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Neurobehavioral Effects of Prenatal Alcohol: Part III. PLS Analyses of Neuropsychologic Tests[1]

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STREISSGUTH, A. P., F. L. BOOKSTEIN, P. D. SAMPSON AND H. M. BARR. *Neurobehavioral effects of prenatal alcohol: Part III. PLS analyses of neuropsychologic tests.* NEUROTOXICOL TERATOL **11**(5) 493–507, 1989.—This paper is the third in a three-part series describing an investigation of the effects of prenatal alcohol exposure on the neurobehavioral functioning of 384 children about 7½ years old. Here we describe the use of Partial Least Squares for data reduction and analysis of 158 neurobehavioral measures as they relate to 13 aspects of prenatal alcohol exposure. A general alcohol latent variable, emphasizing both binge and regular drinking patterns in the period prior to pregnancy recognition as well as during pregnancy, predicts a pattern of neurobehavioral deficit that includes attentional and memory deficits across both verbal and visual modalities; a variety of "process" variables reflecting poor integration and quality of responses; behavior patterns involving distractibility and poor organization; and an inflexible approach to problem-solving. The prominence of poorer spatial organization and arithmetic as primary outcomes of alcohol teratogenesis suggests a possible "nonverbal learning disability" pattern of deficit associated with prenatal alcohol exposure at the level of social drinking.

Fetal Alcohol Syndrome Fetal alcohol effects Behavioral teratology Neuropsychology Memory
Latent variables Birth defects Pregnancy outcome Alcohol teratogenesis Partial Least Squares Longitudinal research

THIS is the third in a three-part series of papers on the 7-year sequelae of prenatal alcohol exposure in a population-based cohort of moderately-exposed children. The first paper (38) reviews the literature on alcohol teratogenesis and presents the rationale, procedures, and distributions of scores for individual tests. The second paper (30) introduces a relatively new statistical methodology (Partial Least Squares—PLS) that is particularly well suited to the richly multivariate data sets generated by human behavioral teratology studies. That paper goes on to analyze data from standardized IQ and achievement tests, classroom behavior ratings, and a laboratory attention task. In this third paper, we use the PLS methodology to analyze an even more complex set of neurobehavioral outcomes, deriving from a large group of neuropsychologic tests, in order to delineate specific patterns of deficit associated with prenatal alcohol exposure.

Neuropsychologic tests are designed to pick up specialized patterns of brain dysfunction even in the presence of normal overall intellectual ability. Traditional batteries of neuropsychologic tests have been developed to characterize the functional deficits associated with specific types of brain-impairing disease processes and head injuries. To our knowledge, there are no existing batteries of neuropsychologic tests designed or used for human behavioral teratology studies, such as this one, for which the goal is to assess the long-term effects of a specific prenatal insult (in this case, alcohol) to the developing brain. Therefore, we assembled a group of tests which we thought would be sensitive markers of prenatal alcohol exposure in the school-age child. As described in Part I (38), decisions about tests to include were based on our clinical experience with neuropsychologic testing of children with Fetal Alcohol Syndrome (FAS), those most severely affected by alcohol teratogenesis (34). We predicted that we might find neurobehavioral effects in children of social-drinking mothers

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similar to, but more subtle than, the severe deficits observed in children with FAS (whose mothers are generally alcoholics).

Our analyses address three basic questions:

1. What patterns of alcohol exposure best explain these neurobehavioral outcomes in 7-year-old children?
2. What patterns of these neurobehavioral outcomes are explained by prenatal alcohol exposure?
3. What relevant covariates, both prenatal and postnatal, modify these associations?

In order to address these questions, we needed a rich and diverse group of neuropsychologic measures and a statistical method capable of handling such an indirect, yet redundant, multivariate data set. Keeping in mind our clinical experience with children with FAS, we cast a broad net of neuropsychologic tests because animal models of alcohol teratogenesis have shown a wide range of effects on brain growth and development (24,48), and because primate research has shown high variability across individuals in the neurobehavioral response to standard binge doses of alcohol during gestation. In one recent primate study (6), although no single test picked out all the exposed animals, all exposed animals were identified on at least one test. Our analysis emphasizes individual scores from a broad group of neuropsychologic tests rather than summary scores. The subsumption of the individual measures in summaries specified a priori, even if appropriate to the diverse populations on which scale development was based, could interfere with our intuition to uncover the particular channels of cognitive deficit associated with specific types and conditions of gestational alcohol exposure. The group of 164 tests on which we settled has been described in Part I of this trilogy (38). There we describe the actual test scores used for analysis, their distribution statistics, and their separate associations with a dichotomous alcohol score and with IQ.

This rich diversity of outcomes would be difficult to handle by traditional multivariate statistical methods. We have adapted a novel statistical procedure, Partial Least Squares (PLS), in order to summarize the relations linking the set of all the alcohol measures to diverse sets (blocks) of outcomes. A PLS analysis combines the alcohol scores into one exposure pattern and combines a set of outcomes into one profile of deficits best explained by the exposure pattern. The exposure pattern and corresponding profile of deficits are viewed as "latent variables" underlying the alcohol scores and the outcomes, respectively. The measure of explanatory power is not the usual R^2 of a multiple regression model, but a more inclusive summary of the pattern of correlation between all the alcohol measures and *all* the outcomes. This PLS methodology is fully described in Part II of this trilogy. There we demonstrated its utility using 43 scores sampling aspects of four outcome blocks—intelligence, achievement, attention and classroom behavior (30). In the present paper, we use PLS for data reduction and analysis of an even more complex set of neuropsychologic tests, comprising 164 scores in 8 separate blocks of related measures.

METHOD

Data in this paper derive from the Seattle Longitudinal Prospective Study on Alcohol and Pregnancy, which was described in detail in Part I (38). A cohort of approximately 500 children was selected at birth according to maternal drinking histories obtained at midpregnancy. The mothers in this population-based study were predominantly white, married, and middle-class, and their reported drinking levels were predominantly moderate. Gestational alcohol exposure was expressed in terms of 13 scores reflecting consumption during two time periods: prior to pregnancy recognition (P) and during midpregnancy (D). Table 2 of Part I presents a full description of these 13 variables, and Table 3 of Part I lists their intercorrelations.

The cohort tested at the 7½-year follow-up included 486 children. Because some tests were added or modified after the testing had begun, not all tests were administered to all children. As latent variables cannot be easily computed with data sets having different sample sizes for different variables, we constructed a data set from 384 subjects who had nearly complete data on all 164 outcome variables. The 102 subjects eliminated were mainly those lacking the CMT (Children's Memory Test) blocks. Within the reduced cohort of 384 subjects, a few missing data were due to changes in the battery or in the examiner instructions; mean values were substituted. Our findings are based on correlations over this set of 384 subjects. Six of the 164 variables show no variation on this subset of 384, reducing the count of outcomes analyzed to 158.

In order to assess possible bias owing to missing data, we computed a second correlation matrix using the largest possible sample size for each pair of variables. (Such a correlation matrix is not necessarily positive-definite, but that is not necessary for the PLS analyses we carried out.) The ordering and magnitude of the saliences (latent variable coefficients) in the many two-block analyses to be reported below differ very little from those derived from the common data set of 384 subjects. We therefore settled upon these 384 subjects as a basis for all further analyses.

Other exposures, covariates, and intervening variables measured pre- and postnatally were considered as relevant predictors for the outcome neurobehavioral latent variables. The selection of these important additional predictor variables is described in Part I (38). From a group of approximately 150 candidates, those covariates selected for analysis in the present paper include other prenatal exposures (nicotine, caffeine, marijuana, aspirin and antibiotics); parental characteristics (paternal and maternal education, maternal age, race, parity and prenatal nutrition); and child characteristics (sex, age and grade at testing). Covariates measured postnatally include marital status (at birth and at 7 years), socioeconomic status, parental status (whether biologic, foster or surrogate parents are at home, parental employment), breast feeding and child nutritional intake, the numbers of children in the household who are less than and greater than 5 years of age, and preschool and/or private school experience.

DATA ANALYSIS: LATENT VARIABLES AND PARTIAL LEAST SQUARES

Our approach to statistical analysis of the effects of alcohol upon behavior is that of Herman Wold's Partial Least Squares (51), as described in Part II (30) of this series. Specific outcome variables are treated as "indicators" of underlying "latent variables" (LV's), or factors, which are the unobserved consequences of the net alcohol dose to the fetus. That dose, in turn, is measured only indirectly by each of our 13 alcohol measures.

At the outset, outcome variables are accumulated into "blocks," specialized lists of indicators sharing a common characteristic. These blocks may derive from the same neuropsychologic test, share an apparent cognitive channel of interest, or represent similar subject behaviors under different conditions. The initial structuring of the blocks is on the basis of face validity. The 158 neuropsychological scores studied here were initially assembled into the eight blocks described in Table 5 of Part I (38). Although each block may have a strong factor structure of its own, this is neither the concern of the PLS analysis nor a factor of its success or failure.

