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Effects of Fetal Cocaine and Tobacco Exposure
on Newborn Information Processing

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August, 1996

A thesis submitted to the Faculty of Graduate Studies and Research in partial
fulfilment of the requirements of the degree of Doctor of Philosophy.

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Abstract

Approximately 10% of women use cocaine and 20% smoke cigarettes during pregnancy. Animal studies indicate that both cocaine and nicotine are neuroteratogenic agents, although findings with humans are inconsistent. Studies with human infants have been plagued by unreliable subject identification procedures, poor control over confounding factors, and invalid measures of CNS integrity. The literature on prenatal cocaine and nicotine use is reviewed and two studies are presented along with an intriguing case report. The effects of maternal prenatal cocaine use (Study 1) and two levels of cigarette smoking (Study 2) on newborn information processing ability were examined using an auditory habituation-recovery paradigm. Case-control designs were employed in which subjects were individually matched on a number of maternal and infant factors. Cocaine exposure was determined by newborn meconium analysis, urine analysis, and maternal self-report. Maternal smoking was determined by self-report and a variation of the bogus pipeline method. Fetal cocaine- and nicotine-exposure were associated with differential impairments in neonatal information processing. Cocaine-exposed newborns exhibited deficits on measures of habituation and recovery to novelty. Dose-response effects of nicotine-exposure were evident on measures of orientation and habituation, but recovery to novelty was not consistently affected. The results imply that fetal cocaine-exposure severely impairs neonatal auditory information processing ability, whereas fetal tobacco-exposure is associated with deficits in information-processing which may be secondary to impairments in arousal regulation. These auditory processing deficits may be related to the later language impairments reported in follow-up studies with cocaine- and tobacco-exposed infants. Following the two studies, a case is presented of an infant born to a woman who

reported using large amounts of cocaine throughout pregnancy, although the infant's meconium and hair tested negative. The mother's hair tested positive for cocaine, confirming her self-report. The infant's performance on the information processing procedure was normal, supporting the validity of the procedure. This case implies that variations in placental handling of cocaine may protect some fetuses from exposure to the drug. Together these studies imply that both cocaine and nicotine are neuroteratogenic although they result in differential outcomes, highlighting the importance of controlling for maternal smoking in studies addressing the impact of prenatal exposure to illicit substances.

Résumé

Approximativement 10% des femmes font usage de cocaïne et 20% fument des cigarettes au cours de leur grossesse. Les études animales indiquent que la cocaïne et la nicotine sont tous deux des agents neurotératogéniques, bien que les résultats chez les humains présentent des irrégularités. Les procédures peu l'invalidité des mesures d'intégrité du SNC ont miné les études auprès de nourrissons humains. Les écrits sur l'usage prénatal de la cocaïne et de la nicotine sont passés en revue et deux études sont présentées ainsi qu'un intrigant rapport de cas. Les effets de l'usage maternel prénatal de la cocaïne (Étude 1) et deux degrés d'inhalation de cigarettes (Étude 2) sur l'habileté de traitement de l'information du nouveau-né furent examinés à l'aide d'un paradigme d'habituation-recouvrement auditif. Des plans de contrôle par cas furent utilisés où les sujets furent mis de pair individuellement sur un nombre de facteurs liés à la mère et au nourrisson. L'exposition à la cocaïne fut déterminée par l'analyse du méconium du nouveau-né, l'analyse d'urine et le compte-rendu de la mère. L'inhalation maternelle fut déterminée par compte-rendu de la mère et par une variante de la méthode de pipeline truquée. L'exposition foetale à la cocaïne et à la nicotine furent associées à différentes altérations de l'habileté néonatale de traitement de l'information. Les nouveaux-nés exposés à la cocaïne présentèrent des déficiences lors de mesures d'habituation et de recouvrement à la nouveauté. Les effets dose-réaction de l'exposition à la nicotine, manifestes aux mesures d'orientation et d'habituation, affectèrent de façon irrégulière le recouvrement à la nouveauté. Les résultats suggèrent que l'exposition foetale à la cocaïne altère sérieusement l'habileté néonatale de traitement de l'information auditive, alors que l'exposition foetale au tabac est associée avec des déficiences dans le traitement de l'information qui peuvent

être secondaires à des déficiences de régulation de l'éveil. Ces déficiences du traitement auditif peuvent être liées à d'ultérieures déficiences de langage rapportées par les études de suivi auprès de nourrissons exposés à la cocaïne et au tabac. Suite aux deux études, le cas est présenté d'un nourrisson né d'une femme rapportant l'usage de larges quantités de cocaïne au cours de toute sa grossesse, bien que le méconium et le cheveu du nourrisson testèrent négatifs. Le cheveu de la mère testa positif pour la cocaïne, confirmant son compte-rendu. La performance du nourrisson à la procédure de traitement de l'information était normale, appuyant la validité de la procédure. Ce cas suggère que des variations dans la réaction placentaire face à la cocaïne peuvent protéger certains fœtus de l'exposition à la drogue. Ensemble, ces études suggèrent que la cocaïne et la nicotine sont tous deux neurotératogéniques bien qu'ils résultent en différents conséquences, soulignant l'importance du contrôle de l'inhalation maternelle de tabac pour les études se penchant sur l'impact de l'exposition prénatale aux substances illicites.

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The studies described in this dissertation could not have been carried out without the assistance of the numerous persons who volunteered their time. I cannot begin to express my appreciation to Grace Valiante ("Amazing Grace") who, in addition to co-ordinating data collection in my absence, was always available to test infants, helped in the recruiting and training of research assistants, made endless treks to the hospital to scrape meconium off diapers, and had a special gift of genuine caring and sensitivity that was pivotal in the recruitment of cocaine-using mothers. And many thanks go to Peta for all her words of encouragement, as well as her technical support. In addition, the studies could not have been completed without the much-appreciated assistance of Caroline Reid, who played a vital role in the organization of the projects as well as in the collection of data. The research projects could not have been carried out without the assistance of the student volunteers who made the data collection possible. Many heartfelt thanks go to (in no particular order) Deb Sinha, Janice Wright, Carys Papageorgiou, Martha Bonin, Julie Tison, Manon, Sophie, Deborah, Leslie, Julie, Jasmine, Cheryl, Yana, and the other students

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Preface and Contributions to Original Knowledge

The information presented in this thesis is unique in several respects. The review of the literature on cocaine use in pregnancy (Chapter 1: Literature I) is the most comprehensive review available and covers the most recent information published in the area. While several reviews of the literature on specific aspects of cocaine use in pregnancy have been published, no reviews are available which integrate the wide variety of important issues relevant to this area of research (e.g., prevalence of prenatal cocaine use, identification of cocaine-exposed neonates, pharmacology of cocaine and its effects on the developing central nervous system, the comparison of animal and human findings, in addition to infant and child outcome studies).

Chapter 2: Literature II covers important issues related to the assessment of early infant intelligence, with a focus on the assessment of auditory information processing in early infancy. Several extensive reviews of this literature have been previously published; however, this paper is the first to address the application of these methods to the assessment of newborns exposed prenatally to cocaine and/or tobacco. The literature reviewed in the introduction to Study 2 (Chapter 5) represents the most complete and up-to-date discussion and critique of studies assessing the effects of prenatal tobacco-exposure on infant and child outcome. Animal studies on the effects of fetal nicotine-exposure on CNS development, and methods of identifying infants whose mothers smoked cigarettes during pregnancy are also reviewed. Although these specific topics have been reviewed elsewhere, these areas have not been integrated into a comprehensive discussion of the important issues which should be addressed in the design of studies assessing the effects of fetal tobacco-exposure on infant outcome.

Study 1 (Chapter 4) is an investigation into the effects of prenatal cocaine-exposure on neonatal information processing ability. Several studies on the effects of fetal cocaine-exposure on neonatal outcome have employed the Neonatal Behavioral Assessment Scale (NBAS). The NBAS measures neurobehavioural functioning rather than information processing ability, and has been heavily criticized for its poor validity and reliability; this study is the first to look at neonatal auditory information processing. While visual information processing ability in cocaine-exposed infants has been examined in two recently published studies with three- and six-month olds, this is the first study to assess newborn infants, thereby examining the effects of fetal cocaine-exposure before the postnatal environment has a chance to impact on infant development. It is also the first study to assess information processing ability in cocaine-exposed infants using the auditory modality. In addition, many methodological improvements were made to address the shortcomings of prior studies. In addition to using a valid measure of information processing ability, an objective measure was used to verify the drug-exposure status of the neonates (meconium analysis), and subjects in each group were individually matched on numerous potentially confounding factors which were not considered in prior studies.

In Study 2, the effects of fetal tobacco-exposure on newborn auditory information processing were assessed. Five studies have examined newborn neurobehavioural functioning in tobacco-exposed neonates using the NBAS, but this is the first study to examine information processing in these infants. In addition, the same methodological improvements, over studies assessing infant outcome in tobacco-exposed infants, were made as described for Study 1. A reliable measure of newborn auditory information processing was used,

meconium analysis in conjunction with a bogus pipeline procedure was employed to ensure that the infants were exposed only to tobacco and not to illicit substances, and numerous confounding factors were controlled. This is also the first study to report the lack of validity of meconium analysis for identifying infants exposed prenatally to maternal cigarette smoking, a potentially important finding since many researchers have begun to use this procedure believing it to be valid.

Studies 1 and 2 yielded differential adverse effects of fetal cocaine and tobacco-exposure on newborn auditory information processing, findings that have not previously been reported. These are the first studies to employ reliable subject identification procedures and valid measures of information processing ability, in addition to individually matching drug-exposed infants with non-exposed controls on several variables. Thus, these two studies represent the most rigorous investigations of the effects of prenatal exposure to cocaine and tobacco on newborn cognitive functioning available to date. These studies make a valuable contribution to the literature by identifying cognitive processes which appear to be disturbed in the newborn period by fetal cocaine and tobacco-exposure, and by highlighting the importance of controlling for maternal cigarette consumption in studies examining the outcome of infants exposed to cocaine and other illicit substances in utero.

In Study 3, an unusual case report is presented which raises issues not previously addressed in the literature on fetal cocaine-exposure. An infant born to a verified cocaine-addict appears to have not been exposed to the maternal cocaine. Although false negative toxicology assays are common, this is the first report of a case where negative infant meconium analysis results were followed up with infant and maternal hair analyses for cocaine to test the hypothesis that

a negative toxicology report may indicate that the infant was not exposed to the drug. In addition, this case report provides unique evidence for the validity of the auditory information processing procedure.

The following outlines my unique contributions to each of the studies presented in this dissertation and the contributions of others. Each of these studies was carried out under the supervision of Dr. Philip Zelazo. With respect to Study 1, the original idea of using the auditory information processing procedure to assess the effects of fetal cocaine-exposure was developed by Drs. Zelazo, Stack, and Papageorgiou. Many of the study design issues were my own idea, such as using subject matching to control for confounding factors, and implementing meconium analysis for the detection of fetal drug exposure (although the idea of using meconium analysis was originally suggested by Dr. Zelazo). I also developed the demographic questionnaire which was used to collect much of the data used in the subject matching procedure. For Study 2, I was responsible for the original conception of the problem, and I designed the study (although the information processing procedure was previously developed by Dr. Zelazo and colleagues), collected and analyzed the data, and reported the results. The same questionnaire which I developed for Study 1 was used in this study. Study 3, the case report, was entirely my own idea. I pursued the unusual data on this infant, arranged for the toxicological analyses, and oversaw the testing and re-testing of this infant on the information processing procedure. The toxicology data presented in Study 3 have been published in collaboration with researchers in Dr. Zelazo's laboratory and at the toxicology laboratory of the Hospital for Sick Children, Toronto, Ontario and the United States Drug Testing Laboratories, Chicago, Illinois (Potter et al., 1994); however, the manuscript was

extensively revised for this dissertation in order to include data which was not included in the published report.

For each of the studies reported in this dissertation, I was responsible for gathering the relevant literature, organizing and writing the literature reviews, collecting the data, recruiting and training volunteer research assistants, enlisting the cooperation of the nursing and social work staff at the hospital where the data was collected, scoring and analyzing the data, and writing the final paper under Dr. Zelazo's supervision. While I received a great deal of assistance from those collaborating on the studies, particularly Dr. Zelazo and Dr. Stack, the work presented in this dissertation can be considered an original, personal contribution to the literature in this area.

Chapter 1: Literature I

Cocaine Use in Pregnancy

In the early 1980's, the U.S. Department of Health and Human Services (DHHS) documented a dramatic increase in the number of individuals using cocaine. Use of cocaine peaked in 1985 when 8.6 million Americans reported occasional use (DHHS, 1993). The fact that approximately 40% of these users were women of child-bearing age (The Blue Sheet, 1995) was of particular concern since little was known about the possible teratogenic effects of cocaine on the developing fetus.

The first descriptions of babies born to cocaine users were alarming. The popular press referred to these infants as a "biological underclass" (Krauthammer, 1989, p. C7), they were described as "brain damaged in ways as yet unknown, oblivious to any affection" (Hopkins, 1990, p. 66), and, according to one journalist, the lucky ones died since those who survived experienced the "agony of withdrawal" in which they "suffered terribly" (Krauthammer, 1989, p. 3B). Even the 1991 president of Boston University, John Silber, in a university symposium on the health care system, denounced cocaine-exposed infants as "babies who won't ever achieve the intellectual development to have consciousness of God" (Saltus, 1991, p. 15).

These sensationalistic descriptions of the effects of prenatal cocaine exposure were based largely on anecdotal reports and misconceptions in the absence of scientific evidence. For example, it is now recognized that the majority of cocaine-exposed newborns do not suffer from withdrawal of the drug and for the small percentage who do, the symptoms are mild (Bateman, Ng, Hansen, & Heagarty, 1993; Besunder & Blumer, 1994; Bingol, Fuchs, Diaz,

Stone, & Gromisch, 1987; Cherukuri, Minkoff, Feldman, Parekh, & Glass, 1988; Fulroth, Phillips, & Durand, 1989; Hadeed & Siegel, 1989; LeBlanc, Parekh, Naso, & Glass, 1987; Madden, Payne, & Miller, 1986; Mayes, Granger, Frank, Schottenfeld, & Bornstein, 1993; Rahbar, Fomufod, White, & Westney, 1993; Spear, 1995). Moreover, recent studies have found that children exposed to cocaine in utero often have intelligence quotients in the normal range at follow-up evaluations ranging from 14 months to 6.5 years of age (Azuma & Chasnoff, 1993; Nulman et al., 1994).

Media reports on the horrors of cocaine use during pregnancy represented a "rush to judgment" (Mayes, Granger, Borenstein, & Zuckerman, 1992, p. 406), and propagated a popular view labelled by one researcher as "the mythology of severe risk" (Neuspiel, 1993, p. 305). Although studies of the newborn period suggest that prenatal cocaine-exposure places the infant at risk for a number of perinatal difficulties (e.g., Chen et al., 1991; Dombrowski, Wolfe, Welch, & Evans, 1991; Dow-Edwards, 1991), the significance of these largely inconclusive findings for the future development of cocaine-exposed infants is not known. Furthermore, many studies have shown that problems observed by some researchers in the neonatal period frequently resolve during the first year of life (Chasnoff, Griffith, Freier, & Murray, 1992; Doberczak, Shanzer, Senie, & Kandall, 1988; Garber, Eisenberg, Yamashita, & Kliegman, 1992; Hurt, Malmud, Brodsky, & Giannetta, 1992; Kaiser, Mooney, & Anday, 1992; Katikaneni, Sallee, & Ibrahim, 1992; Salamy, Eldredge, Anderson, & Bull, 1990; Sparks & Gushurst, 1994; Weathers, Crane, Sauvain, & Blackhurst, 1993).

Despite the lack of scientific evidence that cocaine use during pregnancy produced observable, enduring negative effects on child development, the media reports stirred up fear and public outrage at pregnant drug-users (Zuckerman &

Frank, 1992). Cocaine-exposed infants were said to be taxing the health care system ("Cost of Care", 1991; Phibbs, Bateman, & Schwartz, 1991) and it was predicted that they would soon overwhelm the country's educational system. As the cocaine-exposed babies of the mid-1980's turned five years old, newspapers flourished with headlines warning of an impending educational crisis (e.g., "School's Newest Burden: Cocaine Babies", Griffin & Wiltz, 1991; "Children of Crack: Are the School's Ready? Crack Babies Turn 5, and Schools Brace", Chira, 1990; "First Wave of Crack Kids Hits School", Stone, 1990; "Yesterday's Cocaine Babies are Today's Behavior Problems in School: Can the System Learn to Handle Them?", Shrieves, 1991). The children of cocaine-users were reportedly "creating mayhem in the classrooms of America" (Greig, 1992, p. A1).

In response to the public outrage, several states, 19 by the year 1991, passed legislation requiring mandatory reporting of pregnant drug users, and their prosecution and incarceration under existing state child abuse, and drug distribution and possession laws (Connolly & Marshall, 1991; Garrity-Rokous, 1994; Weber, 1992). Many states also required drug treatment program personnel to report pregnant drug users (Weber, 1992). Cocaine-using pregnant women were incarcerated for minor crimes, often without prenatal care or drug treatment, when under non-pregnant circumstances they would have received probation (Weber, 1992).

This criminalization of gestational cocaine use took place despite the American Medical Association's endorsement of medical rather than punitive approaches to addiction (Chavkin & Kandall, 1990), and the American Psychiatric Association's (1987, 1994) classification of psychoactive drug dependence as a mental disorder rather than a crime. Many health professionals predicted that this punitive approach to the problem would only make matters

worse for pregnant drug addicts and their infants; it was speculated that fear of prosecution would lead pregnant women to avoid prenatal care, conceal their drug use histories from health care workers, and even avoid delivering their babies in hospitals, further jeopardizing the pregnancy outcome (Chavkin & Kandall, 1990; Ostrea & Welch, 1991; Skolnick, 1990; Weber, 1992).

Mandatory reporting laws were also expected to compound the existing difficulties experienced by researchers enlisting subjects for studies examining the outcome of gestational cocaine use (Behnke & Eyler, 1994; Weber, 1992). Identifying cocaine users is a difficult task that is immensely facilitated by maternal self-report; it was speculated that mandatory reporting laws would lead women to deny drug use and refuse to enroll in drug use research projects for fear of being reported. Research on the effects of cocaine on the pregnant woman and developing fetus is needed to determine if the current degree of concern over cocaine use in pregnancy is warranted, and, if it is, to create appropriate prevention and intervention programs for cocaine-using women and their children.

The predictions that punitive laws would aggravate the prenatal drug exposure problem have been at least partially confirmed: in many studies, up to 60% of cocaine-using mothers received no prenatal care (e.g. Cherukuri et al., 1988; Gillogley, Evans, Hansen, Samuels, & Batra, 1990; Ostrea, Brady, Gause, Raymundo, & Stevens, 1992; Singer, Arendt, Song, Warshawsky, & Kliegman, 1994), and self-report rates for cocaine use are extremely low compared to the prevalence rates indicated by objective measures such as meconium analysis (Gillogley et al., 1990; Lurio, Younge, & Selwyn, 1991; McCalla et al., 1991; Neerhof, MacGregor, Retzky, & Sullivan, 1989; Pegues, Engalgau, & Woernle, 1994; Rosengren et al., 1993; Schutzman, Frankenfield-Chernicoff,

Clatterbaugh, & Singer, 1991; Skolnick, 1990). Moreover, in a survey of 22 recipients of grants for the development of treatment programs for drug-using mothers, 15 felt that the punitive measures imposed on pregnant drug-users deterred women from seeking treatment (unpublished report of the Treatment Committee of the Coalition on Alcohol and Drug Dependent Women and Their Children, 1990, as cited in Weber, 1992). The most plausible interpretation of these data is that pregnant women did not disclose their drug use because they feared the punitive consequences. It is also possible that the imposition of punitive measures resulted in decreased cocaine use. Data on the prevalence of gestational cocaine use do not support this explanation, although there are some suggestions that the rapid increase in cocaine use, observed over the course of a decade beginning in the early 1980's, has levelled off (Dicker & Leighton, 1994; DHHS, 1994).

Prevalence of Cocaine Use

According to the United States National Household Survey on Drug Abuse, self-reported cocaine users in the U.S. numbered 1.3 million in 1993, with 500,000 Americans using cocaine weekly (DHHS, 1994). In 1992, more than 7.7% of women (4.5 million) in the child-bearing years, ages 15-44, had used an illicit drug in the past year. Of this group 14% (601,000) had used cocaine (DHHS, 1993). It is likely that these surveys greatly underestimate the actual number of cocaine-users, since one must live in a "household" and possess a telephone in order to be interviewed, factors that would exclude many drug users (Lester & Tronick, 1994). Moreover, the data are based on self-report which is notoriously unreliable. Consequently, an accurate enumeration of cocaine-users has not been available.

The exact percentage of women who use cocaine during pregnancy is also unknown. Estimates of the number of newborns exposed to cocaine prenatally vary widely depending upon the geographical region sampled and the screening methods used. Table 1 summarizes the results of 25 studies (obtained through a search of the Med-line database) which assessed the incidence of drug use in pregnancy between the early 1980's and mid-1990's. Prevalence rates for gestational cocaine use ranged from less than 1% (Castro, Azen, Hobel, & Platt, 1993) to more than 30% (Ostrea et al., 1992). In the majority of studies, cocaine was the most commonly used illicit substance; the prevalence of marijuana use surpassed cocaine in only seven of the 25 studies reviewed (Buchi, Varner, & Chase, 1993; Pegues et al., 1994; Chasnoff, Landress, & Barrett, 1990; Frank et al., 1988; Hollinshead et al., 1990; Schutzman, Frankenfield-Chernicoff, Clatterbaugh, & Singer, 1991; Streissguth et al., 1991). The use of no other illicit drug exceeded the use of cocaine in any of these studies. The data from these 25, primarily U.S. studies, imply that cocaine is the drug of choice among pregnant women (Atkins, 1988).

According to the studies reviewed, the overall estimated prevalence of gestational cocaine use across the U.S. in the last decade was in the order of 10%. The only Canadian incidence study available (Forman et al., 1994) suggests a similar level of use in Canada (12.5% in urban Toronto, 3% in suburban Toronto, 6.25% overall prevalence). The actual prevalence of cocaine use by pregnant women is likely to be somewhat higher than the estimates of the majority of studies due to the limited sensitivity of the screening methods. Furthermore, since nearly all studies have found that the majority of pregnant cocaine-users identified at delivery had no prenatal care (e.g., Gillogley et al.,

Table 1

Studies assessing the prevalence of cocaine use during pregnancy.

Author(s)	Urban/Suburban	Region	Method	Cocaine
Bateman et al. (1993)	Urban	Harlem	U/SR	12.8%
Buchi et al. (1993)	Both	Utah	U	1.1%
Castro et al. (1993)	Urban	Los Angeles	SR	< 1.0%
Chasnoff et al. (1990)	Urban	Florida	U (P)	3.4%
Dombrowski et al. (1991)	Urban	Detroit	U/SR	12.6%
Forman et al. (1994)	Urban	Toronto	U/SR/NH	12.5%
Forman et al. (1994)	Suburban	Toronto	U/SR/NH	3.0%
Frank et al. (1988)	Urban	Boston	U(P)/SR	17.0%
Gillogley et al. (1990)	Urban	Sacramento	U	10.6%
Hansen et al. (1992)	Urban	Sacramento	U	9.5%
Hollinshead et al. (1990)	Both	Rhode Island	U	2.6%
Lurio et al. (1991)	Urban	Bronx	U(P)	7.8%
Matera et al. (1990)	Urban	New York City	U	10.0%
McCalla et al. (1991)	Urban	New York City	U	11.5%
Minkoff et al. (1990)	Urban	New York City	U	12.9%
Nanda et al. (1990)	Urban	Brooklyn	SR	5.8%
Neerhof et al. (1989)	Urban	Chicago	U	8.0%
Osterloh & Lee (1989)	Urban	San Francisco	U	9.0%
Ostrea et al. (1992)	Urban	Detroit	NM	31.0%
Ostrea et al. (1993)	Urban	Detroit	NM	29.2%
Pegues et al. (1994)	Both	Alabama	U(P)	1.3%
Rosengren et al. (1993)	Both	Hartford	NM	3.4%
Schutzman et al. (1991)	Urban	Pennsylvania	NM	11.8%
Skolnick, 1990	Suburban	Delaware	U(P)	9.4%
Spence et al. (1991)	Urban	Philadelphia	U/SR	19.7%
Streissguth et al. (1991)	Urban	Seattle	SR	11.0%

U = Urine screened for cocaine-exposure at delivery; U(P) = Urine screened for cocaine-exposure during a prenatal visit; NM = Newborn meconium screened for cocaine-exposure; NH = Newborn hair screened for cocaine-exposure; SR = Self report of cocaine use at delivery.

1990; Ostrea et al., 1992), assessing the prevalence of gestational cocaine use by screening the small percentage of cocaine-users who attend prenatal clinics (e.g., Chasnoff et al., 1990; Frank et al., 1988; Pegues et al., 1994; Skolnick, 1990) is likely to substantially underestimate the number of pregnant cocaine users.

Based on a DHHS (1994) survey, the number of weekly cocaine users has remained stable at around half a million. However, the number of occasional users (i.e., those who use cocaine less often than monthly) dropped from 8.1 million in 1985 to 3 million in 1993 (DHHS, 1994). Furthermore, while the number of drug-using parturient women discharged from U.S. hospitals increased by 576% between 1979 and 1990 (Dicker & Leighton, 1994), the rate of increase dropped by 13% between 1989 and 1990. These data suggest that the upward trend in the number of pregnant drug-users is levelling off. It is possible that the media's accounts of "cocaine babies", along with the criminalization of gestational drug use, have discouraged a percentage of occasional users from indulging in cocaine during pregnancy. However, the above statistics may simply reflect a decreased willingness on the part of pregnant women and their physicians to report gestational drug use, in light of the hostile social climate associated with the war on drugs. Because the DHHS statistics are based entirely on self-report, any factor that might deter people from reporting drug use, such as a hostile social climate, may result in misleading information on the number of cocaine users. Examination of Table 1 reveals that, in general, when pregnant cocaine users were identified by methods other than self-report, the prevalence of gestational cocaine use did not decrease, according to studies published between 1988 and 1994.

In light of the media reports on the risks associated with prenatal cocaine use and the social hostility towards pregnant cocaine users, one might wonder why such large numbers of women would continue to use cocaine during pregnancy. It is likely that the answer lies partly in the social history of the drug and partly in its psychopharmacology. For example, in the early 1970's, reports by two United States government national commissions on drug abuse stated that cocaine did not cause substantial morbidity (Strategy Council on Drug Abuse, 1973; National Commission on Marijuana and Drug Abuse, 1973, as cited in Gawin, 1988), and, as recently as 1980, cocaine was extolled as a relatively safe, nonaddicting euphoriant (Grinspoon & Bakalar, 1980). Since discontinuation of cocaine does not produce the gross physiological withdrawal symptoms typically seen in opiate addicts, cocaine was considered incapable of producing "dependence" (Jones, 1984, as cited in Johanson & Fischman, 1989).

It is now known that psychological dependence is as detrimental to health and well-being as physical dependence, although at the time of these reports, addiction was defined according to strictly physiological criteria (Gawin, 1991). Withdrawal from cocaine produces severe psychological disturbances including intense cravings for the drug, insomnia, depression, and paranoia (Gawin & Kleber, 1986). These symptoms are immediately relieved by administration of cocaine. Thus, many of the women who began using cocaine believing it to be a relatively safe drug may have found themselves addicted by the time reports of the hazards associated with cocaine use began to appear. As the number of persons using cocaine reached record heights, it became clear that cocaine could no longer be considered "safe" and "non-addicting". Possibly as a consequence of this new awareness of the hazards of cocaine use, many

researchers turned their attention to studying the psychopharmacology of the drug in an effort to understand the phenomenon of cocaine addiction.

Pharmacology of Cocaine

Cocaine belongs to a group of substances that act primarily as central nervous system (CNS) stimulants (Farrar & Kearns, 1989) and is generally sold in the form of cocaine hydrochloride, a white crystalline powder. The most common route of ingestion is intranasally, where cocaine is absorbed through the mucosal membranes of the nasal passages. When taken via this route, cocaine has a half life of 40 - 60 minutes, with peak plasma levels occurring approximately 30 minutes following ingestion (Javaid, Fischman, Schuster, Dekirmenjian, & Davis, 1978), although only 20 to 30 percent of the drug is actually absorbed due to the self-limiting vasoconstrictive action of cocaine on the mucosal vasculature (Julien, 1995). Conversely, intravenous injection results in 100 percent availability of the drug and a rapid onset of action marked by an intense "rush" within one or two minutes of administration (Johanson & Fischman, 1989; Julien, 1995). Whereas cocaine hydrochloride decomposes if burned, the relatively new, alkaloidal "free base", commonly known as "crack", can be smoked (Johanson & Fischman, 1989; Volpe, 1992). Smoking crack results in a similar dose to blood level ratio of the drug, and a similar elimination time course, as intravenous administration of cocaine (Balster, 1988; Spear, 1995). In general, the rate of clearance of cocaine from plasma is related to the rate of uptake (Hutchings & Dow-Edwards, 1991). Therefore, rapid uptake following intravenous injection of cocaine or smoking of crack results in rapid clearance of the drug from the body. Intranasal administration, on the other hand, results in prolonged exposure but at lower plasma concentrations.

In adults, cocaine is rapidly metabolized by plasma and liver cholinesterases to norcocaine, benzoynorecgonine, benzoylecgonine (BE), and ecgonine methyl ester (Konkol, Murphy, Ferriero, Dempsey, & Olsen, 1994; Neuspiel & Hamel, 1991), leading to a rapid decline in drug effect. The resulting brevity of the experience of euphoria often leads to repeated dosing in order to maintain the drug effect, sometimes as often as every 10 minutes (Gawin & Ellinwood, 1988; Rosenak, Diamant, Yaffe, & Hornstein, 1990).

Cocaine exerts its effects through its actions on three different monoaminergic neurotransmitter systems in the CNS, norepinephrine, dopamine, and serotonin, and also on the catecholamines, epinephrine and norepinephrine, of the peripheral nervous system (Mayes, 1994). Cocaine inhibits the reuptake of epinephrine and norepinephrine by presynaptic axon terminals, resulting in an accumulation of these neurotransmitters at the synapses and overactivation of the adrenergic system (Volpe, 1992). The resultant excitation of the sympathetic nervous system is primarily responsible for the hypertension, tachycardia, and vasoconstriction associated with cocaine intoxication (Farrar & Kearns, 1989).

It is through its action on dopaminergic receptors in the mesolimbic and mesocortical pathways (i.e., the reward or "pleasure centres" of the brain), that cocaine produces the powerful sense of euphoria, enhanced alertness, and heightened energy associated with its use (Corbett & Wise, 1980; Goeders, 1988; Goeders & Smith, 1983; Johanson, 1988; Koob & Hubner, 1988). Cocaine exerts its effects at dopaminergic axon terminals by blocking reuptake of dopamine and by facilitating the release of dopamine from the presynaptic vesicles (Kosten, 1990). Upon cessation of cocaine use, a rebound effect occurs in which dopamine becomes progressively depleted from axon terminals,

resulting in the dysphoric state associated with withdrawal from cocaine, and consequential cravings for the drug (Gawin & Ellinwood, 1988; Volpe, 1992).

The serotonin system is also actively involved in the neurochemical effects of cocaine (Carroll, Lac, Asencio, & Kragh, 1990), although the role of serotonin is less well understood (Julien, 1995). While cocaine appears to block the reuptake of serotonin and its precursor, tryptophan, thereby increasing serotonin levels, there is also evidence that cocaine reduces serotonin synthesis (Akbari, Kramer, Whitaker-Azmitia, Spear, & Azmitia, 1992; Knapp & Mandell, 1972). There has been speculation that a disruption in serotonin regulation may account for the disturbances in sleep and wakefulness that accompany and follow cocaine use (Dixon, 1994). Others have suggested that an interaction between the dopamine and serotonin systems in the brain, rather than an increase in dopamine alone, is responsible for the rewarding, euphoric effect of cocaine (Gawin, 1991; Mayes, 1994). This reasoning is partly based on the observation that drugs that selectively stimulate the dopamine and norepinephrine systems but not the serotonin system are not abused by humans and are not self-administered by laboratory animals (Mayes, 1994). Furthermore, serotonin agonists reduce the rewarding properties of cocaine (Carroll et al., 1990), and, as a result, drugs that increase serotonin levels (e.g., fluoxetine) have some efficacy in the treatment of cocaine addiction (Gawin, 1991; Gawin & Ellinwood, 1988).

In summary, cocaine exerts its pharmacological effects through its action on CNS neurotransmitter systems and peripheral catecholamine systems. Its effects on the dopaminergic and serotonergic systems render it a powerfully addictive drug. Moreover, given these mechanisms of action in adults, it is possible that cocaine may adversely affect the developing neurotransmitter

systems in the fetal brain in cases of gestational cocaine use. In addition, the vasoconstrictive effects of cocaine may result in reduced blood supply to the fetus, further compromising normal development. Over the past decade numerous studies have examined the impact of prenatal cocaine use on human fetal development. However, the results of such studies depend on the reliable identification of gestational cocaine users and cocaine-exposed newborns.

Identification of Cocaine-Exposed Newborns

In order to accurately assess the incidence of gestational cocaine use and identify cocaine-exposed newborns for intervention and outcome studies, reliable methods for detecting maternal cocaine use are essential. There are two general methods of identifying prenatal cocaine use: maternal self-report and toxicological analyses of newborn or maternal biological substances for cocaine and its metabolites (Ostrea & Welch, 1991). Toxicological analyses are most often carried out on urine, hair, and meconium (the neonate's first stools). There are benefits and limitations inherent in each of these techniques.

Self-report

Historically, self-report of illicit drug use has been regarded as notoriously unreliable. In a review of 14 studies assessing the validity of drug abusers' self-reports of drug use, Maistro, McKay, and Connors (1990) concluded that the validity of self-report is highly variable, and that the accuracy and reliability of self-report could not be considered high in any of the studies reviewed. In general, self-report of drug use is neither valid nor in-valid, but depends on numerous variables (Babor, Brown, & Del Boca, 1990). These include the sensitivity of the information sought (e.g., cocaine use versus cigarette use), the validation criteria employed (e.g., urine tests, archival records, collateral informants' reports), the personal characteristics of the respondents (e.g., sober,

withdrawing, intoxicated), the time window of the report (recent versus. more distant past), and the demand characteristics of the situation (e.g., anonymous information for research versus identifying information in a region with mandatory reporting laws). Validity of self-report decreases when the information sought is sensitive, the validation criteria are weak or non-existent, the personal characteristics of the respondent interfere with accurate reporting, the events to be recalled occurred in the distant past, and the respondent feels she may be putting herself at risk by answering truthfully.

When parturient women are asked to self-report on their use of illicit drugs, such as cocaine, during pregnancy, the information sought is highly sensitive (i.e., there are strong social sanctions against the use of illicit drugs during pregnancy), the validation criteria (if any) are usually limited in their ability to detect drug use, the respondent is dealing with the many potentially memory-impairing stressors that giving birth entails, she may be intoxicated or experiencing drug withdrawal, and the time window of nine months is relatively long. Moreover, pregnant drug-using women are in a unique position compared to non-pregnant drug-users because, not only do they face the possibility of prosecution and incarceration, they also risk having their infants removed from their custody if they admit to drug use (Chavkin & Kandall, 1990; Connolly & Marshall, 1991; Garrity-Rokous, 1994; Weber, 1992). Taken together, these variables are likely to have a significant impact on the validity of self-reports of cocaine use during pregnancy.

Given the widespread hostility towards pregnant women who use cocaine, and the fear of prosecution and removal of their infants, along with the numerous birth-related situational variables that may influence self-report at the time most pregnant women are screened (i.e., parturition), it is not surprising that the

majority of pregnant cocaine-users deny use. In a study involving 500 consecutively born infants at a suburban medical centre, 11.8% of meconium samples tested positive for cocaine ($n=59$), whereas only 1% of mothers ($n=5$) admitted to cocaine use on an anonymous questionnaire (Schutzman et al., 1991). Similarly, Lurio et al. (1991) found that while maternal urine testing identified 7.8% ($n=14$) of their sample of 179 women screened as cocaine-users, clinical evaluations and detailed drug histories identified only 0.6% ($n=2$) of a sample of 311 women (including the 179 whose urine was also screened) as cocaine users. Comparable findings have been reported by Gillogley et al. (1990), McCalla et al. (1991), Neerhof et al. (1989), Pegues et al. (1994), Rosengren et al. (1993), and Skolnick (1990).

Self-reported use of other drugs used during pregnancy may also be less than accurate. One study which examined the reliability of self-reported alcohol and marijuana use among pregnant women found that, consistent with the studies reviewed by Maistro et al. (1990), reliability was low (Day & Robles, 1989). When subjects were asked at four months gestation about their first trimester alcohol consumption, and again at either seven months gestation or delivery, correlation coefficients between the two reports were .61 and .53 respectively. Interestingly, as time passed, women were more likely to overestimate rather than underestimate their prior alcohol consumption. This phenomenon has also been reported by others (Little, Mandell, & Schultz, 1977, as cited in Day & Robles, 1989). However, it is possible that the subjects under-reported their alcohol consumption when first interviewed at four months gestation, but felt sufficiently comfortable with the researchers by the seventh month of gestation to disclose more accurately the quantities of alcohol consumed earlier in the pregnancy. When asked about marijuana use during the

first trimester of pregnancy, 19% of the estimated users (based on statistical probabilities calculated from previous research on rates of marijuana use) denied use. While these results provide useful data on the reliability of self-reported alcohol and marijuana use, they may not generalize to cocaine.

One method that has been advocated for improving the reliability of self report is the "bogus pipeline" method (Patrick et al., 1994). Before obtaining information concerning substance use, participants are informed that a biological measure will be used to assess whether or not they were exposed to the substance under question; although samples are collected for analysis, they are not usually analyzed. The bogus pipeline method has been shown to enhance the validity of self-reported substance use among adolescents (e.g., Werch, Gorman, Marty, Forbess, & Brown, 1987; Murray, O'Connell, & Schmid, 1987; Murray & Perry, 1987), and at least one study has demonstrated the efficacy of the bogus pipeline procedure for increasing the accuracy of self-reported alcohol consumption among pregnant women (Lowe, Windsor, Adams, Morris, & Reese, 1986). Thus, the bogus pipeline procedure may be a useful technique to enhance the validity of self-report in studies assessing the outcome of infants prenatally exposed to various drugs.

Despite the drawbacks, there are some advantages to using self-report. In contrast to most toxicological methods, self-report is convenient and economical. Moreover, in those who admit to drug use, it is possible to obtain an indication of the timing of exposure and the quantity of drug consumed (Babor et al., 1990; Baker & Brandon, 1990; Behnke & Eyler, 1994; Day & Robles, 1989; Maistro et al., 1990; Sobell & Sobell, 1990), a limitation of most analytic methods. However, because this information is dependent upon memory and a knowledge of drug quantities, the best one can hope to achieve is a rough picture of the mother's

pattern of drug use over the course of pregnancy (Day & Robles, 1989). Even then, knowledge concerning the purity of the drug is nearly always absent.

Overall, the research findings suggest that self-report measures of cocaine use by pregnant women are apt to be of low reliability and validity. As a result, clinicians and researchers relying solely on self-report of drug use (e.g., Castro et al., 1993; Nanda, Feldman, Delke, Chintalapally, & Minkoff, 1990; Streissguth et al., 1991) are likely to underestimate the number of newborns prenatally exposed to cocaine and run the risk of including cocaine-exposed infants in their non-exposed control groups. Nevertheless, when used in conjunction with toxicological drug screening procedures, self-report can provide useful information that would otherwise not be accessible.

Toxicological Measures

When cocaine is ingested into the body, quantities of cocaine, along with its various metabolites, are deposited in all body fluids, tissue, and hair (Farrar & Kearns, 1989). In pregnant women, cocaine has been demonstrated to readily cross the placenta, resulting in the deposition of cocaine and its metabolites throughout the body of the fetus (Dixon, 1994; Kidwell, 1992; Mayes, 1994; Neuspiel & Hamel, 1991; Ostrea et al., 1992; Wiggins, Rolstein, Ruiz, & Davis, 1989), although Study 3 of this dissertation raises the possibility for exception to this finding. Laboratory analyses of such maternal or neonatal biological substances as urine, hair and meconium for the presence of drugs provide an objective alternative to self-report measures of gestational cocaine use.

Nevertheless, even these methods are subject to criticism.

Urine Analysis. Analysis of maternal and/or neonatal urine has been the most common laboratory screening method employed for the detection of prenatal cocaine use. Urine analysis was a popular choice for both prevalence

and outcome studies for a variety of reasons (Behnke & Eyler, 1994; Council on Scientific Affairs, 1987; Lester & Tronick, 1994; Ostrea & Welch, 1991). First, processing by the kidneys often results in higher drug concentrations in urine than in other body fluids such as plasma or neonatal cord blood; second, sufficient quantities of urine can be collected in a relatively non-invasive manner; third, because drugs and their metabolites are usually very stable in frozen urine, long-term storage of samples is possible; and, fourth, urine analysis has the additional advantage of being less expensive than the analysis of other biological substances such as meconium or hair. Because urine is usually free of contaminating protein and cells, complicated extraction procedures are not necessary prior to the toxicological assay. The primary drawback of urine is that cocaine is detectable for only 8 to 12 hours after exposure and benzoylecgonine (BE), the primary metabolite of cocaine, is detectable for a maximum of 5 days, depending upon the analytic method used (Farrar & Kearns, 1989; Hamilton et al., 1977).

The three most commonly used methods for analyzing urine for evidence of cocaine use are the enzyme-multiplied immunoassay technique (EMIT), thin-layer chromatography (TLC), and radioimmunoassay (RIA; Farrar & Kearns, 1989; Hamilton et al., 1977). More recently, fluorescence polarization immunoassay (FPI) has also been applied to drug screening (Kidwell, 1992; Ostrea et al., 1992; Pegues et al., 1994).

When evaluating screening techniques, the sensitivity (the minimum amount of a drug that can be detected) and the specificity (the degree to which compounds other than the drug can yield a false positive result) of each technique must be considered (Council on Scientific Affairs, 1987). Each technique has its inherent advantages and disadvantages. Some techniques can

detect many substances with one assay (e.g., TLC) , whereas others require that separate assays be conducted for each drug or metabolite sought (e.g., EMIT). Moreover, in TLC, RIA, EMIT, and FPI, a number of substances, other than the specific drugs and metabolites for which the specimen is being screened, can cross-react with the reagents used in the toxicological assays and give false positive results. Therefore, it is particularly important that all positive test results be confirmed by a procedure such as gas chromatography/mass spectrometry (GC/MS) or high performance liquid chromatography (HPLC; Council on Scientific Affairs, 1987; Farrar & Kearns, 1989; Kidwell, 1992; Ostrea, 1992). GC/MS and HPLC have very high sensitivity and specificity and will confirm whether or not the drug or metabolite is actually present, or if some other molecular compound caused the positive result. However, use of GC/MS and HPLC increases costs and considerable technical expertise is required to perform these procedures. Table 2 provides a comparison of some advantages and disadvantages of six commonly used analytic techniques.

One of the primary drawbacks of urine analysis is that cocaine use can be detected for a maximum of only 3 to 5 days, depending on the analytical method employed. In a study examining the pattern of excretion of cocaine and its metabolites, Hamilton et al. (1977) assessed the levels of cocaine and BE (the primary metabolite of cocaine) in the urine of six adults following intranasal administration of 1.5 mg/kg body weight of cocaine. Urine specimens were analyzed 11 times over a period of seven days using EMIT, TLC and RIA. Results showed that urine concentrations of cocaine hydrochloride ("cocaine hydrochloride" refers specifically to unmetabolized cocaine) peaked between one and four hours in all subjects and were generally no longer detectable 12 hours after exposure by any of the analytic techniques employed. Thus, it appears that

Table 2

Comparison of Analytic Techniques Used to Detect Cocaine Use

Technique ^a	Major Expertise/ Instrumentation	Detection Limit	Confirmation Required	Simultaneous multiple drug detection
TLC	No	1.000 µg/ml	Yes	Yes
EMIT	Yes	0.025 µg/ml	Yes	No
RIA	Yes	0.001 µg/ml	Yes	No
FPI	Yes	0.005 µg/ml	Yes	No
GC/MS	Yes	0.001 µg/ml	No	Yes
HPLC	Yes	0.020 µg/ml	No	Yes

^a TLC = Thin Layer Chromatography; EMIT = Enzyme Multiplied Immunoassay; RIA = Radioimmunoassay; FPI = Fluorescence Polarization Immunoassay; GC/MS = Gas Chromatography/Mass Spectrometry; HPLC = High Performance Liquid Chromatography.

in human adults, cocaine is broken down into its various metabolites (e.g., BE) within 12 hours of ingestion and is, therefore, no longer detectable in urine. Conversely, BE was detected by EMIT and TLC for two to three days following ingestion of cocaine. The most sensitive measure employed in this study, RIA, detected BE in five of six subjects 120 hours (5 days) after cocaine administration.

In contrast to the findings of Hamilton et al. (1977), a shorter window of detection was found by Van Dyke, Byck, Barash, and Jatlow (1977) in their study of patients receiving cocaine for surgical reasons. BE was no longer detected using the EMIT method by 24 to 36 hours following drug administration in eight of the nine subjects who received 1.5 mg/kg of cocaine intranasally (i.e., the same dose used by Hamilton et al., 1977). This finding indicates that in order to avoid false negatives, urine should ideally be collected within 24 hours of cocaine use if it is to be analyzed for BE using EMIT.

These studies underscore the importance of the timing of urine collection when screening parturient women for cocaine use. Halstead, Godolphin, Lockitch, and Segal (1988) emphasize that urine samples should be collected as soon as possible after admittance to the hospital. Indeed, since cocaine use could be detected by EMIT for only 36 hours in one study (Van Dyke et al., 1977) and EMIT is often the method employed, delays in urine collection would undoubtedly result in a significant risk of false negative results. An additional reason for the immediate collection of urine is to minimize the likelihood of false positives due to drugs administered in the hospital. In Halstead et al.'s study, 12 women with positive urine toxicology reports for opiates had received acetaminophen with codeine for pain postpartum. Confirmatory tests (e.g., HPLC or GC/MS) would indicate whether such positive results were due to the

presence of codeine, morphine, or heroin; however, these tests are often not carried out.

At present, EMIT is the most common urine screening method employed. In 14 of the 18 epidemiological studies presented in Table 1 (page 7) in which urine analysis results served as the basis for prevalence reports, EMIT was the analytic method used (the screening method was not reported in the other four studies). However, only seven studies (50%) reported confirmation of positive EMIT results for at least one of the drugs screened (some studies screened for more than one substance) using a technique with high specificity (Bateman et al., 1993; Buchi et al., 1993; Frank et al., 1988; McCalla et al., 1991; Hollinshead et al., 1990; Osterloh & Lee, 1989; Pegues et al., 1994). The presence of BE was confirmed following positive EMIT results in only two studies (Bateman et al., 1993; Frank et al., 1988). Although BE does not cross-react with other molecules to the same degree as opiates and amphetamine, there is still a risk of false positive results (Behnke & Eyler, 1994; Kidwell, 1992). By not confirming positive EMIT results, 12 of 14 epidemiological studies, relying solely on EMIT analysis of urine, may have included false positive toxicology results in their calculations of gestational drug use prevalence rates. Nevertheless, the rate of false negatives in these studies, due to the short window of detection inherent in urine screening, would likely be substantially higher.

Another important issue in screening for gestational cocaine use at parturition is the question of whether to analyze maternal or neonatal urine, or both. Several studies have reported puzzling discrepancies between toxicology results from maternal and neonatal urine samples (Fulroth et al., 1989; Hansen, Evans, Gillogley, Hughes, & Krener, 1992; Osterloh & Lee, 1989). For example, Fulroth et al. found that in 50% of cases in which the infant's urine tested positive

for cocaine by TLC and EMIT, the mother's urine was negative, and vice versa (it is possible that urine was screened for BE rather than cocaine hydrochloride in this study; many authors fail to make the distinction and state that the specimens were screened for "cocaine").

To improve the reliability of urine screening, urine samples from both the mother and infant should be tested, especially in clinical cases (Osterloh & Lee, 1989; Peterson, Burns, & Widmayer, 1995). Many cocaine-using mothers are likely to escape detection when only one member of the mother-infant pair is screened. Furthermore, prevalence studies typically rely on either maternal or neonatal urine analysis, not both. Prevalence rates, based on Fulroth et al.'s findings, could be as much as 50% higher if urine samples from both mothers and newborns were screened for cocaine and users were identified on the basis of one of the pair testing positive (Peterson et al., 1995).

Various theories have been proposed to explain the observed discrepancies in newborn and maternal urine assays. In cases in which the newborn tests positive and the mother tests negative, it has been suggested that recycling of amniotic fluid (that is, fetal urination deposits cocaine into the amniotic fluid, which is subsequently re-absorbed by the fetus) results in the fetus being exposed to the drug for a longer duration than the mother (Casanova et al., 1994; Dixon, 1994; Jain et al., 1993). Another explanation is based on recent evidence suggesting that the placenta is capable of binding large amounts of cocaine and BE; the subsequent release of these substances over time could prolong fetal exposure to the drug (Simone, Derewlany, Oskamp, Knie, & Koren, 1994). Either of these possibilities could result in a newborn testing cocaine-positive for some time after all traces of the drug have been excreted from the mother's body.

In addition to the cases where a mother tests negative for cocaine while her infant tests positive, it is equally common to find the reverse phenomenon; i.e., the mother tests positive for cocaine while her infant tests negative. One reason for a negative infant urine toxicology assay and concomitant positive maternal assay may be that differences in maternal and fetal metabolism result in cocaine being broken down into different drug metabolites in the mother and fetus (D. Lewis, Director of the United States Drug Testing Laboratories in Chicago, Illinois, personal communication, June 6, 1995; Kidwell, 1992). This view is supported by data suggesting the existence of several sets of fetal enzymes or isozymes that are not present in adults (Slikker & Miller, 1994). For example, a cocaine metabolite, metahydroxybenzoylecgonine (mBE), was recently detected in neonatal urine and meconium, even though BE and cocaine were absent (D. Lewis, Personal communication, June 6, 1995). Because mBE has not been found in adults, the identification of this substance in neonatal meconium implies the existence of specific enzymes which are involved in fetal, but not adult, metabolism of cocaine. Because separate EMIT assays must be run for each drug or metabolite sought, unless one is specifically looking for mBE, the EMIT assay will not detect this metabolite. Thus, false negative results may be obtained for cocaine-exposed neonates in which cocaine was metabolized to mBE.

Recent evidence suggests that cocaine-exposed premature neonates may be likely to test negative on EMIT urine screens for BE, despite recent ingestion of cocaine by the mother. Browne et al. (1992) discovered that in premature neonates the predominant molecular evidence of cocaine exposure was the presence of unmetabolized cocaine hydrochloride, rather than BE. Of six preterm infants (gestational ages 29 - 33 weeks, birthweights 790 - 1400 g), only

one was identified as cocaine-exposed by EMIT urine analysis for BE (Browne et al., 1992). However, when meconium was analyzed for both unmetabolized cocaine and BE, cocaine was detected in all six infants, but BE was not present. Although not reported in their paper, Browne et al.'s sample were very low birthweight in addition to being premature. A comparison of the birthweights and gestational ages of the sample with the Colorado intrauterine growth curves (Lubchenko, Hansman, & Boyd, 1966) reveals that these infants were at or below the 10th percentile for weight by gestational age, indicating significant intrauterine growth retardation (IUGR). Thus, it is possible that Browne et al.'s failure to detect BE was related to the IUGR of these neonates, rather than specifically to prematurity. One could speculate that the failure to detect BE reflects an inability of these fetuses to metabolize cocaine. In support of this hypothesis, a significant relation has been found recently between BE levels in neonatal meconium and cord blood levels of the catabolic enzyme pseudocholinesterase, an enzyme involved in the metabolism of cocaine (Konkol, Murphey, Ferriero, Dempsey, & Olsen, 1994). These data raise the possibility that premature infants with IUGR may be deficient in this enzyme and, if exposed to cocaine in utero, may fail to metabolize cocaine into BE. Unless neonatal toxicology screens specific for unmetabolized cocaine, rather than just BE, are carried out, a negative result may be obtained from the newborn of a mother who tests positive for cocaine use.

Thus, discrepancies between maternal and infant urine toxicology results may be a result of differences between fetal and maternal metabolism of cocaine. However, such discrepancies may also indicate that, relative to the cocaine ingested by the mother, the fetus was not exposed to detectable quantities (cf. Study 3, this dissertation). For example, it has been suggested that

in some cases the placenta may bind the cocaine, preventing it from reaching the fetus (Roe, Little, Bawdon, & Gilstrap, 1990; Simone et al., 1994). In addition, the placenta has been shown to metabolize cocaine resulting in reduced amounts reaching the fetus (Simone, Derewlany, Oskamp, & Koren, 1993). It is also possible that cocaine-induced constriction of placental vessels might result in reduced transport of cocaine to the fetus or poor drug penetration through the placenta (Bingol et al., 1987; Marques, Tippetts, & Branch, 1993; Osterloh & Lee, 1989). Thus, another explanation for discordant mother-infant toxicology results is that in some cases the placenta may protect the fetus from maternal cocaine (Koren, 1990).

In summary, urine has several advantages over other biological markers of cocaine use (Behnke & Eyler, 1994): (a) urine is relatively easy to collect, (b) drug concentrations are higher than in other body fluids, (c) frozen urine specimens can be stored for long periods of time, and (d) it is less expensive than other drug screening techniques. The primary disadvantages of urine analysis for the identification of cocaine-users are : (a) cocaine use can only be detected for one to three days following exposure, by FPI, EMIT or TLC, and a maximum of five days by RIA; (b) up to 50% of recent cocaine users may be missed unless both mother and neonate are tested, which can be costly; (c) the limited specificities of TLC, EMIT, RIA, and FPI require that positive results be confirmed using a high-specificity technique such as GC/MS or HPLC, which can also be costly; (d) positive specimens can be tampered with (e.g., diluted, contaminated with salt, or substituted with a "clean" urine sample) so as to produce a negative test result; and (e) results cannot be quantified; therefore, they provide no indication of how much drug was ingested or how often it was used. Finally, to reduce the high rate of false negatives, neonatal urine should be

screened for three different metabolites (BE, mBE, and cocaine), which can be costly. Thus, although a single urine screen is less expensive than the analysis of other biological substances, if both maternal and neonatal urine are screened, neonatal urine is screened for more than one metabolite, and positive results are confirmed by GC/MS or HPLC, it is possible that the costs associated with urine analysis may approach those of the more sensitive hair or meconium analysis procedures.

Hair Analysis. The analysis of hair for drugs and their metabolites has evolved into a viable alternative to urine testing for the identification of drug users (Baumgartner, Hill, & Bland, 1989; Baumgartner, Jones, Black, & Bland, 1982; Graham, Koren, Klein, Schneiderman, & Greenwald, 1989; Katikaneni et al., 1992; Kintz & Mangin, 1993; Klein, Forman, Eliopoulos, & Koren, 1994; Koren, 1995; Koren, Klein, Forman, & Graham, 1992; Marques, Tippetts, Scott, & Branch, 1993; Nakahara, Ochiai, & Kikura, 1992; Selavka & Rieders, 1995; Strang, 1990). Hair analysis is based on the principle that ingested drugs and metabolites are incorporated from blood and/or sweat into the hair shaft and cuticle during keratinisation (Kidwell, 1992; Ostrea & Welch, 1991; Strang, 1990). Due to the absence of metabolism in hair and its relative structural stability, drugs sequestered in the protein matrix may remain there for an indefinite period of time (Kintz & Mangin, 1993; Marques et al., 1993; Strang, 1990). Furthermore, because hair grows at the relatively uniform rate of approximately 1 cm per month (Meyers & Hamilton, 1951, as cited in Kidwell, 1992), hair has the capacity to provide information concerning an individual's drug use pattern over a period of several months (Baumgartner et al., 1982; Kintz & Mangin, 1993; Koren et al., 1992; Strang, 1990).

