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Neurobehavioral Effects of Prenatal Alcohol: Part I. Research Strategy[1]

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STREISSGUTH, A. P., H. M. BARR, P. D. SAMPSON, F. L. BOOKSTEIN AND B. L. DARBY. *Neurobehavioral effects of prenatal alcohol: Part I. Research strategy.* NEUROTOXICOL TERATOL **11**(5) 461–476, 1989.—This paper, Part I of a three-part series, reviews the literature on the neurobehavioral effects of prenatal alcohol exposure and describes a large group of tests assembled to assess neurobehavioral outcomes of alcohol teratogenesis in 7-year-old children. This paper presents the distribution of these test scores for our sample and discusses their relationships with an alcohol binge score and with full-scale IQ. This group of tests is suitable for children with a wide range of abilities and provides a broad assessment of neurobehavioral deficits. Part II of this series describes a new method of statistical analysis, Partial Least Squares (PLS), which is particularly well suited to complex multivariate data sets such as these, and with its aid, examines the effects of prenatal alcohol exposure on IQ, achievement, vigilance and classroom behavior, a total of 43 outcome scores. Part III examines prenatal alcohol effects on outcomes from the broad group of 164 scores deriving from 17 neuropsychologic tests, using the Partial Least Squares methodology, and summarizes the implications of our findings for the behavioral teratology of alcohol.

Behavioral teratology Alcohol teratogenesis Fetal Alcohol Syndrome Fetal alcohol effects Birth defects
Neuropsychology Memory Alcohol use Partial Least Squares Longitudinal research

THIS is the first in a trilogy of papers describing the effects of prenatal alcohol exposure on the neurobehavioral development of seven-year-old children. This first paper reviews the relevant literature, describes the rationale and methods in the study design, formulates the specific questions to be addressed, and presents descriptive statistics. The second paper (44) has two functions: a) to describe a method of statistical analysis called Partial Least Squares (PLS), which is particularly well suited to the complex multivariate data sets deriving from studies such as this one; and b) to use the PLS methods to analyze standardized outcomes, including IQ and achievement tests, in respect of prenatal alcohol exposure. The third paper (56) applies PLS analyses to a more complex data set deriving from neuropsychological assessment of these 7-year-old offspring.

REVIEW OF THE LITERATURE

Alcohol is well recognized as a teratogenic agent (63,65). It readily crosses the placenta so that fetal blood alcohol levels approximate those of the mothers. Alcohol crosses the blood-brain barrier, so it can alter the development of the central nervous system (CNS) in utero in a fashion depending on the dose, timing, and conditions of exposure (65).

Children with Fetal Alcohol Syndrome (FAS) represent those most severely affected by prenatal alcohol exposure (11, 24, 25, 30). Their mothers abused alcohol during pregnancy or were clearly alcoholic. In addition to growth deficiency and physical anomalies, these children manifest a variety of CNS effects, including mental retardation, hyperactivity, poor impulse control, perceptual/motor problems, and delayed motor development (49). In addition, clinical observations have revealed difficulty with generalizations and abstract thinking, poor problem solving skills, poor social adaptation, and problems with attention and memory (57,58).

Animal research has shown that while many areas of the brain are affected by prenatal alcohol exposure, the hippocampus is particularly at risk (65). Prenatal alcohol exposure produces changes in the mossy fibers of the hippocampus (65), a 20% reduction in the pyramidal cells in the CA1 region of the

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hippocampus, and a reduction in the number of dendritic spines in the CA1 pyramidal neurons (1). Riley *et al.* (41) have speculated that some of the behavioral aberrations associated with alcohol teratogenesis in humans reflect a deficit in response inhibition that has its roots in the hippocampus.

Even in the absence of the physical malformations of FAS, neonatal offspring of alcoholic mothers have been found to have abnormal EEG patterns (9, 18, 19), abnormal visual evoked responses (36),and abnormal auditory brainstem evoked potentials (39). These may all derive from disruption of synaptic transmission or of conduction of action potentials. Autopsy studies indicate that the nature and degree of brain malformations in children of alcoholic and heavy drinking mothers are extremely variable (10), suggesting that a broad spectrum of neurologic, behavioral, and intellectual deficits would be found in survivors. Some of the more frequently noted brain abnormalities included neuroglial heterotopias, cerebral dysgenesis, cerebellar dysgenesis, brainstem dysgenesis, and agenesis of the corpus callosum. Microcephaly was mostly present, and hydrocephalus was observed in most of the autopsied cases without microcephaly. As only about half of the autopsied cases had enough physical characteristics to warrant a diagnosis of FAS, one must conclude that alcohol-related brain abnormalities can occur in the absence of FAS (10). This finding bears important implications for associations of functional deficit with prenatal alcohol exposure in nonclinical populations.

Over the past ten years, a number of epidemiologic studies have investigated the neurobehavioral effects of varying levels and conditions of prenatal alcohol exposure on infant development. After adjustment for relevant covariates, prenatal alcohol exposure has been found to be associated with the following outcomes in neonates: poor sucking, disrupted sleep states, low levels of arousal, tremulousness, unusual body orientation, excessive mouthing, abnormal reflexes, hypotonia, and poor habituation to redundant stimuli (12, 20, 27, 31, 37, 43, 46, 49, 51, 52). In older infants, prenatal alcohol exposure (at levels usually considered social drinking) has been related to disrupted sleep-wake patterns, poor visual recognition memory, and decrements in mental and motor development, spoken language, and verbal comprehension (17, 21, 29, 35, 53). In preschool children, the reported correlates of exposure include attentional deficits, delayed reaction time, IQ decrements, and decrements in fine and gross motor performance (2, 28, 49, 52, 54, 59).

RATIONALE AND SPECIFIC AIMS OF THE PRESENT RESEARCH

To date, no other epidemiologic studies have examined the neurobehavioral effects of prenatal alcohol exposure on nonclinical populations of school-age children. It is the goal of the present research project to do this, particularly with respect to "moderate" levels of exposure.

From the clinical literature on children with FAS, we know that the neurobehavioral manifestations of the prenatal insult continue into adolescence and adulthood (46, 49, 57, 58).The types of neurobehavioral effects vary by stage of development. Hyperactivity and motor problems are more frequently observed in preschool children, while attentional deficits, organizational problems, poor impulse control, and learning problems are more frequently observed during the school-age years (49).

Our epidemiologic studies of alcohol teratogenesis are framed within the context of behavioral teratology (42). That field grew out of experimental studies on laboratory animals, wherein dose and timing of exposure can be controlled in ways not possible in human studies. One of the tenets of behavioral teratology is that the magnitude of effects is related to the magnitude of the dose (62). In the present context, the expectation is that the effects of social drinking during pregnancy are more subtle than those of abusive drinking. While physical effects (growth deficiency, dysmorphology, and congenital malformations) are produced by heavier exposure, neurobehavioral effects may be produced at lower exposure levels, even in the absence of physical effects. Timing of exposure is also important. In rodent studies, the early teratogenic effects of alcohol are affected by even a small difference in gestational age. Therefore, in assessing patterns of alcohol consumption, we obtained information about two time periods: the month or so prior to recognition of pregnancy and the first five months of pregnancy.

Specification of appropriate outcome measures is a critical aspect of behavioral teratology research. We examined the neurobehavioral deficits of children with FAS to find outcomes which might help assess the effects of maternal social drinking on school-age children. As prenatal alcohol exposure is known to produce widespread brain damage, we cast a broad net of behavioral outcomes. Typical neuropsychologic outcomes included tests of intellect and its various components, tests of academic attainment, test of attention, tests of memory, tests of perceptual-motor, tactual performance, auditory-visual integration, verbal fluency, writing fluency, cognitive flexibility, and dominance. Time constraints associated with sample size precluded administration of one of the standard neuropsychologic batteries to all subjects. Extensive language tests were not included because this was not an area of particular deficit in our clinical studies of children with FAS. The 4-year exam from this study had a large battery of motor tasks to evaluate possible cerebellar effects (2), and these were not repeated in the 7-year exam.