The analysis following this organization of outcomes into blocks may be summarized in terms of three steps. First, the association of each of the eight individual blocks with alcohol

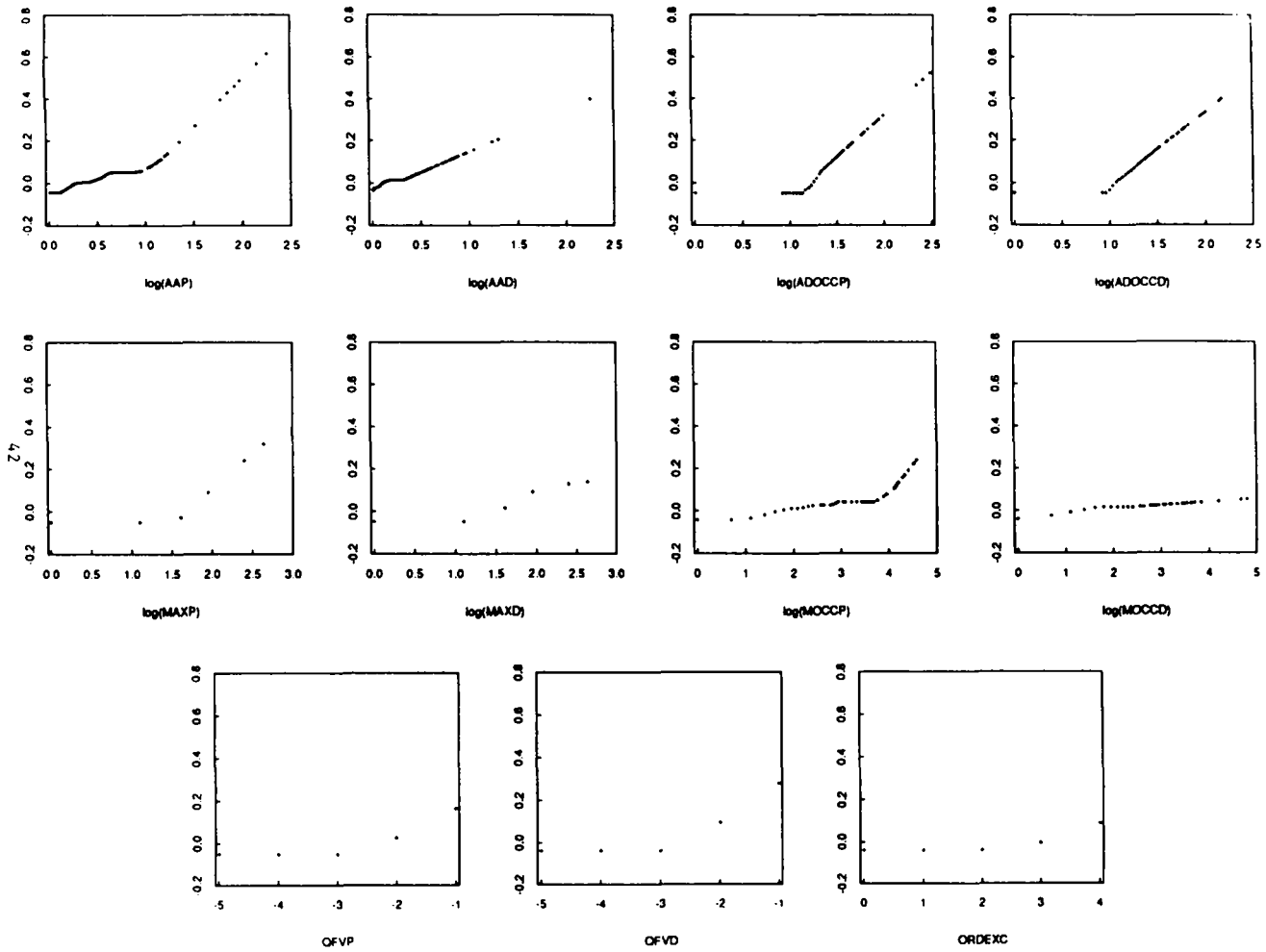

FIG. 1. Monotone nonlinear transformations of eleven of the 13 original alcohol scores (excluding the two binary BINGE measures). These were determined to optimize the correlations of the individual scores with the outcome latent variable in the comprehensive two-block analysis involving all 158 outcome scores. Details of the method are provided in (31). These transformations may be compared with similar ones presented in Fig. 1 of Part II (30).

exposure was analyzed in terms of PLS latent variable models. Second, after noting that the primary alcohol effect (or, alcohol latent variable) was defined similarly in seven of the eight two-block analyses, we proceeded to consider a unitary effect of alcohol across all the outcome blocks by carrying out a comprehensive two-block analysis relating the alcohol scores to the set of all 158 outcomes. At this step we carried out "bootstrap" analyses to assess the precision of our latent variable estimates. Finally, we assessed the extent to which the latent variable correlations computed could be ascribed to joint relations with a set of pre- and postnatal covariates.

In a two-block analysis our goal is to determine whether the matrix of cross-correlations relating the outcome block items to the alcohol items is adequately described by correlations of a single "alcohol latent variable" with a single "neurobehavioral outcome latent variable." To the extent that this is the case, we declare the relationship between alcohol and outcomes to be essentially one-dimensional, and report the dependence of the outcome block upon alcohol in terms of that single underlying correlation, together with the coefficients of the latent variables. These coefficients, which we refer to as "saliences," are correlations of the items of each block, separately, with the (other) latent variable that either predicts them or is predicted by them. If there is evidence that the alcohol-outcome relationship is multidimensional (as explained below) we proceed to interpret the coefficients for a second pair of latent variables. This method of analysis in terms of latent variables differs substantially from the more common approaches of relating a block of variables to one single outcome via multiple regression or to a block of outcomes using canonical correlation analysis or structural equations modeling. For further explanation and comparisons, see Part II of this series (30).

The analyses here, as in Part II, are based on transformed alcohol scores determined so that the transformed scores relate approximately linearly to the outcome latent variable. (Equivalently, they are chosen to optimize the correlation with the outcome latent variable subject to certain constraints of "smoothness" and monotonicity.) The transformations are pictured in Fig. 1. Details of the method are explained in (31). Because these alcohol scores were computed for the comprehensive two-block analysis of the 13 alcohol scores against all 158 outcomes, they are not identical to those used in Part II (which were determined to predict a separate set of 43 outcomes). They are, however, quite similar to those shown in Figure 1 of Part II (30) except for the cases of AAD and

MOCCD. As in Part II, the case with the most extreme alcohol outlier (AAP>25) was dropped because of its relatively large influence on the results (higher estimated associations of alcohol and outcome).

Our interpretation of a two-block analysis is based largely on a pair of statistics provided in the boxes in Appendix Tables A1–A8. For a $p \times q$ cross-correlation matrix, $p<q$, we can compute p pairs of (orthogonal) latent variables. The sum of the squares of the p covariances for these latent variable pairs is equal to the sum of the squares of all $p \times q$ cross-correlations (see Part II (30), Appendix). Thus, the ratio of the squared covariance for the first latent variable pair (LV1) to the total sum of squared correlations is a measure of "explained squared correlation" between the blocks. It provides an informal basis for an assessment of whether or not the relationship(s) between the blocks is well represented using latent variables. (A more formal assessment of structure, reserved for the comprehensive two-block analysis, utilizes bootstrap estimates of coefficient standard errors.) In general we expect better summarization of cross-correlation by latent variables underlying small blocks. We judged the 55 percent of squared correlation explained for the "Magnitude of Dominance" block of four variables too small to warrant interpretation in terms of LVs. The other seven outcome blocks had first LV pairs explaining at least 64% of the squared cross-correlation.

After an assessment of latent variable structure we consider the magnitude of the latent variable correlations (alcohol by each outcome block) as a measure of the strength of the relationship. (It would be possible to have a high correlation based on a single strong element in the cross-correlation matrix, without having a "good" LV structure.) Thus, to interpret a two-block analysis we require both good latent variable structure (high percent of squared correlation explained) and a "reasonable" latent variable correlation. These correlations range from .131 to .289 for the seven two-block relationships with interpretable latent variable structure.

We also examine each two-block relationship for additional dimensions that might be interpretable, i.e., second latent variable pairs (LV2). Our experience with this data set has led us to proceed as follows: if the explained squared correlation is less than 80% for LV1 and at least 10% for LV2, we assess whether the second (and subsequent) latent variable pairs explain a "significant" fraction of the total squared correlations. We claim (informally) that this is the case if these subsequent latent variable pairs have coefficient estimates precise enough to be interpreted. That is, we determine whether two or more of the coefficients defining each latent variable are nominally significant [more than twice their bootstrap standard errors as explained in Part II (30)]. In our study, it is clear that the first LV pairs explain the dominant structure in the correlation matrices; in other data sets, depending on the size of the blocks and how the blocks are constructed, this may not always be the case. Some of the second LV pairs in our analyses meet our informal criteria for interpretation and suggest an additional pattern of alcohol consumption related to factors underlying the neuropsychologic outcomes.