In the past decade, there has been an explosion of literature related to the analysis of hair for cocaine. In an examination of articles cited by a popular toxicology database (NLM-Toxline), a total of 106 papers on the analysis of hair for drugs were published between 1988 and 1993, compared to only 23 between 1981 and 1987 (Selvaka & Rieders, 1995). Furthermore, close to 50% of these articles dealt with the detection of cocaine in hair, while the others were scattered across a wide range of different substances.

The use of hair analysis for the detection of illicit drug-use is a rapidly expanding field of toxicology due to the many attractive features of this medium: (a) the amount of each drug ingested can be quantified; (b) by sectioning a length of hair into segments prior to analysis, it is possible to develop a time-line of drug exposure; (c) the collection of hair is non-invasive; (d) hair is difficult to tamper with so as to produce a negative result; and, (e) compared to body fluids, hair is more easily stored and transported. However, there are several contentious issues concerning the use of hair analysis for the identification of drug-users that have incited a torrent of social, legal, and political debates (Holden, 1990).

One of the primary difficulties with using hair analysis to detect illegal drug use is that hair can be contaminated with cocaine simply through contact with an environment where the drug is present (Holden, 1990; Kidwell, 1992; Koren et al., 1992). For example, Michael Walsh, past acting director of the NIDA division of applied research, stated that in Miami, cocaine could probably be found on every dollar bill (Holden, 1990). Theoretically, a person could handle some money, run a hand through his/her hair, and subsequently test positive for cocaine on a hair analysis test.

Although it has been claimed that all traces of external contamination are removed by the use of specific washing procedures (Koren et al., 1992), others report that extensive washing can still leave behind traces of cocaine (Bailey, 1989; Holden, 1990; Kidwell, 1992). In a study designed to assess the effectiveness of the washing procedure, Koren et al. (1992) exposed three confirmed non-cocaine users to 100 mg crack smoke in a small, unventilated room. Additionally, uncontaminated hair was placed in several 4L beakers and exposed to different levels of dense crack smoke (equivalent to between 5 and 5,000 lines of cocaine smoked in a small, unventilated room) for 60 minutes. Prior to the washing procedure, hair analyses revealed that all hair samples from the individuals exposed to crack smoke contained cocaine, and the hair exposed to the dense smoke in the beakers also contained traces of BE. However, hair analyses conducted after the hair was washed confirmed that all cocaine and BE were removed by the washing procedure.

Other attempts to differentiate between systemic (true) cocaine exposure and external contamination have focused on the presence of cocaine versus its metabolite, BE, in hair (Koren et al., 1992). Theoretically, since hair does not metabolize cocaine, external exposure should result in positive tests for cocaine, but not BE. Thus, even if all traces of external contamination could not be removed by washing, as suggested by the critics of hair analysis, the presence of BE would discriminate between true cocaine-users and non-users. (Although this theory is inconsistent with the results of the experiment in which hair exposed to crack smoke in beakers contained trace amounts of BE, Koren et al. indicate that this was an unrealistic situation [i.e. 5,000 lines of crack smoked in a small room] that would not occur outside of the laboratory setting).

In order to test the theory that externally contaminated hair would not test positive for BE, Koren et al. (1992) compared the concentrations of cocaine and BE in the hair of 10 laboratory workers who claimed to have never used cocaine and had negative urine tests, two individuals who denied cocaine use but were suspected of being in an environment where cocaine was used, and 10 cocaine addicts. Seven of the 10 non-users were found to have trace amounts of cocaine in their hair prior to washing (in the order of .05 ng/g; i.e., barely detectable); this was removed by the washing procedure. The two individuals suspected of environmental exposure had low amounts of cocaine in their hair, removed by washing, but no BE. The cocaine addicts, on the other hand, had significant amounts of cocaine and BE in their hair both before and after washing. While the washing procedure removed some cocaine from the addicts' hair (i.e., cocaine which presumably resulted from external contamination) significant amounts of BE were also removed. If BE is deposited in hair only through internal mechanisms as the authors propose, then BE should presumably not be removed by washing. The fact that BE was removed implies that, in addition to being deposited in hair through internal mechanisms, BE may be deposited in hair through external contamination. It is likely that this contamination resulted from contact of their hair with their own BE-containing bodily fluids such as sweat or saliva; however, if this is the case, then a non-drug-user who comes into contact with the bodily fluids of a cocaine user risks being mis-identified as a cocaine user through hair analysis for BE. These data imply that presence of BE in hair cannot reliably discriminate among cocaine users and individuals who were environmentally contaminated. Therefore, it is imperative that washing procedures be used prior to analyzing hair for BE.

Another mechanism by which external contamination of hair by cocaine could theoretically lead to positive tests for BE is by hydrolysis of the external cocaine molecules. Cocaine can be broken down into BE and other metabolites by hydrolysis with high pH (basic) solutions; that is, hydrolysis mimics metabolism (Kidwell, 1992). Since most shampoos are basic (typically around pH 10), regular shampooing of hair could result in hydrolysis of the cocaine contaminants into "metabolites" (Kidwell, p. 116). However, as Kidwell points out, this is just speculation and has yet to be adequately tested.

An additional problem for the proponents of hair analysis is the variation in the rate of uptake of cocaine and BE among different hair types. Kidwell (1992) compared the hair concentrations of cocaine and BE from two groups of individuals with closely matched drug use histories; one group had brown hair ($n=6$) and the other group had black hair ($n=4$). Dramatic differences were observed in the amount of cocaine detected in each hair type. For example, a black-haired individual and a brown-haired individual each used 250 mg of cocaine once; hair analysis yielded 6.4 ng/10 mg for the black hair, whereas the brown hair was below the detection limit. Similarly, a black-haired person who used 100 mg of cocaine per week had hair analysis results of 2.2 ng/10 mg, whereas a brown-haired person who ingested 250 mg per week was below the detection limit. These data suggest that cocaine may be incorporated into black hair at a higher rate than lighter-coloured hair, and thus indicate a strong potential for racial bias in the use of hair analysis for drug-screening (Holden, 1990).

Another potentially confounding factor in screening hair for cocaine is use of the drug by persons infected with a retrovirus. In a study with pregnant mice, it was found that retroviral infection led to increased serum concentrations of

cocaine, accompanied by a significant increase in the amount of drug incorporated into the hair matrix (Poet, Martinez, & Watson, 1992). Presumably, this would also result in increased drug levels in urine; however, this was not assessed by the authors. The mechanism behind the increased serum and hair drug levels in the presence of retrovirus infection is not known. However, because the human immunodeficiency virus (HIV) is a retrovirus, the hair of HIV positive individuals may also retain higher than normal levels of cocaine, potentially placing this group at risk for bias in drug screening policies.

Whereas the issue of external versus systemic exposure is of significant concern when hair analysis results are used in court cases, custody battles, employee drug screening programs, and analysis of maternal hair for evidence of gestational cocaine exposure, it does not have any serious implications for the analysis of newborn hair (Koren, 1995a; Marques et al., 1993). The issues related to differences in level of drug incorporation, depending upon the type or colour of hair, or in the presence of retrovirus infection, are also not of particular concern in newborn drug screening. The main goal in newborn hair analysis is to establish whether or not cocaine is present in order to best serve the needs of the infant and mother (Marques et al., 1993). Unfortunately, since fetal hair does not grow in sufficient quantities to permit analysis until the sixth to seventh month of gestation, detection of maternal cocaine use is limited to the third trimester of pregnancy.

The validity of newborn and/or maternal hair analysis for assessing cocaine use in pregnancy has been investigated by several researchers. For example, in a comparison of hair analysis and meconium analysis (Ostrea, Martier, Welch, & Brady, 1990), there was 96% concordance in cocaine detection between the two methods. Similarly, Callahan et al. (1992), in a study

of gestational cocaine-users identified by self-report, found the sensitivity of maternal hair analysis at delivery to be 93.5% for first trimester cocaine use and 100% for second and third trimester cocaine use. Newborn hair analysis correctly identified 78% of the infants born to self-declared cocaine-users and meconium analysis identified 74%. In contrast, urine screening identified only 38% of the newborns as cocaine-exposed.

In an attempt to quantify the degree of fetal exposure to cocaine on the basis of degree of maternal exposure, Marques et al. (1993) measured the concentration of cocaine in infant hair and a quantity of maternal hair, roughly corresponding to the last trimester of pregnancy. Subjects were 62 mothers, who reported using cocaine in the last trimester of pregnancy, and their infants. The drug concentrations in maternal and newborn hair were significantly correlated, implying that the last trimester of cocaine use by a mother is reflected in the amount of cocaine found in the hair of her infant. However, when maternal hair was damaged (i.e., due to dyes and other chemical or heat treatments), cocaine levels in the infant and maternal hair were not related. In addition, although all mothers who reported using cocaine had cocaine in their hair, there was no relation between self-report measures of frequency and quantity of use and drug levels in hair. It is likely that these results are yet another example of the poor reliability of self-report measures in yielding a detailed drug history; a dose-response relation between self-reported quantities of drug use and hair analysis results has been documented by several other researchers (e.g., Graham, Koren, Klein, Schneiderman, & Greenwald, 1989; Ostrea et al., 1990; Strang, Marsh, & Desouza, 1990).

For example, Graham, Koren et al. (1989) found that self-reported frequency of cocaine use among 16 cocaine users was highly correlated with the

concentration of BE in their hair. Furthermore, when hair was sectioned before analysis according to the timing of self-reported changes in cocaine-use patterns, these changes in cocaine-use were reflected in the BE concentrations. However, in this study, subjects were asked to classify their drug use as none, occasional, or frequent, whereas Marques et al. (1993) asked for more specific data concerning quantities of cocaine consumed. The reported differences may also be due to the fact that Graham and colleagues analyzed hair for BE whereas Marques and colleagues analyzed hair for cocaine. There is substantial variability in the cocaine to BE ratios in hair across individuals (Koren et al., 1992).

Graham, Koren et al. (1989) also analyzed the hair of seven neonates, four infants between 2.5 and 3.5 months of age, and three toddlers ranging in age from one to three years, with documented intrauterine cocaine exposure. Hair from all seven neonates was positive for BE, as was hair from two of the four infants. However, none of the three toddlers' hair contained BE. This finding suggests that by one year of age, gestational cocaine exposure may no longer be detected by infant hair analysis, and some exposed infants may lose their neonatal hair by 3.5 months of age. Thus, the usefulness of infant hair analysis for detection of cocaine exposure may be limited to the newborn period in many cases.

In summary, hair analysis is a sensitive measure for detecting cocaine use. Maternal hair has the distinct advantage over urine testing of providing estimates of the quantity and pattern of drug use over periods of up to several months. However, in adults, the issues of external contamination and differences among hair types in the uptake of cocaine have yet to be adequately resolved. Nonetheless, for the screening of newborns, hair analysis is a promising

alternative to the less reliable methods of self-report and urine analysis. The primary drawback of neonatal hair analysis is that adequate amounts of hair are often difficult to obtain due to variability in the rate of fetal hair growth. Furthermore, while maternal hair analysis can provide evidence of cocaine use over several months, neonatal hair does not begin growing in sufficient quantity for analysis until the sixth or seventh month of gestation. Thus, the detection of maternal cocaine use by the analysis of newborn hair is limited to the last trimester of pregnancy. Despite criticisms of maternal hair analysis, it remains the only procedure which can provide objective measurements of drug use over the course of the entire pregnancy.

Meconium Analysis. Meconium is a composite of metabolic waste products that collect in the fetal digestive tract during gestation. A method for identifying fetal cocaine exposure on the basis of meconium analysis was first described by Ostrea, Parks, and Brady (1988). These researchers demonstrated that maternal cocaine crossing the placenta is incorporated into fetal meconium, and that high concentrations of cocaine metabolites can be recovered from the meconium of drug-exposed neonates. It was speculated that, as in adults, cocaine was metabolized by the fetus's liver into metabolites that were then transported into the digestive tract in the bile as well as being excreted in urine.

It was also theorized that cocaine and its metabolites could accumulate in meconium through fetal swallowing of amniotic fluid contaminated with cocaine through fetal urination (Jain et al., 1993). Since swallowing begins in the fetus at about the 12th week of gestation, drugs could conceivably be deposited in meconium throughout the last two trimesters of pregnancy (Ostrea, 1992). Thus, any maternal cocaine use during this period could theoretically be detected by meconium analysis, although detection prior to the 17th week has never been

documented. Ostrea, Knapp et al. (1994) recently demonstrated the presence of cocaine in the meconium of a spontaneously aborted 17-week-old fetus. This is the earliest documented gestational age at which maternal cocaine use has been detected by meconium analysis. To date, analysis of meconium excreted by live neonates has detected cocaine use only as far back as 20 weeks gestation (D. Lewis, personal communication, June 6, 1995).

The theory that significant amounts of cocaine and its metabolites, excreted into the amniotic fluid through fetal urination, enter fetal circulation through the swallowing of amniotic fluid has recently been challenged. Mahone, Scott, Sleggs, and Woods (1994) demonstrated that when cocaine was pumped into the amniotic fluid of pregnant ewes whose fetuses had been surgically prevented from swallowing amniotic fluid, significant levels of cocaine and its metabolites were still detected in fetal plasma and meconium. Since swallowing was prevented, these results suggest that the cocaine in the amniotic fluid entered the fetus via some other route. Therefore, the presence of cocaine and its metabolites in meconium is probably not dependent on fetal swallowing, and cocaine could theoretically be detected in the meconium of cocaine-exposed fetuses at any point after meconium begins to form; i.e., at about the 12th week of gestation (Ostrea, Knapp et al., 1994).

Several studies have employed meconium analysis for the detection of gestational cocaine use (Browne et al., 1992; Callahan, et al., 1992; Maynard et al., 1991; Mirochnick, Frank, Cabral, Turner, & Zuckerman, 1995; Ostrea et al., 1989; Ostrea et al., 1990; Ostrea et al., 1992; Ostrea et al., 1993; Rosengren et al., 1993; Ryan et al., 1994). In cases where maternal hair tested positive for cocaine, the sensitivity of meconium analysis ranged from 52% using FPI and 74% using GC/MS in one study (Callahan et al.) to 96% by RIA (Ostrea et al.,

1990). The reason for the relatively low percentage of cases identified by Callahan and colleagues using FPI is not known. Since the authors do not describe the method used to prepare the meconium for analysis, it is possible that the technique employed could have accounted for the rather large percentage of false negatives; the method by which any drugs present are extracted from the meconium is critical in determining the likelihood of drug detection (D. Lewis, personal communication, June 5, 1995). The superior ability of meconium analysis to detect intrauterine cocaine-exposure over conventional drug screening methods has been confirmed by many researchers (e.g., Maynard et al., 1991; Mirochnick et al., 1995; Rosengren et al., 1993; Ryan et al., 1994). When the cocaine detection rates of meconium analysis, urine analysis, and self-report are compared in any given population of mothers and their neonates, meconium analysis invariably detects significantly more cocaine users than urine analysis or self-report, with the exception of one study (Casanova et al., 1994).

In contrast to the results of the majority of studies, Casanova et al. (1994) found meconium analysis to be no more sensitive than urine analysis in detecting cocaine use. In a sample of 30 infants born to women admitting cocaine use, 20 tested positive for cocaine when meconium was analyzed, and the same 20 were identified by newborn urine analysis. In all 20 cases, the drug had been ingested during the three weeks prior to delivery. However, of the 10 subjects testing negative, five had stopped using cocaine in the first trimester of pregnancy. As previously stated, meconium analysis is not sensitive to first trimester drug use and therefore would not be expected to yield positive results in these five cases. Another three subjects had stopped using cocaine in the second trimester; however, if cessation of cocaine use occurred before the 20th

week of gestation, it is unlikely that meconium analysis would identify these cases.

Another possible explanation for the false negative results documented by Casanova et al. (1994) lies in the technique used to prepare the meconium for analysis. The analytic procedure used in this study included diluting the meconium by a factor of five prior to the extraction phase. This significantly reduces the likelihood of detecting low concentrations of cocaine or its metabolites (D. Lewis, personal communication, June 6, 1995). Despite the authors' view that there is a lack of any advantage in using meconium analysis, the fact remains that of the 25 meconium specimens in which cocaine could theoretically be detected, 20 (80%) tested positive. Furthermore, since the frequency of cocaine use varied from one time per month to daily in this study, it is possible that the false-negative cases were those who used cocaine infrequently, and possibly in very small amounts. The 20 mothers identified as cocaine-users by both meconium analysis and urine analysis may have been daily users. With this small sample, it is unlikely that the results would generalize to the larger population of gestational cocaine users. The bulk of the evidence indicates that meconium analysis is much more sensitive than urine analysis for identifying cocaine-users, particularly those who abstained from the drug in the days preceding parturition.

One of the major limitations of meconium analysis has always been that, unlike hair, meconium could not provide any indication of the quantity or frequency of cocaine-use over the course of pregnancy. While meconium specimens collected in the neonatal period are typically pooled into a single, large sample prior to analysis, researchers have recently begun to investigate the possibility that separate analyses of each specimen excreted may provide a

time line of drug exposure. In one such study, the small and large intestines of three spontaneously aborted fetuses were sectioned and the meconium was extracted and analyzed for cocaine (Ostrea, Romero et al., 1994). The mother of one fetus with a gestational age of 22 weeks had significantly reduced her cocaine consumption over the course of her pregnancy. The changes in cocaine use were reflected in the different concentrations of cocaine found along the fetal digestive tract; i.e., the concentrations were substantially greater towards the distal end of the colon, representing more extensive use by the mother earlier in pregnancy. A second mother had stopped using cocaine when she discovered she was pregnant (the number of weeks gestation when the pregnancy was confirmed was not stated). This fetus was still-born at 33 weeks gestation due to an intestinal defect which was determined to be unrelated to the mother's cocaine use (i.e., it occurred at some point after the mother had ceased using cocaine). A small amount of cocaine was found in the meconium in the most distal part of the colon in this fetus, and no cocaine was found elsewhere along the digestive tract. These data are promising as they suggest that cocaine detected in the first meconium excreted may represent drug use early in pregnancy, while the last specimens collected represent more recent drug use. However, there are several limitations to this study. First, as the meconium in this study was obtained post-mortem, the results may not generalize to the meconium excreted from live neonates. Second, the fetuses in this study were very premature, and it is possible that the pattern of drug concentrations throughout the digestive tract may change by the 40th week of gestation. Finally, since meconium is usually collected from diapers and samples vary in size, there would be no precise way of knowing from which part of the digestive tract the excreted meconium originated. Thus, although the findings of this study have

exciting implications, further research is needed with live, full-term neonates before it is possible to determine whether or not meconium analysis is capable of yielding a time line of cocaine exposure.

Another development in meconium analysis research is that the quantity of BE found in meconium has recently been linked to the severity of IUGR (Mirochnick, Frank, Cabral, Turner, & Zuckerman, 1995). In an examination of 95 full-term infants (gestational age > 36 weeks) whose meconium tested positive for BE, the concentration of BE was negatively related to birthweight, length, and head circumference. The relation remained significant after controlling for the effects of gestational age and maternal use of marijuana, cigarettes, and alcohol. These data imply a dose-response relation between cocaine and fetal growth. Interestingly, these findings were based on a single meconium sample taken before 72 hours of age.

Although these data suggest that meconium concentrations of cocaine metabolites may be linked to neonatal outcome, it is not possible to make inferences about the extent of maternal cocaine use based on metabolite concentrations in meconium. Differences in meconium concentrations of cocaine and its metabolites across subjects may be related to individual variations in catabolic enzyme activity rather than to differences in the quantity of cocaine ingested (Konkol et al., 1994).

Additionally, in cases where there has been recent maternal cocaine use, meconium concentrations of cocaine and its metabolites may be significantly augmented through extracorporeal contamination by the infant's cocaine-containing urine (Lombardero, Casanova, Behnke, Eyler, & Bertholf, 1993). Since meconium is nearly always collected from diapers, there is a high probability of extracorporeal urine contamination. In this situation, meconium

samples containing BE or cocaine may reflect recent use of cocaine, rather than the accumulation of drug over time. Since there are numerous reports of pregnant women purchasing cocaine on the erroneous belief that it will shorten their labour (Dombrowski et al., 1991) and "enhance the thrill of delivery" (Skolnick, 1990, p. 306), one cannot assume that a positive result from the analysis of urine-contaminated meconium indicates that the woman used cocaine at other times during her pregnancy. (The belief that cocaine shortens labour has been discredited [Dombrowski et al., 1991; Webheh, Matthews, McCalla, Feldman, & Minkoff, 1995]).

In summary, meconium analysis is a relatively sensitive method for assessing prenatal cocaine exposure beyond the first trimester. Rates of detection are far greater than those of urine analysis and/or self-report, but somewhat lower than those of hair analysis. Meconium is easily collected from diapers and is, therefore, the least invasive of the methods using newborn bodily substances. The primary drawbacks of meconium analysis are that drug-use in the first trimester of pregnancy cannot be detected, and the extraction and analysis of drugs embedded in meconium require expensive equipment and considerable expertise.

Important Issues in the Identification of Gestational Cocaine Use

The validity of any study on the effects of gestational cocaine use ultimately depends, at least in part, on the subject identification methods used. The results of studies relying on urine screening or self-report are of questionable validity. By relying on these measures, there is a substantial probability of including cocaine-users in a "non-cocaine-using" control group, especially when one considers the relatively high prevalence of cocaine use (Graham, Koren et al., 1989). For example, when the sensitivities of four

different subject identification techniques (prenatal or postnatal urine and two forms of self-report) were compared, it was discovered that relying on one method alone would have led to 52% of the drug-exposed sample being misclassified as "controls" (Bergin & Cameron, 1995). According to Bergin and Cameron, " If our sample is typical, half of the 'comparison' infants in similar studies (i.e.; those relying on only one of these four procedures) are actually 'drug-exposed', explaining why research on perinatal consequences of cocaine and other drugs shows inconsistency or insignificance" (p. 296, text in parentheses added).

The implications of subject misclassification are serious. For example, one study assessing the risk of sudden infant death syndrome (SIDS) found no increased risk in a population of 175 cocaine-exposed infants, compared to 821 controls. All subjects were identified through maternal self-report and urine analysis (Bauchner et al., 1988). However, the incidence of SIDS in both groups was very low: one cocaine-exposed infant and four control infants died of SIDS. Given the very low incidence, if only two of the control infants who died of SIDS had been misclassified as non-cocaine-exposed due to maternal denial of drug use and negative urine assays, then maternal cocaine use would be a significant risk factor for SIDS (Graham, Koren et al., 1989). Thus, misclassification may be especially problematic when the incidence of the effect being studied is low. In addition, if the true incidence of an adverse pregnancy outcome is similar for cocaine-exposed and non-exposed infants (i.e., the null hypothesis is true), the probability of erroneously reporting a higher incidence in the cocaine-exposed group is increased if healthy cocaine-exposed infants are mis-classified as controls. For example, in a study of perinatal complications associated with prenatal cocaine use, Spence, Williams, DiGregorio, Kirby-McDonald, &

Polansky (1991) included 18 women, of a total sample of 411, with negative urine screens but self-reported gestational cocaine use in the control group; i.e., a positive urine test was the only criterion for inclusion in the experimental group and a negative urine test was the only criterion for inclusion in the control group. It was not reported whether these 18 women differed in any way from the other 63 cocaine-users, identified by positive urine analyses, in terms of obstetrical outcome. These authors reported a number of adverse pregnancy outcomes associated with prenatal cocaine use. However, if these 18 cocaine-exposed "control" subjects did not experience obstetrical complications, the significance of any complications observed in the cocaine-exposed group would be increased, presumably above "true" significance levels, since it is generally assumed that a mother would not report gestational cocaine use unless she had actually used the drug. Thus, the results of this study, and others with similar questionable subject classification procedures, may be misleading.

Another possible source of error in studies employing self-report is that, given the incentives for participation in some studies, non-users of cocaine may untruthfully report that they used the drug in pregnancy and be erroneously placed in the cocaine-using group. While at first glance such deception seems very unlikely given the potential legal consequences of gestational cocaine-use, there is a relatively strong argument in support of this possibility. First, subjects are often paid for their participation, and self-reported cocaine use almost guarantees inclusion in the study. Receiving financial compensation for responding to interviews and allowing someone to measure their babies may be very attractive to some women. Although this would likely occur only in studies where there is a differential payment schedule for experimental and control subjects, it could also happen in cases where an abundance of control subjects

is available and researchers are specifically attempting to recruit cocaine-using subjects. Second, the cocaine-using subjects in most studies are largely minority-group, inner-city women living in poverty, who have limited access to special services to aid them in coping with the hardships associated with their social status (Coles, 1992; Frank et al., 1988; Freier, 1994; Ostrea et al., 1992). Since many studies incorporate active educational, treatment, and follow-up services into their programs, along with free counselling, prenatal care, and delivery of the infant (e.g., Chasnoff, Burns et al., 1987; Frank et al., 1988; MacGregor et al., 1987; Marques et al., 1993; Mayes et al., 1993), non-drug-using women may be lured into admitting to a non-existent drug problem by the attractive features of these programs. Finally, in some states (e.g., Massachusetts) subjects participating in substance abuse research are protected from criminal prosecution by a writ of confidentiality obtained under Title 42 of US Code Section 242A (Frank et al., 1988). If such legal guarantees of confidentiality are offered by the researchers, there are few negative consequences associated with misrepresenting oneself as a cocaine-user.

Briere (1992) has reviewed several methods for increasing the validity of self-reports in situations where over-reporting is a concern (in his case, sexual abuse histories). One of his recommendations is that researchers should attempt to decrease rewards for providing false information (e.g., avoid the use of providing differential payment or special services when recruiting subjects for experimental versus control groups).

Based on the supposition that inclusion of non-cocaine-using women in the experimental groups is possible in any study classifying subjects on the basis of self-report, and that minority/poverty groups are likely to be over-represented among these "false positives", the finding of cocaine-related effects may be

confounded by the variables associated with poverty and minority group status in these studies. Furthermore, if maternal cocaine use results in adverse outcomes, the inclusion of non-users in the experimental group reduces the likelihood of detecting the negative consequences of cocaine use. Therefore, one must exercise caution in interpreting the results of such studies.

There are a number of steps researchers can take to improve the validity of studies assessing the effects of intrauterine cocaine exposure. First, rigorous experimental designs should include more than one measure for identifying subjects, and at least one of these should be a sensitive measure reflecting cocaine-use at times other than just prior to drug screening, such as meconium or hair analysis. This is especially important for research in which subject follow-up is planned; the validity of longitudinal studies assessing the long-term effects of prenatal cocaine-exposure is to a large extent dependent upon the group identification methods employed during the perinatal period. Second, since cocaine use is often associated with the abuse of other substances, primarily tobacco, alcohol, and marijuana, but also opiates, phenylcyclidine, and amphetamines (Bouknight, 1990; Edmondson & Smith, 1994; Snodgrass, 1994; Struthers & Hansen, 1992), screening measures should be aimed at detecting poly-drug use rather than focusing specifically on cocaine. Third, the potentially confounding effects of poly-drug use and demographic variables should be controlled, preferably through careful matching of experimental and control group subjects along these various dimensions. When control and experimental groups are not matched, the question remains as to whether gestational cocaine use is antecedent to the effects seen in the cocaine-exposed infants, or whether other variables (such as polydrug abuse or demographic factors) are responsible for the overlap between cocaine use during pregnancy and observed effects in the

infant. Some researchers have chosen to use statistical methods to control for the possible mediating effects of such third variables. However, Brier and Elliot (1993) have questioned the validity of such statistical control techniques, cautioning that such analyses are often misleading in quasi-experimental research (i.e., research involving comparisons between non-randomly assigned subjects such as cocaine-using versus non-using mothers). They suggest careful matching of experimental and control subjects on all important potential third variables as an alternative far superior to statistical control procedures.

Early studies on the effects of prenatal cocaine use often lacked reliable subject identification techniques and other control procedures such as those outlined above. Consequently, the results of these studies were often inconsistent. However, as a result of these early efforts, researchers have become increasingly aware of the need for reliable subject identification techniques and rigorous control procedures, and recent clinical studies have begun to expand our knowledge of the effects of prenatal cocaine use.

Effects of Prenatal Cocaine Use

At the time the cocaine epidemic reached its peak in 1985, there was a growing awareness that large numbers of pregnant women were using the drug and many researchers began to study the effects of cocaine on the developing fetus. The number of published studies in this area cited in the Medline database has grown exponentially since the early 1980's (only 12 studies were published between 1980 and 1984 compared to 613 between 1991 and 1995). This change presumably reflects the high priority that researchers, government, and granting agencies have placed on the "cocaine baby" issue.

Given the previously reviewed variety of confounding factors which may affect the results of prenatal cocaine-exposure studies, including characteristics

of the control group, subject identification methods, and poly-drug use, it is not surprising that, to date, no clear picture of the effects of gestational cocaine use has emerged. In many cases, for every positive finding there is a contradictory negative finding. However, some findings are reported more often than others, and in general the research suggests that cocaine is a mild teratogen, although in many cases its effects may be a result of a combination of cocaine use and the constellation of factors associated with prenatal drug use. Nonetheless, cocaine may be associated with normal pregnancy outcomes more frequently than the published studies suggest. In a review of 58 abstracts submitted to the Society for Pediatric Research between 1980 and 1989, Koren and colleagues concluded that in the selection of fetal cocaine studies for presentation at the annual convention there was a "bias against the null hypothesis" (Koren, Graham, Shear, & Einarson, 1989, p. 1440). Studies reporting adverse outcomes were significantly more likely to be accepted for presentation (57%, $n=28$) than studies finding no effect of prenatal cocaine use (11%, $n=1$). Moreover, the studies finding no effects were rated as more scientifically rigorous by judges blind to whether or not they had been accepted for presentation. Rejected studies which found no adverse effects of prenatal cocaine use employed more reliable techniques to verify cocaine use, had larger sample sizes and used better methods to identify drug-free control groups and polydrug users than the studies reporting that prenatal cocaine use resulted in adverse outcomes. Thus, the effects of gestational cocaine use on pregnancy outcome may be less serious than the published literature implies.

Obstetric and Perinatal Outcome

The seven most commonly studied obstetric and perinatal outcomes in gestational cocaine-use research are preterm delivery, IUGR, abruptio

placentae, spontaneous abortion, meconium staining of the amniotic fluid (generally believed to reflect fetal distress), congenital anomalies, and decreased head circumference (an index of brain growth). The results of 27 studies, in which the incidence of at least three of these seven complications was assessed among parturient cocaine-users, are summarized in Table 3. The three most consistent findings across studies are increased risks for preterm delivery, IUGR, and reduced head circumference. Increased incidence of abruption placentae (often associated with perinatal infant death), spontaneous abortion, and meconium staining of the amniotic fluid were also more often reported than not. An increased incidence of congenital anomalies was found in eight studies, although another eight studies reported no increased risk.

The results reported were based on statistically significant differences between the pregnancy outcomes of a cocaine-exposed group, most often a group of women who reported cocaine use and/or tested positive on urine toxicology screens, and those of a comparison group, most often women who denied drug use and/or tested negative on urine screens. In some studies, pregnancy outcomes of cocaine-users were compared with those of groups of women who used other drugs (e.g., heroin, methadone, amphetamine, and marijuana). In most cases poly-drug users who used cocaine fared worse than those using cocaine only. The majority of studies suggest that cocaine is specifically associated with preterm delivery, IUGR and decreased head circumference, independent of other drug use. However, a recent study employing a case-control design in which each of 138 cocaine-exposed infants was paired with two matched controls found that once prenatal care and smoking were taken into account, identifiable differences in birth weight between cocaine-exposed and controls were no longer present; i.e., cocaine was not associated

Table 3
Results of studies assessing fetal cocaine-exposure and perinatal risk.

Authors	PD	IUGR	AP	SA	MS	CA	HC
Bateman et al. (1993)	+	+	+	+	n/a	o	+
Bingol et al. (1987) *	+	+	+	o	n/a	+	+
Burkett et al. (1990)	+	+	o	+	+	+	n/a
Chasnoff et al. (1985) *	o	o	+	+	n/a	n/a	o
Chasnoff et al. (1987) *	+	n/a	n/a	n/a	+	+	o
Chasnoff, Griffith, et al. (1989) *	+	+	+	n/a	n/a	+	+
Chasnoff, Lewis, et al. (1989) *	+	+	+	n/a	+	+	+
Cherukuri et al. (1988) *	+	+	n/a	n/a	o	o	+
Chouteau et al. (1988) *	+	+	o	n/a	n/a	n/a	n/a
Dombrowski et al. (1991)	+	+	+	n/a	n/a	n/a	n/a
Gillogley et al. (1990)	+	+	o	o	o	o	+
Hadeed & Siegel (1989)	o	+	+	+	+	o	+
Handler et al. (1991)	+	+	+	n/a	n/a	o	+
Keith et al. (1989) *	+	+	+	n/a	o	n/a	n/a
Kelley et al. (1991)	+	+	o	o	n/a	n/a	+
Little et al. (1989) *	+	+	o	n/a	+	+	+
Livesay et al. (1989)	+	+	+	n/a	+	o	+
MacGregor et al. (1987) *	+	+	o	+	o	o	n/a
MacGregor et al. (1989)	+	+	+	n/a	n/a	+	n/a
Mastrogiannis et al. (1990)	+	o	o	n/a	+	n/a	n/a
Mayes et al. (1993)	o	+	o	n/a	n/a	n/a	o
Neerhof et al. (1989)	+	+	o	n/a	n/a	o	n/a
Oro & Dixon (1987)	+	+	+	o	o	n/a	+
Singer et al. (1994)	+	+	n/a	+	n/a	n/a	n/a
Spence et al. (1991)	+	+	o	n/a	n/a	n/a	n/a
Weathers et al. (1993)	+	+	n/a	n/a	n/a	n/a	+
Zuckerman et al. (1989) *	+	+	n/a	n/a	n/a	+	+
Total finding increased risk	24	24	12	6	7	8	14
Total finding <u>no</u> increased risk	3	2	10	4	5	8	3
Total studies assessing variable	27	26	22	10	12	16	17

PD = Preterm Delivery; IUGR = Intrauterine Growth Retardation; AP = Abruptio Placentae; SA = Spontaneous Abortion; MS = Meconium Staining; CA = Congenital Anomalies; HC = Head Circumference; + = significant risk; o = no significant risk; n/a = not assessed or incidence too low to determine significance; * Studies included in a meta-analysis by Lutiger, Graham, Einarson, & Koren (1991).

with IUGR (Miller, Boudreaux, & Regan, 1995). Nonetheless, gestational cocaine use continued to be associated with abruptio placentae, vaginal bleeding, premature rupture of membranes, and meconium staining.

It was frequently noted that in cases where the increased incidence of a complication among cocaine-users was not statistically significant, the incidence across all groups was often not high enough for statistical significance to be achieved. However, the number of cases experiencing a particular negative outcome was invariably higher among cocaine-users than among non-drug-using controls. For example, the rate of congenital malformations was typically highest, although often not significantly so, in the cocaine-exposed neonates, even when compared to other drug-exposed groups (Bateman et al., 1993; Gillogley et al., 1990; Handler, Kistin, Davis, & Ferre, 1991; MacGregor et al., 1987; Neerhof et al., 1989; Zuckerman, Frank et al., 1989). The most commonly reported congenital defect among cocaine-exposed infants was malformation of the urogenital tract (Chasnoff, Burns et al., 1987; Chasnoff, Chisum, & Kaplan, 1988; Chasnoff, Lewis, Griffith, & Willey, 1989; Chavez & Mulinare, 1989; Little, Snell, Klein, & Gilstrap, 1989), followed by cardiac defects (Bingol et al., 1987; Burkett, Yasin, & Palow, 1990; Hoyme et al., 1990; Little et al., 1989), skull/brain defects (Bingol et al., 1987; Burkett et al., 1990), and limb reduction defects (Hoyme et al., 1990).

Physiological Outcome in the Neonate

Fetal cocaine-exposure has been linked to a variety of difficulties in the neonatal period, including brain hemorrhages (Kapur, Shaw, & Shepard, 1991; Singer, Yamashita et al., 1994; Spires, Gordon, Choudhuri, Maldonado, & Chan, 1989), neurologically mediated sleep disturbances (Legido, Clancy, Spitzer, & Finnegan, 1992), electroencephalographic abnormalities (Doberczak et al., 1988;

Legido et al., 1992), abnormal cardiac functioning (Frassica, Orav, Walsh, & Lipschultz, 1994; Oriol, Bennett, Rigney, & Goldberger, 1993), ocular abnormalities (Dominguez, Vila-Coro, Slopis, & Bohan, 1991; Isenberg, Spierer, & Inkelis, 1987), increased auditory brain stem transmission time (Anday, Cohen, Schwartz, & Hoffman, 1989; Cone-Wesson & Spingarn, 1993; Jupiter, 1994; Rintelmann, Simpson, Church, & Root, 1994; Salamy et al., 1990), and sleep apnea (Chasnoff, Hunt, Kletter, & Kaplan, 1989; Chen et al., 1991; Davidson Ward, Bautista, Schuetz et al., 1989). The latter may or may not be related to reports of an increased risk of SIDS among cocaine-exposed infants (Chasnoff, Hunt et al., 1989; Davidson Ward et al., 1990; Durand, Espinoza, & Nickerson, 1990).

Although the broad spectrum of hazards that have been associated with prenatal cocaine use is alarming, most of the purported risks have been disputed by other investigators. For example, an increased risk for brain hemorrhage was not found in a cohort study of 323 very low birth weight infants, of whom 86 were prenatally exposed to cocaine (Dusick et al., 1993), nor was there a higher incidence among 115 preterm, cocaine-exposed infants compared to 238 controls (McLenan, Ajayi, & Pildes, 1992). Another study found auditory brain stem transmission time to be comparable to that of controls (Carzoli, Murphy, Hammer-Knisely, & Houy, 1991), and the reported increased risk for SIDS has been challenged by Bauchner et al. (1988), Bauchner (1990), and Zuckerman & Bresnahan (1991).

Despite the long list of adverse effects attributed to prenatal cocaine use, there is no consensus as to which risks are legitimate. A meta-analysis of the 20 studies available for comparison in 1989, was carried out to help solve the controversy existing in the literature at the time. This study assessed the

cocaine-associated risks for 13 different variables, including the seven outlined in Table 2. The only significant findings, when women who used only cocaine were compared to drug-free controls, were an increased risk for genitourinary malformations and for intrauterine death (Lutiger, Graham, Einarson, & Koren, 1991). The use of other drugs in combination with cocaine was determined to also increase the risk for spontaneous abortion. However, when poly-drug users who did and did not use cocaine were compared, the only effect attributable to cocaine was an increased risk for genitourinary malformations. Overall, a medium effect size was found for the continuous variables of gestational age, birthweight, head circumference, and length, when women using cocaine, either alone or in combination with other drugs, were compared to drug-free women. However, the odds ratios for the likelihood of IUGR, low birthweight, and preterm delivery were not significantly different between women using only cocaine and drug-free women. This suggests that a variety of effects commonly attributed to cocaine may actually be caused by other confounding variables such as polydrug use.

Other investigations with cocaine-exposed neonates have focused on the potential neurochemical effects of intrauterine exposure to the drug. Given that in adults cocaine produces its effects by increasing brain levels of monoamine neurotransmitters, there has been some interest in determining if levels of these neurotransmitters are altered in cocaine-exposed neonates as compared to non-exposed controls. The first study to investigate this issue compared the mean plasma levels of epinephrine, norepinephrine, and dopamine, along with adrenoreceptor binding activity, in 20 cocaine-exposed newborns and eight controls at two months of age (Davidson Ward, Bautista, Buckley et al., 1989). Prenatal cocaine-exposure, as determined by a positive urine screen at birth,

was associated with a 2.2-fold increase in plasma norepinephrine levels. Dopamine and epinephrine levels were similar across groups, and there were no group differences in adrenoreceptor activity. The authors speculated that the elevated norepinephrine levels represented increased sympathetic tone, secondary to intrauterine cocaine-exposure. These results were replicated in a second study with a slightly larger sample size of 22 cocaine-exposed and 15 control infants (Davidson Ward et al., 1991).

A similar study examined plasma levels of norepinephrine, dopamine, and dihydroxyphenylalanine (DOPA), the catecholamine precursor, in 12 cocaine-exposed neonates and eight controls (Mirochnick, Meyer, Cole, Herren, & Zuckerman, 1991). While no group differences were observed in dopamine levels, the cocaine-exposed group had significantly higher plasma levels of DOPA, and the mean level of circulating NE was twice that of the control group once an outlier in the control group was removed. The authors speculate that catecholamine levels may be raised directly by blockade of reuptake by cocaine, or indirectly in response to stress associated with IUGR. Norepinephrine is released into the bloodstream by the adrenal medulla in response to stress, following hypothalamic activation of the sympathetic nervous system. Thus, plasma norepinephrine levels do not necessarily reflect CNS levels.

CNS levels of neurotransmitters can be inferred from cerebrospinal concentrations of neurotransmitter precursors and metabolites (Needlman, Zuckerman, Anderson, Mirochnick, & Cohen, 1993). To determine if fetal cocaine exposure resulted in abnormal neurotransmitter levels in the CNS, Needlman and colleagues examined the levels of several catecholamine precursors and metabolites in the cerebral spinal fluid of 11 cocaine-exposed and 20 control neonates undergoing lumbar puncture to rule out infection.

Cocaine-exposed infants were found to have significantly lower levels of homovanillic acid, the principle metabolite of dopamine, present in their cerebrospinal fluid relative to controls. This finding suggests reduced production of dopamine in the CNS.

Together these studies suggest that catecholamine production is altered in infants exposed to cocaine in utero. While norepinephrine levels in plasma are more likely to reflect adrenal response to stress as opposed to CNS production or metabolism of norepinephrine, the reduced levels of dopamine metabolite in cerebrospinal fluid are more convincing evidence of disturbances in CNS dopamine production among cocaine-exposed neonates. It is not known, however, whether dopamine levels throughout the CNS are affected or if reduced dopamine production is limited to specific areas of the brain. Furthermore, the consequences of reduced dopamine levels for CNS functioning in the newborn are also unknown, and, since these studies all assessed catecholamine levels in the neonatal period, it is unknown whether the differences observed between cocaine-exposed infants and controls are transient or are likely to persist. For example, recall that cocaine increases dopamine levels by blocking reuptake, and that withdrawal of cocaine results in depletion of dopamine (a rebound effect). It is possible that cocaine-exposed neonates have reduced levels of dopamine due to withdrawal of the drug and that over time, the dopamine levels will normalize. Alternatively, reduced levels of dopamine may be secondary to a deficient number of dopamine-synthesizing neurons, in which case the effects may be long-lasting.

In summary, a number of studies have linked cocaine with a variety of obstetric and neonatal complications, although the overall findings are inconclusive. However, there is mounting evidence that cocaine is a mild

teratogen that is associated with increased risk for IUGR, urogenital abnormalities, and disturbances in catecholamine production. The next section focuses on the mechanisms through which cocaine exerts its potentially teratogenic effects on the developing fetus.

Effects of Cocaine on Fetal Development

There are two principle mechanisms by which cocaine can influence fetal development (Mayes, 1994; Spear, 1995). The first, is through an indirect effect of maternal cocaine on the placental, umbilical, and fetal vasculature. In this case, developmental effects are believed to be secondary to decreased oxygen and nutrient supply resulting from catecholamine-induced constriction of blood vessels. The primary effects of such vascular constriction include decreased growth, including brain growth, and tissue death in areas where the blood supply is insufficient to supply the necessary life-sustaining factors to the growing cells. Many of the adverse outcomes associated with fetal cocaine-exposure, such as urogenital abnormalities, limb reduction deficits, and intraventricular hemorrhage, are believed to be caused by tissue infarction secondary to cocaine-induced vascular disruption (Hoyme et al., 1990; Jones, 1991; Moore, Sorg, Miller, Key, & Resnik, 1986; Woods, Plessinger, & Clark, 1987; Woods, Plessinger, Scott, & Miller, 1989). The second mechanism by which cocaine can adversely impact on fetal development is through direct effects of cocaine on the developing brain and organ systems. In this case cocaine is believed to directly interfere with such mechanisms as cell proliferation, migration, and differentiation (Rakic, 1992).

Due to ethical limitations in conducting studies on the effects of in utero cocaine-exposure on fetal development in humans and issues related to the control of confounding variables in quasi-experimental designs, most of what is known about cocaine's effects on the developing CNS has been derived from

animal studies. The issue of comparability of findings across species, particularly the question of how well rodent models can be generalized to humans, is, therefore, of concern. This issue was addressed by a 1989 workshop on the "Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity" cosponsored by the Environmental Protection Agency and the National Institute on Drug Abuse (see Spear, 1995, for a detailed description of the proceedings of this workshop). After reviewing the developmental toxicology knowledge base and comparing findings across species, the work group concluded that there was close agreement between animal and human findings for all the neurotoxic agents reviewed (Spear, 1995). Although this does not necessarily imply that the anatomic and neurobehavioural effects of cocaine on human fetal development will mirror the results of animal studies, "it would be highly atypical if good comparability across species also was not evident when assessing the developmental toxicity of cocaine" (Spear, 1995, p. 60). Thus, it is a fair assumption that the most rigorous findings of the animal studies on the developmental toxicity of cocaine will likely also apply to humans.

Effects on the Developing CNS. The CNS has the distinction of being the system in the human body most likely to be affected by developmental insult (Rodier, Cohen, & Buelke-Sam, 1994). For example, while cardiac defects represent one of the most common physical congenital anomalies, abnormalities of the CNS occur at approximately 20 times the rate of cardiac malformations. Whereas the incidence of all cardiac defects combined is approximately 6 per 1000 live births, CNS anomalies occur in approximately 10% of all births when mental retardation and learning disabilities that cannot be accounted for by postnatal environmental insult are included (Rodier et al., 1994).

There are several reasons why the developing CNS is particularly vulnerable to injury relative to other organ systems (Rodier et al., 1994). First, the CNS undergoes a prolonged period of development relative to other organ systems. Whereas the majority of other organs are completely functional in utero or shortly after birth, and continue to grow only in size, the development of the CNS evolves in an elaborate sequence of events beginning by the 4th week of gestation and continuing well past puberty (Nowakowski, 1987). The result is an increased window of opportunity for injurious influences to interfere with CNS development relative to more rapidly forming structures (Rodier et al., 1994). Second, although in many cases the CNS demonstrates remarkable plasticity, neurons do not regenerate. If a neuron is destroyed or fails to form, it is not replaced; repair capabilities are limited to other neurons compensating for the function of the lost cell. In contrast, many other organs (e.g., skin, blood, intestinal tract) are constantly regenerating new cells, and are, therefore, far more resilient to injury. Third, most body structures are made up of numerous repeating units, all performing the same basic function (e.g. kidneys, liver, skin). The result is that damage may occur to a large number of these units before the overall function of the organ is affected. On the other hand, the brain consists of a multitude of functionally specific areas. While there is evidence that some brain regions can take over the function of damaged areas, damage to a discrete area of the brain may have serious consequences relative to damage to discrete areas of other organs (Rodier et al., 1994). Damage to one area not only impairs the behaviour controlled by that specific region, but all behaviours dependent upon the intact connections of neuronal circuits running through that region (Kolb & Wishaw, 1994). For these reasons, the developing CNS is particularly vulnerable to teratogenic influences that typically spare other organ systems.

Thus, if cocaine exerts teratogenic effects on the developing fetus, it is probable that the developing CNS would be the system most likely to be affected.

There are three crucial processes that take place in the development of the CNS, beginning even before the neural tube closes: cell proliferation, cell migration, and cell differentiation (Brittis, Meiri, Dent, & Silver, 1995; Komuro & Rakic, 1992, 1993; Nowakowski, 1987; Rakic & Komuro, 1995). During cell proliferation, neuroblasts (precursors of neurons) multiply until they reach a biologically predetermined number of "young neurons" (cells that are no longer proliferating and have begun to migrate or differentiate). Since regions of the CNS where neuronal proliferation occurs are generally physically remote from the ultimate destination of the neurons produced, young neurons must travel to their previously specified final destination through neuronal migration (Rakic, 1982). Upon reaching their final destination, neuronal differentiation takes place. During this process, each cell's axon grows outwards in search of its appropriate target cell and establishes a synaptic connection with the appropriate branch of the target cell's dendritic tree, in a process known as synaptogenesis (Granger, Tekaia, Le Sourd, Rakic, & Bourgeois, 1995). Generally, many more connections are established between neurons both within and across CNS divisions than are present in the mature CNS. Thus, the final process of differentiation involves the elimination of these transient connections. This is accomplished through reorganization of the axonal and dendritic trees and through neuronal death (Blaschke, Staley, & Chun, 1996; Cowan, Fawcett, O'Leary, & Stanfield, 1984).

In humans, neuronal proliferation generally takes place in the first two to four months of gestation, followed by neuronal migration in the third to fifth months (Mayes, 1994). Neuronal differentiation begins around the sixth month of gestation and continues throughout the first several years of life (Goldman-Rakic,

1987). The processes of cell proliferation, migration, and differentiation can occur simultaneously in every division and subdivision of the CNS (Brittis et al., 1995; Nowakowski, 1987). Therefore, although neuronal proliferation, migration, and differentiation occur in sequence, the stages are not discrete; rather, they involve significant overlap between one phase and the next. However, since these processes take place in sequence, a disruption at one level may have serious consequences for the next step of the process. For example, a disturbance of cell migration typically results in young neurons travelling to the wrong destination. Because these neurons end up residing in the wrong location within the CNS, normal neuronal differentiation cannot take place; that is, displaced neurons may be unable to locate the correct target cells, and instead form connections with neurons other than those originally intended (Rakic, 1982). Abnormalities of cell location have been associated with a variety of disorders including dyslexia and some forms of schizophrenia, and with fetal exposure to a number of teratogenic agents, including ethanol (Miller, 1986; Nowakowski, 1987). If cocaine is neurotoxic to the developing fetus, neuronal proliferation, migration, and differentiation would likely be among the processes susceptible to disruption (Gressens, Kosofsky, & Evrard, 1993; Lidow, 1995).

Neurotransmitters play a key role in defining the structure of neuronal circuits in the developing CNS (Mattson, 1988). Monoamines have been shown to act as "morphogenetic signals" (Lauder, 1988, p. 365), critically influencing neuronal proliferation, migration, differentiation, and synaptogenesis. When cocaine enters fetal circulation, it readily crosses the blood-brain barrier and has been shown to accumulate in the fetal brain at concentrations up to four times as high as peak plasma levels (Wiggins et al., 1989). Since cocaine exerts its effects by altering the regulation of monoamine neurotransmitter systems,

intrauterine cocaine-exposure may ultimately affect the formation and organization of various developing brain structures in the fetus (Mayes, 1994).

Monoamines are present in the embryonic CNS during the very early stages of gestation. Norepinephrine and serotonin have been detected in human fetal peripheral sympathetic neuroblasts as early as 5 weeks gestation, and evidence suggests that by 12 weeks gestation, incompletely differentiated CNS neurons are capable of producing catecholamines (Pickel et al., 1980).

Corresponding rates of development of monoamine neurotransmitter systems have also been reported for laboratory rats (Lidov & Molliver, 1982a, b; Wallace & Lauder, 1983). Monoamine-synthesizing neuron systems develop much earlier than most other neuronal systems, and appear to play a key role in controlling the development of their target areas (Chubakov, Gromova, Konovalov, Sarkisova, & Chumasov, 1986; Lauder, 1981, 1983; Lauder & Krebs, 1978). Moreover, by 20 to 24 weeks gestation, human fetuses have well-developed dopaminergic and noradrenergic innervations in the frontal cerebral cortex (Verney, Milosevic, Alvarez, & Berger, 1993), and at an equivalent point in gestation, rhesus monkey fetuses have similar monoaminergic innervation of the entorhinal cortex, a key structure connecting the hippocampal formation with the rest of the cerebral cortex (Berger, Alvarez, & Goldman-Rakic, 1993). Thus, through its disruptive effects on the regulation of monoamine neurotransmitter systems, cocaine could ultimately affect the development of a wide range of brain structures beginning early in gestation.

Whereas concentrations of cocaine in the fetal brain are generally lower than in the maternal brain, there is evidence that concentrations of BE (the primary metabolite of cocaine) may be more than twice as high in the fetal brain as in the maternal brain (Spear, Kirstein, & Frambes, 1989). BE does not readily

penetrate the blood-brain barrier in adult animals, whereas the immature blood-brain barrier in the fetus is not resistant to penetration by BE. Because BE is known to form molecular complexes with calcium ions, and calcium ions are critically involved in the regulation of a multiplicity of neuronal functions both in adult and developing fetal brains (e.g., Komuro & Rakic, 1992, 1993; Rakic & Komuro, 1995), it is possible that the potential neuroteratogenic effects of cocaine are related in part to a disruption in calcium regulation by BE (Spear, Kirstein, & Frambes, 1989). For example, calcium has been shown to play a crucial, although indirect, role in the migration of cerebellar neurons, and ultimately is involved in controlling the rate of cell movements, the sculpting of their shape, and determination of their structural and functional identities prior to the formation of synaptic connections (Rakic & Komuro, 1995).

Developing neuronal systems have been shown to be particularly vulnerable to the teratogenic influences of drugs, such as cocaine, which interfere with the metabolism of monoamines (Lauder, 1983; Lauder, 1988). Fetal cocaine-exposure has been demonstrated to inhibit the maturation of serotonergic neurons in culture and to inhibit the normal growth of serotonergic fibres to the cerebral cortex and hippocampus in laboratory rats (Akbari, Kramer, Whitaker-Azmitia, Spear, & Azmitia, 1992). These findings are consistent with the early development of monoaminergic neurotransmitter systems in these regions (Berger et al., 1993; Verney et al., 1993). While significant recovery of serotonergic fibre innervation occurred during the first four weeks postnatally, some fibres made inappropriate synaptic connections, and fibre growth remained deficient in some areas, particularly in the hippocampus. Interestingly, when cocaine was administered to rat pups on postnatal days one to five (corresponding to third trimester exposure in humans), the result was a rapid

growth of serotonergic fibres which led to an initial increased fibre density relative to controls.

Fetal cocaine exposure has also been found to increase the density of noradrenergic fibres in the hippocampus and dopaminergic fibres in the anterior cingulate cortex and parietal cortex in 4-week old rats (Akbari & Azmitia, 1992). Cocaine-associated disruptions in the processes underlying corticogenesis in the developing fetal brain have also been demonstrated in mice (Kosofsky, Wilkins, Gressens, & Evrard, 1994). Prenatal cocaine-exposure was found to result in decrements in brain size, disturbances in glial cell distribution, thinning of axonal-dendritic bundles, and abnormal positioning of neurons. Similarly, when chick embryos were administered a single injection of cocaine, the activity of ornithine decarboxylase, a key enzyme in the regulation of brain growth and neuronal differentiation, was significantly suppressed (Beeker, Smith, and Pennington, 1992).

The only human study in which the effects of prenatal cocaine exposure on brain development were examined is a neuropathological study of infants exposed to cocaine in utero who died between one and three months of age (Kaufmann, 1990, as cited in Lidow, 1995). Histological examination of the brains of these infants revealed significant numbers of cortical cells in the white matter, suggesting abnormal migration of cortical neurons. However, since a significant number of cocaine-users also abuse other drugs that impair cerebral development such as alcohol (Miller, 1986), it is possible that the disruptions in cell migration observed in these infants were due to alcohol rather than to cocaine per se (Lidow, 1995).

