^{31}P Magnetic Resonance Spectroscopy in Children at Risk for Substance Abuse

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STATEMENT OF THE PROBLEM

Evidence strongly indicates that the risk for developing a substance abuse (SA) disorder is not randomly distributed in the population. However, the mechanisms underlying this risk are largely unknown. Particularly, little is known about neurobiological mechanisms involved in SA vulnerability. Increased risk for SA has been linked to behavioral disorders such as attention deficit-hyperactivity disorder (ADHD) across the lifespan, conduct disorder (CD) during childhood and adolescence, and adult antisocial personality disorder (ASPD). Previous research has suggested that these latter disorders may be associated with frontal lobe dysfunction. Consequently, it is postulated that a component of the liability to SA is associated with a variant of frontal cortical physiology. Furthermore, it is hypothesized that this physiologic variation will be manifested by abnormalities of brain energy and membrane phospholipid metabolism detectable by in vivo phosphorus 31 (31P) magnetic resonance spectroscopy (MRS).

Specific Aim 1

The first goal of the proposed study is to determine whether boys and girls with a conduct problem (CD+), oppositional defiant disorder (ODD), or CD as defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. rev. (DSM-III-R), and a father with history of psychoactive substance dependence (SA+) can be differentiated from sons and daughters of SA+ fathers who are CD-, and from age-matched normal controls with respect to variations in dorsal prefrontal cerebral energy metabolism measured by in vivo 31P MRS.

Specific Aim 2

The second goal of the proposed study is to determine whether SA+/CD+ children can be differentiated from SA+/CD- boys and girls and from age-matched normal controls on dorsal prefrontal phospholipid metabolism measured by in vivo 31P MRS.

Specific Aim 3

The third goal of the proposed study is to determine the associations in SA+ (both CD+ and CD-) youth between measures of dorsal prefrontal cerebral energy and membrane phospholipid metabolic activity with dimensional measures of aggression, inattention, impulsivity, and hyperactivity. These behaviors are thought to be important components of SA vulnerability.

BACKGROUND AND SIGNIFICANCE

Several lines of evidence converge upon the heuristic value of research directed at clarifying the neurobiological basis of SA vulnerability. The following discussion is a summary of the existing evidence implicating a neurobiological basis of SA vulnerability that is particularly manifest in the anterior cerebral regions. A brief description of MRS and its potential to elucidate aspects of this neurobiologic substrate is also included.

Evidence Suggestive of Anterior Cerebral Disorder in SA Based on Neuropsychologic Studies of ASPD and Its Antecedents

The most prevalent adult psychiatric disorder occurring comorbidly with psychoactive substance abuse is ASPD (Regier et al. 1990). Antisocial individuals demonstrate impulsive, aggressive, and disinhibited behavior similar to that seen among humans and primates with lesions in the anterior cortical region (Pribram 1973). These same features of dysregulated behavior have been frequently shown to predispose to psychoactive substance use disorders (Gorenstein and Newman 1980).

Although similarity in behavior does not necessarily imply commonality in underlying mechanisms, it is important to point out that individuals at high risk for alcoholism and those with CD/ASPD show impairment on neuropsychologic tests of executive functioning (Moffitt 1993). A host of neuropsychological investigations have

suggested that ADHD both in childhood and as a residual disorder in adulthood, CD in adolescence, and ASPD in adulthood are associated with dysfunction of the frontal lobes (Kandel and Freed 1989). ASPD adults have been shown to perform as poorly on neuropsychological tests sensitive to frontal lobe functioning as patients with actual frontal lesions (Gorenstein 1982). However, a replication that studied ASPD and non-ASPD psychoactive substance abusers failed to confirm this finding (Hoffman et al. 1987).

Since SA per se can produce neuropsychological deficits (Grant et al. 1978), and since SA is almost invariably present in ASPD, it is critical to differentiate any central nervous system (CNS) effects of SA from an underlying neurobiological diathesis. This proposed investigation of frontal cerebral high-energy phosphate and membrane phospholipid metabolism in children at high risk for SA affords a unique opportunity to evaluate this putative predisposition for SA disorder without the confounding effects of prior exposure to drugs.

Obviously, not all adults with prefrontal abnormalities have ASPD or SA, and dedicated positron emission tomography (PET) studies of ASPD individuals have yet to be reported. Thus, it is premature to draw con-clusions concerning the relationship between prefrontal anomalies on PET and the syndromal diagnosis of ASPD. In that most psychiatric syndromes are multifactorial, prefrontal dysfunction may be concep-tualized as one aspect of the total liability for ASPD and/or for SA.

