Cognitive Event-Related Potentials in Populations at Risk for Substance Abuse

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STATEMENT OF THE PROBLEM

Cognitive information processing alterations are observed in populations at risk for drug abuse and in patients whose psychiatric disorders are often comorbid with drug abuse and dependence. A common early information processing deficit in these at-risk populations is hypothesized. The hypo-thesis is that the severity of this deficit or changes in this deficit produced by stimulants will be related to the individual's specific vulnerability to drug abuse and will predict subsequent substance abuse.

Specifically, this proposal is to study cognitive processing of 8- to 10-year-old children with attention deficit-hyperactivity disorder (ADHD), overt aggression, and depression. Appropriately matched control subjects and their parents will also be evaluated. Each child will be studied before and after a dose of methylphenidate and placebo in a double-blind, cross-over design. The biological parents of the child will also be tested at baseline. The children will be followed to 12 to 15 years of age with a battery of psychometric, drug history, and demographic questionnaires.

The study employs a cognitive event-related potential (ERP) testing battery sensitive to psychiatric disorders, overt aggression, and the effects of stimulant drugs. The experimental design assesses group differences both at baseline and after a stimulant challenge. Substance abuse detected at 12 to 15 years of age will be predicted from cognitive deficits observed at 8years of age. Comparisons between the cognitive ERPs of the at-risk child and drug-free parent will test for transgenerational mechanisms. Complete demographic, drug history, and psychometric information will be obtained and used to aid in the interpretation of the neurophysiological and outcome data.

BACKGROUND AND SIGNIFICANCE

Cognitive information processing alterations have been described in a number of psychiatric populations. High rates for the diagnosis of depression are observed in substance abusers (Harin and Grant 1987). Substance abusers in treatment who have major depression do more poorly than those with attention deficits (Rounsaville et al. 1987). Depression is often comorbid with substance abuse disorders in adolescents (Lewinsohn et al. 1993). Childhood depression may be a risk factor for substance abuse in both males and females. Neurophysiological measures of cognitive information processing are altered in adult depression. Cognitive ERP components (see below) are reduced in unmedicated depressed patients (Knott and Lapierre 1987; Pfefferbaum, et al. 1984). There are no studies that investigate neurocognitive status of depressed children and the relation of these indices to later substance abuse.

ERP research in populations at risk for substance abuse has been promising, but the effort has been focused on the sons of alcoholics. However, children with ADHD, aggressive boys, sons of drug abusers, and children with intrauterine exposure to abused drugs reportedly have altered sensory and cognitive ERPs (Brigham et al. 1993; Guo et al. 1994; Herning et al. 1989; Satterfield et al. 1987, 1988, 1990). These children are also at risk for substance abuse (Davis and Templer 1988; Kofoed and MacMillian 1986; Mannuzza et al. 1993; Weiss et al. 1985). The sensory and cognitive ERPs of these at-risk children are reviewed in an attempt to determine a common underlying deficit. Whether infor-mation processing deficits are associated with or predict a greater risk for drug abuse is not known.

Information processing can be evaluated in children as well as adults by noninvasive electrophysiological methods. Brain potentials or ERPs reflecting neural events related to sensory transmission of the stimuli or endogenous processing of task-related stimuli can be extracted from scalp recorded electroencephalogram (EEG). The brain potentials that are time-locked to sensory or endogenous events in the brain are extracted by signal-averaging techniques (Johnson 1993). The resulting waveforms have a sequence of peaks (positive activity) and valleys (negative activity) repre-senting the different stages of information processing. The peaks or valleys (ERP components) are named for their polarity (P for positive components, N for negative components) and the peak or valley number or latency. Thus, P3 would be the third positive component in the ERP waveform.

Family History of Alcoholism

Alcoholism research has focused on a reduced P3 as a marker of increased vulnerability to substance abuse. P3 is an endogenous component elicited by task-relevant auditory, visual, and somatosensory stimuli. It is thought to represent the updating of recent memory (Donchin and Coles 1988; Johnson 1993). A reduced P3 component would suggest limited evaluation of the task-relevant stimulus. Elmasian and colleagues (1982) were first to note a reduced P3 component in the auditory ERP of 18- to 26-year-old men who had a family history of alcoholism. The P3 component of the ERP in a visual discrimination task was reduced in 7- to 10-year-old boys who had alcoholic fathers as compared with boys with normal fathers (Begleiter et al. 1984).

