ELSEVIER

Neurotoxicology and Teratology, Vol. 20, No. 3, pp. 293–306, 1998

0892-0362/98 $19.00 + .00

PII S0892-0362(97)00091-3

Differential Effects on Cognitive Functioning in 9- to 12-Year Olds Prenatally Exposed to Cigarettes and Marihuana

PETER A. FRIED, BARBARA WATKINSON AND ROBERT GRAY

Department of Psychology, Carleton University, Ottawa, Ontario, Canada

Received 28 February 1997; Accepted 30 July 1997

FRIED, P. A., B. WATKINSON AND R. GRAY. *Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana.* NEUROTOXICOL TERATOL **20**(3) 293–306, 1998.—Cognitive performance was examined in 131 9–12-year-old children for whom prenatal marihuana and cigarette exposure had been ascertained. The subjects, participants in an ongoing longitudinal study, were from a low-risk, predominantly middle class sample. The tasks included the WISC-III and a series of tests assessing aspects of cognition subsumed under the rubric of executive function. Consistent with results obtained at earlier ages, discriminant function analysis revealed a dose-dependent association, which remained after controlling for potential confounds (including secondhand smoke), between prenatal cigarette exposure and lower global intelligence scores with the verbal subtests of the WISC maximally discriminating among levels of in utero exposure. In contrast, prenatal marihuana exposure was not associated with global intelligence or the verbal subtests. Rather, this drug was negatively associated with the executive function tasks that require impulse control and visual analysis/hypothesis testing and with a number of WISC subtests requiring the same abilities. The interpretation of these results is discussed in terms of executive function and is related to earlier observations of this sample and to the extant prefrontal and general marihuana literature. © 1998 Elsevier Science Inc.

Marihuana Cigarettes Prenatal Children Executive function Cognition

AMONG the estimated 4 million women delivering live births in the United States, 20.4% smoked cigarettes at some time during pregnancy and 2.9% reported use of marihuana (39). Although these are the most recent figures available they are based on 1992 data and likely represent a conservative estimate of current use as, reversing a downward trend noted in the late 1980s and early 1990s, the use of both cigarettes and marihuana is increasing among women of reproductive age (28). These two substances are among the most widely used nonmedicinal drugs during pregnancy. For over a decade findings arising from the Ottawa Prenatal Prospective Study (OPPS) have been reported describing the neurobehavioral and developmental outcomes in the offspring of women who used marihuana and/or cigarettes during pregnancy.

Several investigators have reported lower scores on tests of general cognitive performance in preschool and school-aged children born to women who smoked cigarettes during pregnancy (14,16,17,40,47). These observations, which appear to be dose related, persisted after statistically controlling for such potentially confounding variables as demographic factors and other drug use. An additional link between the negative association of prenatal smoking and the cognitive performance of offspring was evident in the report by Sexton et al. (47) in which 3-year-old children born to mothers who quit smoking early in pregnancy were compared to the offspring of mothers who continued to smoke throughout pregnancy. The authors reported that the children of the former group performed at a higher level of intellectual functioning than the children of the latter group.

In both the OPPS between the ages of 3 and 6 (17,14) and in the sample of Sexton et al. (47) the overall cognitive assessment was carried out utilizing the McCarthy Scales of Children's Abilities (35). In all cases, the primary variables that discriminated between the children of smokers with those born to women who quit smoking or nonsmokers were subtests in the verbal domain. The association between in utero

Requests for reprints should be addressed to Peter A. Fried, Department of Psychology, Carleton University, Ottawa, Ontario, Canada K1S 5B6. Tel: (613) 520-2676; Fax: (613) 520-3667; E-mail: pfried@ccs.carleton.ca

cigarette exposure and auditory/language outcomes has been continuously noted in the OPPS sample from the neonatal stage (15,18), infancy (16), early childhood (14,17), middle childhood (33,36), to early adolescence (21).

The longitudinally consistent and relatively robust observations pertaining to in utero cigarette use and poorer performance in auditory domains and tests of global intelligence in offspring have not been observed in the relatively few studies examining the children born to maternal marihuana users. In children involved in the OPPS, at ages 2 (16) and 3 (17), after controlling for potentially confounding variables, maternal marihuana use was not found to be associated with cognitive outcome variables. However, at 4 years of age (17), several cognitive domains distinguished the children of heavy (daily) marihuana users from the remainder of the sample after adjusting for confounding variables. In particular, memory and verbal outcome measures were negatively associated with maternal marihuana use. These observations are strikingly similar to those reported by Day et al. (6) in which the 3-year-old offspring of marihuana users were impaired on the short-term memory, verbal and abstract/visual reasoning subscales of the Stanford-Binet Intelligence Test. Griffith et al. (25) also noted, in 3-year-old offspring, that maternal marihuana use was predictive of poorer performance on abstract/visual reasoning although use during pregnancy was not associated with an overall lowered IQ.

Published data focusing upon the cognitive effects of prenatal marihuana exposure in offspring older than 3 years is limited to material derived from the OPPS. In 5- and 6-year-old children, maternal use of marihuana was not found to be associated with deficits on global cognitive skills (14), although at 6 years of age prenatal marihuana habits were associated with increased omission errors on a vigilance task, possibly reflecting a deficit in sustained attention (20). Furthermore, parental ratings of children at that age indicated greater problems, particularly in the area of inattention and conduct.

Recently, it was speculated (13) that in utero marihuana exposure may impact upon certain behaviors/cognitive abilities that fall under the construct termed executive function. The types of behaviors thought to reflect this function [e.g., (7,8,32)] include cognitive flexibility in problem solving, focused attention, inhibiting prepotent responses, monitoring, evaluating, and adjusting self-directed responses, and working memory (the temporary storage of information while processing incoming data). Thus, executive function is a shorthand to describe a multiple, nonunitary set of cognitive/behavioral abilities critical in effortful, nonroutine, goal-oriented situations. A number of the components of executive function appear to be behaviors that differentiate the offspring of marihuana users from comparison children born to both cigarette smokers and nondrug users. These behaviors include lessened self-regulatory abilities (possibly manifested as behavioral problems), lower scores on tasks of sustained attention, abstract/visual reasoning, and facets of language and memory.

The lack of association between prenatal exposure to marihuana and a lowering of general IQ (13,14,17,25) is consistent with the proposed link between in utero exposure to cannabis and its impact upon aspects of executive function in the offspring. Most researchers, in describing executive function, point out that this construct is not associated with measures of global intelligence [e.g., (55,62)]. As traditional intelligence tests are structured in such a way as to set up specific tasks and goals they may obscure the assessment of such key aspects of executive function as integration of domains of functioning, goal setting, planning, and self-monitoring. Furthermore, global IQ tests evaluate well-learned information and established cognitive sets (9), which may not require facets of executive functioning. However, as emphasized by some (8,11), when tests evaluate novel problem-solving abilities ("fluid intelligence") as contrasted to knowledge ("crystallized intelligence"), there is an association between executive function and intelligence.

The present report has two objectives: First to examine, in 9–12-year-old children, the impact of in utero cigarette and marihuana exposure on a series of cognitive tasks and, second, to examine whether the two drugs have differential effects on global intelligence compared with tasks that are thought to assess executive function.

The tests described in the present work were part of a large battery administered to 9–12-year-old children as part of the OPPS with the overall objective of examining potential effects of in utero exposure to cigarettes and marihuana with particular attention to domains that had been impacted at earlier ages. The present report describes those aspects of the overall battery that assess global cognitive ability and certain specific cognitive tasks. The speculation of a possible link between prenatal marihuana usage and its potential impact upon executive function was not part of the consideration when this battery was originally designed and the testing initiated. However, somewhat fortuitously, the battery does contain a number of measures that have been traditionally used to measure executive function or that assess behaviors thought to be part of executive function.

METHOD

Ottawa Prenatal Prospective Cohort and Pregnancy Information

The Ottawa Prenatal Prospective Study (OPPS), an ongoing longitudinal study, began in 1978 with the objective of examining the association between several socially used drugs consumed during pregnancy and the effects upon offspring. Marihuana and cigarettes have been the primary drugs of interest in recent reports. Six hundred and ninety-eight women, who volunteered after learning of the Study through the media or through notices in obstetricians' offices, have been interviewed during their pregnancies. During the pregnancy, neonatal, early and late childhood time frames the Study has collected data for over 4000 variables.

Interviews were conducted, usually in the home of the volunteer subject, during each trimester remaining in the pregnancy at the time of entrance into the study. The use of the same female interviewer throughout the pregnancy and the repetition of interviews enhanced the rapport between the subject and the interviewer and provided an opportunity to assess the consistency of the self-report (19). Data were collected pertaining to the amounts and patterns of maternal drug use, maternal caffeine use, maternal age, height, prepregnancy weight, weight gained during pregnancy, regular maternal exposure to the cigarette smoke of others, general health (both present and prior to pregnancy), and history of previous pregnancies. At each interview, a 24-h dietary recall was requested of the mother and was evaluated in reference to a recommended standard (10). The father's medical history, parents' level of education, and the family's socioeconomic level were also recorded.

For cigarette use, a nicotine score was derived by multiplying the daily average of the number of cigarettes smoked by the nicotine content of the brand specified. Marihuana use was recorded in terms of number of joints per week. Measure-

ment of alcohol consumption included beer, wine, and liquor use: both the quantity and pattern of consumption were recorded and converted to ounces of absolute alcohol (AA) per day.

Of the 698 pregnant women who were interviewed, a cohort of children was selected for follow-up beyond birth. Among this cohort were 140 children of women who reported any use of marihuana during pregnancy, children of women who drank alcohol beyond a daily average of 0.85 ounces AA, and children whose mothers smoked an average of at least 16 mg of nicotine per day during pregnancy. In addition to these 140 children, children of 50 women who were nonusers of marihuana, who abstained or drank little alcohol, and who were nonsmokers were randomly selected to be included in the follow-up study.