Evidence Suggestive of Anterior Cerebral Disorder in SA Based on Neuroimaging Research

Attentional and cognitive impairments have been implicated as risk factors for SA disorders (Tarter et al. 1985). To date, neuroimaging investigations has been conducted on youth with ADHD; this group of individuals has syndromal attentional deficits and have been frequently documented in longitudinal investigations as being at increased risk for SA. Youth with ADHD, particularly those who have comorbid CD or ODD, are at signi-ficant risk for developing SA disorders, as well as ASPD in adulthood (Biederman et al. 1990; Cantwell and Baker 1988; Gittelman et al. 1985). Furthermore, among adult substance abusers, up to 40 percent meet diagnostic criteria for ADHD-residual type (Wood et al. 1983).

An early neuroanatomical investigation of ADHD used computerized axial tomography (CAT), but was hampered by the inclusion of a

large number of subjects who already had an SA disorder, thereby confounding the interpretation (Nasrallah et al. 1986). Nonetheless, investigators observed a significant degree of anterior cerebral atrophy. However, another study that also used CAT technology to evaluate neuroanatomic features reported no significant structural differences between ADHD cases and controls (Shaywitz et al. 1983).

Regional cerebral blood flow (rCBF) studies provided a significant methodologic improvement over static neuroanatomic examination of the brain because they inform about cerebral metabolic activity in specific brain regions and neural structures. In the normal brain, cerebral blood flow and cerebral glucose metabolism correlate in an almost 1:1 ratio, and both are closely related to brain function (Mathew et al. 1985; Raichle et al. 1976). Early rCBF studies of ADHD children using the xenon-133 inhalation method revealed hypoperfusion and low metabolic activity in the white matter of the frontal lobes and the caudate nuclei (Lou et al. 1984). However, a practical drawback to this method is the exposure of prepubertal children to a significant dose of ionizing radiation, which has the potential for long-term adverse sequelae.

Recently, Zametkin and colleagues (1990), cognizant of the problems inherent in exposing children to ionizing radiation, reported results of a PET study of regional cerebral glucose metabolism in adults who had ADHD since childhood but no history of SA or CD in adolescence. Significant reductions in cerebral glucose metabolism were demonstrated in the premotor cortex (control of motor activity) and the superior prefrontal cortex (regulation of attention), consistent with deficits in neuropsychologic tests of children with ADHD. This study supports the notion that reduced anterior cerebral metabolism may be an important indicator for the risk of ADHD and, by implication, for the risk of SA.

Evidence Suggestive of Anterior Cerebral Disorder in SA Based on Dispositional Behavior

Several specific dispositional propensities have been linked to heightened risk for SA. These include negative mood states, sensation-seeking behavior (Zuckerman 1972), and impulsivity (Jones 1968; McCord et al. 1960). Each of these propensities has been linked to anterior cerebral function.

The experience of negative mood states may be mediated through dys-function of the prefrontal cortex. For example, Grafman and

colleagues (1986) investigated the effects of lateralized orbitofrontal and dorsolateral prefrontal injuries on mood regulation. Lesions of the right orbitofrontal region were associated with increased irritability, anxiety, and depression, while left dorsolateral lesions were associated with greater anger and hostility. These affective characteristics have been implicated to presage SA (Jaffe et al. 1988; Kandel et al. 1986; Kellam et al. 1982). Sensation-seeking or risk-taking behavior has been linked to reduced behavioral inhibitory capacity. Associated with this behavioral characteristic is impulsivity. This propensity, like sensation seeking, has been frequently related to SA (Cadoret et al. 1986) and is manifest following an anterior cerebral injury (Mattson and Levin 1990). Nonalcoholic offspring of alcoholics not only exhibit these latter behavioral propensities but also demonstrate a pattern of evoked potential abnormalities, which have been interpreted to reflect maturational retardation in the anterior cerebral region (Hill et al. 1990).

Actions of Drugs of Abuse on Anterior Cortical Structures

Several drugs of abuse exert actions on the anterior structures of cerebral cortex. High doses of alcohol (Volkow et al. 1988) appear to increase cerebral blood flow, while low doses of benzodiazepines (Mathew et al. 1985) decrease cerebral blood flow to this area. Both drugs produce effects that are more pronounced in the right frontal cortex. Amphet-amines have been reported to bilaterally reduce cerebral metabolic rates in the frontal regions (Wolkin et al. 1987). Cocaine has been found to reduce glucose metabolism in most brain regions, including the frontal lobes (London et al. 1990).