To determine if the results of rodent studies generalize to primates, and to examine the effects of cocaine on the development of the primate cerebral

cortex independent of other neurotoxic substances commonly used in conjunction with cocaine by pregnant women, Lidow (1995) examined the effects of prenatal cocaine on cortical development in rhesus monkeys. Pregnant monkeys were administered cocaine twice daily for 60 days during midgestation (days 40 to 102 of a 165-day gestation), obtaining blood plasma levels of cocaine similar to those found in chronic cocaine users. The brains of their offspring were examined two months postnatally. Visual examination of the brains of the cocaine-exposed infants revealed that they were normal in appearance (i.e., there was no evidence of insult and the pattern of sulci was normal). However, histological examination revealed that, compared to the non-exposed controls, the cortices of the cocaine-exposed monkeys had a number of highly abnormal characteristics. First, cocaine-exposure significantly disrupted the laminar organization of the cerebral cortex with complete blending of the distinction between the individual layers of the cortex in some cases. Second, substantial numbers of cortical cells were discovered in the white matter and inappropriate cortical layers, implying an inability of cortical cells to reach their proper destination. Third, the overall number of cortical neurons was dramatically reduced. Fourth, cocaine had a severe effect on the glial fibres normally evident in the upper cortical layers, with practically no glial fibres observed in some cases. Since glial fibres play a crucial role in guiding migrating neurons to their final destinations, reduction of glial fibres may have been partially responsible for the disturbances in cell migration. However, Lidow points out that this problem is probably secondary to cocaine's disregulatory effect on the monoaminergic neurotransmitter systems.

In summary, the evidence from studies with chicks, rodents, non-human primates, and deceased infants converges to imply that cocaine is a

neuroteratogenic substance. Fetal exposure to cocaine appears to cause significant alterations in the lamination, neural density, and organization of the developing brain.

Effects on Neuronal Activity. In addition to neuronal development, intrauterine cocaine-exposure also appears to have detrimental effects on neuronal activity (Dow-Edwards, Freed, & Fico, 1990). When glucose utilization was used as an index of brain activity, significantly lower levels of activity were found in adult male rats prenatally exposed to cocaine than controls. The hippocampus, hypothalamic structures, motor system, and nigrostriatal pathways were particularly adversely affected, while the sensory systems were spared. In addition, a significant increase in dopamine receptor activity was observed in the substantia nigra. Although the implications of these findings are not clear, it has been suggested that the combination of decreased metabolic activity in the nigrostriatal tract and increased receptor activity in the substantia nigra are similar to the functional changes in this pathway seen in patients with Parkinson's disease, and may be related to the tremors sometimes reported in clinical descriptions of cocaine-exposed infants (e.g., Chasnoff et al., 1985).

In a study in which glucose metabolism was used as a measure of brain activity, it was found that when cocaine was administered in the first 10 days postnatally, brain glucose metabolism was not affected in male rats (Dow-Edwards, 1989). However, in female rats, postnatal cocaine-exposure significantly increased metabolism in highly dopaminergic brain regions, with concurrent increases in dopamine receptor binding activity in these areas. In a second study, prenatal cocaine administration was found to reduce brain activity in male rats (Dow-Edwards et al., 1990). Thus, while the brain activity of male rats was sensitive to the effects of cocaine administered prenatally (Dow-

Edwards et al., 1990), female rats appeared to be particularly sensitive to postnatal administration of cocaine (Dow-Edwards, 1989). Others have also reported more marked effects of cocaine on female rat behaviour compared to males (Barron & Irvine, 1995; Glick, Hinds, & Shapiro, 1984), although the implications of the male-female differences remain unclear.

Attenuation in dopamine activity associated with fetal cocaine-exposure has also been observed, and it has been suggested that reductions in dopamine functioning may be related to hyperactivity and attentional deficits in humans (Spear et al., 1989). Increases in dopamine receptor activity reported in some studies (e.g., Dow-Edwards, 1989; Dow-Edwards et al., 1990) may be a compensatory mechanism, secondary to the reductions in dopamine neuronal activity; although the true nature of the disturbance in dopaminergic functioning is likely to be far more complex (Spear, 1995). However, reductions in dopamine functioning in laboratory animals are consistent with the findings of a study with human neonates. Needleman et al. (1993) examined the concentration of dopamine metabolites in the CSF of cocaine-exposed neonates and determined that the production of dopamine by the CNS was deficient relative to controls.

Overall, a variety of disturbances in neuronal architecture and monoaminergic neurotransmitter activity in laboratory animals have been attributed to the effects of intrauterine cocaine-exposure on the developing fetal brain. Typically, these abnormalities were caused by doses of cocaine that were not high enough to have adverse effects on fetal growth or to induce obstetrical complications. These studies also suggest that the timing of cocaine exposure is critical in determining neurodevelopmental outcome, although systematic investigation of this phenomenon has not been the focus of animal studies.

Neurobehavioural Effects in Animals

An important question is whether abnormalities in brain structure resulting from fetal cocaine-exposure are associated with alterations in neurobehavioural functioning. Since dopamine has been implicated in the modulation of arousal and activity levels, and cocaine affects the metabolism of dopaminergic neurons, several studies have examined the effect of prenatal cocaine-exposure on measures of arousal and activity (Mayes, 1994). When cocaine was administered to laboratory rats during the first 10 days postnatally, a period associated with synaptogenesis in the forebrain, roughly equivalent to the third trimester of gestation in humans, the level of motor activity exhibited by the animals was generally reduced (Church, Holmes, Overbeck, Tilak, & Zajac, 1991; Dow-Edwards, 1989). Conversely, when cocaine was administered prenatally, the rat offspring tended to demonstrate increased motor activity relative to controls, although this typically occurred only at the higher doses (Barron & Irvine, 1995; Hutchings, Fico, & Dow-Edwards, 1989). Thus, the timing of administration of cocaine appears to play an important role in determining its effects on activity level.

While the majority of studies have examined post-natal behaviour, Simonik and colleagues developed a procedure which allowed fetal rats to be directly observed (Simonik, Robinson, & Smotherman, 1994a, 1994b). The technique involved submersing the maternal rat's abdomen in saline solution and surgically opening the uterus to expose the fetuses. Injection of cocaine into the fetal CNS resulted in significant increases in motor activity (Simonik et al., 1994a). Cocaine also disrupted the cyclic organization of motor activity in the fetal rat (Simonik et al., 1994b). Since cyclic motor behaviour is believed to reflect a fundamental property of the developing CNS, such cocaine-induced

early disturbances in motor regulation may be related to later disturbances in the neurobehavioural organization of motor behaviour.

Wall-climbing in the presence of an aversive stimulus is another motor behaviour which appears to be dependent upon catecholaminergic activity (Mayes, 1994). Rat pups exposed prenatally to cocaine have been observed to exhibit a significant reduction in wall-climbing behaviour in response to foot-shock relative to controls, suggesting alterations in catecholaminergic activity (Spear, Kirstein & Frambes, 1989; Spear, Kirstein, Bell, et al., 1989).

Animals prenatally exposed to cocaine also show difficulty with associative learning and retention tasks. Deficits have been observed on appetitive conditioning (Spear, Kirstein, & Frambes, 1989; Spear, Kirstein, Bell, et al., 1989), aversive conditioning (Kosofsky et al., 1994; Smith, Mattran, Kurjan, & Kurtz, 1989; Spear, Kirstein, & Frambes, 1989), and water maze tasks (Smith et al., 1989). However, others have found no effect of cocaine on paired associative learning (Barron & Irvine, 1995; Church et al., 1991).

Since cocaine is often taken in conjunction with alcohol, one study examined the effects of intrauterine cocaine and alcohol exposure, both together and independently, on activity level and passive and active avoidance behaviours in rat pups (Church et al., 1991). Interestingly, it was found that while prenatal cocaine-exposure was associated with hypoactivity, alcohol and alcohol-plus-cocaine exposure were associated with hyperactivity. No drug treatment had any effect on active or passive avoidance behaviours in this study.

In summary, there is evidence that a number of behaviours believed to be mediated by monoaminergic neurotransmitter systems are altered among animals exposed to cocaine in utero or in the first days postnatally. For some behaviours, the type of alteration observed is mediated by the timing of exposure

and the gender of the fetus. In general, motor behaviours are the most consistently affected in laboratory animals. Impairments in memory and learning have also been demonstrated, although there is inconsistency across studies. However, unlike humans, cognitive ability is a somewhat elusive concept to assess in laboratory animals.

Cognitive-Behavioural Effects in Humans

Effects on the Newborn. Studies examining the relation between intrauterine cocaine exposure and infant cognitive-behavioural outcome have been limited in both number and quality, and for the most part, have focused on behaviour during the neonatal period. The measure that has been most frequently employed in the study of newborn neurobehavioural functioning is the Neonatal Behavioural Assessment Scale (NBAS; Brazelton, 1984). This scale consists of items assessing 27 newborn behaviours and 20 reflexes, typically summarized according to seven cluster-scores: Habituation, Orientation, Motor Behaviour, Range of State, State Regulation, Autonomic Stability, and Abnormal Reflexes (Brazelton, 1984; Lester & Brazelton, 1982).

A number of studies have reported finding abnormal response patterns on the NBAS (Brazelton, 1984) among newborns prenatally exposed to cocaine (Black, Shuler, & Nair, 1993; Chasnoff, Burns, Schnoll, & Burns, 1985; Chasnoff, Burns et al., 1987; Chasnoff, Griffith, MacGregor, Dirkes, & Burns, 1989; Chasnoff, Lewis et al., 1989; Eisen et al., 1991; Griffith, Chasnoff, Dirkes, & Burns, 1988; Mayes et al., 1993; Tronick, Frank, Cabral, & Zuckerman, 1994). However, as with obstetrical outcome measures, there is considerable variation in the type and number of abnormal behaviours found, and when each behaviour cluster is individually considered, the majority of studies have found no effect of fetal cocaine-exposure on NBAS scores. The results of 16 studies in which the

NBAS was used to assess the behaviour of cocaine-exposed newborns are summarized in Table 4. These represent all NBAS studies involving cocaine-exposed newborns cited by the med-line data base as of July 1, 1995.

The most commonly reported abnormalities on the NBAS (Brazelton, 1984) among cocaine-exposed neonates are poor state regulation, abnormal reflexes, depressed scores on measures of orientation to various visual and auditory stimuli, and impaired motor ability (Chasnoff et al., 1985; Chasnoff, Griffith et al., 1989; Chasnoff, Lewis et al., 1989; Griffith et al., 1988). Deficits in orientation and ability to achieve an alert state were found in one study even when the mother used cocaine only during the first trimester (Chasnoff, Griffith, et al., 1989). Others have found adverse effects of cocaine on newborn habituation (Eisen et al., 1991; Mayes et al., 1993; Tronick et al., 1994), and increased stress behaviours among cocaine-exposed newborns, particularly abnormal reflex behaviour and autonomic instability (Eisen et al., 1991). However, when the confounding effects of obstetric complications and maternal alcohol use were statistically controlled in the latter study, only the habituation measures continued to be associated with prenatal cocaine-exposure.

Whether or not differences have been found between cocaine-exposed infants and controls on the NBAS (Brazelton, 1984) has to some degree been dependent upon the extent of control over confounding factors (Neuspiel, 1994). For example, maternal cigarette smoking represents one confounding factor that was frequently not considered. Moreover, as pointed out by Neuspiel, even among research designs that attempted to control for group differences in smoking behaviour, the method used was not always adequate. For example, several studies used a dichotomous classification system, where smoking was simply considered to be present or absent (e.g., Chasnoff et al., 1985; Neuspiel,

Table 4.

Results of Studies Using the Neonatal Behavioral Assessment Scale to Assess Neurobehavioural Functioning in Cocaine-exposed Newborns and Controls

Authors	HAB	OR	MB	RS	REG	AS	AR
Black et al. (1993)	o	o	o	o	o	+	o
Chasnoff et al. (1985)	o	+	+	n/a	+	o	+
Chasnoff et al. (1987)	o	o	o	o	+	o	o
Chasnoff, Griffith, et al. (1989)	o	+	+	+	+	o	+
Chasnoff, Lewis, et al. (1989)	o	+	+	o	+	o	o
Coles et al. (1992)	o	o	o	o	o	o	o
Eisen et al. (1991)	+	o	o	o	o	+	+
Eyler et al. (1995)	o	o	o	o	o	o	o
Griffith et al. (1988)	o	+	+	o	+	o	+
Hawley et al. (1992)	o	o	o	o	o	o	o
Mayes et al. (1993)	+	o	o	o	o	o	o
Myers et al. (1995)	o	o	o	o	o	o	o
Neuspiel et al. (1991)	o	o	o	o	o	o	o
Richardson & Day (1991)	o	o	o	o	o	o	o
Tronick et al. (1994)	+	o	o	o	+	o	o
Woods et al. (1993)	o	o	o	o	o	o	o
Total # finding an effect	3	4	4	1	6	2	4
Total # finding <u>no</u> effect	13	12	12	14	10	14	12
Total # assessing the measure	16	16	16	15	16	16	16

Hab = Habituation; OR = Orientation; MB = Motor Behaviour; RS = Range of State;
REG = Regulation of State; AS = Autonomic Stability; AR = Abnormal Reflexes.

Hamel, Hochberg, Greene, & Campbell, 1991; Woods, Eyler, Behnke, & Conlon, 1993). It is possible that deleterious effects on newborn behaviour may be more likely to occur among infants born to heavy smokers than among those born to light smokers. Two studies that did not even take into account maternal smoking reported adverse effects of prenatal cocaine-exposure on NBAS scores (Eisen et al., 1991; Mayes et al., 1993). Since maternal tobacco use has been shown to result in depressed scores on the orientation, habituation, regulation of state, motor behaviour, and reflex measures of the NBAS (Picone, Allen, Olsen, & Ferris, 1982), the results of these studies are seriously confounded by potential group differences in maternal smoking behaviour. Moreover, the most frequently reported deficit among cocaine-exposed neonates on the NBAS was impaired regulation of state, yet prenatal tobacco exposure has consistently been shown to affect regulation of state scores, with two studies finding increased irritability (Saxton, 1978; Picone et al., 1982) and two studies finding decreased irritability among smokers' infants (Fried & Makin, 1987; Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984).

In addition to maternal smoking, control over several other potentially confounding factors has been lacking in many of the studies employing the NBAS (Brazelton, 1984). Factors such as group differences in birthweight and/or gestational age (Chasnoff, Lewis, et al., 1989; Chasnoff, Griffith et al., 1989), neurological insults such as brain haemorrhages and seizures (Chasnoff, Burns et al., 1987; Chasnoff, Lewis et al., 1989; Chasnoff, Griffith, et al., 1989), and obstetric complications such as abruptio placentae and fetal distress (Chasnoff, Lewis, et al., 1989) have not been controlled. Any of these factors could potentially result in poor performance on the NBAS, seriously limiting the ability to delineate those neurobehavioural effects specific to cocaine.

Another problem with studies employing the NBAS (Brazelton, 1984) is the extent to which experimenter bias can influence scores. For example, during orientation and habituation tasks the infant is typically held by the examiner, who is aware of the particular stimulus being presented and its location (Muir & Field, 1979). Thus, it is possible for examiners to, intentionally or unintentionally, influence the infant's responses. This issue is clearly illustrated by a study using the NBAS to examine the effects of prenatal alcohol, marijuana, and tobacco exposure on newborn behaviour (Richardson, Day, & Taylor, 1989). In this study it was found that, when examiners were aware of the infants' group membership, they were the best predictor of NBAS scores. This occurred despite the extensive training and practice that examiners must undergo before becoming certified to administer the NBAS.

Although most studies using the NBAS (Brazelton, 1984) report that examiners were "blind" to infant group membership, in many cases the methods used may not have ensured total "blindness". For example, a number of studies reported that the examiners were not informed of the infants' prenatal history (Chasnoff et al., 1985; Chasnoff et al., 1987; Chasnoff, Lewis et al., 1989; Chasnoff, Griffith et al., 1989) or were unaware of the infants' urine toxicology results (Eisen et al., 1991). These precautions reduce the likelihood that an experimenter will be aware of an infant's status, but often there are other indicators of an infant's group membership which are difficult to control. Examples of instances where an infant's cocaine-exposed status may be evident include cases where: (a) a seemingly healthy, full-term infant is under observation in the intensive care nursery; (b) the infant has an obvious genitourinary malformation such as prune-belly syndrome (for example, Chasnoff, Griffith et al. (1989) reported that 9 of 52 cocaine-exposed infants in

their sample had genitourinary tract abnormalities); (c) the infant has been abandoned by the mother; or, (d) the infant's drug-exposure is discussed among hospital staff within ear-shot of the examiner. Although it is unlikely that NBAS examiners would be aware of the group membership of all infants in the study if precautions were taken to prevent this, it is possible that awareness of infant status may occur with enough frequency in some studies to bias the overall NBAS results.

Despite the general lack of control over potential confounding variables, seven of 16 studies reviewed found no effect of fetal cocaine-exposure on any of the NBAS (Brazelton, 1984) cluster-scores. Only five studies reported differences on more than two cluster-scores and these tended to be studies that reported significant group differences on important confounding variables such as neurological insults, gestational age and/or birthweight, obstetrical complications, and/or maternal cigarette consumption (Chasnoff et al., 1985; Chasnoff, Griffith et al., 1989; Chasnoff, Lewis et al., 1989; Eisen et al., 1991). The studies employing more stringent control over confounding factors have, in general, reported minimal findings (Black et al., 1993; Eyler, Behnke, Conlon, Woods, & Wobie, 1995; Hawley, Brodsky, Gianetta, & Hurt, 1992; Mayes, Granger, Frank, Schottenfeld, & Bornstein, 1993; Myers et al., 1995; Richardson & Day, 1991; Woods et al., 1993). For example, Mayes et al. (1993) found that poor habituation was the only NBAS measure related to cocaine exposure whereas state regulation problems and abnormal reflexes were associated with low birthweight. However, even these results are suspect because, like Eisen (1991) who also found effects of cocaine on habituation, Mayes et al. (1993) did not take into account maternal cigarette smoking.

The inconsistencies in the results of behavioural studies on the effects of prenatal cocaine-exposure are also likely to be at least partly due to the interaction of cocaine with other substances ingested by the mother. In all studies described above, the mother used at least one other substance during pregnancy, most often alcohol, tobacco, and/or marijuana, but occasionally opiates and other street drugs. In a comparison of infants born to mothers who used primarily cocaine, and not opiates, with infants born to mothers who used both cocaine and methadone, Chasnoff et al. (1985) found that whereas the cocaine-only group had significant deficits in auditory and visual orientation, the cocaine-methadone group had normal scores. Although, as the authors point out, the results may reflect a Type II error, they also raise the possibility of an antagonistic drug interaction in which the effects of a CNS depressant (methadone) modified the effects of a CNS stimulant (cocaine). Thus, the extent of control over the use of other substances by mothers in the sample is an important consideration in judging the validity of the outcome of any study examining the effects of prenatal cocaine-exposure on infant behaviour.

Measures other than the NBAS (Brazelton, 1984) have also been used to distinguish between the direct effects of fetal cocaine exposure and secondary effects, such as IUGR. Based on an examination of the effects of fetal cocaine exposure on newborn acoustical cry characteristics, Lester et al. (1991), posited the existence of two distinct neurobehavioural syndromes: excitable and depressed. In an analysis of the cries of 80 cocaine-exposed infants and 80 controls, it was found that excitable cry characteristics seemed to be a direct result of cocaine-exposure, whereas depressed cry characteristics appeared to be related to the indirect effects of cocaine-exposure secondary to IUGR. However, in a second study in which the acoustical cry characteristics of 404

cocaine-exposed newborns were compared with those of 373 controls, fetal cocaine-exposure was found to be associated with cry patterns indicative of a pattern of underaroused neurobehavioural functioning (Corwin et al., 1992). Although cocaine-exposed newborns were of significantly lower birthweight and head-circumference, the differences in cry characteristics persisted when the effects of these variables were statistically controlled. The authors suggest that the observed differences in neurobehavioural functioning represent CNS injury.

Overall, the results of these studies suggest that fetal cocaine-exposure may result in some abnormal behavioural responses during the newborn period, particularly when cocaine is used in conjunction with other substances. Difficulty in maintaining appropriate arousal levels is the most commonly reported disturbance, and this in turn may influence performance on orientation and habituation measures. However, many studies have found no effect of prenatal cocaine-exposure on newborn behaviour as measured by the NBAS. Despite the suggestions in the animal literature that cocaine disrupts fetal brain development, there have been no consistently reported adverse effects of gestational cocaine use on newborn neurobehavioural functioning, as measured by the NBAS, when adequate control has been exercised over potentially confounding factors. However, it is possible that the NBAS is not sufficiently sensitive to detect the neurobehavioural effects of cocaine.

Of the various subtests of the NBAS (Brazelton, 1984), the orientation and habituation cluster scores appear at face value to be the most reflective of early information processing ability. However, it is questionable whether the simple orientation and habituation measures of the NBAS are sufficiently complex to tap into true cerebral processing of information. More sophisticated procedures for assessing newborn information processing are available in which controlled

conditions reduce experimenter bias, a serious limitation of the NBAS, and assess recovery to novelty following orientation and habituation. Recovery to novelty appears to involve more complex processing than simple orientation and habituation, and future research using these techniques may resolve the controversy over the effects of fetal cocaine exposure on infant cognitive ability. Procedures for assessing infant information processing ability will be discussed in more detail in Chapter 2.

Effects Beyond the Neonatal Period. Relative to the number of studies examining the effects of intrauterine cocaine-exposure in the newborn period, few published studies currently exist on the long-term outcome of infants exposed to cocaine in utero. This is partly because the oldest children from the newborn studies are now only seven years old, and partly because follow-up studies with this population are very difficult to conduct. The subject attrition rate is high for several reasons. First, the infants are often placed in foster care and may be moved from one foster home to another, making follow-up difficult. Second, in many jurisdictions (e.g., in Montreal, Que.), written informed consent is required from the natural mother, even if the child is in foster care. Since it is often hard to locate the mothers, consent is extremely difficult to obtain. Third, if the child is placed in the custody of the mother, these mothers often take their infants and disappear into the "underground", where contacting them is virtually impossible. Fourth, even if the mother is located, many obstacles must often be overcome before the infant can be brought into the laboratory for testing; for example, transportation must be arranged, along with care of the mother's other children. Finally, even after all the arrangements have been made, there is a good chance that the mother will not keep her appointment. Thus, while a fair

number of researchers have examined development in the newborn period, long-term follow-up studies are scarce.

Among the handful of longitudinal studies that are available, the strength of the association between fetal cocaine-exposure and child outcome is limited by the original sample selection criteria and control of confounding variables. The results of the follow-up studies recently published are generally based on samples selected in the early days of prenatal cocaine use research, when group identification methods were often of questionable sensitivity and confounding factors were frequently not considered. Thus, both positive and negative findings should be interpreted with caution.

One such longitudinal study used the Fagan Test of Infant Intelligence (FTII; Fagan & Singer, 1983) to determine the effects of prenatal cocaine exposure on visual memory in 6 and 12 month old infants (Struthers & Hansen, 1992). Thirty-six infants, prenatally exposed to cocaine and/or amphetamines, were compared with 26 controls matched on race and SES. Only 47% of the drug-exposed sample were exposed to cocaine and not amphetamines, and a number of the mothers had also used significant quantities of alcohol, marijuana, and opiates. Cigarette use was not even documented. Although attempts were made to test all infants on two occasions (at ages 6 and 12 months), a substantial number in both groups were tested only once. Overall, FTII scores were significantly lower among the drug-exposed infants relative to controls, with 17 of the 36 drug-exposed infants scoring in the "at-risk" range compared to only 3 of the 26 controls. Ten of these at-risk, drug-exposed infants had two tests, with five infants scoring in the at-risk range on the first test and five scoring in the at-risk range on the second test; i.e., no drug-exposed infant tested in the at-risk range at both ages. The authors point out that poor scores on the FTII may be

secondary to the high level of distractibility, extreme activity, and exaggerated responses to stimulation (such as movement of the screen on which the visual stimuli were projected) observed among the drug-exposed group, rather than being a true reflection of information processing ability. However, if such behaviours are due to prenatal cocaine exposure, the infants would be expected to exhibit a similar pattern of performance during both testing sessions. Furthermore, since less than half of the infants were exposed to cocaine in utero, and multiple drug use was not taken into account, it is impossible to draw conclusions from the results of this study about the effects of fetal cocaine-exposure on infant information processing ability.

Mayes, Bornstein, Chawarska, and Granger (1995) assessed the development of 61 cocaine-exposed infants and 47 controls at age three months with an information processing paradigm involving habituation-recovery-dishabituation to visual stimuli. No group differences were found on the information processing measures among those infants who completed the procedure. However, a significantly greater number of cocaine-exposed infants failed to complete the information processing procedure relative to controls due to state regulation problems. For 51% of the cocaine-exposed infants, testing had to be abandoned due to inconsolable crying, compared to 28% of the control infants. The inability of such a large number of cocaine-exposed infants to begin or complete the testing procedure was interpreted as a cocaine-related problem with the regulation of arousal. Thus, in a second study, hypothesizing that cocaine is associated with impaired regulation of arousal, and that arousal is increased in the context of novelty, the affective states of cocaine-exposed and non-exposed infants were compared in response to visual stimulation (Mayes, Bornstein, Chawarska, Haynes, & Granger, 1996). Three novel visual stimuli

(i.e., in this study, the first time a stimulus was presented it was referred to as the novel stimulus) were presented consecutively, with each remaining on the screen for as long as the infant looked at it. Following these presentations, the same stimuli were presented in sequence a second time. While the groups did not differ on the amount of time spent looking at the stimuli, the cocaine-exposed infants reacted with more negative affect to the novel stimuli than controls and negative affect decreased when the stimuli were presented a second time.

The studies by Mayes and colleagues (Mayes et al., 1995; 1996) suggest that cocaine-exposed infants have impaired regulation of arousal. However, they do not rule out the possibility that information processing ability is also impaired in cocaine-exposed infants. It is possible that in the information processing study (Mayes et al., 1995) the infants who failed to start or complete the procedure would have exhibited impairments in information processing ability had they completed the procedure; i.e., there is no way of knowing if these infants had information processing deficits in addition to impaired regulation of arousal. For example, it is possible that the same brain structures involved in the regulation of arousal are also involved in information processing in infancy; i.e., even if the infant did maintain an alert, non-agitated state for the entire procedure, information processing may still have been impaired. Thus, while regulation of arousal may be impaired in some cocaine-exposed infants, this does not supersede the possibility that information processing ability is also impaired, as suggested by Bornstein (in press) in his discussion of these studies.

While the studies by Mayes and colleagues (1995, 1996) imply that cocaine-exposed infants find novelty aversive, Karmel and Gardner (1996) found the opposite pattern – that cocaine-exposed infants preferred high intensity visual stimuli both at birth and one month of age. Karmel and colleagues

developed a paradigm in which infant arousal levels were manipulated by testing infants either immediately before or after feeding, swaddled or unswaddled and either with or without external sources of stimulation. Using these techniques, they repeatedly demonstrated that under high arousal conditions, normal infants prefer to look at low intensity stimuli, and under low arousal conditions high intensity stimuli are preferred (Karmel, Gardner, and Magnano, 1991; Gardner & Karmel, 1984; Karmel et al., 1991; Lawson & Turkewitz, 1980; Lewkowicz & Turkewitz, 1981). However, cocaine-exposed neonates and one-month-old infants preferred high intensity stimuli regardless of their arousal level (Karmel & Gardner, 1996). While these effects were less evident at four months of age (Karmel, Gardner, & Freedland, in press), the authors caution that the stimuli used at this age may have been insensitive to the effects of cocaine.

Thus, while many researchers agree that fetal cocaine-exposure has detrimental effects on the regulation of arousal, the findings are inconsistent with respect to the manner in which impaired regulation of arousal is expressed in cocaine-exposed infants. It is possible that the differences in reaction to stimulation among the cocaine-exposed infants in the studies by Mayes et al. (1995, 1996) and Karmel and colleagues (Karmel & Gardner, 1996; Karmel, Gardner, & Feedland, in press) are a result of differences in the ages of the samples, or in the procedures used.

While arousal modulation and information processing among cocaine-exposed infants have only recently begun to receive attention, several groups of researchers have used conventional tests such as the Bayley Scales of Infant Development (BSID; Bayley, 1969) to determine if prenatal cocaine-exposure has adverse effects on infant intelligence. Mayes et al. (1995), in addition to assessing visual information processing (as previously described), administered

the BSID to a group of cocaine-exposed and control infants at three months of age. On the Mental Development Index (MDI), scores were similar for both groups. Cocaine-exposed infants initially scored significantly lower on the Psychomotor Development Index (PDI); however, group differences did not persist after controlling for birthweight and length, maternal tobacco use, and prenatal care.

Graham et al. (1992) compared the BSID (Bayley, 1969) scores of thirty 18-month-old toddlers, born to mothers who described themselves as "social cocaine users", with 20 well-matched toddlers born to cannabis users and 30 drug-free controls. The mothers of the cocaine-exposed group were non-addicted cocaine users who stopped all drug use when they discovered they were pregnant, generally towards the end of the first trimester. At 18 months the BSID and the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984) were administered by examiners blind to the subjects' group membership. No group differences were found on either scale.

Similarly, when the BSID (Bayley, 1969) was administered every six months, between the ages of 6 and 24 months, to a group of cocaine-exposed infants and controls, matched for low SES and gestational age, no group differences were found at any of the four ages (Hurt, Malmud, Brodsky, and Giannetta, 1992). Kaiser et al. (1992) extended these findings to a group of premature cocaine-exposed infants who had exhibited abnormal sensorineural reactivity at birth. At ages 6 and 12 months the cocaine-exposed group did not differ from controls on BSID developmental quotients.

Chasnoff, Griffith, Freier, and Murray (1992) also found no direct effects of prenatal cocaine exposure on BSID (Bayley, 1969) scores. In this study, infants of mothers who used cocaine, often in combination with marijuana and alcohol,

were compared to a group of infants whose mothers used alcohol and marijuana but not cocaine during pregnancy, and a drug-free control group. Infants were tested at 3, 6, 12, and 24 months. All drug-using mothers had been enrolled in a comprehensive prenatal drug treatment program by the 15th week of gestation, although most continued to use cocaine throughout pregnancy. At age six months, the cocaine/polydrug group and the alcohol/marijuana group scored significantly lower than the drug-free controls on the MDI and PDI; however, the mean scores of all groups were higher than 100, the standardized mean. There were no differences between the groups at any of the other ages. A significantly greater number of cocaine-exposed infants than controls scored more than one standard deviation below the standardized mean, although this was partly due to the fact that not one control infant scored more than one standard deviation below the standardized mean. The percentages of cocaine-exposed infants scoring more than one standard deviation below the mean ranged from 5% (MDI at 3 and 6 months, PDI at 3 months) to 14% (PDI at 24 months). However, in a normal distribution, 16% of scores would be expected to fall more than one standard deviation below the mean. Thus, neither the scores of the control infants (n s ranged from 78 at 3-months to 50 at 24-months) nor the cocaine-exposed infants (n s ranged from 82 at 3-months to 29 at 24-months) were normally distributed, with abnormally low numbers of infants scoring less than one standard deviation below the mean. It seems that the control infants in particular were a select group of high-functioning infants and cocaine-exposure did not reduce scores below what would be expected in a normal distribution. Nonetheless, collapsed across groups, a significant correlation was found between head circumference and BSID scores, and cocaine-exposure was the single best predictor of decreased head circumference.

In a follow-up study by Azuma and Chasnoff (1993), these groups were assessed again at 3 years of age (approximately 50% of the subjects in each group were lost to attrition over the one-year interval and an unspecified number of these children were replaced with new subjects). On the Stanford-Binet Intelligence Scale, 4th edition (Thorndike, Hagen, & Sattler, 1986), prenatal cocaine-exposure was associated with a slight, but non-significant, decrement in cognitive development at three years of age. Whereas the mean IQ scores of all three groups were within the normal range, the two drug-exposed groups had IQ scores an average of four to five points lower than the controls. The authors attributed the differences in IQ to an interaction between environmental factors and the direct consequences of prenatal drug exposure. The drug-exposed groups also had smaller head circumferences than the controls; however, head circumference was not related to cognitive ability in this sample. In addition, maternal smoking may have been a confounding factor in this study. Although maternal smoking was not considered in the data analyses, only 20% of the control mothers smoked compared to 84% of the cocaine-using mothers and 38% of the other-drug-using mothers (in the sample at age 2 years 49%, 71%, and 54% respectively, had smoked). Thus, while the authors claim that their findings indicate that cocaine-exposure is associated with reduced cognitive ability, it is questionable whether a four point-decrement in IQ is clinically meaningful in this group of disadvantaged children whose IQ scores were in the normal range. Moreover, because maternal cigarette smoking has been associated with similar decrements in IQ (e.g., Olds, Henderson, & Tatelbaum, 1994) and maternal smoking was not controlled, cognitive deficits cannot be attributed to fetal cocaine-exposure.

While the studies available to date suggest that, overall, fetal cocaine-exposure does not adversely affect intelligence as measured by conventional intelligence tests, a number of studies have found evidence of language delays among cocaine-exposed children (Angelilli et al., 1994; Bruce & Wallace, 1994; Johnson, Rinard, Krkovich, Seikel, & Madison, 1994; Lewis, Freebairn, & Singer, 1994; Malakoff, Mayes, Schottenfeld, 1995; Nulman et al., 1994). For example, Johnson et al. (1994) administered the BSID (Bayley, 1969), the Sequenced Inventory of Communication Development (SICD; Hedrick, Prather, & Tobin, 1975) and the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn & Dunn, 1981) to a group of 20 prenatally cocaine-exposed preschoolers (the cocaine-using mothers generally used other substances in addition to cocaine), and 20 non-exposed controls. The SICD measures both expressive and receptive language ability and the PPVT-R measures receptive vocabulary. All children were tested twice over a period of 18 months, at varying ages. At the first testing, the cocaine-exposed group had significantly lower scores on the SICD and PPVT-R, but not on the BSID. By the second testing, the gap between the subjects' scores on the language measures and those expected for their age had grown wider among the cocaine-exposed children, indicating that the severity of language delay increased as the children grew older. Although the observed language impairments might be a direct result of cocaine's effects on fetal brain development, the role of environment must also be considered.

Bruce and Wallace (1994) reported similar results for expressive language delays but not receptive language, as measured by the SICD (Hedrick, et al., 1975). However, the subjects in this study consisted of only six cocaine-exposed children, and scores were compared with the standardized norms for the test. In another study, thirty-five two-year-olds with prenatal cocaine-exposure were

found to exhibit delays in both expressive and receptive language on the SICD compared to matched controls (Lewis et al., 1994). Similarly, Angelilli et al. (1994) found a history of prenatal cocaine-exposure among 21% of all language delayed pre-schoolers attending a primary-care clinic over a one-year period. Collectively, these results suggest that the conventional intelligence tests (BSID & Stanford-Binet), may not be sufficiently sensitive to detect the effects of in utero cocaine-exposure on the processes involved in language development.

One of the biggest challenges facing researchers conducting longitudinal studies with infants prenatally exposed to cocaine is differentiating between environmental effects on development and the effects of intrauterine cocaine-exposure (Brooks, Zuckerman, Bamforth, Cole, & Kaplan-Sanoff, 1994; Brown & Zuckerman, 1991; Lester & Tronick, 1994; Neuspiel, 1994). The quality of the postnatal environment can have a significant effect on the development of the drug-exposed child, with maternal responsiveness and sensitivity to the needs of the child potentially buffering the adverse effects of prenatal drug-exposure (Beckwith et al., 1994; Johnson, Glassman, Fiks, & Rosen, 1992). Many of the factors associated with maternal cocaine use can adversely influence the mother's parenting ability (Barabach, Glazer, & Norris, 1992). Impoverished environments, including deficient parenting, may exacerbate the effects of cocaine or result in negative outcomes that may be erroneously attributed to fetal cocaine exposure.

In support of the detrimental effects of adverse environmental factors on the development of cocaine-exposed infants, many researchers have documented poor attachment and impoverished interactions among cocaine-exposed infants and their mothers. For example, Tronick, Weinberg, Olson, & Zuckerman (1995) found that the face-to-face interactions of six-month-old

cocaine-exposed infants and their mothers were dominated by mutual negative affect. Cocaine-using mothers have also been found to be unresponsive to their infants' cues (Barabach et al., 1992; Zuckerman & Bresnahan, 1991), to have unrealistic expectations concerning their infants' competencies (Griffith, 1988), to be more likely to suffer from depression (Zuckerman, Amaro, Bauchner, & Cabral, 1989), and to be intolerant of their children's behaviour (Brooks et al., 1994) compared to controls. Furthermore, in cocaine-using families, money and time are often diverted away from meeting children's needs, to seeking, using, being high on, and recovering from drugs (Bays, 1990). As a result of the parenting difficulties associated with maternal drug-use, cocaine-exposed children are at risk for neglect and abuse (Kelley, Walsh, & Thompson, 1991; Zuckerman & Bresnahan, 1991).

Further compounding the difficulty in attributing any observed adverse child outcomes to fetal cocaine-exposure, independent of post-natal environmental effects, is the observation that, in addition to the effects of poverty and parental neglect, these infants may continue to be exposed to cocaine following birth. Cocaine has been ingested by infants through breast milk (e.g., Chasnoff, Lewis et al., 1987), passive inhalation of crack smoke (Mirchandani et al., 1991; Randall, 1992), and even deliberate, or accidental, administration of cocaine (Kharasch, Glotzer, Vinci, Weitzman, & Sargent, 1991; Krug, Marble, Lubitz, & Long, 1991; Rosenberg, Meert, Knazik, Yee, & Kauffman, 1991; Shannon, Lacouture, Roa, & Woolf, 1989). For example, Rosenberg et al. (1991) conducted urine tests to detect occult (i.e., hidden or not suspected) cocaine exposure in a sample of 460 children between one and 60 months of age. The children had presented at a pediatric emergency department for routine complaints (e.g., fever, abdominal pain, vomiting, diarrhea). Subjects who were

suspected of cocaine-exposure by history were excluded from the prevalence results. BE was identified in the urine of 5.4% of the children, indicating exposure to cocaine in approximately one of every 18 children under the age of five in whom cocaine-exposure was not suspected. In one coroner's report, 16 cases of infant death were associated with exposure to environments that contained crack smoke (Mirchandani et al., 1991). In all cases, toxicological post-mortem analyses revealed the presence of cocaine or BE in the blood, urine, or tissue of the infants. These studies raise the possibility that adverse outcomes among children of cocaine-using mothers may be due to postnatal cocaine exposure as well as prenatal exposure.

Given the large number of confounding variables, determining the effects of in utero cocaine-exposure on child development is a difficult and complex task. However, two recently conducted studies have attempted to meet this challenge (Malakoff et al., 1995; Nulman et al., 1994). Malakoff et al. examined language skills among a group of 21 inner-city preschool children living with cocaine-dependent mothers. Eight of these 21 children were not exposed to cocaine in utero, allowing for comparison of the effects of prenatal cocaine-exposure and environment on language development. Children were assessed using the SICD (Hedrick et al., 1975), the Peabody Picture Vocabulary Test (Dunn, 1965), and the Expressive One Word Picture Vocabulary Test (Gardner, 1979). Results indicated that 70% of the children had severe language delays, with only one child achieving scores above the 50th percentile. There was no difference in the extent of language delay between children prenatally exposed to cocaine and those who were not exposed. The single child who showed no language delay had a history of prenatal cocaine-exposure. Although these results suggest that a cocaine-using environment may be more important in

predicting child language delays than in utero cocaine-exposure, the sample size was small and comprised entirely of the children of impoverished, inner-city cocaine addicts. In this case, the detrimental effects of the environment on language development may have masked any direct effects of fetal cocaine-exposure; thus, the results may not generalize to other groups of cocaine-users.

The second study to control for environmental effects on development involved children who were exposed to cocaine in utero but adopted shortly after birth by middle to upper class families (Nulman et al., 1994). Twenty-three adopted children, ranging in age from 14 months to 6.5 years, who were exposed to cocaine in utero were compared with controls, matched for SES and IQ of the adoptive mother. General intellectual development was assessed using either the BSID (Bayley, 1969) if under 30 months of age, or the McCarthy Scales of Children's Abilities (McCarthy, 1972) if over 30 months of age. In addition, both groups were administered the Reynell Developmental Language Scales-Revised (Reynell, 1977), which assesses speech quality, output, and maturity of language. Results showed that global IQ scores tended to fall at the upper end of the Average range for the cocaine-exposed group and in the High Average range for the control group. No significant group differences in IQ were found, despite the fact that the cocaine-exposed children had significantly smaller head circumferences than the controls. However, the cocaine-exposed group had significant language delays as determined by scores on the expressive and verbal comprehension tests of the Reynell language scales. This was the first study to demonstrate adverse effects of fetal cocaine exposure on development, presumably without confounding post-natal environmental factors. However, although adopted children whose mothers had a history of heavy alcohol use during pregnancy (concomitant with cocaine use) were excluded, the

majority of cocaine-users also smoked cigarettes and consumed moderate amounts of alcohol during pregnancy, unlike the control mothers. As the authors point out, it is unlikely that a cohort of women who used solely cocaine during pregnancy will ever be available. In light of this fact, however, researchers should attempt to control for these factors using subject matching procedures if they wish to delineate any effects specific to cocaine. Determining whether observed adverse effects are directly attributable to cocaine is a worthwhile research goal considering the previously discussed social and legal consequences that are imposed on pregnant cocaine-users on the grounds that the drug damages the fetus.

In summary, although well-designed follow-up studies with children exposed to cocaine in utero are few in number, the results suggest that cocaine-exposed children have global IQs in the normal range, despite findings of persistent decrements in head circumference. However, prenatal cocaine-exposure seems to be associated with an increased incidence of both expressive and receptive language delays. Since language delays are often associated with cognitive delays (Zelazo, 1988), it is possible that cognitive deficits may become more evident as the children grow older.

Summary

Approximately one in 10 babies born in North America was exposed to cocaine in utero. If the early media reports portraying cocaine-exposed infants as severely emotionally, behaviourally, and cognitively impaired had been supported by scientific investigation, then clinicians, educators, and social service agencies would indeed have been faced with a crisis of epidemic proportions. However, the most rigorous studies of cocaine-exposed newborns have generally failed to produce consistent findings of adverse outcome.

Nevertheless, there is some evidence that cocaine-exposed fetuses may be at increased risk for urogenital abnormalities, prematurity, IUGR, and reduced head circumference.

Animal studies investigating the effects of cocaine on the developing fetal brain imply that cocaine interferes with a number of important neuronal events, including cell proliferation, migration, differentiation, and synaptogenesis. Disruption of these processes may be a result of cocaine's effects on monoaminergic neurotransmitter levels. These neurotransmitters play a crucial role in directing the processes of cell proliferation, migration, differentiation, and synaptogenesis. Furthermore, in animals, cocaine-induced disruptions in brain development are associated with abnormalities in brain activity, motor behaviour, and possibly associative learning. Although such disruptions in brain development in human infants have been identified in only one, poorly controlled neuropathology report, there is evidence that intrauterine cocaine-exposure is associated with alterations in CNS dopamine levels and plasma norepinephrine levels in newborns. Thus, the data suggest that, as in animals, human fetal brain development may also be adversely affected by cocaine.

Gross insults to the fetal brain are often reflected by abnormalities in newborn neurobehavioural functioning. The most commonly used test of neurobehavioural functioning in cocaine-exposed human neonates has been the NBAS (Brazelton, 1984). Early studies using this measure found that cocaine-exposure was associated with a variety of abnormal responses; however, there was much inconsistency in results across studies, possibly due to poor control over confounding variables and unreliable subject identification procedures. Studies in which attempts were made to control for confounding variables such as maternal poly-drug use, SES, and newborn gestational age and birthweight,

failed to find impairments on the NBAS among cocaine-exposed newborns. Maternal cigarette smoking is rarely considered in the data analyses or interpretation of the results, yet infants whose mothers smoked during pregnancy also exhibit impaired neurobehavioural functioning on the NBAS and slight decrements in childhood IQ scores. Thus, whether cocaine causes aberrations in brain development serious enough to impair neurobehavioural functioning is a matter of controversy. However, more subtle influences of cocaine on brain development may be reflected in deficits in newborn information processing – a domain of mental ability for which the validity of the NBAS is questionable.

In longitudinal studies where cocaine-exposed infants have been followed into the preschool years, cocaine-exposed children perform in the normal range on conventional measures of intelligence relative to controls matched on SES. However, studies examining language development have consistently reported language impairments in cocaine-exposed children and one study raises the possibility that these impairments may occur independent of postnatal environmental effects (although not independently of prenatal exposure to tobacco and moderate levels of alcohol). Although there is no way to verify whether or not the observed deficits in language ability are directly attributable to fetal cocaine-exposure, this argument is partially supported by the consistency of the finding across studies and the disruptive effects of cocaine on neural organization in the developing brain observed repeatedly in animal studies.

Conclusion

The goal of research into the effects of gestational cocaine-use should be the identification of those factors which are most predictive of adverse outcomes for the mother and child in order that prevention and intervention strategies can be designed. Studies which do not take into account confounding factors tend to

find adverse pregnancy outcomes, indicating that maternal cocaine use, either directly or through its association with other harmful factors, complicates pregnancy outcome. However, researchers have been unable to determine whether it is cocaine itself or the constellation of other factors associated with its use that poses the greatest risk for pregnancy outcome. This question is particularly relevant for public policy-makers. Lester & Tronick (1994) sum up the question as follows:

"We know that poverty affects development. What would be the public implications if, at the end of the second generation of research on cocaine, we learned that what we thought were drug effects are actually due to poverty and not to drugs per se?" (p. 119).

The issue is undeniably complex. For example, low birth weight and prematurity are associated with increased infant mortality and morbidity (McCormick, 1985; Petersen, Greisen, Kovacs, Munck, & Friis-Hansen, 1990; The Infant Health and Development Program, 1990); thus, any study attempting to separate the effects of confounding factors from the direct effects of cocaine must control for group differences in birth weight and gestational age, among other factors. While it is possible that prematurity and low birthweight may be mediating variables in the causal pathway between fetal cocaine-exposure and infant mortality and morbidity, it is possible that prematurity and low birthweight are due to factors other than cocaine.

Cocaine-exposed infants are not a homogeneous group; differences in metabolism, degree of placental protection, and genetic constitution undoubtedly play a significant role in determining the degree of impact of cocaine. While a number of infants may be significantly harmed by in utero cocaine-exposure, a percentage are also likely to develop unscathed. By careful control over confounding variables, and the use of measures sensitive to any potential

adverse effects of cocaine, the factors most influential in determining adverse outcome may be identified. Although it is tempting to conclude on the basis of the numerous poorly controlled studies that have been published to date, that cocaine is likely to be less important in predicting infant outcome than other factors associated with poverty, it remains possible that intrauterine cocaine exposure is a major risk factor for adverse infant and child outcome, particularly language impairments.

In recent years there has been a movement away from the study of cognitive development among infants prenatally exposed to cocaine towards a greater emphasis on the post-natal environment and poor maternal-child interactions as the primary cause of adverse developmental outcomes (Beeghly & Tronick, 1994; Freier, 1994; Lester & Tronick, 1994). Despite this trend, even though both cocaine-exposed and control children fare better when raised in healthy environments, prenatal cocaine-exposure remains the best predictor of developmental delays (Beckwith et al., 1994). The term "developmental delays" is appropriate at this point in time because it is not known if the problems observed in early childhood are transient or long-term.

The movement away from studying cognitive development has resulted partly from a lack of consistent evidence that prenatal cocaine-exposure adversely affects information processing ability assessed with the poorly controlled habituation measures of the NBAS (Brazelton, 1984). The NBAS may not be sensitive to the effects of cocaine on the developing brain and further study using more sensitive measures is warranted. For example, early maternal-child interactions may be compromised not only by a lack of appropriate parenting ability on the part of the mother, but also by deficient information processing on the part of the infant; that is, if the infant has difficulty processing

information and organizing responses to stimulation, the mother's ability to respond appropriately to the infant's cues may be further compromised (Griffith, 1988). If newborn information processing ability is found to be impaired among infants exposed to cocaine in utero, then interventions aimed at stimulating cognitive development might improve child outcome. Since cocaine appears to disrupt the processes of neuronal growth and CNS organization, and since the brain exhibits remarkable plasticity, particularly in the first few years of life, such interventions may positively influence post-natal brain development and help the child overcome the effects of disturbances in neuronal development. However, for this to occur, cognitive deficits should be identified as early as possible, ideally in the newborn period (Lester, 1988; Zelazo, 1989). Failure to identify cognitive difficulties until potential language delays become evident in the later preschool years may reduce the success of attempts to ameliorate such delays.

The next chapter focuses on the information processing procedures that have been developed over the last two decades to assess intelligence in early infancy. These measures have far greater predictive validity for childhood cognitive ability than neurobehavioural measures such as the NBAS and conventional measures of infant intelligence such as the BSID. Therefore, it is possible that such information processing measures may be valuable instruments for determining in early infancy whether or not fetal cocaine exposure compromises cognitive ability.

Chapter 2: Literature II

Assessment of Newborn Information Processing Ability

Over the past two decades as more and more premature newborns are surviving infancy, developmental psychologists have been faced with the challenge of developing valid instruments for identifying those infants at risk for developmental delay. Conventional measures for assessing infant intelligence in the first 2½ years of life, such as the BSID (Bayley, 1969), are primarily measures of sensorimotor functioning and have no predictive validity for later intelligence, at least prior to 18 to 24 months of age (McCall, 1979; McCall & Carriger, 1993). The lack of continuity in mental development from infancy to later childhood as assessed by conventional measures is partly a result of the fact that such tests invariably confound physical ability and verbal expressiveness with central processing ability (Zelazo, 1979, 1988, 1989). These tests fail to identify infants who, despite impaired sensorimotor or expressive development or serious behaviour problems, have intact cognitive functioning. For example, infants with cerebral palsy are likely to be mislabelled as cognitively impaired on the basis of depressed scores derived from conventional tests that require intact sensorimotor functioning.

Conventional tests for assessment of the newborn are even more problematic than those used with older infants. Such tests were designed to identify infants at risk and in need of intervention, and their emphasis is on assessing neurological integrity (Prechtl & Beintema, 1965) and the overall behavioural organization and physiological condition of the infant (Brazelton, 1984). Item selection was typically influenced by Gesell (1925) whose focus was on the gathering of extensive normative data on infant behavioural development

rather than on intelligence *per sé*. Gesell espoused a maturational view of development and maintained that by establishing the integrity of the infant's central nervous system one could infer normality (Zelazo, 1989). In the past decade, the NBAS (Brazelton, 1984) has been the most widely used newborn screening instrument. The NBAS is primarily a measure of overall neurobehavioural organization and functioning, although the orientation and habituation measures often are used to infer cognitive processing ability. However, the orientation and habituation scores of the NBAS have little predictive validity for concurrent or later infant scores on more robust information processing measures (Dubowitz, Dubowitz, Morante, & Verghote, 1980; Frankel, Shapira, Arbel, Shapira, & Ayal, 1982; Moss, Colombo, Mitchell, & Horowitz, 1988).

There are several limitations inherent in the NBAS (Brazelton, 1984) orientation and habituation procedures. For example, because the examiner both holds the infant and delivers the stimulus, such as shaking a rattle, it is possible for the experimenter to influence the head-turning response of the infant that reflects either orientation or habituation. In addition, visual cues may play a role in the orientating response as the rattle is shaken within the infant's peripheral visual field. Experimenter bias has been shown to have a profound impact on neonatal NBAS scores (Richardson et al., 1989).

Muir and Field (1979) made substantial improvements to the NBAS (Brazelton, 1984) orientation and habituation procedures. First, they reduced the possibility of experimenter bias. This was accomplished by preventing the experimenter from knowing the location of the sound source by tape-recording the auditory stimuli and using headphones to deliver the stimuli to both ears simultaneously. Second, visual cues to the direction of the auditory stimuli were

eliminated by presenting them to the infant through stereo speakers. Third, the method of holding the infant was modified to facilitate free movement of the head to both the left and right. Using this technique, 72-hour-old infants oriented to an auditory stimulus, turning their heads toward the sound source on an average of 74% of the eight trials presented. By using this technique, Muir and Field demonstrated that neonates were capable of orienting to auditory stimuli under highly controlled conditions.

Along with the development of well-controlled procedures for measuring newborn orientation, the phenomena of habituation to a repeated stimulus and recovery of responding to a novel stimulus were investigated as potential indices of infant cognitive ability (e.g., Adkinson & Berg, 1976; Clifton & Nelson, 1976; Fagan, 1970; McCall, Hogerty, Hamilton, & Vincent, 1973; Miranda, 1970; Pancratz & Cohen, 1970). The application of orientation-habituation-recovery paradigms to infancy research was based on the model presented by Sokolov (1963). Sokolov proposed that with repeated presentations of a stimulus, the salient features of the stimulus, including its intensity, duration, and temporal relation to other stimuli, are encoded by the cortex in the form of a neuronal model (Clifton & Nelson, 1976). The organism initially responds to the stimulus (orients) and habituates over repeated presentations as the neuronal representation of the stimulus develops. Following habituation, incoming stimuli are compared with the existing model and a mismatch results in recovery of responding. Thus, if a novel stimulus is introduced, or some aspect of the original stimulus is altered, or the stimulus is not presented for a period of time, recovery of responding occurs. Failure to habituate or recover responding, therefore, implies a breakdown in the formation of the neuronal representation of the initial stimulus, in the first case, or a failure in the discrimination process in

the latter case (Bornstein & Sigman, 1986; Cohen & Gelber, 1975; Zelazo, Weiss, Randolph, Swain, & Moore, 1987). Because Sokolov's (1963) theory implied the development of cortical representations or memory traces of a stimulus, and active comparisons between incoming stimuli and existing cortical representations, developmental psychologists investigated the constructs of orientation, habituation, and recovery to novelty as potential measures of infant information processing ability (Clifton & Nelson, 1976).

Bornstein (in press) describes an adult analog of infant habituation based on the writings of the French philosopher, Condillac, in 1780:

Condillac invited his reader to imagine arriving at a chateau at night. In the morning, the shutters of the bedchamber are opened for just an instant, permitting the visitor a glimpse at a magnificent landscape. A second glimpse, or a third, each time would yield exactly the same sense impressions as the first, the impression that the landscape would yield if the shutters were left open. Just one glimpse is *insufficient*, Condillac argued, for the visitor to become familiar with the countryside; he could hardly recount what he had seen. But successive inspections allow the visitor to sort out the major features of the view, then to distinguish and relate more and more minor features to these, and finally to embrace the landscape (p. 6).

With repeated presentations of the landscape, a mental representation would be formed. Once the landscape was fully encoded, attention to the view would likely wane. However, if the shutters were then opened to reveal a novel landscape, attention to the view would no doubt be recovered. However, in order for habituation and recovery to occur, the original view must have been encoded and a memory trace formed. Thus, failure to habituate implies that the stimulus was not fully encoded. Failure to recover to the novel stimulus implies a failure in the comparison process; i.e., the new stimulus was not recognized as being

different from the first. While the processes involved in the adult are qualitatively different from those involved in the infant (i.e., in the adult, the stimulus is likely to evoke other stored memories, verbal processes, etc.), the basic mechanisms of encoding and comparing stimuli are similar.

Using fixed trials and infant-controlled habituation procedures with both visual and auditory stimuli, researchers have repeatedly demonstrated that infants from the newborn period through 36 months of age habituate to repeated stimuli and recover attention to novel stimuli (e.g., Brody, Zelazo, & Chaika, 1984; Colombo, Mitchell, & Horowitz, 1988; McCall et al., 1973; Rose, Feldman, & Wallace, 1988; Tarquinio, Zelazo, & Weiss, 1990; Weiss, Zelazo, & Swain, 1988; Zelazo, Kearsley, & Stack, 1995; Zelazo et al., 1987; Zelazo, 1988; Zelazo, Weiss, & Tarquinio, 1991). Infant habituation and preferences for novelty became valuable tools for making predictions about the cognitive development of high-risk infants and for determining the continuity of intelligence from infancy to later childhood (Cohen, 1988; Bornstein, 1989; Bornstein & Tamis-LeMonda, 1994; Fagan, 1988; Fagan & McGrath, 1981; Fagan, Singer, Montie, & Shepherd, 1986; Lecuyer, 1989; Lewis & Brooks-Gunn, 1981, 1984; Miranda & Fantz, 1973; Rose, 1983; Rose & Wallace, 1985; Sigman, Cohen, Beckwith, Asarnow, & Parmelee, 1991; Slater, Cooper, Rose, & Morison, 1989; Sternberg, 1981; Tamis-LeMonda & Bornstein, 1993; Thompson, Fagan, & Fulker, 1991; Zelazo et al., 1989).