We gave particular emphasis to those outcomes which reflect meaningful brain-behavior relationships in terms of the extensive animal literature on the neuroteratogenicity of alcohol and congruent clinical observations of patients with FAS. Hippocampal effects have frequently been produced by prenatal alcohol exposure in animal studies (1,65) and some of the behavioral problems observed in patients with FAS have been thought to be similar to behaviors observed in hippocampally-damaged patients. Rats prenatally exposed to alcohol have visual-spatial memory and response inhibition deficits similar to hippocampally-damaged rats (41). Therefore, we included a number of memory tasks in the 7-year exam, namely visual memory [Memory for Designs from the Children's Memory Test (13)]; Memory for Faces Test (already associated with hippocampal damage in adult patients (32)]; Verbal Memory: Children's Memory Test (13), Digit Span Subtest of the WISC-R; and Auditory Memory: Seashore Rhythm Test (45). Response inhibition was also assessed in several ways, such as through the AX Task of the Vigilance Test (Continuous Performance Test) and the behavior ratings of impulsivity and executive functions such as organization, persistance, etc. Thus, through careful selection of neuropsychologic tests, it may be possible to understand the long-term consequences of prenatal alcohol exposure in terms of brain-behavior relationships, particularly with regard to hippocampal function.

In epidemiologic studies of moderate levels of alcohol exposure, we do not expect large effects in individual children, but rather, subtle effects that will be observable as mean deficits across groups of similarly exposed offspring. Although we use neuropsychologic tests as outcomes, we do not expect alcohol effects to be of clinical significance for these subjects individually. As epidemiologists use birthweight, we use neurobehavioral tests as sensitive indicators of population differences attributable to a specific cause in a group comparison.

As any behavioral measure can measure "brain damage" only indirectly, we use a variety of tests to assess individual level and quality of function. Furthermore, as behavior is modified by the immediate situation in which it is measured, we measure neurobehavioral outcomes in a variety of settings. Thus, we measured

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF 7-YEAR SAMPLE (N=486)

Characteristic	n	(%)	Characteristic	n	(%)
Maternal race			Maternal education		
White	421	(87%)	Grad. school	35	(7%)
Black	34	(7%)	College grad.	103	(21%)
Am. Indian	4	(1%)	Some college	141	(29%)
Other	27	(5%)	H.S. grad.	143	(29%)
			Some H.S.	46	(10%)
Maternal age			Jr. H.S.	18	(4%)
15 - 19	51	(10%)	< 7th grade	0	
20 - 24	116	(24%)			
25 - 29	208	(43%)	Socioeconomic status (SES)		
30 - 34	96	(20%)	Upper	45	(9%)
35 - 39	13	(3%)	Upper middle	90	(19%)
≥ 40	2	(<1%)	Middle	124	(25%)
			Lower middle	173	(36%)
Marital status			Lower	54	(11%)
Single	50	(10%)			
Married	418	(86%)	Birth order		
Separated	9	(2%)	First born	212	(44%)
Divorced	8	(2%)	Other	274	(56%)
Widowed	1	(<1%)			

Note: These data pertain to the fifth month of pregnancy. SES is calculated using the education of mother and the occupation of head of household, according to the system developed by Hollingshead.

behavior in the laboratory with clinical neuropsychologic tests, a standardized IQ test, a standardized test of academic achievement, and a computerized vigilance test. We obtained qualitative ratings of behavior from examiners who administered the clinical tests and from the individual school teachers who observed these children in the classroom. The extent to which the effects of prenatal alcohol exposure can be measured across tests and across situations will strengthen our conclusions about the veridicality of findings. The pattern of alcohol effects across tests, situations and observers will help us understand the functional effects of prenatal alcohol on the developing brain.

Analyses in Parts II and III to follow (44,56) assume that no single outcome measure can adequately reflect the impact of alcohol on the neurobehavioral development of the child and, likewise, that no single alcohol score can reflect the full impact of prenatal alcohol on the fetus. In our view, traditional (well-known) statistical methods are not suitable for analyses of alcohol-induced brain damage as measured indirectly using hundreds of variables. In Part II of this series (44) we describe the rationale and application of Partial Least Squares (PLS) methods for the assessment of such large multivariate data sets. We analyze conventional IQ and achievement test data, classroom ratings, and laboratory attention measures in relation to 13 measures of prenatal alcohol exposure. In Part III of this series (56) we apply PLS methods to analyze an even larger data set of neuropsychologic outcome measures.

The analyses imply that "alcohol exposure" and its consequence, (neurobehaviorally assessed) "brain damage," are best construed as "latent variables" underlying the large batteries of individual tests and test scores. Latent variables are computed and interpreted in terms of patterns of weights (coefficients) applied to the individual alcohol scores and to the outcome measures. We explain how the weights are determined so as to best explain the entire pattern of correlations between the alcohol scores and the outcome measures. In both papers we demonstrate how these analyses serve our principal goal: the summarization of vast numbers of correlations in terms of patterns of alcohol scores (representing an alcohol exposure latent variable) associated with patterns of alcohol effects in the outcome variables (reflecting neurobehavioral response or brain damage latent variables).

The basic questions to which our analyses are addressed are these:

1. What patterns of alcohol scores best account for neurobehavioral outcomes in seven-year-old children?
2. What patterns of neurobehavioral outcomes are explained by this prenatal alcohol exposure?
3. What relevant covariates modify these assessments?

METHOD

The Seattle Longitudinal Prospective Study on Alcohol and Pregnancy began in 1974 as an assessment of the long-term effects of moderate levels of prenatal alcohol exposure. Details of the study design have been published previously (60); original references pertaining to the early methodology are not included in the present paper.

Study Design

The 486 singleton-born children examined in the present study were the 7½-year-old follow-up cohort of a longitudinal prospective study initiated when their mothers were pregnant. During a one-year interval, all women in prenatal care by the fifth month of pregnancy at two Seattle hospitals were asked to participate in the study. Those accepting (85%) were interviewed in their homes during the fifth month of pregnancy regarding beverage and drug use, diet, pregnancy history, and demographics. From this screening sample of 1529 pregnant women, a follow-up cohort of

TABLE 2
ALCOHOL BLOCK DEFINITION AND DESCRIPTIVE STATISTICS (N=486)

Alcohol Scores	Abbreviation	Mean	S D	Min	Med	Max
Average ounces of absolute alcohol/day						
Prior to pregnancy recognition	AAP	0.61	1.55	0	0.13	25.76
During mid-pregnancy	AAD	0.26	0.55	0	0.05	8.55
Binge ≥5: ≥ 5 drinks/occasion						
Prior to pregnancy recognition	BINGE P	0.29	0.45	0	0.0	1.00
During mid-pregnancy	BINGE D	0.19	0.39	0	0.0	1.00
Average drinks per occasion						
Prior to pregnancy recognition	ADOCCP	1.84	1.68	0	1.50	13.00
During mid-pregnancy	ADOCCD	1.71	1.40	0	1.50	13.00
Maximum drinks reported on any occasion						
Prior to pregnancy recognition	MAXP	2.98	2.88	0	2.00	13.00
During mid-pregnancy	MAXD	2.81	2.76	0	2.00	13.00
Monthly occasions of drinking						
Prior to pregnancy recognition	MOCCP	12.64	20.97	0	3.50	240.00
During mid-pregnancy	MOCCD	6.47	11.55	0	1.00	120.00
Quantity-Frequency-Variability Index						
Prior to pregnancy recognition	QFVP	2.87	1.45	1	3.00	5.00
During mid-pregnancy	QFVD	2.58	1.20	1	3.00	5.00
Ordered Experimental Code (combines timing/dose/pattern)	ORDEXC	2.23	1.57	0	2.00	4.00

Note: See text for a fuller description of these scores and pertinent references.
AA is a continuous variable; AA ≥ 1.00 = average of ≥ 2 drinks per day of wine, beer, liquor, or combination.
BINGE is a dichotomous variable representing whether or not 5 or more drinks were reported on at least one occasion.
ADOCC represents the average number of drinks reported for any drinking occasion.
MAX is the maximum number of drinks reported per drinking occasion.
MOCC is the number of occasions per month in which drinking is reported.
QFV is a three dimensional categorical score (Quantity, Frequency, Variability) deriving from Cahalan [7], but the order has been reversed for consistency with the other drinking scales, so that 5 is the heaviest.
ORDEXC is an *a priori* code (Ordered Experimental Categories) developed at the outset of this study [59] to describe the presumed risk to the fetus of different drinking patterns, in order to enroll women in the follow up study. A score of 4 represents the highest presumed risk.
P refers to the month or so prior to pregnancy recognition, D to drinking during mid-pregnancy, assessed at the 5th month of pregnancy.

approximately 500 was selected, stratified for heavier drinkers and smokers, infrequent drinkers and abstainers, and over-sampled for heavier drinkers and smokers. Additional subjects from the screening sample were added to the follow-up cohort from time to time to keep the total sample size around 500.

