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.

REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3d ed. (rev.) Washington, DC: American Psychiatric Association, 1987.

Bell, B.; Mednick, S.; Gottesman,O.; and Sergent, J. Electrodermal parameters in young, normal male twins. In: Mednick, S., and Christiansen, K.O., eds. Biosocial Bases of Criminal Behavior. New York: Gardner Press, 1977. pp. 217-225.

Begleiter, H.; Porjesz, B.; Bihari, B.; and Kissin, B. Event-related brain potentials in boys at risk for alcoholism. Science 225:1493-1496, 1984.

Bernstein, A.S.; Riedel, J.A.; Graae, F.; Seidman, D.; Steel, H.; Connolly, J.; and Lubowsky, J. Schizophrenia is associated with altered orienting activity: Depression with electrodermal (cholinergic?) deficit and normal orienting responses. J Abnorm Psychol 97:3-12, 1988.

Buchsbaum, M.S. Average evoked response and stimulus intensity in identical and fraternal twins. Physiol Psychol 2:365-370, 1974.

Cleckley, H. The Mask of Sanity. 5th ed. St. Louis: Mosby, 1976.

Dustman, R.E., and Beck, E.C. The visually evoked potential in twins. Electroencephalogr Clin Neurophysiol 19:570-575, 1965.

Finn, P.R.; Kessler, D.N.; and Hussang, A.M. Risk for alcoholism and classical conditioning to signals for punishment: Evidence for a weak behavioral inhibition system? J Abnorm Psychol 103:293-301, 1994.

Finn, P.R., and Pihl, R.O. Men at high risk for alcoholism: The effect of alcohol on cardiovascular response to unavoidable shock. J Abnorm Psychol 96:230-236, 1987.

Finn, P.R.; Ramsey, S.E.; and Earleywine, M. "Orienting to Relevant and Irrelevant Stimuli in Individuals at High Risk for Alcoholism." Paper presented at the annual meeting of the Society for Psychophysio-logical Research, Boston, MA, October 17-21, 1990a.

Finn, P.R.; Zeitouni, N.; and Pihl, R.O. Effects of alcohol on psycho-physiological hyperreactivity to nonaversive and aversive stimuli in men at high risk for alcoholism. J Abnorm Psych 99:79-83, 1990b.

Fowles, D.C. The three arousal model: Implications of Gray's two-factor learning theory for heart rate, electrodermal activity and psychopathy. Psychophysiology 17:87-104, 1980.

Gabrielli, S.G.; Mednick, S.A.; Volavka, J; Pollock, V.E.; Schulsinger,F.; and Itil, T.M. Electroencephalograms in children of alcoholic fathers. Psychophysiology 19:404-407, 1982.

Gough, H.G. Manual for the California Psychological Inventory. Palo Alto, CA: Consulting Psychologists Press, 1964.

Hare, R.D. Acquisition and generalization of conditioned fear responses in psychopathic and nonpsychopathic criminals. J Psychol 59:367-370, 1965.

Hare, R.D. Electrodermal and cardiovascular correlates of psychopathy. In: Hare, R.D., and Schalling, D., eds. Psychopathic Behavior: Approaches to Research. Chichester, UK: Wiley, 1978. pp. 107-144.

Hare, R.D., and Craigen, D. Psychopathy and physiological activity in a mixed-motive game situation. Psychophysiology 11:197-206, 1974.

Hare, R.D.; Frazelle, J.; and Cox, D.N. Psychopathy and physiological responses to threat of an aversive stimulus. Psychophysiology 15:165-172, 1978.

Hare, R.D.; Hart, S.D.; and Harpur, T.J. Psychopathy and the DSM-IV criteria for antisocial personality disorder. J Abnorm Psychol 100:391-398, 1991.

Hume, W.I. Physiological measures of twins. In: Claridge, G.S.; Canter,S.; and Hume, W., eds. Personality Differences and Biological Variation: A Study of Twins. Oxford: Pergamon Press, 1973. pp.87-114.