The development of measures for the assessment of information processing in infancy provided a great improvement over conventional measures which, without exception, confounded cognitive ability with neuromotor development. In comparison with conventional measures such as the BSID (Bayley, 1969), a recent meta-analysis revealed that assessments of habituation

and recognition memory in the first year of life have substantial predictive validity for IQ measured between 2 and 8 years of age, with a raw median correlation of .45 (McCall & Carriger, 1993). These findings confirm those of an earlier review of the literature which found similar levels of predictive validity for infant information processing measures (Bornstein & Sigman, 1986).

Visual Information Processing

The majority of studies investigating information processing in infancy have employed visual stimuli (Bornstein, 1989a, 1989b, 1990; Bornstein & Sigman, 1986; Bornstein & Tamis-LeMonda, 1994; Colombo, Mitchell, O'Brien, & Horowitz, 1986; Colombo et al., 1988; Fagan, 1970; Fagan & McGrath, 1981; Fagan & Singer, 1983; Fagan et al., 1986; Fagan & Montie, 1988; Kaplan, Werner, & Rudy, 1990; Karmel et al., 1991; Kopp, Sigman, Parmelee, & Jeffrey, 1975; Lewis & Brooks-Gunn, 1981, 1984; Mayes & Kessen, 1989; McCall & Carriger, 1993; McCall et al., 1973; Miranda, 1970; Miranda & Fantz, 1973; Moss et al., 1988; Pancratz & Cohen, 1970; Rose, 1980, 1983; Rose & Wallace, 1985; Sigman et al., 1991; Slater et al., 1989; Slater, Morrison, & Rose, 1982, 1984; Tamis-LeMonda & Bornstein, 1993; Thompson et al., 1991; Zelazo, Hopkins, Jacobson, & Kagan, 1974; Zelazo et al., 1995). With young infants, stimuli were typically geometric shapes or pictures of faces projected onto a screen facing the infant (e.g., Bornstein & Tamis-LeMonda, 1994; Colombo et al., 1986; Rose, 1980). With older infants, actual objects, moving or stationary, were often used in place of pictures (e.g., Rose, 1983; Zelazo et al., 1974; Zelazo et al., 1995).

In visual habituation paradigms, a single "look" at the stimulus is typically the unit of analysis (Bornstein, 1989a, 1989b, in press). Most infants will initially attend to the stimulus; however, with repeated presentations, looking time decreases. Infant-control procedures are often used in these procedures; i.e.,

the stimulus continues to be presented for as long as the infant looks at it. Usually, the average length of the first two or so looks is considered the baseline looking time and the criterion for habituation was defined as two or so successive looks less than or equal to one half of the baseline (Bornstein, in press). In studies of visual information processing, dependent measures included the length of the longest look, cumulative looking time, the rate of decrement in looking, the slope, number of looks to habituation criterion, and so on. Following habituation, a novel stimulus was often introduced as a control measure to ensure that habituation was not due to changes in state or arousal levels (e.g., Pancratz & Cohen, 1970). However, response to novelty received attention as an index of more complex information processing ability than habituation (e.g., Fagan, 1970; McCall et al., 1973). A number of researchers, most notably Fagan and colleagues, developed information processing paradigms based on visual habituation and preference for novelty that involved simultaneous presentations of pairs of stimuli rather than consecutive presentations of single stimuli (e.g., Fagan, 1970; Fagan & McGrath, 1981; Fagan & Singer, 1983; Fagan et al., 1986; Fagan & Montie, 1988). In the paired stimulus paradigm, two examples of the same visual stimulus are presented simultaneously side by side. Following habituation, one of the stimuli is replaced with a novel stimulus and presented simultaneously with the familiarized stimulus, with the side of presentation alternating from one trial to the next. Following repeated presentations of the familiarization stimulus, normal infants prefer to look at the novel stimulus. Novelty preference has been reliably demonstrated with infants as young as six weeks of age (Slater et al., 1982, 1984). Visual habituation and recovery to novelty are moderately predictive of intelligence in childhood, with average

correlations in the order of .45 (Bornstein & Sigman, 1986; McCall & Carriger, 1993).

Information Processing Versus Selective Receptor Adaptation

Despite the predictive validity of infant habituation-recovery measures for later intelligence, habituation studies attempting to demonstrate information processing in the first three or four months of life were criticized on the grounds that the results could be accounted for by a neuronal fatigue model (Dannemiller & Banks, 1983). This theory was presented in opposition to information processing interpretations of visual habituation and recovery in young infants, although the implications also apply to auditory information processing measures (e.g., Kisilevsky & Muir, 1993). According to the selective receptor adaptation (SRA) theory, infant habituation to repeated presentations of a stimulus occurs as a result of adaptation of a selective set of feature-specific neurons; recovery occurs because a novel stimulus excites a different set of neurons. For example, habituation to a visual stimulus was explained by the neuronal fatigue of a set of specific feature detectors in the visual striate cortex; i.e., following repeated excitation, the neuron would cease to fire in response to stimulation. Recovery to a novel stimulus was due to the excitation of a different set of feature detectors. Similarly, habituation to an auditory stimulus presumably involved the fatigue of feature-specific neurons in the auditory cortex with novel stimuli exciting different, non-fatigued neurons (Zelazo et al., 1991). However, a series of studies by Zelazo and colleagues employing auditory stimuli have provided evidence that a selective receptor adaptation (SRA) model cannot account for habituation and recovery to novelty (e.g., Swain et al., 1993; Tarquinio et al., 1990, 1991; Weiss et al., 1988; Zelazo et al., 1989; Zelazo et al., 1987).

Auditory Information Processing

In the infant-control auditory information processing procedure developed by Zelazo and colleagues, auditory stimuli are presented under the controlled conditions developed by Muir and Field (1976). An infant is presented with an auditory familiarization stimulus which is repeated every three seconds in trials of 30 seconds duration. Infant head turns toward and away from the sound source comprise the dependent measure. Normal infants exhibit an initial high level of head-turning toward the sound source when the familiarization stimulus is presented. Head-turning towards the stimulus typically declines over repeated trials and normal infants begin to turn away from the sound source after repeated presentations of the stimulus. Trials continue until the infant meets specific criteria for orientation and habituation, at which point the second phase begins and, depending upon the experiment and group assignments, a novel stimulus may be introduced. Normal infants recover responding to novelty; that is, they once again respond with a high frequency of head-turning toward the new stimulus which again declines over repeated presentations of the stimulus, culminating in head-turning away from the redundant stimulus. Following habituation to the novel stimulus, the familiarization stimulus may be re-introduced in the dishabituation phase, and again normal infants recover responding. Thus, the procedure has up to three phases depending upon the experimental design: a) familiarization, b) novelty, and c) dishabituation.

Several experiments using this procedure, among others, have provided evidence contradicting the SRA model of infant habituation and recovery to novelty. First, newborn infants have been shown to recover responding to a decrement in sound pressure level of an auditory familiarization stimulus (Tarquinio et al., 1990, 1991). An SRA model would predict that, because a

decrease in sound pressure level does not excite a different set of receptors, recovery of responding should not occur. Using a two-phase procedure (familiarization and novelty), Tarquinio et al. (1991) habituated 96 neonates (average age of 41 hours) to an auditory stimulus, the repeated phonemes "nana" or "titi" spoken by a female voice, played at either 72 or 78 dB sound pressure level (SPL). Following habituation, the infants in each group were randomly assigned to receive the same stimulus at a SPL of either 66, 72, or 78 dB. Contrary to SRA theory, the infants who heard the same stimulus at an augmented or reduced SPL recovered responding. The infants who continued to hear the stimulus at the same SPL did not recover responding. Recovery was greatest among the infants who heard a 72 dB stimulus followed by a 66 dB stimulus. These results are inconsistent with an SRA model which predicts recovery to stimuli of increased, but not decreased, intensity (Dannemiller & Banks, 1983). The fact that the groups who continued to hear the stimulus at previous SPL levels did not recover responding indicates that recovery to the decreased SPL was not due to spontaneous recovery.

Contrary to the findings of Tarquinio et al., (1991), increased responding to a novel decrement in SPL following habituation to an auditory stimulus was not found by Kisilevsky and Muir (1993). While recovery of responding was observed to an increase in stimulus intensity, a decrease in SPL did not elicit recovery. However, the two studies differed in several respects. First, the auditory stimuli used by Tarquinio et al. were speech sounds, whereas Kisilevsky and Muir used short bursts of white noise. Second, Tarquinio et al. tested the infants only when they were in a quiet, alert state, whereas Kisilevsky and Muir tested infants immediately after feeding, partially swaddled, and in the first epoch of sleep. Third, the dependent measure in the study by Tarquinio et al. was

head-turning toward the sound source, whereas Kisilevsky and Muir measured face and limb movements. Finally, the criteria for habituation to the familiarization stimulus differed in the two studies. While the findings of Kisilevsky and Muir can be explained by an SRA model, Tarquinio et al.'s data imply active processing of the stimuli and cannot be accounted for by an SRA model. The inconsistency in the results may be related to the type of auditory stimuli used, variables associated with infant state, or other procedural differences between studies. Despite the fact that the results of Kisilevsky and Muir are consistent with an SRA interpretation, there is other mounting evidence which suggests that young infants are capable of active information processing.

A second line of evidence contradicting the SRA theory is that infants can retain memory traces of habituated stimuli over periods far exceeding the refractory period of fatigued neurons (Slater & Morison, 1985).

Neurophysiological studies indicated that the neuronal refractory period is typically in the order of milliseconds (Ackles & Karrar, 1990). However, neonates can remain habituated to an auditory stimulus for up to 55 seconds (Tarquinio et al., 1991; Zelazo et al., 1987), a phenomenon which cannot be explained by the SRA model. Moreover, several studies have demonstrated that newborns retain information to which they are repeatedly exposed over periods ranging from hours to days. For example, DeCasper and Fifer (1980) showed that neonates preferred to listen to tape-recordings of their mothers' voices than to recordings of other women's voices, including newborns with little postnatal exposure to their mothers' voices. Newborns also preferred to listen to a story they had heard in utero during the last six weeks of pregnancy than a story they had not previously heard (DeCasper & Spence, 1986). These studies imply that newborns retain memory traces for auditory information to which they were

exposed prenatally. Similarly, Bushnell, McCutcheon, Sinclair, & Tweedlie (1984) demonstrated that five- and nine-week-old infants remembered aspects of visual information related to colour and form after a 24-hour delay. Following familiarization to a coloured, geometric shape, during two 15-minute sessions per day for 14 days, the infants demonstrated a reliable preference for forms of a different colour and/or shape.

The studies by DeCasper, Bushnell, and colleagues (Bushnell et al., 1984; DeCasper & Fifer, 1980; DeCasper & Spence, 1986) involved repeated familiarization with stimuli over periods of two to six weeks. However, using an habituation-recovery paradigm with two- to three-day old neonates, Swain et al. (1993) found evidence that an auditory stimulus, familiarized during one session, was partially retained over a 24-hour period. An SRA model would predict that orientation and habituation to a stimulus should occur at the same rate on the second day it is heard, regardless of exposure to the stimulus the previous day. Contrary to SRA theory, neonates who were habituated to an auditory stimulus (a spoken word) on day one, and heard the same word on day two, exhibited less recovery than neonates who heard a novel word on day two. Moreover, unlike the other group, the neonates who heard the same stimulus on day two began turning systematically away from the sound source during the first half of the procedure. Contrary to SRA theory, these data indicate that newborn infants actively encode and store auditory information and compare incoming stimulation with the stored representation. Moreover, evidence for a partial memory trace can be found 24 hours after exposure to the stimulus.

One of the most robust findings of studies employing the auditory information processing procedure developed by Zelazo and colleagues is that habituated infants do not just cease turning towards a repeated stimulus; they

actively turn away from it (Swain et al., 1993; Tarquinio et al., 1990, 1991; Weiss, 1986; Weiss et al., 1988; Zelazo et al., 1989; Zelazo et al., 1987). Turning away from a stimulus after repeated exposure implies that infants actively avoid redundant information (Zelazo et al., 1991). According to an SRA model, repeated stimulation would result in receptor fatigue and, therefore, a lack of systematic head-turning in either direction. Thus, an SRA model cannot account for the observation that infants turn away from repeated stimulation. Turning away from the stimulus implies active processing and systematic avoidance of the redundant sound.

In response to evidence refuting the SRA model summarized by Slater and Morison (1985), particularly the retention of information over delays of 24 hours, Dannemiller and Banks (1986) conceded that the SRA theory was of diminished attractiveness. However, at that time they did not consider the contradictory evidence sufficiently persuasive to abandon the SRA model in favour of information processing interpretations of infant habituation and recovery.

Validity of the Auditory Information Processing Procedure

Using auditory stimuli, Zelazo and colleagues have now provided clear evidence of active information processing in neonates less than two days old (Brody et al., 1984; Swain et al., 1993; Tarquinio et al., 1990, 1991; Weiss, 1986; Weiss et al., 1988; Zelazo et al., 1989; Zelazo et al., 1987; Zelazo et al., 1991). The data imply that newborns, like older infants, create mental representations for events, retain a memory trace, and actively compare new information with the mental representation (Bornstein & Sigman, 1986; Cohen, 1973; Zelazo, 1989).

The practical application of the neonatal information processing procedure was demonstrated when it was shown that the head turning procedure

discriminated among newborns at three levels of risk (normal, moderate and high) for subsequent delays in mental development (Zelazo et al., 1989). Differential recovery of head turning in response to a novel auditory stimulus, following orientation and habituation to the previous auditory stimulus, discriminated among groups, with the high risk group showing the poorest recovery to novelty. Furthermore, it was demonstrated that all three groups were similar in terms of head-turning ability, and maintained a high level of positive state (i.e., awake and not fretting) throughout the procedure. Moreover, in follow-up testing, neonatal head-turning toward the sound source was found to predict visual information processing at 4 months of age, with r 's ranging from .51 to .62 (Zelazo, 1989). Since information processing measures at four months have good predictive validity for later intelligence (Bornstein & Sigman, 1986; McCall & Carriger, 1993), it is likely that the newborn information processing procedure also has good predictive validity for later childhood intelligence.

Given the validity of this procedure with its sound methodology for testing predictions from information processing models, it is one of the most appropriate procedures available to determine whether fetal cocaine exposure effects development of neonatal information processing ability. Measures of information processing are better predictors of later intelligence than conventional indices (Bornstein & Sigman, 1986; McCall & Carriger, 1993) and may be more sensitive to the neurotoxic effects of fetal cocaine exposure. Furthermore, while cocaine-exposed newborns do not show deficits on the NBAS (Brazelton, 1984) measures of orientation and habituation in the better-controlled studies (e.g., Black et al., 1993; Eyler et al., 1995; Hawley et al., 1992; Myers et al., 1995), the NBAS does not include measures of recovery to novelty. Since the high-risk infants assessed by Zelazo et al. (1989) were indistinguishable from controls on

measures of orientation and habituation to the familiarization stimulus, cocaine-exposed newborns would not be expected to show deficits on the orientation and habituation measures of the NBAS. If prenatal cocaine-exposure compromises the development of neural structures on which intact information processing ability relies, recovery to novelty may be the best measure for detecting this effect.

Chapter 3: Rationale for the Current Studies

Statement of the Problem

The research presented in the following chapters was aimed at determining the impact of fetal cocaine- and tobacco-exposure on newborn information processing. Because the majority of cocaine-users also smoke cigarettes, it is necessary to evaluate the impact of maternal smoking in order to distinguish the effects of fetal cocaine-exposure from those of fetal tobacco-exposure. Previous studies on the effects of prenatal cocaine-exposure on infant cognitive development have been plagued by a number of serious problems, including insensitive measures, questionable subject identification techniques, and lack of control over potentially confounding factors. To avoid adding to the large body of contradictory reports based on less-than-optimal experimental designs, attempts were made to overcome the problems of previous studies. Thus, the following limitations of previous studies were addressed in this research: (a) inadequate subject identification techniques, (b) poor control over confounding variables, (c) lack of consideration of the effects of maternal smoking on newborn information processing independent of cocaine use, and (d) the poor validity of measures used to assess newborn information processing ability. In addition, an intriguing case study illustrates the importance of considering individual differences when assessing the risks associated with gestational cocaine use.

Subject Identification

One of the primary criticisms of studies employing unreliable subject identification procedures is that cocaine-exposed infants may be inadvertently included in the control group, and, although less likely, that control infants may

be misclassified as cocaine-exposed. In Study 1 (Chapter 4), cocaine-exposed infants were classified on the basis of meconium analysis, in addition to self-report and/or urine analysis. In order to reduce the possibility of misclassifying drug-exposed infants as controls, meconium analysis was also carried out for control infants. The introduction of meconium analysis for subject classification overcomes the primary limitation of urine analysis: the fact that the rate of false negatives is in the order of 70% due to cocaine's rapid clearance from the body (Ostrea et al., 1989). Furthermore, whereas in most studies urine samples were screened for BE only, meconium samples in the present studies were screened for cocaine and its metabolites, BE and mBE. In order to control for poly-drug use in these studies, meconium was also analyzed for the presence of cannabinoids, opiates, cotinine (a metabolite of nicotine), and cocaethylene (a compound that is formed when cocaine is taken in conjunction with alcohol).

The primary drawback of meconium analysis is that first-trimester drug use cannot be detected. At present, the only objective technique available for the detection of first trimester drug use is analysis of maternal hair. Unfortunately, the controversial issues surrounding the use of maternal hair analysis for the detection of drug use precluded the use of this technique as a measure for confirming the non-drug-exposed status of control infants. However, mothers who ceased use of cocaine during the first trimester might be more likely to report their first trimester drug use than chronic users. Because cessation of cocaine use may be associated with concern for the well-being of the infant, the mother may be anxious to know if her first-trimester drug-use could have harmed the infant; thus, she may be likely to reveal her drug-use history in order to seek information. In addition, drug-use that is stopped once the mother becomes aware of the pregnancy is not associated with the same social hostility as drug-

use throughout pregnancy, another factor which may increase the probability of truthful self-report. Furthermore, mothers were not aware that the meconium analysis they were agreeing to by signing the consent form would be unlikely to detect first trimester drug use. Finally, in Montreal, Quebec, where this study was carried out, punitive measures are limited to the protection of the infant in extreme cases by removing him or her from the mother's custody, unlike some U.S. states where the mother may face prosecution and incarceration for admitting to drug use. Thus, by analyzing the meconium of control infants in addition to seeking drug use histories through self-report, it is unlikely that cocaine-exposed infants would be inadvertently included in the control group.

In Study 2 (Chapter 5), an investigation of the effects of maternal cigarette smoking on newborn information processing ability, it was not possible to analyze meconium samples from all infants due to financial limitations. However, mothers were informed that by consenting to participate in the study, permission would be granted for newborn meconium to be analyzed for evidence of drug use during pregnancy, and meconium samples were collected wherever possible. As this is a variation of the "bogus pipeline" method which has proven to be a moderate deterrent to concealing drug use (i.e., believing that a biological marker will be used to confirm self-reports increases their accuracy), it is probable that few infants in this study were exposed to illicit drugs in utero. Infants born to mothers who admitted to use of any illicit drug during pregnancy were excluded.

Control over Confounding Variables

Potentially confounding factors were carefully controlled through subject matching procedures. Cocaine-exposed neonates and controls were matched on a number of variables including birthweight, gestational age, SES, maternal

weight gain, and maternal cigarette consumption. Furthermore, poly-drug use was not common in the sample studied, alcohol consumption was comparable across groups, and infants with obvious neurological insults were excluded from the study.

Despite attempts to match experimental and control infants on all important variables, it proved impossible to match the cocaine-exposed and control infants on the degree of prenatal care received by the mothers. To assess the impact of this variable on information processing ability, analyses were conducted in which the cocaine-exposed group with no prenatal care was compared with the group who received prenatal care.

Effects of Maternal Cigarette Smoking on Newborn Information Processing

In the majority of outcome studies finding adverse effects of fetal cocaine exposure in humans, maternal cigarette smoking has consistently confounded the results. Significantly more cocaine-users than controls smoked in most prior studies and researchers occasionally attempted to control for this factor using statistical techniques. When smoking was statistically controlled, effects associated with cocaine use often disappeared. Because control over maternal smoking behaviour was either not possible or was not considered by the researchers in many studies, the relative impact of cocaine versus tobacco exposure on infant outcome is not known.

In Study 1 (Chapter 4), cocaine-exposed and control infants were matched on maternal cigarette smoking. In Study 2 (Chapter 5), newborns exposed to various levels of tobacco smoke, but not other drugs, were compared on the information processing measures in order to assess the impact of fetal tobacco-exposure independent of cocaine-exposure.

Assessment of Newborn Information Processing Ability

Information processing was assessed using a sensitive measure previously demonstrated to discriminate among infants at high, moderate, and low risk for subsequent developmental delay (Zelazo et al., 1989). This procedure relies on newborn orientation, habituation, and recovery of responding to novelty, using auditory stimuli, in a partial infant-controlled design. Since the NBAS (Brazelton, 1984) does not include measures of recovery to novelty, and recovery of responding was previously found to be the best discriminator among infants at different levels of risk for developmental delay (Caron & Caron, 1981; Cohen, 1981; Fagan & Singer, 1983; Sigman & Parmelee, 1974; Werner & Siqueland, 1981; Zelazo et al., 1989), it was hypothesized that this measure would be more sensitive to the effects of fetal cocaine-exposure on newborn information processing ability. Moreover, the only studies attempting to assess information processing among cocaine-exposed infants have used visual stimuli (Mayes et al., 1995; Struthers & Hansen, 1992). Because there is mounting evidence that fetal cocaine-exposure is associated with childhood language impairments (Angelilli et al., 1994; Bruce & Wallace, 1994; Johnson et al., 1994; Lewis, Freebairn et al., 1994; Malakoff et al., 1995; Nulman et al., 1994), the assessment of newborn auditory information processing may be more relevant than visual processing in this population.

Individual Differences

In most studies finding adverse effects of maternal drug use on infant outcome, in which groups of drug-exposed infants are compared with non-drug-exposed controls, there are usually a number of drug-exposed infants who perform at the same level as non-exposed controls. Such individual differences are often obscured by the overall performance of the drug-exposed group as a

whole. In the first and second studies of this dissertation, the sample size did not permit a thorough analysis of individual differences in performance. However, Study 3 (Chapter 6) presents the case of one particular infant born to a cocaine addict who performed in the normal range despite the daily ingestion of large amounts of cocaine by the mother throughout pregnancy. Possible explanations and implications of such individual differences are discussed.

In summary, the studies presented in Chapters 4 and 5 represent efforts to delineate the effects of prenatal cocaine and nicotine exposure on newborn auditory information processing ability. Subjects were classified as drug-exposed or non-drug-exposed using one of the most reliable methods available to date, a multitude of potentially confounding factors were controlled by careful subject matching procedures, and valid measures of newborn information processing ability were used. An intriguing case study is presented in Chapter 6 with potential reasons for the resilience of some drug-exposed infants. A general discussion, along with conclusions, is presented in Chapter 7.

Chapter 4: Study 1

Effects of Fetal Cocaine-Exposure on Newborn Information Processing

With the increasing popularity of cocaine in North America, the number of pregnancies complicated by maternal abuse of cocaine increased substantially over the course of the 1980s (Dicker & Leighton, 1994). Studies conducted in urban hospitals showed that upwards of 10% of all newborns test positive for cocaine (e.g., Bateman et al., 1993; Matera, Warren, Moomjy, Fink, & Fox, 1990; Minkoff et al., 1990; Ostrea et al., 1992; Schutzman et al., 1991) and that cocaine appears to be the drug of choice for pregnant women (Atkins, 1988). It is known that cocaine can penetrate the placenta and accumulate in the fetal brain at concentrations up to four times greater than those observed in plasma (Wiggins et al., 1989). Furthermore, prenatal cocaine-exposure has been shown by animal studies to disrupt fetal CNS development by interfering with the processes of neuronal proliferation, migration, and differentiation (Akbari & Azmitia, 1992; Akbari, Kramer, et al., 1992; Beeker et al., 1992; Kosofsky et al., 1994; Lidow, 1995). Fetal cocaine-exposure also leads to significant alterations in brain activity among laboratory animals (Dow-Edwards, 1989; Dow-Edwards et al., 1990; Spear, 1995; Spear, Kirstein, & Frambes, 1989). On the assumption that these findings are to some extent generalizable to humans, deficits in brain functioning can be expected among newborns exposed to cocaine in utero.

Numerous studies have documented language delays among children exposed to cocaine in utero (Angelilli et al., 1994; Bruce & Wallace, 1994; Johnson et al., 1994; Lewis, Freebairn et al., 1994; Malakoff et al., 1995; Nulman et al., 1994). Although the results of an adoption study suggested that language

deficits in cocaine-exposed children are not a result of postnatal environmental influences (Nulman et al., 1994), the impact of environment on language development is likely to be an important factor in studies where cocaine-exposed infants were raised by their natural mothers. The relative contributions of intrauterine cocaine-exposure and postnatal environment are virtually impossible to discriminate in the majority of studies finding language impairments in the offspring of prenatal cocaine users. However, if impairments in language development are a result of disturbances in fetal brain development among children exposed to cocaine in utero, then such disturbances may be detectable at birth.

The purpose of this study was to determine whether deficits in the brain functioning of cocaine-exposed newborns are evident at birth, before the postnatal environment has a chance to impact on their functioning. Although cocaine-exposed newborns generally fail to show abnormalities in the organization of neurobehavioural functioning as measured by the NBAS (Brazelton, 1984), and they have been shown to have normal intelligence quotients in the preschool years when assessed by conventional measures of intelligence, such measures may not be sensitive to the subtle effects of cocaine on the integrity of brain functioning. Unlike conventional measures of infant intelligence which have virtually no predictive validity before 18 months of age (McCall, 1979), information processing measures are moderately predictive of later intelligence ($r=.45$; Bornstein & Sigman, 1986; McCall & Carriger, 1993). Moreover, Moss and colleagues demonstrated that the neonatal orientation and habituation measures of the NBAS were not related to information processing scores at 3 months of age, and replicated these findings with an independent sample of infants (Moss et al., 1988).

The information processing procedure developed by Zelazo and colleagues (Weiss, Zelazo, & Swain, 1988; Zelazo et al., 1989; Zelazo, Weiss, & Tarquinio, 1991) was used to assess newborn central processing ability in this study. Not only has the validity of this measure of newborn information processing ability been established through numerous studies, but given that the primary deficit associated with fetal cocaine exposure is subsequent language delay, this approach has the distinct advantage of measuring neonatal auditory rather than visual processing. Presumably normal language development would be more dependent on intact auditory information processing ability than visual processing ability. Thus, it is likely that an auditory information processing procedure would be more likely to detect the effects of fetal cocaine-exposure than visual processing paradigms.

Several other short-comings of previous research into the effects of intrauterine cocaine-exposure on infant outcome were addressed in this study. First, by carefully matching cocaine-exposed and control infants on several of the most important confounding factors identified by Nuespiel (1994), the probability that any differences between cocaine-exposed and control infants on the information processing procedure are due to cocaine is increased. Cocaine-exposed and control infants were carefully matched for birthweight, gestational age, number of cigarettes smoked by the mother per day, SES, and maternal weight gain during pregnancy. Second, the most reliable subject identification procedures currently available were used to ensure that the control infants had not been exposed to cocaine in utero and that all of the experimental group infants were the offspring of gestational cocaine users. Specifically, meconium analysis and/or infant and maternal urine analysis, in conjunction with maternal self-report were used to classify subjects as cocaine-exposed or non-exposed.

Third, meconium analysis and self-report allowed for the documentation of polydrug use.

Finally, studies assessing information processing in newborns are often plagued by a high rate of subject attrition due to the neonate's labile state (Clifton & Nelson, 1976; Richardson & McCluskey, 1983). Some researchers speculate that published results may be biased because the "uncooperative" nature of some newborns may be an important variable related to developmental outcome, including differential orienting and habituating; thus, the neonate's uncooperative nature may not be merely an obstacle to testing (Colombo & Horowitz, 1987; Wachs & Smitherman, 1985). However, it has been argued that by careful attention to the choice of test times, selection of stimuli, methods used to encourage an alert state (Zelazo et al., 1989) and time of testing in relation to feeding (Muir & Field, 1979), subject attrition can be minimized. Given the reports of significant state lability among cocaine-exposed neonates (e.g., Chasnoff et al., 1985; Chasnoff, Burns et al., 1987; Chasnoff & Griffith, 1989; Griffith, 1988; Tronick et al., 1994), the alerting procedure was considered to be of critical importance in the present study for eliciting the best possible infant performance on the information processing task. Thus, testing was only attempted when the infant was in a quiet, alert state.

Hypotheses

It was predicted that due to cocaine's potentially disruptive effects on fetal brain development, cocaine-exposed infants would show deficits in information processing ability. Specifically, cocaine-exposed newborns would fail to recover responding to a novel stimulus following habituation to the previously presented stimulus. More detailed hypotheses can be found on pp. 148-149.

Method

Participants

Cocaine-exposed Group. Forty-four cocaine-exposed neonates were recruited from the Sir Mortimer B. Davis Jewish General and St. Mary's Hospitals, Montreal, Quebec between 1991 and 1995. In most cases, these newborns had already been identified by physicians, nurses or social work staff as cocaine-exposed by maternal self-report, urine testing, or both. In two cases where the mother denied drug use and urinalysis yielded negative results, but where maternal cocaine use was still suspected, meconium analysis was requested by the attending physician. In both cases, the meconium tested positive for cocaine. Following confirmation of gestational cocaine use, the mother was invited to participate in the study. Approximately 15% of the identified cocaine abusing mothers ($n=6$) refused to participate. Those who agreed provided written informed consent (Appendix A). An additional 10 of the identified cocaine-exposed neonates were unable to participate in the study as their mothers had abandoned them in the hospital and were not available to give informed consent. Cocaine-exposed neonates with brain haemorrhages or any other clear neurological insults were excluded ($n=2$). Thus, of the original 44 cocaine-exposed infants recruited, 26 participated in the study.

Of the 26 who participated in testing, one infant was excluded from the cocaine-exposed group prior to data analysis. In this case the infant was extremely premature (gestational age 27 weeks) with IUGR (birthweight = 765 g), and a matched control could not be found. Furthermore, the infant tested negative for cocaine-exposure by meconium analysis, the mother and infant both tested negative by urine analysis, and the mother reported using a very small amount of cocaine (0.25 g), one time only, in the first trimester of pregnancy.

After exclusion of this infant, 25 cocaine-exposed neonates, 15 females and 10 males, remained in the final sample.

All infants participating in the study had five-minute Apgar scores (Apgar, Holoday, James, Weisbrot, & Berrien, 1958) of seven or greater. With the exception of one infant, all were normal in appearance and had no obvious physical anomalies. The exception was one cocaine-exposed infant who was born without lower limbs; however, cranial ultrasound and CAT scans conducted on this infant were normal.

Control Group. 120 healthy infants without a documented history of cocaine exposure, recruited from the maternity ward of the Sir Mortimer B. Davis Jewish General Hospital in Montreal, Quebec, were tested on the information processing procedure. These infants formed a pool from which 25 matched controls were selected for the cocaine-exposed neonates. This pool of potential control infants was generally not representative of the population of infants born at this hospital, however. In order to provide good potential matches for the cocaine-exposed infants, infants with birthweights and gestational ages below the 50th percentile, who were otherwise healthy, were selectively recruited. If no such infants were available for testing on any given day, other healthy infants were then recruited.

Thirty-one of the 120 potential control neonates were excluded from the pool of controls because meconium was either not excreted prior to discharge or, more commonly, was inadvertently thrown away by the nursing staff. Of the remaining sample, nine were excluded because of high levels of untestable state (i.e.; fretting and sleeping), 16 were excluded due to a head-turning bias in one

direction¹ (to the right in all cases except one), and three were excluded because information concerning maternal smoking was not provided by the mother. Another control infant was excluded because a documented history of maternal drug use during a previous pregnancy along with the mother's current lifestyle raised the possibility that the mother also used cocaine during the current pregnancy, and first trimester cocaine use cannot be determined by meconium analysis. This left a total of 60 potential controls. From this group, the closest match for each cocaine-exposed neonate based on gestational age (GA), birthweight (BW), number of cigarettes smoked per day (CIGS), maternal socioeconomic status (SES), and maternal weight gain during pregnancy (WG) was selected for inclusion in the data analysis. Other factors documented for comparison between groups included corrected gestational age at the time of testing (TA = GA + postnatal age), infant weight at the time of testing (TW), Apgar scores at five minutes (APG), maternal age (MA), extent of prenatal care (CARE), and alcohol and drug use during pregnancy.

Subject Matching Procedure. With the exception of WG, matching criteria were chosen to allow matching of the maximum number of infants possible while remaining within one standard deviation of the grand mean for each variable. The control infant who was the closest match was selected for each cocaine-exposed infant according to the following matching criteria: a) GA within two weeks (.73 of one SD); b) BW within 450 grams (.72 of one SD); c) CIGS within five cigarettes per day (.5 of one SD); d) for SES, household income within \$10,000 per year (.63 of one SD); and e) WG within five kilograms (1.2 Sds).

¹ All but two of these infants were held by one particular experimenter; it was, therefore, assumed that the bias in the direction of head-turning was related to the way the infants were held, rather than to infant factors.

Information concerning smoking was not available for two cocaine-exposed newborns, and information concerning WG was missing for seven cocaine-exposed and two control subjects. In these cases, the missing values were replaced by group means. As a result, it is possible that the cocaine-exposed and control infant pairs may not match on the CIGS and WG variables.

The first step in the matching procedure consisted of dividing the data from the potential controls and cocaine-exposed infants into two groups according to whether or not the mothers smoked cigarettes during pregnancy (the mothers of 20 cocaine-exposed infants and 26 potential controls smoked throughout pregnancy). Then, within the smoking and non-smoking groups, cocaine-exposed infants were matched with potential controls according to GA, followed by BW, CIGS (in the smoking group), SES, and WG, respectively. If more than one potential control could be matched with a cocaine-exposed neonate on a given variable, the one with the closest match on the subsequent variable was chosen. By the time the last matching variable was reached, no cocaine-exposed infant had more than one possible control, although not all cocaine-exposed/control infant pairs matched on all five variables. The raw data for each of the five matching variables for the 25 cocaine-exposed/matched control pairs is shown in Table 5. Of the 25 control/cocaine-exposed infant pairs, all 25 matched according to criteria on at least three of the five variables; 18 pairs matched on at least four variables, and 10 pairs matched on all five variables. The variables most difficult to match were the last two entered into the process: SES and WG. Although sex was not included as a matching variable based on previous research showing no sex differences on the information processing procedure, the matched controls consisted of 16 female infants and 9 males and the cocaine-exposed group was comprised of 15 females and

Table 5

Raw Data on Subject Matching Variables for Cocaine-exposed Infants and their Matched Controls

Gestational Age (weeks-days)		Birthweight (g)		Cigarettes (# per day)		SES (x \$1,000/year)		Pregnancy Weight Gain (Kg)	
cocaine	control	cocaine	control	cocaine	control	cocaine	control	cocaine	control
36-0	37-4	2710	2460	25	25	5	5	(12.0)	14.1
37-4	39-1	2680	2700	20	25	5	15	7.3	8.2
37-0	37-3	2460	2665	15	14	5	15	8.2	9.1
34-4	34-0	1770	1775	5	2	50	55	9.1	13.6
40-1	39-1	3090	2975	0	0	15	15	15.9	(12.6)
38-4	39-5	3115	3260	4	4	5	5	15.9	13.6
40-0	38-3	3175	2890	0	0	15	15	(12.0)	9.1
38-6	38-5	2590	3000	10	10	5	5	11.4	10.0
41-0	39-1	2710	2840	15	20	25	15	15.5	10.9
39-0	37-0	3470	3385	0	0	5	15	13.6	16.8
39-1	39-3	3400	3565	0	0	35	35	19.5	11.4*
40-4	40-0	3880	3630	0	0	15	15	22.7	11.8*
39-1	40-2	2895	3110	15	8	25	15	6.8	18.2*
35-0	36-3	2175	2570	8	10	15	5	1.0	18.2*
28-5	30-0	1230	1525	(14.2)	10	5	5	(12.0)	18.2*
33-3	34-6	2275	2530	20	25	5	25*	(12.0)	11.8
40-0	39-5	3145	3295	20	8*	15	5	15.9	14.5
36-0	37-0	2330	2610	50	25*	5	15	9.1	13.2
36-6	37-6	2455	2980*	25	25	25	55*	13.6	9.1
36-0	38-0	2440	3600*	20	5*	5	15	(12.0)	13.2
36-0	33-4*	2010	2015	(14.2)	6*	5	15	(12.0)	(12.6)
36-0	38-4*	3175	3120	20	10*	5	5	9.1	6.8
28-5	28-0	1250	1280	15	12	50	25*	9.1	16.8*
38-0	38-0	2950	3190	30	25	15	55*	(12.0)	20.5*
41-0	41-2	3360	3390	10	10	45	65*	13.6	4.1*

* Matched control subject is outside the limits of the matching criterion for that particular variable.
Values in parentheses represent group means substituted for missing values.

10 males. In 16 of the matched pairs, the cocaine-exposed and control infants were of the same sex.

Age at Testing. The majority of infants were tested on the information processing procedure between 18 and 72 hours of age ($n = 13$ for the cocaine-exposed newborns, $n=21$ for the control newborns). Premature neonates (four cocaine-exposed neonates and five control neonates had gestational ages below 36 weeks), and cocaine-exposed neonates requiring observation in the neonatal intensive care unit, were tested as soon as medically stable. Of the 12 cocaine-exposed infants who were not tested within 72 hours of birth, five were tested within eight days, and the remaining seven were tested between two and six weeks of age. Of the four control infants who were not tested within 72 hours of birth, two were tested between one and three weeks of age, and the remaining two were tested at four and six weeks of age.

The most common reason for delay in the testing of the cocaine-exposed newborns was difficulty in obtaining consent from the mother. These mothers often left the hospital soon after giving birth and returned to visit their infants infrequently. A less common reason was admission to the neonatal intensive care nursery for observation ($n=5$). Once it was determined that the infant was medically stable, the infant was tested on the information processing procedure.

Collection of Demographic Information

Mothers were approached and invited to participate in the study as soon after giving birth as possible, in order to obtain written consent for the collection of infant meconium. At this time mothers were given a Demographic Questionnaire to complete (Appendix B), which asked questions concerning drug and alcohol use as well as cigarette smoking during pregnancy, household income, pregnancy weight gain, and number of prenatal doctor visits, among

other things. Information concerning the newborn was obtained from the infant's birth records; this included GA, BW, sex, and APG. The corrected gestational age of the infant at the time of testing (GA + postnatal age) and infant weight at the time of testing were also documented.

Six of the 25 mothers who used cocaine during pregnancy failed to complete the demographic questionnaire. In order to match the infants of these six mothers with appropriate controls, information concerning smoking, drug and alcohol use, SES, and CARE was obtained from the hospital social services records. Group means and standard deviations for the five subject matching variables (GA, BW, CIGS, SES, and WG) and the five other demographic control variables (TA, TW, APG, MA, and CARE) are shown in Table 6.

The data concerning the use of alcohol and other substances during pregnancy is summarized in Table 7. Although the data suggest moderate levels of marijuana/hashish and alcohol use among the cocaine-users, none of the mothers in either group reported heavy drinking or extensive use of marijuana/hashish, with the exception of one cocaine-user who reported drinking eight beers per occasion, twice per month. Apart from this subject, the maximum reported regular use of alcohol was two drinks per occasion, once a week throughout pregnancy, reported by one control mother and three cocaine-using mothers. Additionally, only two of the cocaine-using mothers and two of the control mothers reported using marijuana/hashish beyond the first trimester of pregnancy, and in all cases, the amounts were small (e.g., one "joint" every two weeks). In fact, qualitative analysis of the self-reports on substance use (and also informal conversations with the mothers) suggest that the vast majority of cocaine-users stopped using marijuana/hashish and alcohol once

Table 6

Group Means and Standard Deviations for Cocaine-exposed and Control Neonates on the Five Matching and Five Control Demographic Variables.

Variable ^a	Cocaine (n=25)	Controls (n=25)
<u>Subject Matching Variables</u>		
Gestational age (wks)	37.3 (2.8)	37.5 (2.7)
Birthweight (g)	2679 (636)	2827 (597)
# cigarettes smoked / day ^b	13.7 (10.1)	10.6 (8.8)
SES (\$1,000 per year)	16.2 (14.2)	19.9 (17.5)
Maternal weight gain (Kg)	12.1 (4.2)	12.7 (4.0)
<u>Control Variables</u>		
Corrected gestational age at testing (wks)	39.0 (2.5)	38.1 (2.0)
Weight at testing (g)	2887 (577)	2832 (489)
Apgar at 5 minutes	8.8 (0.6)	9.1 (0.5)
Mother's age (yrs)	27.2 (4.3)	27.0 (5.9)
# who received prenatal care	14 / 25	24 / 25

^a Standard deviations are listed in brackets beside each group mean.

^b Includes all subjects with non-smokers receiving a score of 0.

Table 7

Number of Cocaine-using and Control Mothers Who Used Other Substances.

Substance used ^a	Cocaine (n=21) ^b	Controls (n=23) ^c
Any alcohol use	15	12
Alcohol use throughout pregnancy	7	3
Marijuana / Hashish (any use) ^d	8	2
Heroin (any use) ^d	3	0

^a Based on self-report, although use of cannabinoids and heroin after 20 weeks gestation was confirmed by meconium analysis. ^b Missing data for 4 of the 25 subjects.

^c Missing data for 2 of the 25 subjects. ^d Cocaine, marijuana, hashish, and heroin were the only illicit substances reportedly used; heroin was used regularly by only 1 subject.

pregnancy was confirmed. However, few were able to give up cocaine or cigarettes.

Based on self-report, three of the cocaine-using mothers also used heroin, although use was largely limited to the first trimester. One subject took one "point" on two occasions in the first trimester and again in the third trimester; another subject took one quarter of one point daily during the first trimester; and the third subject reported heroin use in the first trimester only, but did not specify the quantity or frequency. Heroin, marijuana, and cocaine were the only illicit substances reportedly used by the women in this study.

The quantity and frequency of cocaine use varied widely across the cocaine-using mothers. Table 8 summarizes the estimated average extent of cocaine use by the subjects, classified along a four point continuum with a value of 1 representing light use, 2 representing moderate use, 3 representing heavy use, and 4 representing very heavy use. The highest reported use of cocaine was 2 to 3 grams per day throughout gestation and the lowest reported use was less than 0.25 g once per month in only the first trimester. Considerable fluctuations in the pattern of cocaine use were common. Three mothers had extended periods of abstinence (2 - 4 months), due to incarceration. Thus, the values presented in Table 8 are approximate, with quantities averaged across gestation.

Drug Screening Procedures

Self-reported cocaine use, positive meconium analysis results, or one cocaine-positive urine sample from either the mother or the infant were criteria for inclusion in the cocaine-exposed group. Meconium analysis was the primary method of detecting and confirming prenatal drug use for this study; urine

Table 8

Classification of Cocaine-users by Quantity and Frequency of Use

Cocaine use	Light ^a	Moderate ^b	Heavy ^c	Very heavy ^d
n out of 25 ^e	8	8	6	3
% of users	32	32	24	12

^a Cocaine use limited to first trimester: less than 0.5 g, less than once per week.

^b Use throughout gestation: 0.5 g or less, between 1 and 3 times per week.

^c Use throughout gestation: 0.25 - 1 g daily.

^d Use throughout gestation: more than 1 g daily.

^e Extent of cocaine use was estimated from social work records of 3 mothers who failed to complete the demographic questionnaire.

analysis was often requested by the attending physician and the results were used to confirm drug use in cases where meconium analysis was not available.

Meconium Analysis. Plastic bags for the collection of meconium-stained diapers were attached to the infants' bassinets. Meconium was collected from diapers for the first three days following birth, or until the baby was discharged. Meconium was collected for 24 of the 25 control infants; however, drug analyses could not be carried out on three of these samples due to a shortage of funds (analysis of each meconium sample cost approximately \$110). In each of the four cases in which meconium was not analyzed, the mother had no prior history of drug use and reported that she did not use any illicit drugs during pregnancy, and neither mothers nor infants showed any signs of drug intoxication or withdrawal. Thus, there was no reason to suspect that these mothers used cocaine during pregnancy, although the possibility cannot be completely ruled out. In the one control infant who did not produce a meconium sample prior to discharge, maternal and infant urine samples were available for analysis; both tested negative for cocaine and opiates. These four cases were included in the study only because good matched controls with meconium analysis results could not be found for four of the cocaine-exposed neonates, and these infants provided the best available matches. For the cocaine-exposed infants, meconium analysis was carried out in all cases where a meconium sample was available ($n=15$ of 25). The meconium analysis procedure was instituted when the study was already underway; the first six cocaine-exposed infants tested were identified solely on the basis of urine analysis and maternal self-report since meconium analysis was not part of the procedure at that time. Non-drug-

exposed infants who were tested prior to the institution of meconium analysis were excluded from the pool of potential controls.

All meconium collected from each infant was kept in a freezer located in the testing room, which was kept locked at all times. Samples were clearly marked with the infant's code number, the mother's initials, and the date of collection. The meconium was sent periodically by courier to the United States Drug Testing Laboratories in Chicago, Illinois for drug analysis. Since drugs reaching the infant are not distributed evenly throughout the meconium (D. Lewis, personal communication, March, 1992), several meconium specimens were collected where possible from each infant, although records were not kept on the number of samples collected from each infant.

Upon reaching the laboratory, the meconium specimens from each infant were pooled and hydrogenated prior to drug analysis. An allocot from the homogenate was then concentrated by a factor of four and screened for cocaine, BE, cocaethylene (an indication of whether or not the mother also consumed alcohol in addition to cocaine), opiates, cannabinoids, and cotinine (a metabolite of nicotine). The last 12 samples (three cocaine-exposed and nine controls) to be sent for analysis were also screened for mBE (a recently identified fetal metabolite cocaine). Analysis for mBE was carried out only for the last 12 meconium samples because the technique was not available when the first specimens were analyzed.

Initial drug screenings were carried out using fluorescence polarization immunoassay (FPI). In order to rule out the possibility of false positives, all samples which yielded positive results for any illicit substance were further analyzed by GC/MS. The limit of quantization was 5 ng/g and the limit of detection was 2 ng/g. Positive cotinine results using FPI were not subjected to

confirmatory analysis with GC/MS. Consequently, maternal self-reports concerning cigarette smoking could not be completely validated by the meconium analysis results.

One control infant tested positive for mBE and was subsequently excluded from the analyses and replaced with another control. Since the levels of mBE were low in this case, and the validity of low levels of mBE for indicating cocaine use has yet to be established, this infant was also not included in the cocaine-exposed group.

Urine Analysis. All urine analyses were performed by the laboratories of the Sir Mortimer B. Davis Jewish General and St. Mary's Hospitals at the request of the attending physician. When a mother was suspected of using drugs, maternal and neonatal urine samples were sent for analysis. Criteria for requesting urine drug screening included maternal self-report of drug use, documented history of drug use, lack of prenatal care, and physical symptoms suggestive of intoxication or withdrawal at the time of delivery. Analyses of infant and maternal urine were each repeated with three separate urine specimens; one positive sample was the criterion for inclusion in the cocaine-exposed group. Analyses were conducted by means of a commercial radioimmunoassay with high sensitivity and specificity.

Comparison of Subject Identification Techniques. Table 9 shows the percentage of cocaine users identified by each identification procedure. While the data imply that self-report is the most reliable method of detecting prenatal cocaine use, the numbers presented in Table 9 are somewhat misleading because the hospital policy was to conduct urine tests only if there was a strong indication that the mother was a drug-user. The most common reason for ordering a urine test was self-reported drug use. Thus, urine analysis

detected the greatest percentage of cocaine users because in 84% of the cases, the women were screened because they reported cocaine use. Furthermore, although one might conclude, based on the data in Table 9, that meconium analysis is not a reliable method for detecting cocaine use, the relatively low success rate of meconium analysis is misleading. First, the mothers of six of the seven infants whose meconium tested negative for cocaine ceased using cocaine during the first trimester of pregnancy; although one of the six claimed to have taken cocaine when she went into labour, after remaining abstinent for six months. Since meconium does not form until the end of the first trimester, meconium analysis would not be expected to detect this use. This mother had a positive urine test, while the neonate's urine and meconium tested negative, lending credence to her self-report. The remaining infant whose meconium was negative for cocaine was born to a mother who had at least one positive urine test during pregnancy, one week before delivery, according to social work records. At birth both the mother and infant tested negative for cocaine by urine screening. This infant's meconium had been expected to test positive for cocaine/BE. The most likely explanation for the negative result was that the meconium collected was not a representative specimen. Since records were not kept on how many meconium samples were collected from each infant, it is impossible to determine whether this was the case.

Second, the validity of meconium analysis is partially demonstrated by the fact that two subjects who denied drug use and had negative urine screens were identified as cocaine users via meconium analysis. This number is increased to three when the infant whose meconium tested positive for

Table 9

Percentage of Gestational Cocaine Users Detected by Self-report, Urine Analysis, and Meconium Analysis

Cocaine use detected	Self-report (n)	Urine (n)	Meconium (n)
Yes	21	16	8
No	4	9	7 ^a
Total	25	25	15
% of users detected	84%	64%	53%

^a Six of the 7 infants who tested negative via meconium analysis were born to mothers who used cocaine only in the first trimester; thus, identification by meconium analysis would not be expected.

mBE, and was subsequently excluded from the study, is considered. These infants may have been misclassified as controls if meconium analysis had not been carried out. Thus, without meconium analysis, cocaine-exposed infants would have comprised 12% of the control group.

Once informed consent had been obtained from the mother, bags were provided for meconium-stained diapers and the infant's nurse was notified that the infant would be participating in the study and that diapers should be saved. The mother was provided with the demographic questionnaire and testing on the information processing procedure was scheduled.

Information Processing Procedure

Apparatus and Stimuli. The information processing procedure employed auditory stimuli played on two four-track cassette players, amplified and presented through Fischer stereo speakers at a sound pressure level of 72 decibels. Output volume levels were checked with a sound pressure level meter prior to the testing of each infant. The stimuli consisted of two words, "tinder" and "beagle", chosen because of their comparable low frequency of occurrence (Kucera & Francis, 1967), comparable length, and phonetic content, segments of which were demonstrated previously to be discriminable by two- and three-month-old infants (Eimas, 1975) and neonates (Brody et al., 1984; Zelazo et al., 1989). Each word was approximately 1 second in duration and was repeated at a rate of one word every 2 seconds. Each word was recorded on two of four stereo tape tracks, and a silent switch box connecting the tape player and stereo amplifier allowed either pair of tape tracks to be played.

Infant responses were coded by a hand-held button box connected to the computer. The box contained four coding buttons, one for each of four possible infant responses: head turn to the right, head turn to the left, fretting, and eyes

closed. Infant responses were delivered on-line to the computer which was programmed to keep track of trial duration, and duration of each of the four possible infant responses.

Infant Testing. Testing took place in a quiet, dimly lit room across the hall from the nursery at the Sir Mortimer B. Davis Jewish General Hospital. Infants were tested 30 to 60 minutes after feeding in order to minimize fretting due to hunger, and extreme sleepiness due to a full stomach. Infants were brought into the room, usually asleep, and awakened. A series of behaviours including face-to-face looking, Moro, Palmer, Babinski, and tonic-neck reflexes were elicited until the infant was fully awake and in an alert, non-agitated state. If this state could not be achieved, the infant was returned to the mother and the procedure was attempted later the same or the next day.

Throughout the information processing procedure, the infant was held by the first experimenter (E1) at a 45 degree angle between vertical and supine, with the infant's head and shoulders supported in one hand and the lower back and buttocks in the other hand, as recommended by Muir and Field (1979). The infant was held over a warming table on which the experimenter holding the infant rested his/her elbows. Stereo speakers delivering the stimuli were located approximately 30 cm to either side of the infant's ears. A second experimenter (E2) stood behind the holder and recorded the infant's responses by depressing the corresponding buttons on the button box. A head turn was coded when the infant rotated the sagittal midline of the head 45 degrees to either side. The criterion of a 45 degree rotation to qualify as a turn is conservative relative to the criterion of 6 degrees used by Muir & Field (1979) and the 15 degree criterion used by Clifton, Morrongiello, Kulig, & Dowd (1981) and was chosen to reduce

the probability of spurious head movements, as recommended by Zelazo et al. (1989).

A third experimenter (E3) controlled the computer and apparatus delivering the stimuli. In order to eliminate experimenter bias, E1 and E2 wore stereo headphones which delivered all auditory stimuli simultaneously to both ears through a six-channel audio mixer, giving the impression of central location of the sound. Thus, only E3 was aware of the direction of the sound source, the particular stimuli being delivered, or changes from one phase of the procedure to the next. Although experimenters were occasionally aware of the infant's group membership, the headphones served to reduce experimenter bias during the testing procedure.

Each infant participated in three phases of the information processing procedure in a partial infant-control design (Zelazo et al., 1989): (a) Familiarization Phase: The familiarization stimulus word was presented until criteria for orientation and habituation were achieved, or for 16 trials if the infant failed to orient; (b) Novelty Phase: A novel stimulus word was played until the infant oriented and habituated, or for 12 trials if the infant failed to orient; and (c) Dishabituation Phase: The initial familiarization stimulus was presented again until the infant oriented, or for 9 trials if the infant failed to orient.

The criterion for orientation in each phase was defined as three head turns toward the sound source within four consecutive trials. The criterion for habituation was defined as any combination of head turns away from the sound source and/or lack of head turn within three consecutive trials. If an infant began to orient or habituate on the last trial of each phase, up to two additional trials were allowed to provide a final opportunity for the infant to orient or habituate. The orientation and habituation criteria and the maximum number of trials in

each phase were chosen on the basis of previous research with this procedure (Zelazo et al., 1989).

In each phase, one stimulus (i.e., either "tinder" or "beagle") was presented to the infant repeatedly at a rate of a stimulus word every two seconds in trials of 30 seconds maximum duration. If the infant turned his/her head toward or away from the sound source and sustained the turn for three seconds before 30 seconds had elapsed, the trial ended. Inter-trial intervals varied depending upon the amount of time required to regain an alert state in cases where the infant had begun to fret or fall asleep. However, attempts were made to keep inter-trial intervals below 10 seconds duration. In general, inter-trial intervals were approximately 5 to 10 seconds in length, during which time the infant's head was recentred by E1, and E3 recorded the infant's head-turning response from the computer (i.e., E3 could not see the infant, and information concerning the direction of head-turn was transmitted by the coder to the computer, with responses recorded on paper by E3 at the end of each trial). One of three responses was possible for each trial: (a) head turn toward the sound source, (b) head turn away from the sound source, or (c) no head turn. When the infant reached the criterion for orientation and habituation or the maximum number of allowable trials for each phase, the stimulus word was changed and the next phase began. Upon completion of testing, the infant was returned to the mother and the length of each trial, along with time spent fretting and with eyes closed, was recorded from the computer.

Study Design

A multivariate design with one between group independent variable (cocaine exposure/control) and three measures of central information processing (orientation, habituation, and recovery to novelty) was used to assess whether

fetal cocaine exposure adversely affected neonatal information processing ability. Multivariate and univariate analyses of variance were used to assess between group differences on the following measures of central information processing: (a) orientation to the stimuli in each of the three phases, (b) habituation to the familiarization and novelty phase stimuli, and (c) recovery of responding to the stimuli in the novelty and dishabituation phases. In addition, between group differences were assessed on a number of control variables. These consisted of (a) the five subject matching variables, (b) five other demographic control variables, (c) percentage of time in a positive state, and (d) overall percentage of head turns.