Many attempts have been made to replicate these findings, but the results have been mixed. Polich and colleagues (1994) have performed a meta-analysis on data from the 30 studies evaluating the P3 in sons of alcoholics and found that the P3 is more often reduced when a complex visual task is used. In a prospective study, the sons of alcoholics with smaller P3 ampli-tudes at age 13 had a greater risk of becoming a substance abuser at age 16 (Berman et al. 1993).

Reduced P3 amplitude was also observed in schizophrenia, depression, Parkinsonism, dementia, ADHD, persons with excellent pitch discrimination, and children with learning disorders (Ebmeier et al. 1992; Holcomb et al. 1986; Morstyn et al. 1983; Pfefferbaum et al. 1984; Polich 1991; Satterfield et al. 1990). Whether individuals with reduced P3 amplitude who are not sons of alcoholic fathers are at increased risk for alcohol and drug abuse is not known. The focus on P3 may preclude the study of other aspects of sensory and cognitive processing in sons of alcoholics. Table 1 summarizes ERP studies of children of alcoholic fathers wherein com-ponents other than P3 were analyzed. N1, P2, N2, and late waves are also altered in these children.

ADHD and Learning Disorders

Children with ADHD and learning disorders have increased risk for substance abuse (Mannuzza et al. 1993; Weiss et al. 1985). Cognitive ERP deficits were found in children with reading disorders (Conners

TABLE 1. Cognitive ERPs in individuals at risk for alcoholism: Studies investigating brain components other than the P300.

Population	Task: ERP	Results	Study
7-15 year olds, FHA+, FHA-	Oddball (a): N1, P2, N2	P2 in FHA+	Begleiter et al. 1987
11-12 year olds, FHA+, FHA-	Discr(v): N2	Trend toward smaller N2 in FHA+	Sponheim and Ficken 1990
8-14 year olds, FHA+, FHA-	Oddball(a): N1, P2, N2	Trend toward smaller N1 in FHA+ N2 at Fz in FHA+	Hill et al. 1990
8-18 year olds, FHA+, FHA-	Discr(v): N1, P2, N2	N1 latency in FHA+	Hill and Steinhauer 1993
7-11 year olds, FHA+, FHDA+, controls	Oddball(a): LW	LW latency for FHA+ and FHDA+	Brigham et al. 1993

KEY: LW = Late waves; Discr = discrimination task; a = auditory;
v = visual; FHA = family history of alcoholism; FHDA = family history of drug abuse.

1970; Holcomb et al. 1986; Preston et al. 1974), dyslexia (Taylor and Keenan 1990), and ADHD (Halliday et al. 1976; Prichep et al. 1976; Satterfield et al. 1987, 1988, 1990). Table 2 lists studies comparing the ERPs of these children to those of controls. Various ERP components were reduced in amplitude or increased in latency in these disorders.

Methylphenidate reverses these alterations of ERP in children with ADHD. Table 3 lists studies evaluating the acute or chronic effects of methylphenidate on cognitive information processing and clinical out-come in ADHD children. The stimulus intensity/ERP amplitude slope was reduced in children with ADHD who clinically responded to amphetamine or methylphenidate (Buchsbaum and Wender 1973; Klorman et al. 1983; Saletu et al. 1975). Prichep and colleagues (1976) observed that the P2 component was depressed in ADHD children, and that methylphenidate normalized the reduced P2.

TABLE 2. Cognitive ERPs in ADHD, dyslexia, and reading disorders: Comparisons with matched controls.