Attrition of subjects across the 7½ years of the study was 14% for the heavier drinkers and 14% for the rest of the sample; 95% of those seen at 4 years were seen again at age 7½. This high rate of follow up (86% overall) was achieved through extensive outreach activities (15).

Subjects

At the 7½-year examination, 486 subjects were evaluated: 261 boys and 225 girls. They ranged in age from 6½ to 8½ years, with a mean of 7½ years. As shown in Table 1, mothers were primarily white (87%), married (86%), and middle-class (81%). Average maternal age during pregnancy was 26, and average maternal education was 13½ years.

Assessment and Categorization of Prenatal Alcohol Exposure

Alcohol exposure was measured by maternal report in the fifth month of pregnancy. A quantity-frequency-variability (QFV) interview (8) assessed the consumption of beer, wine, and liquor for two time periods: during midpregnancy (D), and for the month or so prior to pregnancy recognition (P). The rationale for the P scores derives from the fact that whereas the period of organogenesis is extremely important for teratogenesis, women have generally not yet altered their normal habits because they usually are not aware of being pregnant during this first month. We obtained information about exposures during this period by asking about drinking prior to pregnancy or prior to pregnancy recognition.

The primary alcohol scores are characterized in Table 2 and

TABLE 3

CORRELATIONS AMONG THE 13 ALCOHOL SCORES REFLECTING DIMENSIONS OF MATERNAL ALCOHOL INTAKE (N = 486)

	LAAP	LAAD	BINGE P	BINGE D	LADOCCP	LADOCCD	LMAXP	LMAXD	LMOCCP	LMOCCD	QFVP	QFVD	ORDEXC
LAAP	1.00	0.67	0.54	0.39	0.63	0.50	0.65	0.52	0.88	0.69	0.73	0.67	0.73
LAAD	0.67	1.00	0.39	0.48	0.47	0.48	0.49	0.53	0.69	0.87	0 56	0.73	0.62
BINGE P	0.54	0.39	1.00	0.60	0.66	0.51	0.75	0.58	0.53	0.44	0.73	0.59	0.66
BINGE D	0.39	0.48	0.60	1.00	0.48	0.53	0.51	0.64	0.40	0.44	0.51	0.70	0.50
LADOCCP	0.63	0.47	0.66	0.48	1.00	0.80	0.97	0.78	0.74	0.62	0.91	0.78	0.84
LADOCCD	0.50	0.48	0.51	0.53	0.80	1.00	0.76	0.95	0.61	0.61	0.72	0.83	0.77
LMAXP	0.65	0.49	0.75	0.51	0.97	0.76	1.00	0.79	0.77	0.65	0.93	0.78	0.86
LMAXD	0.52	0.53	0.58	0.64	0.78	0.95	0.79	1.00	0.64	0.66	0.75	0.85	0.80
LMOCCP	0.88	0.69	0.53	0.40	0.74	0.61	0.77	0.64	1.00	0.84	0.86	0.78	0.89
LMOCCD	0.69	0.87	0.44	0.44	0.62	0.61	0.65	0.66	0.84	1.00	0.72	0.84	0.80
QFVP	0.73	0.56	0.73	0.51	0.91	0.72	0.93	0.75	0.86	0.72	1.00	0.81	0.91
QFVD	0.67	0.73	0.59	0.70	0.78	0.83	0.78	0.85	0.78	0.84	0.81	1.00	0.84
ORDEXC	0.73	0.62	0.66	0.50	0.84	0.77	0.86	0.80	0.89	0.80	0.91	0.84	1.00

Note: Variable names beginning with "L" refer to scores transformed by log(x +1). These log transformations were computed to lessen the effects of skewness and extreme values in the alcohol scores. Definitions in text and on Table 2.

their distributions summarized for the mothers of this cohort of children. When this study began, we did not know which alcohol variables might be critical to certain offspring effects. We therefore generated a variety of alcohol scores incorporating aspects of level, pattern, and timing of exposure. Average ounces of absolute alcohol consumed per day (AA), calculated according to Jessor *et al.* (23), reflects the overall level of exposure. An AA score of 1.0 represents average consumption of about two drinks per day, but the pattern of consumption might be a regular daily drinking pattern or an occasional heavy binge. To clarify the effects of these various drinking patterns, several "binge" scores were calculated, including BINGE, MAX, and ADOCC. The BINGE scores is a dichotomous score for subjects who have reported drinking 5 or more drinks on some occasion in the time period in question. MAX (maximum drinks any occasion) and ADOCC (average drinks any occasion) (38) are simple counts of the maximum and average drinks, respectively, reported separately by time period. We also calculated a 5-point QFV score (8), which derives from a 3-dimensional quantity-frequency-variability scheme for averaging both daily and binge drinking, and a general frequency score (MOCC), the count of the monthly occasions of drinking (38). Finally, we included a derived a priori drinking score (ORDEXC: Ordered Experimental Categories) developed at the outset of the study to select mothers for the follow-up phase. This is an a priori ordering of the various alcohol scores calculated in 1974, according to what we presumed was their risk to the fetus (60). The ORDEXC score of 4 represents highest presumed risk. The coding for the 5-point QFV scores was reversed so that for all 13 alcohol scores, a higher score represents more alcohol.

The correlations among these 13 alcohol scores, as presented in Table 3, range from .39 to .97. The variability in patterns of alcohol consumption is not one-dimensional (as is shown by a principal components analysis of this matrix not included here), and there is far too much collinearity for these scores to be used as joint predictors in multiple regression analyses. Unfortunately, in human teratology studies, it is not possible to measure actual exposure or individual differences in maternal and fetal ethanol metabolism, nor is it feasible to assess alcohol through blood or urine studies throughout pregnancy. Drinking behavior has many facets, and scores based on self-report can capture these dimensions, but are subject to (intentional and unintentional) reporting bias. Nevertheless, test-retest reliability was good when the interview was readministered one week later to 78 mothers (60). Test-retest correlations of the alcohol scores were between .84 and .90, the same range as for the caffeine scores (3). As the prenatal interviews were conducted before general knowledge that drinking could be harmful to the fetus, we assume that a more candid self-report was obtained than could be obtained today.

This basically middle-class cohort represents a broad range of alcohol exposures (see Table 2). The mean AA score is 0.61 (a little over one drink per day) with a median of 0.13 (less than one-half drink per day) for the period prior to pregnancy recognition and a mean of 0.26 (half a drink per day) with median 0.05 during the fifth month of pregnancy. Approximately 27% of the follow-up sample mothers were nondrinkers at the outset of pregnancy, and 23% were nondrinkers at the fifth month. For the mothers who drank at all, the mean and median drinking occasions per month (MOCC) were 17 and 9 for the period prior to pregnancy recognition, and 8 and 5, respectively, during midpregnancy. The mean numbers of drinks per occasion (ADOCC, for drinkers only) for the two time periods were 2.5 and 2.2, while the mean maxima of drinks (MAX) were 4.4 and 4.0, respectively. The BINGE score identified 40% of the drinkers for the period prior to pregnancy recognition and 25% at midpregnancy.

Other Exposures, Covariates, and Intervening Variables

Nicotine use was calculated as the product of the reported number of cigarettes smoked per day by the milligrams of nicotine per cigarette for the brand smoked. Nicotine scores ranged from 0 to 77, with the 148 smokers averaging 17.7 mg (over three-fourths of a pack of moderate nicotine cigarettes per day); 70% of the sample were nonsmokers, and 60% of the heavier drinkers (AAP≥1) did not smoke. Caffeine scores were determined from self-reported use of coffee, tea, cola beverages, and chocolate, converted to mg/day (3). Caffeine use prior to pregnancy recognition ranged from 0 to 2053 mg per day,with a mean of 262 mg, the equivalent of about 3.5 cups of coffee. Only 5 mothers abstained from caffeine. Aspirin and acetaminophen (the most frequently reported drugs after alcohol), and other drugs (marijuana, Valium, etc.) were coded as times used per month. Antibiotic use, which was studied to control for possible illness and infection

TABLE 4

DISTRIBUTION STATISTICS ON INDIVIDUAL ITEMS COMPRISING THE FOUR OUTCOME BLOCKS USED FOR THE PLS ANALYSIS IN PART II. COLUMNS 2 AND 3 COMPARE SCORES OF CHILDREN BORN TO BINGEING AND NON-BINGEING MOTHERS. COLUMNS 4 - 8 PRESENT DISTRIBUTION STATISTICS FOR THE FULL SAMPLE. COLUMN 9 PRESENTS THE SIMPLE CORRELATIONS OF THE INDIVIDUAL ITEMS WITH WISC-R IQ.