Post hoc analyses were carried out to ensure that (a) sex differences in the effects of cocaine-exposure did not exist, and (b) that lack of prenatal care among the cocaine-exposed group could not account for any observed group differences.

Data Reduction

To prepare the data for analysis, the trials in the familiarization phase were first divided into two equal or nearly equal blocks of trials. In general, the first block represents orientation trials, and the second block represents habituation trials, with some overlap in the middle. When a trial block was made up of an odd number of trials, turns toward the sound source were included in the trial block closest to the beginning of the phase, and turns away from the sound source, or no-turns, were included in the trial block closest to the end of the phase. This procedure was repeated for the novelty phase. Trial blocks were used to assess changes in response patterns between phases (within group variable). The two trial blocks of the familiarization phase, each containing approximately 50% of the trials of that phase, were then subdivided to produce

four approximately equal quartiles of trials. This procedure was repeated for the novelty phase. Thus, each phase was broken down into four quartiles of trials each approximating one quarter of the trials of each phase. Reducing trial blocks to quartiles allowed for changes in the direction of head-turning to be assessed within each phase (within group variable). In the following pages, with respect to the familiarization and novelty phases, the term "trial block" always refers to one half (or very close to one half) of the total number of trials in that phase; i.e., each phase consists of two blocks of trials. The term "quartile" always refers to one quarter (or very close to one quarter) of the trials of that phase; i.e., each phase is broken down into four quartiles of trials.

For the dishabituation phase, a trial block consisting of the first three to six trials was used in all data analyses involving the dishabituation phase. The first three to six trials were chosen on the basis of previous research using this procedure which demonstrated that infants generally orient within six trials in this phase (Zelazo et al., 1989). If an infant oriented in fewer than six trials, the trial block consisted of the number of trials available; i.e., if an infant oriented in three trials, thereby ending the procedure, the dishabituation block would consist of only three trials and all values for the dishabituation phase would be calculated on the basis of those three trials. In the following pages, this block of trials will be referred to as the "dishabituation block". (See Appendix C for a sample scoring sheet). This method of data reduction is similar to the method used in previous studies by Zelazo and colleagues (e.g., Zelazo et al., 1989; Zelazo et al., 1991).

Since the amount of time infants were in a "positive state" (i.e., not fretting and with eyes open) during testing could influence their performance on the information processing measures, it was important to check for group differences on this variable. The amount of time spent in a negative state was calculated

first, by adding up the time (in seconds) that the infant was fretting or had eyes closed during each trial and dividing this sum by the total sum of all trial lengths. The percentage of time spent in a positive state was then derived by subtracting the percentage of time spent in a negative state from 100%. This process was carried out separately for each phase of the procedure.

Dependent Measures. Three dependent measures were used to assess information processing ability, and two control measures were employed to ensure that the groups did not differ on head-turning ability and degree of positive state. The three primary dependent measures were as follows: (a) in each trial block and quartile, and in the dishabituation block, the percentage of trials with head turns toward the sound source; (b) the number of trials required to reach criterion for orientation in the familiarization, novelty and dishabituation phases, and habituation in the familiarization and novelty phases; and (c) a "difference score" calculated by subtracting the number of head turns away from the stimulus from the number of head turns toward, within the first and last quartiles of each phase (a measure of preferential head-turning toward or away from the stimulus). The two control variables consisting of (a) the overall percentage of trials with head turns during the procedure (to ensure that both groups were equally capable of producing head turns), and (b) the percentage of time the infant was in a "positive state" (i.e., not fretting and with eyes open) in each phase.

Specific Hypotheses Related to the Information Processing Dependent Measures. Given the current inconsistencies in the literature regarding the effects of cocaine on infant outcome, it was impossible to predict in advance if the cocaine-exposed infants would differ from controls on the information processing measures. However, there was no reason to expect that fetal cocaine

exposure would enhance infant performance. Thus, the null hypothesis was that group differences would not be found on any of the information processing measures. The alternative hypothesis was that if cocaine was a neurotoxic substance, fetal cocaine-exposure would compromise information processing ability leading to differences between the cocaine-exposed and matched control groups as follows:

1. Familiarization Phase: Based on the findings of previous research with infants at risk for developmental delay (Zelazo et al., 1989), it was hypothesized that cocaine-exposed infants would not differ from controls on the familiarization phase measures. First, both groups would be expected to show a high level of head turning towards the sound source in the first two quartiles (or first trial block), decreasing to lower levels towards the end of the phase (third and fourth quartiles, or second trial block). Second, group differences were not expected on the number of trials required to meet the criteria for orientation and habituation in this phase. Third, in both groups, difference scores were expected to be greater than zero for the first quartile (indicating preferential turning toward the stimulus) and less than zero in the fourth quartile (indicating systematic turning away from the stimulus).

2. Novelty Phase: Specific group differences were expected in this phase. It was hypothesized that: (a) the percentage of head turns toward the sound source in the initial two quartiles (1st trial block) of the novelty phase would be lower among the cocaine-exposed infants compared with controls, (b) the cocaine-exposed infants would require a greater number of trials to reach the criteria for orientation and habituation, (c) the degree of recovery to the novel stimulus, as determined by comparisons of the second trial block of the familiarization phase with the first trial block of the recovery phase, would be

lower for the cocaine-exposed infants compared with controls, and (d) whereas control infants were expected to show a systematic pattern of frequent turns toward the stimulus in the first quartile of the novelty phase and frequent turns away in the last quartile (as determined by positive and negative difference scores, respectively), cocaine-exposed infants were expected to respond randomly, as reflected by difference scores approaching zero. In addition, it was expected that when subjects who failed to habituate to the familiarization stimulus were excluded from the analysis, group differences in the percentage of head turns towards the novel stimulus in the first trial block of the novelty phase would continue to be significant.

3. Dishabituation Phase: The following group differences were hypothesized for the dishabituation phase: (a) whereas the control infants would recover responding to the dishabituation stimulus, the cocaine-exposed infants would not (assessed by comparing the groups on the percentage of head turns towards the stimulus in the 2nd block of the novelty phase with the percentage of head turns towards the stimulus in the dishabituation block), (b) fewer cocaine-exposed infants would reach the criterion for orientation compared to controls, (c) the cocaine-exposed infants who reached the criterion for orientation would require a greater number of trials to do so than controls, and (d) that difference scores would be greater than zero for controls and not different from zero for the cocaine-exposed infants for the first three trials of the dishabituation block.

Results

An alpha level of 0.05 was used as the criterion for significance in all analyses. Only statistically significant results are reported in the text of this section; summary tables for all analyses can be found in Appendix D. Topics in the results section will be discussed in the following order:

1. General approach to the analysis of the data.
2. Results of preparatory analyses including: (a) preparation of data for analysis by identification of missing values, outliers, and violations of the assumptions of MANOVA, (b) results of analyses of demographic variables (to determine whether the groups differ on potentially confounding factors), and (c) results of between group comparisons on the two information processing control measures, degree of overall head-turning and degree of positive state.
3. Between group comparisons on information processing ability as assessed by the information processing measures in the (a) familiarization phase, (b) novelty phase, and (c) dishabituation phase.
4. Post hoc analyses to assess (a) sex differences in performance among cocaine-exposed newborns (based on reports from animal studies that fetal cocaine-exposure affects males and females differently), and (b) the performance of infants whose mothers received prenatal care compared with those whose mothers did not receive prenatal care.

General Approach to the Data Analyses

Three statistical techniques were used to analyze the data: multivariate and univariate ANOVAs, χ^2 tests, and one-sample t tests. Each of these techniques was used to analyze specific types of data.

Repeated measures MANOVAs were used to assess between group differences on the demographic control variables, changes in positive state across phases of the information processing procedure, and changes in the percentage of head turning towards the stimulus across quartiles and trial blocks of the information processing procedure. Following the rules and conventions of MANOVA, if the multivariate Wilk's lambda F was significant for the effect of

Group or the Variable x Group interaction, then univariate F tests for the effect of Group were conducted to determine the source of the significance.

Group differences in degree of orientation to the stimulus in each of the familiarization, novelty and dishabituation phases were assessed by first using χ^2 tests to determine if the frequency of cases meeting the criterion for orientation differed between groups. Following the χ^2 tests, ANOVA was used to determine if the groups differed on the number of trials required to reach the criterion for orientation, with infants who did not reach the criterion excluded prior to the analysis. The same process was used for the analyses of degree of habituation to the familiarization and novelty phase stimuli.

Because the measure of recovery of head turning toward the novel stimuli in the novelty and dishabituation phases was to some degree a function of the degree of habituation to the preceding stimulus, analyses of recovery to novelty were carried out twice: first, with all infants included in the analysis, and a second time with the infants who failed to habituate to the preceding stimulus excluded. This ensured that, if ANOVA revealed a lack of recovery to novelty among the infants in one group relative to the other, the scores of infants who habituated and recovered were not masked by a lack of habituation to the preceding stimulus among the infants who failed to recover.

The difference score measure (number of head turns toward the stimulus minus the number of head turns away) was used to determine whether the infants in each group differed in terms of preferential direction of head turns in the first and last quartiles of each phase. The difference scores were compared with a mean of zero using one-sample t tests within each group. A score significantly greater than zero indicated that the infants turned toward the stimulus more often than they turned away. A score less than zero indicated that

they preferentially turned away from the stimulus, and a score not different from zero indicated random responding. Thus, difference scores greater than zero would be expected at the beginning of a phase (orientation) and scores less than zero would be expected near the end of a phase (habituation).

Preparatory Analyses

Preanalysis. Prior to analysis, the distributions of all demographic and information processing variables were examined for missing values. Second, the scores of outliers were identified. Third, the assumption of normality was determined on the basis of the degree of skewness and kurtosis for each variable, examined separately for the 25 cocaine-exposed neonates and the 25 controls. With a moderate sample size and equal n 's, the assumption of homogeneity of variance was not likely to be violated (Tabachnick & Fidell, 1996).

The data set for the control group was missing two values for WG, two values for APG, and one value for MA. Among subjects in the cocaine-exposed group, three demographic variables had missing values: WG was missing for seven subjects, CIGS was missing for two subjects, and APG was missing for one subject. There were no missing values on any of the information processing measures with the exception of the dishabituation phase scores for two cocaine-exposed subjects who did not complete the procedure (in one case, the parents were watching and decided to terminate the testing procedure at the end of the novelty phase; in the second case the infant fell into a deep sleep after fretting through the first few trials of the dishabituation phase, and a decision was made to exclude the data for this phase). In order to include all subjects in the data analyses, group means were used as the best estimate of the missing values, as recommended by Tabachnick and Fidell (1996).

Outliers were identified on a number of demographic and information processing variables. Outliers were defined as data points more than two standard deviations away from the mean (i.e., z -score > 2.00), with the standard deviations used in the z -score transformations being those calculated before any missing values were replaced by group means. Since ANOVA is sensitive to extreme outliers (Tabachnick & Fidell, 1996; Wilkinson et al., 1992), the outliers' scores in each case were replaced with scores calculated to be two standard deviations away from the mean. In all cases, the new score was still the most extreme score of the group on the variable in question. This technique is more conservative than the method proposed by Tabachnick and Fidell (1996) who suggest replacing the outlying score with a score one unit higher than the next highest score on the measure. However, because replacement of outlying scores with less extreme scores, in some cases, would have worked in favour of improving the performance of the control group relative to the cocaine-exposed group, scores two standard deviations from the mean were used to reduce the probability of Type I errors.

Skewness and kurtosis values were calculated for each variable and those with z -scores greater than 3.0 were considered to violate the assumption of normality required for ANOVA (Tabachnick & Fidell, 1996). Once the extreme scores of the outliers had been replaced by less extreme scores, no variable was significantly skewed or had high kurtosis.

Demographic Control Variables. Subsumed under the heading "demographic characteristics" were the maternal and infant characteristics which served as control variables. These included the five variables used in the subject matching procedure (GA, BW, CIGS, SES, and WG), and an additional five control variables (TW, TA, APG, MA, and CARE). For the CARE variable,

mothers were coded as receiving adequate prenatal care if they had received three or more prenatal health check-ups over the course of their pregnancy; conversely, they were coded as not receiving prenatal care if they had received two or less prenatal health check-ups.

Prior to MANOVA for group differences on the five variables used in the subject matching procedure, the inter-correlations of the variables were checked for multicollinearity. BW and GA were highly correlated ($r(48) = .86$). Although neither BW nor GA was correlated with Group, the correlation coefficient for BW and Group ($r(48) = .12$) was slightly higher than that of GA and Group. Thus, BW was used in the between group analyses. A 2 (Group) x 4 (Matching Variables) MANOVA on the remaining four subject matching variables (BW, SES, WG, and CIGS) revealed no group differences (Appendix D, Table D1), indicating that the groups were well-matched on these variables.

Prior to analyses on the other five control variables (TW, TA, APG, MA, and CARE), multicollinearity was assessed. TA and TW were highly correlated ($r(48) = .77$), and although neither TA nor TW was correlated with Group, the correlation coefficient for TA ($r(48) = .19$) was slightly higher than the correlation of TW with Group. Thus, TA was used in the analyses. A 2 (Group) x 4 (Control Variable) MANOVA yielded a Group x Variable interaction, $F(3, 46) = 7.22$, $p < .001$, and an effect of Group, $F(4, 45) = 7.97$, $p < .001$. Univariate F -tests indicated that the groups differed only on CARE, $F(1, 48) = 22.79$, $p < .001$ (Appendix D, Table D2). Whereas the two groups were similar in terms of TW, TA, APG, and MA, there were significant differences in the extent of prenatal care between the cocaine-exposed and control infants. Specifically, only 14 of 25 (56%) cocaine-using mothers received prenatal care compared to 24 of 25 (96%) control mothers.

Since lack of prenatal care is generally considered to be a risk factor in itself for a variety of adverse pregnancy outcomes, this group difference was of particular concern. Furthermore, the group differences in prenatal care could not be statistically controlled due to violation of most of the assumptions of multivariate analysis of covariance (e.g., linearity, normal distribution, homogeneity of variance; Tabachnick & Fidell, 1989). As this variable had the potential to seriously confound the information processing results, post hoc analyses were conducted in which the cocaine-exposed infants whose mothers had received prenatal care were compared with those who had not received prenatal care. The results of these analyses are presented following the main findings of the cocaine-exposed versus control group analyses on the information processing measures.

Control Measures for Information Processing Assessment. To rule out the possibility that as a result of fetal cocaine-exposure, the cocaine-exposed infants might be less capable of making head turns than the control infants, the cocaine-exposed and control infants were compared on the overall percentage of trials ending with a head turn. The percentage of trials with head turns in either direction (as opposed to trials with no turn) was collapsed across the three phases of the procedure. Between group differences were examined by a one-way Group x Head-turning ANOVA. No significant group differences in the overall percentage of head-turning were found (Appendix D, Table D3), indicating that cocaine-exposed and control infants were equally capable of making head turns. Cocaine-exposed and control infants turned on an average of 74.2% and 77.9% of trials, respectively.

The amount of time spent in positive state was the second information processing control variable. Because group differences in the time spent in a

positive state would represent a serious confounding variable, it was important to ensure that any group differences on the information processing measures could not be attributed to differences in degree of positive state. The group means and standard deviations for the percentage of time spent in a positive state in each phase are shown in Table 10. A 2 (Group) x 3 (Phase) repeated measures MANOVA revealed that, collapsed across groups, positive state tended to decrease in a linear fashion across phases, although the effect was only marginally significant, $F(2, 47) = 2.09$, $p = 0.05$ (Appendix D, Table D4). The Group x Phase interaction was not significant, indicating that the groups did not differ on the percentage of time spent in a positive state across the three phases of the information processing procedure. Collapsed across groups, a high level of positive state was achieved in all three phases of the procedure with grand means for the familiarization, novelty and dishabituation phases of 87.1%, 84.0%, and 81.6%, respectively.

Analyses of Information Processing Ability

Figure 1 illustrates the percentage of head-turning toward the sound source across the three phases of the procedure for the cocaine-exposed and control infants. The familiarization phase is broken down into four quartile trial blocks as shown in Panel a, the scores for the novelty phase trial blocks are shown in Panel b, and the first three to six trials of the dishabituation phase are shown in Panel c.

Familiarization Phase. In order to assess whether the cocaine-exposed and control infants showed an initial high percentage of turns toward the stimulus that decreased across the familiarization phase, the percentage of turns toward the familiarization stimulus across the four quartiles of the phase was assessed by a 2 (Group) x 4 (Quartiles) repeated measures MANOVA (Appendix D, Table D5).

Table 10

Group Means and Standard Deviations for Positive State Across Phases, for Cocaine-exposed and Control Infants

Group	Familiarization	Novelty	Dishabituation
Cocaine-exposed	86.3 (14.1)	84.1 (16.5)	83.3 (20.0)
Controls	87.8 (13.5)	83.9 (13.7)	79.9 (18.8)

Note: Standard deviations in parentheses.

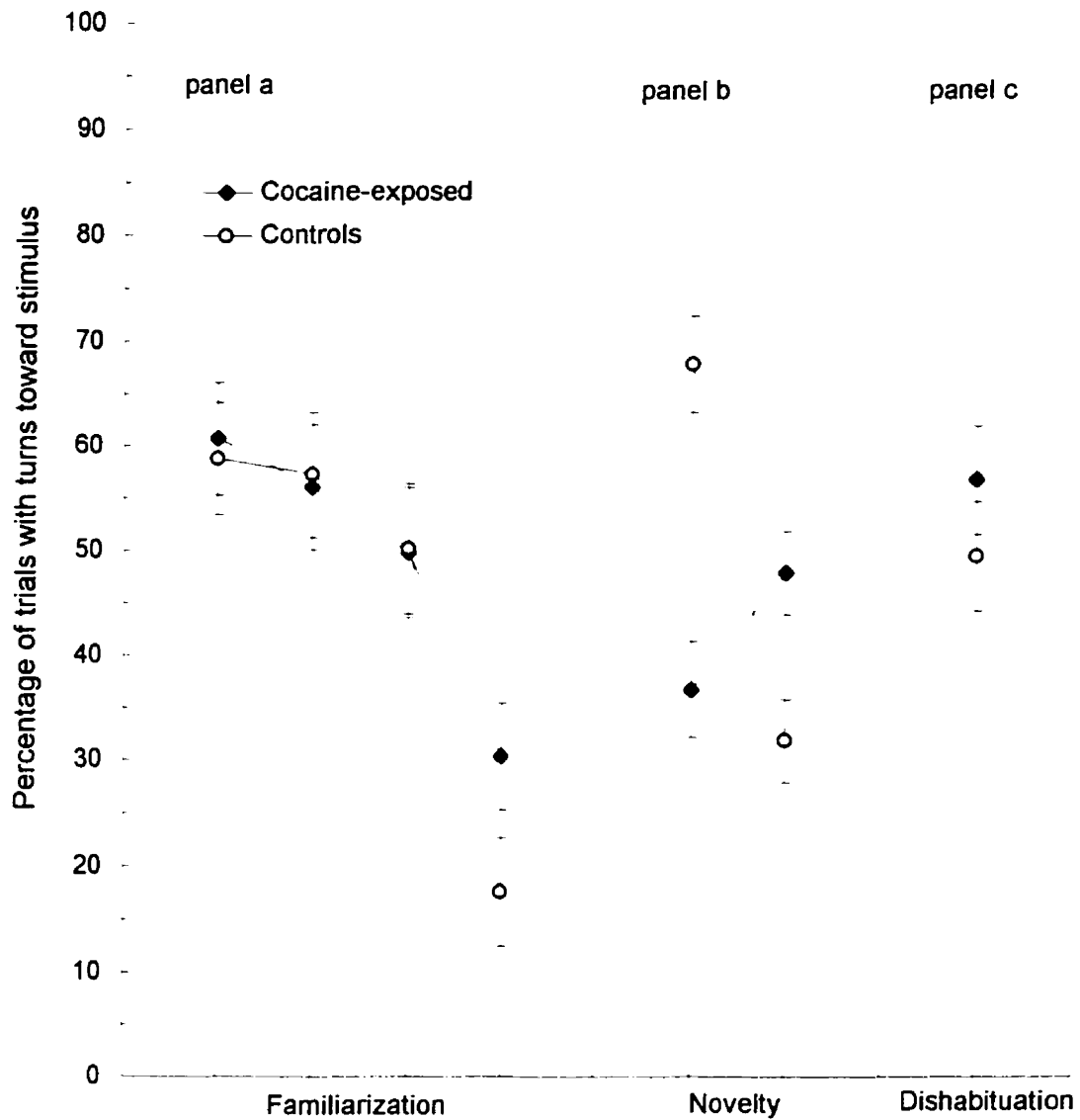


Figure 1. Mean percentages of head-turning toward the sound source for cocaine-exposed and control neonates during: familiarization phase quartile blocks (panel a); novelty phase trial blocks (panel b); and the dishabituation phase trial block (panel c).

The multivariate effect of Quartiles was significant, $F(3, 46) = 15.52, p < .000$, indicating that collapsed across groups, the percentage of turns toward the stimulus changed across the four quartiles. Inspection of the means revealed that the percentage of turns toward the stimulus decreased in a linear fashion from 59.8% in the first quartile to 24.0% in the fourth quartile. There was no Quartiles x Group interaction, indicating that both groups demonstrated similar levels of turns toward the stimulus across the four quartiles of the familiarization phase. The mean percentage of turns toward the stimulus for each group across the four quartiles is illustrated in Figure 2.

To assess whether turns toward or away from the familiarization stimulus exceeded chance levels at the beginning and end of the familiarization phase, difference scores (turns toward - turns away) were compared with a mean of zero in the first and last quartiles for each group. One-sample t tests were used to determine whether the mean difference scores for each group were significantly different from zero (Appendix D, Table D6). Analyses revealed that both the cocaine-exposed group, $t(24) = 5.17, p < .001$, and the control group, $t(24) = 3.62, p < .01$, turned preferentially toward the stimulus in the first quartile of the familiarization phase. However, in the last quartile, the mean difference score for the cocaine-exposed group was not different from zero, indicating that the direction of head-turning was random. However, the control infants turned systematically away from the stimulus in the last quartile, $t(24) = -3.73, p < .01$, signifying habituation.

To determine if the cocaine-exposed and control infants exhibited similar levels of orientation and habituation to the stimulus, between-group comparisons on the number of infants reaching orientation and habituation criteria were carried out using χ^2 analyses. No group differences were found for the

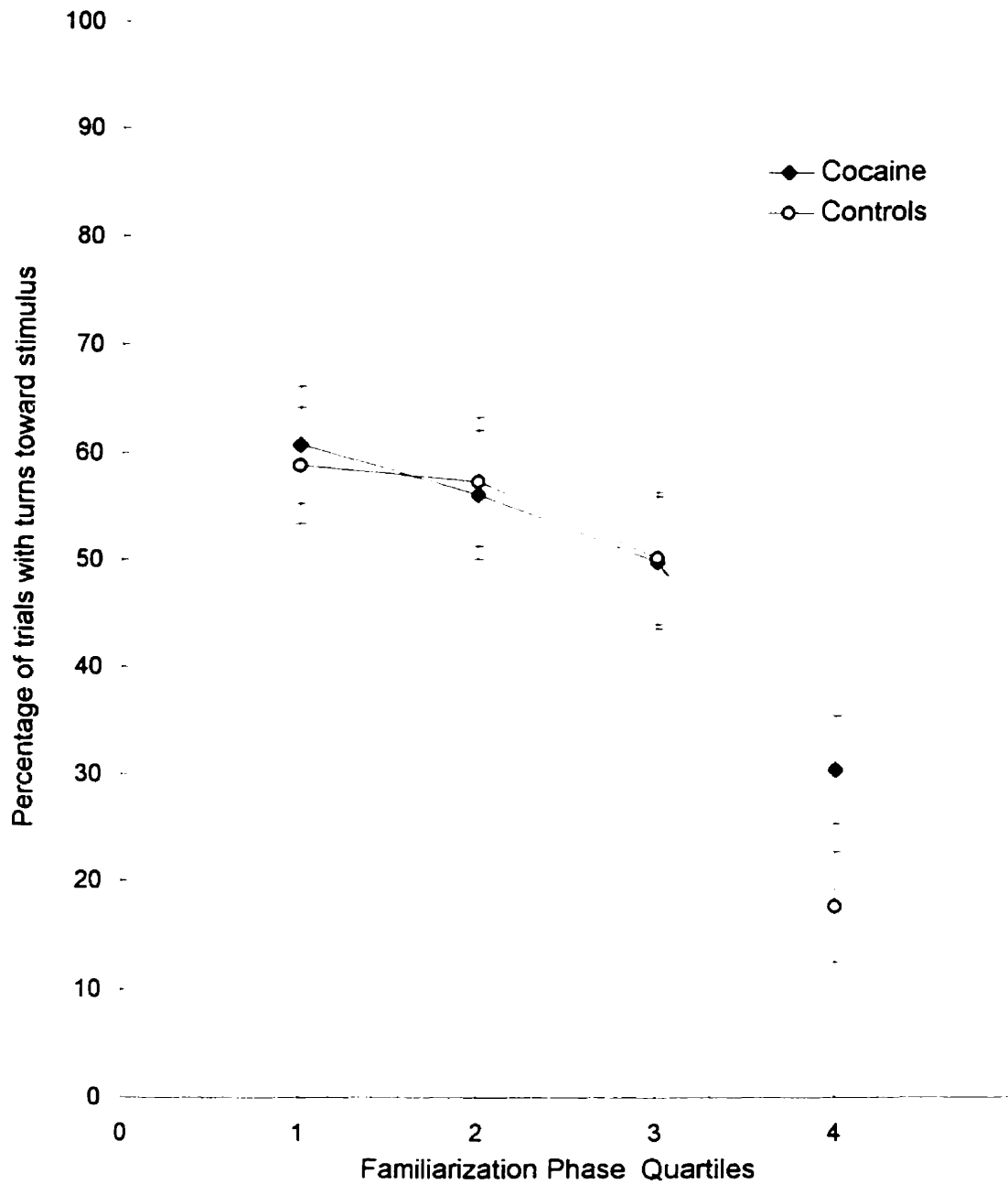


Figure 2. Mean percentages of head-turning toward the sound source during the 4 quartile blocks of the familiarization phase, for cocaine-exposed and control neonates.

percentage of infants who reached the criterion for orientation (Appendix D, Table D7), with 80% of the cocaine-exposed infants reaching criterion and 88% of controls reaching criterion. As shown in figure 3 (panel a), of the infants who oriented, there were no group differences in the number of trials required to reach criterion for orientation (Appendix D, Table D8). The cocaine-exposed infants oriented in an average of 6.0 trials, and the control infants oriented in an average of 6.6 trials.

Cocaine-exposed infants were less likely to reach the criterion for habituation (Appendix D, Table D9), $\chi^2(1) = 5.333$, $p < .05$. Of the infants who habituated, there was no difference between groups in the number of trials required to reach criterion (Appendix D, Table D10). As shown in Figure 3 (panel a), cocaine-exposed and control neonates habituated within an average of 11.1 and 12.8 trials, respectively.

Together, the results of the data analyses for the familiarization phase indicate that the cocaine-exposed neonates performed at the same level as matched controls on measures of orientation to the familiarization stimulus. However, the cocaine-exposed infants were less likely than controls to reach the criterion for habituation.

Novelty Phase. To examine the pattern of head turning towards the novel stimulus by the cocaine-exposed and control infants, a 2 (Group) x 4 (Quartiles) repeated measures MANOVA was conducted (Appendix D, Table D11). As with the familiarization stimulus, the multivariate effect of Quartiles was significant, $F(3, 46) = 8.03$, $p < .001$, indicating that the percentage of turns toward the stimulus decreased across quartiles. Collapsed across groups, the percentage of turns toward the stimulus decreased in a linear fashion from 52.7% in the first

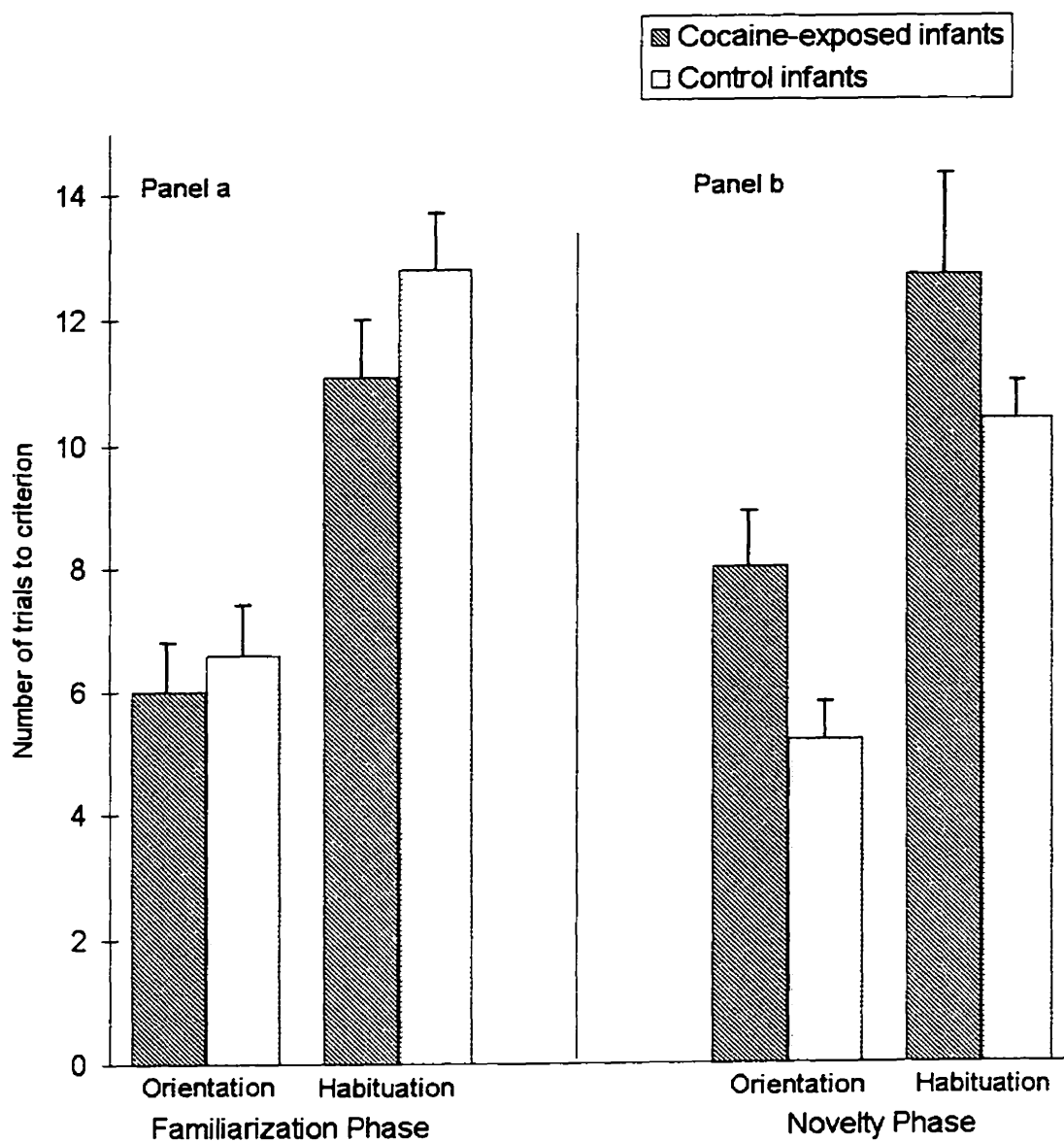


Figure 3. Number of trials required to reach the criteria for orientation and habituation in the familiarization (Panel a) and novelty (Panel b) phases among cocaine-exposed and control neonates who reached the criteria.

quartile to 31.1% in the last quartile. However, this effect was qualified by a Group x Quartile interaction, $F(3, 46) = 21.06$, $p < 0.001$, indicating that the responses of the cocaine-exposed and control infants differed across quartiles. Univariate F tests for the effect of Group revealed group differences in the percentage of turns toward the stimulus in the first quartile, $F(1, 48) = 11.39$, $p < 0.01$, the second quartile, $F(1, 48) = 19.35$, $p < 0.001$, and the fourth quartile, $F(1, 48) = 34.82$, $p < 0.001$. Inspection of the group means showed that whereas the initial high percentage of head turns toward the novel stimulus exhibited by the control group decreased across the phase, the percentage of turns toward exhibited by the cocaine-exposed infants remained relatively stable. These results are illustrated in Figure 4.

To assess turns toward the stimulus relative to turns away at the beginning and end of the novelty phase, the difference scores for the first and last quartiles were compared with a mean of zero within each group (Appendix D, Table D12). Analyses indicated that the control infants turned systematically toward the stimulus in the first quartile of the novelty phase, $t(24) = 6.26$, $p < .001$, and turned systematically away from the stimulus in the last quartile, $t(24) = -4.06$, $p < .001$. In contrast, the difference scores of the cocaine-exposed infants in the first quartile were not different from zero, indicating that they responded in a random fashion upon introduction of the novel stimulus. Furthermore, in the last quartile of the novelty phase, when habituation would be expected, the cocaine-exposed infants turned systematically toward the stimulus, $t(24) = 3.73$, $p < .01$.

Since recovery to novelty following habituation to a familiarization stimulus has been demonstrated by previous research to be the best information processing measure for discriminating among infants at high, moderate, and low

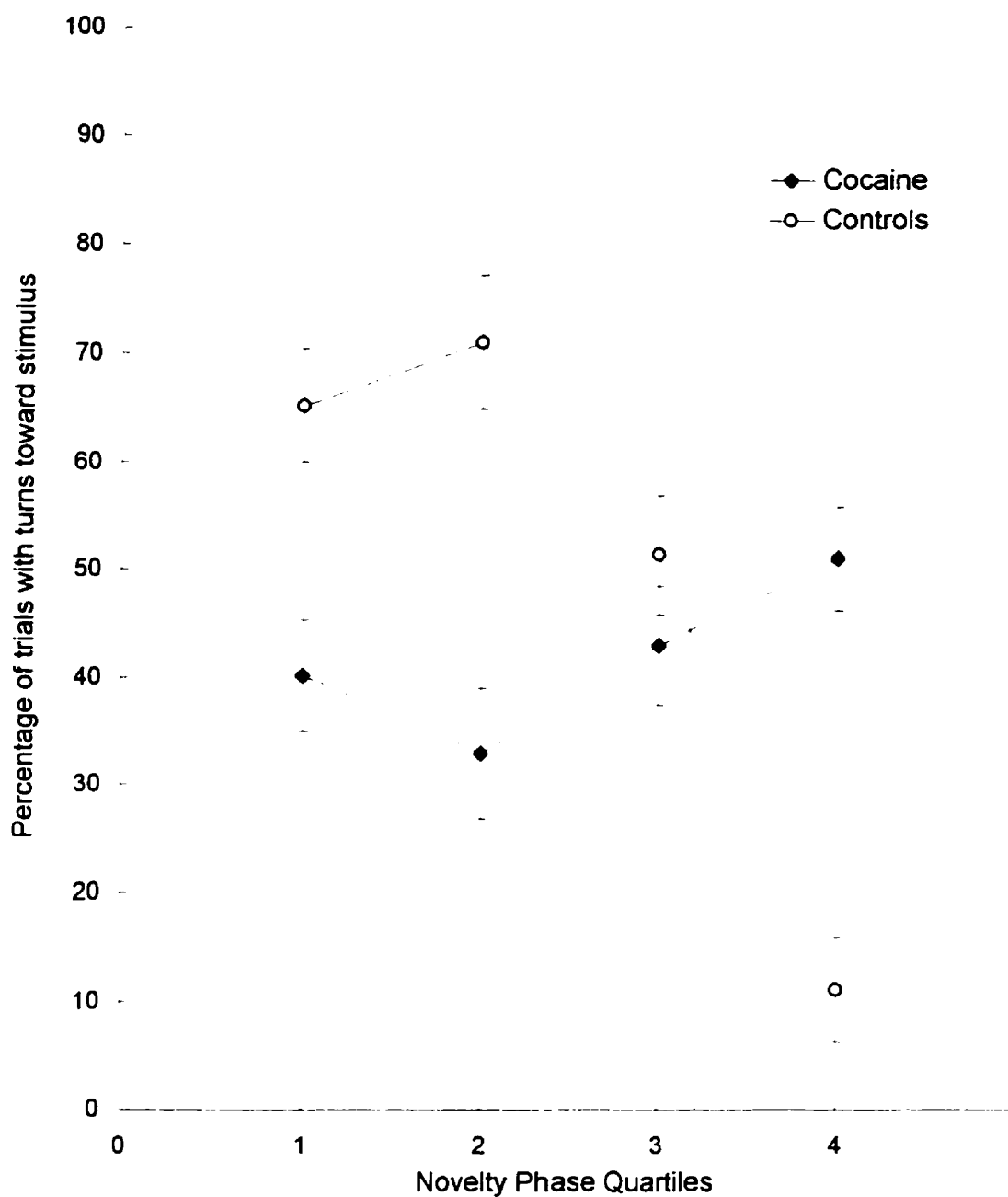


Figure 4. Mean percentages of head-turning toward the sound source during the 4 quartile blocks of the novelty phase, for cocaine-exposed and control neonates.

risk for developmental delay (Zelazo et al., 1989), analyses assessing recovery to a novel stimulus were of particular importance in this study. To assess recovery of head turning to the novel stimulus, the percentage of head turns toward the stimulus in the last trial block of the familiarization phase was compared with that in the first trial block of the novelty phase. A 2 (Group) x 2 (Trial Block) repeated measures ANOVA (Appendix D, Table D13) revealed an effect of Trial Block, $F(1, 48) = 13.75$, $p < 0.01$, and a Group x Trial Block interaction, $F(1, 48) = 21.07$, $p < 0.001$. These results suggest that while, collapsed across groups, the overall percentage of turns toward the stimulus increased between the last trial block of the familiarization phase and the first trial block of the novelty phase, the pattern of head turning across trial blocks discriminated between groups. A multivariate test for the effect of Group (Appendix D, Table D14) was significant, $F(2, 47) = 12.65$, $p < 0.001$, and univariate F tests revealed that the overall increase in the percentage of head turns toward the novel stimulus was entirely due to an increase in responding among infants in the control group, as illustrated in Figure 5. Whereas the cocaine-exposed and control infants responded with a similar percentage of turns toward the stimulus in the last trial block of the familiarization phase, the cocaine-exposed infants exhibited a lower percentage of turns toward the stimulus in the first trial block of the novelty phase, $F(1, 48) = 22.75$, $p < 0.001$. Whereas the percentage of turns toward the stimulus exhibited by the control infants increased from a mean of 34.4% in the last trial block of the familiarization phase to 67.9% in the first trial block of the novelty phase, the percentage of turns toward exhibited by the cocaine-exposed infants remained relatively stable. Thus, whereas the control infants recovered responding to the novel stimulus, the cocaine-exposed infants did not.

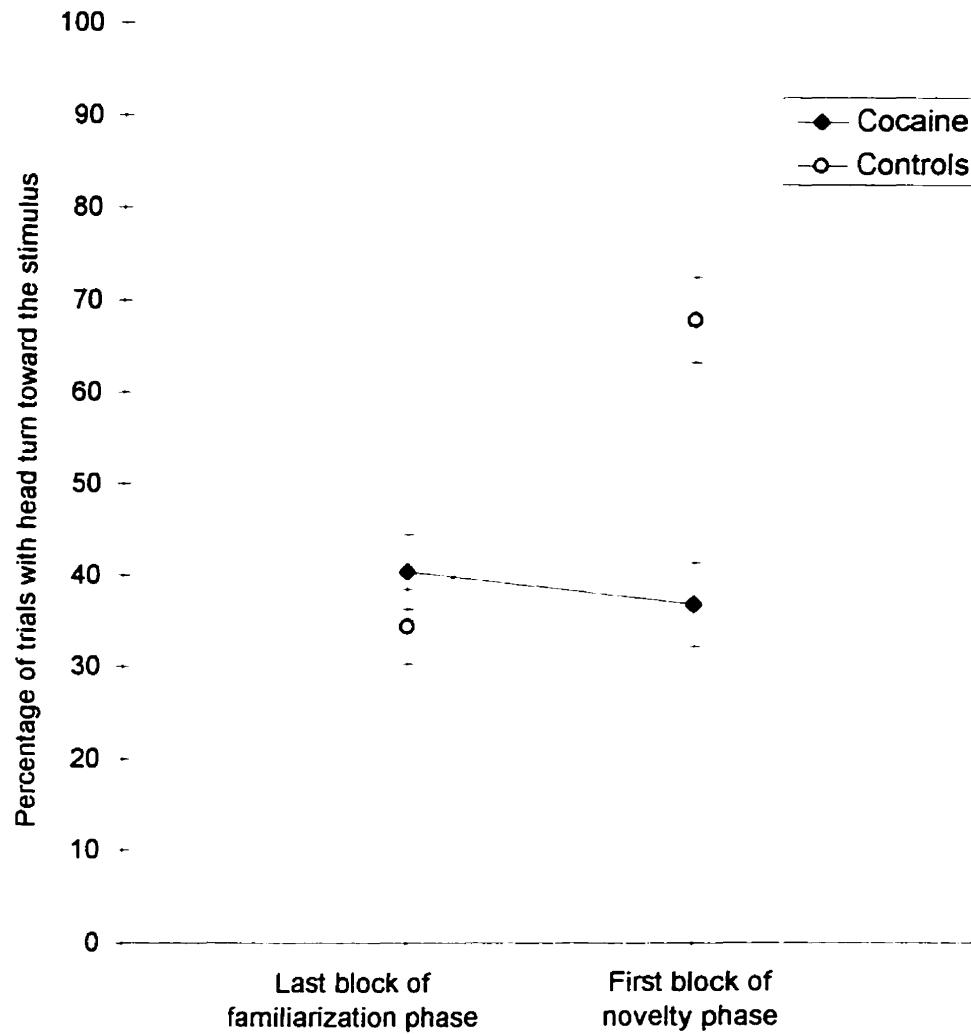


Figure 5. Response to novelty among cocaine-exposed and control infants as determined by change in head turns toward the stimulus between the last block of the familiarization phase and the first block of the recovery phase.

To determine if the lack of recovery to novelty displayed by the cocaine-exposed infants was a function of the poor performance exhibited by those infants who failed to habituate to the familiarization stimulus (i.e., the poor performance of the cocaine-exposed infants who failed to habituate may have masked the performance of those who did habituate), response to novelty was re-assessed with all infants who did not reach the criterion for habituation in the familiarization phase excluded. A Group x Trial Block ANOVA (Appendix D, Table D15) was used to compare the cocaine-exposed and control infants on the percentage of turns toward the stimulus in the first trial block of the novelty phase. Excluding the infants who failed to habituate to the familiarization stimulus did not change the results; the cocaine-exposed infants continued to show a lack of recovery to novelty relative to controls, as indicated by group differences in the percentage of turns toward the stimulus in the first trial block of the novelty phase, $F(1, 28) = 9.07, p < 0.01$.

Although the group differences in the percentage of turns toward the stimulus in the first block of the novelty phase suggest a lack of recovery to the novel stimulus, it was important to determine if these group differences translated into differences in the frequency of orientation to the novel stimulus. A between group comparison of the number of infants who reached the criterion for orientation (Appendix D, Table D16) indicated that cocaine-exposed newborns were less likely than controls to orient to the novel stimulus, $\chi^2(1) = 11.52, p < 0.01$. Whereas 92% of the controls oriented, only 48% of the cocaine-exposed newborns oriented. Furthermore, as shown in Figure 3 (panel b), of the infants who oriented, the control infants reached criterion in an average of 5.2 trials, whereas the cocaine-exposed infants required an average of 8.0 trials, $F(1, 33) = 6.72, p < 0.05$ (Appendix D, Table D17).

Similar results were found for the number of infants who reached the criterion for habituation to the novel stimulus, $\chi^2(1) = 18.47$, $p < 0.001$ (Appendix D, Table D18). Whereas 72% of the controls habituated, only 12% of the cocaine-exposed newborns habituated. Of the infants who habituated, cocaine-exposed infants required a somewhat greater number of trials to reach criterion relative to controls (M 's = 12.8 and 10.4 respectively), although with only 3 cocaine-exposed infants habituating, the cell sizes were too small for statistical analysis (Figure 3, panel b).

In summary, the results for the novelty phase imply impairments in information processing ability among the cocaine-exposed infants. First, these infants did not demonstrate a normal pattern of responding across the novelty phase. Whereas the control infants showed an initial high level of head turning toward the stimulus that declined across the phase, the cocaine-exposed infants showed a random pattern of responding at the beginning of the phase and a higher level of head turning toward the stimulus at the end of the phase, when the control infants were turning away from the stimulus. Second, the cocaine-exposed neonates were less likely than controls to orient and habituate to the novel stimulus, and required more trials to reach criterion than controls. Third, and most importantly, the cocaine-exposed infants failed to recover responding upon introduction of the novel stimulus. A failure to recover responding has been previously associated with risk for developmental delay (Zelazo et al., 1989).

Dishabituation Phase. In the dishabituation phase, the original stimulus used in the familiarization phase was reintroduced. To determine if the dishabituation stimulus would elicit recovery of head-turning, the percentage of head turns toward the stimulus during the second block of the novelty phase was compared with the percentage of head turns toward the stimulus in the

dishabituation trial block. A 2 (Group) x 2 (Trial Block) repeated measures ANOVA (Appendix D, Table D19) indicated that, collapsed across groups, the percentage of head turns toward the stimulus was greater at the beginning of the dishabituation phase than at the end of the novelty phase, $F(1, 48) = 8.11, p < 0.01$. There was a multivariate effect of Group, $F(2, 47) = 4.48, p < .05$ (Appendix D, Table D20), reflecting the fact that, collapsed across trial blocks, the cocaine-exposed infants made a higher percentage of head turns toward the stimulus than the controls. However, univariate analyses indicated that the groups differed only on the percentage of head turns toward the stimulus during the second trial block of the novelty phase, $F(1, 48) = 8.14, p < .01$ (Appendix D, Table D20). There were no group differences in the percentage of head turns toward the stimulus during the dishabituation trial block.

Because the pattern of responding illustrated in Figure 1 (Panels b and c) suggests that the pattern of head-turning toward the sound source among the cocaine-exposed infants was simply following the same trajectory, increasing across the novelty phase and into the dishabituation phase, further exploratory analyses were conducted to assess recovery to the dishabituation stimulus. Within each group, t tests were used to compare the percentage of head turns toward the stimulus during the last trial block of the novelty phase with the dishabituation trial block (Appendix D, Table D21). This analysis indicated that the control infants recovered responding, $t(24) = 2.33, p < .03$, whereas the cocaine-exposed infants did not, $t(24) = 1.63, p > .1$.

Analysis of difference scores for the first three trials of the dishabituation phase (a similar number of trials as in the first quartile of the novelty phase) were compared with a mean of zero (Appendix D, Table D22). The results indicated

that both the cocaine-exposed and control infants turned randomly toward and away from the stimulus.

When a χ^2 analysis was conducted to determine whether the cocaine-exposed and control infants differed in the frequency of orientation to the dishabituation stimulus, no between group difference was found (Appendix D, Table D23). Of the 48 infants who completed the procedure, 70% of the cocaine-exposed infants and 76% of the control infants reached the criterion for orientation. A one-way ANOVA (Appendix D, Table D24) indicated that, of the infants who reached criterion, the groups did not differ on the number of trials required. The cocaine-exposed infants oriented in an average of 5.3 trials and the control infants oriented in an average of 5.9 trials.

In summary, the results of the dishabituation phase analyses indicate that the control infants recovered responding to the dishabituation stimulus whereas the cocaine-exposed infants did not. However, the groups did not differ on the percentage of infants who oriented to the dishabituation stimulus or the number of trials required. In addition, during the first three trials of the dishabituation phase, neither group turned systematically toward the stimulus.

Summary. Whereas the performance of the cocaine-exposed infants was similar to that of the control infants on the orientation measures of the familiarization phase, the cocaine-exposed infants were less likely to habituate. In the novelty phase, cocaine-exposure was associated with a failure to recover to the novel stimulus, and impairments were evident on both the orientation and habituation measures. Upon introduction of the dishabituation stimulus, the control infants recovered responding whereas the cocaine-exposed infants did not. These results are summarized in Figure 1. Overall, cocaine-exposure was

associated with impairments in habituation to a repeated stimulus and recovery of responding to a novel stimulus.

Post Hoc Analyses

Sex. Based on reports of sex differences in neuronal activity following fetal cocaine exposure in laboratory animals, post hoc analyses were carried out to determine if male and female cocaine-exposed neonates differed in terms of habituation and response to novelty. Analyses which yielded significant differences between the cocaine-exposed and control infants were repeated for the cocaine-exposed infants with sex as a between-group independent variable. Because human studies with cocaine-exposed infants have not reported sex differences on cognitive measures, sex differences were not expected on the information processing procedure. Habituation measures included the percentage of infants in each group who reached criterion for habituation to the familiarization stimulus (Appendix D, Table D25) and novel stimulus (Appendix D, Table D26), the relative frequency of turns toward versus turns away from the sound source (difference scores) in the last quartiles of the familiarization phase (Appendix D, Table D27) and novelty phase (Appendix D, Table D28), and the percentage of head turns toward the stimulus in the second trial blocks of the familiarization phase (Appendix D, Table D29) and novelty phase (Appendix D, Table D30). There were no sex differences on any of these measures, except for the difference scores of the last quartile of the novelty phase. Previous analyses had revealed that, as a group, the cocaine-exposed infants had turned systematically toward the stimulus whereas the controls had turned systematically away from the stimulus. Post hoc analyses for sex differences indicated that only the male infants turned systematically toward the stimulus during the last quartile of the novelty phase, $t(9) = 4.88$, $p < .001$, whereas the

direction of head turns among the females was random. Neither of these patterns of responding was evident among the control infants -- numerous studies have shown that normal infants turn away from the stimulus during the last quartile. Thus, all analyses for sex differences on measures of habituation showed that both the male and female cocaine-exposed infants showed deficits in habituation to the familiarization and novel stimuli.

Sex differences in recovery to the novel stimulus were assessed by comparing the groups on the percentages of head turns toward the stimulus in the last trial block of the familiarization phase and the first trial block of the novelty phase (Appendix D, Table D31); recovery to the dishabituation stimulus was assessed by comparing the percentage of head turning toward the stimulus in the second trial block of the novelty phase with the dishabituation trial block (Appendix D, Table D32). In addition, t tests were used to compare the percentage of head turning toward the stimulus in the second trial block of the novelty phase with the percentage of turns toward the stimulus in the dishabituation trial block within each group (Appendix D, Table D33). No sex differences were found for any of these measures. All results indicated that both sexes failed to recover responding to the novel and dishabituation stimuli.

Prenatal Care. To determine if lack of prenatal care had a negative impact on information processing measures independent of the effects of cocaine, a separate set of analyses was carried out on the cocaine-exposed infants only. The cocaine-exposed sample was divided into two groups according to whether or not the mother had received adequate prenatal care. Lack of prenatal care was defined as fewer than three prenatal health check-ups. This criterion was chosen instead of zero prenatal check-ups because a few of the mothers had been to see a doctor once or twice during their pregnancy, most often because

they had come into contact with a sexually transmitted disease. However, it was doubtful whether this would qualify as "prenatal care". Second, since it was common for cocaine-users to be unaware of their pregnant state until as late as four months gestation, if they had regular once-monthly check-ups at this point and gave birth prematurely, three doctor visits might constitute regular prenatal care. All mothers who were classified as receiving prenatal care had seen a doctor at least once per month after the pregnancy was confirmed. Based on this criterion, 14 of the 25 cocaine-users were classified as receiving prenatal care ("care" group), and 11 as receiving no prenatal care ("no care" group).

The same analyses as for sex differences were carried out for prenatal care. Care and no care groups were compared first on measures of habituation, followed by measures of recovery to novelty.

Chi-square tests revealed no differences in the number of care and no care infants who reached criterion for habituation to the familiarization and novel stimuli (Appendix D, Tables D34 and D35). Difference scores were not different from zero during the last quartile of the familiarization phase for both groups (Appendix D, Table D36), and during the last quartile of the novelty phase (Appendix D, Table D37), the difference scores indicated that both groups turned preferentially toward the stimulus (care: $t(13) = 2.63$, $p < .03$; no care: $t(10) = 2.59$, $p < .03$). Prenatal care also had no effect on the percentages of head turns toward the stimulus during the second trial blocks of the familiarization and novelty phases (Appendix D, Tables D38 and D39). Overall, the care and no care groups exhibited similar patterns of performance on all measures of habituation. Thus, lack of prenatal care among a high number of cocaine-exposed infants did not explain the deficits in habituation observed among the

cocaine-exposed infants relative to the non-exposed infants.

Between group comparisons on recovery to the novel stimulus, using repeated measures MANOVA to compare the percentage of head-turning toward the stimulus during the second trial block of the familiarization phase with the first trial block of the novelty phase, yielded no significant effects of prenatal care (Appendix D, Table D40). The care and no care groups both failed to recover to the novel stimulus. Similarly, there were no differences in recovery to the dishabituation stimulus, assessed by comparing the second trial block of the novelty phase with the dishabituation trial block using repeated measures MANOVA (Appendix D, Table D41). Both groups failed to recover responding as determined by t tests for within group comparisons of the mean percentages of head-turning toward the stimulus in the second trial block of the novelty phase with the dishabituation trial block (Appendix D, Table D42). Thus, whether or not the mothers of the cocaine-exposed infants received prenatal care did not affect their infants' performance on measures of recovery to novelty.

Overall, between-group comparisons of the cocaine-exposed infants whose mothers received and did not receive prenatal care indicated that whether or not a mother received prenatal care did not impact on the information processing ability of her infant. Cocaine appears to have detrimental effects on neonatal information processing ability independent of factors associated with lack of prenatal care.

Discussion

Information Processing

Summary of Findings. As hypothesized, recovery of localized head-turning to a novel stimulus following repeated exposure to the previous stimulus discriminated between newborn infants exposed to cocaine in utero and non-

exposed infants. In addition, fetal cocaine-exposure was associated with impaired habituation to the familiarization stimulus whereas orientation was not adversely affected. Both groups systematically turned toward the stimulus during the initial trials of the familiarization phase indicating orientation; however, during the last quartile, the control infants turned systematically away from the stimulus indicating habituation, whereas the cocaine-exposed infants turned randomly toward and away from the stimulus. Turning away from a redundant stimulus is a robust finding that has been demonstrated repeatedly with normal infants during habituation and implies active processing of the stimulus (Swain et al., 1993; Tarquinio et al., 1990, 1991; Weiss, 1986; Weiss et al., 1988; Zelazo et al., 1989; Zelazo et al., 1987). Failure to turn away from the stimulus during the last quartile of the familiarization phase implies delayed information processing. This interpretation is supported by the fact that the cocaine-exposed infants were also less likely to reach criterion for habituation.

Following repeated exposure to the familiarization stimulus, the novel stimulus was introduced and the control infants displayed a high percentage of head turns toward the sound source, indicating recovery of responding. In contrast, the cocaine-exposed infants did not increase their head-turning toward the sound source when the novel stimulus was introduced. This lack of recovery among the cocaine-exposed infants was not a function of poor habituation to the familiarization stimulus; lack of recovery to the novel stimulus was also observed among the cocaine-exposed infants who habituated to the familiarization stimulus. Differences in recovery to the novel stimulus were also illustrated by the fact that the control infants systematically turned toward the novel stimulus during the initial trials of the novelty phase, whereas in the familiarization trials immediately preceding the onset of the novel stimulus, they had turned

systematically away from the sound source. Thus, the control infants switched from turning away to turning toward the sound source when the novel stimulus was introduced, whereas the cocaine-exposed infants continued to turn randomly; i.e., there was no change in responding when the novel stimulus was presented.