Population	Task: ERP	Results	Study
Good and poor readers	Discr: N1, P2	N1 in poor readers	Conners 1970
Reading disorder (RD)	Discr: N1, P2	N1 in RD	Preston et al. 1974
Dyslexia (D)	Discr: N1, P2	N1-P2 in D RT in D	Sobotka and May 1977
ADHD 12-14 years	Selective attention task: N1, P2	N1 in ADHD	Zambelli et al. 1977
ADHD 12-14 years	Selective attention task: N1, P3	N1 and P3	Loiselle et al. 1980
ADHD and reading disorder (RD)	Complex oddball: N2, P3, SW, Pc, Nc	P3 in ADHD P3 latency in ADHD and RD P3 latency over blocks	Holcomb et al. 1986
ADHD, ADHD and aggression	Passive task: N1, P2, N2	N2 in ADHD with aggression	Satterfield et al. 1987
ADHD	Attention task: P2, N2, ND	N2 & ND in ADHD	Satterfield et al. 1988
ADHD	Selective attention task: PN, P3	P3b in ADHD PN in ADHD	Satterfield et al. 1990
Dyslexia (D)	3 Reading-related tasks: N2, P3	N2 and P3 latency P3 in D	Taylor and Keenan 1990

KEY: Discr = visual flash sensory discrimination task.

TABLE 3. Cognitive ERPs in ADHD and stimulant challenges.

Population	Task: ERP	Results	Study
MBD	Aug/Red: P1, N1, P2	VEP in MBD. A slope in nonresponders and in responders	Buchsbaum and Wender 1973
ADHD 6-13 years	Visual flash: 12 peaks	A latency and amplitude	Saletu et al. 1975
ADHD 6-11 years	Aug/Red: P1, N1, P2	Failed to replicate Buchsbaum	Hall et al. 1976
ADHD X = 9.3 years	Mixed oddball: N1, P2	N1 and P2 in ADHD Normalized in responders with M	Halliday et al. 1976
ADHD 8-11 years	Click guess: N1, P2, N2, P3	P2 and N2 in ADHD M P2 P3 in ADHD	Prichep et al. 1976
ADHD X = 9.5 years	CPT: P3	P3 with M in ADHD M errors	Klorman et al. 1979
ADHD X = 8 years	Aug/Red: CPT: P3b Oddball: P3b (visual) Oddball: P3b (auditory)	M P2 slope M P3b and reduced errors M reaction time	Klorman et al. 1983
ADHD X = 10.6 years	Mixed oddball: N1, P2	N1-P2 with M in clinical responders	Halliday et al. 1984b
ADHD 6-12 years	Attention task: PN, N1	M PN and N1	Klorman et al. 1990
ADHD	CPT	M P2/N2 and P3	Overtoom et al. 1993

KEY: CPT = Continuous performance task; Aug/Red = augmenting reducing task; A = amphetamine; M = methylphenidate; X=mean; MBD = minimal brain dysfunction; VEP = visual evoked potential.

Halliday and colleagues (1976) also found reduced N1 and P2 components in ADHD children; methylphenidate normalized these components in children who responded clinically to methylphenidate. Overtoom and colleagues (1993) found a P2 deficit in ADHD; methylphenidate reversed it. Methylphenidate increased the amplitude of two ERP components specifically linked to attention in children with ADHD (Klorman et al. 1990). Methylphenidate normalized P3 amplitude and latency in ADHD children (Klorman et al. 1979, 1983; Overtoom et al. 1993).

The effect of methylphenidate on ERPs of normal subjects is less clear (seetable 4). Peloquin and Klorman (1986) observed a small increase in P2 and P3b at one electrode site following methylphenidate administration in normal children. In normal adults, task fatigue is sufficient to lower P3 amplitude and increase its latency, but methylphenidate normalizes these alterations. Methylphenidate affects the ERPs of ADHD children who clinically respond to it, but does not have clear effect on the ERPs of normal children or ADHD children who do not respond clinically. Methyl-phenidate also produces a mixed response on the ERP of normal adults, which may reflect the variable clinical response. The basis for this differential response to methylphenidate is not known.

It is important to note that cognitive processing components of the ERP occurring before the P3 are altered in children with ADHD are consistent with the altered sensory processing observed in this population. For example, Camp and colleagues (1983) reported the brainstem auditory evoked response (BAER) components were delayed in children with ADHD, but this effect was reversed by methylphenidate. Mason and Mellor (1984) found BAER, middle latency, and cognitive ERP components altered in children with speech and language disorders.