Of these 190 subjects, 146 children ranging in age from 9 to 12 years inclusive were available for testing with the cognitive battery. Of the remaining 44 not tested, most involved families who had moved out of the Ottawa area. In addition, two families withdrew from the study and a few children were unavailable for the testing. No differential loss of subjects with respect to drug variables occurred. The data for four children whose primary language was French and for six children who attended French school were omitted from the analyses because the language emphasis at school and/or at home was thought to influence the outcome variables in the present report. Five children were on Ritalin medication. Concern regarding the effect of Ritalin on the children's performance in the cognitive/executive function area led to the decision to exclude the data for these five children from the analysis. Of these, three were born to heavy smokers, one to a light smoker, and one to a nonsmoker. One of the mothers who was a heavy smoker was also a infrequent/moderate marihuana user. None of the mothers of the children on Ritalin was a heavy drinker. The final sample included 131 nine- to 12-year-old children that included 3 nine-year-olds, 70 ten-year-olds, 34 eleven-year-olds, and 24 twelve-year-olds.

Instruments and Procedure

From a large battery of tests administered to the 9–12-year-old children, measures that assessed cognitive and executive functioning were selected (Table 1). The instruments that are included in this manuscript are the Wechsler Intelligence Scale for Children-III (WISC-III) with its subscales, composite and derived scores (60), the Gordon Diagnostic Delay and Vigilance Tasks (24), the Category test (44), the Auditory Working Memory test (49), the Fluency test (53), and the total time taken to perform the Tactual Performance test (44). Together, these tests result in a total of 29 outcomes measures. All of the tests had norms available for the age range tested and these standardized scores were used in the tables and the analyses. The WISC-III was used as a measure of general intelligence with the subscales measuring various cognitive abilitites. The other tests from the large battery given at this age assess aspects of behavior that, traditionally, are considered to be indicants of executive function. The Gordon Delay and the Gordon Vigilance tasks examine inhibition of prepotent responses and sustained attention, respectively. The Category test involves visually deducing abstract categories and the ability to adjust behavior on the basis of negative and positive feedback. Working memory was examined in both the Auditory Working Memory and the Fluency tasks. The Tactile Performance task assesses the ability to recall previous information and monitoring and correcting self-directed responses. Two brief psychological questionnaires were also given to the children that examined anxiety (45) and depression levels (46).

TABLE 1

TEST BATTERY GIVEN TO THE CHILD

WISC-III (60): One of the most widely used tests of general intellectual abilities. All 13 subtests were used (Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Coding, Picture Arrangement, Block Design, Object Assembly, Symbol Search & Mazes) as well as the composite Verbal and Performance IQ, Full Scale IQ, and the derived Verbal Comprehension, Perceptual Organization, Freedom from Distractibility and Processing Speed Factor scores.

Fluency Test (53): A measure of oral fluency in which the subject was required, within 60 seconds, to produce as many words as possible beginning with a specific consonant sound. This was done twice; with the sound 'c' as in cat and 'p' as in play.

Auditory Working Memory (49): A measure of the ability to retain information in short-term memory while processing incoming information and retrieving information from long-term storage. The subject was read aloud blocks of 2, 3, 4, or 5 sentences and asked to fill in the missing word at the end of each sentence within a block. The subject was then required to remember, within each block, the missing words.

Tactual Performance Task (44): The blindfolded subject must place wooden blocks of varying shapes into their proper place on a form board, first with the dominant hand, then with the other hand and finally with both hands. The length of time to complete the entire task is the outcome reported in this article.

Category Test (44): A test of concept formation requiring non-verbal abstract reasoning and mental flexibility. A computer controlled projector presented 208 images making up 7 subtests. On the subject's lap was a console with 4 coloured buttons. The child was required to abstract principles in each subtest based on variables of size, shape, number and position of objects and press the appropriate response button. A bell and a buzzer provided immediate feedback (positive and negative, respectively). The total number of errors is reported in this article.

Gordon Delay Task (24): In this test of impulsivity, the ability to withhold responding was assessed using an on-button solid state console and a six second DRL (differential reinforcement of low rate of responding) schedule. Under this regimen a child received a reinforcement (points on a screen) when a button press occurred 6 seconds after the emission of a previous button press. The absolute number of responses, the number of rewarded responses and an efficiency ratio (number of rewarded responses divided by the total number of responses) were obtained.

Gordon Vigilance Task (24): The same apparatus as in the Delay Task was utilized to examine sustained attention. A series of single-digit numbers were shown at a rate of 1 per second and for a duration of 200 milliseconds with the entire task lasting 9 minutes. The subject was required to press the response button when the target stimulus (a "1" if it was preceded by a "9") appeared. The total correct responses and the number of commission errors are reported in this article.

The child's postnatal smoke exposure, which included any sources within or outside the home, was determined for each year of the child's life up to the date of testing by asking the mother if her child during each year had been exposed to cigarette smoke on a regular basis (i.e., at least 2 h a day). Data for this variable were available for 115 subjects. In addition to the current smoking status of the family, family income, maternal education, and maternal marihuana use (average number of joints per week in last year) at the time of the child's assessment was determined by a questionnaire given to the family. This information was available for 121 of the 131 subjects. The Home Environment Questionnaire (HEQ) (50) was mailed to the families and yielded 10 scales: Achievement, Aggression-External, Aggression in the Home, Aggression Total, Supervision, Change, Affiliation, Separation, Sociability, and Socioeconomic Status. Nine of the 131 subjects did not return the Home Environment Questionnaire. The NEO Five Factor Inventory (5) was used to assess the mother's personality and provides measures of Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness. One hundred and twenty-one complete inventories were obtained.

All of the tests were administered in a blind fashion with respect to prenatal drug exposure.

Statistical Analysis

As described in previous publications using the OPPS sample [e.g., (14,15)], multivariate analyses were run to reduce Type 1 error and to study the relationships among the variables. To avoid potential problems with multicollinearity and singularity and yet retain all outcome variables for analysis, stepwise Discriminant Function Analysis (DFA) was used to examine the relationship between the drug groups and the cognitive tasks. With the three smoking and three marihuana groups, DFA produces, for each drug condition, two independent sets of discriminant scores, by means of weighting the outcome variables. The means of these discriminant scores (group centroids) for each level of maternal drug use are then compared. Stepwise DFA allows variables that discriminate across drug levels to enter in order of predictive power. If two highly correlated predictors are considered for entry, the more powerful would enter first, bringing both a unique contribution and the explanatory variance shared with the less powerful predictor. This latter variable rarely has sufficient remaining explanatory power to enter the equation. However, with DFA, structure coefficients are available for additional interpretation. These coefficients represent the correlation between each predictor variable and the discriminant function(s). Therefore, if a variable fails to enter because of a high correlation with another predictor variable that does step into the equation, its relative predictive power for the discriminant function is apparent when the structure coefficient is examined. Another possible source for determining the importance of individual predictors is the size and direction of the Discriminant Function coefficients associated with the variables that step into the DFA. However, these latter coefficients are not beneficial for interpretive purposes if the variables are correlated (3).

Tolerance for inclusion ($1 - R^2$ where R^2 is the relationship between the variable considered for inclusion and the variables already stepped into the equation) was set to ≥ 0.05 to protect against multicollinearity and singularity. Classification results for the DFAs were based on using the sample size for each group to estimate probabilities for group membership.

Because stepwise analyses capitalize on chance, cross-validation procedures were undertaken to examine the stability of the discriminant functions. Sixty percent of the sample was randomly selected and the coefficients obtained were applied to the remaining 40%. Shrinkage of correct classification rates was then examined.

For analytic purposes, maternal cigarette smoking (average use across pregnancy) was categorized into three groups: nonsmoking, light, heavy ($\geq$16 mg nicotine/day, which is approximately a minimum of one package of average strength). Maternal average marihuana use across pregnancy was categorized into three groups: no use; infrequent/moderate use (>0 and <6 joints/week); heavy use ($\geq$6 joints/week). Separate DFAs were conducted for each drug group.

Using three categories for both the nicotine and marihuana analyses with a sample of 131 allowed the detection of an effect size of one-third of a standard deviation with 90% power (4).

Confounding Variables

Potentially confounding prenatal variables that were considered were family income, mother's age at delivery, mother's weight before pregnancy, average level of parental education, other maternal drug use, and prenatal passive smoke exposure. Postnatal variables considered as potentially moderating or intervening in the relationship between maternal prenatal cigarette smoking and outcomes were the sex of the child, the home environment, the mother's personality, the child's level of depression and anxiety, the secondhand smoke exposure of the child, current maternal sociodemographic characteristics (family income and maternal education), and marihuana use at the time of the child's testing. Any variables related to the drug of interest at an alpha level of 0.10 or less were selected as potential confounds or intervening variables. Subsequently, using analyses of covariance (ANCOVA), the prenatal potentially confounding variables were examined for association with individual outcomes and the discriminant scores forming the predictive function(s) as identified by DFA, and if related ($p \leq 0.05$) were retained as covariates. Thus, for separate analyses, the covariates may differ. Alcohol and the drug that was not of primary interest (marihuana or cigarettes) were also always included as covariates. Potentially intervening postnatal variables were then assessed for their influence on the discriminant scores and individual outcomes. If related ($p \leq 0.05$), these variables were added as covariates in the ANCOVA containing the prenatal potentially confounding covariates.

Trend analysis was employed to study the shape of the relationships between the adjusted outcome variables and the drug groups (58). Trend analysis requires equal spacing across levels of maternal drug use or a selection of coefficients that takes into account the unequal spacing (12). Ordinal categories (e.g., 0, 1, 2) assigned to the three levels of cigarette smoking or marihuana use would assume equal spacing, which is not representative of the data. Instead, the means of nicotine in mg/day for each level of smoking and marihuana in joints/day were substituted as coefficients in the polynomial analysis for linear and quadratic trends.

