

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

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SUMMARY

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

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

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

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

STRENGTHS OF THE PROPOSED RESEARCH

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

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

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

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

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

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

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

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

WEAKNESSES OF THE PROPOSED RESEARCH

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

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

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

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

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

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

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

ALTERNATE IDEAS

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

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

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

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