After repeated presentations of the novel stimulus, the control infants habituated, and during the last few trials of the novelty phase, they turned systematically away from the stimulus as predicted. However, an unusual and aberrant pattern of responding was observed among the cocaine-exposed infants. Following the random head-turning observed during the initial trials of the novelty phase, the cocaine-exposed infants turned systematically toward the stimulus during the last trials of the phase. Moreover, only 3 of the 25 cocaine-exposed infants reached criterion for habituation to the novel stimulus, and whereas 12 eventually reached criterion for orientation to the novel stimulus, many oriented near the end of the phase. This indicates that the performance of the cocaine-exposed infants was consistently affected and that the poor performance of the group as a whole was not simply the result of a few impaired infants reducing the overall mean scores.

In addition to being associated with a lack of recovery and impaired habituation to the novel stimulus, fetal cocaine-exposure was also associated with a lack of recovery to the dishabituation stimulus. While the scores of the cocaine-exposed and control infants on the various measures assessing processing of the dishabituation stimulus were similar, the percentage of head turning toward the sound source increased significantly among the control infants when the dishabituation stimulus was introduced. Conversely, the response pattern of the cocaine-exposed infants did not change; the increased head-

turning toward the sound source observed across the novelty phase simply followed the same trajectory into the dishabituation phase (see Figure 1, Panels b and c). Thus, while the change in the percentage of head turning toward the sound source among the control infants implied recovery of responding and processing of the stimulus, this can not be inferred for the cocaine-exposed infants.

It was somewhat surprising to observe a lack of systematic head-turning toward the dishabituation stimulus during the first trials of the dishabituation phase among both the control and cocaine-exposed infants. While random turning was expected for the cocaine-exposed infants, studies have repeatedly shown that normal infants turn systematically toward the stimulus during the initial trials of the dishabituation phase (e.g., Zelazo et al., 1989; Zelazo et al., 1991). However, as mentioned previously, the control infants in this sample were not representative of the general population. As a group, their birthweights and gestational ages were below average and 80% of the mothers smoked cigarettes. These factors may have adversely affected the performance of the control infants relative to the performance that has previously been observed among samples that are more representative of the population of infants born at this hospital.

The differences between the cocaine-exposed and control infants cannot be attributed to differences in positive state or ability to make head turns. The two groups were similar in terms of the percentage of time spent in a positive state and there were no group differences in the overall percentage of trials with head turns. In addition, the fact that group differences were not observed on measures of orientation to the familiarization stimulus implies that both groups were equally capable of localizing the sound and organizing the appropriate

head turning response. The group differences appear to reflect differences in information processing ability.

To improve the probability that observed group differences could be attributed to cocaine rather than to other variables, the infants in each group were individually matched on birthweight, gestational age, number of cigarettes smoked per day by the mother, SES, and maternal pregnancy weight gain. In addition, the groups were similar in terms of weight and corrected gestational age at the time of testing, five-minute Apgar scores, and the mother's age. By controlling for these potential confounds, the probability that the observed information processing deficits are a result of fetal cocaine-exposure are increased substantially. Moreover, while the percentage of mothers receiving prenatal care was much lower among the cocaine-exposed infants, whether or not the mother received prenatal care had no impact on her infant's information processing ability.

A number of animal studies have found sex differences in neural activity among cocaine-exposed offspring (Barron & Irvine, 1995; Dow-Edwards, 1989; Dow-Edwards et al., 1990; Glick et al., 1984), although the type of effect as well as the sex most adversely affected varies from one study to the next and appears to be at least partially related to the timing of cocaine administration. Human studies assessing the cognitive development of cocaine-exposed infants have not reported sex differences. To determine whether cocaine had differential effects on the information processing of male and female infants in the present study, male and female cocaine-exposed infants were compared on the measures that discriminated between cocaine-exposed and non-exposed infants. Sex had no effect on information processing ability, with the exception that males turned systematically toward the stimulus at the end of the novelty

phase whereas females turned randomly. Because a normal response is to turn away from the stimulus at this point during the procedure, this male-female difference did not affect the interpretation of the results.

Interpretation of Findings. Numerous studies conducted by Zelazo and colleagues using the auditory information processing procedure have demonstrated that normal, healthy newborn infants orient and habituate to a familiarization stimulus, recover responding and subsequently habituate to a novel stimulus, and dishabituate (recover) to the return of the familiarization stimulus (e.g., Brody et al., 1984; Swain et al., 1991; Tarquinio et al., 1990; Tarquinio et al., 1991; Zelazo et al., 1984; Zelazo et al., 1987; Zelazo et al., 1989). In addition, habituation is marked not only by a lack of head-turning toward the stimulus, but systematic turning away from the stimulus. Turning away from the sound source after repeated presentations of a stimulus is a robust finding that implies that newborns actively process auditory stimuli and that habituation is not simply a result of selective receptor adaptation or effector fatigue (Zelazo et al., 1991).

Orientation, habituation and recovery to a novel stimulus are separate behavioural responses which all rely on one common cognitive phenomenon: the creation of mental representations (Bornstein, in press; Bornstein & Sigman, 1986; Weiss et al., 1988; Zelazo, 1988; Zelazo et al., 1991). The initial orientation observed upon presentation of the familiarization stimulus has been described as a primarily reflexive behaviour (Kisilevsky & Muir, 1993; Muir & Clifton, 1985; Muir, Clifton, & Clarkson, 1989; Zelazo et al., 1991), although the response may take several stimulus presentations to occur. With repeated exposure to the stimulus, the infant creates a mental representation of the stimulus. Each stimulus presentation is actively compared with the mental

representation and, depending on the strength of the memory trace and the parameters of the stimulus, the infant may respond by turning toward the stimulus, turning away from the stimulus, or by not turning at all (Zelazo et al., 1991). Turning away from the stimulus after repeated presentations implies the creation of a mental representation and recognition that the stimulus is familiar. The consistency of the finding that newborns turn away from a redundant stimulus suggests that an affective component is elicited that results in the infants attempting to actively avoid the redundant sound (Zelazo et al., 1991). Failure to habituate implies a deficit in the ability to create an accurate representation of the stimulus, while failure to turn systematically away from the stimulus (recall that, in addition to turning away, the criterion for habituation can be attained by three consecutive trials with no turn) implies deficits in the processing of the stimulus.

Recovery of responding to a novel stimulus involves the recognition that the stimulus is different than the one presented previously. An active comparative process is hypothesized to take place, in which the novel stimulus is compared with the mental representation. If a mismatch results, recovery of responding occurs. In cases where an infant previously habituated to a familiarized stimulus but failed to recover responding to a novel stimulus, as was the case in the high risk sample assessed by Zelazo et al. (1989), a breakdown in the comparative process may be inferred. That is, a mental representation of the previous stimulus was created as evidenced by habituation; however, the novel stimulus was not processed as a mismatch and recognized as different from the previous stimulus.

In the present study, the cocaine-exposed infants decreased their responding to the familiarization stimulus but failed to habituate to the same

degree as controls. The decrement in responding suggests that a partial representation of the stimulus was created. The fact that the novel stimulus differed from the familiarization stimulus primarily in phonetic content (i.e., stimulus length, sound pressure level, and the voice speaking the word were the same) suggests that the stimulus characteristics that were retained were related primarily to the non-phonetic properties of the stimulus. Had phonetic content been partially encoded, then some degree of recovery to the novel stimulus would be expected; however, no recovery was noted.

Sophian (1980) has argued that while recovery of responding to a novel stimulus following habituation to a previous stimulus implies memory for the previous stimulus, failure to observe recovery to novelty does not necessarily imply a lack of memory for the previous stimulus. This is because, in order for the infant to recover responding to novelty, the infant must not only recognize the discrepancy between the familiar and novel stimulus, but must also prefer the novel stimulus. Thus, a failure to recover responding to a novel stimulus may be related to stimulus preference rather than an information processing deficit. However, head-turns toward the sound source among cocaine-exposed infants increased at the end of the novelty phase, a pattern which would not be expected if the infants simply did not "prefer" the novel stimulus. Furthermore, while such a theory may help to explain individual differences in response to novelty, it is unlikely that stimulus preference could account for one whole group of infants failing to respond to the novel stimulus. Also, the order of presentation of the stimuli were counterbalanced across groups; therefore, just in case cocaine-exposure should result in a whole group of infants preferring "beagle" over "tinder" or vice versa for reasons unknown, counterbalancing would have eliminated this confound. Contradictory evidence for Sophian's stimulus

preference theory is also found in the responses of the cocaine-exposed infants to the dishabituation stimulus. This was the same stimulus heard during the familiarization phase; thus, if preference for this particular stimulus was the reason behind the lack of recovery to the novel stimulus, systematic head-turning toward the sound source should have been observed upon the return of the familiarization (dishabituation) stimulus, and it was not.

An alternative explanation for the poor habituation and lack of recovery to novelty among cocaine-exposed neonates is that processing of all stimuli was delayed. More specifically, following repeated presentations of the familiarization stimulus, the infant created a partial mental representation of the stimulus; had more trials been allowed it is possible that full habituation would have been observed. Because the mental representation of the familiarization stimulus was incomplete, the infant failed to discriminate between the novel stimulus and the partial neuronal representation of the familiarization stimulus. This is supported by the observation that head-turns toward the sound source continued to decline until the second quartile of the novelty phase (see Figure 4). After repeated presentations of the novel stimulus, it may have eventually been processed as a "mismatch" when compared to the partial neuronal representation of the familiarization stimulus. However, because newborn infants are not able to retain a memory trace of an auditory stimulus for longer than 55 seconds in the current paradigm (Tarquinio et al., 1991; Zelazo et al., 1987), it is unlikely that the increased head-turning toward the sound source near the end of the novelty phase reflected delayed recognition that this stimulus was different from the familiarization stimulus.

At the end of the novelty phase, the cocaine-exposed infants began to turn toward the sound source. If more presentations of the novel stimulus had been

allowed, it is possible that the cocaine-exposed infants would have eventually oriented and habituated. However, if the dishabituation stimulus was introduced just when the infants were in the process of orienting to the novel stimulus, the result might be that the infants would continue to turn toward the sound source giving the impression of orientation to the dishabituation stimulus. This theory receives partial support from the fact that head-turns toward the stimulus were steadily increasing among the cocaine-exposed infants at the point where the dishabituation stimulus was introduced (Figure 1, Panels a and b). During the second block of the novelty phase the toward-away difference scores for the cocaine-exposed infants indicated that they were making significantly more head-turns toward the stimulus than away, a trend that did not continue in the first three trials of the dishabituation phase. The fact that the systematic head-turning toward the sound source did not continue might indicate that the dishabituation stimulus was introduced at a point where the infants were beginning to habituate to the novel stimulus. If this is the case, then it is further evidence that the dishabituation stimulus was not processed as being different from the novel stimulus.

Interestingly, Zelazo et al.'s (1989) high risk sample exhibited a similar pattern of responding as the cocaine-exposed infants, demonstrating a higher level of recovery to the dishabituation stimulus than to the novel stimulus. However, unlike the cocaine-exposed infants, the high-risk infants demonstrated a slight increase in head-turns toward the sound source upon introduction of the novel stimulus relative to levels of habituation to the familiarization stimulus. Furthermore, the percentage of head-turns toward the stimulus decreased significantly by the last quartile of the novelty phase, indicating that, unlike the

cocaine-exposed infants, the high-risk infants habituated to some degree to the novel stimulus.

Given the complete lack of recovery to the novelty phase stimulus following habituation to the familiarization stimulus, it is unlikely that the cocaine-exposed infants' response to the dishabituation stimulus could be interpreted as evidence of normal information processing. Even if one adopts a conservative standpoint and assesses the lack of group differences on the dishabituation measures as evidence of recovery of responding, there is evidence from studies with older infants that processing of the dishabituation stimulus is easier than processing of the novel stimulus since a memory trace has been previously laid down (e.g., Zelazo et al., 1995). Most importantly, the response of the cocaine-exposed infants to the dishabituation stimulus cannot be interpreted as evidence of recovery since these infants did not habituate to the preceding stimulus.

The results of previous studies assessing habituation and recovery of responding to novelty among newborns (Brody et al., 1984; Swain & Zelazo, 1987; Weiss et al., 1988; Tarquinio et al., 1991; Tarquinio et al., 1990; Zelazo et al., 1989) imply that this behaviour is dependent upon intact information processing ability (Zelazo, 1979, 1986; Zelazo et al., 1989, 1991). Thus, the results imply that prenatal cocaine-exposure, either alone or in combination with other pre- and peri-natal factors, adversely affects information processing ability in the newborn period.

Relation to Previous Research

To date, researchers attempting to assess the mental status of cocaine-exposed newborns have employed the NBAS (Brazelton, 1984). The present study is the first to examine the effects of cocaine on auditory information processing, and the first to assess information processing in any modality during

the neonatal period. In 13 of 16 prior studies reviewed in Chapter 1 (see Table 4), cocaine-exposed neonates performed normally on the habituation measures of the NBAS. Only three studies found cocaine-associated deficits in habituation (Eisen et al., 1991; Mayes et al., 1993; and Tronick et al., 1994) and two of these studies failed to control for maternal smoking (Eisen et al., 1991; Mayes et al., 1993). Failure to control for maternal smoking renders the results suspect as several studies have shown that maternal smoking impairs performance on the habituation measures of the NBAS (Fried & Makin, 1987; Picone et al., 1982; Richardson, Day, & Taylor, 1989; Saxton, 1978). However, the study by Tronick et al. (1994) was well-controlled and demonstrated that exposure to both high and low doses of maternal cocaine adversely affected habituation scores independent of tobacco-exposure, consistent with the findings of the present study.

The fact that the majority of studies did not find cocaine-associated deficits on the habituation measures of the NBAS suggests that the NBAS habituation measures may not be sensitive to the effects of cocaine. Simple, poorly controlled measures of orientation and habituation, such as those included in the NBAS, may not be sufficiently sensitive to detect the effects of cocaine on newborn cognitive functioning. The present study demonstrated that, in order to detect the effects of cocaine, an information processing procedure incorporating assessment of habituation and recovery to novelty has greater discriminant validity. For example, Moss et al. (1988) demonstrated in two studies that the NBAS orientation and habituation measures were not related to visual information processing ability in three-month-old infants. Regulation of state was the only measure related to information processing ability. Interestingly, impaired regulation of state was the most frequently reported finding among studies

assessing the effects of fetal cocaine exposure on NBAS scores. Six of the 10 studies assessing regulation of state reported deficits on this measure (Chasnoff et al., 1985; Chasnoff, Burns et al., 1987; Chasnoff, Griffith et al., 1989; Chasnoff, Lewis et al., 1989; Griffith et al., 1988; Tronick et al., 1994).

While it has been argued that deficits in performance on information processing tasks among cocaine-exposed newborns may be secondary to state regulation problems (Bornstein, in press; Chasnoff et al., 1985; Chasnoff, Griffith et al., 1989; Griffith et al., 1988; Mayes et al., 1995, 1996; Tronick et al., 1994), often characterized by vacillations between intense irritability and extreme sleepiness (Griffith, 1988), this pattern was not observed in the present sample. Both cocaine-exposed and control infants showed comparable high levels of alert wakefulness with minimal fretting throughout the procedure. The high levels of positive state were elicited, in part, by careful attention to the time of testing in relation to feeding, and by ensuring that each infant was in an awake, calm, and alert state before beginning the procedure. Previous research has demonstrated the importance of these factors in eliciting cooperation from the infant (Zelazo et al., 1989; Muir & Field, 1976).

A number of researchers have addressed the question of whether fetal cocaine exposure impairs regulation of state using measures other than the NBAS. Mayes et al. (1995) attempted to assess visual habituation and recovery to novelty in a group of cocaine-exposed and non-exposed three-month old infants. No group differences were found on habituation or recovery to novelty among the infants who finished the procedure; however, testing had to be stopped in the cases of more than 50% of the cocaine-exposed sample due to inconsolable fretting. In a second study, negative affect and behavioural state in response to visual stimulation were assessed in three-month-old infants (Mayes

et al., 1996). Cocaine-exposed infants exhibited high levels of negative state (e.g., crying, grimacing, fretting) when a visual stimulus was presented for the first time, but the second time the stimulus was presented, significantly less negative state was observed. The results of these two studies were interpreted to imply that fetal cocaine-exposure leads to impairments in ability to regulate arousal, and that novelty increases arousal levels beyond the cocaine-exposed infants' abilities to self-regulate.

This theory was also investigated by Karmel and colleagues (Karmel & Gardner, 1996; Karmel, Gardner, & Freedman, in press). However, contrary to the findings of Mayes et al. (1995; 1996), cocaine-exposed infants preferred high intensity visual stimulation over low intensity stimulation at birth and one-month of age, regardless of arousal level (Karmel & Gardner, 1996). The effect was less apparent at four-months of age (Karmel, Gardner, & Freedman, in press), and it is possible that age differences may explain the inconsistency between the findings of Mayes et al. (1996) and Karmel and Gardner (1996).

While the studies of Mayes et al. (1995, 1996) and Karmel and colleagues (Karmel & Gardner, 1996; Karmel, Gardner, & Freedman, in press) imply that fetal cocaine-exposure has detrimental effects on arousal level, their findings do not eliminate the possibility that cocaine is also associated with impairments in information processing. The data from the current study suggest that, when care is taken to elicit an optimal level of arousal, as evidenced by a calm, alert state prior to testing, information processing ability is compromised among cocaine-exposed neonates. In the studies conducted by Mayes et al. (1995, 1996) the infants were brought to a laboratory for testing and it is likely that the experimenters did not have the luxury of waiting for the baby to be in an optimal state for testing. Because the current study was conducted on a hospital

maternity ward, if an infant could not be brought to an alert, non-fretful state, he or she was returned to the mother and testing was attempted again one hour after the next feeding, or the next day, if necessary. Because of this benefit to testing in the hospital, attrition due to fretting was very low.

The results of the present study are inconsistent with those of Karmel and Gardner (1996) who found that cocaine-exposed neonates preferred high intensity stimuli, and with the results of Mayes et al. (1996) who found that cocaine-exposed infants find novel stimulation aversive. If the cocaine-exposed infants in the present study had preferred high intensity stimulation, one could hypothesize that they would have recovered responding to the novel stimulus (i.e., relative to the redundant familiarization stimulus, the novel stimulus could be construed as having a higher intensity); and if novelty is aversive, then they should have failed to orient to the familiarization stimulus and exhibited more negative state than the controls during the first trial blocks of the familiarization and novelty phases (Mayes et al. defined a novel stimulus as one that was presented for the first time; thus, the familiarization stimulus in the present study was akin to their "novel" stimulus). However, in the present study, no differences were noted between the cocaine-exposed and control infants on degree of positive state, and while the cocaine-exposed infants oriented to the familiarization stimulus, they did not recover responding to the novel or dishabituation stimuli. While age differences may explain the inconsistency between the present results and those of Mayes et al. (1996), Karmel & Gardner's (1996) sample were initially tested as neonates; thus, the discrepancy in findings must be due to something other than age.

One possibility is that the differences in results across studies may be a function of the modality in which the stimuli were presented. Karmel & Gardner

(1996) and Mayes et al. (1996) used visual stimuli, whereas the current study used auditory stimuli. Auditory and visual stimulation may have differential effects on arousal and the processing of these two types of stimuli may be differentially affected by cocaine. Because a number of studies suggest that prenatal cocaine-exposure is associated with subsequent language deficits (Angelilli et al., 1994; Bruce & Wallace, 1994; Johnson et al., 1994; Lewis, Freebairn et al., 1994; Malakoff et al., 1995; Nulman et al., 1994), the auditory information processing procedure may be more apt to reveal any information processing difficulties than a visual processing paradigm. Presumably, language development is more closely linked to auditory than visual information processing and, therefore, an auditory information processing procedure may be more sensitive to the effects of cocaine. The results suggest that auditory information processing was impaired, whereas Mayes et al. (1995) found that the cocaine-exposed infants who completed a visual information processing procedure did not differ from controls on measures of habituation and recovery to novelty, and Karmel and Gardner (1996) found that cocaine-exposed infants prefer intense stimuli (and possibly, therefore, novelty). Without a comparison of the two procedures on the same sample of cocaine-exposed infants, it is impossible to determine if the inconsistent results are due to modality-specific effects of cocaine or to other procedural or sampling variables. However, preliminary data from the laboratory of D. Lewkowicz, involving the same cocaine-exposed infants tested by Karmel and Gardner (1996) indicates that fetal cocaine-exposure may be associated with impairments in auditory-visual cross-modal transfer (D. Lewkowicz, personal communication, August 14, 1996). This finding raises the possibility that cocaine may adversely affect one modality (probably auditory) more than the other (probably visual).

Study Design Issues

Control of Confounding Factors. Many earlier studies in which adverse effects of intrauterine cocaine-exposure on NBAS scores were demonstrated (e.g., Chasnoff, Griffith et al., 1989; Chasnoff, Lewis, et al., 1989; Eisen et al., 1991; Griffith et al., 1988; Mayes et al., 1993) have been criticized for attributing cocaine-exposed/non-exposed group differences to prenatal cocaine exposure while failing to control for important confounding factors, most notably maternal smoking (Nuespiel, 1994). Furthermore, studies in which more stringent controls were exercised failed to find any detrimental effects of intrauterine cocaine-exposure on NBAS scores (e.g., Coles et al., 1992; Eyler et al., 1995; Myers et al., 1995; Richardson & Day, 1991; Woods et al., 1993). Maternal smoking remains a confounding factor in the more recent studies assessing the effects of cocaine on infant information processing and arousal regulation (Karmel & Gardner, 1996; Karmel, Gardner, & Freedman, in press; Mayes et al., 1995, 1996) since a greater proportion of cocaine-exposed infants than controls were also prenatally exposed to tobacco. This lack of control over maternal smoking is particularly problematic because prenatal tobacco exposure has independent effects on NBAS regulation of state scores (Fried & Makin, 1987; Jacobson et al., 1984; Picone et al., 1982; Saxton, 1978) and habituation scores (Fried & Makin, 1987; Picone et al., 1982; Richardson et al., 1989; Saxton, 1978). Maternal prenatal smoking is also associated with reduced childhood IQ scores (e.g., Olds et al., 1994). Thus, because cocaine-exposed and control infants were not matched on maternal smoking in previous studies, difficulties in arousal regulation or visual information processing specific to cocaine-exposure cannot be determined.

In contrast to earlier studies which failed to control for confounding factors (e.g., Chasnoff, Griffith et al., 1989; Chasnoff, Lewis, et al., 1989; Eisen et al., 1991; Griffith et al., 1988; Mayes et al., 1993, 1995), in the present study, cocaine-exposed and control infants were individually matched on numerous variables, including gestational age and birthweight, SES, pregnancy weight gain, and number of cigarettes smoked during pregnancy. The cocaine-exposed and control groups were also similar in terms of the mothers' age, the age and weight of the infant at the time of testing, and infant Apgar scores at five minutes (Apgar et al., 1958). Although it was impossible to match cocaine-exposed and control infants on the extent of prenatal care received by the mother, separate analyses comparing the infants of cocaine-users who received prenatal care with those who did not, indicated that prenatal care had no apparent effect on information processing ability. Fetal cocaine-exposure resulted in a lack of habituation and recovery to novelty whether or not the mother had received prenatal care. By controlling for numerous potentially confounding variables, the probability that the observed deficits are attributable to fetal cocaine-exposure is increased.

Subject Identification. In the past, researchers studying the effects of intrauterine cocaine-exposure on infant outcome had to depend on unreliable measures of gestational cocaine use, namely self-report and urine analysis, to identify cocaine-exposed infants. As a result, cocaine-exposed infants may have frequently been unwittingly included in the "control" group. With the advent of meconium analysis, the likelihood of such errors has been significantly reduced. In the present study, meconium analysis was carried out on 88% of the control infants, and a combination of meconium analysis, urine analysis, and/or maternal self-report was used to identify cocaine-exposed infants. While this does not rule

out the possibility of unreported cocaine use during the first trimester of pregnancy leading to misclassification of cocaine-exposed infants as "controls" (since meconium analysis cannot detect first trimester drug use), the likelihood of subject misclassification was substantially reduced. It is possible that mothers may be more likely to admit to cocaine use during the first trimester since cessation of drug use is an indication of concern for the health of the baby. Moreover, all mothers consented to toxicological analysis of their infants' meconium for prenatal substance use. This variation of the bogus pipeline procedure (i.e., believing that a laboratory test for substance use will be conducted, whether or not it is actually carried out) has been shown to increase the validity of self-reports in adolescents (Murray et al., 1987; Murray & Perry, 1987; Werch et al., 1987) and pregnant women (Lowe et al., 1986). Since mothers were not aware that meconium analysis could not detect first trimester drug use (unless, of course, they were familiar with the meconium analysis literature), the likelihood that first trimester drug use would be reported was increased. In addition, the use of the bogus pipeline procedure increased the likelihood that, for the 12% of control infants whose meconium was not analyzed, maternal self-reports of no prenatal drug use were accurate. Thus, whereas the unreliable subject identification procedures used in the majority of prior studies may have resulted in misclassification of a substantial number drug-exposed infants as controls, the present study addressed this problem by using a combination of meconium analysis and self-report with the addition of a bogus pipeline procedure to ensure that control infants were not prenatally exposed to cocaine.

Cocaine and Polydrug Use. Because fetal cocaine exposure is nearly always part of a constellation of risk factors including cigarette smoking and the

use of alcohol and other drugs, it is impossible to extricate the relative contributions of these various factors to infant outcome. However, since cocaine-exposed and control infants in the present study were in most cases well-matched on a number of these confounding variables, the likelihood that the observed deficits in information processing are primarily attributable to cocaine-exposure is increased. Nevertheless, since the majority of cocaine using mothers also smoked cigarettes, it is possible that the constituents of tobacco interacted with cocaine in a synergistic fashion to produce the observed outcome. Thus, on the basis of this study, it would be incorrect to assume that the observed deficits in information processing among the cocaine-exposed infants are due to solely to cocaine; rather, it possible that they are due to a combination of maternal use of cocaine, low to moderate levels of alcohol, and, in some cases, low to moderate levels of cannabis.

Unlike the cocaine-using mothers in the majority of previous studies, the mothers in the present sample generally did not use narcotics such as heroin. Inspection of the data from the three cocaine-exposed infants whose mothers used heroin shows that two of the three performed similarly to the rest of the cocaine-exposed infants. These two infants' mothers also used cannabis. However, the one infant whose mother used heroin and cocaine but not cannabis performed more like the control infants. This particular case is interesting because it is consistent with the findings of Chasnoff et al. (1985). These researchers reported that whereas the infants in their sample who were exposed prenatally to cocaine but not narcotics were impaired on the orientation, habituation, and consolability measures of the NBAS (Brazelton, 1984), the infants exposed to a combination of cocaine and methadone (a narcotic similar to heroin) achieved normal scores. Although it is impossible to draw any

inferences on the basis of one case, it is possible that, as Chasnoff et al. suggested in their report, that the combination of cocaine and heroin in this one particular infant resulted in an antagonistic drug interaction where one substance ameliorated the effects of the other. A. Van Baar (personal communication, August 14, 1996) noted a similar pattern in her sample of drug-exposed infants -- children whose mothers had ingested both cocaine and heroin or methadone during pregnancy were not as cognitively impaired at 10 years of age as children whose mothers had ingested either of the drugs alone. In the present study, in the two infants whose mothers used cannabis along with cocaine and heroin, the addition of cannabis to the drug interaction may have reduced the antagonistic effect of heroin on cocaine, although again it is impossible to draw any conclusions on the basis of two cases. However, these data raise the possibility that antagonistic and agonistic drug interactions may account for some of the individual differences observed in the outcomes of cocaine-exposed infants born to polydrug users.

In future research, it may be useful to attempt to separate cocaine-users into different groups according to which other substances were used, rather than simply having a "cocaine use only" and a "polydrug use" group as is often the procedure. Unfortunately, sample sizes and the number of possible combinations of polydrug use often make this task impossible. Individual case descriptions are useful; if many researchers report the results of unusual cases, a pattern may become evident across studies. However, the low level of polydrug use among the cocaine using mothers in the present study increases the likelihood that the observed deficits in information processing ability are attributable to cocaine and smoking, rather than to a combination of street drugs.

One possibility that was not addressed in the current study is that infant performance may be partially related to genetic endowment; specifically, the mother's drug-taking may be related to genetic factors that she passed on to her infant that influenced his or her performance on the information processing procedure. For example, Khantzian (1985) suggested that the drug an individual comes to rely on is not a random choice, but is influenced by a host of dispositional factors, many of which may have genetic origins. Factors which appear to predispose an individual to cocaine abuse include pre-existing chronic depression, ADHD, and/or bipolar illness (Khantzian, 1985). It is possible that the genetic endowment of the infant interacts with fetal exposure to cocaine to produce the resultant outcome. For example, the genetic factors that predispose an individual to developing ADHD or major mood disorders may involve genetically determined abnormal fetal development of specific brain regions that might also affect information processing ability in the neonatal period. Fetal exposure to cocaine may interact with such genetic vulnerabilities which may partially account for the variability in infant outcome. Nevertheless, the results of the current study imply that the auditory information processing ability of the majority of cocaine-exposed newborns is adversely affected.

Implications

Although the results indicate that fetal cocaine-exposure compromises newborn central processing ability, the significance of these results for the future development of the infant are unknown. For example, it is possible that poor performance on the information processing measures is related to the increased brain stem transmission time for auditory stimuli that has been associated with fetal cocaine-exposure in some studies (Anday et al., 1989; Cone-Wesson & Spingarn, 1993; Jupiter, 1994; Rintelmann et al., 1994; Salamy et al., 1990),

although Carzoli et al. (1991) found no differences between cocaine-exposed and control infants on auditory brain stem transmission time in the perinatal period.. Delays in the transmission of auditory stimuli to the cerebral cortex could conceivably result in delayed encoding and storage of auditory stimuli. However, Salamy et al. (1990) found that on measures of auditory brain stem transmission time, by ages 3 to 6 months, cocaine-exposed infants were indistinguishable from controls. The fact that the cocaine-exposed infants showed the same degree of orientation to the familiarization stimulus as the controls suggests that the group differences on the other information processing measures are likely due to more than delays in brain stem auditory transmission time.

It is not known whether the observed deficits in the central processing of auditory information would generalize to other sensory modalities, such as the processing of visual information. However, it is possible that the auditory information processing deficits observed among cocaine-exposed newborns may be related to the reported impairments in language ability observed in the preschool and primary school years (Angelilli et al., 1994; Bruce & Wallace, 1994; Johnson et al., 1994; Lewis, Freebairn et al., 1994; Malakoff et al., 1995; Nulman et al., 1994). Since language impairments are the most consistently reported long-term effect of fetal cocaine-exposure, the auditory information processing procedure has the advantage of a direct link to language processing and may, therefore, be more sensitive to the effects of prenatal cocaine-exposure on the neonate. The information processing deficits observed in the newborn period may be an early manifestation of brain dysfunction that gives rise to impairments in language ability in later years. At present it is not known if the language delays observed in early childhood by a number of researchers will persist into adult life. However, if the deficits observed in the central processing

of auditory information among cocaine-exposed newborns are indeed an early manifestation of cerebral dysfunction, then the fact that these deficits were observed before the postnatal environment had a chance to impact on infant development implies that fetal cocaine exposure plays a causal role in the development of the observed childhood language impairments, independent of postnatal environment, as suggested by Nulman et al. (1994).

Fetal Cocaine and CNS Development. The current data indicate that fetal cocaine-exposure impacts adversely on neonatal information processing, implying abnormal CNS development. Both animal and human studies have demonstrated that cocaine disrupts fetal brain development through its effects on a number of different neurodevelopmental processes. Cocaine interferes with the three primary processes of CNS development: neuronal proliferation, migration, and differentiation (Akbari & Azmitia, 1992; Akbari, Kramer, et al., 1992; Beeker et al., 1992; Kaufmann, 1990, as cited in Lidow, 1995; Kosofsky et al., 1994; Lidow, 1995).

Disruption of neuronal proliferation, migration, and differentiation could occur through cocaine's interference with a number of different mechanisms regulating these processes (Lidow, 1995). The adverse effects of cocaine on two mechanisms crucial to the normal proliferation, migration, and differentiation of neurons, and, therefore, of normal brain development have been well-documented. First, cocaine disrupts the regulation of monoaminergic neurotransmitter systems, and monoamines play a crucial role in neural development, ultimately determining the cytoarchitecture of the brain (Chubakov et al., 1986; Lauder, 1981, 1983, 1988; Lauder & Krebs, 1978; Lidov & Molliver, 1982a, 1982b; Mattson, 1988; Wallace & Lauder, 1983). Second, the primary metabolite of cocaine, BE, is found in high concentrations in the fetal brain,

where it binds to calcium ions (Spear, Kirstein, & Frambes, 1989). Calcium ions play a key role in the development and regulation of neural circuits and brain architecture (Komuro & Rakic, 1992, 1993; Rakic & Komuro, 1995). Since monoaminergic neurotransmitter and calcium ion regulation of neuronal development are involved at all stages and in diffuse areas of brain growth and organization, cocaine-associated disruptions in these processes are likely to adversely affect a wide range of neural structures and functions (Lidow, 1995). For example, it is likely that alterations in brain cytoarchitecture are related to the disturbances in neural activity observed among laboratory animals prenatally exposed to cocaine (Dow-Edwards, 1989; Dow-Edwards et al., 1990; Spear, 1995; Spear, Kirstein, & Frambes, 1989).

Because, in the animal studies reviewed, cocaine was administered to pregnant animals continuously and at moderate to high doses, it is possible that the severity of the observed disturbances in brain development would generalize only to the most chronic users of cocaine. Nonetheless, given the wide variety of cocaine-associated detrimental effects on brain development demonstrated in animal studies, it is possible that even light or moderate users of cocaine place their fetuses at a high risk for at least minimal disturbances in brain development. Factors related to maternal, fetal and placental metabolism as well as the dosage, route of administration, timing of exposure, and other substances used no doubt interact to determine infant outcome. However, the data from the current study suggest that auditory information processing ability is adversely affected even among light and moderate users of cocaine and those who ceased using the drug during the first trimester (given that only 3 of the 25 cocaine-exposed infants habituated to the novel stimulus). However, the sample size was

too small, and the dose and timing of exposure too variable, to allow for analysis of these effects.

The precise area of the brain affected by cocaine that would result in information processing deficits and possibly subsequent language delays cannot be accurately pinpointed given the diffuse effects of cocaine and the numerous structures involved in auditory processing. However, one could speculate that since the cocaine-exposed infants oriented to the familiarization stimulus, the auditory receptors and the auditory nerve were developed, as they are in normal infants at birth (Hecox, 1975). It would seem logical to infer that cocaine results in disruptions in the development of the auditory cortex; however, it is likely that a normal performance on the auditory information processing procedure relies on the functioning of numerous other brain structures including the hippocampus, thalamus, cerebellum, and the various neural networks that connect these diverse regions of the brain. Thus, the information processing impairments cannot be localized to a specific region of the brain, although the data imply disturbances in neural function.

Limitations of the Present Study

Although the data clearly indicate that fetal cocaine-exposure has an adverse effect on information processing ability, this study is not without limitations that must be considered in evaluating the implications of the findings. First, although attempts were made to control for experimenter bias during the testing procedure by having E1 and E2 wear headphones so that they could not hear the stimulus being played or the direction of the sound source, the experimenters were often aware of the infants' group membership. Thus, it is possible that knowledge of the infants' group membership may have influenced the results through some other means than awareness of the stimulus and

direction of the sound source. One possible way this could happen is if head turns were coded less often among the cocaine-exposed group than the control group. However, this is unlikely since the overall percentage of head turns across the procedure was the same for both groups.

Second, because the data for this study were collected over a four year period without funds to pay for a research assistant, several students volunteered over the years as experimenters for testing the infants. Thus, because the research team changed several times during the period of data collection, it was not possible to conduct inter-rater reliability coefficients for the coding of head turns. Although all experimenters received thorough training before testing infants for this study, it is possible that there were individual variations among coders in coding head turns. However, inter-rater reliability has been greater than .9 in previous studies employing the same procedure and it is unlikely that the inter-rater agreement would be any lower in this study. More importantly, differences between coders would be unlikely to selectively affect one group of infants because the same experimenters were the coders for both cocaine-exposed and control infants. Thus, although the situation was unavoidable and care was taken to ensure that all experimenters were trained to carry out their tasks in a similar manner, the lack of inter-rater reliability measurements is a limitation of this study that should be considered when interpreting the results.

Finally, because meconium analysis cannot detect first trimester drug use, and because meconium analysis was not carried out for three of the control infants, it is possible that some of the control infants were exposed to drugs in utero. Unfortunately, there was no way to overcome this problem, since money was simply not available to analyze three of the meconium samples, and there

are no valid and reliable techniques for assessing first trimester drug use. Although this could be accomplished by analysis of maternal hair, the issues of external contamination and differences in the rate of drug uptake in different coloured hair precluded the use of this procedure. In addition, hair analysis was more expensive than meconium analysis.

Despite these limitations, it is unlikely that any one of them could completely account for the observed differences in performance between the cocaine-exposed and control infants on the information processing procedure. Moreover, it is doubtful that the limitations outweigh the improvements that have been made over prior studies, including (a) the use of the current auditory procedure rather than the NBAS for assessing information processing; (b) the use of meconium analysis, in addition to urine analysis and self-report with the bogus pipeline method, for ensuring that control infants were not cocaine-exposed and for documenting polydrug use; (c) controlling for a number of confounding factors through subject matching techniques; and (d) taking care to ensure each infant was in an alert, responsive state before beginning the testing procedure. Thus, despite its limitations, a number of procedures were implemented in the current study to increase scientific rigour, thereby increasing the probability that the observed effects are related to fetal cocaine-exposure.

Conclusion

This study examined the effects of fetal cocaine-exposure on newborn information processing ability. Cocaine-exposed and control infants were well-matched on five important variables that have confounded the results of previous studies. A valid measure of auditory information processing ability was used to determine the effects of fetal cocaine exposure. Cocaine-exposed infants exhibited deficits in habituation and recovery to novelty, measures which have

previously been shown to have good discriminant validity among infants at different levels of risk for developmental delay. It is possible that the deficits in the processing of auditory stimuli observed in the present study may be related to the reported impairments in language development among preschool and primary school aged children exposed to cocaine in utero. Thus, while maternal cocaine use does not often result in observable defects in fetal development, more subtle effects on cognitive functioning may be evident in the newborn period. The results of this study imply that cocaine has adverse effects on brain development independent of the effects of postnatal environment. However, it is not known whether these effects are transient in nature or of long term consequence for the development of the child.

Chapter 5: Study 2

Effects of Fetal Tobacco Exposure on Newborn
Information Processing

According to recent surveys, approximately 20% of women smoke cigarettes during pregnancy, with prevalence rates ranging from 10 to 32% depending on the geographic region sampled (Bardy, Seppälä, Lillsunde, Koskela, & Gref, 1994; The Blue Sheet, 1994; Castro et al., 1993; DHHS, 1995; Ernster, 1993; Windsor, Li et al., 1993; Windsor, Lowe et al., 1993). For nearly four decades it has been known that maternal cigarette smoking during pregnancy is associated with an increased risk for adverse pregnancy outcome.

The first report on the harmful effects of smoking during pregnancy appeared in 1957, when Simpson identified an association between gestational tobacco use and decreased birthweight among a sample of 7,499 patients (Simpson, 1957). Since then, numerous studies have confirmed this finding (Ahlborg & Bodin, 1991; Bardy et al., 1993; Castro et al., 1993; Comstock, Shah, Meyer, & Abbey, 1971; Davies, Gray, Ellwood, & Abernethy, 1976; Eskenazi, Prehn, & Christianson, 1995; Lieberman, Gremy, Lang, & Cohen, 1994; McDonald, Armstrong, & Sloan, 1992; Meredith, 1975; Meyer & Tonascia, 1977; Morrison, Williams, Najman, Andersen, & Keeping, 1993; Naeye, 1978, 1981; Olsen, 1992; Picone et al., 1982; Roquer, Figueras, Botet, & Jimenez, 1995; Rush, 1974; Walsh, 1994). Since low birthweight increases the risk for adverse infant outcome (e.g., McCormick, 1985; Petersen et al., 1990; The Infant Health and Development Program, 1990), this finding alone is enough to warrant concern over the vast numbers of infants exposed to the by-products of tobacco smoke in utero.

It is now known that the risks of maternal smoking extend well beyond its effects on birthweight. Smoking during pregnancy has been associated with an increased risk for fetal (Ahlborg & Bodin, 1991; Walsh, 1994) and neonatal death (Comstock et al., 1971; Kullander & Källén, 1971; Meredith, 1975; Walsh, 1994), including sudden infant death syndrome (DiFranza & Lew, 1995; Haglund & Cnattingus, 1990; Milerad & Sundell, 1993; Kleinman, Pierre, Madans, Land, & Schramm, 1988; Mitchell, et al., 1993; Schoendorf & Kiely, 1992; Taylor & Sanderson, 1995). Gestational cigarette smoking has been linked to abnormalities of the placenta (Naeye, 1978; Rush, Kristal, & Blanc, 1986; Sastry, Janson, Ahmed, Knots, & Schinfeld, 1989; Spira, Philippe, & Spira, 1977), pediatric respiratory problems (Fergusson, Horwood, Shannon, & Taylor, 1981; Hanrahan et al., 1992; Moessinger, 1989; Schulte-Hobein, Schwartz-Bickenbach, Abt, Plum, & Nau, 1992; Tager, Weiss, Munoz, Rosner, Speizer, 1983), cardiovascular disturbances in the infant (Abdul-Khaliq, Segerer, Luck, & Obladen, 1993; Asmussen & Kjeldsen, 1975; Russel et al., 1971), hypertonicity and increased nervous system excitation in the first month of life (Fried, Watkinson, Dillon, & Dulberg, 1987), and child behaviour problems similar to those observed in attention deficit-hyperactivity disorder (Denson, Nanson, & McWatters, 1975; Kristjansson, Fried, & Watkinson, 1989; Naeye & Peters, 1984; Weitzman, Gortmaker, & Sobol, 1992). Despite the plethora of risks associated with maternal smoking, prenatal tobacco exposure does not seem to be associated with an increased incidence of congenital malformations (Kullander & Källén, 1971; McDonald et al., 1982b; Nash & Persaud, 1988). However, a recent study suggests that prenatal exposure to tobacco smoke may increase the risk for congenital malformations in fetuses who are already genetically predisposed (Seller & Bnait, 1995).

Animal studies have provided evidence for both direct and indirect effects of nicotine and other constituents of tobacco on the developing fetus. The combustion of tobacco at the end of a cigarette produces more than 4,000 different chemical compounds (Naeye, 1981; Nash & Persaud, 1988), and nicotine is only one of the 2,000 toxic substances so far identified (Baghurst, Tong, Woodward, & McMichael, 1992). For example, the biologically active components of greatest concentration in mainstream cigarette smoke so far identified are, in order of decreasing concentration, carbon monoxide, nicotine, acetaldehyde, acetic acid, nitrogen oxides, formic acid, hydrogen cyanide, acetone, and methanol (Mactutus, 1989).

Nicotine is a powerful vasoconstrictor which acutely and chronically reduces placental blood flow, by as much as 38% immediately following nicotine administration (Nash & Persaud, 1988; Philipe, Pateinky, & Endler, 1984; Suzuki, Minel, & Johnson, 1980). This has the effect of drastically reducing the supply of oxygen and nutrients to the developing fetus (Walsh, 1994). While nicotine deprives the fetus of oxygen by reducing fetal blood supply, carbon monoxide intensifies this effect by binding to fetal haemoglobin, producing carboxyhemoglobin which is incapable of carrying oxygen to the developing fetal cells (Benowitz, 1991; Bureau et al., 1982; Suzuki et al., 1980). Furthermore, carboxyhemoglobin concentrations in the fetus are higher than those in the mother and the elimination half-time may be as much as three times longer (Bureau et al., 1982; Mactutus, 1989; Nash & Persaud, 1988). A similar phenomenon has been observed with nicotine in both animals (Nash & Persaud, 1988; Suzuki, et al., 1974) and humans (Luck, Nau, Hansen, & Steldinger, 1985). When a biochemical marker of tissue oxygen deprivation, erythropoietin, was measured in the cord blood of newborns whose mothers smoked cigarettes

during pregnancy, the results indicated that approximately one in five fetuses who are exposed to tobacco smoke is in a state of chronic hypoxia (Varvarigou, Beratis, Makri, & Vagenakis, 1994).

In addition to its indirect effect on the developing fetal brain through reduced oxygen and nutrient supply, nicotine readily crosses the blood-brain barrier and has been shown to interfere directly with fetal brain development. Animal studies have shown that prolonged fetal exposure to nicotine increases the number of nicotinic cholinergic binding sites (Navarro et al., 1989; Slotkin, Orband-Miller, & Queen, 1987), delays cell maturation (Navarro et al., 1989; Slotkin, Greer, Faust, Cho, & Seidler, 1986), reduces neuronal proliferation (Navarro et al., 1989) and differentiation (Slotkin et al., 1986), and increases forebrain levels of dopamine and norepinephrine (Lichtensteiger, Ribary, Schlumpf, Odermatt, & Widmer, 1988). Among rats prenatally exposed to nicotine, the metabolism of central catecholamine systems has been shown to remain disturbed into adulthood (Lichtensteiger et al., 1988). By interfering with early biochemical events that regulate the growth and development of the CNS, nicotine-exposure may ultimately result in various functional and structural abnormalities of the CNS (Nash & Persaud, 1988). In addition, there has been speculation that the catecholamine disturbances induced by prenatal nicotine exposure may be linked to both behavioral and learning problems (Lichtensteiger et al., 1988). Lesions of the dopamine system have been shown to result in motor hyperactivity and decreased performance in young rats, whereas lesions of the norepinephrine systems produced learning deficits (Raskin, Shaywitz, Shaywitz, Cohen, & Anderson, 1984, as cited in Lichtensteiger et al., 1988).

Although it should not be assumed that the results of studies with rats will generalize to humans (Tong & McMichael, 1992), the evidence suggests that

maternal smoking during pregnancy may interfere with fetal brain development. If these effects occur in humans, it is possible that such disturbances in normal brain development may be manifested in impairments of higher order brain processes.

Maternal Smoking and Child Cognitive Development

Adverse effects of fetal tobacco-exposure on newborn neurobehavioural functioning have been examined in a number of studies, with inconsistent results (Fried & Makin, 1987; Jacobson et al., 1984; Picone et al., 1982; Richardson et al., 1989; Saxton, 1978). Saxton (1978) published the first study employing the NBAS (Brazelton, 1984) to investigate the effects of maternal smoking on newborn neurobehavioural functioning. Infants born to mothers who smoked 15 or more cigarettes per day had depressed scores on measures of orientation and habituation to auditory stimuli relative to controls, and were more difficult to console (Saxton, 1978). The two groups were matched for SES, maternal age, and parity, and all were of normal birthweight.

Saxton's (1978) results were replicated by Picone et al. (1982) who also found deficits on measures of orientation and habituation to auditory stimuli, along with difficulties in autonomic regulation, among the infants of smokers. These effects occurred independent of birthweight and maternal weight gain. It was implied that the same potential covariates controlled by Saxton were also controlled in this study, but this was not explicitly stated.

Deficits on the auditory habituation measures of the NBAS (Brazelton, 1984) were also associated with maternal smoking in a prospective study involving 250 infants (Fried & Makin, 1987). In this study, the offspring of smokers were less irritable, although they exhibited more tremors, than the offspring of non-smokers. It is important to note that among the mothers of the

infants of this sample, 19% smoked marijuana, and 40% were classified as moderate to heavy drinkers (i.e., more than .14 ounces of absolute alcohol per day, with 5% drinking more than .85 ounces per day). Although the effects of maternal smoking on the NBAS measures were different from the effects observed for marijuana and alcohol, and the tobacco-associated deficits in habituation to auditory stimuli persisted after statistically controlling for these covariates, it is possible that an interaction between tobacco constituents and alcohol or marijuana could account for the observed effects. However, it is not clear why the infants in this study were less irritable whereas Saxton (1978) described them as more difficult to console.

Other studies employing the NBAS (Brazelton, 1984) have not supported the existence of tobacco-associated deficits in infant performance. Jacobson et al. (1984) failed to find group differences on measures of auditory orientation and habituation, although the previously reported decreased irritability among infants of smokers (Fried & Makin, 1987) was replicated. While orientation to auditory stimuli was initially impaired among infants born to smokers, the effect did not reach significance after controlling for group differences on SES and caffeine consumption.

Richardson et al. (1989) found that smoking in the third trimester of pregnancy was related to poorer scores on habituation to auditory stimuli, although smoking during the first and second trimesters resulted in no harmful effects, and smoking at any time during pregnancy was not associated with performance deficits on any other NBAS (Brazelton, 1984) measures. However, 45% of the mothers in the total sample drank alcohol, and 27% smoked marijuana, at least one to six times per week during the first trimester of pregnancy, with the percentage of users declining from the first trimester to

delivery. Moreover, examiner effects (observer biases) were the best predictor of infant performance in this study, suggesting that the infant scores on the NBAS measures may have been unreliable.

Overall, the results of studies employing the NBAS (Brazelton, 1984) to assess newborn neurobehavioural functioning suggest that maternal smoking during pregnancy may adversely effect infant responses to auditory stimuli, although the evidence is not entirely consistent. Deficits on both orientation and habituation to auditory stimuli have been found, whereas responses to visual stimuli were normal. These data suggest that fetal exposure to the constituents of tobacco may selectively affect the development of the auditory system.

While studies with newborns are relatively free from the confounding effects of postnatal life on infant development, the long-term effects of prenatal tobacco exposure on cognitive development are very difficult to separate from the effects of numerous other variables. For example, maternal factors associated with cigarette smoking include maternal age, race, SES, education level, intelligence, mental health, and marital status, to name but a few. Other confounding factors from the child's postnatal environment include postnatal exposure to cigarette smoke, quality of the home environment (including parenting style and opportunities for stimulation), number of siblings, and day care and/or preschool experience, among other things (Baghurst et al., 1992; Olds et al., 1994). When the multitude of pre- and perinatal confounds are considered, the list of potential covariates is endless. While it would be impossible to control for all potential confounds, the most rigorous studies have attempted to control for group differences on at least several factors that distinguish smokers from non-smokers.

Because it is very rare for a mother who has smoked cigarettes during pregnancy to quit smoking after giving birth, passive exposure of the infant to tobacco smoke generally continues postnatally. With large sample sizes it is occasionally possible to distinguish between the developmental effects attributable to prenatal versus postnatal tobacco exposure by comparing infants born to mothers who began smoking after the birth of the baby with those whose mothers smoked both during and after pregnancy. However, in many studies this was not possible, and the effects of prenatal tobacco exposure were confounded by the effects of postnatal exposure.

The effects of prenatal tobacco exposure on development in infancy have been assessed in four studies using the BSID (Bayley, 1969). In a large scale follow-up study of 400 families, infant IQ at 12 months of age was not found to be affected by maternal prenatal or postnatal smoking after controlling for group differences in social class, maternal education, maternal IQ assessed with the PPVT (Dunn, 1965), caregiving qualities and conditions in the home environment (Olds et al., 1994).

The results of Olds et al. (1994) were corroborated by a case-control study involving 69 infant pairs matched on maternal race, parity, age, and SES (Schulte-Hobein et al., 1992). The BSID (Bayley, 1969) was administered at ages 6 and 12 months, to 69 infants born to mothers who smoked five or more cigarettes per day and 69 infants whose mothers did not smoke. To verify maternal self-reports concerning smoking, infant urine was analyzed for cotinine content at each test age. There were no differences between groups on the psychomotor or mental development scales, despite the fact that the smokers' infants were of significantly lower birthweight and experienced more lower respiratory tract infections.

A third study, involving 548 infants tested at 24 months of age, also failed to find deficits on BSID (Bayley, 1969) scores among infants whose mothers smoked during pregnancy (Baghurst et al., 1992). However, when 72 mothers who began smoking after pregnancy were added to the sample of 160 mothers who smoked both during and after pregnancy, there was a significant effect of postnatal exposure to tobacco smoke on the Mental Development Index of the BSID; effects of prenatal smoking had no effect on BSID scores.

In contrast to the findings of these studies, Gusella and Fried (1984) found an association between maternal smoking and a decrease in BSID (Bayley, 1969) Motor Scale scores in a sample of 84 infants assessed at 13 months of age. Maternal smoking was also associated with a decline in verbal comprehension and fine motor skills (cluster scores derived from the BSID item scores). The effects remained significant after controlling for maternal prenatal alcohol consumption, paternal education and birthweight.

Three out of four studies employing the BSID (Bayley, 1969) to assess the effects of prenatal smoking on infant development failed to find any adverse effects. However, it is possible that the BSID is not sufficiently sensitive to detect subtle alterations in brain functioning. Although the BSID claims to announce normality (Bayley, 1967), it has virtually no predictive validity for later intelligence before two years of age (McCall, 1979; Zelazo, 1989). However, all but one of the studies relied entirely on maternal self-report to identify smokers. If some mothers falsely reported that they did not smoke during pregnancy and their infants were included in the non-exposed control group, the probability of detecting any true group differences associated with prenatal maternal smoking would be reduced.

Studies in which children were followed into the preschool and middle childhood years suggest that exposure to tobacco smoke, both prenatally and postnatally, has mild detrimental effects on child cognitive development. For example, Sexton, Fox, & Hebel (1990) administered the McCarthy Scales of Children's Abilities (1972) to 101 three-year-old children whose mothers had quit smoking between the 18th and 32nd weeks of pregnancy and 263 children whose mothers smoked 10 or more cigarettes per day throughout pregnancy. In addition, mothers completed a preschool version of the Minnesota Child Development Inventory (Ireton, Thwing, & Currier, 1977). Self-reports of smoking were verified with analyses of saliva for thiocyanate, a marker of smoking status. Compared to the offspring of women who quit smoking, the offspring of women who continued to smoke throughout pregnancy scored significantly lower on all the McCarthy subscales (General Cognitive Index, Perceptual-Performance, Quantitative, Verbal, and Motor) except the Memory scale. The Verbal scale and General Cognitive Index were the most severely affected. These findings were further supported by scores on the MCDI, on which the children of smokers received lower scores on the General Development, Expressive Language, and Comprehension-Conceptual subscales. The results of this study suggest that maternal smoking throughout pregnancy compromises the cognitive development of the child compared to quitting smoking by the 8th month of gestation. Although postnatal exposure to cigarette smoke was not addressed in this study, it is likely that the majority of children exposed to tobacco prenatally were also exposed postnatally, thereby confounding the effects of prenatal exposure with those of postnatal exposure.

Similar effects of prenatal tobacco exposure on the cognitive development of preschoolers were reported by Fried & Watkinson (1990). The McCarthy

Scales of Children's Abilities (McCarthy, 1972) and Reynell Developmental Language Scales-Revised (Reynell, 1977) were used to compare the cognitive development of 72 children whose mothers smoked during pregnancy and 61 children whose mothers were non-smokers. At three years of age, children born to smokers scored significantly lower on the Verbal subscale of the McCarthy, with the effect remaining significant after controlling for a number of covariates. At four years of age, smoking was found to be associated with decreased scores on the Verbal scale of the McCarthy, the expressive component of the Reynell, and the PPVT-R (Dunn & Dunn, 1981). Although the effects of multiple drug-exposure were statistically controlled, 53% of the mothers drank more than .14 ounces of absolute alcohol per day and 23% smoked marijuana on a weekly or daily basis during pregnancy. Thus, the observed relation between prenatal tobacco exposure and child cognitive development may actually be due to an interaction between alcohol, marijuana, and tobacco in the developing fetus. In addition, postnatal exposure to tobacco smoke was not considered in the analyses.