Antisocial Personality Disorder (ASP) and Aggression

The relationship between antisocial behavior and substance abuse has been known for some time. Impulsive, aggressive, and shy-aggressive individuals have been shown to be at risk for drug abuse (Kellam et al. 1980; Kofoed and MacMillan 1986; Lewis 1984; Sutker 1984). Most ERP research with antisocial and aggressive individuals has been with adults in passive tasks and with warning rather than target stimuli (Jutai

TABLE 4. Cognitive ERPs in normal subjects given stimulants: Placebo-controlled design.

Population	Task: ERP	Results	Study
Young adults	SAT: N1, P3	No change in any measure with M	Hink et al. 1978
Young adults	CPT: P3 Choice RT Task: P3, CNV	M P3 amplitude late in the session. M RT No change in P3 with M M RT	Coons et al. 1981
Adults	SE/RS: P3	M RT	Callaway et al. 1983
Young adults	Vigilance: P2, P3 P-A: P3	M blocked the in P3 amplitude and in P3 latency seen with placebo. M RT No change in P3 with M	Strauss et al. 1984
Children 8-14 years	CPT: P2, P3b Sternberg: P3b	M P2. M P3b M RT and errors M errors	Peloquin and Klorman 1986
Young adults	Sternberg: P3b Sternberg: P3b	M RT and error M P3b latency and RT	Brumaghim et al. 1987
Old adults	SE/RS: P3	A RT	Halliday et al. 1984a
Young adults	Sternberg: P3	M RT	Fitzpatrick et al. 1980
Young adults	SE/RS: P3	A RT	Halliday et al. 1984a

KEY: A = Amphetamine; CNV = contingent negative variation; CPT = continuous performance task-visual; M = methyl-phenidate; RT= reaction time; SE/RS = stimulus evaluation/response selection task-visual; SAT = selective attention task-auditory; P-A = paired-associate learning task.

and Hare 1983; Raine and Venables 1987; Satterfield et al. 1988; Syndalko 1979; Syndalko et al. 1975). The findings are summarized in table 5. The P3 evoked by a warning tone was larger in noninstitutionalized delinquent adolescents than in controls, but the P3 to the target tone was not measured (Raine and Venables 1987). However, the P3 to a target was similar to that of control boys in the author's sample of overtly aggressive adolescents (Herning et al. 1989). When Raine and Venables (1990) compared crimi-nality in this sample 10 years later with the earlier brain potentials, N1, not P3, predicted incarceration. N1 amplitude is related to changes in attention.

ERPs at various stages in the auditory information processing system differed significantly between the more delinquent, overtly aggressive adolescents compared with neighborhood-matched control boys (Herning et al. 1989). The latency of wave V of the BAER was longer, N1 was earlier during high background noise, and frontally the slow wave was abnormal in the aggressive boys. These differences were not due to psychiatric disorders other than conduct disorder (CD) as measured by a computerized version of the "Diagnostic and Statistical Manual of Mental Disorders," 3d ed. (DSM-III). These ERP differences were also not the result of drug use since the limited drug use in the sample had been statis-tically removed. These patterns of ERP alterations are similar to those observed in children with ADHD.

A second study compared the EEG and BAERs of 125 adult drug abusers who entered the Addiction Research Center's (ARC's) Inpatient Research Unit for variety of different drug studies (Fishbein et al. 1989). Electro-physiological and psychometric data were collected when the subjects were drug free. An extensive psychometric evaluation included a computerized DSM-III interview, Addiction Severity Inventory, Buss-Durkee Hostility Inventory (Buss and Durkee 1985), and delinquent behavior questionnaire developed by Dunford and Elliott (1984). After statistically correcting for drug use and age, greater aggression scores were associated with longer latency BAER peaks. Thus, aggressive adults, like aggressive adolescents, have longer latency BAER peaks.

ERP alternations in aggressive individuals also occur at many stages of information processing system starting as early as 3 to 5 milliseconds (ms). Although few studies have looked at aggressive children, the ERP alterations are similar to those observed in children with ADHD.

TABLE 5. Cognitive ERPs in ASP and aggression: Comparisons with matched controls.

