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

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SUMMARY

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

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

STRENGTHS OF THE PROPOSED RESEARCH

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

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

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

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

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

WEAKNESSES OF THE PROPOSED RESEARCH

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

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

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

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

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

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

ALTERNATE IDEAS

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

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

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

REFERENCES

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