Iacono, W.G.; Lykken, D.T.; Peloquin, L.J.; Lumry, A.E.; Valintine,R.H.; and Tuason, V. Electrodermal activity in euthymic patients with affective disorders: A possible marker for depression. Arch Gen Psychiatry 40:557-565, 1983.

Iacono, W.G.; Lykken, D.T.; Haroian, K.P.; Peloquin, L.J.; Valintine,R.H.; and Tuason, V. Electrodermal activity in euthymic patients with affective disorders: One-year retest stability and the effects of stimulus intensity and significance. J Abnorm Psychol 93:304-311, 1984.

Lader, M.H., and Wing, L. Physiological Measures, Sedative Drugs, and Morbid Anxiety. London: Oxford University Press, 1966.

Lang, P.J.; Bradley, M.M.; and Cuthbert, B.N. Emotion, attention, and the startle reflex. Psychol Rev 97:377-398, 1990.

Lewis, E.G.; Dustman, R.E.; and Beck, E.C. Evoked response similarity in monozygotic, dizygotic and unrelated individuals: A comprehensive study. Electroenceph Clin Neurophysiol 23:309-316, 1972.

Lund, T.; Sponheim, S.; Clementz, B.A.; and Iacono, W.G. Internal consistency reliability of resting EEG power spectra in schizophrenic and normal subjects. Psychophysiology 32:66-71, 1995.

Lykken, D.T. A study of anxiety in the sociopathic personality. J-Abnorm Psychol 55:6-10, 1957.

Lykken, D.T.; Iacono, W.G.; Haroian, K.; McGue, M.; and Bouchard,T.J., Jr. Habituation of the skin conductance response to strong stimuli: A twin study. Psychophysiology 24:4-15, 1988.

Lykken, D.T.; Macindoe, I.; and Tellegen, A. Perception: Autonomic response to shock as a function of predictability in time and locus. Psychophysiology 9:318-333, 1972.

Lykken, D.T.; Tellegen, A.T.; and Iacono, W.G. EEG spectra in twins: Evidence for a neglected mechanism of genetic determination. Physiol Psychol 10:60-65, 1982.

Lykken, D.T.; Tellegen, A.; and Thorkelson, K.A. Genetic determination of EEG frequency spectra. Biol Psychol 1:245-259, 1974.

Ogloff, J.P.R., and Wong, S. Electrodermal and cardiovascular evidence of a coping response in psychopaths. Criminal Justic Behav 17:231-254, 1990.

Osborne, R.T. Heritability estimates for the visual evoked response. Life Sci 9:481-490, 1970.

Patrick, C.J.; Bradley, M.M.; and Lang, P.J. Emotion in the criminal psychopath: Startle reflex modulation. J Abnorm Psychol 102:82-92, 1993.

Pihl, R.O.; Finn, P.; and Peterson, J. Autonomic hyperreactivity and risk for alcoholism. Prog Neuro Psychopharmacol Biol Psychiatry 13:489-496, 1989.

Polich, J., and Bloom F.E. P300 and alcohol consumption in normals and individuals at risk for alcoholism: A preliminary report. Prog Neuro Psychopharmacol Biol Psychiatry 10:201-210, 1986.

Polich, J., and Bloom, F.E. P300 from normals and adult children of alcoholics. Alcohol 4:301-305, 1987.

Polich, J., and Bloom, F.E. Event-related brain potentials in individuals at high and low risk for developing alcoholism: Failure to replicate. Alcohol Clin Exp Res 12:368-373, 1988.

Polich, J., and Burns, T. P300 from identical twins. Neuropsychologia 25:299-304, 1987.

Polich, J.; Pollock, V.E.; and Bloom, F.E. Meta-analysis of P300 amplitude from males at risk for alcoholism. Psychol Bull 115:44-73, 1994.