Population	Task: ERPs	Results	Study
Adult psychopaths	Warned RT: CNV	CNV	McCallum 1973
Adult psychopaths	Warned RT: CNV	CNV equal controls	Syndalko et al. 1975
Adult psychopaths	Oddball: P3	P3 equal controls	Syndalko et al. 1979
Adult psychopaths	Passive: N1, P2	N1	Jutai and Hare 1983
Adult: ASP	Warned RT: CNV	CNV	Howard et al. 1984
Adult: ASP	BAER: I-V	II-IV latency	Josef et al. 1983
15 year olds	Warned RT: P3, N1, CNV	P3 for warning stimulus	Raine and Venables 1987
15 year olds	Warned RT: P3, N1, CNV	N1 amplitude predicts criminality at 24	Raine and Venables 1990
Adult psychopaths	CPT: P3	P3 latency	Raine and Venables 1988
11 to 18 year olds aggressive	BAER: I-V Oddball: N1, P2, P3, SW	V latency N1 latency SW	Herning et al. 1989
Adult substance abusers	BAER: I-V	III latency ASP and aggression	Fishbein et al. 1989

KEY: RT = Reaction time; BAER = brainstem auditory evoked response; CRT = continuous performance task; Aug/Red=augmenting reducing task; ASP = antisocial personality disorder.

Aggressive children may have an information processing system that is more sensitive to stimulants than nonaggressive children, and thus may differentially respond to methylphenidate. The neurophysiological response to methylphenidate may predict subsequent drug abuse, other factors notwithstanding.

Intrauterine Drug Exposure

Children with intrauterine exposure to illicit drugs are at risk for substance abuse. School-aged children with intrauterine heroin exposure were impulsive, had poor self-control, paid poor attention, and were hyperactive (Bauman and Levine 1986; Kaltenbach and Finnegan 1989; Lifschitz et al. 1985; Wilson 1989; Wilson et al. 1979, 1981). It has been reported that in utero exposure to marijuana produced attention deficits (Fried et al. 1992) and that both in utero and environmental factors place these children at risk for drug abuse (Chasnoff et al. 1986; Davis and Templer 1988). A similar argument could be made for intrauterine exposure to licit drugs, but further research is required.

Few studies have used ERP methodology or task performance only to investigate cognitive processing in school-aged children with intrauterine drug exposure. Table 6 lists studies measuring cognitive processing by in utero drug-exposed children. Two prospective studies investigating the in utero effects of marijuana (Fried, in press) and methadone (Hans 1989, in press) found altered attention processing on a continuous performance task (CPT). These CPT findings are consistent with the author's retrospective ERP study of boys born to opiate-using mothers.

Cognitive ERP components and task performance were altered in 7- to 12-year-old sons of opiate-abusing mothers (Guo et al. 1994). The P2 component of auditory ERP, as well as P2 and N2 components of the visual ERP, were smaller in sons of opiate-using mothers as compared with the same components in boys from similar socioeconomic status (SES). The sons of opiate-using mothers made more errors than the control boys. The boys who had no in utero opiate exposure but lived with an opiate-using mother were impaired on P2 and N2 components on the oddball task and the Sternberg tasks. This pattern of deficits suggests the involvement of environmental factors or poor mother-child inter-actions (Bauman and Levine 1986). Here again, the ERP deficit was similar to that found by others in ADHD children.

TABLE 6. Cognitive processing in children exposed to drugs in utero: Comparison to matched controls.

Population/Drug	Task: ERP	Results	Study
7-10 year olds/ Marijuana	CPT	Exposed made more errors	Fried, in press
7-10 year olds/ Methadone	CPT	Exposed made more errors	Hans 1989,in press
7-11 year olds/ Opiates	Oddball (a): N1, P2, N2, P3 Sternberg (v): N1, P2, N2, P3	P2 P2 and N2 Exposed made more errors	Guo et al. 1994

KEY: CPT = continuous performance task; a = auditory; v = visual.

Children of Drug Abusers

Transgenerational and environmental factors place children of drug abusers at greater risk for substance abuse. The ERPs as well as event-related EEG alpha synchronization and desynchronization (stimulus-induced changes in the ongoing EEG) of young sons of substance abusers and alcoholics in the auditory oddball task were studied by Brigham and colleagues (1993; in press). N1 was delayed in the sons of substance abusers, but not sons of alcoholics, when compared with the control boys. Boys with a family history of substance abuse had smaller N2 amplitudes than control boys, but a longer latency. Event-related EEG alpha synchronization and synchronization measured in the auditory oddball task differed between the risk groups and the control group at various times after the stimuli. As with the other at-risk populations, the sons of substance abusers have neurocognitive alterations at a number of information-processing stages.