Individual differences in the subjective and objective responses to drugs of abuse may account for the variability in outcomes for those adolescents who experiment with drugs. One possible mechanism for these individual differences is an interaction between the premorbid neurobiologic substrate of the adolescent with the actions of the drug. It is reasonable to hypothe-size that the frontal cortex is the site of this interaction. Drug-induced reductions in the already diminished frontal activity of individuals at heightened risk for SA may further disinhibit these individuals, thereby augmenting affective and behavioral dysregulation and increasing the propensity for continued drug use.

Description and Utility of In Vivo 31P Magnetic Resonance Spectroscopy

Although nuclear MRS was discovered more than 30 years ago, the technique has only recently been applied to the study of metabolic functions of the living human brain (Bottomley et al. 1984; Welch 1989). Subsequently, this noninvasive technique has been used to study a variety of clinical conditions affecting human brain functioning (Pettegrew 1991). Simply stated, MRS takes advantage of the fact that many specific atomic nuclei align in a particular direction under the influence of an external magnetic field. In order to detect this alignment, the magnetic moment of these nuclei must first be disturbed by a brief pulse of radiowaves at a specific and unique frequency that causes the nuclei to precess. After the pulse is switched off, the precessing nuclei briefly induce an alternating voltage at a fixed frequency in a receiving coil until the precession decays. In complex biological materials, the particular nuclei of interest produce characteristic shifts in signal resonance frequency (called chemical shifts) due to slight differences in the chemical structures of the associated molecules. The voltage changes from these shifts are detected and amplified so that the signals can be digitized and stored in computer memory. The frequencies associated with the chemical shifts can be analyzed by Fourier transforms, making possible the identification of specific molecules of interest.

Phosphorus is present in molecules of living tissue and is critically important for transformation and use of energy by neurons and glia and synthesis and degradation of phospholipids that comprise neuronal and glial membranes. 31P MRS brain spectra are sensitive to the presence of these phosphorus-containing molecules in which concentrations are 0.1-millimole and above. As seen in figure 1, these spectra manifest as resonance signal peaks that quantify the presence of phosphocreatine (PCr), inorganic phosphates (Pi), phosphomonoesters (PME), phospho-diesters (PDE), and the g, a, and ß phosphates of adenosine triphosphate (ATP). Biochemical inferences are made based upon the contribution of each resonance signal to the total phosphate resonance signal and the changes in their areas under the curve (Welch 1989).

ATP is a critically important energy-transporting molecule that links energy sources such as nutrients (e.g., glucose) to energy-requiring cellular processes such as biosynthesis and membrane transport. In mammalian brain, the ß and gATP 31P MRS signals reflect additive contributions by the major energy-carrying compounds ATP, adenosine diphosphate (ADP), and adenosine monophosphate (AMP) (Pettegrew et al. 1986). The a-ATP signal is less specific since it also contains contributions from dinucleotides. The PCr signal reflects the concen-tration of a high-energy phosphate compound catalyzed by creatine kinase, which functions as a buffer to keep brain levels of ATP constant.

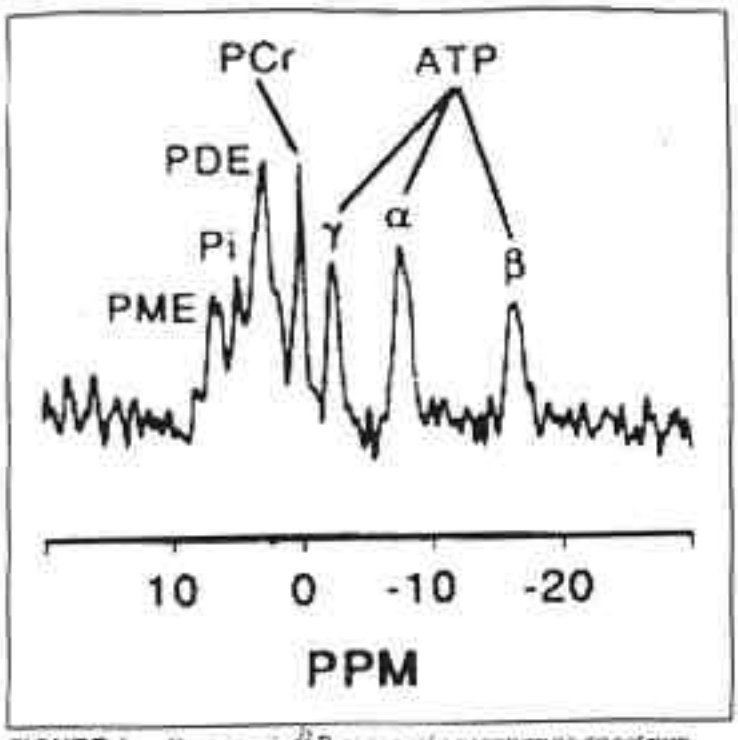

FIGURE 1. *Prototypic ^{31}P magnetic resonance spectrum.*

The Pi signal reflects concentrations of one of the catabolic breakdown products of ATP metabolism. Thus, the PCr/Pi ratio may indicate ATP synthesis relative to catabolism.