The consistency of the principal (first) Alcohol LV's across the 2-block analyses (with high coefficients emphasizing a binge pattern of drinking and the lowest coefficients emphasizing high frequency patterns) suggests that we concatenate all eight outcome blocks for the comprehensive two-block PLS analysis which is carried out in the same way as the individual two-block analyses. Table 2 provides a summary of this analysis, listing only those outcomes with apparently significant contributions to the principal latent variable pair according to bootstrap standard errors computed from 100 bootstrap replications. The selected outcomes are not those which happen to show a high correlation with some one of the alcohol measures; they are, instead, the variables showing the greatest sensitivity to (correlation with) the Alcohol LV whose coefficients are listed in the left-hand column. Precisely those outcomes with relatively highest latent variable coefficients for blocks 1–7 (Tables A1–A7) are among the items most weighted in this comprehensive two-block analysis. For this large analysis the estimated latent variable correlation is .319, and 69% of the total of 13×158 squared correlations is explained by the covariance between this pair of latent variables.

TABLE 1

SUMMARY TWO-BLOCK ANALYSES FOR THE BLOCK OF 13 ALCOHOL SCORES TOGETHER WITH EACH OF THE EIGHT BLOCKS OF NEUROBEHAVIORAL OUTCOMES

Block (Number of items)	Correlation with Alcohol LV	Percent of Total Squared Correlation Explained by 1st LV
4. CMT Copy Designs (42)	0.289	73%
3. CMT Memory for Designs (42)	0.239	75%
1. Miscellaneous Memory (18)	0.191	64%
2. CMT Verbal Memory (20)	0.186	72%
5. Miscellaneous Neuropsychologic (11)	0.171	67%
7. Namewriting Speed (4)	0.133	92%
6. Behavior Ratings (17)	0.131	65%
8. Magnitude of Dominance (4)	0.086	55%

Note: The data from which these summary scores derive are presented in the Appendix, Tables A1 - A8.

The second latent variable pair (LV2) for this comprehensive analysis similarly identifies those outcomes with the highest latent variable coefficients in the LV2's reported in Tables A1–A7. The LV2 correlation appears substantial (.357), but explains only 11% of the squared correlation in the cross-correlation matrix. Only four or five outcomes out of the 158 are clearly identified in this pattern.

As a final step we adjusted the correlation between the first pair of LV's for covariates as in Part II (30). We began with the same list of fundamental covariates: sex, age, and grade of child; examiner effects; other prenatal exposures (nicotine, caffeine, marijuana, aspirin, and antibiotics); and parental characteristics (paternal and maternal education, maternal age, race, and prenatal nutrition, parity). We then considered covariates measured postnatally and/or reflecting primarily the postnatal environment: marital status (at birth and at seven years), socioeconomic status, whether biological, foster, or surrogate parents are at home, whether parents are employed, breast feeding and child nutritional intake, the numbers of children less than and greater than 5 years of age in the household, and preschool and private school experience. Specific covariates from this list were chosen using an all-subsets-regression procedure applied first to the prenatal covariates and other exposures, then to the postnatal family environment measures. (Missing data on some of these covariates for the 384 subjects of this analysis were filled in with mean values for the corresponding values. The variable with the most missing data was child nutrition, for which 14 values were filled in. No other variable had more than seven missing values for these 384 cases.)

RESULTS

Results of the eight two-block PLS analyses are presented in Appendix Tables A1–A8. Table 1 summarizes data from the first

TABLE 2

SUMMARY OF THE COMPREHENSIVE 2-BLOCK PLS ANALYSIS

Alcohol Coefficients			Neurobehavioral Coefficients			
Item	LV	±SE	Block	Item	LV	±SE
AAP	0.281	±0.05	1	Miscellaneous Memory		
AAD	0.141	±0.06		Seashore C. Errors	0.197	±.05
BINGEP	0.304	±0.03		TPT Memory	-0.127	±.06
BINGED	0.307	±0.03		TPT Location	-0.120	±.04
ADOCCP	0.362	±0.03	2	CMT Verbal Memory		
ADOCCD	0.315	±0.03		# Recalled St.4	-0.121	±.05
MAXP	0.327	±0.03		Sequence St. 2	0.143	±.05
MAXD	0.280	±0.03		Sequence St. 4	0.134	±.05
MOCCP	0.212	±0.04	3	CMT Memory Designs		
MOCCD	0.066	±0.05		# Recalled D.1	-0.167	±.05
QFVP	0.303	±0.03		# Recalled D.5	-0.165	±.05
QFVD	0.325	±0.03		Quality D.2	0.125	±.05
ORDEXC	0.231	±0.03		Quality D.3	0.124	±.05
				Reversals D.1	0.168	±.05
				Distortions D.2	0.124	±.04
				Integration D.1	0.140	±.05
			4	CMT Copy Designs		
				Quality D.3	0.176	±.07
				Reversals D.1	0.256	±.07
				Distortions D.2	0.143	±.05
				Substitutions D.5	0.133	±.05
				Integration D.2	0.129	±.05
				Integration D.4	0.131	±.04
				Perseverations D.5	0.126	±.05
			5	Miscellaneous Neuro		
				Progressive Figures Time	0.155	±.05
			6	Behavior Ratings		
				BR.Distraction	0.130	±.05
			7	Name Writing Speed		
				1st NDomTime	0.130	±.05
				Whole NDom Time	0.141	±.05

Simple:	-.319
Adjusted:	-.297
Squared Covariance:	5.058
Total Squared Corr:	7.295
Percent Explained:	69.3%

Note: SE = Bootstrap Standard Error

See text Part I [27] for a fuller description of these scores and pertinent references.

Alcohol Scores: 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 per drinking occasion.

MAX is the maximum number of drinks reported for any 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, 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 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.

TPT refers to the Tactual Performance Test

CMT refers to the Children's Memory Test

St. refers to the four stories in CMT Verbal

D. refers to the five designs in CMT Memory Designs

NDom = Non-Dominant Hand

LV's from these analyses. The percent of squared correlation explained ranges from 64% to 75% for six of these blocks, and reaches 92% for the small block of four assessments of name-writing speed. The correlation of outcome latent variables with their separate Alcohol LV's ranged from .131 for the Behavior Ratings block to .289 for the CMT Copy Designs block. By contrast, the Magnitude of Dominance block differed substantially from the other blocks, in that only 55% of the squared correlation was explained and the correlation with alcohol was only .086. We conclude that this small block of laterality outcomes (Block 8)

does not incorporate a latent variable with respect to alcohol exposure. The other seven two-block relationships are interpretable and do reflect an underlying structure with alcohol. These include Miscellaneous Memory, CMT Verbal Memory, CMT Memory for Designs, CMT Copy Designs, Miscellaneous Neuropsychologic and Behavior Ratings. The Alcohol LVs correlating with these seven outcome blocks are fairly consistent in that they emphasize binge patterns of consumption: ADOCC (average drinks per occasion), MAX (maximum drinks per occasion), and BINGE (5 or more drinks on any occasion). The two alcohol scores contributing least to these outcome LV's are frequency and average scores, particularly during midpregnancy: MOCC (monthly occasions of drinking) and AA (average ounces of absolute alcohol per day).

Five blocks show evidence of an interpretable second latent varible pair according to the criteria set out above (Blocks 1, 2, 3, 5, and 7). Performance on Miscellaneous Memory, Verbal Memory, Memory for Designs, Miscellaneous Neuropsychologic, and Behavior Ratings was also associated with an alcohol pattern contrasting measures of binge drinking (primarily ADOCCP and MAXP) with frequent drinking during pregnancy (AAD and MOCCD). However, very few items from the outcome blocks are loaded on this second LV pair. Because this possible second dimension appears difficult to interpret, and explains less than 12% of the total squared correlation in the comprehensive two-block analysis, we do not discuss it further at this time.

The comprehensive two-block analysis sought the underlying alcohol latent variable most associated with a neurobehavioral latent variable underlying the complete set of 158 seven-year neurobehavioral outcomes. The results of this analysis are presented in Table 2. The Alcohol LV is very similar to the one we observed in most of the two-block analyses, with a strong binge component, particularly in the "P" period. Of the thirteen original alcohol indicators, only AAD and MOCCD failed to persist as significant elements of this single latent variable. We note that the magnitude of the correlation of the Alcohol LV with the Neurobehavioral LV is higher in this comprehensive analysis than in any of the two-block correlations presented in Tables A1–A8. However, it is not much higher than that based on the CMT Copy Designs block alone, suggesting that additional data do not change this association much once the best blocks of outcomes have been determined.

After consideration of a broad list of possible covariates, as described under Data Analysis, the following were identified as the first covariates to include in the analysis: paternal and maternal education, prenatal aspirin exposure, and the age, grade and sex of the child. Paternal education was the single most important covariate of the outcome latent variable. The correlation between the alcohol and outcome latent variables dropped only slightly, from $-.319$ to $-.291$ as a result of these adjustments. The postnatal covariates having nominally significant coefficients for prediction of the resulting adjusted outcome latent variable included number of children greater than 5 years of age in the household and breast feeding. This list is somewhat arbitrary, as it selected from certain highly intercorrelated clusters of alternate environmental measures. The resulting partial correlation between the alcohol and outcome latent variables now increases in magnitude to $-.297$. This continues to be highly significant according to a conventional multiple regression analysis of the outcome latent variable. Indeed, the Alcohol LV has the most significant regression coefficient in the regression model including all of the pre- and postnatal covariates just noted.