RESULTS

The age, family income, and parity of the present sample are similar to those of women who gave birth at the participating hospitals in the same years that the sample women were

recruited (19). Most of the demographic, behavioral, and personality characteristics considered did not vary across either cigarette smoking or marihuana drug levels. However, a few significant differences were found among the various drug groups, which included aspects of socioeconomic status, parental education, home environment, mother's personality, and the degree of secondhand smoke exposure both by the mother during pregnancy and by the child postnatally. These differences plus the drug usage during pregnancy are presented in Table 2.

Assumptions regarding singularity, lack of factor by covariate interactions, and homogeneity of variance–covariance matrices were satisfied for the DFA and ANCOVA analyses. One nicotine and two marihuana and alcohol values were extreme univariate outliers with respect to their distributions (z score > 4). Each score was adjusted to one unit greater than the next heaviest user in the distribution, while maintaining their rank order (58) to retain the cases for analysis but to reduce their influence. When used as continuous variables (i.e., potential confounds), drug values were log transformed to reduce positive skewness.

Cigarette Smoking

Table 3a presents the unadjusted means and SDs as well as the means and SEs adjusted for prenatal and postnatal covariates across the three smoking groups. Most of the cognitive variables were linearly associated with prenatal maternal smoking before adjustment for covariates. After controlling for prenatal potential confounds, dose–response relationships were again observed, many of which demonstrated a statistically significant linear trend ($p < 0.05$): WISC Full Scale, Verbal IQ, Digit Span, Picture Arrangement, Information, Freedom from Distractibility, Fluency. Control for postnatal intervening covariates led to the lack of association between smoking groups and outcomes except for the linear trend retained with the WISC Picture Arrangement and Freedom from Distractibility. Observation of the postnatally adjusted means indicates that these intervening variables did moderate smoking effects with the Auditory Working memory and Fluency tasks and with the WISC-Picture Completion. However, with most of the WISC variables, which had retained association with smoking groups after controlling for prenatal covariates, the differences across the means for smoking levels remained similar, suggesting that the number of postnatal covariates requiring control may have handicapped power to detect a difference across the groups.

The WISC and executive function variables used in stepwise DFA were significantly associated with the smoking groups [$\chi^2(8, n = 131) = 32.9, p < 0.001$; Wilks' lambda = 0.77]. The first discriminant function accounted for 85% of the total discriminatory variance and discriminated in a linear dose-related manner maximally distinguishing the heavy smoking from the control group (Table 4). The means of the

TABLE 2
DRUG USAGE AND CHARACTERISTICS UPON WHICH DRUG GROUPS DIFFER

	Smoking (mg/day)			Marihuana (joints/week)		
	None 0 Group 1	Light >0 & <16 Group 2	Heavy ≥16 Group 3	None 0 Group 1	Infrequent/Moderate >0 & <6 Group 2	Heavy ≥6 Group 3
N	57	48	26	92	19	20
Nicotine (mg/day)	0.0	6.5	27.1[d,†]	8.1	6.9	7.1
Marijuana (joints/week)	3.1	2.6	2.4	0.0	1.9	16.1[d,¶]
Alcohol (oz. AA/day)	0.19	0.18	0.19	0.19	0.22	0.13
Family status (% together)	73	60	67	75	58	40[c,‡]
Family income while pregnant ($cdn)	34,190	31,329	28,385	35,240	24,720	24,187[c,‡]
Average parent education*	3.0	2.6	2.1[d,†]	2.8	2.5	1.9[d,¶]
Mother's age at delivery (year)	29.6	27.5	26.8[b]	29.6	25.8	24.6[d,§]
Prenatal secondhand cigarette smoke exposure (% responding yes)	28	67	100[c,†]	51	53	85[b]
Child's postnatal passive exposure (proportion of life)	0.23	0.52	0.79[c,†]	0.38	0.47	0.76[c,‡]
NEO agreeableness *T*-score	53.1	49.4	50.0	52.9	47.8	46.9[a]
NEO conscientiousness *T*-score	54.2	49.8	45.4[c,‡]	51.7	52.2	46.2
HEQ aggression total *T*-score	47.1	49.8	52.6[a]	48.2	50.1	52.3
HEQ supervision *T*-score	50.7	46.9	43.0[b,‡]	47.6	48.2	48.6
HEQ affilliation *T*-score	53.9	51.7	49.2	53.8	48.2	48.9[b]
HEQ socioeconomic status *T*-score	60.9	57.6	51.5[d,§]	57.9	59.4	56.4
Current family income ($cdn × 1000)	44	44	39	44	46	33[c,¶]
Current mother's education*	3.0	2.6	2.1[c,†]	2.8	2.6	2.2[c,‡]
Current mother's marijuana (joints/week)	0.2	0.7	0.9	0.0	1.2	2.3[d,§]

*Education coded as: 1, did not finish high school; 2, graduated from high school; 3, graduated from college or university; 4, obtained a postgraduate degree.

Note: Statistical tests were one-way between-subjects ANOVAs with the Scheffé test (alpha = 0.05) used for post hoc comparisons of continuous data and χ^2 analysis of frequency data. [a]$p \leq 0.10$, [b]$p \leq 0.05$, [c]$p \leq 0.01$, [d]$p \leq 0.001$.

†All pairwise comparisons differ. ‡Group 1 differs from group 3. §Group 1 differs from groups 2 and 3. ¶Groups 1 and 2 differ from group 3.

TABLE 3a

UNADJUSTED AND ADJUSTED OUTCOME VARIABLES ACROSS SMOKING GROUPS

	Smoking (mg/day)								
	Unadjusted [Mean (sd)]			Adjusted for Prenatal Covariates [Adj. Mean (se)]			Adjusted for Prenatal and Postnatal Covariates [Adj. Mean (se)]		
	None 0	Light >0 & <16	Heavy ≥16	None 0	Light >0 & <16	Heavy ≥16	None 0	Light >0 & <16	Heavy ≥16
N	57	48	26	57	48	26	57	48	26
WISC									
Information	12.1 (2.7)	11.7 (2.2)	10.2^{L,c} (2.4)	11.9 (0.37)	11.7 (0.35)	10.4^{L,b} (0.56)	11.8 (0.42)	11.6 (0.41)	10.4 (0.67)
Similarities	13.0 (2.4)	12.1 (2.8)	11.5^{L,b} (2.2)	12.7 (0.35)	12.1 (0.36)	11.8 (0.53)	12.3 (0.37)	12.1 (0.39)	11.9 (0.62)
Arithmetic	12.4 (2.9)	11.7 (2.9)	10.4^{L,c} (3.2)	11.9 (0.44)	11.7 (0.42)	10.9 (0.66)	11.9 (0.47)	11.9 (0.46)	11.0 (0.75)
Vocabulary	12.2 (3.0)	11.0 (2.8)	10.4^{L,b} (2.4)	12.0 (0.40)	11.0 (0.41)	10.6^{L,a} (0.60)	11.7 (0.45)	11.0 (0.47)	10.9 (0.75)
Comprehension	12.1 (3.4)	11.4 (3.0)	10.1^{L,b} (2.9)	11.5 (0.42)	11.3 (0.44)	10.7 (0.65)	11.4 (11.6)	11.7 (11.9)	10.8 (11.0)
Digit Span	12.2 (2.7)	11.1 (2.8)	9.9^{L,d} (1.9)	11.9 (0.36)	11.0 (0.37)	10.3^{L,b} (0.55)	11.8 (0.38)	11.0 (0.39)	10.6 (0.58)
Picture Completion	12.3 (2.4)	11.1 (2.7)	11.4^{Q,b} (3.0)	12.2 (0.35)	11.2 (0.38)	11.5^{Q,a} (0.52)	11.9 (0.39)	11.2 (0.41)	11.9 (0.59)
Coding	11.5 (2.4)	10.1 (2.8)	9.8$^{L,b;Q,b}$ (3.0)	11.2 (0.37)	10.1 (0.38)	10.2^{Q,a} (0.56)	11.1 (0.42)	10.1 (0.43)	10.4 (0.66)
Picture Arrangement	12.2 (3.2)	11.4 (3.4)	10.2^{L,b} (4.3)	12.2 (0.47)	11.4 (0.51)	10.2^{L,b} (0.69)	12.2 (0.49)	11.4 (0.52)	10.1^{L,b} (0.77)
Block Design	13.4 (3.5)	12.0 (3.5)	11.2^{L,c} (2.5)	12.6 (0.48)	12.0 (0.46)	12.0 (0.72)	12.4 (0.51)	11.7 (0.51)	12.1 (0.83)
Object Assembly	12.2 (2.7)	11.2 (2.8)	10.6^{L,b} (2.4)	11.7 (0.39)	11.2 (0.38)	11.1 (0.58)	11.3 (0.44)	10.9 (0.44)	11.4 (0.71)
Symbol Search	12.8 (3.2)	12.1 (3.7)	11.3^{L,a} (4.1)	12.8 (0.48)	12.1 (0.52)	11.3^{L,a} (0.71)	12.4 (0.55)	12.1 (0.59)	11.7 (0.85)
Mazes	11.9 (2.8)	10.5 (3.3)	10.4$^{L,a;Q,a}$ (3.6)	11.4 (0.43)	10.5 (0.45)	10.4 (0.66)	11.0 (0.49)	10.6 (0.51)	11.3 (0.81)
Verbal IQ	114.0 (12.7)	109.5 (12.0)	103.4^{L,d} (12.6)	112.6 (1.8)	109.3 (1.7)	105.0^{L,b} (2.7)	112.0 (2.0)	110.1 (2.0)	105.3 (3.2)
Performance IQ	115.7 (11.9)	108.0 (13.1)	104.3$^{L,d;Q,b}$ (12.7)	113.5 (1.9)	108.1 (1.8)	106.4 (2.8)	111.6 (2.1)	107.1 (2.0)	107.7 (3.4)
Full Scale IQ	116.1 (11.3)	109.4 (11.9)	104.1$^{L,d;Q,a}$ (11.4)	114.2 (1.7)	109.3 (1.7)	106.0^{L,b} (2.6)	113.0 (1.9)	109.3 (1.9)	106.7 (3.2)
Verbal Comprehension Index	113.4 (12.8)	108.9 (11.7)	103.3^{L,d} (10.4)	111.6 (1.6)	108.7 (1.7)	105.3^{L,a} (2.5)	110.5 (1.9)	109.5 (1.9)	105.8 (3.0)
Perceptual Organization Index	115.9 (12.2)	109.2 (13.7)	105.7$^{L,c;Q,a}$ (12.3)	113.8 (1.9)	109.3 (1.8)	107.6 (2.8)	111.9 (2.1)	108.4 (2.1)	108.2 (3.4)
Freedom from Distractibility Index	114.2 (12.9)	108.9 (12.8)	101.9^{L,d} (11.2)	112.6 (1.9)	108.7 (1.8)	103.7^{L,b} (2.8)	112.9 (1.9)	108.8 (1.8)	104.7^{L,a} (3.0)
Processing Speed Index	112.1 (12.7)	106.8 (15.3)	103.8^{L,b} (16.5)	111.1 (2.0)	106.7 (2.1)	104.8 (3.1)	109.7 (2.3)	106.7 (2.3)	106.7 (3.6)
Gordon Delay									
Total Rewards	98.1 (15.2)	97.0 (17.3)	94.9 (13.4)	94.9 (2.3)	97.0 (2.3)	98.1 (3.3)	*	*	*
Total Responses	104.7 (13.5)	105.6 (17.4)	105.9 (12.2)	104.7 (2.0)	105.6 (2.1)	106.0 (2.9)	*	*	*
Total Efficiency Ratio	91.0 (15.5)	90.1 (19.4)	86.8 (18.2)	88.6 (2.6)	90.3 (2.6)	89.1 (3.8)	88.9 (2.6)	90.0 (2.6)	90.4 (3.9)
Gordon Vigilance									
Correct	100.6 (21.0)	99.0 (21.2)	85.5^{L,c} (29.9)	95.7 (3.5)	98.8 (3.3)	90.6 (5.3)	93.4 (3.5)	99.7 (3.5)	94.9 (5.4)
Commissions	109.0 (27.3)	105.7 (18.6)	121.6^{L,b} (30.8)	112.2 (3.8)	106.2 (3.6)	118.0^{Q,a} (5.3)	113.2 (3.8)	106.8 (3.8)	117.4 (5.7)
Auditory Working Memory	113.8 (12.8)	110.2 (13.2)	103.8^{L,c} (14.6)	112.2 (1.8)	110.1 (2.0)	105.7^{L,a} (2.9)	108.3 (2.0)	108.7 (2.1)	109.6 (3.3)
Fluency std	98.7 (14.7)	96.6 (14.4)	90.2^{L,b} (16.5)	98.7 (2.0)	96.5 (2.2)	90.2^{L,b} (2.9)	95.4 (2.2)	95.8 (2.4)	92.7 (3.4)
Tactual Performace Test Total	100.5 (15.6)	101.4 (16.2)	99.9 (17.6)	99.4 (2.1)	101.7 (2.4)	100.6 (3.2)	*	*	*
Category Test Total Errors	84.4 (16.1)	86.4 (15.6)	90.3 (17.4)	87.6 (2.6)	86.5 (2.4)	87.1 (3.9)	88.3 (2.9)	87.4 (2.7)	87.7 (4.5)
Discriminant Composite Scores	0.46	−0.10	−0.84^{L,d}	0.27	−0.11	−0.63^{L,d}	0.22	−0.16	−0.56^{L,b}