Implications of ERP Research

The focus of ERP research in populations at risk for drug abuse differs greatly from that in populations at risk for alcoholism. ERP research in alcoholism attempted to understand why young sons of alcoholics have smaller P3 amplitudes. By contrast, the ERP research in populations at risk for drug abuse tried to characterize sensory and cognitive processing at different levels in the different at-risk populations per se. This latter research was not focused on the P3

component. Individuals at risk for drug abuse have alterations in sensory and cognitive ERP components that occur throughout the poststimulus period.

Findings from diverse research groups point to a common deficit in stimulus processing in individuals at risk for drug abuse. A deficit in early sensory processing and attention was observed in children with ADHD, aggressive children, intrauterine drug-exposed children, and children of substance abusers. Stimulants have reversed these ERP alterations in children with ADHD and may reverse them in the other populations at risk for drug abuse. The mechanism by which the early sensory and cognitive alterations may lead to subsequent drug abuse is not known. Drugs such as methylphenidate may be useful as probes to assess individual differences in vulnerability of these children. A prospective study relating deficits in information-processing components or stimulant-induced changes in these components to subsequent drug abuse is needed.

DESIGN AND EXPERIMENTAL METHODS

The proposed study would examine sensory and cognitive processing in three groups of children exhibiting behaviors that often lead to substance abuse: overt aggression, ADHD, and current depression. Both ERPs andtask performance will be assessed at baseline and after stimulant (methylphenidate) challenge when the children are in the age range of 8to 10. Drug use will be determined after a 4-year interval. This proposed research will clarify and extend what is known about early sensory processing and attention in children with ADHD and aggressive children of both sexes, as well as explore the possibility of childhood depression as a risk factor for substance abuse in a prospective study. Appropriate control children and parents of both index and control children will be evaluated to tease apart transgenerational factors. The goal will be to determine whether the altered ERP components in the at-risk populations will predict future drug use.

Experimental Design

Children with at-risk behavior disorders and their parents will be assessed on neurophysiological variables and task performance. The children will be tested a second time during a challenge session with methylphenidate. At the time of testing, extensive demographic and family data will be collected. Four years later, demographic and family data will again be collected along with drug use history and psychometric data from both the child and the parents.

Five groups of children will be recruited: overtly aggressive (N = 100), ADHD without aggression (N = 100), ADHD with aggression (N = 100), depressed (N = 100), and matched control children (N = 100). Each group will be racially balanced and composed of equal numbers of females and males. The children with ADHD and depressed children will be tested on a neurophysiological battery when medication free. ADHD children are likely to be already on medication. This methodological problem may be circumvented in two ways: The subjects can be tested after a fixed washout period, or newly identified ADHD children can be tested before they are placed on medication. The overtly aggressive children will meet the criteria of "high" delinquency, reporting 25 or more lifetime self-reported delinquent acts on the Dunford and Elliott (1984) questionnaire. The control children will be obtained from the same neighborhoods or schools as the at-risk children. Social, economic, legal, educational, psychometric, medical, drug history, and family interaction information will be obtained from all subjects.

Neurophysiological Assessment

After the demographic, psychiatric, and psychometric screen, appropriate children and their parents will undergo a 2-day neurophysiological testing. Methylphenidate (0.3 milligrams per kilogram (mg/kg)) or placebo will be administered to the child in a double-blind crossover design. The parents will be expected to abstain from alcohol and illicit drugs for 24hours before a baseline testing. Compliance will be determined by urine toxicologies and breath alcohol monitoring. It is recognized that complete neurophysiological data may not be obtained from all parents because of positive urine toxicologies. In previous outpatient work, about 10 to 15 percent of the subjects failed to comply with similar restrictions. These patients will be dropped from the study. Thus, the sample size to test the similarity of ERPs of the parent to those of the child will be slightly less than the comparisons between groups of children.

The battery of neurophysiological tests (table 7) will be administered before the oral ingestion of placebo or methylphenidate and at 1 and 2hours postingestion. The tasks in this battery have previously been used successfully with adults and 7- to 11-year-old children. Both ERPs and performance will be obtained on these tasks. Heart rate and blood pressure will be measured, and the visual-analog drug effects scale and Profile of Mood State questionnaire will be administered before and at 45, 90, 150, and 210 minutes after the drug administration.