Perceptual motor problems and memory are the two areas most strongly associated with prenatal alcohol exposure. In copying designs, exposed children have more difficulty with the qualitative aspects of performance. They make more reversals and distortions of design elements and produce designs of poor quality and poor integration. The generalization of these problems to their school work is manifested by their greater difficulty in writing their own names. Poorer memory is noted in auditory memory (the Seashore) and in the perceptual memory component of the TPT (Tactual Performance Test). Problems with verbal memory and drawing designs from memory are also noted as correlates of alcohol exposure, along with difficulty in shifting set and in maintaining a flexible problem-solving attitude (Progressive Figures). Prenatal alcohol is also associated with distractibility in the testing situation, as determined by Examiner Behavior Ratings.

If we turn now to examine the actual tests that were the most sensitive to alcohol teratogenesis we see that the design copying tasks (CMT Copy Designs), the Seashore Rhythm Test, and the Children's Memory Test were particularly successful. Additionally, several neuropsychologic tests from the Reitan Neuropsychologic Battery for younger children were very good: Progressive Figures, Name Writing, and the TPT. Distractibility from among the Examiner Behavior Ratings was also sensitive to our measures of prenatal alcohol exposure. The diversity of significant findings across the group of tests administered justifies our decision to consider a very wide diversity of outcome measures rather than focusing on one or two well-known tests. Among the five designs of the Children's Memory Test, designs 1, 2, 5 and 3 appear to be the most sensitive. For the Verbal Memory components of the CMT, stories 2 and 4 are clearly the best. Furthermore, the qualitative scores (Quality, Reversals, Substitutions, Integration, Sequence, and so forth) were as sensitive indicators as were simple counts of items recalled correctly.

DISCUSSION

Methodologic Reflections

We noted at the outset that the task of examining, organizing and analyzing data on 207 outcome variables (Parts II and III) by 13 alcohol predictors and around 150 potential covariates assessed prospectively from the prenatal period to age 7 years was not a simple one. We agree with Rutter (29) and others who argue that the traditional univariate and multivariate correlational analyses have a variety of shortcomings for large-scale longitudinal child development studies. In this trilogy we hope we have demonstrated the utility of the latent varible modeling technique called Partial Least Squares (PLS). This methodology permits us to detect the basic underlying signal or pattern of associations and substantially reduces the possibility of chance associations and their erroneous interpretation.

Additionally, we touch briefly on the question of statistical vs. clinical significance. In human behavioral teratology studies we examine large groups of exposed and nonexposed offspring and look for small perturbations on neurobehavioral outcomes. Although we may use neuropsychologic tests as outcomes, we do not use them in a traditionally clinical manner to look for individual clinical disability. Population studies of "low dose" risk factors do not assume that individually exposed offspring will be severely handicapped from these low dose exposure levels; rather we evaluate statistically whether groups of exposed offspring function differently from nonexposed groups. In behavioral teratology studies, we predict a dose-response relationship with increasing effects at higher doses.

Questions Addressed

Now we examine the findings from this trilogy of papers in terms of the three questions to which these analyses have been addressed. Then we discuss these results in light of current principles of behavioral teratology, other risk-assessment studies

with children, and recent neuropsychologic correlates of learning disability. Finally, we speculate on possible long term consequences of these alcohol-related neurobehavioral deficits.

1. What patterns of alcohol scores best predict neurobehavioral effects in 7-year-old children?

Binge scores of prenatal alcohol exposure emerge as the most consistent predictors of neurobehavioral effects upon both the four blocks of Part II and the eight blocks reported here. ADOCC (average drinks per occasion), MAX (maximum drinks per occasion), and the BINGE score (ever drinking 5 or more drinks on one occasion within the designated time period) were better predictors of neurobehavioral effects than either the frequency score MOCC (monthly occasion of drinking), or the average score AA (average ounces of absolute alcohol per day), particularly in the during pregnancy period. The systematically greater salience of the binge scores suggests that massed doses of alcohol are the most damaging to the fetus, so that even infrequent occasions of binge drinking can have lasting effects. Our finding accords with primate research showing neurobehavioral offspring effects from a weekly binge model of maternal drinking (6) and with recent rodent research showing that a given amount of alcohol was more damaging when administered in a binge pattern than in regular doses once or twice daily (15).

The PLS analysis also permits us to ascertain the relative salience of the two periods of exposure for these outcomes. While, pattern by pattern, both P and D ratings are associated with neurobehavioral effects, the associations with the P scores are usually the stronger. This suggests that while drinking during either period may be deleterious, the association of neurobehavioral deficits with early first trimester drinking is stronger (the period here referred to as "prior to pregnancy recognition"). This is in keeping with earlier findings from this project (36) and other epidemiologic studies of prenatal alcohol effects on birthweight (19) and sleep disruption (32).

2. What patterns of neurobehavioral deficits are associated with prenatal alcohol exposure?

The PLS analyses in Part II revealed a pattern of neurobehavioral deficit spanning memory, problem solving (arithmetic), and attention/impulsivity. These decrements were observed in three separate settings: on standardized IQ and achievement tests, on a laboratory vigilance task, and by teachers in the classroom. Part III showed similar findings with respect to a large group of neuropsychologic tests. Here, prenatal alcohol was most strongly related to memory, susceptibility to distraction, perceptual motor functioning, and to flexibility and organization in problem solving. Altogether, these alcohol-related deficits were observed across a broad band of neuropsychologic tasks, under a variety of conditions (classroom, computer lab, and clinical testing situations), and according to the records of three independent observers (psychometrist, computer lab examiner, and classroom teacher).

Deficits of memory and attention were also not limited to one modality, but were observed on the WISC-R as auditory memory deficits (Digit-Span); on the Children's Memory Task as both spatial memory deficits (difficulty drawing designs from memory) and verbal memory deficits; on the Seashore Rhythm Test as decrements in recall of rhythmical patterns; on the computerized vigilance test as impulsive errors on a visual attention task; and on perceptual-motor tasks as process errors. Children who were relatively more exposed also performed more poorly on TPT Memory and TPT Location, which require nonvisual, tactile identification and recall of the spatial relationship of three-dimensional forms. Alcohol-related arithmetic decrements were observed on both intelligence and achievement tests. Impulsivity was observed both in the vigilance laboratory (increased errors of commission on the AX task) and by classroom teachers. Just as the PLS analyses allowed us to rank the diverse alcohol measures by their salience for predicting these outcomes, so it provided saliences for each neurobehavioral score according to its predictability by the net alcohol latent variable.

Verbal tasks [such as vocabulary and comprehension subtests from the WISC-R (Part II), spelling accuracy from the WRAT-R (Part II), and Animal Naming, a measure of verbal fluency (Part III)] are not as strongly associated with prenatal alcohol exposure as are the perceptual-motor, memory/attention outcomes. The verbal component of the Children's Memory Test is not as strongly related to alcohol as the Memory for Designs or Copy Designs component (see Table 1). This finding is congruent with the evaluation of this same cohort at 4 years of age (39). At that time, PIQ (Performance Scale IQ) was more substantially associated with prenatal alcohol exposure than was VIQ (Verbal Scale IQ). Likewise, fine motor/neuropsychologic functioning was also associated with prenatal alcohol exposure in this cohort at four years of age (2). At eight months of age, the same findings had emerged on the Bayley Psychomotor Development Index (37).

The association of prenatal alcohol with attention deficits has been observed previously with this cohort at earlier ages, and in other studies as well. As neonates, alcohol-exposed offspring functioned more poorly on an attentional task of habituation from the Brazelton Neonatal Behavioral Scale (35). When confronted with redundant stimuli (either auditory or visual), exposed neonates took longer to "tune out" the redundant stimuli and to stop responding. Another study found poorer performance on visual recognition memory at four months to be associated with prenatal alcohol exposure (14). Two separate studies, one upon the present sample, have shown poorer attention at four years to be associated with prenatal alcohol exposure (17,41), as did our earlier analysis of the 7-year attention data by a regression method (40).

3. To what degree are these alcohol-related deficits modified by covariates?

In Part II (30) we described two methods of adjusting a PLS analysis for concomitant pre- and postnatal determinants of the same outcomes affected by alcohol. For all four of the outcome latent variables described in Part II (IQ, Achievement, Classroom Behavior, and Vigilance), the best single predictor is father's education. Our alcohol latent variable remains a significant predictor of these outcomes even after considering this stronger effect: that is, the partial correlation of the alcohol latent variable and each outcome, adjusting for paternal education, is still significant. The other covariates have very little additional effect on these partial correlations either separately or together. Other prenatal exposures (smoking, marijuana, for example) are not significant correlates of the neurobehavioral latent variables correlated with alcohol, and so cannot alter our assessment of the alcohol effect.

Although no drug interactions were found between alcohol and other prenatal exposures, certain postnatal environmental interactions were observed. As noted in Part II, the alcohol effects on the IQ latent variable are somewhat stronger in families with poorly educated parents or families with larger numbers of older children. The alcohol effects on the Classroom Behavior latent variable appeared stronger in families in which the child was born to an unmarried mother. Similarly, a significant interaction indicated greater alcohol effects on the neurobehavioral latent variable summarized here in Table 2 for families with larger numbers of older children. Thus, the effects of alcohol upon the 7-year-old child may be exacerbated by certain postnatal environmental conditions and ameliorated by others. We had not found such interactions in studies of this cohort as younger children; perhaps it takes 7 years for the ameliorations or exacerbations due to environment to accumulate.

