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

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SUMMARY

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

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

STRENGTHS OF THE PROPOSED RESEARCH

One of the major strengths of this procedure is that the technique is not invasive and does not use ionizing radiation. The noninvasive nature of this procedure readily allows it to be used in populations (e.g., children) that are typically protected from relatively new and unproven techniques. The lack of the need for ionizing radiation is another important strength because it allows for repeated assessments over a relatively short period of time, if necessary. This approach permits a repeated measure design to be used and subjects can easily serve as their own controls. There are restrictions on the amount of ionizing radiation that can be given to an individual subject; without such restrictions, MRS offers the researcher an opportunity to be more creative with the experimental designs.

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

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

Another strength of the proposed research is the extensive measures of dysregulated behaviors that will be collected. The study will include assessments of aggression, inattention, hyperactivity, and impulsivity. A further strength is the procedure for relating the acquired 31P spectra to the localized individual image. Identification and calculations of the peak areas for adenosine triphosphate (ATP), phosphomonoesters (PME), phosphodiesters (PDE), and the phosphocreatine/inorganic phosphate (Pcr/Pi) ratios will be performed under the supervision of experts in the field. These state-of-the-art procedures should result in extremely accurate measures of these substances. A separate validation procedure utilizing the difference in chemical shifts between the gamma ATP and the alpha ATP and using the method described by Pettegrew and colleagues (1991) represents another significant strength of the application.

WEAKNESSES OF THE PROPOSED RESEARCH

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

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

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

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

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

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

ALTERNATE IDEAS

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

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

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

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ACKNOWLEDGMENT

This review and commentary was supported, in part, by grant DA 00115 from the National Institute on Drug Abuse.

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