TABLE 7. Neurophysiological Performance Assessment Battery.

Sensory evaluation1
- Brainstem auditory evoked response procedure
- Pattern reversal visual evoked response procedure

Cognitive evaluation2
- Auditory rare event monitoring task (oddball task)
- Auditory selective attention task
- Continuous performance tasks (visual)
  - Single target letter task
  - Paired letter task
- Sternberg memory tasks (visual)
  - Short memory set (2 letters for child, 3 for adult)
  - Long memory set (4 letters for child, 6 for adult)

KEY: 1American Electroencephalographic Society (1984) guidelines will be followed for these clinical tests.
2Military guidelines will be followed for these tests (Reeves et al. 1991).

ERP Recording and Measurement

The ERPs will be recorded from 13 locations (Fz, Cz, Pz, F3, F4, C3, C4, T3, T4, P3, P4, O1, and O2) based 10-20 International System. An electro-oculogram (EOG) will be recorded from the side of the left eye and from above the left eye and referred to the left eartip in order to monitor eye movement artifacts. Silver/silver chloride electrodes will be used at all locations. Testing will be performed in a sound-attenuated, electrically shielded chamber. Each EEG or EOG channel will sample at 2.0 ms intervals using software developed inhouse for this purpose. Faster sampling rates will be used with the sensory procedures. The inter-channel sampling time was 40.0

microseconds (μs). The raw EEG and EOG data will be saved on magnetic media for subsequent analysis.

The EEG and EOG will be processed for artifact. Artifact-free single trials will be averaged according to stimulus type after the test session. ERPs will be measured by an individual who is blind to the subject's group. The auditory ERP peaks will be measured in the following latency ranges for N1 (50 to 180 ms), P2 (100 to 250 ms), N2 (181 to 400 ms), and P3 (250 to 700 ms). The visual ERP peaks will be measured in latency ranges for P1 (80 to 120), N1 (50 to 180 ms), P2 (100 to 250 ms), N2 (181 to 400 ms), and P3 (250 to 700 ms). BAER and pattern reversal evoked responses will be measured in accordance with American Electroencephalographic Society guidelines (1984). In addition, the cognitive ERP components will be extracted by principal component analysis (Herning et al. 1989).

Analysis and Expected Results

The first major hypothesis to be tested is whether the three at-risk groups have similar sensory and cognitive ERP alterations and performance levels and whether these neurocognitive alterations differ from those of controls at baseline and after methylphenidate challenge. The three at-risk groups at baseline are expected to have delayed BAER waves, delayed P1 in the pattern-reversal evoked response task, and reduced or delayed N1, P2, and P3 components of the auditory and visual cognitive ERPs when compared with control children.

Not all children in the risk groups will respond to the methylphenidate challenge in a similar manner. For some children, no ERP components would change with the drug challenge; for ADHD children, some of the baseline ERP alterations would be reversed; and for still other children, the drug challenge would produce greater ERP alterations than in the baseline condition. Which particular pattern is related to subsequent substance abuse is the focus of this research. These three patterns will be observed in the three risk groups. Little or no change is expected in control children.

These predictions are based on ADHD research findings that some ADHD children respond clinically to methylphenidate and some do not (Buchsbaum and Wender 1973; Klorman et al. 1983; Saletu et al. 1975). The ERPs of those who respond are also normalized by methylphenidate. The other risk groups have similar ERP alterations and may also respond to methylphenidate in a similar fashion. The

intent is to determine which children are at greater risk for drug abuse: those with altered ERPs that are normalized, those with altered ERPs that are not affected, or those with altered ERPs that are further modified by the methylphenidate challenge.

The hypothesis that the ERPs of child and parent are similar will be tested. Some similarities are expected in the deficits observed in the at-risk children and their parents. Both aggressive boys and aggressive men have some similar BAER deficits (Fishbein et al. 1989; Herning et al. 1989). Children with intrauterine heroin exposure as well as their mothers were impulsive, had poor self-control, paid poor attention, and were hyperactive (Bauman and Levine 1986). The transgenerational transmission of ADHD has been suggested. The evaluation of ERPs of child and parents will aid in understanding the nature of the trans-generational mechanism.