*No postnatal covariates were identified for these tasks.

^{L}linear trend, ^{Q}quadratic trend.

$^{a}p \leq 0.10$, $^{b}p \leq 0.05$, $^{c}p \leq 0.01$, $^{d}p \leq 0.001$.

TABLE 3b

UNADJUSTED AND ADJUSTED OUTCOME VARIABLES ACROSS MARIHUANA GROUPS

	Marihuana (joints/week)								
	Unadjusted [Mean (sd)]			Adjusted for Prenatal Covariates [Adj. Mean (se)]			Adjusted for Prenatal and Postnatal Covariates [Adj. Mean (se)]		
	None 0	Infrequent/ Moderate >0 & <6	Heavy ≥6	None 0	Infrequent/ Moderate >0 & <6	Heavy ≥6	None 0	Infrequent/ Moderate >0 & <6	Heavy ≥6
N	92	19	20	92	19	20	92	19	20
WISC									
Information	11.7 (2.7)	11.8 (1.9)	10.6[L,a] (2.0)	11.6 (0.26)	11.9 (0.58)	10.7 (0.61)	11.4 (0.28)	11.3 (0.65)	11.0 (0.76)
Similarities	12.3 (2.6)	12.9 (2.9)	12.4 (2.1)	12.1 (0.27)	12.8 (0.57)	12.7 (0.62)	12.1 (0.28)	12.4 (0.63)	12.4 (0.72)
Arithmetic	11.8 (2.9)	11.8 (3.4)	11.7 (3.3)	11.4 (0.31)	11.8 (0.67)	12.1 (0.74)	11.5 (0.32)	11.4 (0.74)	12.5 (0.85)
Vocabulary	11.6 (3.0)	11.8 (3.0)	10.5 (2.4)	11.4 (0.30)	11.7 (0.65)	10.7 (0.70)	11.4 (0.32)	11.3 (0.74)	11.0 (0.84)
Comprehension	11.4 (3.2)	12.1 (2.9)	10.7 (3.2)	10.8 (0.32)	12.0 (0.69)	11.4 (0.74)	10.7 (0.35)	12.6 (0.78)	11.9[Q,b] (0.90)
Digit Span	11.3 (2.6)	11.6 (2.8)	11.5 (3.3)	11.0 (0.28)	11.5 (0.60)	11.9 (0.65)	11.0 (0.28)	11.6 (0.64)	12.2 (0.67)
Picture Completion	11.9 (2.8)	10.9 (2.0)	11.3 (2.5)	11.8 (0.28)	10.9 (0.62)	11.5 (0.61)	11.7 (0.29)	10.8 (0.69)	11.6 (0.71)
Coding	10.8 (2.9)	10.4 (2.6)	10.5 (1.9)	10.5 (0.29)	10.4 (0.61)	10.8 (0.66)	10.3 (0.31)	10.5 (0.70)	11.2 (0.81)
Picture Arrangement	11.4 (3.7)	12.4 (3.1)	11.2 (3.5)	11.4 (0.36)	12.4 (0.80)	11.2 (0.78)	11.0 (0.37)	12.1 (0.86)	11.4 (0.85)
Block Design	12.8 (3.3)	12.7 (2.8)	10.9[L,b] (4.1)	12.5 (0.35)	12.3 (0.75)	11.5 (0.81)	12.3 (0.36)	12.3 (0.86)	10.5[L,a] (0.96)
Object Assembly	11.4 (2.6)	12.9 (2.4)	10.6[Q,b] (3.0)	11.3 (0.26)	12.8 (0.58)	10.8[Q,b] (0.59)	11.2 (0.29)	12.7 (0.67)	10.4[Q,b] (0.72)
Symbol Search	12.2 (3.8)	12.6 (3.5)	12.2 (3.0)	12.2 (0.38)	12.6 (0.83)	12.1 (0.81)	11.9 (0.40)	13.2 (0.95)	12.4 (0.98)
Mazes	11.2 (3.4)	10.7 (2.2)	10.9 (3.1)	10.8 (0.33)	10.5 (0.72)	11.4 (0.77)	10.6 (0.35)	10.2 (0.81)	12.3[L,a] (0.92)
Verbal IQ	110.5 (12.9)	112.5 (12.1)	107.1 (11.1)	109.1 (1.3)	112.3 (2.7)	108.7 (3.0)	101.0 (1.4)	110.7 (3.1)	110.4 (3.6)
Performance IQ	111.1 (14.1)	112.8 (9.3)	106.3 (12.5)	110.7 (1.3)	112.2 (2.8)	107.3 (3.1)	109.8 (1.4)	112.2 (3.2)	105.2 (3.7)
Full Scale IQ	111.6 (13.2)	113.7 (9.8)	107.2 (10.1)	110.7 (1.2)	113.2 (2.6)	108.6 (2.9)	110.1 (1.3)	112.9 (3.0)	107.6 (3.5)
Verbal Comprehension Index	110.0 (13.2)	112.3 (10.6)	106.0 (9.7)	108.7 (1.3)	111.8 (2.7)	107.9 (2.9)	108.4 (1.3)	110.4 (3.1)	109.3 (3.6)
Perceptual Organization Index	111.8 (13.8)	114.2 (9.5)	106.8 (13.6)	111.9 (1.3)	113.5 (2.8)	107.4 (3.1)	111.0 (1.4)	113.1 (3.2)	104.8 (3.7)
Freedom from Distractibility Index	109.5 (12.7)	110.5 (14.8)	110.4 (15.0)	107.7 (1.3)	110.3 (2.9)	112.4 (3.2)	107.5 (1.4)	110.8 (3.1)	112.9 (3.3)
Processing Speed Index	108.5 (15.8)	108.7 (13.3)	108.1 (10.7)	107.6 (1.6)	108.7 (3.4)	108.9 (3.6)	106.5 (1.7)	110.6 (3.8)	110.9 (4.4)
Gordon Delay									
Total Rewards	97.2 (14.9)	98.1 (12.5)	95.5 (21.0)	96.1 (1.7)	97.2 (3.6)	97.6 (3.6)	*	*	*
Total Responses	103.8 (13.5)	107.4 (13.1)	109.8[L,a] (20.3)	104.5 (1.5)	107.4 (3.3)	109.8 (3.3)	105.1 (1.7)	107.4 (3.5)	108.4 (3.6)
Total Efficiency Ratio	91.2 (16.5)	88.5 (15.2)	85.5 (23.1)	90.4 (1.8)	87.6 (4.1)	87.1 (4.1)	*	*	*
Gordon Vigilance									
Correct	96.9 (23.4)	96.6 (17.6)	97.9 (30.3)	91.8 (2.4)	95.4 (5.3)	94.3[L,a] (3.8)	91.9 (2.3)	98.4 (5.3)	107.8[L,b] (5.6)
Commissions	111.1 (26.6)	108.0 (22.8)	108.6 (25.4)	114.9 (2.7)	110.1 (5.7)	102.9[L,a] (6.2)	116.5 (2.7)	112.3 (6.3)	98.5[L,b] (6.8)
Auditory Working Memory	109.8 (13.7)	111.7 (14.1)	112.6 (14.0)	108.3 (1.5)	111.3 (3.0)	114.7[L,a] (3.3)	107.4 (1.5)	111.4 (3.3)	114.3 (3.8)
Fluency std	95.9 (14.3)	95.4 (20.8)	98.4 (13.6)	96.0 (1.58)	95.7 (3.49)	98.1 (3.40)	96.5 (1.69)	94.3 (3.80)	96.3 (4.54)
Tactual Performace Test Total Time	100.9 (16.5)	101.1 (15.9)	99.0 (15.0)	98.8 (1.8)	102.0 (3.8)	100.2 (3.8)	*	*	*
Category Test Total Errors	83.8 (17.0)	88.5 (14.7)	95.5[L,c] (19.1)	86.2 (1.8)	88.5 (3.9)	93.0 (4.2)	86.5 (2.0)	90.7 (4.4)	96.4[L,a] (5.1)
Discriminant Composite Scores	−0.29	0.68	0.71[L,d;Q,c]	−0.27	0.71	0.65[L,c;Q,c]	−0.22	0.70	0.61[L,a;Q,c]