Outcome Blocks		Alcohol Exposure (Mean Scores) Binge P (n=140)	No Binge (n=346)	Total Sample (N)	M	±	SD	Min - Max	IQ r
Block 1. WISC-R (standard scores and IQ)									
Information	*	10.37	10.97	(482)	10.79	±	2.93	2 - 19	.754
Similarities	*	11.46	11.90	(482)	11.77	±	3.22	2 - 19	.743
Arithmetic	*	9.19	10.46	(481)	10.10	±	3.05	2 - 19	.701
Vocabulary	*	11.31	11.54	(482)	11.47	±	3.18	2 - 19	.724
Comprehension	*	10.79	11.10	(482)	11.01	±	3.11	1 - 19	.694
Digit span	*	9.51	10.30	(482)	10.07	±	2.66	1 - 19	.412
Pic comp	*	10.84	11.30	(482)	11.17	±	2.53	4 - 18	.593
Pic arrange	*	11.34	11.83	(482)	11.68	±	3.00	2 - 19	.613
Blk designs	*	11.16	12.15	(482)	11.86	±	3.21	1 - 19	.642
Obj assembly	*	11.20	11.34	(482)	11.30	±	2.62	2 - 19	.578
Coding	*	9.34	9.86	(482)	9.71	±	3.13	2 - 19	.427
Full Scale IQ	*	104.78	108.72	(482)	107.58	±	14.45	54 - 152	
Verbal IQ	*	103.55	107.19	(482)	106.13	±	15.48	52 - 155	
Performance IQ	*	105.28	108.82	(482)	107.79	±	13.94	64 - 145	
Block 2. WRAT-R (standard scores)									
Reading	*	108.66	114.73	(482)	112.96	±	17.52	57 - 156	.563
Spelling	*	102.89	107.60	(482)	106.23	±	16.28	48 - 155	.573
Arithmetic	*	100.47	105.59	(482)	104.10	±	10.93	52 - 152	.591
Block 3. Myklebust Scales (scores)									
Comprehend-words	*	3.22	3.48	(469)	3.41	±	.76	1 - 5	.548
Follow-instructs	*	3.25	3.43	(469)	3.38	±	.86	1 - 5	.498
Conprehend-disc	*	3.34	3.50	(469)	3.45	±	.96	1 - 5	.453
Retain-info	*	3.22	3.53	(468)	3.44	±	.82	1 - 5	.538
Vocabulary	*	3.22	3.38	(469)	3.34	±	.68	1 - 5	.488
Grammar	*	3.17	3.40	(469)	3.34	±	.79	2 - 5	.463
Word-recall	*	3.24	3.50	(469)	3.43	±	.79	1 - 5	.467
Relate-experience	*	3.30	3.47	(467)	3.42	±	.81	1 - 5	.452
Formulate-ideas	*	3.15	3.39	(469)	3.32	±	.77	1 - 5	.536
Judge-time	*	3.22	3.38	(469)	3.33	±	.98	1 - 5	.313
Spatial-orient	*	3.57	3.70	(469)	3.67	±	.77	2 - 5	.308
Judge-relations	*	3.50	3.66	(469)	3.61	±	.91	1 - 5	.478
Knows-directions	*	3.21	3.32	(469)	3.29	±	.88	1 - 5	.441
Coordination	*	3.21	3.29	(469)	3.27	±	.76	1 - 5	.208
Balance	*	3.24	3.29	(469)	3.28	±	.61	1 - 5	.217
Manual-dexterity	*	3.08	3.28	(469)	3.22	±	.80	1 - 5	.268
Coop/impulsivity	*	3.21	3.63	(469)	3.51	±	1.11	1 - 5	.359
Attention	*	3.17	3.45	(469)	3.37	±	1.00	1 - 5	.431
Organization	*	2.99	3.23	(469)	3.16	±	.96	1 - 5	.332
Flexibility	*	3.14	3.34	(469)	3.28	±	.90	1 - 5	.354
Social-acceptance	*	3.33	3.42	(469)	3.40	±	.82	1 - 5	.299
Responsibility	*	3.17	3.32	(469)	3.28	±	.83	1 - 5	.385
Finish-tasks	*	3.26	3.56	(469)	3.48	±	.95	1 - 5	.330
Tactfulness	*	3.44	3.68	(469)	3.62	±	.87	1 - 5	.297
Total Scores	*	77.72	82.54	(465)	81.19	±	14.76	42 - 116	.542
Learning Disabled (Myklebust PRS-R score < 65)	*	18 %	11 %	(465)	13 %			0 - 100%	.407

TABLE 4
(CONTINUED)

Outcome Blocks		Alcohol Exposure (Mean Scores) Binge P (n=140)	No Binge (n=346)	Total Sample (N)	M	±	SD	Min - Max	IQ r
Block 4. CPT Vigilance									
Errors Omission (X)	*	4.41	4.14	(454)	4.22	±	4.57	0 - 31	-.343
Errors Commission (X)	*	9.98	8.02	(454)	8.58	±	11.75	0 - 94	-.204
Mean Reaction Time (X)	*	71.53	71.43	(454)	71.46	±	6.02	54 - 91	.012
Errors of Omission (AX)	*	5.83	4.56	(454)	4.92	±	4.72	0 - 26	-.344
Errors of Commission (AX)	*	7.91	5.15	(454)	5.93	±	8.70	0 - 80	-.285

* A mean difference in the anticipated direction, with the children of binge drinkers showing poorer performance than children whose mothers did not drink 5 or more drinks on any occasion during pregnancy.

during pregnancy, was a binary indicator of use of any of a number of antibiotics. Only 8 of the mothers reported use of "street drugs" (heroin, methadone, and others), 84 reported marijuana use,and 12 had used drugs considered to be "possibly teratogenic" at the time the study began [hydantoins, hydrochlorothiazide, chlordiazepoxide hydrochloride (Librium), and meprobamate]. Maternal nutrition was assessed with a 24-hour recall during pregnancy and quantified by summarizing the number of basic food groups for which a mother's dietary intake was adequate according to recommended allowances.

Genetic and demographic characteristics included race, age, education, and parity of the mother, education of the father, sex of the child, and exact age of the child (in days) at the 7-year exam. As the correlations between child IQ and parental education [r = .46 and .43, respectively, for mothers and fathers (54)] are comparable to those reported in the literature between parent IQ and child IQ [between .38 and .46 (7)], we view parental education as a surrogate for parental IQ, which could not be measured in this study. The postnatal events coded included illnesses, accidents, hospitalizations, medical problems, any minor illness on the day of the 7-year exam, preschool attendance, and major life changes in household (at ages 8 months, 18 months, 4 years and 7 years). Mother-child interaction was assessed by nine global assessments at 8 and 18 months of age, each rated on a 5-point scale (50).

Covariate Selection

In assessing possible causal associations between prenatal alcohol exposure and later neuropsychologic functioning of the child, we must consider whether observed relationships involving alcohol can be attributable to confounding with other causal factors. Beginning with the prenatal interview and continuing at each postnatal assessment, we recorded as many potentially confounding and/or intervening variables as possible. A list of approximately 150 such covariates and the rationale for their selection have been published previously (61). This list includes three types of measures: some "genetic" variables which may directly affect the outcome measures; other exposure variables which are sometimes correlated with alcohol use and which could, if ignored, be responsible for spurious relationships with alcohol exposure; and selected postnatal factors which predict behavior and may serve as intervening variables between alcohol exposure and outcome.

Covariates were selected for the analyses in Parts II and III (44,56) if they were substantially (usually "significantly") correlated with some of the outcome measures and/or alcohol exposure measures, or if the literature suggested possible effects on the fetus. Note that the only covariates to bias our estimates of alcohol-outcome relationships are those substantially correlated with both alcohol exposure and outcome. Variables which are predictive of the outcomes (but are not related to alcohol exposure) are considered, however, in order to reduce the "noise" in the assessment of neuropsychological response and so obtain more precise estimates of alcohol-outcome correlations. The covariates that meet these criteria include parental education; maternal age, race and parity; maternal use of cigarettes, marijuana, caffeine, and nutrition during pregnancy; family history of learning disabilities; and child's sex, grade and age at testing.

Some of the covariates reflect postnatal conditions. We are interested not in the ability of these postnatal covariates to predict outcomes per se, but rather in whether the causal route is a direct path from alcohol to outcome or an indirect path by route of a certain postnatal covariate. After assessing the significance of the relation between alcohol exposure and behavioral measures, we considered the "adjustments" owing to such postnatal environmental variables as number of children in the household, preschool experience, nursing, and mother-infant interaction.