When the 4-year assessments are complete, a stepwise discriminant analysis will be used to determine which ERP measures collected at 8-years of age predict substance abuse at age 12 for each group separately and for all the children pooled together. The significant ERP predictor measures will also be combined with identical ERP measures from the parent to determine whether prediction can be improved. If, indeed, genetic or other transgenerational factors are operating, the addition of the parent's neurophysiological data would enhance the prediction. Models and theory in this area are rather sparse. However, there is reason to believe ERP measures will be useful in predicting substance abuse. An ERP component, N1, measured in childhood, successfully predicted criminality as a young adult (Raine and Venables 1990). The amplitude of P3 in sons of alcoholics predicted substance abuse 4 years later (Berman et al. 1993).

One possible outcome would be that the children who had the largest neurocognitive change (specific changes are noted below) to the methylphenidate challenge at an early age would be substance abusers at the time of followup. On the other hand, the at-risk children who have the largest neurocognitive deficits as compared with control children in baseline recording may be substance abusers at followup. The strength of the study is that both predictions are tested. It is possible that a combination of baseline and drug challenge neurocognitive measures may best predict drug and alcohol use. Although it is hypothesized that the neurocognitive deficits in the four at-risk groups are similar, different neurocognitive deficits may exist in each of the groups that may predict subsequent drug use for that

group. Little is known about the ERPs of depressed children and their response to methylphenidate. Likewise, it is not known whether the ERP alterations observed in aggressive children will normalize with methylphenidate. This study is intended to clarify these points. The study is designed with a sufficient sample size in each group to separately predict substance abuse from baseline or methyl-phenidate challenge neurocognitive measures for each group.

While it is difficult to foretell whether baseline or drug challenge measures would predict subsequent drug use, some predictions can be made as to which ERP components may predict subsequent drug use. The neurocognitive alterations currently observed in at-risk populations occur at a number of ERP components starting as early as 3 to 5 ms after the onset of the stimulus. Alterations at earlier stages of information processing may produce deficits in later stages. Alterations in ERP components up to 250 ms were found in populations at risk for substance abuse and were sensitive to the effects of stimulants. Alterations in these components which reflect early sensory processing and attention, are most likely to predict subsequent drug abuse.

Many outcomes are possible, and all outcomes will provide useful information about neurocognitive factors that place an individual at risk for substance abuse. The design of the study is based on the hypothesis that certain underlying cognitive deficits are common to populations at risk for substance abuse and that specific changes in these neurocognitive alterations after a stimulant challenge will predict subsequent drug abuse.

STRENGTHS AND WEAKNESSES

Populations at risk for substance abuse to be tested in this prospective study have been clearly identified in many epidemiological studies and carefully characterized in terms of their sensory and cognitive ERPs in numerous neurophysiological studies. Alterations in information processing are clearly defined in these populations, and patterns of processing appear to be similar across different samples. Stimulants normalize these alterations in some individuals. What remains is to understand why there is a differential response to stimulants and its relationship to subsequent drug use.

An additional strength is that the study attempts to identify a neuro-physiological mechanism common to different at-risk populations,

which makes these individuals vulnerable to drug abuse. While information processing deficits common to individuals in an at-risk group may not by themselves place an individual at risk, they may be linked at the neural substrate level and be responsible for this vulnerability.

There are some methodological weaknesses. First, only a single dose of a single challenge drug, methylphenidate, is administered, and this drug affects more that one transmitter system. Unfortunately, only a limited number of drugs may be given to children. Methylphenidate is one such drug and its effects on ADHD are well known.

A second weakness is that only stimulant abuse may be predicted from a challenge with a stimulant. However, this was not the case in the study by Berman and colleagues (1993), where the sons of alcoholics with smaller P3 amplitudes at age 13 were found to have a greater risk of becoming substance abusers rather than just alcohol abusers.

PUBLIC HEALTH SIGNIFICANCE

This study identifies neurocognitive deficits in grade school children which predict subsequent drug and alcohol use. The early identification and treatment of these neurocognitive deficits may both enrich the educational and cognitive development and reduce the risk of substance abuse in these children.

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