The PME signal reflects the presence of precursors of membrane phospholipids primarily including phosphocholine, phosphoethanolamine, and alpha-glycerophosphate. The PDE signal reflects concentrations of degradative products after membrane phospholipid breakdown. The PDE region includes glycerophosphodiesters, phosphorylated glycolipids, and glycoproteins (Pettegrew et al. 1986, 1987). Thus, the PME/PDE ratio may reflect membrane phospholipid synthesis relative to catabolism. Importantly, preclinical and clinical studies have demonstrated that 31P MRS can provide valuable heuristic insights into both the bioenergetic status of the brain and the dynamic biologic membrane synthetic processes occurring within the brain during development and maturation (Hida et al. 1992; Holtzman et al. 1991; Minshew et al. 1992; Pettegrew et al. 1987, 1990). For example, it has been established that the frontal cerebral cortex undergoes a maturational decline in synaptic density (sometimes

called synaptic pruning) between ages 2 to 16 years (Huttenlocher 1979). Preliminary research suggests that this synaptic pruning is reflected in a decrease in synthesis of membrane phospholipids and an increase in their degradation, which can be monitored using 31P MRS (Minshew et al. 1992). Although speculative, this technology may ultimately be useful in testing hypotheses concerning the presence of a putative delay (or dys-function) in the chronological attainment of stages of cerebral maturation among youth at high risk for psychoactive substance abuse disorders (Hudspeth and Pribram 1992).

Significance

This initial investigation will be used to determine if 31P MRS of the frontal brain region is a heuristic strategy able to delineate the neuro-biologic substrate of the risk for a SA disorder, which can present prior to a child's actual exposure to drugs of abuse. 31P MRS provides a unique picture of in vivo brain energy metabolism and the metabolic status of neural membranes' structural constituents without the drawbacks associated with more invasive techniques involving exposure to ionizing radiation. The elucidation of a neurobiologic risk factor for the develop-ment of SA can lead to novel biopsychosocial models for SA etiology with significant ramifications for prevention and treatment. To the author's knowledge, this technology has yet to be applied to either cross-sectional or longitudinal research on SA vulnerability.

Preliminary Evidence for Disturbances in Executive Functions in the Proposed Study Population

Table 1 summarizes some selective findings to date from a preliminary study on a sample of prepubertal boys comparing SA+/CD+, SA+/CD-, and control boys (as previously defined) on measures of behavioral deviation implicative of disturbances in executive functions that are associated with the prefrontal cortical regions. Elevations on these same neuropsychological dimensions have been implicated in the liability for later SA in several longitudinal studies (Kandel et al. 1986; Kellam et al. 1982; McCord et al. 1960). On the majority of measures the SA+/CD+ group differs significantly from the other two groups. This observation supports a gradient of SA risk such that SA+/CD+ boys > SA+/CD- boys > SA-/CD- boys. The study sample from which these data were collected will constitute the males in this proposed study; females will be recruited from a similar population.

TABLE 1. Evidence for disturbances in executive functioning postulated to be localized to prefrontal cortex.

Measure	Group I: SA+/CD+ (N = 27)	Group II: SA+/CD- (N = 64)	Group III: Normal (N = 69)	F-ratio; 2-tailed probability
Behavioral Dysregulation Scales (Martin et al. 1994)	mean±SD	mean±SD	mean±SD	
Aggression	0.71±0.5	-0.11±0.6	-0.80±0.6	F = 24.5, p< 0.00001
Inattention	0.57±0.6	-0.01±0.7	-0.20±0.6	F = 14.4, p< 0.00001
Hyperactivity	0.19±0.4	-0.03±0.4	-0.05±0.4	F = 3.9, p < 0.02
Impulsivity	0.42±0.7	0.06±0.6	-0.20±0.6	F = 7.5, p < 0.0008
Distraction episodes observed during written arithmetic test	5.20±4.4	2.40±3.2	2.58±3.4	F = 5.6, p < 0.0047
Response bias (impulsivity) during computerized vigilance task	0.01±0.01	0.01±0.01	0.006±0.0	F = 4.7, p < 0.01

NOTE: In post-hoc comparisons, group I differs from group II and group III for all measures except impulsivity, where group I differs from group III only.