Pollock, V.E.; Volavka, J.; Goodwin, D.W.; Mednick, S.A.; Gabrielli,W.F.; Knop, J.; and Schulsinger, F. The EEG after alcohol administration in men at risk for alcoholism. Arch Gen Psychiatry 40:857-861, 1983.

Propping, P. Genetic control of ethanol action in the central nervous system: An EEG study in twins. Hum Genet 35:309-334, 1977.

Propping, P.; Kruger, J.; and Mark, N. Genetic disposition of alcoholism. An EEG study in alcoholics and their relatives. Hum Genet 59:51-50, 1981.

Raine, A.; Venables, P.H.; and Williams, M. Autonomic orienting responses in 15-year-old male subjects and criminal behavior at age-24. Am J Psychiatry 147:933-937, 1990a.

Raine, A.; Venables, P.H.; and Williams, M.A. Relationships between central and autonomic measures of arousal at age 15 years and criminality at age 24 years. Arch Gen Psychiatry 47:1003-1007, 1990b.

Robins, L.M.; Babor, T.; and Cottler, L.B. Composite International Diagnostic Interview: Expanded Substance Abuse Module. 1987. (Available from the authors.)

Robins, L.N.; Wing, J.; Wittchen, H.U.; Helzer, J.E.; Babor, T.F.; Burke,J.; Farmer, A.; Jablenski, A.; Pickens, R.; Regier, D.A.; Sartorius, N.; and Towle, L.H. The composite international diagnostic interview. Arch Gen Psychiatry 45:1069-1077, 1988.

Rust, J. Genetic effects in the cortical auditory evoked potential: A twin study. Electroencephalogr Clin Neurophysiol 39:321-327, 1975.

Spitzer, R.L.; Williams, J.B.W.; and Gibbon, M. Structural Clinical Interview for DSM-III-R. New York: New York State Psychiatric Institute, 1987.

Stassen, H.H.; Bomben, G.; and Propping, P. Genetic aspects of the EEG: An investigation into the within-pair similarity of monozygotic and dizygotic twins with a new method of analysis. Electroencephalogr Clin Neurophysiol 66:489-501, 1987.

Stassen, H.H.; Lykken, D.T.; Propping, P.; and Bauben, G. Genetic determination of the human EEG. Hum Genet 80:165-176, 1988.

Surwillo, W.W. Cortical evoked potentials in monozygotic twins and unrelated subjects: Comparisons of exogenous and endogenous components. Behav Genet 10:201-209, 1980.

Tellegen, A.; Lykken, D.T.; Bouchard, T.J., Jr.; Wilcox, K.; Segal, N.; and Rich, S. Personality similarity in twins reared apart and together. JPers Soc Psychol 54:1031-1039, 1988.

Tharp, U.K.; Maltzman, I.; Syndulko, K.; and Ziskind, E. Autonomic activity during anticipation of an aversive tone in noninstitutionalized sociopaths. Psychophysiology 17:123-128, 1980.

Vogel, G. The genetic basis of the normal human electroencephalogram (EEG). Humangenetik 110:91-114, 1970.

Volavka, J. Electroencephalogram among criminals. In: Mednick, S.A.; Moffitt, T.E.; and Stack, S.A., eds. The Causes of Crime: New Biological Approaches. Cambridge: Cambridge University Press, 1987.

Welner, Z.; Reich, W.; Herjanic, B.; Jung, K.; and Amado, H. Reliability, validity, and parent-child agreement studies of the Diagnostic Interview for Children and Adolescents (DICA). J Am Acad Child Adolesc Psychiatry 26:649-653, 1987.

Whipple, S.C.; Berman, S.M.; and Noble, E.P. Event-related potentials in alcoholic fathers and their sons. Alcohol 8:321-327, 1991.

Zahn, T.P. Autonomic nervous system characteristics possibly related to a genetic pre-disposition to schizophrenia: An overview. Schizophr Bull 6:49-60, 1977.

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