Procedures

For the 7½ year exam, each child was examined by two psychometrists. One administered the neuropsychological tests and made the behavior ratings; the other administered the computerized vigilance test. At no time did the psychometrists have any information about the child's exposure history, family situation, or performance on prior tests. The examiners were trained to a high level of reliability maintained with monthly reliability checks. The children were examined at the study offices at the University of Washington during the summer in which, according to birth date, they might be expected to have finished first grade. In order to keep the psychometrists "blind" with respect to the families, an outreach worker did all the scheduling and rescheduling of appointments.

Order of the tests was standardized across all children: the WISC-R, the WRAT-R, the neuropsychologic tests, and the vigilance paradigm. As it is not feasible to randomize the order of test administration in behavioral teratology studies, we exploited

TABLE 5

ITEMS IN THE NBT BATTERY: DISTRIBUTION STATISTICS BY PRENATAL ALCOHOL (BINGE P)

Outcome Blocks		Alcohol Exposure (Mean Scores) Binge P (n=140)	No Binge (n=346)	Total Sample (N)	M	±	SD	Min - Max	IQ r
Block 1. Miscellaneous Memory									
Memory for Faces Test									
Faces.#Correct	*	5.56	5.75	(453)	5.70	±	2.17	0 - 12	.122
Faces.#Chosen	*	9.24	9.46	(453)	9.40	±	4.03	0 - 25	.024
Faces.Correct/Chosen		.63	.63	(451)	.63	±	.17	.3 - 1	.107
Faces.Chosen-Correct		3.68	3.71	(453)	3.70	±	2.49	0 - 13	-.068
Seashore Rhythm Test									
Seashore A.Errors	*	2.17	1.87	(482)	1.95	±	1.83	0 - 9	-.275
Seashore B.Errors	*	2.99	2.89	(482)	2.92	±	1.87	0 - 10	-.288
Seashore C.Errors	*	4.48	3.84	(482)	4.02	±	1.75	0 - 9	-.199
Tactual Performance Test (TPT)									
TPT.Time Dom (sec)		373.26	380.04	(479)	378.10	±	172.02	83 - 1112	-.183
TPT.Time NDom (sec)	*	262.88	262.33	(479)	262.49	±	145.45	44 - 915	-.186
TPT.Time Both H.	*	150.04	134.92	(479)	139.24	±	98.40	22 - 600	-.223
TPT.#Blocks Dom	*	5.09	5.21	(479)	5.18	±	1.63	0 - 6	.214
TPT.#Blocks NDom	*	5.38	5.60	(479)	5.54	±	1.28	0 - 6	.214
TPT.#Blocks Both H.		5.84	5.83	(478)	5.83	±	.82	0 - 6	.173
TPT.Memory	*	3.46	3.82	(480)	3.72	±	1.49	0 - 6	.381
TPT.Localization	*	2.05	2.25	(480)	2.19	±	1.71	0 - 6	.373
Animal Naming Test									
An.Naming.#Best 60 Sec		12.14	11.80	(464)	11.90	±	3.73	2 - 25	.442
An.Naming.#Worst 30 Sec		2.66	2.66	(464)	2.66	±	1.84	0 - 10	.321
Incidental Learning Test									
Inci.Learng.#Correct	*	2.00	2.17	(484)	2.12	±	.97	0 - 4	.278
Block 2. Verbal Memory (CMTV)									
Children's Memory Test (CMT)									
CMTV.#Recalled St.1		9.74	9.63	(484)	9.66	±	3.21	0 - 15	.287
CMTV.#Recalled St.2	*	11.88	12.07	(483)	12.02	±	4.14	0 - 20	.288
CMTV.#Recalled St.3	*	8.69	9.01	(484)	8.92	±	2.92	0 - 15	.230
CMTV.#Recalled St.4	*	13.62	14.59	(484)	14.31	±	4.07	0 - 20	.365
CMTV.Accuracy St.1	*	78 %	83 %	(474)	81 %			1 - 3	.176
CMTV.Accuracy St.2	*	73 %	80 %	(474)	78 %			1 - 3	.192
CMTV.Accuracy St.3	*	78 %	82 %	(477)	81 %			1 - 3	.101
CMTV.Accuracy St.4	*	82 %	86 %	(478)	85 %			1 - 3	.123
CMTV.Sequence St.1		63 %	59 %	(474)	60 %			1 - 3	.192
CMTV.Sequence St.2	*	41 %	50 %	(474)	47 %			1 - 3	.169
CMTV.Sequence St.3		54 %	53 %	(477)	53 %			1 - 3	.100
CMTV.Sequence St.r	*	57 %	66 %	(478)	64 %			1 - 3	.311
CMTV.Unusual Fea.St.1		87 %	85 %	(474)	85 %			1 - 3	.182
CMTV.Unusual Fea.St.2	*	81 %	85 %	(474)	84 %			1 - 3	.236
CMTV.Unusual Fea.St.3	*	84 %	85 %	(477)	85 %			1 - 3	.121
CMTV.Unusual Fea.St.4	*	80 %	87 %	(478)	85 %			1 - 3	.209
CMTV.Extra Idea St.1	*	28 %	32 %	(484)	31 %			0 - 1	.148
CMTV.Extra Idea St.2		61 %	58 %	(483)	59 %			0 - 1	.248
CMTV.Extra Idea St.3	*	50 %	54 %	(484)	53 %			0 - 1	.144
CMTV.Extra Idea St.4	*	>99 %	>99 %	(483)	>99 %			0 - 1	-.037

TABLE 5
(CONTINUED)

Outcome Blocks		Alcohol Exposure (Mean Scores) Binge P (n=140)	No Binge (n=346)	(N)	Total Sample M	±	SD	Min - Max	IQ r
Block 3. Memory for Designs (CMTM)									
Children's Memory Test (CMT)									
CMTM.#Recalled D.1	*	3.66	3.99	(485)	3.90	±	1.06	0 - 5	.338
CMTM.#Recalled D.2	*	4.13	4.19	(483)	4.17	±	1.15	0 - 6	.241
CMTM.#Recalled D.3	*	2.99	3.24	(486)	3.17	±	1.41	0 - 5	.260
CMTM.#Recalled D.4	*	7.22	7.34	(485)	7.30	±	1.12	2 - 8	.243
CMTM.#Recalled D.5	*	5.10	5.32	(448)	5.25	±	1.40	0 - 8	.443
CMTM.Magnitude D.1	*	89 %	92 %	(485)	92 %			0 - 1	.085
CMTM.Magnitude D.2	*	92 %	94 %	(485)	93 %			0 - 1	.054
CMTM.Magnitude D.3		93 %	93 %	(486)	93 %			0 - 1	.054
CMTM.Magnitude D.4		93 %	92 %	(486)	93 %			0 - 1	.034
CMTM.Magnitude D.5	*	85 %	88 %	(447)	87 %			0 - 1	.025
CMTM.Quality D.1	*	65 %	70 %	(485)	68 %			0 - 2	.223
CMTM.Quality D.2	*	52 %	60 %	(485)	58 %			0 - 2	.323
CMTM.Quality D.3	*	68 %	79 %	(486)	76 %			0 - 2	.156
CMTM.Quality D.4	*	71 %	79 %	(486)	77 %			0 - 2	.130
CMTM.Quality D.5	*	39 %	48 %	(447)	45 %			0 - 2	.350
CMTM.Rotations D.1	*	78 %	82 %	(485)	81 %			0 - 2	.088
CMTM.Rotations D.2		95 %	94 %	(485)	94 %			0 - 1	.041
CMTM.Rotations D.3		97 %	97 %	(486)	97 %			0 - 1	.014
CMTM.Rotations D.4	*	36 %	40 %	(486)	39 %			0 - 2	.021
CMTM.Rotations D.5		69 %	66 %	(447)	67 %			0 - 4	.061
CMTM.Reversals D.1	*	64 %	68 %	(485)	67 %			0 - 2	.168
CMTM.Reversals D.2	*	84 %	87 %	(485)	86 %			0 - 2	-.027
CMTM.Reversals D.3	*	96 %	98 %	(486)	97 %			0 - 1	.019
CMTM.Reversals D.4		96 %	95 %	(486)	95 %			0 - 2	-.001
CMTM.Reversals D.5		82 %	79 %	(447)	80 %			0 - 4	-.006
CMTM.Distortions D.1	*	65 %	66 %	(485)	66 %			0 - 3	.196
CMTM.Distortions D.2	*	46 %	56 %	(485)	53 %			0 - 2	.378
CMTM.Distortions D.3	*	91 %	95 %	(486)	94 %			0 - 1	-.043
CMTM.Distortions D.4	*	67 %	70 %	(486)	69 %			0 - 1	.118
CMTM.Distortions D.5	*	25 %	26 %	(447)	26 %			0 - 6	.141
CMTM.Substitutions D.1		100 %	>99 %	(485)	>99 %			0 - 1	.008
CMTM.Substitutions D.2		70 %	68 %	(485)	69 %			0 - 3	.153
CMTM.Substitutions D.3	*	59 %	67 %	(486)	65 %			0 - 1	.082
CMTM.Substitutions D.4		86 %	83 %	(486)	84 %			0 - 1	.157
CMTM.Substitutions D.5	*	52 %	61 %	(447)	58 %			0 - 3	.087
CMTM.Integration D.1	*	74 %	85 %	(485)	82 %			0 - 1	.137
CMTM.Integration D.2	*	87 %	92 %	(485)	91 %			0 - 1	.178
CMTM.Integration D.3	*	99 %	>99 %	(486)	>99 %			0 - 1	.016
CMTM.Integration D.4	*	85 %	86 %	(486)	86 %			0 - 1	.095
CMTM.Integration D.5	*	40 %	44 %	(447)	43 %			0 - 1	.007
CMTM.Perseveration D.1		100 %	100 %	(485)	100 %			1 - 1	n.c.
CMTM.Perseveration D.2		69 %	66 %	(485)	67 %			0 - 2	-.033
CMTM.Perseveration D.3	*	69 %	72 %	(486)	71 %			0 - 2	.015
CMTM.Perseveration D.4		100 %	100 %	(486)	100 %			1 - 1	n.c.
CMTM.Perseveration D.5	*	76%	80 %	(447)	79 %			0 - 2	.001