*No postnatal covariates were identified for these tasks.

[L]linear trend, [Q]quadratic trend.

[a]$p \leq 0.10$, [b]$p \leq 0.05$, [c]$p \leq 0.01$, [d]$p \leq 0.001$.

discriminant scores for each smoking group (group centroids) were 0.46, −0.10, and −0.84 for the nonsmoking, light, and heavy smoking groups, respectively. The primary predictors on the first discriminant function were WISC variables, that is, the WISC Full Scale, Verbal IQ, Freedom from Distractibility, Verbal Comprehension (structure coefficients: 0.82, 0.77, 0.77, 0.72, respectively). The four variables that stepped into the discriminant function were correlated (Pearson product-moment correlation coefficients ranged from 0.06 to 0.69) and therefore their associated discriminant function coefficients were unreliable for interpretative purposes (2).

Of the potentially confounding variables that were related to the smoking groups (Table 2), average parental education and prenatal secondhand smoke exposure were associated with the discriminant scores. After controlling for these two variables as well as maternal marihuana and alcohol use in a ANCOVA procedure, the association between smoking groups and the discriminant scores forming the first function persisted, $F(2, 124) = 4.6$, $p < 0.05$, with a strong linear association [linear trend: $F(1, 124) = 8.3$, $p < 0.01$].

Postnatal intervening variables that were associated with maternal prenatal smoking (Table 2) and also the discriminant scores were the child's postnatal smoke exposure, the maternal education level current at the time of testing, and Aggression-Total and Socioeconomic Status elements of the HEQ. The association between maternal smoking and discriminant scores persisted after the addition of the child's postnatal smoke exposure to the ANCOVA that included the four prenatal covariates (maternal alcohol and marihuana usage, prenatal secondhand smoke exposure, and average parental education), $F(2, 107) = 3.2$, $p < 0.05$. The subsequent addition of current maternal education level, and the Aggression-Total and the Socioeconomic Status subscales of the HEQ to the ANCOVA marginally reduced the overall associ-

TABLE 4
RESULTS OF DISCRIMINANT FUNCTION ANALYSIS

	Cigarettes		Marihuana	
Predictor Variables	Structure Coefficient	Discriminant Function Coefficient	Structure Coefficient	Discriminant Function Coefficient
WISC				
Information	0.57	0.11	−0.17	
Similarities	0.58		−0.01	
Arithmetic	0.57		0.00	
Vocabulary	0.61		−0.05	
Comprehension	0.51		0.07	
Digit Span	0.69	0.43	0.12	
Picture Completion	0.41		−0.30	−0.41
Coding	0.46		−0.02	
Picture Arrangement	0.34		0.12	0.51
Block Design	0.51		−0.30	−0.60
Object Assembly	0.30		0.10	0.52
Symbol Search	0.36		0.07	
Mazes	0.21		−0.06	
Verbal IQ	0.77		−0.04	
Performance IQ	0.64		−0.12	
Full Scale IQ	0.82	0.56	−0.08	
Verbal Comprehension Index	0.72		−0.04	
Perceptual Organization Index	0.55		−0.12	
Freedom from Distractibility Index	0.77		0.07	0.44
Processing Speed Index	0.44		0.03	
Gordon Delay				
Total Rewards	0.16		0.06	
Total Responses	−0.01		0.34	0.54
Total Efficiency Ratio	0.15		−0.29	
Gordon Vigilance				
Correct	0.47	0.39	−0.09	
Commissions	−0.29		0.12	
Auditory Working Memory	0.35		−0.07	
Fluency	0.31		−0.02	
Tactual Performance Test Total Time	−0.16		0.22	
Category Test Total Errors	−0.34		0.49	0.75
Group Centroids				
Control	0.46		−0.29	
Light Cig; Infreq/Mod Mar	−0.10		0.68	
Heavy	−0.84		0.71	

ation between maternal smoking and the discriminant scores, $F(2, 98) = 2.7, p = 0.07$, with the linear trend remaining statistically significant [linear trend: $F(1, 98) = 4.4, p < 0.05$].

Cross validation of the DFA, which compared 60% of the sample with the remaining data, indicated that the function was stable. The median shrinkage (from a distribution of seven procedures conducted) was 58% to 50%, which is considerably above the 34% correct classification calculated if the classification was based on chance alone.

The influence of secondhand smoke exposure was examined further. The two measures of secondhand smoke exposure were 1) the mother's prenatal exposure recorded as a dichotomous variable indicating the presence or absence of regular exposure, and 2) the child's smoke exposure measured as a continuous variable and expressed as a proportion of the number of years exposed relative to their age at the time of testing. Both the mother's prenatal and child's secondhand smoke exposure were associated with the scores from the first discriminant function (Pearson product-moment correlation coefficients: $r = -0.3, p < 0.01$ and $r = -0.28, p < 0.01$, respectively). However, these relationships between secondhand smoke exposure and the outcome measure may be misleading because all of the women who smoked heavily during pregnancy were also exposed, on a regular basis, to secondhand smoke and had children who were exposed to secondhand smoke. Thus, the apparent effects of secondhand smoke exposure may be due to prenatal maternal smoking. To overcome this confounding relationship, the data of the children born only to nonsmokers were selected, thereby allowing the influence of secondhand smoke exposure to be examined independently of the effects of active smoking by the mother. Of the 57 mothers in the nonsmoking group, 16 were exposed prenatally to secondhand smoke. Data for the child's passive exposure was available for 52 children of the nonsmoking mothers and, of these, 17 were exposed to secondhand smoke. Using the nonsmoking data only, neither the mother's prenatal nor the child's secondhand smoke exposure was associated with the discriminant scores.

To determine whether the influence of secondhand smoke exposure was dependent on the age of the child when exposed, secondhand smoke exposure for the children in all of the smoking groups was stratified into three time periods: 0–3, 4–6, and 7–9 years of age. Correlations between the discriminant scores and the child's smoke exposure revealed no difference across the three time frames.

Lower socioeconomic status and parental education are associated with maternal smoking (Table 2) and were used as covariates in the ANCOVAs. Although, after their control, maternal smoking remained associated with the outcome scores, further measures were undertaken to ensure that the relationship between maternal smoking and outcome was not due to SES variables. An approach used with data for the 5- and 6-year-old children and described in an earlier article (14) was applied to the current data. Parental education was selected as a marker variable for SES because it displayed the greatest differences across smoking groups among our SES variables (Table 2). A subsample of the heavy and abstainer smoking groups was selected by eliminating the extreme categories of parental education. In this way, average parental education did not statistically differ (using a conservative alpha of 0.1) across the heavy and control groups. The resulting subsample retained 35 of 57 in the control group and 18 of 26 in the heavy group. Following this adjustment for the major potentially confounding variable, parental education, the important discriminating outcome variables (i.e., WISC Full Scale, Verbal IQ, Verbal Comprehension, Vocabulary) remained associated with maternal smoking ($p < 0.05$).

Marihuana

The relationship between marihuana exposure and the cognitive/executive function variables was examined with the same approach used for maternal smoking. Table 3b presents the unadjusted means and SDs as well as the means and SEs adjusted for prenatal and postnatal covariates across the three marihuana groups for the outcomes. At a univariate level, the strongest negative associations were observed with the Category test, the WISC Block Design and Information, and the total number of responses on the Gordon Delay task. None of these relationships remained statistically significant after controlling for potentially confounding prenatal covariates.