DESIGN AND EXPERIMENTAL METHODS

Overview of Design

This study will use a case-control design in which the two risk groups will consist of 10- to 12-year-old boys and girls who are the offspring of fathers who meet DSM-III-R criteria for a psychoactive substance dependence disorder (above and beyond nicotine dependence) and either have a conduct problem (SA+/CD+) (defined as meeting DSM-III-R criteria for ODD or CD) or do not have a conduct problem or any other psychiatric disorder (SA+/CD-). The subjects will be matched and contrasted with medically and psychiatrically normal sons and daughters of fathers who do not meet DSM-III-R criteria for any disorder (SA-/CD-). Fathers with psychoactive substance dependence will be selected for sampling in order to ensure an adequate severity of SA to confer significant risk to their offspring. The groups will be compared on magnetic resonance spectra derived from 31P MRS scans of the dorsal prefrontal cortex.

Hypotheses

Based upon the results of prior investigations in subjects with disruptive behavior and using technologies such as rCBF studies (Lou et al. 1984) or PET (Zametkin et al. 1990), and based on PET studies of normal CNS maturation (Chugani et al. 1987), it is hypothesized that SA+/CD+ children will show evidence of reduced dorsal prefrontal metabolism and increases in CNS biomembrane breakdown (possibly reflecting greater synaptic decline) in comparison with matched SA+/CD- subjects and normal control children. Specifically, the following hypotheses will be tested.

1. Ten- to 12-year-old SA+/CD+ children will be differentiated from age, sex, and socioeconomic status (SES) matched SA+/CD- children and psychiatrically and medically normal children of psychiatrically normal parents (SA-/CD-) on the basis of reduced dorsal prefrontal bioenenergetic metabolic activity as indicated by increased 31P MRS signal for ATP (suggesting reduced ATP utilization) and a greater PCr/Pi ratio (suggested reduced catabolism relative to synthesis).

2. SA+/CD+ children will be differentiated from age, sex, and SES-matched SA+/CD- and SA-/CD- subjects on the basis of reduced dorsal prefrontal PME/PDE ratios (suggestive of increased membrane catabolism).

3. Within the SA risk groups (SA+/CD+ and SA+/CD-), subject scores on composite measures of impulsivity, aggression, hyperactivity, and inattention will directly predict dorsal prefrontal 31P MRS signals for ATP and the PCr/Pi ratio (indicative of reduced dorsal prefrontal metabolism) and inversely predict with the PME/PDE ratio recorded over the dorsal prefrontal region (indicative of increased membrane catabolism).

Subjects

Inclusionary Criteria. The highest risk group (SA+/CD+) will include 16 boys and 16 girls (ages 10 to 12 years) who meet DSM-III-R criteria for either ODD or CD and whose fathers meet lifetime DSM-III-R criteria for psychoactive substance dependence disorder (in addition to nicotine dependence, if present). The moderate risk group (SA+/CD-) will comprise 16 boys and 16 girls whose fathers are SA+ but the subjects do not meet any DSM-III-R diagnostic criteria. Normal daughters and sons of control fathers who met no DSM-III-R criteria will be studied as a normal control group (SA-/CD-). The groups will be matched on age, sex, race, physical maturation (Tanner stage), intelligence, and family SES. The sample will be drawn from a community population (rather than treatment programs) using advertising and reverse telephone book solicitation in order to maximize representativeness of the sample.

Exclusionary Criteria, Children. Children will be excluded for the following criteria:

1. Any current diagnosis or history of a DSM-III-R psychoactive substance abuse disorder or any significant history of experimentation with alcohol or drugs. To further rule out drug use, quantity/frequency indices will be obtained from the Substance Use Questionnaire (Tarter, unpublished data). The validity of self-reports of drug use are enhanced through the implementation of a "bogus pipeline" procedure (Evans et al. 1977) using hair samples. Specifically, subjects are told that self-reports of drug use will be reconciled with results obtained from the analysis of a hair sample. However, no such hair analysis actually takes place. Urine drug screens utilizing standard immunoassay methods are also used to provide collaborative evidence of abstinence from recent drug use both during subject ascertainment and on the day of the scan.

2. Any current or lifetime diagnosis of autistic disorder or psychosis.

3. Prior history of open or closed head injury with or without loss of consciousness (e.g., concussion).

4. The presence of a seizure disorder or any other neurologic illness or neurodevelopmental disability.

5. Current administration of any neurologically active drugs (e.g.,-tran-quilizers, antidepressants, neuroleptics, or anticonvulsants).