TABLE 5
(CONTINUED)

Outcome Blocks		Alcohol Exposure (Mean Scores) Binge P (n=140)	No Binge (n=346)	(N)	Total Sample M	±	SD	Min - Max	IQ r
Block 4. Copy Designs (CMTC)									
Children's Memory Test (CMT)									
CMTC.Recalled D.1	*	4.52	4.62	(447)	4.59	±	.73	1 - 5	.224
CMTC.Recalled D.2	*	4.55	4.57	(448)	4.56	±	.98	0 - 6	.325
CMTC.Recalled D.3	*	4.24	4.38	(448)	4.34	±	1.05	0 - 5	.361
CMTC.Recalled D.4		7.70	7.70	(448)	7.70	±	.67	2 - 8	.366
CMTC.Recalled D.5	*	6.80	6.84	(448)	6.83	±	1.07	0 - 8	.411
CMTC.Magnitude D.1		95 %	91 %	(447)	92 %			0 - 1	.029
CMTC.Magnitude D.2		92 %	90 %	(448)	90 %			0 - 1	-.079
CMTC.Magnitude D.3	*	94 %	95 %	(448)	94 %			0 - 1	-.011
CMTC.Magnitude D.4	*	92 %	95 %	(448)	94 %			0 - 1	.018
CMTC.Magnitude D.5		94 %	94 %	(448)	94 %			0 - 1	.003
CMTC.Quality D.1	*	77 %	83 %	(447)	81 %			0 - 2	.138
CMTC.Quality D.2	*	68 %	72 %	(448)	71 %			0 - 2	.289
CMTC.Quality D.3	*	88 %	93 %	(448)	92 %			0 - 2	.213
CMTC.Quality D.4	*	80 %	86 %	(448)	84 %			0 - 2	.216
CMTC.Quality D.5	*	70 %	72 %	(448)	71 %			0 - 2	.356
CMTC.Rotations D.1	*	88 %	90 %	(447)	89 %			0 - 1	.004
CMTC.Rotations D.2		96 %	96 %	(448)	96 %			0 - 1	.111
CMTC.Rotations D.3	*	95 %	97 %	(448)	96 %			0 - 1	-.015
CMTC.Rotations D.4	*	42 %	50 %	(448)	48 %			0 - 2	.183
CMTC.Rotations D.5	*	78 %	81 %	(448)	80 %			0 - 2	.169
CMTC.Reversals D.1	*	90 %	97 %	(447)	95 %			0 - 2	.180
CMTC.Reversals D.2		88 %	86 %	(448)	87 %			0 - 1	-.050
CMTC.Reversals D.3		100 %	>99 %	(448)	>99 %			0 - 1	.006
CMTC.Reversals D.4		98 %	98 %	(448)	98 %			0 - 1	.078
CMTC.Reversals D.5		95 %	92 %	(448)	93 %			0 - 3	.097
CMTC.Distortions D.1	*	78 %	80 %	(447)	79 %			0 - 2	.163
CMTC.Distortions D.2	*	67 %	74 %	(448)	72 %			0 - 1	.311
CMTC.Distortions D.3	*	97 %	98 %	(448)	98 %			0 - 1	-.054
CMTC.Distortions D.4		72 %	72 %	(448)	72 %			0 - 2	.102
CMTC.Distortions D.5		48 %	46 %	(448)	47 %			0 - 6	.304
CMTC.Substitutions D.1		100 %	100 %	(447)	100 %			1 - 1	n.c.
CMTC.Substitutions D.2	*	75 %	76 %	(448)	76 %			0 - 3	.238
CMTC.Substitutions D.3	*	84 %	89 %	(448)	87 %			0 - 1	.202
CMTC.Substitutions D.4		90 %	89 %	(448)	89 %			0 - 2	.179
CMTC.Substitutions D.5	*	52 %	64 %	(448)	60 %			0 - 2	.078
CMTC.Integration D.1		88 %	87 %	(447)	87 %			0 - 1	.192
CMTC.Integration D.2	*	87 %	92 %	(448)	90 %			0 - 1	.177
CMTC.Integration D.3		100 %	>99 %	(448)	>99 %			0 - 1	.019
CMTC.Integration D.4	*	71 %	79 %	(448)	76 %			0 - 1	.085
CMTC.Integration D.5	*	32 %	38 %	(448)	37 %			0 - 1	.035
CMTC.Perseverations D.1	*	99 %	>99%	(447)	>99 %			0 - 1	.006
CMTC.Perseverations D.2		83 %	76 %	(448)	78 %			0 - 2	.082
CMTC.Perseverations D.3		97 %	97 %	(448)	97 %			0 - 2	.200
CMTC.Perseverations D.4		100 %	100 %	(448)	100 %			1 - 1	n.c.
CMTC.Perseverations D.5	*	80 %	86 %	(448)	85 %			0 - 2	.168

TABLE 5
(CONTINUED)