Contrary to the findings of Fried & Watkinson (1990), Baghurst et al. (1992) found that scores on the McCarthy Scales of Children's Abilities (1972) were not affected by prenatal maternal smoking. In a study in which 548 children were followed to 4 years of age, prenatal tobacco exposure was not associated with lower scores on the McCarthy. Although there were initial effects of postnatal exposure to cigarette smoke on the General Cognitive Index scores, these were no longer significant after controlling for covariates. The variables identified as having independent effects on children's cognitive abilities included gender, SES, quality of the home environment, maternal intelligence, birthweight, feeding style, and number of siblings in the household. However, the findings of this

study were limited by the fact that smoking was based entirely on self-report, women who reported smoking up to 5 cigarettes during their pregnancy were included in the non-smoking group, and maternal consumption of alcohol and other drugs was not considered.

In the cohort followed by Olds et al. (1994), scores on the BSID (Bayley, 1969) at 12 months and the Catell Scales (Catell, 1940) at 24 months did not differentiate between smokers and non-smokers. However, at ages 36 and 48 months, children whose mothers smoked during pregnancy had significantly lower scores on the Stanford-Binet Intelligence Test (Terman & Merrill, 1960). Scores of smokers' children were an average of 9.44 points lower than those of non-smokers' children, although the difference in IQ was reduced to 4.35 points (still significant) after controlling for maternal age, education, SES, gender, number of cigarettes smoked per day at 48 months postpartum, quality of diet, gestational age at initiation of prenatal care, number of prenatal visits, maternal intelligence (assessed by the PPVT; Dunn, 1965), maternal depression and sense of control, and quality of the home environment. (Other potential covariates such as alcohol and other drug use were examined, but were not associated with the outcome measures). Postnatal exposure to tobacco smoke in the absence of prenatal exposure did not significantly effect child IQ scores. The greatest effect was observed among children whose mothers smoked 10 or more cigarettes per day beyond 34 weeks gestation (IQ was lowered by 5.25 points after controlling for confounding factors). The IQ scores remained virtually unchanged after controlling for infant factors including birthweight, head circumference, and gestational age. In contrast to the majority of other studies, an attempt was made in this study to verify the reliability of maternal self-reported smoking status by performing serum cotinine assays on a subsample of

95 women. Self-report was found to be more accurate near the end of pregnancy (34th week of gestation) than at the beginning of pregnancy (17th week of gestation) when the women registered for the study, although the percentage of smokers who denied smoking was not reported. Thus, in one of the best-controlled studies available, prenatal cigarette smoking was found to have a small but significant effect on child intelligence at 3 and 4 years of age, independent of postnatal exposure to tobacco smoke. Unfortunately, only global IQ scores were reported; therefore, it is not known if maternal smoking had a greater adverse effect on verbal scores than performance scores as was found in a number of other studies.

Several studies have assessed the effects of prenatal tobacco exposure on cognitive ability in school-aged children. Dunn, McBurney, Ingram, & Hunter (1977) administered a test battery that included the Wechsler Intelligence Scale for Children (WISC; Wechsler, 1949), Bender Visual-Motor Gestalt test (Bender, 1946), the Vocal Encoding test from the Illinois Test of Psycholinguistic Ability (Kirk, McCarthy, & Kirk, 1968), and the Goodenough-Harris Draw-a-Man test (Harris, 1963) to 151 children at 6½ years of age. Children were classified according to whether or not the mothers smoked during pregnancy, and according to whether they were full-term and of normal weight, small-for-gestational-age, or premature with appropriate birthweight. The scores of children born to smokers were consistently lower than those of children born to non-smokers, in all birth categories. Significant differences in favour of non-smokers' children were found for the WISC Full-Scale, Verbal, and Performance IQ's, Bender Gestalt test, and Vocal Encoding tests, in at least one birth category. This study also found that boys born to smokers exhibited more behaviour problems than boys born to non-smokers. All effects occurred

independent of family social status, and maternal age, parity, height and weight. However, the use of alcohol and other drugs was not documented, and smoking was based on self-report.

Deficits on the Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler, 1975) among 6 to 9-year-old children prenatally exposed to tobacco have been reported by Makin, Fried, and Watkinson (1991). Children of smokers also achieved significantly lower scores on the PPVT-R (Dunn & Dunn, 1981), the Syntax Quotient of the Language Development-Primary test (Newcomer & Hammill, 1982), and the Goodenough-Harris Draw-a-Man test (Harris, 1963). Smokers' children also had higher behaviour problem ratings on the Connor's Parent Questionnaire (Connors, 1970). These findings suggest that prenatal cigarette exposure compromises the normal development of speech and language skills, intelligence, visual/spatial abilities, and behaviour regulation (Makin et al., 1991). However, a percentage of mothers in this study also consumed alcohol and smoked marijuana on a regular basis, and substance use was based on self-report.

In contrast to Makin et al's (1991) findings of an association between lower WISC-R (Wechsler, 1975) scores and maternal cigarette smoking in pregnancy, one well-controlled study failed to find these effects among 8 to 12-year-olds after controlling for confounding factors (Fergusson & Lloyd, 1991). More than 800 children were tested on the WISC-R, Burt Word Reading Test (Gilmore, Croft, & Reid, 1981), and the Progressive Achievement Tests (PAT) in Reading Comprehension and Reading Vocabulary (Elley & Reid, 1969) and the PAT Mathematics Test (Reid & Hughes, 1974). While there was a dose-related decline in performance on nearly all measures for each age group (ages 8, 9, 10, 11, and 12 years) for each trimester of pregnancy in which the mother smoked,

none of the effects remained significant after controlling for covariates. In this study, covariates included family SES, quality of mother/child interaction, maternal avoidance of restriction and punishment, average family standard of living from birth to 10 years, maternal education, number of changes of school from entry to seven years, and number of years of preschool education. Adjustments were also made to control for selection bias due to subject attrition. Thus, while children born to smokers achieved lower scores than children whose mothers did not smoke, the differences were attributable to factors other than maternal smoking.

One way to address the issue of confounding factors is to control for them directly through subject selection procedures rather than using statistical control techniques during data analysis. Naeye & Peters (1984) were able to control a large number of confounding factors by comparing the academic achievement, assessed by the Wide-Range Achievement Test - Revised (Jastak & Jastak, 1965), and attentional and behavioral problems at 7 years of age among 578 sibling pairs whose mothers had smoked during one but not in the other of the two pregnancies. An equal number of women smoked in the first as in the second of the two pregnancies. Prenatal smoking was associated with significantly lower scores on Spelling, Reading, and Attention Span, and a significantly higher Motor Activity score. Despite the statistical significance of the differences in scores, achievement test scores were only 2 to 5% lower and behavioural abnormalities 2% more frequent when the mothers had smoked. Neonatal haemoglobin levels were also measured in this study. Haemoglobin levels increased with the number of cigarettes smoked by the mother during pregnancy. Interestingly, among the children born to smokers, those who were identified as hyperactive and having short attention spans at age seven had

significantly higher haemoglobin levels at birth than children with normal behaviour; the same correlation did not exist among the children of non-smokers. Because this study employed a matched-pair design with siblings from the same family, the impact of numerous demographic factors and genetic influences on intellectual ability were controlled, increasing the likelihood that the decrements in academic achievement scores and the increase in behaviour problems were due to prenatal tobacco exposure.

Similar decrements in achievement scores among the offspring of smokers had been reported more than 20 years earlier by Butler and Goldstein (1973) in a follow-up study of more than 12,000 children. Children were given a reading test at age 7, and reading, mathematics, and general ability tests at age 11 (the names of the specific tests administered were not reported). The children were divided into three groups according to the number of cigarettes smoked per day by the mother after the fourth month of pregnancy (non-smokers, 1 to 9 cigarettes per day, and 10 or more cigarettes per day). Smoking-related deficits were found on all measures, and persisted after controlling for the mother's height, age, social class, number of older and younger children in the household, and the sex of the child. Although various other confounding factors that have been found to distinguish between smokers and non-smokers were not addressed, the very large sample size and the control of a number of confounding factors increase the credibility of the findings. One of the primary limitations of this study is that the use of alcohol and other drugs was not taken into account. Although maternal smoking was identified through self-report, self-reported smoking may have been more reliable at the time the data were collected than it would be today. Because these children were born in the early 1960's, before the risks of smoking during pregnancy were widely publicized, and

before there were the current social sanctions against smoking during pregnancy, women may have been more likely to report smoking than they would be today. It is likely that due to the strong social sanctions of the 1980s and 1990s against all smoking, and the even greater sanctions against smoking during pregnancy, that self-reports concerning gestational cigarette smoking would be highly unreliable in more recent studies, with large proportions of smokers denying smoking or under-reporting the number of cigarettes smoked.

Identifying Gestational Cigarette Smokers

The majority of studies published to date which assessed the effects of maternal smoking on infant outcome relied on self-reports of smoking during pregnancy. However, there is a wide-spread belief that self-reports of cigarette consumption are unreliable. For example, in a confidential survey of 211 outpatients at a general hospital, 121 (43%) said they currently smoked cigarettes. However, 21 (18%) of the self-reported non-smokers had levels of biochemical markers suggestive of cigarette smoking.

In another study, Windsor, Morris, & Cutter (1989) measured levels of thiocyanate (a metabolite of nicotine) in the saliva of pregnant women and reported that the reliability of self-report was low. However, the use of thiocyanate as a biochemical marker of cigarette smoking has been criticized since thiocyanate can be present in the saliva of non-smokers (Patrick et al., 1994). In addition, there is a degree of error inherent in any biochemical measure assessing levels of the by-products of cigarettes; classification error could be due to either error in the self-reports, or error in the biochemical measures (Murray, Connett, Lauger, & Voelker, 1993).

Recent studies and literature reviews have suggested that in most studies, self-reports of smoking are as accurate in identifying smokers as laboratory

analyses for the by-products of cigarette smoke (Gilpin et al., 1994; Kozlowski & Heatherington, 1990; Patrick et al., 1994). The sensitivity and specificity of self-report are in the order of 88% for non-pregnant individuals, similar to the sensitivity and specificity of analysis of saliva for cotinine (Patrick et al., 1994). This means that in any given sample, it can be expected that approximately 12% of smokers will be misclassified as non-smokers. Nevertheless, reliability decreases as the social desirability of reporting not smoking increases (Murray et al., 1993). Such might be the case with pregnant women; in one literature review which led to the conclusion that the reliability of self-reported smoking is generally high, studies involving pregnant women were deliberately excluded from the analysis (Patrick et al., 1994).

The use of biochemical markers to verify self-report is recommended for any study where the reliable identification of smokers and non-smokers is crucial to the aims of the study (Patrick et al., 1994), and with pregnant women, this may be particularly important since the social desirability of reporting not smoking is high (Eskenazi et al., 1995). Thus, in studies on the effects of prenatal tobacco use, biological markers with high sensitivity and specificity should be used to verify maternal self-report.

Of the various biochemical markers of cigarette smoking, cotinine (the primary metabolite of nicotine) has the highest sensitivity and specificity (Jarvis, et al., 1987; Murray et al., 1993; Patrick et al., 1994), particularly when measured in plasma as opposed to saliva or urine. Serum cotinine levels in pregnant women have been shown to be more closely related to newborn birthweight than maternal self-reports of smoking (Eskenazi et al., 1995; Haddow, Knight, Palomaki, McCarthy, & Foss, 1989).

Recently, cotinine has been shown to collect in the meconium of fetuses whose mothers smoked cigarettes during pregnancy (Ostrea, Knapp, Romero, Montes, & Ostrea, 1994). Since cotinine levels in serum, saliva, and urine can only identify exposure to nicotine within one day of sample collection (Haddow et al., 1989; Luck et al., 1985), meconium analysis has the potential to identify newborns whose mothers smoked at any time beyond the first trimester of pregnancy, the point at which when meconium begins to form.

Ostrea et al. (1994) demonstrated that analysis of meconium for cotinine using radioimmunoassay could distinguish between infants of mothers who smoked more than one pack of cigarettes per day and non-smokers. However, cotinine levels were similar for infants whose mothers smoked less than one pack per day and those exposed to second-hand cigarette smoke. Others have also found significant levels of cotinine in the plasma of individuals exposed to second-hand smoke (Eskenazi et al., 1995). Thus, while the analysis of meconium holds promise as a method for identifying infants exposed to maternal tobacco smoke in utero, it may not be possible to distinguish between infants born to mothers who were light smokers and those who were exposed to second-hand smoke. Since few mothers smoke more than one pack of cigarettes per day during pregnancy, the utility of this measure is questionable. However, D. Lewis, of the United States Drug Testing Laboratories, reported that although the methods for analyzing meconium for cotinine were still in the experimental stage, the method used in his laboratory was somewhat different than the method used by Ostrea and should discriminate among true smokers and those exposed to second-hand smoke (Personal communication, June 5, 1995).

The previously described bogus pipeline method has been advocated for improving the reliability of self report in cases where it is not possible to carry out toxicological analyses (Patrick et al., 1994). Believing that an objective measure of substance use (in this case, meconium analysis) will be used to confirm self-reports has been shown to increase their reliability (e.g., Lowe et al., 1986; Murray et al., 1987; Murray & Perry, 1987; Werch et al., 1987). Thus, the bogus pipeline procedure may be a useful technique to enhance the validity of self-report in studies assessing the outcome of infants prenatally exposed to tobacco. The lack of inclusion of such methods in studies assessing the impact of maternal smoking on child development may account for some of the inconsistencies in the findings across studies.

Summary and Rationale for the Present Study

The research findings suggest that smoking during pregnancy has a small but measurable detrimental effect on cognitive ability in childhood, although it is not clear whether the effects are due prenatal exposure, or a combination of pre- and postnatal exposure, of the child to maternal smoking. Although deficits have been reported for both verbal and non-verbal ability, verbal skills seem to be more sensitive to the effects of tobacco exposure. It is possible that the weaker verbal skills of children whose mothers smoked during pregnancy may be a later manifestation of the impairments in responsiveness to auditory stimuli seen on the NBAS (Brazelton, 1984) among tobacco-exposed neonates. However, no study has been published to date in which the cognitive ability of infants prenatally exposed to tobacco was assessed using the newer, more valid information processing procedures now available. Researchers have relied on the NBAS and the BSID (Bayley, 1969) to assess the development of infants

born to smokers, conventional measures which have virtually no predictive validity for later cognitive ability.

Of the five studies employing the NBAS (Brazelton, 1984) to compare the behaviour of neonates born to mothers who smoked during pregnancy with those born to non-smokers, four found that maternal smoking was related to deficits in responsiveness to auditory stimuli (Fried & Makin, 1978; Picone et al., 1982; Richardson, Day, & Taylor, 1989; Saxton, 1978). These findings suggest that maternal smoking selectively impairs auditory functioning. However, because the NBAS does not include measures of central processing of auditory stimuli, it is not known whether the observed effects are the result of a reduced auditory threshold or impairments in the central processing of auditory stimuli. Since there have been no reports that children exposed prenatally to tobacco are more likely to be deaf than children born to non-smokers, it is possible that the lower NBAS scores are a result of difficulties in the active processing of the stimuli. However, it is also possible that the obtained results are a consequence of the shortcomings of the NBAS as an assessment instrument. As previously stated, examiner bias may be the best predictor of an infant's scores (Richardson et al., 1989). This is due, among other things, partly to the subjective nature of the behavioural ratings and the fact that the examiner both holds the infant, delivers the stimuli, and determines the score. In addition, the auditory orientation and habituation tasks are delivered in such a way as to allow visual cues to guide the infant's head turning response that is used to determine orientation or habituation. Thus, the NBAS has several shortcomings that weaken the findings of the studies in which it is employed. However, by using procedures sensitive to deficits in the central processing of auditory stimuli, the question of whether fetal

tobacco exposure has detrimental effects on fetal brain development can be addressed.

In the present study, the previously described (Chapter 4) method of assessing newborn information processing was used to compare newborns whose mothers smoked cigarettes during pregnancy with newborns whose mothers did not smoke. The auditory information processing procedure was developed to overcome the weaknesses of the NBAS by assessing information processing under highly controlled conditions, including: (a) delivering the stimuli through stereo speakers to remove the visual cues provided in the NBAS; (b) having separate experimenters deliver the stimuli, hold the infant, and record the head-turning responses; (c) having the holder and coder wear headphones delivering stimuli simultaneously to both ears to reduce the likelihood of experimenter bias; and (d) only assessing information processing ability when the infant is in an alert, responsive state. The validity of this method for discriminating among newborns at different levels of risk for developmental delay has been demonstrated by Zelazo et al. (1989), and Study 1 of this dissertation demonstrated its ability to discriminate among cocaine-exposed and non-exposed infants. If the reported decrements in verbal ability, and IQ and achievement test scores among tobacco-exposed children are due to the influence of maternal cigarette smoking on fetal brain development, these effects may be manifested in reduced auditory information processing ability in the newborn.

Because the effects of prenatal tobacco-exposure on child development are most often confounded by postnatal exposure to cigarette smoke, the detection of information processing deficits in the neonate would provide further support for the direct effects of prenatal tobacco exposure on the developing fetal brain.

One important issue which challenges the validity of the majority of studies on the effects of maternal smoking on child outcome is that self-report was used as the primary means of classifying infants as tobacco-exposed or non-exposed (Tong & McMichael, 1992). In addition to the fact that a number of smokers are likely to be misclassified as non-smokers when self-report is the sole means of subject classification, infants whose mothers used other drugs during pregnancy are likely to be included in the sample. In the few studies where laboratory analyses have been used to verify maternal self-report, these analyses have been limited to nicotine metabolites for the verification of self-reports of cigarette smoking. No study assessing the effects of prenatal cigarette smoking used laboratory measures to assess the prevalence of illicit drug use among the participants. In the 1970's and 80's marijuana use was common; in one study on the effects of prenatal tobacco exposure, more than 40% of mothers used marijuana in the first trimester of pregnancy and more than 20% used it in the second and third trimesters (Richardson et al., 1989). In the cohort followed by Fried and colleagues (e.g., Fried & Makin, 1987; Fried, Watkinson et al., 1987; Fried & Watkinson, 1990), more than 23% of mothers reported using marijuana prenatally. In more recent years, there is evidence to suggest that, relative to marijuana, pregnant women are equally or more likely to use cocaine. Prevalence studies conducted in the 1980's and 90's show that more than 10% of North American infants were exposed to cocaine in utero (see Chapter 1, Table 1) and an equal or lesser percentage were exposed to marijuana. Therefore, unless multiple drug use is assessed using reliable methods (e.g., meconium analysis), and polydrug users are excluded, the effects of tobacco may be either augmented or masked by the effects of other drugs.

In the present study, meconium was analyzed for approximately half of the sample to ensure that the infants were not exposed to cannabis, cocaine, or opiates in utero. Meconium was also analyzed for cotinine (a metabolite of nicotine) to verify maternal reports of smoking status. Although a lack of funds prevented the analysis of all meconium samples, the mothers were made aware, before signing the consent form, that meconium would be collected and analyzed for drugs. This "bogus pipeline" method has been shown to increase the accuracy of self-reported substance use (Lowe, Windsor, Adams, Morris, & Reese, 1986; Werch, Gorman, Marty, Forbess, & Brown, 1987; Murray, O'Connell, & Schmid, 1987; Murray & Perry, 1987). By collecting meconium samples and informing the mothers that meconium would be analyzed for drugs, it is likely that the overall accuracy of self-report would be enhanced.

Whereas the results of a number of studies examining the effects of maternal smoking on infant outcome have been confounded by the presence of illicit drug users in the study samples (Fried & Makin, 1987; Fried & Watkinson, 1990; Makin, Fried, & Watkinson, 1989; Olds et al., 1994), in the present study, all infants born to known or suspected illicit drug users were excluded. Unfortunately, the percentage of women who used alcohol during pregnancy was too high to exclude all drinkers; however, none of the mothers in the present study were heavy drinkers, with most reporting drinking less than one drink per month.

In summary, the present study employed one of the most valid measures of newborn information processing available to assess the effects of prenatal tobacco-exposure on fetal brain development. In many cases fetal exposure to illicit drugs was assessed via meconium analysis and in other cases a "bogus pipeline" method was used to increase the validity of maternal self-report. The

detection of any effects of prenatal tobacco exposure on newborn information processing would lend support to the theory that the reported lower IQ and achievement scores among children of smokers are at least partially attributable to the influence of the various constituents of tobacco smoke on the developing fetal brain.

Hypotheses

Because the evidence suggests that the constituents of tobacco are mildly neuroteratogenic and exposed children exhibit mild decrements in IQ and academic achievement, it was hypothesized that the tobacco-exposed newborns would show mild deficits in information processing ability. It was hypothesized that, relative to controls, tobacco-exposed neonates would show reduced recovery of responding to a novel stimulus following habituation to a previously presented stimulus. Although there are consistent reports that prenatal tobacco-exposure is associated with deficits in orientation and habituation to auditory stimuli on the NBAS (Brazelton, 1984), tobacco-exposed infants were not expected to exhibit deficits in orientation and habituation to the familiarization stimulus on the present procedure; such deficits were not evident among newborns at high risk for developmental delay in a previous study (Zelazo et al., 1989). More detailed hypotheses can be found on pp. 238-240.

Method

The present study consists of two parts. In Part I, healthy infants born to mothers who smoked cigarettes (but did not use illicit drugs) during pregnancy were compared on the information processing measures with healthy, non-drug-exposed infants born to non-smokers. In Part II, dose-response effects of smoking on information processing ability were explored; the infants born to smokers were divided into two groups based on the number of cigarettes

smoked per day by the mother and compared with infants born to non-smokers. To control for differences in birthweight and SES among the infants born to smokers and non-smokers, infants in each group were individually matched on these variables in Part II. The participants, method, and results for Part I are described first, followed by the participants and results for Part II. The method was the same for Parts I and II.

Part I

Participants

All participants were recruited from the maternity ward of the Sir Mortimer B. Davis Jewish General Hospital in Montreal, Quebec. Of the original sample of 120 non-cocaine-exposed infants tested on the information processing procedure for Study 1 (Chapter 4) a number of infants were excluded, as previously mentioned, for the following reasons: nine exhibited high levels of untestable state (i.e.; fretting and sleeping), 16 had a head-turning bias in one direction that was attributed to the holding position of one particular experimenter, and in three cases information concerning maternal smoking was not provided by the mother. Another six infants were excluded because of maternal self-reported cannabis use or a history of cocaine use prior to pregnancy. The remaining 86 infants were divided into two groups according to maternal self-reports of cigarette smoking during pregnancy (infants born to 18 smokers and five non-smokers from this sample also served as matched controls for cocaine-exposed neonates in Study 1).

Of the total sample, 34 infants, 20 females and 14 males, were born to mothers who reported cigarette smoking during pregnancy (tobacco-exposed group). The number of cigarettes smoked per day by the mothers of the tobacco-exposed infants ranged from 2 to 25 ($M=10.8$), with 17 mothers

smoking 10 or more cigarettes per day during pregnancy, and 17 smoking less than 10 cigarettes per day. The control group consisted of 52 healthy newborns, 23 females and 29 males, born to self-reported non-smokers. Table 11 provides the means and standard deviations for birthweight (BW), weight at testing (TW), gestational age (GA), corrected gestational age at time of testing (TA = GA + postnatal age), socioeconomic status (SES), maternal weight gain during pregnancy (WG), Apgar score at 5 minutes (APG), mothers' age (MA), parity (PAR), gravidity (GRAV), and the mothers' highest level of education achieved (ED). Maternal education was coded on a five point scale where 1 = did not complete high school and 5 = graduated from university, with other levels of education falling in between. All infants were normal in appearance (i.e.; had no visible birth defects) and had five-minute Apgar scores of at least eight, with 97% ($n=33$) of the tobacco-exposed and 98% ($n=51$) of the control infants having Apgar scores of nine or ten.

Meconium analysis was carried out for 19 (56%) of the 34 tobacco-exposed infants and 21 (40%) of the 52 control infants to rule out fetal exposure to cocaine, cannabis, and opiates during the second and third trimesters of pregnancy. Although meconium samples were available for 23 (68%) of the tobacco-exposed infants and 44 (85%) of the controls, 27 meconium samples could not be analyzed due to a lack of funds. Urine analysis results were available for two infants born to smokers for whom meconium was not available. All analyzed meconium and urine samples tested negative for cocaine, cannabis, and opiates. Infants born to mothers who reported using, or were suspected of using, illicit drugs during pregnancy had been excluded previously.

Table 11

Group Means and Standard Deviations for Tobacco-exposed and Control Neonates on Demographic Control Variables.

Variable ^a	Tobacco (n=34)	Controls (n=52)
BW (g)	2812 (508)	3077 (470)
TW (g)	2850 (421)	3086 (445)
GA (weeks-days)	38-1 (2-5)	38-5 (2-1)
TA (weeks-days)	38-4 (2-0)	38-6 (1-5)
SES (\$1000 per year)	27.4 (22.8)	37.5 (22.7)
WG (kg)	14.7 (5.8)	13.3 (5.8)
APG (score out of 10)	9.1 (0.4)	9.1 (0.4)
MA	26.5 (5.7)	29.5 (4.3)
PAR	1.7 (0.8)	1.9 (1.0)
GRAV	2.5 (1.4)	2.4 (1.5)
ED ^b	2.8 (1.4)	3.0 (1.3)

^a Standard deviations are listed in brackets beside each group mean.

^b Maternal education: 1=did not complete high school, 2=high school graduate, 3=CEGEP, some college, or technical training, 4=graduated from college program, or some university, 5=university graduate. BW=birthweight; TW=weight at testing; GA=gestational age; TA=corrected gestational age at testing (GA + postnatal age); SES=socioeconomic status; WG=maternal pregnancy weight gain; APG=APGAR score at 5 minutes; MA=age of mother; PAR=parity; GRAV=gravida; ED=mother's highest level of education achieved.

It was originally intended that maternal reports concerning smoking or not smoking cigarettes during pregnancy would be confirmed by meconium analysis for cotinine (a metabolite of nicotine); however, meconium analysis proved unreliable for discriminating between infants born to smokers and non-smokers. Statistical analyses assessing the reliability of meconium analysis for determining gestational cigarette smoking are presented in the results section. Because meconium analysis proved unreliable, maternal self-reports concerning cigarette smoking could not be validated. However, the previously described bogus pipeline method was employed to increase the reliability of maternal self-reports of tobacco use.

Information concerning self-reported alcohol consumption during pregnancy among the smoking and non-smoking mothers is presented in Table 12. Alcohol consumption was low among all mothers. Among those who reported drinking alcohol during pregnancy, the majority drank one glass of wine or beer less often than once per month. The highest rate of alcohol consumption reported was two drinks, twice per week throughout pregnancy, by a non-smoking mother.

Age at Testing. For 88% ($n=30$) of the tobacco-exposed infants and 94% ($n=49$) of the control infants, testing on the information processing procedure took place between 18 and 72 hours of age. Premature neonates (four tobacco-exposed and three control infants) were tested as soon as medically stable. Of the four tobacco-exposed infants who were not tested within 72 hours of birth, one was tested at age 10 days, two were tested within two weeks of age, and one was tested at 5½ weeks of age. Of the four control infants who were not tested within 72 hours of birth, two were tested within 1½ weeks of age, and one was tested at four weeks of age.

Table 12

Number of Smokers and Control Mothers Who Drank Alcohol During Pregnancy

	Smokers	Controls
Any alcohol use during pregnancy	11 (32%)	11 (21%)
Alcohol use throughout pregnancy	2 (6%)	3 (6%)
No alcohol during pregnancy	17 (50%)	38 (73%)
Information missing or not clear ^a	6 (18%)	3 (6%)

^a Information was missing for 1 smoker and 1 control mother. It was not clear if the mothers did or did not drink alcohol during pregnancy in the case of 5 smokers and 2 control mothers.

Procedure

The procedures for obtaining written informed consent and collecting demographic information were identical to those described in Study 1, with the exception that social service records were not used as a source of demographic information. Mothers completed the demographic questionnaire (Appendix B) and information was gathered from the infants' hospital birth records. Meconium was collected and analyzed as described in Study 1; the information processing procedure was also identical to that used in Study 1.

Study Design

A multivariate design with one between-group independent variable (tobacco-exposure/control) and three measures of central information processing (orientation, habituation, and recovery to novelty) was used to assess whether fetal tobacco-exposure adversely affects information processing ability in the neonate. Analysis of variance, χ^2 tests, and t tests were used to assess between group differences on the following measures of central information processing: (a) orientation to the stimuli in each of the three phases, (b) habituation to the familiarization and novelty phase stimuli, and (c) recovery of responding to the stimuli in the novelty and dishabituation phases. In addition, between group differences were assessed on a number of control variables. These consisted of (a) 10 demographic control variables (BW, TW, GA, TA, SES, WG, MA, PAR, GRAV, and ED), (b) the percentage of time the infants spent in a positive state during the testing procedure, and (c) the overall percentage of head turns.

Data Reduction

To prepare the data for analysis, the trials in the familiarization and novelty phases were broken down into four quartiles and two trial blocks, and

the dishabituation phase trial block was made up of the first three to six trials, depending on the number required to reach the criterion for orientation, as described in Study 1.

Dependent Measures. The three primary dependent measures described in Study 1 were used in the current analyses: (a) in each trial block and quartile, the percentage of trials with head turns toward the sound source; (b) the number of trials required to meet the criterion for orientation in the familiarization, novelty and dishabituation phases, and habituation in the familiarization and novelty phases; and (c) a "difference score" calculated by subtracting the number of head turns away from the sound source from the number of head turns toward the sound source within each trial block (a measure of the degree to which infants turned preferentially toward, as opposed to away from, the stimulus). In addition, two control variables were analyzed consisting of: (a) the overall percentage of trials with head turns toward or away from the sound source during the procedure (to ensure that both groups were equally capable of producing head turns), and (b) the percentage of time the infant was in a "positive state" (i.e., not fretting and with eyes open) in each phase.

Specific Hypotheses Related to the Information Processing Dependent Measures. The null hypothesis was that group differences would not be found on any of the information processing measures. It was predicted that the null hypothesis would be rejected. The alternative hypothesis was that fetal tobacco-exposure would compromise information processing ability leading to differences between the tobacco-exposed and control groups as follows:

1. Familiarization Phase: Based on the findings of previous research with infants at risk for developmental delay (Zelazo et al., 1989), it was

hypothesized that tobacco-exposed infants would not differ from controls on the familiarization phase measures. First, both groups would be expected to show a high level of head turning toward the sound source in the first two quartiles (or first trial block), decreasing to significantly lower levels toward the end of the phase (third and fourth quartiles, or second trial block). Second, group differences were not expected on the number of trials required to meet the criteria for orientation and habituation in this phase. Third, in both groups, difference scores were expected to be significantly greater than zero for the first quartile (indicating preferential head turning toward the stimulus) and less than zero in the last quartile (indicating head turning away from the stimulus).

2. Novelty Phase: Specific group differences were expected in this phase. It was hypothesized that (a) the percentage of head turns toward the stimulus in the initial quartiles of the novelty phase would be significantly lower among the tobacco-exposed infants compared to controls, (b) the tobacco-exposed infants would require a significantly greater number of trials to reach the criteria for orientation and habituation, (c) the degree of recovery to the novel stimulus, as determined by comparisons between the second trial block of the familiarization phase and the first trial block of the recovery phase, would be significantly lower for the tobacco-exposed infants compared with controls, and (d) whereas control infants would show a systematic pattern of frequent turns toward the stimulus in the first quartile of the novelty phase and frequent turns away in the fourth quartile (as determined by positive and negative scores, respectively), tobacco-exposed infants would respond randomly, as reflected by difference scores approaching zero.

3. Dishabituation Phase: The following group differences were hypothesized for the dishabituation phase: (a) whereas the control infants

would recover responding to the dishabituation stimulus, the tobacco-exposed infants would show less recovery (assessed by comparing the percentage of head turns toward the stimulus in the second block of the novelty phase with the percentage of head turns toward the stimulus in the dishabituation block), (b) fewer tobacco-exposed infants would reach the criterion for orientation compared to controls, (c) the tobacco-exposed infants who reached the criterion for orientation would require a greater number of trials to do so than controls, and (d) difference scores would be significantly greater than zero for controls (indicating preferential turning toward the stimulus) and not different from zero for the tobacco-exposed infants (indicating random head-turning) in the dishabituation block.

Results

Because a large effect size was not expected (based on the performance of the control infants in Study 1, who were mostly born to smokers, and the relatively small decrements in IQ and achievement test scores associated with maternal tobacco use), an alpha level of 0.05 was used as the criterion for significance in all analyses. Only statistically significant results are reported in the text of this section; summary tables for all other analyses can be found in Appendix E. Topics in the results section will be discussed in the following order:

1. General approach to the analysis of the data.
2. Preparatory analyses including: (a) the reliability of meconium analysis for identifying infants born to mothers who smoked cigarettes during pregnancy, (b) preparation of data for analysis by the identification of missing values, outliers, and violations of the assumptions of MANOVA, (c) results of analyses of demographic control variables (to determine whether the groups

differed on potentially confounding factors), and (d) results of between group comparisons on the two information processing control measures, degree of overall head-turning and degree of positive state.

3. Most importantly, between group comparisons on the information processing measures in the (a) familiarization phase, (b) novelty phase, and (c) dishabituation phase.

General Approach to the Data Analyses

The data were analyzed using the same approach described in Study 1. The only exception was that, in addition to the other statistical techniques employed in these studies, correlational analyses were used in assessing the reliability of meconium analysis.

Preliminary Analyses

Reliability of Meconium Analysis for Determining Cigarette Smoking During Pregnancy. For the purpose of assessing the reliability of the presence of cotinine in newborn meconium as a marker of maternal cigarette smoking during pregnancy, the meconium analysis results for all infants (including those born to cocaine-users and infants who were excluded from the information processing data analyses) were analyzed. Meconium samples from a total of 65 infants were analyzed for the presence of cotinine, the primary metabolite of nicotine.

Four variables were employed in the current analyses: (a) maternal self-report of smoking or not smoking cigarettes during pregnancy was coded as a dummy variable (SMOKE-YN) with "no smoking" coded as 0 and "smoking" coded as 1; (b) the number of cigarettes smoked per day during pregnancy represented a second variable (CIGS), with non-smokers receiving a score of zero; (c) whether or not cotinine was detected in meconium was coded as a

dummy variable (COT-YN) with "cotinine not detected" coded as 0 and "cotinine detected" coded as 1; and (d) the quantity of cotinine detected (nanograms per gram) made up the fourth variable (COT-Q). Unfortunately, the laboratory conducting the meconium analysis did not provide quantification of cotinine for 12 of the 32 meconium samples in which cotinine was detected; data on this variable were available for the remaining 20 cotinine-positive samples, with the 33 negative samples receiving a score of zero.

Pearson product-moment correlation coefficients were calculated for the relation between SMOKE-YN, CIGS, and COT-YN for all 65 subjects, and for COT-Q for the 53 subjects for whom COT-Q scores were available. As shown in Table 13, maternal self reports of smoking and the results of meconium analysis for cotinine were not related (r 's ranged from .05 to .14). The relation between SMOKE-YN and COT-YN was further examined using a χ^2 test to compare the percentage of smokers and non-smokers with positive meconium analysis results for cotinine. No between group differences were found, $\chi^2(1)=.423$, $p=.52$, with 44% ($n=12$) of the 27 non-smokers testing positive for cotinine, and 53% ($n=20$) of the smokers testing positive.

To address the possibility that the above findings reflected invalid maternal self-reports of smoking rather than invalid meconium analysis results, the relation between smoking and the presence of cotinine in meconium was examined further with the mothers who reported not smoking excluded. It was assumed that mothers who did not smoke during pregnancy would not falsely report that they had smoked; thus, the self-reports of smokers would presumably be more accurate. For self-reported smokers, there was, again, no relation between the number of cigarettes smoked per day and either the

Table 13

Correlation Coefficients for the Relation Between Maternal Cigarette Smoking During Pregnancy and Cotinine in Newborn Meconium

Variable	SMOKE-YN	CIGS
COT-YN ($n=65$)	.08	.14
COT-Q ($n=53$)	.05	.14

COT-YN = Cotinine detected - yes/no (yes=1, no=0); COT-Q = Quantity of cotinine detected (ng/g); SMOKE-YN = Smoking reported - yes/no (yes=1, no=0); CIGS = Number of cigarettes smoked per day (based on self-report).

presence of cotinine in newborn meconium, $r(37) = .17$, or the quantity of cotinine detected, $r(19) = .18$.

Because Ostrea et al. (1994) found that the levels of cotinine in newborn meconium were similar for infants whose mothers smoked up to a pack of cigarettes per day and infants whose mothers were exposed to second-hand smoke, the relation between the presence or absence of cotinine and maternal reports of exposure to second-hand smoke was examined. Information was not available for a number of infants, since questions about exposure to second-hand smoke were added to the procedure after approximately half of the infants had been tested. In addition, the relation between exposure to second-hand smoke and the quantity of cotinine detected could not be examined since the number of infants with information available on both of these variables was too small to permit analysis. However, the relation between the presence or absence of cotinine in meconium and the presence or absence of exposure to second-hand smoke (on at least a weekly basis) was assessed for 49 infants. Mothers who reported smoking cigarettes were coded as being exposed to second-hand smoke. In contrast to the findings of Ostrea et al. (1994), the Pearson product-moment correlation indicated that in the present sample there was no relation between exposure to second-hand smoke and the presence of cotinine in meconium, $r(47) = .07$. Infants of mothers who were exposed to second-hand smoke were no more likely to have cotinine in their meconium than infants whose mothers were not exposed. However, only five of the 49 mothers were not exposed to second-hand smoke.

In summary, the presence or absence of cotinine in newborn meconium did not serve as a reliable marker for maternal cigarette smoking or exposure to second-hand smoke during pregnancy. In addition, among mothers who reported

smoking during pregnancy, neither the quantity of cotinine detected nor the presence of cotinine in newborn meconium was related to the number of cigarettes smoked per day.

Preanalysis of Data. Prior to analysis, the distributions of all demographic and information processing variables were examined for missing values. Second, within each group, the scores of outliers were identified. Third, the distributions of scores to be analyzed by (M)ANOVA were assessed for normality on the basis of skewness and kurtosis values for each variable, within each group.

The control and tobacco-exposed group data were each missing three values for WG, one value for SES, and two values for APG, MA, PAR, GRAV, and ED. One control infant was missing positive state scores for the three phases of the procedure due to a problem with the coding apparatus. However, the infant was included in the study as the data were otherwise useful, and it was noted that the infant exhibited a high level of positive state throughout the procedure. There were no missing values on any of the information processing measures. In order to include all subjects in the data analyses, missing values were replaced by group means, as recommended by Tabachnick and Fidell (1996). Outliers, defined as data points more than two standard deviations away from the mean, were identified on a number of demographic and information processing variables. Since ANOVA is sensitive to extreme outliers (Tabachnick & Fidell, 1996; Wilkinson et al., 1992), the outliers' scores in each case were replaced with scores calculated to be two standard deviations away from the group mean. In all cases, the new scores were still the most extreme scores of the group.

The distribution of scores on each variable was considered to violate the assumption of normality if the z-scores for skewness and kurtosis were greater

than 3.0, as recommended by Tabachnick and Fidell (1996). Once the extreme scores of the outliers had been replaced by less extreme scores, the two variables representing the last quartiles of the familiarization and novelty phases remained significantly positively skewed, and the positive state scores for the three phases remained significantly negatively skewed. The skewed quartile scores could not be corrected by transformation. The positive state scores for each phase were transformed using square root transformations. Following transformation, all positive state scores were within acceptable limits for skewness and kurtosis.

Analysis of Demographic Control Variables. Subsumed under the heading "demographic control variables" were the ten maternal and infant characteristics on which it was predicted that potential group differences might exist: BW, GA, TW, TA, WG, SES, MA, PAR, GRAV, and ED. Multicollinearity was assessed prior to MANOVA through examination of the intercorrelations among the variables; where the correlation between two variables was higher than $r=.7$, the variable most closely associated with tobacco-exposure status (Group) was included in the analysis of variance (Tabachnick & Fidell, 1996). GA was highly correlated with TA, and BW was highly correlated with TW; of these variables, GA and BW were entered into the analysis of variance. A 2 (Group) x 8 (Control Variables) repeated measures MANOVA was performed on the demographic control variables (Appendix E, Table E1), yielding a Group x Control Variable interaction, $F(7, 78) = 3.36, p < .01$, and a multivariate effect of Group, $F(8, 77) = 2.91, p < .01$. Univariate tests revealed that, compared to controls, tobacco-exposed infants weighed less at birth, $F(1, 84) = 7.02, p < .05$, were born to mothers with lower SES, $F(1, 84) = 4.18, p < .05$, and had mothers

who were younger, $F(1, 84) = 7.89, p < .01$. The groups did not differ on GA, WG, PAR, GRAV, or ED.

Since low birthweight is a mediating variable in the pathway between maternal gestational cigarette smoking and infant outcome, rather than a confounding factor (Kiely, 1991), group differences in birthweight were not statistically controlled in the analyses of the information processing measures. The inter-correlations between SES, MA and the information processing variables were examined to determine the extent to which information processing scores were influenced by these potential covariates. None of the information processing variable scores was significantly correlated with either SES or MA, with the exception that the difference scores in the first quartile of the familiarization phase were significantly correlated with MA, $r(84) = -.23, p < .05$. Because a large number of correlations were generated, and only one was significant, this was likely a spurious correlation that represented a Type I error. Therefore, on the basis of the lack of relation between SES and MA and the information processing measures, the group differences on SES and MA were not statistically controlled. However, to isolate the effects of smoking independent of BW and SES, two variables which have been repeatedly demonstrated in the literature to be associated with maternal cigarette smoking, these factors were more stringently controlled in Part II of this study using subject matching procedures.

Control Measures for Information Processing Ability. To rule out the possibility that as a result of fetal tobacco-exposure, the tobacco-exposed infants might be less capable of making head turns than the control infants, the tobacco-exposed and control infants were compared on the overall percentage of trials ending with a head turn toward or away from the stimulus. A one-way Group x

Head-turns ANOVA revealed no significant group differences in the overall percentage of head-turning (Appendix E, Table E2), indicating that tobacco-exposed and control infants were equally capable of making head turns. Tobacco-exposed and control infants turned on an average of 78.1% and 81.3% of trials, respectively.

The amount of time spent in positive state was the second information processing control variable. Because group differences in the time spent in a positive state would confound the information processing results, it was important to ensure that any group differences on the information processing measures could not be attributed to differences in degree of positive state. A 2 (Group) x 3 (Phase) repeated measures MANOVA on the transformed positive state variables revealed that, collapsed across groups, positive state decreased in a linear fashion across phases, $F(2, 83) = 9.05, p < .001$ (Appendix E, Table E3). The Group x Phase interaction and the Multivariate effect of Group were not significant, indicating that the groups did not differ on the percentage of time spent in a positive state across the three phases of the information processing procedure. Collapsed across groups, a high level of positive state was achieved in all three phases of the procedure with grand means (on the non-transformed variables) for the familiarization, novelty and dishabituation phases of 91.4%, 87.8%, and 84.3%, respectively.

Analyses of Information Processing Ability

The performance of the tobacco-exposed and non-exposed neonates was compared for the three phases of the information processing procedure. Figure 6 shows the pattern of responding across the four quartiles of the familiarization phase, the two trial blocks of the novelty phase, and the first three to six trials of the dishabituation phase.

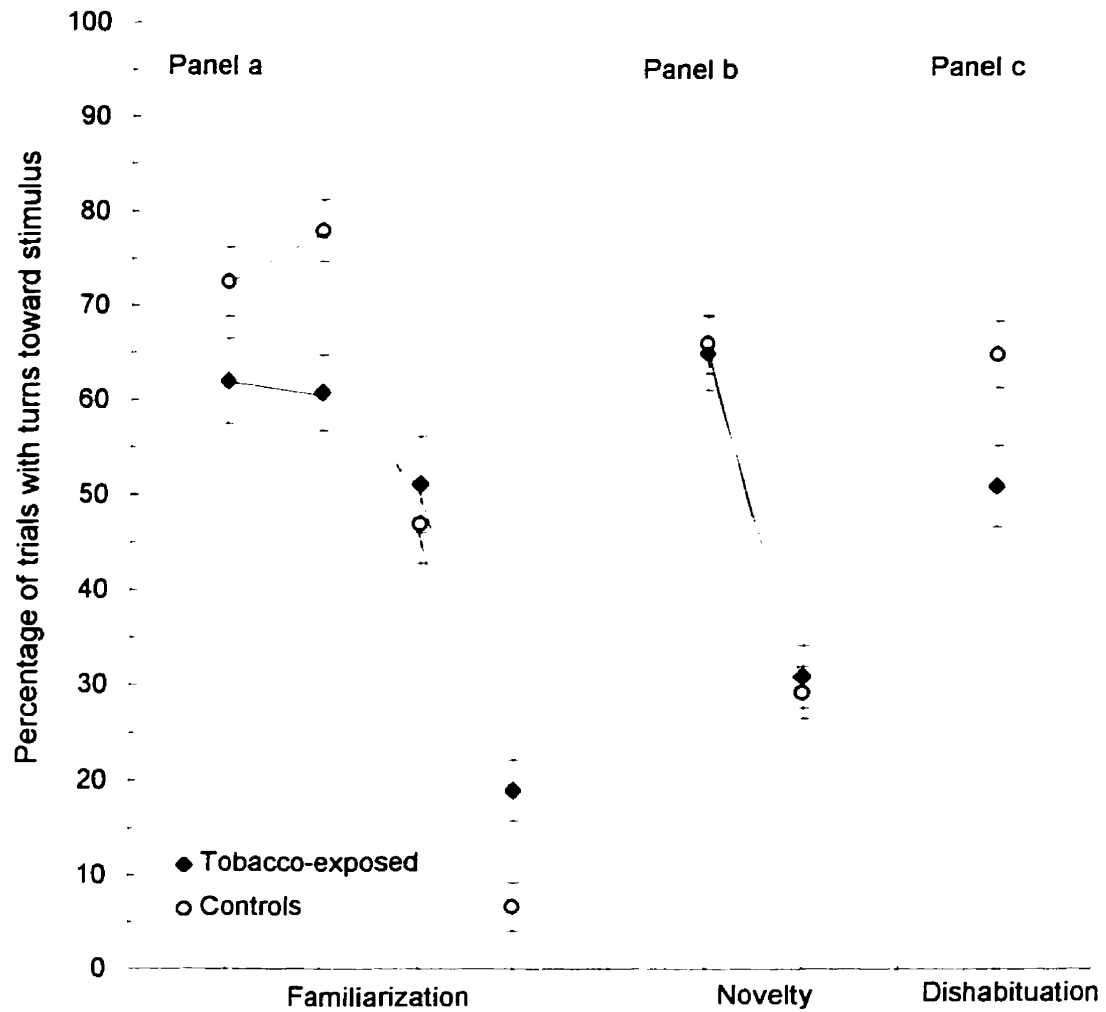


Figure 6. Mean percentages of head turns toward the sound source for tobacco-exposed and control neonates during: familiarization phase quartiles (Panel a); novelty phase trial blocks (Panel b); and the dishabituation phase trial block (Panel c).

Familiarization Phase. To assess whether the tobacco-exposed and control infants showed an initial high percentage of turns toward the familiarization stimulus (orientation) that decreased across the phase (habituation), the percentage of turns toward the stimulus in each of the four quartiles of the familiarization phase was assessed in a 2 (Group) x 4 (Quartiles) repeated measures MANOVA (Appendix E, Table E4). The multivariate effect of Quartiles was significant, $F(3, 82) = 116.53, p < .000$, reflecting the observation that collapsed across groups, the percentage of turns toward the stimulus decreased in a linear fashion from 68.3% in the first quartile to 11.5% in the fourth quartile. However, a Group x Quartile interaction, $F(3, 82) = 6.21, p < .01$, and multivariate effect of Group, $F(4, 81) = 4.69, p < .01$, revealed that the groups differed in the percentage of head turns toward the stimulus across the four quartiles. Univariate analyses indicated that, as shown in Figure 7, compared to the control infants, the tobacco-exposed infants responded to the stimulus with a lower percentage of head turns toward the stimulus in the second quartile, $F(1, 84) = 11.08, p < .01$, and a higher percentage of head turns toward the stimulus in the fourth quartile of the familiarization phase, $F(1, 84) = 9.18, p < .01$.

Because the skewed distribution of scores in the fourth quartile of the familiarization phase violated the assumption of normality for analysis of variance, the above analyses were repeated using trial blocks in place of quartiles. A 2 (Group) x 2 (Trial Block) repeated measures MANOVA (Appendix E, Table E5) yielded a Group x Trial Block interaction, $F(1, 84) = 12.86, p < .01$, and multivariate effect of Group, $F(2, 83) = 6.68, p < .01$. As shown in Figure 8, the initial level of head-turning toward the stimulus (Block 1) was lower among tobacco-exposed infants than controls, $F(1, 84) = 11.57, p < .01$, and the

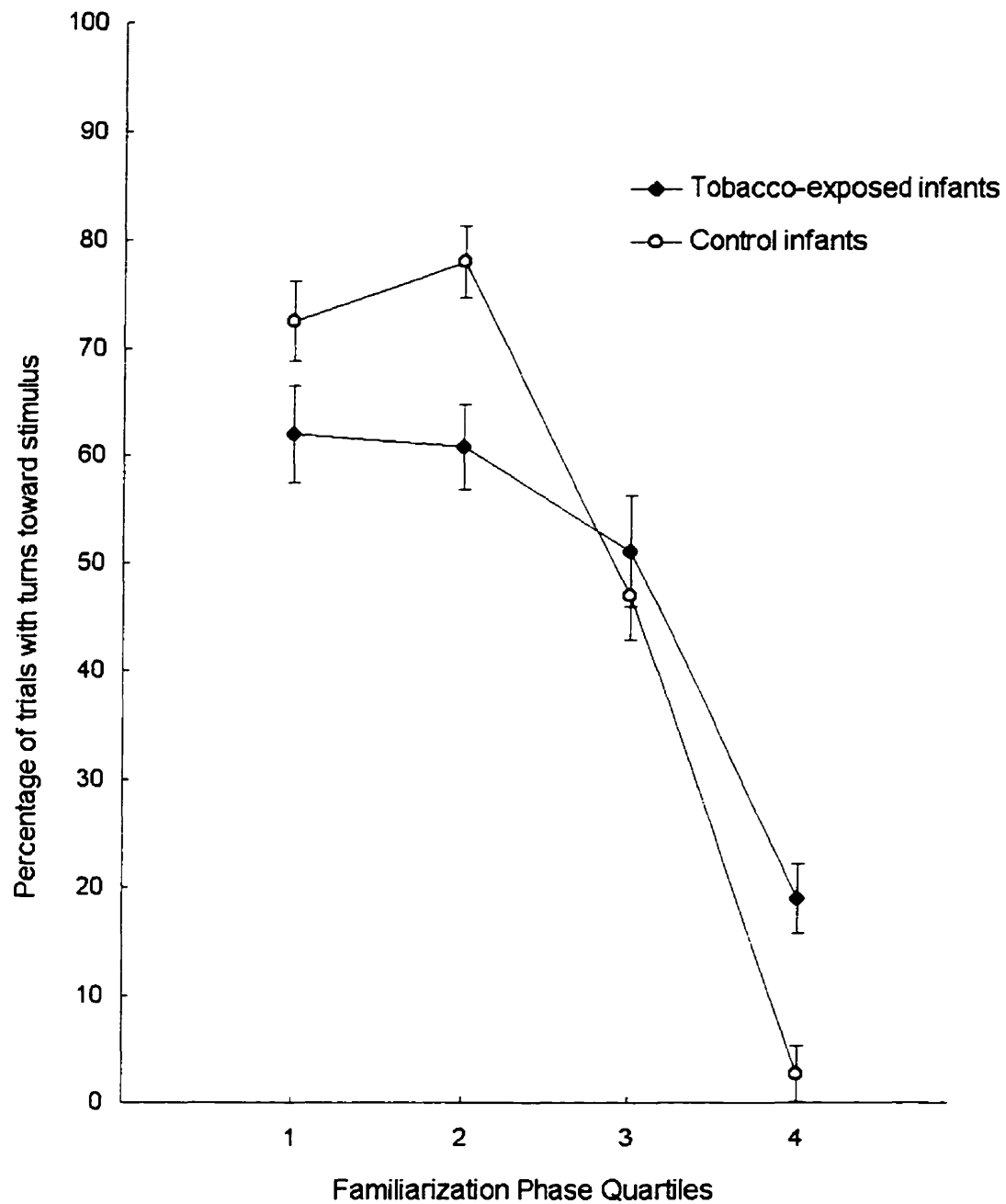


Figure 7. Mean percentages of head-turning toward the sound source during the 4 quartile blocks of the familiarization phase, for tobacco-exposed and control infants.

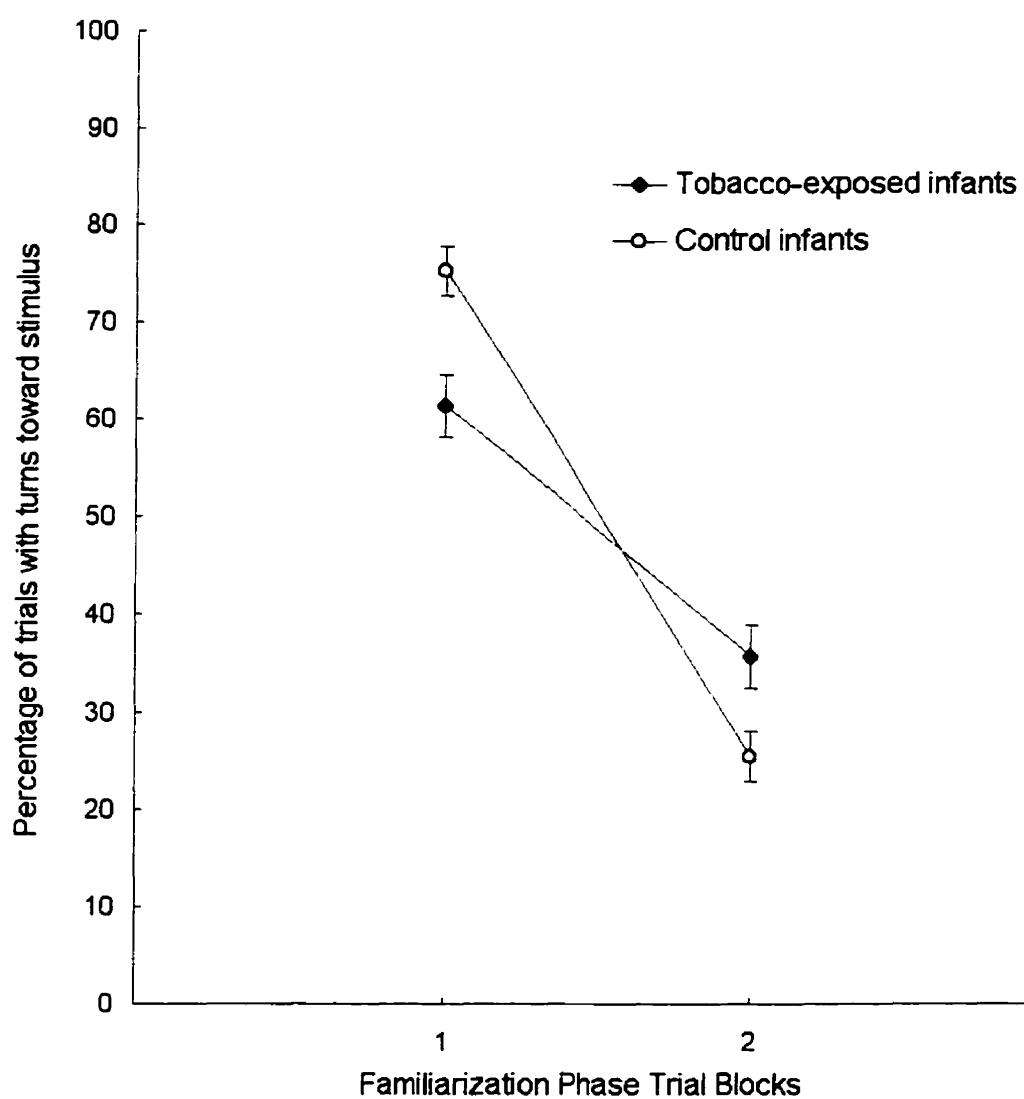


Figure 8. Mean percentage of head turns toward the sound source during the two trial blocks of the familiarization phase, for tobacco-exposed and control infants.

percentage of head turns toward the stimulus in the second half of the familiarization phase (Block 2) was higher among tobacco-exposed infants than controls, $F(1, 84) = 6.21, p < .05$.