Using stepwise DFA, a significant relationship was found between maternal marihuana use and the variables that are associated with aspects of executive function [$\chi^2(14, n = 131) = 33.7, p < 0.01$; Wilks' Lambda = 0.76]. The first discriminant function accounted for 72% of the total discriminatory variance and served primarily to distinguish the marihuana users from the control group (Table 4). The means of the discriminant scores for each marihuana group (group centroids) were −0.29, 0.68, and 0.71 for the control, infrequent/moderate, and heavy groups, respectively. The main discriminating measures were the Category Test, the Gordon Delay total number of responses, the WISC-Block Design, WISC-Picture Completion and the Gordon Delay efficiency ratio (structure coefficients: 0.49, 0.34, −0.30, −0.30, −0.29, respectively) on which the marihuana users performed more poorly than the control group. The variables that stepped into the discriminant function were correlated (Pearson product-moment correlation coefficients ranged from 0.0008 to 0.45) and therefore the discriminant function coefficients were limited in their usefulness for interpretative purposes (3).

Of the potentially confounding variables associated with maternal marihuana use (Table 2), only mother's age at the time of pregnancy was associated with the discriminant scores. After controlling for mother's age as well as maternal cigarette smoking and alcohol use, the relationship between maternal marihuana use and the discriminant scores persisted, $F(2, 125) = 10.2, p < 0.001$, with both a linear, $F(1, 125) = 9.1$, $p < 0.01$, and quadratic, $F(1,125) = 11.3, p < 0.01$, component. After controlling for mother's current marihuana use, the only postnatal potentially intervening variable related to the discriminant scores, maternal marihuana use during pregnancy remained associated with the discriminant scores, $F(2, 124) = 7.0, p < 0.01$, again with linear, $F(1, 124) = 3.9, p = 0.05$, and quadratic trends, $F(1, 124) = 10.1, p < 0.01$.

Cross-validation procedures that compared the DFA results of 60% of the sample with the remaining data revealed that the function was stable. The median change in correct classification (from a distribution of seven procedures conducted) for the DFA was 69% to 68%. Both figures are greater than 53%, which is the correct classification by chance alone using prior probabilities based on the number of subjects in each marihuana group.

DISCUSSION

The present report continues the presentation of findings arising from the OPPS—a long-term prospective study of the effects of in utero exposure to cigarettes and marihuana. The results described here are in the domain of cognition obtained from 9- to 12-year-old children with the findings both parallel-

ing and considerably extending earlier observations with the same Ottawa sample at younger ages. A major new finding reported here is the observation of marked differences in cognitive outcomes associated with the maternal use of each of the two drugs examined.

In the OPPS sample at the ages of 3 through 6 (14,17), the General Cognitive Index derived from the McCarthy Scales of Children's Abilities (35) was related to maternal use of cigarettes in a negative dose–response manner after statistically controlling for potentially confounding variables. Paralleling this, in the present work among the 9–12 year olds, the Full Scale IQ of the WISC was linearly and negatively associated with in utero exposure to cigarettes. In addition to the WISC Full Scale, the composite Verbal IQ, Verbal Comprehension Index, and the Digit Span, Picture Arrangement, and Information subscales were also associated in a significant, negative linear fashion with maternal cigarette smoking. The results of a Discriminant Function Analysis (DFA) indicated that the WISC variables that provided the best discriminatory power were the WISC Full Scale, Verbal IQ and Verbal Comprehension.

The finding that the verbal domain within the IQ battery was the dimension that maximally discriminated among the different levels of in utero exposure is similar to the observations made at earlier ages with this sample (14,17). Further, the present findings extend the association between in utero cigarette exposure and auditory/language outcomes that has been continually noted in the OPPS sample. Such negative relationships with maternal smoking have been observed in the offspring in the neonatal stage (15) in which poorer habituation to auditory stimuli was evident, in infancy (16) in which responses to auditory related behavior were altered, in early childhood (14,17) and middle childhood (33,36) in which language, vocabulary and central auditory processing were negatively impacted, and in early adolescence (21) in which the phonological aspects of reading in 9–12 year olds were negatively associated with maternal smoking. The continuity over approximately 12 years in the relationship between auditory/language variables and in utero exposure to cigarette smoke suggests that these aspects of behavior are affected, at least to some degree, by the direct consequences of maternal smoking. This of course does not preclude the possible interactive effects of postnatal life-style habits and/or exposure to secondhand smoke that may influence directly or indirectly performance on the auditory/language related variables.

In the present study, the results of the tests, which were not part of the WISC but rather purported to examine aspects of executive function, are consistent with the cigarette results noted in the intelligence test described above. In the linear trend analysis the two tests that were significantly associated with cigarette smoking were the two auditory-based assessments: fluency and auditory working memory. In the DFA of maternal cigarette use, these two tests also had moderately high structure coefficients. This association of in utero exposure to cigarette smoke with these two language-based tests is consistent with the observations made in these children since birth that was described earlier in the Discussion.

Although not a primary focus of the present study, a preliminary examination of the possible effects of either maternal passive smoke exposure or the child's secondhand smoke exposure was undertaken. After controlling for prenatal and postnatal covariates, neither type of involuntary smoking appeared to influence the cognitive variables assessed in this present work. This finding differs from a recent report with the same subjects in which the child's exposure to secondhand smoke adversely influenced language but not reading (21). In interpreting this absence of effect it must be noted that, although the measures of secondhand smoke included when the exposure occurred and whether it was on a regular basis, no measurement of the magnitude of such exposure was ascertained.

The results obtained from those children exposed to marihuana in utero differed in numerous ways from the data arising from those children exposed in utero to cigarette smoke. An important finding arising from the present data pertains to differences between the two drugs used during pregnancy and the WISC outcomes. The results of the linear trend analysis revealed that, unlike with smoking, there was no association between either the Full Scale IQ or the composite Verbal IQ and in utero marihuana exposure. Further differences between the smoking and marihuana groups on the WISC scores were revealed by the structure coefficients of the DFA. In the discrimination across the three cigarette groups, all of the subtests were negatively related to maternal smoking and all but one contributed moderately or strongly to the function. With the one exception (mazes), the structure coefficients for the WISC subtests ranged from 0.30 to 0.69. Notably, the Full Scale IQ was the most discriminating variable (structure coefficient of 0.82), suggesting that the major effect of in utero cigarette exposure is upon overall cognitive performance. In contrast, the DFA carried out on the WISC data of the marihuana groups indicated that the Full Scale IQ was not a predictive variable (structure coefficient of −0.08). Rather, the negatively impacting disciminating variables with structure coefficients of at least 0.30 were limited to the Block Design and Picture Completion subtests suggesting that in utero marihuana exposure affects particular rather than global aspects of intelligence.

In the Block Design subtest, subjects are directed to assemble blocks to form a design identical to one presented in a picture. This nonverbal concept formation task requires the ability of perceptual organization, spatial visualization, and abstract conceptualization. The Picture Completion subtest requires the subject to identify a missing portion of an incompletely drawn picture and tests the ability to differentiate essential from nonessential details.

These two subtests of the WISC are multifactorial, potentially involving basic visuo-spatial and visuo-motor abilities as well as higher order cognitive processes including planning, impulse control, visuo-construction and visuo-analysis. To examine whether prenatal marihuana exposure impacts upon basic visual motor and spatial functioning the following procedure was implemented. As part of the overall battery given to these children at the time of cognitive testing, the Developmental Test of Visual-Motor Integration (2) was administered. This widely used instrument consists of 24 geometric forms to be copied in an untimed fashion. Performance on this task was not associated with maternal marihuana use. Furthermore, when this task was used as a covariate, it did not diminish the association between maternal marihuana use and the discriminant outcome scores. That the marihuana findings on the two WISC subtests persisted after statistically controlling for basic spatial and motor abilities supports the interpretation that the impact of prenatal marihuana exposure on these WISC subtests is upon "higher order" cognitive processes.

The negative relationship between these two subtests and maternal marihuana use in the present work is consistent with the finding of poorer abstract/visual reasoning in 3 year olds exposed in utero to marihuana (6,25). It may also be noteworthy that, when the children in the OPPS were less than a week

old, prenatal marihuana exposure was associated with poorer habituation to visual but not auditory stimuli.

The findings from the WISC data suggest that different aspects of cognitive functioning are impacted by maternal use of the two drugs. Prenatal cigarette exposure resulted in a negative, dose–response relationship and maximum discriminability in both overall global intelligence and verbal scores as well as most individual subscale scores. Many, although not all, of the individual subscales affected can be characterized as assessing learned information and established cognitive sets. However, with marihuana, not only was there no association in the 9–12-year-old offspring with overall, psychometrically determined intelligence but only Block Design and Picture Completion of the various individual subtests of the WISC differentiated among the marihuana groups.

In the present study, the results of the non-WISC outcome measures, which assessed aspects of executive function, were consistent with the observations for the marihuana groups gleaned from the WISC tasks. The primary variables (in addition to the Block Design and Picture Completion subtests of the WISC) that were associated with the composite score that maximally discriminated among the marihuana groups were the Category test, the total number of responses measuring impulsivity on the Gordon Delay task, and the efficiency ratio on the Gordon Delay task. The Category test requires the subject visually to identify abstract categories and shift cognitive sets as response criteria change. The Gordon test of impulsivity is a measure of the ability to inhibit a prepotent response in a differential reinforcement of low rate of responding task with the efficiency ratio reflecting the proportion of rewarded (correct) responses relative to the total number of responses.

Thus, of the six tests thought to assess aspects of executive function the two that were found to be associated with marihuana involve impulse control, visual analysis and hypothesis testing. This is consistent with the WISC results as the two subtests in that battery associated with prenatal marihuana use—Block Design and Picture Completion—require visual analysis and hypothesis testing.