The fact that parental education is the strongest predictor of childhood learning and behavioral disorders is not surprising. This

finding has been reported many times before [e.g., (25,47)]. What is of more interest here is that the effects of alcohol remain substantial (significant) even after these other well-known social/environmental variables have been adjusted for as covariates in the present analyses. Likewise, larger family size has previously been associated with poorer child outcome, particularly learning disabilities [e.g., (1, 3, 8)]. Of particular interest here is the interaction of prenatal alcohol with larger family size. That prenatal injury is subject to postnatal environmental modification is one of the tenets of behavioral teratology (44).

Finally, we note that the effect of covariate adjustment on the alcohol-neurobehavioral latent variable relationships was substantially greater for the standardized tests examined in Part II of this series in contrast to the neuropsychological tests analyzed in Part III. Specifically, we saw that covariate adjustment in Part II reduced the magnitude of the latent variable correlation for the comprehensive two-block analysis from $-.24$ to $-.12$, while in Part III, covariate adjustment had negligible effect, changing the correlation only from about $-.32$ to $-.30$. The greater resistance of neuropsychologic tests to sociodemographic influences is of considerable interest. Neuropsychologic tests are designed to measure the processes of brain functioning rather than the products, and thus may provide more sensitive measures of the long-term consequences of prenatal exposures than IQ and achievement tests.

Relationship of Findings to Neurobehavioral Teratology in General

In formulating this research design, we drew heavily on the senior author's observations of children with Fetal Alcohol Syndrome (FAS) across the life span (34). As FAS is a birth defect caused by maternal alcohol abuse during pregnancy, we thought that more moderate levels of prenatal alcohol exposure might be associated with effects similar to those found in latency-age children with FAS, but milder: this is, of course, an example of the dose-response tenet of teratology (44,50). The tests we assembled were intended both to tap attentional and memory problems across a variety of modalities and settings and to assess the traditional dimensions of intelligence and achievement. As we expected, the effects of alcohol upon behavior in any of these settings are similar to, but less severe than, those which characterize children with a diagnosis of FAS. Broadly summarized, these include attentional and memory problems, distractibility, impulsivity, and problems with organization, persistence, cooperation, and flexible problem solving.

Similar results have been observed in animal models of alcohol teratogenesis, including hyperactivity, learning deficits, and response-inhibition deficits. [See (21, 26, 45) for recent reviews.] Of particular interest have been two recent studies showing spatial-learning deficits in rodents prenatally exposed to alcohol (4,12). A number of animal studies have suggested that prenatal alcohol exposure particularly damages the hippocampal area of the brain (15, 16, 26, 49). Similarities between the behavior of hippocampal-damaged rodents and that of pups prenatally exposed to alcohol has led to some speculation (21,26) that, in fact, the hippocampal effects mediate the behavioral deficits.

While some of the behavioral deficits observed in the present study could result from hippocampal damage, there is no reason to suspect that this is the only affected site. There is, in fact, little evidence from human FAS studies that prenatal alcohol damage is localized only in one part of the brain. Autopsy reports on deceased patients with FAS have shown widespread anomalies, many of which may be associated with disruption in the migration and integration of neural and glial cells during embryogenesis (5).

The findings from our present study of long-term effects of prenatal alcohol are in keeping with the broader behavioral teratology and behavioral toxicology literature, which indicates that neurobehavioral outcomes are sensitive indicators of "low-dose" toxicologic or teratogenic effects. The classic lead-toxicology study by Needleman and colleagues (23) found dose-dependent relationships between lead and some of the outcome measures used in the present study, such as the Seashore Rhythm Test, WISC-R subtests, including Digit Span, and negative classroom behaviors as rated by teachers (particularly distractibility, disorganization, and difficulty following directions).

Studies on another established behavioral teratogen, methyl mercury, show some interesting parallels to our study. Not only does prenatal mercury produce a diffuse pattern of lesions, but the birth defect known as Minamata disease points up the dramatic discrepancy between the vulnerability of the adult compared to the embryo, fetus and child. Mothers exposed to mercury at doses high enough to produce Minamata disease in their offspring, with accompanying severe and lifelong mental and neurologic defects, did not themselves sustain serious sequelae of mercury exposure (45). The same could be said for alcohol. In this study, for example, less than 1% of the mothers reported any problems (medical, social, occupational, or legal) with alcohol. Thus we see that what mothers perceived to be nonproblem social drinking had long-lasting subtle effects on offspring.

Implications of the Neuropsychologic Findings

The results from the present study fit comfortably with other recent studies of early childhood neuropsychologic deficits having a known etiology, such as birth trauma and anoxia (13), head injuries (18), seizure disorders (9), meningitis and other brain diseases (43), and side effects of central nervous system prophylaxis for childhood leukemia (20,22). These studies have all suggested that such brain insults produce effects across a wide range of neuropsychologic and cognitive functions, and that the earlier the insult, the more severe are the sequelae. One might speculate, then, that sequelae of a prenatal insult would be observed across a wide array of behavioral and performance tasks, such as found in the present study. The pattern of WISC-R subtest performance deficits (Digit Span, Arithmetic, and to a lesser extent, Block Designs), observed in Part II (30), is the same as the pattern of performance deficits reported in follow-up studies of other types of early CNS insult such as meningitis (43) or closed head injury (18). Similar neuropsychologic performance deficits have also been reported in patients receiving CNS prophylaxis for acute lymphocytic leukemia (11) even in the absence of low IQ scores (20,22) or CAT scan abnormalities (10). In these studies as well as our alcohol studies, this pattern of performance deficits occurs even in the presence of above average IQ. That is, the pattern of performance decrements is a more sensitive indicator of CNS insult than is the full-scale IQ by itself. Such findings strongly support our decision to analyze individual scores rather than aggregating them into conventional summary scores.

Several tests were unrelated to the outcome latent variable defined by prenatal alcohol exposure. Of particular interest is the Animal Naming Test from the Boston Aphasia Screening Battery. Absence of findings on this task (and similar rapid-naming tests) has been noted in several other studies of brain injury sequelae, particularly those with a primarily right hemisphere or nonlanguage pattern of deficits [e.g., (7,46)]. The Memory for Faces Test was included because in adults it has been sensitive to hippocampal lesions. However, the task was somewhat difficult for these young children and problems with administration may have decreased its sensitivity. Attempts to derive additional scores were apparently unsuccessful (Faces Chosen, Faces Correct/Faces Chosen, Faces Correct-Faces Chosen).

The persistent pattern of arithmetic decrement (across both the WISC-R and the WRAT-R) relative to language tasks is particularly interesting and may have clinical implications warranting further investigation. This same pattern of academic performance (arithmetic more affected than reading) has been observed in earlier studies of children with Fetal Alcohol Syndrome and children of alcoholic mothers (34), although, of course, the level of performance was lower in the latter studies in keeping with the dose-response tenet of behavioral teratology (44,50). While the present study examined only group effects, one cannot help speculating on the possible relationship between this pattern of group decrements and the pattern of individual deficits described by Strang and Rourke (33) as "Specific Arithmetic Disability." Children with this pattern of disability also have poor visual perceptual organization, including difficulty with speeded eye-hand coordination and tests of motor steadiness [in particular, performance on the Wisconsin Fine Motor Steadiness Battery, on which our cohort also did poorly at their 4-year exam (2)]. More recently, Rourke (27) has termed this pattern of neuropsychologic deficits "nonverbal learning disability" and noted accompanying hyperactivity and emotional disturbance. Children who exhibit this pattern of central processing abilities are particularly at risk for psychopathology as adolescents (28,33). Our studies indicate that the long-term neurobehavioral consequences of prenatal alcohol exposure are not attenuating with age. Further evaluation of this cohort in adolescence is presently under way.

CONCLUSIONS

The pattern of childhood neurobehavioral deficit demonstrated in this study reveals the diverse, lasting, and statistically significant effects of prenatal alcohol exposure on subtle measures of attention, memory, and cognitive processing in school age children. We believe that these functional deficits represent the sequelae of CNS perturbation during embryonic and fetal development. The pattern of correlations between the alcohol exposure measures and these deficits suggests that drinking prior to recognition of pregnancy is the more critical time for these effects and that the drinking pattern most detrimental to the developing nervous system is the binge pattern. The observed effects cannot be attributed to any of a wide variety of prenatal and postnatal covariates that also affect offspring development. The findings from both parts of the present study [this paper and (30)] are consistent with findings from this same cohort at earlier ages (37, 42, 44). While animal studies can explicitly examine brain-behavior relationships in the absence of the many possible mediating influences that must be confronted in human studies, the congruent findings across both human and animal domains strengthens our conclusions regarding the neuroteratogenic effects of prenatal alcohol. We believe we have demonstrated how a broad battery of neurobehavioral tests and measurements may detect subtle but long-lasting sequelae of teratogenic exposure at levels generally too low to produce physical signs in the offspring. The statistical technique of Partial Least Squares serves very well in studies of the pattern of relationship between such sets of neurobehavioral outcome measures and the diverse measurements of teratogenic exposure on which they may depend. Further examination of this cohort will reveal the consequences of these subtle neurobehavioral deficits for social, emotional, and academic functioning during adolescence.