6. Cigarette smoking or other habitual use of nicotine products.

7. Intelligence quotient (IQ) below 90 as determined by the Weschler Intelligence Scale for Children (WISC-III) (Weschler 1991) or Weschler Adult Intelligence Scale, revised (WAIS-R) (Weschler 1981) to eliminate confounding effects of mental deficiency.

8. The presence of metallic plates or pins anywhere in the body.

In addition, all subjects must be abstinent from caffeine for at least 12hours and over-the-counter cold medicine or any other medications that possess a psychoactive effect for 24 hours prior to MRS scanning.

Exclusionary Criteria, Parents. Subjects will be assigned to high-risk or low-risk SA group status based upon the presence or absence of a psychoactive substance dependence disorder (besides nicotine dependence) in the father. However, subjects will be excluded if:

1. Substance-abusing fathers have (a) a life-threatening medical illness, (b) a chronic neurologic disorder, or (c) a psychotic illness;

2. If nonabusing fathers have (a) any past or current DSM-III-R axis I or II disorder, (b) a life-threatening medical illness, or (c) a chronic neurologic disorder; or

3. Any of the mothers have (a) any past or current DSM-III-R axis I disorder, (b) a life-threatening medical illness, (c) a history of alcohol and/or drug use during the research subject's gestation, and (d) a chronic neurologic disorder.

Mothers of high-risk subjects who themselves have a DSM-III-R psychoactive substance use disorder would be included in order to allow for an exploratory analysis of the effects of bilineal versus unilineal familial substance abuse on their offspring. However, if mothers of high- risk subjects report that drugs were used during the index pregnancy, they would be excluded.

Sample Size and Power Requirements

In order to test hypotheses 1 and 2 (i.e., the SA+/CD+, SA+/CD-, and SA-/CD- comparisons), the proposed sample size of 32 per group (16-boys and 16 girls) would be sufficient to achieve benchmark statistical power= 0.8 at a one-tailed a = 0.05, for a moderate effect size= 0.32.

In order to test hypothesis 3, the combined SA+/CD+ and SA+/CD- groups sample size of 64 would be sufficient for a benchmark statistical power = 0.8 at a one-tailed a = 0.05, assuming a moderate correlational effect size of 0.32.

Independent Variables: Psychiatric and Substance Abuse Diagnoses of Father and Child

At the time of ascertainment, substance-abusing and nonabusing fathers will be administered an expanded version of the Structured Clinical Interview for Diagnoses (SCID). Best-estimate DSM-III-R diagnoses are generated using data obtained from the SCID, confirmatory information from the spouse, and any available clinical records. This diagnostic approach is in accordance with the method described by Leckman and colleagues (1982), and was recently validated by Kosten and Rounsaville (1992). Index boys and girls (10 to 12 years of age) will be assessed using an expanded version of the Children's Schedule for Affective Disorders and Schizophrenia (K-SADS) administered to both the child and mother (reporting on child). The expanded K-SADS contains a detailed inquiry about deviant, aggressive, and illegal behavior. DSM-III-R diagnostic formulations for index children will be based chiefly upon maternal reports of the child's behavior with confirmation through the child's self-report and any available clinical records. Both adult and child best-estimate diagnoses will be compiled and ultimately finalized after case presentations at a diagnostic consensus conference. At such conferences only numerical identifiers are used so that psychiatric diagnoses of children are made blind with respect to the psychiatric status of their parents.

Composite Measures of Dysregulated Behaviors

Numerous measures from multiple data sources will be used to construct indices of aggression, inattention, hyperactivity, and impulsivity (Martin et al. 1994). Data sources include mother's report on child, child's self-reports, teacher's reports on child, and child laboratory test measures. "Mother reports on child" data use item

endorsements from the disruptive behavior disorder symptoms on the K-SADS-E (Orvaschel et al. 1982), the Child Behavior Checklist (Achenback and Edelbrock 1983), and a minimal brain dysfunction questionnaire (Tarter et al. 1977). Child self-report data will be primarily taken from symptoms endorsed on the K-SADS-E (Orvaschel et al. 1982). Teacher reports will be taken from responses on the Child Behavior Checklist-Teacher Version (Achenback and Edelbrock 1983), the Disruptive Behavior Disorders Rating Scale (Pelham and Murphy, unpublished data), and the Connors Behavior Rating Scale (Connors 1969).