Outcome Blocks		Alcohol Exposure (Mean Scores) Binge P (n=140)	No Binge (n=346)	(N)	Total Sample M	±	SD	Min - Max	IQ r
Block 5. Miscellaneous Neuropsychologic									
Progressive Figures Test									
Progressive Figures.Time	*	.94	.82	(483)	.85	±	.71	.2 - 5.6	-.411
Progressive Figures. Errors	*	.59	.42	(484)	.47	±	1.65	0 - 22.0	-.268
Auditory-Visual Integration Test									
AV.Integration.Errors	*	3.98	3.58	(442)	3.70	±	2.36	0 - 9.0	-.508
Verbal Fluency (Blueberries Said)									
#Said (in 30 sec)	*	6.86	7.04	(479)	6.99	±	2.34	.5 - 14.0	.309
Errors	*	7.35	6.92	(479)	7.04	±	5.53	0 - 60.0	-.262
Torque Test									
Torque.Dom (#Clockwise)?		.88	.83	(463)	.84	±	1.28	0 - 3.0	.023
Torque.NDom (#Clockwise)?		.92	.91	(463)	.91	±	1.30	0 - 3.0	-.012
Torque.Consistent Dom		92 %	91 %	(463)	91 %			0 - 1.0	-.058
Torque.Consistent NDom		91 %	88 %	(463)	89 %			0 - 1.0	.009
Lateral Dominance Test									
Dom.Writ. (right hand for writing)	?	86 %	89 %	(480)	88 %			0 - 1.0	-.003
Lateral Dominance	?	80.53	81.59	(448)	81.28	±	23.61	0 - 100.0	.009
Block 6. Name Writing Speed									
Nam Writ.1st Dom Time	*	2.31	2.01	(461)	2.10	±	1.29	.4 - 14.5	-.188
Nam Writ.1st NDom Time	*	4.65	4.06	(460)	4.23	±	2.23	1.0 - 25.0	-.228
Nam Writ.Whole.Dom Time	*	2.53	2.17	(446)	2.27	±	1.29	.5 - 13.0	-.215
Nam Writ.Whole.NDom Time	*	4.36	3.98	(446)	4.09	±	1.69	1.4 - 15.5	-.228
Block 7. Magnitude of Dominance (calculated from other tests)									
TPT Dom/NDom	?	1.82	1.76	(479)	1.78	±	1.14	.3 - 8.5	.034
TPT.NDom/Both	?	2.23	2.46	(479)	2.40	±	1.54	.5 - 10.8	.106
Nam.Writ.Dom/NDom	?	.58	.56	(446)	.57	±	.22	.1 - 1.7	-.011
Lateral dominance Consistency		36.56	36.30	(448)	36.37	±	14.57	7.0 - 50.0	-.017
Block 8. Behavior Ratings									
BR.Fear of New Situations		2.55	2.68	(412)	2.64	±	1.77	1 - 7	-.227
BR.Uninhibited	*	4.84	4.95	(472)	4.92	±	1.84	1 - 7	.288
BR.Too Uninhibited	*	8 %	7 %	(472)	7 %			0 - 1	-.094
BR.Happy	*	4.84	4.90	(483)	4.88	±	1.37	1 - 7	.213
BR.Aware		5.32	5.10	(403)	5.16	±	1.48	1 - 7	.208
BR.Too Aware		7 %	7 %	(403)	7 %			0 - 1	-.166
BR.Seeks Reassurance	*	3.28	3.18	(483)	3.21	±	1.76	1 - 7	-.109
BR.Cooperation	*	5.11	5.42	(481)	5.33	±	1.49	1 - 7	.299
BR.Performance anxiety		3.69	3.70	(482)	3.70	±	1.74	1 - 7	-.211
BR.Endurance	*	4.93	5.21	(479)	5.13	±	1.92	1 - 7	.367
BR.FinishesTask	*	5.22	5.39	(469)	5.34	±	1.67	1 - 7	.326
BR.Organization	*	4.82	5.01	(479)	4.96	±	1.65	1 - 7	.463
BR.Distractability	*	3.05	2.67	(480)	2.78	±	1.85	1 - 7	-.216
BR.Persistence	*	4.69	4.92	(462)	4.86	±	1.82	1 - 7	.392
BR.Too Persistent		7 %	3 %	(462)	4 %			0 - 1	-.229
BR.Frustration	*	3.50	3.03	(484)	3.17	±	1.85	1 - 7	-.269

TABLE 5
(CONTINUED)

Outcome Blocks		Alcohol Exposure (Mean Scores) Binge P (n=140)	No Binge (n=346)	(N)	Total Sample M	±	SD	Min - Max	IQ r
Block 8. Behavior Ratings (continued)									
BR.Impulsivity		3.24	3.25	(483)	3.25	±	1.68	1 - 7	-.204
BR.Activity	*	3.83	3.82	(484)	3.82	±	1.17	1 - 7	.019
BR.Spontaneous Verbalization		3.71	3.48	(214)	3.54	±	2.09	1 - 7	.152
BR.Appropriateness of Spontaneous Verbalization	*	6.02	6.07	(334)	6.06	±	1.47	1 - 7	.141
BR.Verbal Interruptions	*	3.58	3.35	(308)	3.42	±	1.84	1 - 7	-.037
BR.Intuitiveness of Verbal Interruptions		1.97	2.16	(317)	2.10	±	1.77	1 - 7	-.106
BR.Organization Under Stress	*	3.66	4.16	(258)	4.02	±	2.21	1 - 7	.280

Note: Logarithm transformations were computed for 8 of the most highly skewed distributions: all 4 Name Writing Scores, Progressive Figures Time and Errors, and Blueberries Errors. The variation in sample size among individual items, is for the most part, due to missing data resulting from certain items being added after testing had begun, or modifications in the scoring or administration procedures, which invalidated some early scores.

Definitions: An * indicates that the differences are in the expected direction. n.c. means not computable (no variability). Percent Error Free is presented in lieu of mean ± SD for variables where: 1) a large number of the scores were zero, and 2) for binary variables.

the testing order to enhance the effects of fatigue. Because vigilance studies depend to some extent on fatigue, we placed that test at the end of the session.

Appropriate permission having been obtained, the child's primary classroom teacher filled out a behavior rating form on the child's classroom behavior. This classroom phase was carried out approximately three months after the child should have begun second grade. The return rate on teacher questionnaires was 96.5%.

The average testing time for the IQ, achievement, and neuropsychologic tests (excluding CPT vigilance) was 2 hours 45 minutes. Testing time was not associated with alcohol exposure, demographic variables, ambient temperature, time of day, type of school attended,or other child variables. Testing time was associated with individual examiners and with the presence of an observer for reliability studies.

Outcome Variables

The wide variety of tests and ratings assessed the many types of neurobehavioral outcomes that we believed (based on the literature and our own clinical experience) might be affected by prenatal alcohol exposure. We focussed on those with particular significance for understanding the brain/behavior relationships involved in alcohol teratogenesis. Altogether, we administerd 17 neuropsychologic tests to the children and used two sets of rating scales,one filled out by the psychometrist, the other by the classroom teacher.

Because our goal was to examine the pattern of neurobehavioral deficits associated with prenatal alcohol exposure, the unit that we analyzed was the individual test or subtest score rather than the summary score. This procedure allowed us to take advantage of the fact that not all subtests were equally effective in detecting the effects of alcohol. The 17 tests and 2 rating scales yielded a total of 164 individual scores which constituted the outcome variables. For convenience, these 164 scores have been classified into a priori "blocks" based on their face validity.

For the analyses in Parts II and III (44,56), these outcomes have been divided into two sets: Set 1 includes the standardized IQ and Achievement Tests, our laboratory vigilance test, and the classroom behaviors rated by the teachers. We use these relatively circumscribed sets of variables to introduce the PLS method in Part II (44). In Part III (56), we apply the same method to the more complex neurobehavioral data sets.

The analyses in Part II (44) refer to four "blocks" or groups of variables for the PLS analysis. These include:

Block 1. Intelligence. Eleven subtest scores from the Wechsler Intelligence Scale for Children-Revised (WISC-R) (64).

Block 2. Achievement. Standard scores for Reading, Spelling and Arithmetic from the Wide Range Achievement Test-Revised (WRAT-R) (22).

Block 3. Classroom Behavior. Twenty-four teacher ratings of the child's classroom behavior, rated on the Myklebust Pupil Rating Scale-Revised (PRS) (33). This is a screening instrument for identifying children at high risk for school failure. Each item is rated on a 5-point scale from very poor to superior.

Block 4. Vigilance. Four error scores (Errors of Omission and Errors of Commission from two conditions, the X and the AX task), and a mean reaction time score from a computerized vigilance test (Continuous Performance Test, CPT), a measure of sustained attention, described previously (55).

For the analyses in Part III (56), the neurobehavioral outcomes are organized into eight "blocks" by face validity:

Block 1. Miscellaneous Memory Tests (18 scores).

a. The Memory for Faces Test, developed by Milner (32), is a short-term memory test which discriminates adults with hippocampal and temporal damage. Four scores were analyzed: the total number of faces chosen by the child, the number of faces correctly identified as having been previously viewed, the ratio of number

correct to number chosen, and the number correct minus the number incorrectly chosen.

b. The Seashore Rhythm Test (45), part of the Reitan-Indiana Battery (40), is an auditory discrimination test in which one must distinguish whether pairs of rhythmic patterns are the same or different. This test is a sensitive indicator of exposure to lead (34). Errors in each of 3 trials are scored.

c. The Tactual Performance Test (TPT), also part of the Reitan-Indiana Battery (40), requires that the subject complete a wooden formboard using only tactile cues. The time to complete 3 trials of the task is observed for the dominant hand, the nondominant hand, and both hands together. Other scores include the numbers of blocks placed (out of 6 possible) with each hand and with both hands, the number of forms correctly drawn after the test ("TPT Memory"), and the number of forms drawn in the correct location ("TPT Location").

d. Animal Naming is a test from the Boston Aphasia Battery (16), which measures verbal fluency. We used the number of animals named in the most productive 60 second period and the number named in the worst 30 second period.

e. Incidental Learning is a simple 4-item test in which the subjects were asked at the end of the 2½-hour session to recall things the examiner had said or done at the outset, including the examiner's name, the name of her dog, her favorite color, and where her pencil was kept. The score is the total correct out of 4.