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REFERENCES

1. Alberman, E. The early prediction of learning disorders. Dev. Med. Child Neurol. 15:202–204; 1973.
2. Barr, H. M.; Streissguth, A. P.; Darby, B. L.; Sampson, P. D. Prenatal exposure to alcohol, caffeine, tobacco, and aspirin: Effects on neuropsychological, fine motor, and gross motor function in 4-year old children. Dev. Psychol.; in press.
3. Belmont, L.; Stein, Z. A.; Wittes, J. T. Birth order, family size and school failure. Dev. Med. Child Neurol. 18:421–430; 1976.
4. Blanchard, B. A.; Riley, E. P.; Hannigan, J. H. Deficits on a spatial navigation task following prenatal exposure to ethanol. Neurotoxicol. Teratol. 9:253–258; 1987.
5. Clarren, S. K. Neuropathology in the Fetal Alcohol Syndrome. In: West, J. R., ed. Alcohol and brain development. London: Oxford University Press; 1985.
6. Clarren, S. K.; Astley, S. J.; Bowden, D. M. Physical anomalies and developmental delays in nonhuman primate infants exposed to weekly doses of ethanol during gestation. Teratology 37:561–569; 1988.
7. Copeland, D. R.; Fletcher, J. M.; Pfefferbaum-Levine, B.; Jaffe, N.; Ried, H.; Maor, M. Neuropsychological sequelae of childhood cancer in long-term survivors. Pediatrics 75(4):745–753; 1985.
8. Davie, R.; Butler, N.; Goldstein, H. From birth to seven: A report of the national child development study. London: Longman; 1972.
9. Fedio, P.; Mirsky, A. F. Selective intellectual deficits in children with temporal lobe or centrencephalic epilepsy. Neuropsychologia 7:287–300; 1969.
10. Gluck, R. S.; Baron, I. S.; Brallier, D. R.; Fink, J.; Leikin, S. L. Follow-up of central nervous system (CNS) prophylaxis in acute lymphocytic leukemia (ALL). Pediatr. Res. 14(4):534; 1980.
11. Goff, J. R.; Anderson, H. R.; Cooper, P. F. Distractibility and memory deficits in long-term survivors of acute lymphoblastic leukemia. Dev. Behav. Pediatr. 1(4):159–163; 1980.
12. Goodlett, C. R.; Kelly, S. J.; West, J. R. Early postnatal alcohol exposure that produces high blood alcohol levels impairs development of spatial navigation learning. Psychobiology 15:64–74; 1987.
13. Graham, F. K.; Ernhart, C. B.; Thurston, D.; Craft, M. Development three years after perinatal anoxia and other potentially damaging newborn experiences. Psychol. Monogr. 76(3):1–53; 1962.
14. Jacobson, S. W.; Jacobson, J. L.; Dowler, J. K.; Fein, G. G.; Schwartz, P. M. Sensitivity of Fagan's recognition memory test to subtle intrauterine risk. Paper presented at the American Psychological Assn. meeting. Anaheim, CA; 1983.
15. Kelly, S. J.; Black, A. C.; West, J. R. Changes in the muscarinic: Cholinergic receptors in the hippocampus of rats exposed to ethyl alcohol during the brain growth spurt. J. Pharm. Exp. Ther. 249: 798–804; 1989.
16. Kelly, S. J.; Goodlett, C.R.; Hulsether, S. A.; West, J. R. Impaired spatial navigation in adult female but not adult male rats exposed to alcohol during the brain growth spurt. Behav. Brain Res. 27:247–257; 1988.
17. Landesman-Dwyer, S.; Ragozin, A. S.; Little, R. E. Behavioral correlates of prenatal alcohol exposure: A four-year follow-up study. Neurobehav. Toxicol. Teratol. 3:187–193; 1981.
18. Levin, H. S.; Eisenberg, H. M.; Wigg, N. R.; Kobayashi, K. Memory and intellectual ability after head injury in children and

adolescents. Neurosurgery 11(5):668–673; 1982.
19. Little, R. E. Alcohol consumption during pregnancy and decreased birthweight. Am. J. Public Health 67:1154–1156; 1977.
20. Meadows, A. T.; Massair, D. J.; Dergusson, J.; Gordon, J.; Littman, P.; Moss, K. Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukemia treated with cranial irradiation. Lancet 2:1015–1018; 1981.
21. Meyer, L. S.; Riley, E. P. Behavioral teratology of alcohol. In: Riley, E. P.; Vorhees, C. V., eds. A handbook of behavioral teratology. New York: Plenum Press; 1986:101–140.
22. Moss, H. A.; Nannis, E. D.; Poplack, D. G. The effects of prophylactic treatment of the central nervous system on the intellectual functioning of children with acute lymphocytic leukemia. Am. J. Med. 71:47–52; 1981.
23. Needleman, H. L.; Gunnol, C.; Leviton, A.; Reed, R.; Peresie, H.; Maher, C.; Barrett, P. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N. Engl. J. Med. 300:689–695; 1979.
24. Porter, R.; O'Conner, M.; Whelan, J., eds. Mechanisms of alcohol damage in utero. CIBA Foundation Symposium #105. London: Pitman; 1984.
25. Ramey, C. T.; Stedman, D. J.; Borders-Patterson, A.; Mengel, W. Predicting school failure from information available at birth. Am. J. Ment. Defic. 82:524–534; 1978.
26. Riley, E. P.; Barron, S.; Hannigan, J. H. Response inhibition deficits following prenatal alcohol exposure: A comparison to the effects of hippocampal lesions in rats. In: West, J. R., ed. Alcohol and brain development. New York: Oxford University Press; 1986.
27. Rourke, B. P. Socio-emotional disturbances of learning-disabled children. J. Consult. Clin. Psychol. 56:801–810; 1988.
28. Rourke, B. P.; Young, G. C.; Leenaars, A. A. A childhood learning disability that predisposes those afflicted to adolescent and adult depression and suicide risk. J. Learn. Dis. 22:169–175; 1989.
29. Rutter, M. Continuities and discontinuities from infancy. In: Osofsky, J., ed. Handbook of infant development. New York: John Wiley & Sons; 1987.
30. Sampson, P. D.; Streissguth, A. P.; Barr, H. M.; Bookstein, F. L. Neurobehavioral effects of prenatal alcohol: Part II. Partial Least Squares analysis. Neurotoxicol. Teratol. 11:477–491; 1989.
31. Sampson, P. D.; Streissguth, A. P.; Vega-Gonzalez, S. C.; Barr, H. M.; Bookstein, F. L. Predicting classroom behavior ratings by prenatal alcohol exposure: Latent variable modeling & non-linear scaling. Seattle: University of Washington, Department of Statistics, Technical Report #103; 1987.
32. Scher, M.; Richardson, G.; Coble, P.; Day, N.; Stoffer, D. The effects of prenatal alcohol and marijuana exposure: Disturbances in neonatal sleep, cycling, and arousal. Pediatr. Res. 24:101–105; 1988.
33. Strang, J. D.; Rourke, B. P. Adaptive behaviors of children who exhibit specific arithmetic disabilities and associated neuropsychological abilities and deficits. In: Rourke, B. P., ed. Neuropsychology of learning disabilities: Essentials of subtype analysis. New York: Guilford Press; 1985.
34. Streissguth, A. P. The behavioral teratology of alcohol: Performance, behavioral and intellectual deficits in prenatally exposed children. In: West, J. R., ed. Alcohol and brain development. New York: Oxford University Press; 1986:3–44.
35. Streissguth, A. P.; Barr, H. M.; Martin, D. C. Maternal alcohol use and neonatal habituation assessed with the Brazelton Scale. Child Dev. 54:1109–1118; 1983.
36. Streissguth, A. P.; Barr, H. M.; Martin, D. C. Alcohol exposure in utero and functional deficits in children during the first four years of life. In: Porter, R.; O'Conner, M.; Whelan, J., eds. Mechanisms of alcohol damage in utero. CIBA Foundation Symposium No. 105. London: Pitman; 1984:176–196.
37. Streissguth, A. P.; Barr, H. M.; Martin, D. C.; Herman, C. S. Effects of maternal alcohol, nicotine and caffeine use during pregnancy on infant mental and motor development. Alcohol: Clin. Exp. Res. 4:185–189; 1980.
38. Streissguth, A. P.; Barr, H. M.; Sampson, P. D.; Bookstein, F. L.; Darby, B. L. Neurobehavioral effects of prenatal alcohol: Part I. Research strategy. Neurotoxicol. Teratol. 11:461–476; 1989.
39. Streissguth, A. P.; Barr, H. M.; Sampson, P. D.; Darby, B. L.; Martin, D. C. IQ at age 4 in relation to maternal alcohol use and, smoking during pregnancy. Dev. Psychol. 25(1):3–11; 1989.
40. Streissguth, A. P.; Barr, H. M.; Sampson, P. D.; Parrish-Johnson, J. C.; Kirchner, G. L.; Martin, D. C. Attention, distraction, and reaction time at age 7 years and prenatal alcohol exposure. Neurobehav. Toxicol. Teratol. 8(6):717–725; 1986.
41. Streissguth, A. P.; Martin, D. C.; Barr, H. M.; Sandman, B. M.; Kirchner, G. L.; Darby, B. L. Intrauterine alcohol and nicotine exposure: Attention and reaction time in 4-year-old children. Dev. Psychol. 20:533–541; 1984.
42. Streissguth, A. P.; Martin, D. C.; Martin, J. C.; Barr, H. M. The Seattle longitudinal prospective study on alcohol and pregnancy. Neurobehav. Toxicol. Teratol. 3:223–233; 1981.
43. Taylor, G.; Michaels, R.; Mazurs, P.; Bauer, R.; Linden, C. Intellectual, neuropsychological, and achievement outcomes in children six to eight years after recovery from haemophilus influenza meningitis. Pediatrics 74(2):198–205; 1984.
44. Vorhees, C. V. Principles in behavioral teratology. In: Riley, E. P.; Vorhees, C. V., eds. Handbook of behavioral teratology. New York: Plenum Press; 1986:23–48.
45. Vorhees, C. V.; Mollnow, E. Behavioral teratogenesis: Long term influences on behavior from early exposure to environmental agents. In: Osofsky, J. D., ed. Handbook of infant development, 2nd edition. New York: John Wiley and Sons; 1987:913–971.
46. Weintraub, S.; Mesulam, M. Developmental learning disabilities of the right hemisphere: Emotional, interpersonal and cognitive components. Arch. Neurol. 40:463–485; 1983.
47. Werner, E. E. Environmental interaction in minimal brain dysfunction. In: Rie, H. E.; Rie, E. D., eds. Handbook of minimal brain dysfunction: A critical review. New York: Wiley; 1980.
48. West, J. R., ed. Alcohol and brain development. London: Oxford University Press; 1986.
49. West, J. R.; Dewey, S. L.; Pierce, D. R.; Black, A. C. Prenatal and early postnatal exposure to ethanol permanently alters the rat hippocampus. In: Mechanisms of alcohol damage in utero. CIBA Foundation Symposium, 105. London: Pitman; 1984.
50. Wilson, J. G. Current status of teratology. In: Wilson, J. G.; Fraser, F., eds. Handbook of teratology: General principles and etiology, vol. 1. New York: Plenum Press; 1977:47–74.
51. Wold, H. Soft modeling: The basic design and some extensions. In: Systems under indirect observation: Causality-structure-prediction, vol. 2. Amsterdam: North Holland Publishing Company; 1982:1–54.