Laboratory test data on the child will be obtained from a computerized provocation-to-aggression task (Pelham et al. 1991), objective measure of motor activity during specific tasks (Tryon 1991), a computerized vigilance task (Schneider and Detweiler 1987), and subtests of the WISC-III (Weschler 1991). Summary score indicators and their covariances will be examined on the basis of data type and data source in a systematic fashion. Indicators will first be evaluated on measures from specific informants; indicators that show good convergent validity (e.g.,high Cronbach's alpha) will be retained. Then, the convergence of summary scores from different data sources will be evaluated. Next, factor and construct scores derived from this procedure will be subjected to concurrent validity analysis using variables that are not used in the data reduction procedure.

This structural approach to data reduction will minimize the possibility that a particular instrument or a particular data source wields an undue degree of influence on resultant construct scores. The convergent validity of the resultant constructs and the estimation of method variance parameters were tested using a latent variable approach (Jöreskog and Sörbom 1989) in a multitrait, multimethod model (Campbell and Fiske 1959). The results indicated that the covariance between these indicators is best represented by the four specified traits and four specified methods. The majority of significant factor loadings stemmed from the underlying traits rather than the method factors, providing further evidence for the validity of these measures.

Dependent Measure: 31P Magnetic Resonance Spectra

This procedure will involve first generating a morphologic image using standard longitudinal relaxation time (T1)-weighted spin-lattice proton magnetic resonance imaging (MRI) scans in order to define the anatomic region of the dorsal prefrontal cortex and its volume that

are the desired signal sources (volumes of interest) for 31P MRS. The magnetic field strength will be 1.5 Tesla tuned to a phosphorus nuclear magnetic resonance frequency of 25.895 megahertz (MHz) and a proton frequency of 63.970 MHz. The 31P nuclear magnetic spectra will be obtained utilizing a magnetic field strength (B1) field gradient as described by Bendall (1990), but without phase cycling.

The 31P spectra will be acquired using the same set of surface coils used to obtain the morphologic image, and will be reconciled with this image using the image-processing capabilities of the scanning system in order to ensure an accurate determination of the spectral signal source. The imaging and spectroscopy scans will be obtained using the surface coil technique with coils mounted over the frontal region of the head of the supine subject. For 31P MRS, surface coils are used to transmit the radio frequency impulse and receive the resulting voltage oscillations. To maximize the signal-to-noise ratio in the shortest time possible from a well-defined spatial focus, which in this case is the prefrontal cortex, surface coils will be dual-tuned to detect both the proton and 31P frequencies. Specifically, a 20-centimeter (cm) 31P surface coil and a coplanar 7.5 cm surface coil will be used. Hydrogen (proton) images for spectral localization will be obtained by transmitting with the Helmholtz surface body coil and receiving with the 7.5 cm coplanar surface coil. This will permit a uniform excitation of the head, but with a receptivity profile based on the 7.5 cm coil. The 31P spectra will be acquired by transmitting with the 20 cm coil and receiving with 7.5cm coil. The 20cm coil is sufficiently large (compared with the 7.5cm coil) to produce the same radio frequency homogeneity in the area of interest as that of the body coil used for the proton images of the brain. Conse-quently, the acquired 31P spectra can be directly related to the localized proton image. Other acquisition parameters will be the same as described by Pettegrew and colleagues (1991).

Identification and Calculation of Peak Areas for ATP, PME, PDE, and the PCr/Pi Ratios

All spectra will be processed on a data station with a 5 hertz (Hz) exponential multiplication, first- and second-order phase correction to bring all peaks into absorption mode, and with baseline correction by means of linear tilts known as baseline points. Integrated areas would then be calculated using a program that fits the spectrum with a series of Lorentzian lines. Known doublets, such as the ionized ends regions, will be fitted with two Lorentzian lines, and known triplets, such as the middle region, will be fitted with three Lorentzian lines.

The PME and PDE peaks will then be fitted with one, two, or three Lorentzian lines to obtain the most accurate fit.

The accuracy of fit will be assessed by determining if the difference between experimentally observed and simulated spectra yield a flat line. For each spectrum, the integrated areas of the PME, Pi, PCr, ionized ends (g-ATP), and esterified ends (a-ATP) and middles (ß-ATP) will be determined. From these integrated areas, the mole percents of PME, Pi, PDE, PCr, and ATP will be measured. The signals will be expressed as mole percentages of the total 31P MRS signal, thereby giving relative amounts of these molecules in the brain region.