Block 2. Children's Memory Test—Verbal (CMTV). This test was developed by Carl Dodrill and Bonnie Miller (Regional Epilepsy Center, Seattle, WA) as a children's version of the Wechsler Memory Test. The scores are the total number of elements recalled by the child after hearing each of 4 stories read by the examiner. In addition, we developed a qualitative scoring system whereby each of the child's 4 stories was given a score for Accuracy, Sequence, Unusual features, and Extra ideas, for a total of 20 scores.

Block 3. Memory for Designs, Children's Memory Test (CMTM). This test was developed by Dodrill and Miller and modified in our laboratory; a detailed scoring manual is available (13). The scores are the total number of elements correctly drawn from memory immediately after viewing each of five line drawings. Each design was additionally scored with eight qualitative codes which we designed deriving from the Koppitz Scoring System (26) for the Bender Gestalt Test: Magnitude, Quality, Rotations, Reversals, Distortions, Substitutions, Integration, and Perseveration. The total number of scores for this block is 45.

Block 4. Copying Designs, Children's Memory Test (CMTC). This test is our modification of the CMT in which the child is asked to copy the same designs he/she had earlier drawn from memory. The scores are the same as for CMTM.

Block 5. Miscellaneous Neuropsychologic Tests (11 scores).

a. Progressive Figures, another test from the Reitan-Indiana Test Battery, measures cognitive flexibility. The child is required to connect eight designs with a pencil line, progressing from a small internal design to the identical shape used as a large exterior design. Time to completion and errors were recorded.

b. The Auditory-Visual Integration Test developed by Birch (4,5) measures the ability to recognize the relationship between auditory patterns (taps) and visual patterns (dots). The score is the number of errors in 10 trials.

c. Blueberries Said is a verbal fluency test requiring the rapid repetition of the phrase "The big blue bucket of blue blueberries." The scores are the number of repetitions of the phrase in 30 seconds and the number of errors.

d. The Torque Test developed by Blau (6) and subsequently modified (14) is a motor test in which the direction of drawing circles is scored for each hand. The scores are the number of clockwise circles drawn with each hand and binary indicators for consistency of direction (all clockwise or all counterclockwise) for each hand.

e. Lateral Dominance is part of the Reitan-Indiana Battery (40). The score is the percent of tasks which show a right-sided preference. We also included a binary indicator for those children who wrote with their right hand.

Block 6. Name-Writing Speed. This task is also part of the Reitan-Indiana Battern (40). Scores are seconds per letter taken to write the first name and the full name with the dominant and the nondominant hand.

Block 7. Magnitude of Dominance. These scores were calculated as ratios of scores from the TPT (Dom/NonDom and NonDom/Both) and Name Writing (Dom/NonDom) Tests. In addition, a Lateral Dominance Consistency Score was derived from Reitan's Lateral Dominance test (40), with 50 representing complete consistency for either the right or left side, across all 7 items, and 0 representing no consistency across trials.

Block 8. Behavior Ratings. These rating scales were filled out by the examiners following the testing session with each child. Fifteen behaviors (Cooperation, Performance anxiety, Organization, Distractibility, Persistence, and so forth) were rated on 7-point scales, from low to high. Three of the scales (Uninhibitedness, Awareness and Persistence) were coded additionally for inappropriate behavior.

RESULTS/DISCUSSION

In risk-prediction studies such as these, two characteristics of the tests themselves deserve attention: a) it is important to select tasks that are not so difficult that they cannot be carried out by the entire cohort (to avoid missing data on what might be the highest-risk subjects); and b) it is also important that the tests are sufficiently difficult to provide a suitable range of scores without excessive skewing of the distributions. The standardized tests in Table 4 (Myklebust PRS, WRAT-R and WISC-R) accomplish requirement (b) better than the CPT error scores, which were somewhat skewed toward a perfect performance, thus making them less sensitive. In terms of requirement (a), we note that only one subject had difficulty comprehending the directions, although 14 of the children had IQ scores below 80. The most stressful test, the TPT, was terminated for two children who could not tolerate the stress. One of these children was heavily exposed to alcohol in utero; the other was moderately exposed and had a history of child abuse. The latter child also refused two other tests (Progressive Figures and the Seashore Rhythm). Two additional children had difficulty performing the Seashore test.

Tables 4 and 5 present data on the individual outcome scores comprising, respectively, the 4-block analyses described in Part II (44) and the 8-block analyses described in Part III (56). Three types of data are presented on each table: mean scores for binge-exposed (BINGE P) and nonbinge-exposed children, distribution statistics for the whole sample (means, standard deviations, and range of scores), and correlations of each individual item with the full-scale IQ score. The use of the BINGE-P score as a grouping variable is for convenience; it does not imply that it is the "best" alcohol predictor [see Parts II and III (44,56)].

From these data we see that the scores obtained span a wide range of values. Population values on the standardized tests (IQ, achievement and learning disabilities) are in line with expectations considering the generally well-educated middle-class homes from which these children derive. The mean WISC-R IQ of 108 is congruent with the WPPSI IQ obtained on this cohort at 4 years 3 months of age (54). According to Myklebust's criteria (33), 13% of this population is at risk for learning disabilities based on the ratings of classroom teachers on the PRS. This figure may be somewhat elevated compared to other populations due to the

disproportionate number of children in this cohort who were prenatally exposed to alcohol. (Recall that the follow-up cohort intentionally maximized the number of children of heavier drinkers from the population-based sample of 1529 pregnant women interviewed.)

Tables 4 and 5 also present the simple correlations of these neurobehavioral scores with the full-scale IQ score. Naturally, the subtests of the IQ test and the achievement tests are the most highly correlated with IQ. Yet the correlations are not so high that any one of these scores could be thought of as surrogate for IQ. Some of the teacher ratings such as "comprehends words," "retains information" and "formulates ideas" are also quite highly correlated with IQ, but most show only a modest relationship with IQ. The vigilance scores are modestly correlated with IQ (except for reaction time, which is uncorrelated). Some of the neurobehavioral tests are modestly correlated with IQ, but others, particularly the qualitative "process" variables, are only minimally correlated.

Simple comparisons of the mean scores of binge-exposed vs. nonbinge-exposed children show that the binge-exposed have lower IQ scores and achievement scores, and that a greater proportion (18% vs. 11%) have a PRS score less than 65 [Myklebust's (33) criterion for being "at risk for learning disabilities"]. Also, the binge-exposed children make more errors on the computerized vigilance task (CPT), particularly on the second subtest, which is sensitive to impulsive errors.

Pondering these descriptive findings was not the primary aim of this research. Our goal was not simply to ask about IQ differences between the binge-exposed and the nonbinge-exposed children. We wished, instead, to find the underlying dimensions of behavior and performance that are affected by our best cumulative measure of "dose." Remember that we measured 13 patterns and levels of prenatal alcohol exposure. BINGE P was only one convenient dichotomous score that separated out a sizeable number (140) of binge-exposed children. We could as easily have presented our other dichotomous score, BINGE D, in Tables 4 and 5. If we had done that, we would have cut the sample at $n = 92$ binge-exposed children. (In fact, the distributions are quite similar.) Practically, it would never be possible to scan the individual distributions or carry out multiple regression analyses using all 13 of these alcohol predictors, against the 164 outcomes of potential interest.

Therefore, rather than pursuing these separate investigations further, we present in Parts II and III of this trilogy the application of a new statistical methodology to this complex multivariate problem. Using the standardized tests from Table 4 we demonstrate in Part II (44) how the Partial Least Squares (PLS) methodology determines the underlying "signal" of alcohol exposure and the corresponding signal of performance deficit. In Part III (56) we apply this methodology to the even more complex group of neuropsychologic tests listed in Table 5.

That alcohol causes brain alterations and performance deficits has been confirmed by hundreds of experiments on laboratory animals [e.g., (41,63)] and by clinical observations and studies on children of alcoholic mothers (49). It is not the fact of this causation that is under investigation here. We are seeking instead to characterize the *patterns* of prenatal exposure that produce behavioral deficits in 7-year-old children, and the *patterns* of behavioral deficit that are most associated with these patterns of alcohol "dose." Because behavioral deficits are multiply determined, we must also examine the influence of selected covariates upon this causal association. These concerns lead us directly into the analyses of Parts II and III (44,56).

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