APPENDIX

TABLE A1
PLS ANALYSIS: ALCOHOL BLOCK VERSUS MISCELLANEOUS MEMORY BLOCK

Alcohol Coefficients			Miscellaneous Memory Coefficients		
Item	LV1	LV2	Item	LV1	LV2
AAP	0.225	-0.153	Inci.Learng.#Correct	-0.195	0.047
AAD	0.035	-0.589	Faces.#Correct	-0.188	0.410
BINGEP	0.361	0.108	Faces.#Chosen	-0.188	0.387
BINGED	0.275	-0.012	Seashore A.Errors	0.255	0.478
ADOCCP	0.459	0.224	Seashore B.Errors	0.092	0.535
ADOCCD	0.291	-0.098	Seashore C.Errors	0.576	-0.116
MAXP	0.375	0.181	TPT.Memory	-0.392	-0.096
MAXD	0.246	-0.143	TPT.Location	-0.358	0.008
MOCCP	0.124	-0.351	TPT.#Blocks Dom	-0.071	-0.036
MOCCD	-0.008	-0.553	TPT.#Blocks NDom	-0.264	-0.073
QFVP	0.351	0.098	TPT.#Blocks Both H.	0.050	-0.196
QFVD	0.272	-0.185	TPT.Time Dom	0.153	-0.154
ORDEXC	0.184	-0.179	TPT.Time NDom	0.191	-0.071
			TPT.Time Both H.	0.245	0.137
			An.Naming.# Best 60 Sec.	-0.065	-0.103
			An. Naming # Worst 30 sec.	-0.024	-0.131
			Faces. Correct/Chosen	0.040	0.117
			Faces Chosen-Correct	-0.025	0.094

Singular Value:
LV1: 0.770 LV2: 0.440
Correlations: Alcohol by Misc. Mem:
LV1: 0.191 LV2: 0.217
Percent of Squared Correlation Explained:
LV1: 64% LV2: 21%

Note: Abbreviations in Appendix are defined on Table 2 and in the text of Part I [38].

TABLE A2
PLS ANALYSIS: ALCOHOL BLOCK VERSUS CMT VERBAL MEMORY BLOCK

Alcohol Coefficients			CMT Verbal Memory Coefficients		
Item	LV1	LV2	Item	LV1	LV2
AAP	0.252	-0.191	CMTV.#Recalled St.1	0.145	-0.394
AAD	0.157	-0.531	CMTV.#Recalled St.2	-0.313	-0.165
BINGEP	0.292	0.221	CMTV.#Recalled St.3	-0.146	-0.333
BINGED	0.349	0.127	CMTV.#Recalled St.4	-0.375	-0.117
ADOCCP	0.278	0.151	CMTV.Accuracy St.1	0.302	-0.238
ADOCCD	0.276	0.096	CMTV.Accuracy St.2	0.104	0.234
MAXP	0.291	0.189	CMTV.Accuracy St.3	-0.071	0.266
MAXD	0.345	0.182	CMTV.Accuracy St.4	0.026	0.343
MOCCP	0.265	-0.298	CMTV.Sequence St.1	-0.155	0.182
MOCCD	0.161	-0.640	CMTV.Sequence St.2	0.442	0.053
QFVP	0.315	0.119	CMTV.Sequence St.3	-0.036	0.058
QFVD	0.285	-0.018	CMTV.Sequence St.4	0.415	0.012
ORDEXC	0.268	-0.053	CMTV.Unusual Fea St.1	-0.064	0.133
			CMTV.Unusual Fea St.2	0.110	0.199
			CMTV.Unusual Fea St.3	0.045	0.176
			CMTV.Unusual Fea St.4	0.100	0.265
			CMTV.Extra Idea St.1	0.353	-0.047
			CMTV.Extra Idea St.2	-0.034	-0.333
			CMTV.Extra Idea St.3	0.193	-0.257
			CMTV.Extra Idea St.4	-0.165	0.128

Singular Values:
LV1: 0.741 LV2: 0.336
Correlations: Alcohol by CMTV:
LV1: 0.186 LV2: 0.149
Percent of Squared Correlation Explained:
LV1: 72% LV2: 15%

TABLE A3

PLS ANALYSIS: ALCOHOL BLOCK VERSUS CMT MEMORY DESIGNS BLOCK

Alcohol Coefficients			CMT.Memory Designs Coefficients		
Item	LV1	LV2	Item	LV1	LV2
AAP	0.249	-0.151	CMTM.#Recalled D.1	-0.317	-0.066
AAD	0.204	-0.444	CMTM.#Recalled D.2	-0.119	-0.281
BINGEP	0.293	0.049	CMTM.#Recalled D.3	-0.160	-0.383
BINGED	0.276	0.088	CMTM.#Recalled D.4	-0.102	-0.356
ADOCCP	0.351	0.269	CMTM.#Recalled D.5	-0.317	0.005
ADOCCD	0.344	0.201	CMTM.Magnitude D.1	0.081	-0.018
MAXP	0.313	0.178	CMTM.Magnitude D.2	0.072	-0.029
MAXD	0.283	0.063	CMTM.Magnitude D.3	-0.181	0.153
MOCCP	0.173	-0.400	CMTM.Magnitude D.4	-0.085	0.082
MOCCD	0.052	-0.626	CMTM.Magnitude D.5	-0.015	-0.069
QFVP	0.298	-0.031	CMTM.Quality D.1	0.216	0.067
QFVD	0.362	0.072	CMTM.Quality D.2	0.236	0.135
ORDEXC	0.249	-0.250	CMTM.Quality D.3	0.238	-0.089
			CMTM.Quality D.4	0.205	0.102
			CMTM.Quality D.5	0.204	0.060
			CMTM.Rotations D.1	0.015	0.063
			CMTM.Rotations D.2	-0.110	0.120
			CMTM.Rotations D.3	0.087	0.160
			CMTM.Rotations D.4	-0.045	0.220
			CMTM.Rotations D.5	0.050	-0.021
			CMTM.Reversals D.1	0.317	0.065
			CMTM.Reversals D.2	0.023	-0.036
			CMTM.Reversals D.3	0.017	0.051
			CMTM.Reversals D.4	-0.147	0.163
			CMTM.Reversals D.5	-0.057	0.185
			CMTM.Distortions D.1	-0.079	0.293
			CMTM.Distortions D.2	0.235	0.129
			CMTM.Distortions D.3	-0.001	0.088
			CMTM.Distortions D.4	0.055	0.072
			CMTM.Distortions D.5	0.068	0.006
			CMTM.Substitutions D.2	0.026	0.007
			CMTM.Substitutions D.3	0.190	0.035
			CMTM.Substitutions D.4	-0.011	0.228
			CMTM.Substitutions D.5	0.052	0.087
			CMTM.Integration D.1	0.270	-0.142
			CMTM.Integration D.2	0.209	-0.293
			CMTM.Integration D.3	0.242	-0.230
			CMTM.Integration D.4	0.045	0.132
			CMTM.Integration D.5	0.064	-0.010
			CMTM.Perseverations D.2	-0.079	0.036
			CMTM.Perseverations D.3	-0.063	0.075
			CMTM.Perseverations D.5	-0.055	0.202