The WISC subtests and non-WISC tests that are associated with the highly discriminating composite score from the DFA do not retain statistically significant relationships with the marihuana groups after controlling for potential confounds. Much more predictive and stable, after controlling for both prenatal and postnatal covariates, in discriminating across the marihuana groups was the composite score from the DFA representing a combination of test outcomes. The meaning of this composite score can be interpreted from the structure coefficients. The higher the structure coefficients the more the composite score is represented by the associated task. The composite score from the marihuana DFA has only moderately high associations (structure coefficients) with the Category task, the Gordon Impulsivity test, and both the Block Design and Picture Completion subtests of the WISC. The absence of a high correlation with these variables suggests that the composite score taps only an aspect of each of these tasks but an element that is an underlying dimension shared and common to all. That common element for all four tasks appears to be a facet of executive function that involves visual analysis, hypothesis testing, and inhibition of prepotent responses. This type of integrative, "top-down" (8) behavior is considered to be an important facet of the neurocognitive domain of executive function [e.g., (62)].

The finding that only particular facets of executive function appear to be associated with maternal marihuana use can be interpreted as consistent with substantial evidence suggesting that behaviors predicated upon successful executive functioning are not of a singular nature. This position arises from diverse findings. Using a factor analytical approach to executive function in children, Welsh et al. (62) reported that, in a battery of tests of this construct administered to a normative sample of children from 3 to 12, three independent factors were revealed. One factor was labeled Hypothesis Testing and Impulse Control. This identified a convergence of cognitive processes that were strikingly similar to those associated with prenatal marihuana exposure in the present work with the factor being defined by requiring visual analysis and inhibition of prepotent responses. Of the other two factors identified by Welsh et al. (62), the first was referred to as a Fluid and Speeded Response factor and included verbal fluency and motor sequencing. The final factor was labelled as Planning and involved a spatial positioning problem-solving task relying heavily on working memory with no visual cues or alternatives to select from. In the present report, those tasks that assessed cognitive processes contributing to what Welsh labelled as the Fluid and Speeded Response factor (Verbal Fluency, Tactile Performance Task) and Planning factor (Auditory Working Memory, Tactile Performance Task) were not found to be associated with maternal marihuana use.

In the present work impulse control and visual hypothesis testing appear to be negatively impacted. Whether the failure to find an association with other aspects of executive function may be due to the selective nature of marihuana's putative in utero effect of acting upon particular anatomical/synaptic mechanisms or whether it is an artifact of the particular tests used, the age of the subjects or some other factor(s) remains to be determined.

The developmental literature provides additional support for viewing executive function skills as a nonunitary construct and, furthermore, is consistent with observations reported previously with the OPPS sample. Executive functioning is a multistage process with different functions maturing at different ages (1,41) reflecting, at least in part, the differential development of areas in the prefrontal portion of the brain (55). Although precursors or rudimentary aspects of executive function are present in infants and toddlers (e.g., object search and object permanence behavior), spheres of executive functioning are not apparent or are difficult to test until the children approach or reach school-age and continue to develop at least until puberty (29,61,62). Observations at younger ages with the OPPS sample are consistent with this developmental course of executive functioning and the proposed association with prenatal marihuana exposure. Neurobehavioral effects of marihuana were not noted beyond the neonatal period until the child was 4 years of age (17). Furthermore, at 6 years of age and not at earlier ages, prenatal marihuana exposure was associated with behavioral problems, aspects of attention and visual perceptual tasks (20). With respect to the data reported in this article, the findings in the normative-developmental study of executive function (62) are particularly germain. In that investigation, competence in hypothesis testing and impulse control, in contrast to other aspects of executive function, were found to be achieved at 10 years of age (62)—a finding that is consistent with the present study's observation of marihuana's negative effect on this dimension of executive function manifest in the 9–12 year olds.

That the construct of executive function involves components that may be neuropsychologically separable also comes from research examining prefrontal lobe functioning. Not all executive function is prefrontally mediated nor are all pre-

frontal functions consistent with the term executive function [e.g., (8,59)]. However, there is little question that the prefrontal cortical regions are intimately involved in the modulation of cognitive capacities subsumed under the term executive function (30,57). Many authors have emphasized the anatomical heterogeneity of the prefrontal areas in ascribing different functions to different regions of this portion of the brain (22,23,56). Furthermore, on the basis of studies both of injury to different parts of the frontal area [reviewed in (57)] and of regional blood flow in intact subjects (42), aspects of executive function are clearly differentially associated with different areas of the prefrontal region.

The speculation that in utero marihuana may impact upon aspects of executive function is supported, in an indirect fashion, by several different findings from the general marihuana literature suggesting an association between cannabis, frontal lobe activity, and executive function. In work carried out in the early 1970s, injected tritiated Δ^9-tetrahydrocannabinol in the squirrel monkey (37) and in the rat (48) was found in high concentrations in the frontal regions of the cortex. In more recent work (27,38) it was reported that, within the different regions of the rat's cortex, the frontal area contained the highest density of cannabinoid binding sites. In humans, frontal lobe activity appears to be affected by marihuana usage. Chronic daily use of marihuana resulted in marked alteration of alpha activity, primarily in the frontal region even after prolonged cessation of use (54) and cerebral blood flow was significantly increased, especially in the frontal region during marihuana smoking in experienced users (34).

In adult chronic marihuana users, behaviors that appear impacted by the long-term use of cannabis are consistent with executive function. These include fragmentation of thought, difficulty in short-term memory tasks, disturbances in attention, concentration, and judgment (26,31,51,52). Perseverative responding has also been reported as a residual executive function effect in heavy users who had been abstinent for at least 24 h (43). These findings implicating marihuana with prefrontal cortical regions and executive function skills are consistent with the speculation of an association between prenatal exposure to marihuana and components of executive function.

Not only did the effects of in utero marihuana or cigarette exposure reported in this study differ but the results of the DFA indicated that the relationship across levels of use within each drug differed. With maternal cigarette use, the group centroids indicated the maximum group differences were between the heavy smoking group and the control group and a significant linear trend was observed across the discriminating composite score. Among the three maternal marihuana categories (no use, up to 6 joints per week, greater or equal to 6 joints per week), this consistent linear reationship was not observed. The results from both the DFA and the linear trend analysis are consistent in that they indicate that the offspring of the heavy marihuana users differ from the offspring of the abstainers, particularly on tests that require visual analysis and synthesis and on the test of response inhibition.

The interpretation of the effect of infrequent/moderate maternal marihuana use is not as clear. The group centroids of the composite score indicate a similar negative effect of infrequent/moderate and heavy marihuana use during pregnancy. However, the examination of the four individual tasks most highly associated with the composite score indicates that this pattern of effect is only evident with Picture Completion. The infrequent/moderate group mean for the Category test, the Gordon impulsivity task, and the Block Design subtest is intermediate between the control and heavy groups. Despite this poorer level of performance on several individual executive function tasks and the composite score, a pattern of better performance by the infrequent/moderate marijuana group compared to the control and heavy groups is evident with approximately half of the tests administered in this battery (Table 3b), although many differences are not statistically significant. The tests on which the infrequent/moderate group perform better than controls are predominantly from the cognitive, nonexecutive function battery. It is interesting that this group of children, while well-functioning on most of the cognitive battery, show poorer performance on the four executive function tasks relative to controls that make up the composite score.

In summary, the present findings indicate that, in the 9–12-year-old offspring, maternal cigarette usage has markedly different associations compared with maternal marihuana use in the domain of cognition. The results were relatively robust, with both maternal smoking and marihuana use retaining predictive power for different combinations of outcomes after controlling for potentially confounding prenatal variables. Furthermore, the inclusion of postnatal variables exerted only a small moderating effect. The present results extend to older ages the negative dose–response association between an overall intelligence score and prenatal exposure to cigarettes observed at earlier ages. Also, the observation that subtests based on verbal functioning maximally discriminated among levels of maternal smoking in the 9–12 year olds parallels and extends the observations made in this sample and others at earlier ages. On the other hand, maternal use of marihuana was not related to global intellegence. This lack of association is consistent with findings in this sample at earlier ages. In further contrast, whereas maternal cigarette use was associated with impairments in specific content domains, marihuana use during pregnancy was negatively associated with a composite score representing an on-line integrative ability based on visual analysis, visual hypothesis testing, and impulse control. These findings coupled with observations made with younger children were interpreted as suggesting that in utero exposure to marihuana may impact, in a negative manner, upon aspects of neurocognitive competence that fall under the umbrella of executive function.

ACKNOWLEDGEMENTS

The authors thank H. Linttell for her continuing invaluable assistance in data collection and S. Gmora for his insightful comments and criticisms. This research was supported by a grant to P.A.F. from the National Institute on Drug Abuse.

REFERENCES

1. Becker, M. G.; Isaac, W.; Hynd, G. W.: Neuropsychological development of nonverbal behaviors attributed to 'frontal lobe' functioning. Dev. Neuropsychol. 3:275–298; 1987.
2. Beery, K.: Developmental test of visual-motor integration. Cleveland: Modern Curriculum Press; 1982.
3. Borgen F. H.; Seling, M. J.: Uses of discriminant analysis following MANOVA: Multivariate statistics for multivariate purposes. J. Appl. Psychol. 63:689–697; 1978.
4. Cohen, J.: Statistical power analysis for the behavioral sciences. New York: Academic Press; 1977.

