Massachussetts Mental Health Center and
Brockton/West Roxbury VAMC (116A)
940 Belmont Street
Brockton, MA 02401

Michael J. Lyons, Ph.D.
Assistant Professor
Psychology Department
Boston University

and

Lecturer and Research Psychologist
Department of Psychiatry
Harvard Medical School at Brockton/West Roxbury VAMC (116A)
940 Belmont Street
Brockton, MA 02401