Singular Values:
LV1: 1.184 LV2: 0.435
Correlations: Alcohol by CMTM:
LV1: 0.239 LV2: 0.226
Percent of Squared Correlation Explained:
LV1: 75% LV2: 10%

TABLE A4

PLS ANALYSIS: ALCOHOL BLOCK VERSUS CMT COPY DESIGNS BLOCK

Alcohol Coefficients			CMT Copy Designs Coefficients		
Item	LV1	LV2	Item	LV1	LV2
AAP	0.339	-0.349	CMTC.#Recalled D.1	-0.181	-0.005
AAD	0.188	-0.037	CMTC.#Recalled D.2	-0.178	-0.366
BINGEP	0.269	-0.130	CMTC.#Recalled D.3	-0.081	-0.133
BINGED	0.319	0.376	CMTC.#Recalled D.4	0.014	-0.188
ADOCCP	0.316	0.065	CMTC.#Recalled D.5	-0.111	-0.025
ADOCCD	0.314	0.376	CMTC.Magnitude D.1	-0.174	0.241
MAXP	0.295	-0.061	CMTC.Magnitude D.2	-0.116	0.178
MAXD	0.273	0.241	CMTC.Magnitude D.3	-0.048	0.134
MOCCP	0.268	-0.421	CMTC.Magnitude D.4	0.260	0.057
MOCCD	0.117	-0.242	CMTC.Magnitude D.5	-0.038	0.005
QFVP	0.263	-0.253	CMTC.Quality D.1	0.113	-0.020
QFVD	0.322	0.382	CMTC.Quality D.2	0.160	0.097
ORDEXC	0.238	-0.256	CMTC.Quality D.3	0.313	-0.135
			CMTC.Quality D.4	0.135	0.008
			CMTC.Quality D.5	0.055	0.141
			CMTC.Rotations D.1	-0.003	0.073
			CMTC.Rotations D.2	0.015	-0.216
			CMTC.Rotations D.3	0.100	-0.181
			CMTC.Rotations D.4	0.089	-0.023
			CMTC.Rotations D.5	0.103	0.061
			CMTC.Reversals D.1	0.447	-0.092
			CMTC.Reversals D.2	0.004	0.194
			CMTC.Reversals D.4	-0.047	-0.208
			CMTC.Reversals D.5	-0.099	0.104
			CMTC.Distortions D.1	0.051	0.061
			CMTC.Distortions D.2	0.250	0.112
			CMTC.Distortions D.3	0.175	-0.058
			CMTC.Distortions D.4	-0.068	-0.023
			CMTC.Distortions D.5	-0.042	0.177
			CMTC.Substitutions D.2	-0.017	-0.046
			CMTC.Substitutions D.3	0.198	-0.159
			CMTC.Substitutions D.4	-0.050	0.284
			CMTC.Substitutions D.5	0.230	-0.136
			CMTC.Integration D.1	0.081	0.200
			CMTC.Integration D.2	0.224	-0.137
			CMTC.Integration D.3	-0.029	0.006
			CMTC.Integration D.4	0.224	0.195
			CMTC.Integration D.5	0.117	0.307
			CMTC.Perseverations D.1	0.049	0.026
			CMTC.Perseverations D.2	-0.145	-0.121
			CMTC.Perseverations D.3	-0.141	0.127
			CMTC.Perseverations D.5	0.203	0.253

Singular Values:
LV1: 1.307 LV2: 0.495
Correlations: Alcohol by CMTC
LV1: 0.289 LV2: 0.328
Percent of Squared Correlation Explained:
LV1: 73% LV2: 10%

TABLE A5

PLS ANALYSIS: ALCOHOL BLOCK VERSUS MISCELLANEOUS NEUROPSYCHOLOGIC BLOCK

Alcohol Coefficients			Misc. Neuro Coefficients		
Item	LV1	LV2	Item	LV1	LV2
AAP	0.159	-0.181	Lateral Dominance	0.177	-0.259
AAD	-0.043	-0.508	Dom Hand Writing	0.022	0.0
BINGEP	0.257	-0.044	Blueberries.#Said	-0.525	-0.473
BINGED	0.375	-0.075	Blueberries.Errors	-0.156	0.021
ADOCCP	0.466	0.138	Torque.Dom	-0.003	0.106
ADOCCD	0.356	0.158	Torque Consistent.Dom	-0.175	0.166
MAXP	0.322	0.137	Torque.NDom	-0.216	-0.239
MAXD	0.304	0.019	Torque Consistent .NDom	0.042	-0.619
MOCCP	0.059	-0.377	AV.Integration.Errors	0.380	0.204
MOCCD	-0.049	-0.564	Progressive Figures.Time	0.642	-0.354
QFVP	0.292	-0.116	Progressive Figures.Errors	0.182	-0.250
QFVD	0.339	-0.121			
ORDEXC	0.140	-0.388			

Singular Values:
LV1: 0.529 LV2: 0.260
Correlations: Alcohol by Misc.Neuro:
LV1: 0.171 LV2: 0.149
Percent of Squared Correlation Explained:
LV1: 67% LV2: 16%

Note: AV = Audio-Visual Integration

TABLE A6

PLS ANALYSIS: ALCOHOL BLOCK VERSUS BEHAVIOR RATINGS BLOCK

Alcohol Coefficients			Behavior Ratings Coefficients		
Item	LV1	LV2	Item	LV1	LV2
AAP	0.304	-0.191	BR.Fear of New Situation	-0.203	0.247
AAD	0.022	-0.230	BR.Uninhibited	0.003	-0.260
BINGEP	0.389	0.236	BR.Too Uninhibited	0.009	0.016
BINGED	0.216	-0.482	BR.Happy	0.065	-0.239
ADOCCP	0.337	0.130	BR.Too Aware	0.006	-0.018
ADOCCD	0.237	-0.221	BR.Seeks Reassurance	0.350	0.058
MAXP	0.437	0.161	BR.Cooperation	-0.264	0.095
MAXD	0.239	-0.176	BR.Performance Anxiety	-0.031	0.508
MOCCP	0.242	-0.086	BR.Endurance	-0.171	-0.142
MOCCD	-0.067	-0.208	BR.Finishes Tasks	-0.148	-0.117
QFVP	0.333	0.358	BR.Organization	-0.373	-0.144
QFVD	0.219	-0.523	BR.Distractability	0.501	-0.247
ORDEXC	0.262	0.221	BR.Persistence	-0.302	-0.174
			BR.Too Persistent	0.358	0.138
			BR.Frustration	0.310	0.078
			BR.Impulsivity	-0.058	-0.082
			BR.Activity	0.025	-0.605

Singular Values:
LV1: 0.593 LV2: 0.269
Correlations: Alcohol by Behavior Ratings
LV1: 0.131 LV2: 0.147
Percent of Squared Correlation Explained
LV1: 65% LV2: 13%

TABLE A7

PLS ANALYSIS: ALCOHOL BLOCK VERSUS NAME WRITING SPEED BLOCK

	Alcohol Coefficients			Name Writing Speed Coefficients	
Item	LV1	LV2	Item	LV1	LV2
AAP	0.262	0.435	Nam Writ.1st Dom Time	0.299	-0.868
AAD	-0.127	0.581	Nam Writ.1st NDom Time	0.579	0.320
BINGEP	0.328	-0.109	Nam Writ.Whole.Dom Time	0.455	-0.234
BINGED	0.300	-0.008	Nam Writ Whole.NDom Time	0.607	0.298
ADOCCD	0.500	-0.218			
ADOCCP	0.242	0.093			
MAXP	0.383	-0.258			
MAXD	0.168	-0.048			
MOCCP	0.155	0.519			
MOCCD	-0.039	0.049			
QFVP	0.358	0.113			
QFVD	0.265	0.145			
ORDEXC	0.098	0.177			

Singular Values:
LV1: 0.541 LV2: 0.140
Correlations: Alcohol by Nam.Writ.
LV1: 0.133 LV2: 0.107
Percent of Squared Correlation Explained:
LV1: 92% LV2: 6%

TABLE A8

PLS ANALYSIS: ALCOHOL BLOCK VERSUS MAGNITUDE OF DOMINANCE BLOCK

	Alcohol Coefficients			Magnitude of Dominance Coefficients	
Item	LV1	LV2	Item	LV1	LV2
AAP	0.110	0.565	TPT Dom/NDom	0.435	-0.556
AAD	0.250	0.327	TPT.NDom/Both	-0.770	0.122
BINGEP	0.355	-0.078	Nam.Writ.Dom/NDom	-0.354	-0.806
BINGED	0.249	-0.102	Lateral Dominance Consistency	0.304	0.164
ADOCCP	0.401	-0.168			
ADOCCD	0.314	-0.023			
MAXP	0.322	-0.211			
MAXD	0.201	-0.074			
MOCCP	0.043	0.612			
MOCCD	0.028	-0.036			
QFVP	0.168	0.297			
QFVD	0.545	-0.035			
ORDEXC	0.084	0.118			

Singular Values:
LV1: 0.239 LV2: 0.179
Correlations: Alcohol by Magn.Dom.
LV1: 0.086 LV2: 0.138
Percent of Squared Correlation Explained:
LV1: 55% LV2: 31%