5. Costa, P.; McCrae, R.: The NEO five factor inventory. Odessa, FL: Psychological Assessment Resources Inc.; 1989.
6. Day, N.; Richardson, G.; Goldschmidt, L.; Robles, N.; Taylor, P.; Stoffer, D.; Cornelius, M.; Geva, D.: The effect of prenatal marijuana exposure on the cognitive development of offspring at age three. Neurotoxicol. Teratol. 16:169–175; 1994.
7. Denckla, M. B.: Measurement of executive function. In: Lyon, G. R., ed. Frames of reference for the assessment of learning disabilities: New views on measurement issues. Baltimore: Paul H. Brookes; 1993:117–142.
8. Denckla, M. B.: A theory and model of executive function. In: Lyon, G. R.; Krasnegor, N. A., eds. Attention, memory and executive function. Baltimore: Paul H. Brookes; 1996:263–278.
9. Dennis, M.: Frontal lobe function in childhood and adolescence: A heuristic for assessing attention regulation, executive control and the intentional states important for social discourse. Dev. Neuropsychol. 7:327–358; 1991.
10. Dietary standards of Canada. Ottawa, Ontario, Canada: Department of Health & Welfare; 1975.
11. Duncan, J.; Burgess, P.; Emslie, H.: Fluid intelligence after frontal lobe lesions. Neuropsychologia 33:261–268; 1995.
12. Ferguson, G. A.; Takane, Y.: Statistical analysis in psychology and education (6th ed.) New York: McGraw-Hill; 1989:333.
13. Fried, P. A.: The Ottawa Prenatal Prospective Study (OPPS): Methodological issues and findings—it's easy to throw the baby out with the bath water. Life Sci. 56:2159–2168; 1995.
14. Fried, P. A.; O'Connell, C. M.; Watkinson, B.: 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes and alcohol: Cognitive and language assessment. J. Dev. Behav. Pediatr. 13:383–391; 1992.
15. Fried, P. A.; Makin, J. E.: Neonatal behavioural correlates of prenatal exposure to marihuana, cigarettes and alcohol in a low risk population. Neurotoxicol. Teratol. 9:1–7; 1987.
16. Fried, P. A.; Watkinson, B.: 12- and 24-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes and alcohol. Neurotoxicol. Teratol. 10:305–313; 1988.
17. Fried, P. A.; Watkinson, B.: 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes and alcohol. J. Dev. Behav. Pediatr. 11:49–58; 1990.
18. Fried, P. A.; Watkinson, B.; Dillon, R. F.; Dulberg, C. S.: Neonatal neurological status in a low-risk population after prenatal exposure to cigarettes, marijuana and alcohol. J. Dev. Behav. Pediatr. 8:318–326; 1987.
19. Fried, P. A.; Watkinson, B.; Grant, A.; Knights, R. K.: Changing patterns of soft drug use prior to and during pregnancy: A prospective study. Drug Alcohol Depend. 6:323–343; 1980.
20. Fried, P. A.; Watkinson, B.; Gray, R.: A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes and alcohol. Neurotoxicol. Teratol. 14:299–311; 1992.
21. Fried, P. A.; Watkinson, B.; Siegel, L. S.: Reading and language in 9 to 12-year-olds prenatally exposed to cigarettes and marijuana. Neurotoxicol. Teratol. 19:171–183; 1997.
22. Fuster, J. M.: The prefrontal cortex. Anatomy, physiology and neuropsychology of the frontal lobe, 2nd ed. New York: Raven Press; 1989.
23. Goldman-Rakic, P. S.: Development of cortical circuitry and cognitive function. Child Dev. 58:601–622; 1987.
24. Gordon, M.; McClure, D. F.: Gordon Diagnostic System: Interpretative supplement. Golden, CO: Clinical Diagnostics; 1984.
25. Griffith, D. R.; Azuma, S. D.; Chasnoff, I. J.: Three-year outcome of children exposed prenatally to drugs. J. Am. Acad. Child Adolesc. Psychiatry 33:20–27; 1994.
26. Hall, W.; Solowij, N.; Lemon, J.: The health and psychological consequence of cannabis use. Monograph Series #25. Canberra: Australian Government Publishing Service; 1994.
27. Herkenham, M.; Lynn, A. B.; Johnson, M. R.; Melvin, L. S.; de Costa, B. R.; Rice, K. C.: Characterization and localization of cannabinoid receptors in rat brain: A quantitative in vitro autoradiographic study. J. Neurosci. 11:563–583; 1991.
28. Johnston, L.; O'Malley, P.; Bachman, J.: National survey results on drug use from the Monitoring the Future study, 1975–1994 vol 2 college students and young adults. NIH Publication Number 96-4027. Rockville, MD: NIDA; 1996.
29. Levin, H. S.; Culhane, K. A.; Hartmann, J.; Evankovich, K.; Mattson, A. J.; Harward, H.; Ringholz, G.; Ewing-Cobbs, L.; Fletcher, J. M.: Developmental changes in performance on tests of purported frontal lobe functioning. Dev. Neuropsychol. 7:377–395; 1991.
30. Lezak, M. D.: Neuropsychological assessment (2nd ed.) New York: Oxford University Press; 1983.
31. Lundqvist, T.: Specific thought patterns in chronic cannabis smokers observed during treatment. Life Sci. 56:2141–2144; 1995.
32. Luria, A. R.: Higher cortical functions in man. New York: Basic; 1966.
33. Makin, J.; Fried, P. A.; Watkinson, B.: A comparison of active and passive smoking during pregnancy: Long-term effects. Neurotoxicol. Teratol. 13:5–12; 1991.
34. Mathew, R. J.; Wilson, W. H.: Acute changes in cerebral blood flow after smoking marijuana. Life Sci. 52:757–767; 1993.
35. McCarthy, P.: McCarthy scales of children's abilities. New York: The Psychological Corporation; 1972.
36. McCartney, J. S.; Fried, P. A.; Watkinson, B.: Central auditory processing in school-age children prenatally exposed to cigarette smoke. Neurotoxicol. Teratol. 16:269–276; 1994.
37. McIsaac, W. M.; Fritchie, G. E.; Idanpäan-Heikkila, J. E.; Ho, B. T.; Englert, L. F.: Distribution of marihuana in monkey brain and concomitant behavioral effects. Nature 230:593–594; 1971.
38. Musty, R. E.; Reggio, P.; Consroe, P.: A review of recent advances in cannabinoid reserach and the 1994 International Symposium on cannabis and the cannabinoids. Life Sci. 56:1933–1940; 1995.
39. National Pregnancy and Health Survey. Drug use among women delivering live births: 1992. NIH Publication Number 96-3819. Rockville, MD: NIDA; 1996.
40. Olds, D. L.; Henderson, C. R., Jr.; Tatelbaum, R.: Intellectual impairment in children of women who smoke cigarettes during pregnancy. Pediatrics 93:221–227; 1994.
41. Passler, M. A.; Isaac, W.; Hynd, G. W.: Neuropsychological development of behavior attributed to frontal lobe functioning in children. Dev. Neuropsychol. 1:349–370; 1985.
42. Petrides, M.; Alivisatos, B.; Evans, A. C.; Meyer, E.: Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc. Natl. Acad. Sci. USA 90:873–877; 1993.
43. Pope H. G., Jr.; Yurgelun-Todd, D.: The residual cognitive effects of heavy marijuana use in college students. J. Am. Med. Assoc. 275:521–527; 1996.
44. Reitan, R.; Davison, L.: Clinical neuropsychology. New York: John Wiley & Sons; 1974.
45. Reynolds, C. R.; Richmond, B. O.: What I think and feel: A revised measure of children's manifest anxiety. J. Abnorm. Child Psychol. 6:271–280; 1978.
46. Reynolds, W. M.: Reynolds child depression scale: Professional manual. Odessa, FL: Psychological Assessment Resources Inc.; 1989.
47. Sexton, M.; Fox, N. L.; Hebel, J. R.: Prenatal exposure to tobacco: II effects on cognitive functioning at age three. Int. J. Epidemiol. 19:72–77; 1990.
48. Shannon, M. E.; Fried, P. A.: The macro- and microdistribution and polymorphic electroencephalographic effects of 9-tetrahydrocannabinol in the rat. Psychopharmacologia 27:141–156; 1972.
49. Siegel, L. S.; Ryan, E. B.: The development of working memory in normally achieving and subtypes of learning disabled children. Child Dev. 60:973–980; 1989.
50. Sines, J.: The home environment questionnaire. Iowa City, IA: Psychological Assessment and Services; 1983.
51. Solowij, N.: Do cognitive impairments recover following cessation of cannabis use? Life Sci. 56:2119–2126; 1995.
52. Solowij, N.; Michie, P. T.; Fox, A. M.: Effects of long-term cannabis use on selective attention: An event-related potential study. Pharmacol. Biochem. Behav. 40:683–688; 1991.

53. Spreen, O.; Strauss, E.: A compendium of neuropsychological tests: Administration, norms and commentary. London: Oxford University Press; 1991.
54. Struve, F. A.; Straumanis, J. J.; Patrick, G.; Price, L.: Topographic mapping of quantitative EEG variables in chronic heavy marihuana users: Empirical findings with psychiatric patients. Clin. EEG 20:6–23; 1989.
55. Stuss, D. T.: Biological and psychological development of executive functions. Brain Cogn. 20:8–23; 1992.
56. Stuss, D. T.; Benson, F.: Neuropsychological studies of frontal lobes. Psychol. Bull. 95:3–28; 1984.
57. Stuss, D. T.; Eskes, G. A.; Foster, J. K.: Experimental neuropsychological studies of frontal lobe functions. In: Boller, F.; Grafman, J., eds. Handbook of neuropsychology, vol. 9. Amsterdam: Elsevier; 1994:149–185.
58. Tabachnik, B. G.; Fidell, L. S.: Using multivariate statistics, 2nd ed. New York: Harper & Row; 1989.
59. Tranel, D.; Anderson, S. W.; Benton, A. L.: Development of the concept of 'executive function' and its relationship to the frontal lobes. In: Boller, F.; Grafman, J., eds. Handbook of neuropsychology, Vol. 9. Amsterdam: Elsevier; 1994:125–148.
60. Wechsler, D.: Weschler intellegence scale for children, 3rd ed. New York: The Psychological Corporation; 1991.
61. Welsh , M. C.; Pennington, B. F.: Assessing frontal lobe functioning in children: Views from developmental psychology. Dev. Neuropsychol. 4:199–230; 1988.
62. Welsh, M. C.; Pennington, B. F.; Groisser, D. B.: A normative-developmental study of executive function: A window on prefrontal function in children. Dev. Neuropsychol. 7:131–149; 1991.