Analysis and Expected Results

Following a graphic display of the raw data, assessment for normality (with appropriate transformation of data to induce normality, when appropriate), and testing for outliers, descriptive statistics will be generated for all independent and dependent variables. Dependent variables will also be assessed for homogeneity of variance and significant intercorrelation. Between-group tests of matching variables will be conducted to assure group comparability. Should between-group differences in matching variables be found, analyses of covariance (ANCOVA) will be employed using the differentiating variable as covariate. Should there be significant correlations between dependent MRS measures, a multivariate analysis of variance (MANOVA) procedure will be used instead of the analysis of variance (ANOVA) approach to test hypotheses 1 and 2. If multi-collinearity is found in multiple regression analyses, then ridge regression procedures will be utilized.

The general linear model ANOVA will be employed to test research hypotheses 1 through 3. This approach was chosen because it permits an evaluation of the extent to which variation in one or more of the quanti-tative or qualitative independent variables is associated with variation in a quantitative dependent variable.

To test hypothesis 1 (proposing group differences in dorsal prefrontal bioenergetic metabolic activity), a one-way ANOVA or MANOVA will be performed across three groups with the high-energy phosphate metab-olites and ratios (PCr/Pi and ATP) as dependent variables. The null hypothesis of no between-group differences will be rejected if the variance ratio (F) is significant at the 5 percent level. Post-hoc comparisons will be conducted using the Sheffé test.

Similarly, to test hypothesis 2 (proposing group differences in membrane catabolism), a one-way ANOVA or MANOVA will be performed across the three groups, and the membrane phospholipid metabolites PDE and PME will be treated as dependent variables. The null hypothesis of no between-group differences will be rejected if F is significant at the 5per-cent level. Post-hoc comparisons will be conducted using the Sheffé test.

In order to test hypothesis 3 (proposing that personality and behavior variables predict prefrontal metabolism and membrane catabolism), separate multiple regression analyses will be employed for bioenergetic and membrane metabolite effects. If high-energy phosphate metabolites or membrane phospholipid metabolites, as dependent variables, are highly intercorrelated, then multivariate multiple regression will be used. The following linear model will be used:

MRS variables = ß0 + ß1Impulsivity + ß2Hyperactivity
+ ß3Inattention + ß4Aggression + error

All variables will be entered simultaneously. Should multicollinearity beobserved, redge regression will be used. If significant effects of impulsivity, hyperactivity, inattention, or aggression are found at the 5percent level or better, then the null hypothesis of no association will be rejected. The sign(s) of the significant unstandardized regression coefficient(s) will be indicative of a direct or inverse association.

Expected Results

The author anticipates that the analysis will reveal that the CD+/SA+ children have the lowest frontal energy metabolism, as well as the greatest frontal phospholipid metabolism, as measured by 31P MRS.

Impulsivity and inattention are expected to predict both the MRS bio-energetic and phospholipid metabolic variables in a negative direction. That is, the lower the frontal energy metabolism and the greater the phospholipid metabolism, the more impulsive and inattentive behaviors will be manifest. Aggression and hyperactivity will not predict any of the MRS variables; these behaviors are less salient to frontal executive functioning.

PUBLIC HEALTH SIGNIFICANCE

The results from this investigation will clearly demonstrate the presence of a neurobiological diathesis associated with the liability for an SA disorder. It will thereby confirm the extant data from neuropsychologic and neuro-physiologic studies of populations at risk for SA. The results will provide molecular geneticists with a narrower field in which to search for candidate genes that influence SA liability. However, the most important ramifi-cations will be in the realm of SA prevention. Few prevention efforts, if any, have attempted to identify high-risk individuals based upon neurobio-logical profiles and employ interventions directed towards neurocognitive remediation. In other contexts, such programs have been quite effective in improving aggressive and impulsive behavior, attention, and memory. Furthermore, both EEG and event-related potentials (ERPs) can be modified through the processes of classical and operant conditioning (Begleiter and Platz 1969; Kamiya 1969; Rosenfeld et al. 1984). Research has also shown that it is possible to normalize ERPs through pharmaco-logical intervention (Brumaghim et al. 1987).

Behaviorally dysregulated and antisocial substance abusers, as a group, exact a significant social cost. There is a clear need to develop identifi-cation and intervention strategies that are specific to the characteristics of this dysregulated population at substantial risk for SA. Neurobiologic risk factors may be an important component of their liability. The elucidation of a neurobiologic risk factor for the development of SA can lead to novel biopsychosocial models for SA etiology with significant ramifications for prevention and treatment. The characterization of a putative neurobiologic diathesis would ultimately lead to the development of novel prevention approaches that are specific, efficient, and efficacious.

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