Examination of the relative frequency of head turns toward versus away from the stimulus during the first and last quartiles of the familiarization phase was carried out by analysis of difference scores (turns toward - turns away). Difference scores were compared with a mean of zero for each group using one-sample t tests to determine if turns toward or away from the stimulus exceeded chance levels (Appendix E, Table E6). Analyses indicated that in the first quartile of the familiarization phase, both groups of infants turned preferentially toward the stimulus (tobacco-exposed group: $t(33) = 5.01, p < .001$; control group: $t(51) = 8.44, p < .001$), and in the last quartile both groups turned preferentially away from the stimulus (tobacco-exposed group: $t(33) = -3.67, p < .01$; control group: $t(51) = -6.34, p < .001$).

However, χ^2 analyses revealed that the tobacco-exposed infants were less likely than controls to reach the criterion for orientation, $\chi^2(1) = 4.75, p < .05$ (Appendix E, Table E7), and habituation, $\chi^2(1) = 7.02, p < .01$ (Appendix E, Table E8), to the familiarization stimulus. Whereas all the control infants oriented ($n=52$) and 90.4% ($n=47$) habituated, fewer tobacco-exposed infants (91.2%, $n=31$) oriented and only 67.7% ($n=23$) habituated. In addition, as illustrated in Figure 9 (Panel a), among those infants who reached criterion, the groups also differed on the number of trials required to orient, $F(1, 81) = 14.71, p < .001$ (Appendix E, Table E9), and habituate, $F(1, 68) = 5.06, p < .05$ (Appendix E, Table E10).

Together, the results of the data analyses for the familiarization phase indicate that the information processing ability of the tobacco-exposed neonates

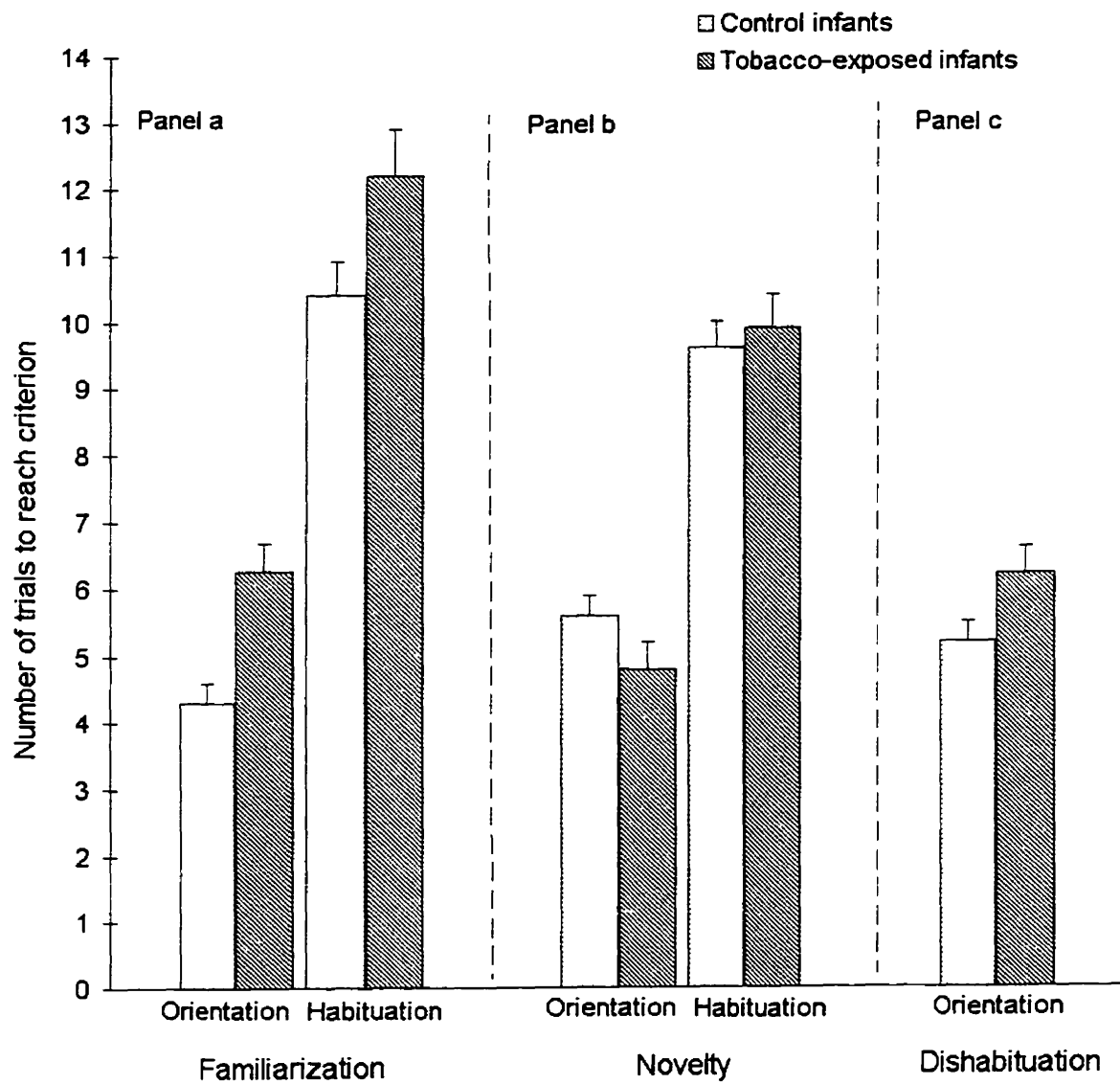


Figure 9. Number of trials required to reach criterion for orientation and habituation in the familiarization and novelty phases, and orientation in the dishabituation phase, for tobacco-exposed and control infants.

is compromised relative to controls. Specifically, upon presentation of the familiarization stimulus the tobacco-exposed infants responded with a lower percentage of head turns toward the sound source relative to controls, and they were less likely to reach the criterion for orientation. Among the infants who oriented, the tobacco-exposed infants required a greater number of trials to reach criterion. They also responded with a higher percentage of head turns toward the stimulus during the second half of the familiarization phase relative to controls, and were less likely to habituate to the stimulus. Moreover, among those infants who habituated, the tobacco-exposed infants required a greater number of trials to reach criterion. Despite these group differences, when performance was analyzed by comparing difference scores at the beginning and end of the phase with a mean of zero, the tobacco-exposed infants performed similarly to controls, turning preferentially toward the stimulus in the first quartile and away from the stimulus in the last quartile of the familiarization phase.

Novelty Phase. A 2 (Group) x 4 (Quartiles) repeated measures MANOVA was used to compare the tobacco-exposed and control infants on the percentage of head turns toward the stimulus across the four quartiles of the novelty phase (Appendix E, Table E11). The multivariate effect of Quartiles was significant, $F(3, 65) = 109.09$, $p < 0.001$, reflecting a decrease in the percentage of turns toward the stimulus across quartiles. Collapsed across groups, the percentage of turns toward the stimulus decreased in a linear fashion from 63.0% in the first quartile to 9.0% in the last quartile. Neither a Group x Quartile interaction nor a main effect of Group was found, indicating that the responses of the tobacco-exposed and control infants to the novel stimulus were similar across the novelty phase quartiles, as shown in Figure 10. To ensure that the

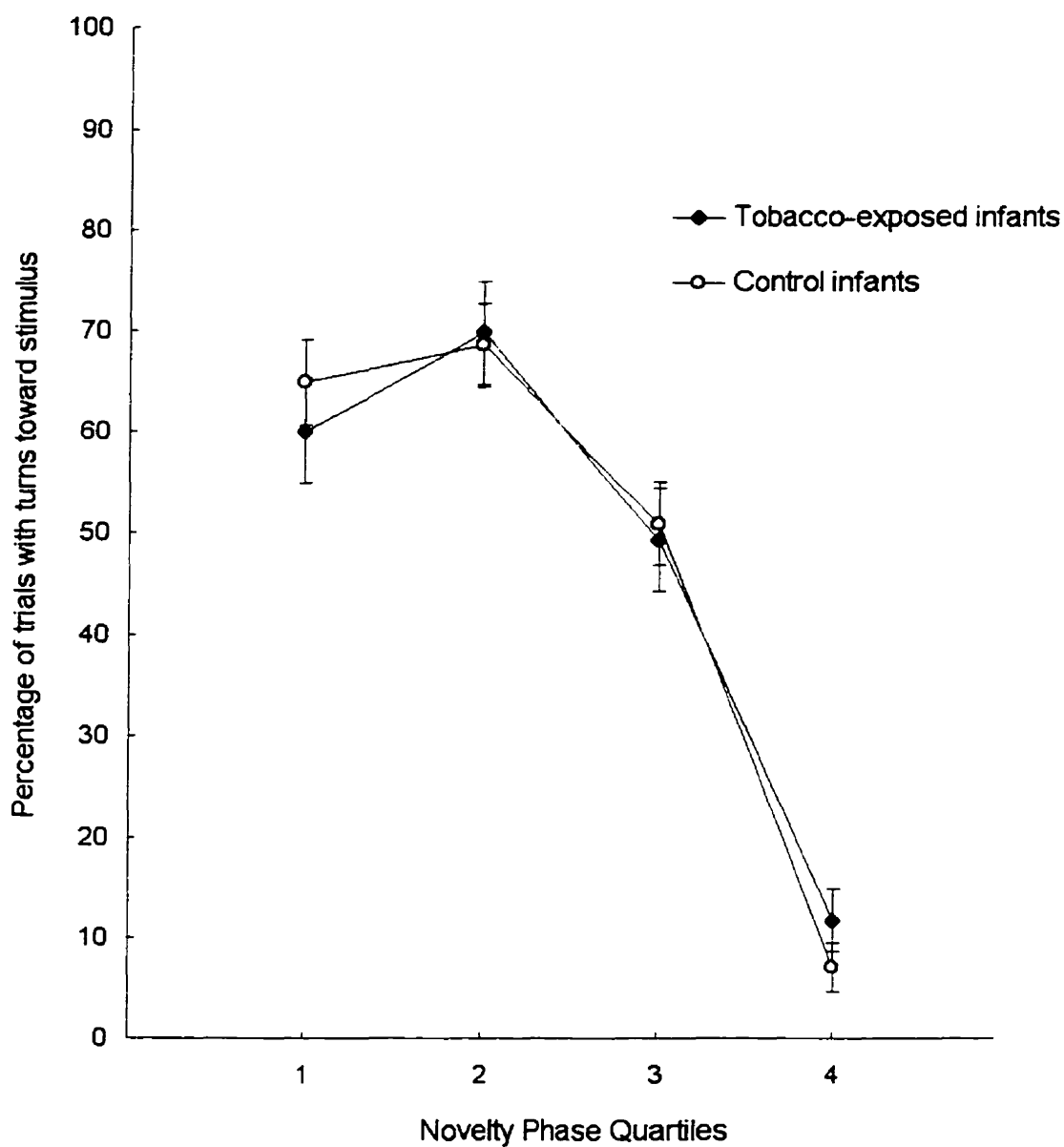


Figure 10. Mean percentages of head-turning toward the sound source during the 4 quartile blocks of the novelty phase, for tobacco-exposed and control neonates.

skewed distribution of the fourth quartile scores did not mask significant between-group differences, the analyses were repeated using the two trial blocks in place of quartiles (Appendix E, Table E12). Again, no significant between-group differences were found.

To assess the number of turns toward the stimulus relative to turns away at the beginning and end of the novelty phase, the difference scores for the first and last quartiles of the novelty phase were compared with a mean of zero for each group (Appendix E, Table E13). Analyses indicated that both the tobacco-exposed infants, $t(33) = 5.56$, $p < .001$ and control infants, $t(51) = 7.77$, $p < .001$, turned systematically toward the stimulus in the first quartile of the novelty phase, and turned systematically away from the stimulus in the last quartile, $t(33) = -4.01$, $p < .001$ for the tobacco-exposed infants, $t(51) = -7.01$, $p < .001$ for the control infants.

Recovery of head turning upon introduction of the novel stimulus was assessed by comparing the percentage of head turns toward the stimulus in the last trial block of the familiarization phase with the percentage of head turns toward the stimulus in the first trial block of the novelty phase. A 2 (Group) $\times$ 2 (Trial Block) repeated measures ANOVA (Appendix E, Table E14) revealed an effect of Trial Block, $F(1, 84) = 111.07$, $p < 0.001$, indicating that collapsed across groups, the overall percentage of turns toward the stimulus increased between the last trial block of the familiarization phase and the first trial block of the novelty phase. The Group $\times$ Trial Block interaction did not reach significance, $F(1, 84) = 2.88$, $p = .093$. The multivariate effect of Group was marginally significant, $F(2, 83) = 3.07$, $p = .052$, and univariate analyses indicated that this was due to the previously reported between-group difference in head turning toward the stimulus during the last trial block of the familiarization phase (Appendix E, Table

E15). The groups did not differ in the percentage of head turns toward the stimulus in the first trial block of the novelty phase. To determine whether the effect of Group on recovery to the novel stimulus was largely due to the influence of the infants who failed to habituate to the familiarization stimulus, the analysis was repeated with the infants who failed to habituate excluded (Appendix E, Table E16). The effect of Group was no longer significant and the previous near-significant Group x Trial Block interaction was no longer apparent.

The percentage of infants in each group who reached the criterion for orientation (Appendix E, Table E17) and habituation (Appendix E, Table E18) to the novel stimulus were compared using χ^2 analyses. No between-group differences were found. Ninety-six percent of the control infants and 88% of the tobacco-exposed infants oriented; 79% of the control infants and 68% of the tobacco-exposed infants habituated. As illustrated in Figure 9 (Panel b), the groups were also similar in terms of the number of trials required to reach the criterion for orientation (Appendix E, Table E19) and habituation (Appendix E, Table E20).

In summary, the data analysis results for the novelty phase indicate that the tobacco-exposed and control infants were similar in their responses to the novel stimulus. However, a near significant Group x Trial Block interaction for recovery to novelty indicated that there was a tendency for the tobacco-exposed infants to exhibit less recovery than the non-exposed infants, although this effect was largely due to the performance of the infants who failed to habituate to the familiarization stimulus.

Dishabituation Phase. To determine if the introduction of the dishabituation stimulus (following habituation to the novelty phase stimulus) would elicit recovery of head-turning, the percentage of head turns toward the

stimulus during the second trial block of the novelty phase was compared with the percentage of head turns toward the stimulus in the dishabituation phase trial block. A 2 (Group) x 2 (Trial Block) repeated measures MANOVA (Appendix E, Table E21) indicated that, collapsed across groups, the percentage of head turns toward the stimulus increased between the two trial blocks, $F(1, 84) = 58.89$, $p < 0.001$, from 29.9% in the second block of the novelty phase to 59.4% in the dishabituation phase trial block. However, as shown in Figure 6 (Panels b and c), there was a Group x Trial Block interaction, $F(1, 84) = 4.63$, $p < .05$, and multivariate effect of Group, $F(2, 83) = 3.20$, $p < 0.05$. Univariate analyses indicated that the percentage of head turns toward the stimulus in the dishabituation phase trial block was greater among the control infants than the tobacco-exposed infants, $F(1, 84) = 6.46$, $p < .05$. Moreover, when the relative number of turns toward versus turns away from the dishabituation stimulus was examined for each group using t tests to compare difference scores with a mean of zero (Appendix E, Table E22), the results indicated that the control infants turned systematically toward the stimulus, $t(51) = 5.83$, $p < .001$, whereas the tobacco-exposed infants turned randomly toward and away from the stimulus, $t(33) = 1.54$, $p > .1$. Thus, unlike the control infants, the tobacco-exposed infants failed to recover responding to the dishabituation stimulus.

Although χ^2 analysis for the percentage of infants in each group who reached criterion for orientation to the dishabituation stimulus only approached significance, $\chi^2(1) = 3.07$, $p = .08$ (Appendix E, Table E23), of the infants who oriented, the tobacco-exposed infants required a greater number of trials to reach criterion, $F(1, 73) = 4.56$, $p < .05$ (Appendix E, Table E24), as shown in Figure 9 (Panel c). Whereas 92% ($n = 48$) of the control infants oriented, and did

so in an average of 5.2 trials, a relatively smaller percentage of tobacco-exposed infants (79%, $n=27$) oriented, requiring 6.2 trials to reach criterion.

In summary, the results of the dishabituation phase analyses indicate that, upon introduction of the dishabituation stimulus, the tobacco-exposed infants failed to recover responding to the same degree as controls. Moreover, whereas the controls turned systematically toward the sound source upon introduction of the dishabituation stimulus, the tobacco-exposed infants did not. They required a greater number of trials to orient to the dishabituation stimulus, and tended to be less likely to reach the criterion for orientation.

Summary

Compared to infants born to non-smokers, those born to smokers weighed less at birth and their mothers were of lower SES. The two groups achieved similar levels of head-turning and positive state during the information processing procedure. However, infants born to smokers exhibited deficits on a number of information processing measures relative to controls. In the familiarization phase, infants born to smokers exhibited lower levels of head-turning toward the stimulus in the first half of the phase, implying poorer orientation, and higher levels of head-turning toward the stimulus in the second half of the phase, implying poorer habituation. Tobacco-exposed infants were less likely to orient and habituate to the familiarization stimulus and, those who oriented and habituated required a greater number of trials to reach criterion. The relatively high level of head-turning toward the stimulus at the end of the familiarization phase among the tobacco-exposed infants led to marginally significant group differences in the degree of recovery to the novel stimulus, although there were no group differences in the percentage of head turns toward the novel stimulus or measures of habituation to the novel stimulus. The

infants whose mothers smoked during pregnancy did not recover responding to the dishabituation stimulus, exhibited lower levels of head-turning toward the sound source, turned randomly toward and away from the dishabituation stimulus, and required a greater number of trials than control infants to reach the criterion for orientation.

Part II: Dose-Response Effects of Tobacco-exposure

When the results of the analyses comparing the infants born to smokers with those born to non-smokers indicated that the groups differed on a number of important information processing measures, the data were further analyzed to determine if infant performance was related to the degree of fetal exposure to tobacco. Tobacco-exposed infants were divided into two groups according to the number of cigarettes smoked per day by the mothers and compared with control infants born to non-smokers. Because the group differences between the infants born to smokers and non-smokers in Part I may have been partially mediated by group differences in BW, a case-controlled, matched pairs design was used to examine the effect of tobacco exposure on information processing ability independent of the effects of birthweight. In addition, although SES was not related to the information processing measures in Part I, SES has been consistently associated with maternal smoking in the literature; therefore, infants were matched on SES in this analysis.

Participants

The 34 tobacco-exposed infants were divided into two groups according to the side of the median on which they fell for the number of cigarettes smoked per day by their mothers during pregnancy. This resulted in two equal groups of 17 infants: the mothers in the first group smoked less than 10 cigarettes per day

(light smokers = LS), and the mothers in the second group smoked 10 or more cigarettes per day (heavy smokers = HS). The LS mothers smoked an average of 4.7 cigarettes per day, and the HS mothers smoked an average of 16.9 cigarettes per day.

Each LS infant was matched with an HS infant on BW within 500 g (this was the smallest difference that allowed the matching of all infants; it represents ± 1.1 standard deviations from the grand mean) and SES within \$10,000/year (household income was used as an index of SES, and \$10,000 was one unit of increment on the questionnaire; it represents $\pm .5$ standard deviations from the grand mean). After the infants in the two smoking groups were matched as closely as possible on these variables, the control infant who was the closest match for each pair was selected from the original sample of 52 control infants. All 17 triplets (HS/LS/Control) were matched on BW within 500 g, and 16 were matched on SES within \$10,000 (although the data for SES were missing for one HS and one control infant). The raw data for the matching variables are presented in Table 14. The HS group consisted of 8 males and 9 females, the LS group consisted of 6 males and 11 females, and the control group consisted of 11 males and 6 females. Because the small sample size precluded the use of covariate analysis to control for potential sex differences in performance, correlational analyses were planned for all variables on which the smoking groups differed to ensure that sex was not a confound. This analysis follows the information processing analyses. Group means for the demographic control variables are shown in Table 15.

Table 14
Matching Variable Scores for Infants Born to Heavy Smokers, Light Smokers,
and Non-Smokers

	BW (g)			SES (x \$1000/yr)		
	HS	LS	NS	HS	LS	NS
1	3390	3575	3640	65	65	65
2	3190	3460	3260	55	65	55
3	3120	3600	3280	5	15	15
4	3000	3295	3295	5	5	15
5	2980	3465	3260	55	45	45
6	2780	3110	3220	15	15	5
7	2840	3260	2975	15	5	15
8	2825	3120	3140	35	25	25
9	2700	2970	2890	15	5	15
10	2660	2835	2835	--	35	25
11	2620	2430	2665	5	15	5
12	2610	2800	2500	15	5	15
13	2610	2805	3050	55	55	45
14	2570	2850	2610	5	5	5
15	2530	2065	2440	25	55*	35
16	2460	2015	2095	5	5	--
17	1280	1775	1550	55	55	55
<u>M</u>	2747	2908	2876	26.3	28.5	27.5
(SD)	(351)	(554)	(469)	(22.3)	(23.2)	(19.2)

BW=birthweight; SES=socioeconomic status; HS=heavy smokers' infants;
 LS=light smokers' infants, NS=non-smokers' infants (controls).

* The infant was outside the limits of the matching criterion for SES.

Table 15

Group Means and Standard Deviations for the Demographic Matching and Control Variables for Infants Born to Heavy Smokers (HS), Light Smokers (LS), and Non-smokers (NS)

Variable	HS	LS	NS
BW (g)	2447 (351)	2909 (554)	2877 (469)
TW (g)	2765 (305)	2939 (498)	2886 (449)
GA (weeks-days)	38-2 (2-2)	38-2 (2-3)	38-2 (2-2)
TA (weeks-days)	38-4 (2-2)	38-5 (2-0)	38-4 (2-0)
MA (years)	26.4 (6.9)	26.7 (4.2)	27.6 (3.2)
WG (kg)	12.9 (5.3)	16.3 (4.4)	10.3 (3.8)
GRAV	2.5 (1.3)	2.4 (1.5)	1.9 (1.0)
PAR	1.8 (0.8)	1.7 (0.8)	1.9 (1.0)
ED ^a	2.6 (1.4)	3.0 (1.4)	2.6 (1.4)

BW=birthweight; TW=weight at testing; GA=gestational age; TA=corrected age at testing; MA=mother's age; WG=maternal pregnancy weight gain; GRAV=gravidity; PAR=parity; ED=maternal educational level (^ascored on a 5-point scale where 1=did not complete high school, 2=high school graduate, 3=CEGEP, some college, or technical training, 4=graduated from college program, or had some university, 5=university graduate).

Results

Prealysis

As in Part I, missing values were replaced with group means, and outliers on each variable were replaced with scores two standard deviations away from the group mean. The kurtosis and skewness values for each variable were examined for deviation from the normal distribution. The variables representing the percentage of head turns toward the stimulus in the last quartile of the familiarization phase and the novelty phase were positively skewed and could not be normalized by transformation. All other variables were within acceptable limits for skewness and kurtosis.

General Approach to the Data Analysis

The general approach to the data analysis was the same as in Part I. However, because there were three groups in this study, planned orthogonal comparisons between group means were carried out using Fisher's least-significant-difference test following all significant or near-significant univariate analyses of the information processing measures. For the analyses of the control variables, Tukey's post hoc test was used to compare group means.

Analyses of Demographic Control Variables

To ensure that the matching process was successful, a 3 (Group) x 2 (Matching Variable) repeated measures MANOVA was conducted for BW and SES. No group differences were found (Appendix F, Table F1). To control for potentially confounding group differences on TW, GA, TA, WG, MA, PAR, GRAV, and ED a second repeated measures MANOVA was carried out for these variables. However, a check for multicollinearity indicated that TA, GA, and TW were all highly intercorrelated with r 's greater than .7. Since TW was the most highly correlated with Group, it was entered into the MANOVA. Thus, a 3 (Group)

x 6 (Control Variables) repeated measures MANOVA was carried out for TW, WG, MA, PAR, GRAV, and ED (Appendix F, Table F2). The multivariate F for the Group x Control Variable interaction was marginally significant, $F(10, 88) = 1.93$, $p = .051$, and there was a main effect of Group, $F(12, 86) = 1.90$, $p < .05$.

Univariate analyses indicated that the groups were similar on TW, MA, PAR, GRAV, and ED, but differed on WG, $F(2, 48) = 7.42$, $p < .01$. Tukey's post hoc pairwise comparisons between group means, indicated that the pregnancy weight gain of the LS mothers was greater than that of the control mothers ($p < .05$). No other comparisons were significant. Whereas mothers of the LS infants gained an average of 16.3 kilograms, the mothers of the control infants gained an average of 10.3 kilograms; mothers of the HS infants gained an average of 12.9 kilograms. Since maternal weight gain during pregnancy was used as an index of caloric intake and the purpose of group comparisons was to ensure that the mothers who smoked had gained at least as much weight as the control mothers, the group differences on WG were considered to be of little consequence for the information processing results. To test this assumption, the correlations between WG and the information processing variables were examined; all were non-significant.

Information Processing Control Measures

To ensure that the infants in the three groups were equally capable of making head turns, the groups were compared on the overall percentage of head turns during the procedure in a 3 (Group) x 1 (Head turns) ANOVA Appendix F, Table F3). No significant differences were found, with the HS infants turning on 77.2% of the trials, LS infants turning on 78.9% of the trials, and the controls turning on 80.2% of the trials, on average.

The groups were compared on the percentage of time spent in a positive state during the three phases of the procedure by way of a 3 (Group) x 3 (Phase)

repeated measures MANOVA (Appendix F, Table F4). Collapsed across groups, the percentage of time spent in a positive state decreased across the three phases of the procedure, $F(2, 47) = 4.89, p < .05$. There was a high percentage of positive state throughout the procedure, with means of 90.6%, 86.9% and 84.0% for the familiarization, novelty, and dishabituation phases, respectively. Although there was no Group x Phase interaction, the effect of Group approached significance, $F(6, 92) = 1.88, p = .093$. Tukey's post hoc pairwise comparisons test was used to explore this effect, since positive state is an important control variable. These analyses indicated that the LS infants exhibited less positive state than the control infants in both the novelty phase ($p < .05$) and dishabituation phase ($p < .05$). The lowest mean level of positive state observed was 75.4%, among the LS infants in the dishabituation phase.

Information Processing Measures

The HS, LS, and control infants were compared on the information processing measures across the three phases of the procedure. Figure 11 shows the percentage of head turns toward the sound source during the familiarization quartiles, novelty trial blocks, and the dishabituation trial block.

Familiarization Phase. Between group comparisons on the percentage of head turns toward the stimulus in each of the four quartiles of the familiarization phase were conducted in a 3 (Group) x 4 (Quartiles) repeated measures MANOVA (Appendix F, Table F5). The multivariate F was significant for the effect of Quartiles, $F(3, 46) = 44.05, p < .001$, with the percentage of head turns toward the stimulus declining across quartiles. A Group x Quartiles interaction, $F(6, 92) = 2.45, p < .05$, indicated that the groups differed on the percentage of turns toward the stimulus across quartiles. Univariate analyses revealed group differences on

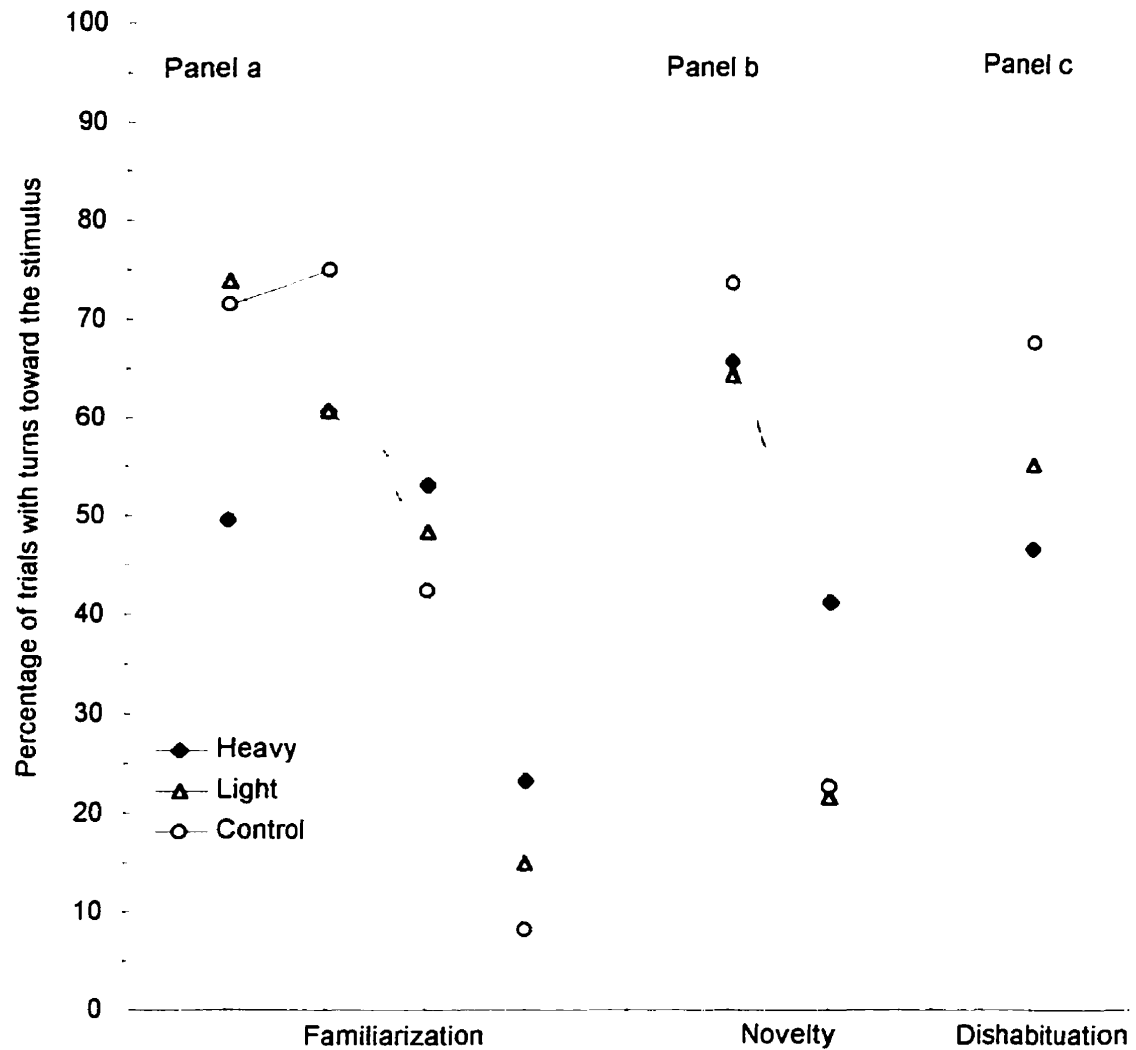


Figure 11. Mean percentages of head turns toward the sound source for infants born to heavy smokers, light smokers, and non-smokers (controls) during: familiarization phase quartiles (Panel a); novelty phase trial blocks (Panel b); and the dishabituation phase trial block (Panel c). Note: Standard error bars are omitted to improve clarity.

the first quartile only, $F(2, 48) = 4.44, p < .05$. As shown in Figure 12, planned comparisons between group means indicated that the percentage of head turns toward the stimulus during the first quartile of the familiarization phase was significantly lower among the HS infants than the LS infants ($p < .05$) and the non-smokers ($p < .01$); the means of the LS infants and non-smokers were similar. These results suggest a dose-response effect of maternal smoking on the infants' initial head-turning response to the familiarization stimulus.

Because the distribution of scores in the last quartile of the familiarization phase was skewed, violating the assumptions of ANOVA, the above analyses were repeated using the two trial blocks of the familiarization phase in place of quartiles (Appendix F, Table F6). A 3 (Group) x 2 (Trial Block) repeated measures ANOVA revealed an effect of Trial Block, $F(1, 48) = 67.87, p < .001$, qualified by a Group x Trial Block interaction, $F(2, 48) = 5.61, p < .01$, and multivariate effect of Group, $F(4, 94) = 2.70, p < .05$. Thus, although the percentage of head turns toward the stimulus declined from the first to the second trial block, the pattern was not the same for the three groups. As illustrated in Figure 13, univariate F tests revealed significant group differences on both the first trial block, $F(2, 48) = 3.48, p < .05$, and the second trial block, $F(2, 48) = 3.90, p < .05$. Planned comparisons indicated that the percentage of head turns toward the stimulus was greater for the control infants than the HS infants in the first trial block ($p < .05$), and lower for the control infants than the HS infants in the second trial block ($p < .01$). The LS infants were not significantly different from the HS infants or the controls.

To examine the direction of head-turning at the beginning and end of the familiarization phase, the difference scores for the first and last quartiles were compared with a mean of zero for each group (Appendix F, Table F7). The results

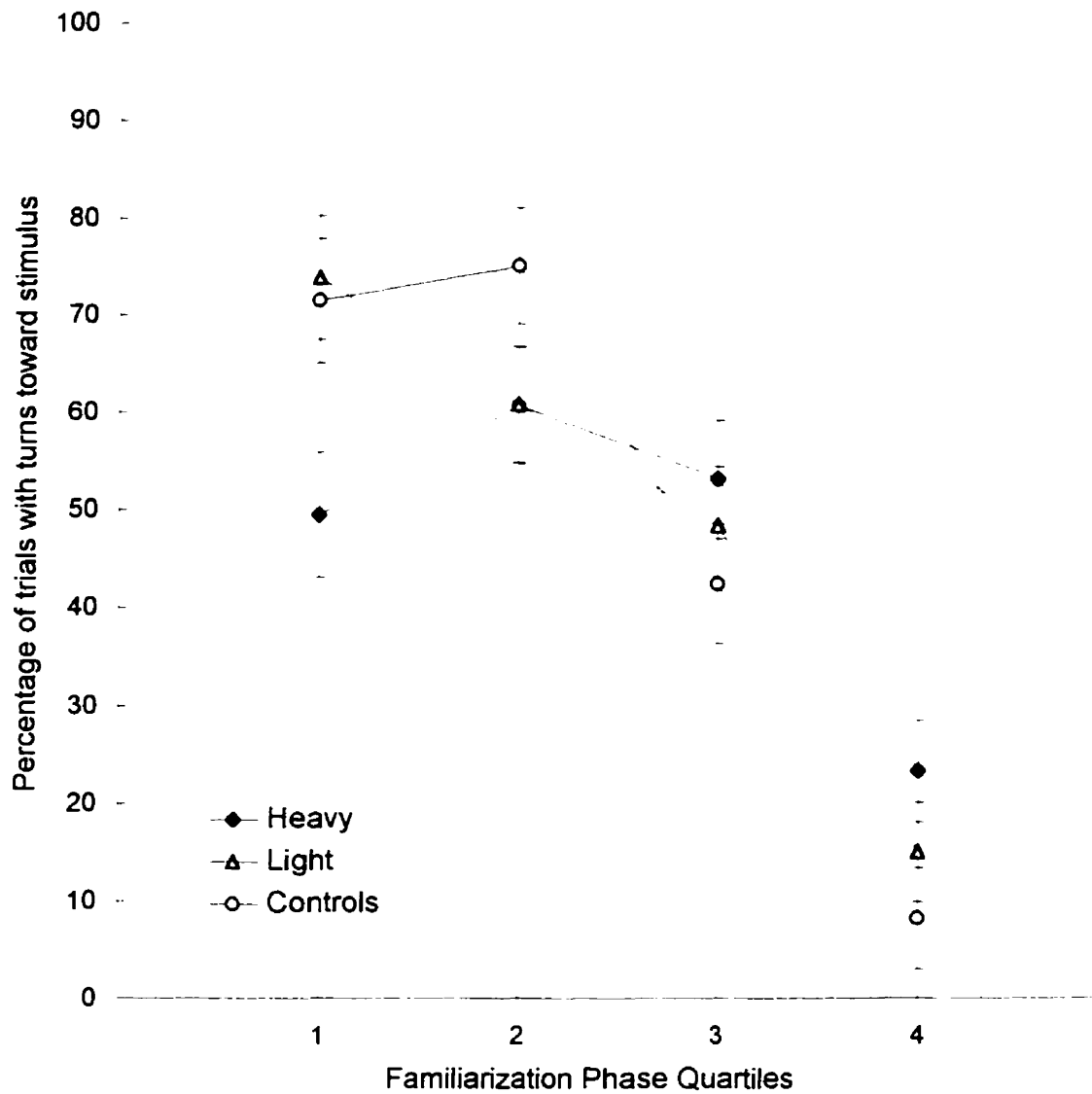


Figure 12. Mean percentages of head turns toward the sound source during the 4 quartile blocks of the familiarization phase, for infants born to heavy smokers, light smokers, and non-smokers (controls).

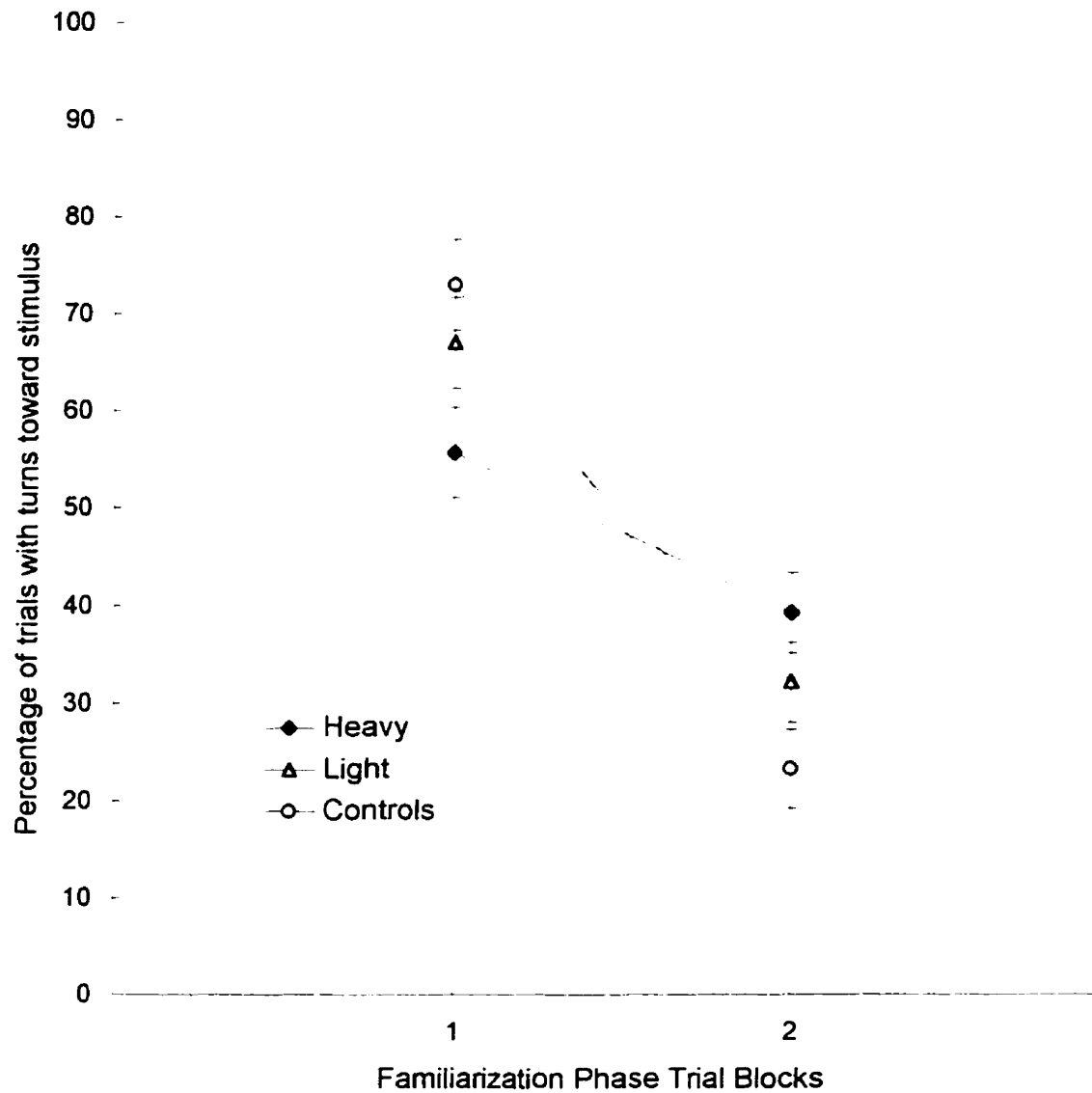


Figure 13. Mean percentages of head-turning toward the sound source during the 2 trial blocks of the familiarization phase, for infants born to heavy smokers, light smokers, and non-smokers (controls).

indicated that systematic head-turning toward the stimulus was exhibited by the control infants, $t(16) = 5.18$, $p < .001$, and LS infants, $t(16) = 4.59$, $p < .001$, and to a lesser extent by the HS infants, $t(16) = 2.48$, $p < .05$. In the fourth quartile of the familiarization phase, all three groups turned systematically away from the stimulus (controls: $t(16) = -2.75$, $p < .05$; LS infants: $t(16) = -2.87$, $p < .05$; HS infants: $t(16) = -2.19$, $p < .05$).

To determine if the three groups differed in the number of infants who reached the criterion for orientation to the familiarization stimulus, a χ^2 analysis was carried out (Appendix F, Table F8). No significant differences between groups were found, with all 17 control infants, 16 LS infants, and 15 HS infants reaching the criterion for orientation. However, of the infants who oriented, a one-way ANOVA (Appendix F, Table F9) indicated that the groups differed in the number of trials required to reach criterion, $F(2, 45) = 4.99$, $p < .05$. Planned comparisons of group means revealed differences between the HS infants and controls ($p < .01$), and a near-significant difference between the HS and LS infants ($p = .061$). As shown in Figure 14 (Panel a), the controls oriented in an average of 4.2 trials, whereas the LS infants required 5.3 trials and the HS infants required 7.1 trials, on average.

Group differences in the number of infants who reached the criterion for habituation were also assessed by way of a χ^2 analysis (Appendix F, Table F10). The results were non-significant, with 16 controls, 12 LS infants, and 11 HS infants habituating to the familiarization stimulus. A one-way ANOVA indicated that, among the infants who reached criterion for habituation, the groups were similar in terms of the number of trials required (Appendix F, Table F11). As shown in Figure 14 (Panel a), controls habituated in 10.9 trials, LS infants in 11.2 trials, and the HS infants in 13.4 trials.

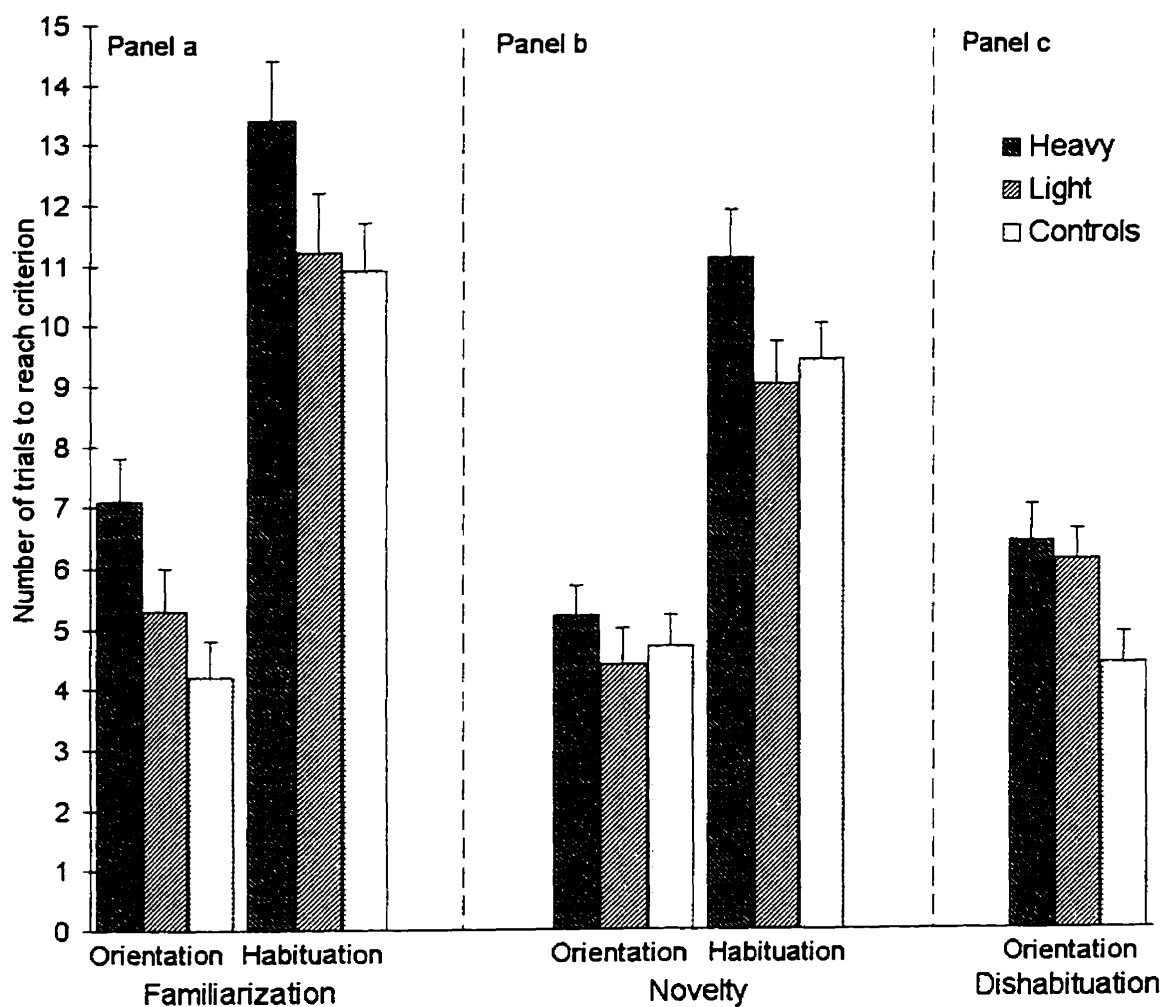


Figure 14. Number of trials required to reach criterion for orientation and habituation in the familiarization and novelty phases, and orientation in the dishabituation phase, for infants born to heavy smokers, light smokers, and non-smokers (controls).

In summary, the analyses of the familiarization phase data revealed dose-response effects of maternal smoking on newborn responses to the familiarization stimulus. The HS infants exhibited a lower percentage of head turns toward the stimulus during the first half of the familiarization phase and a greater percentage of head turns toward the stimulus during the second half of the familiarization phase than either the LS infants' or controls. In addition, the HS infants required more trials to reach criterion for orientation to the familiarization stimulus compared with the controls; the LS infants fell between the two groups. These results suggest that smoking during pregnancy has adverse effects on newborn information processing as assessed by the familiarization phase measures, and that the decrement in performance is related to the number of cigarettes smoked per day.

Novelty Phase. The performance of the three groups during the novelty phase was first assessed by comparing the percentage of head turns toward the stimulus across the four quartiles of the phase (see Figure 15). A 3 (Group) x 4 (Quartiles) repeated measures MANOVA (Appendix F, Table F12) revealed a significant effect of Quartiles, $F(3, 46) = 63.17, p < .001$, with the percentage of head turns toward the stimulus decreasing across quartiles. There was no Group x Quartile interaction, although the main effect of Group approached significance ($p = .061$). Univariate analyses indicated that the groups differed only on the percentage of head turns toward the stimulus in the fourth quartile, and planned comparisons between group means revealed that the HS infants made fewer turns toward the sound source than either the LS infants ($p < .01$) or the control infants ($p < .01$). However, because the distribution of the data in the fourth quartile was skewed, in violation of the assumptions of ANOVA, the analysis was

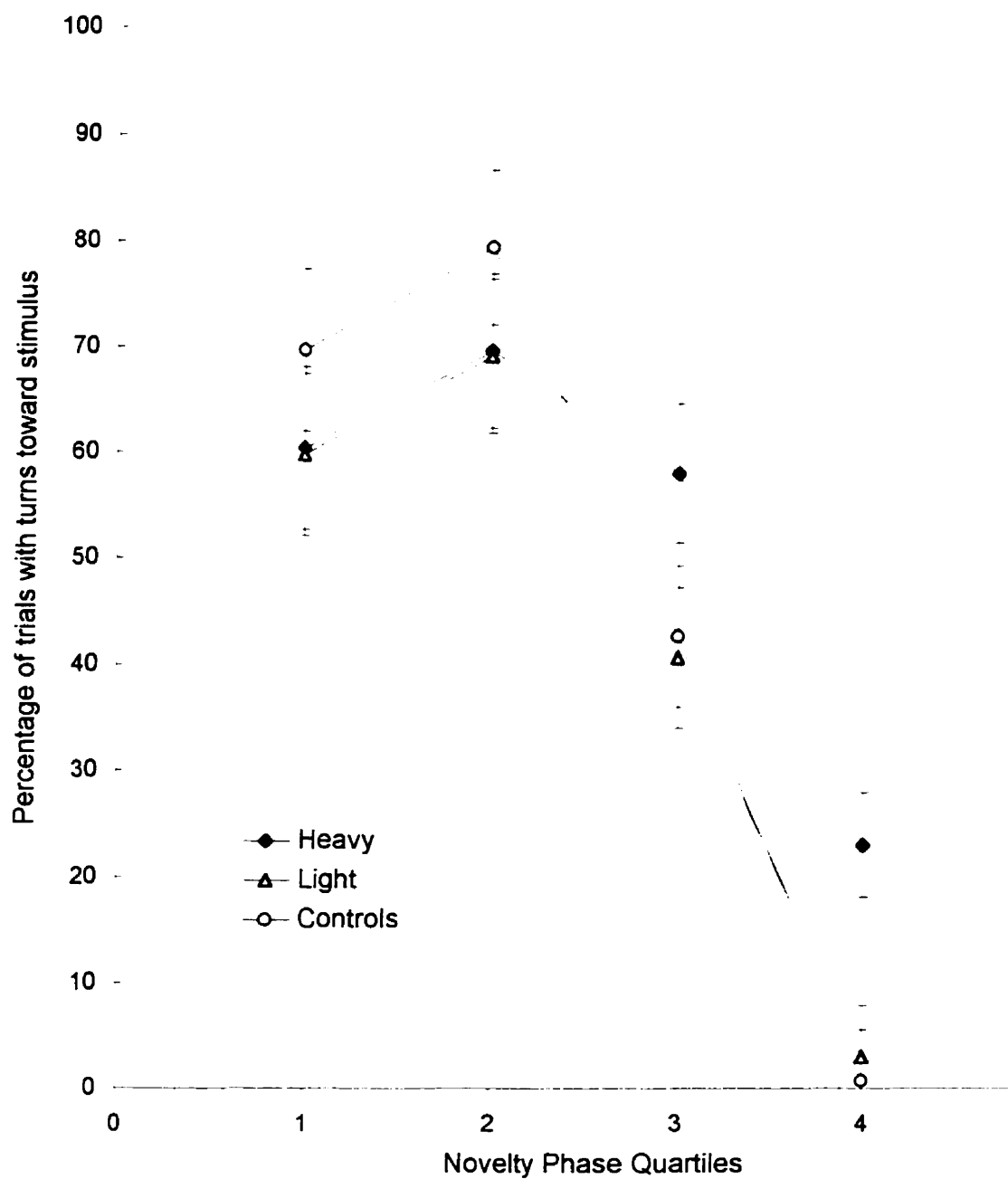


Figure 15. Mean percentages of head turns toward the sound source during the 4 quartile blocks of the novelty phase, for infants born to heavy smokers, light smokers, and non-smokers (controls).

repeated using novelty phase trial blocks in place of quartiles. A 2 (Group) x 2 (Trial Block) repeated measures MANOVA (Appendix F, Table F13) yielded multivariate effects of Trial Blocks, $F(1, 48) = 57.71, p < .001$, and Group, $F(4, 94) = 3.62, p < .01$, indicating that, although head-turning toward the stimulus decreased, the responses across trial blocks were not the same for the three groups. Univariate analyses revealed group differences on the second trial block, $F(2, 48) = 5.77, p < .01$. Planned comparisons between group means indicated differences between the HS and LS infants ($p < .01$), and the HS and control infants ($p < .01$); the LS infants and controls did not differ. As shown in Figure 11 (Panel b) the HS infants turned toward the stimulus on an average of 41.2% of trials in the second block of the novelty phase whereas the LS infants and controls turned toward the stimulus on an average of 21.6% and 22.7% of trials, respectively.

Recovery to the novel stimulus was assessed by comparing the percentage of head turns toward the stimulus in the last trial block of the familiarization phase with the percentage of head turns toward the stimulus in the first trial block of the novelty phase. A 3 (Group) x 2 (Trial Block) repeated measures MANOVA (Appendix F, Table F14) revealed an effect of Trial Block, $F(1, 48) = 72.65, p < .001$, indicating that collapsed across groups the percentage of head turns toward the novel stimulus increased over trial blocks. The Group x Trial Block interaction approached significance, $F(2, 48) = 2.90, p = .065$, and similar results were found for the effect of Group, $F(4, 94) = 2.10, p = .09$, suggesting that the degree of recovery differed among the three groups. Planned comparisons of group means revealed that the previously described group differences on the percentage of head turns toward the stimulus in the second block of the familiarization phase accounted for the near-significant interaction;

i.e., HS infants responded with a higher percentage of head turns toward the stimulus in the second block of the familiarization phase than either the LS infants or controls. The groups did not differ on the percentage of head turns toward the stimulus in the first block of the novelty phase.

To determine if the tendency for the groups to differ on the degree of recovery to the novel stimulus was primarily due to the poorer habituation of the HS infants, the analysis was repeated with the infants who failed to habituate to the familiarization stimulus excluded (Appendix F, Table F15). The previous tendency toward a Group x Trial Block interaction and main effect of Group were no longer apparent. This suggests that differences between groups on recovery to the novel stimulus were a function of the group differences on the habituation measures of the familiarization phase.

Because recovery to novelty is one of the most important variables for discriminating among infants at risk for developmental delay (Zelazo et al., 1989), further exploratory analyses were carried out to determine whether the infants recovered responding to the novel stimulus. *t* tests indicated that the percentages of head turns toward the stimulus in the first block of the novelty phase were different from the percentages of head turns toward the stimulus in the second block of the familiarization phase for all three groups (Appendix F, Table F16). These results imply that the HS, LS, and control groups all recovered responding to the novel stimulus.

The degree of head-turning toward the stimulus relative to turns away was assessed for each group during the first and last quartiles of the novelty phase by comparing the difference scores with a mean of zero (Appendix F, Table F17). Analyses for direction of head turns during the first quartile of the novelty phase indicated that all three groups turned systematically toward the stimulus (controls:

$t(16) = 4.31, p < .01$; LS infants: $t(16) = 3.77, p < .01$; HS infants: $t(16) = 4.15, p < .01$). However, during the last quartile, only the controls and LS infants turned systematically away from the stimulus (controls: $t(16) = -5.74, p < .001$; LS infants: $t(16) = -5.64, p < .001$), while for the HS infants the difference scores were not significantly different from zero, $t(16) = -1.07, p = .299$.

When χ^2 analysis was used to compare groups on the number of infants reaching the criterion for orientation (Appendix F, Table F18), group differences were found, $\chi^2(2) = 8.68, p < .05$. Whereas all controls and HS infants oriented, only 13 LS infants oriented. When a one-way ANOVA was carried out to determine if the groups differed on the number of trials required to reach the criterion for orientation, no group differences were found (Appendix F, Table F19). As illustrated in Figure 14 (Panel b), the controls oriented in 4.7 trials, the LS infants in 4.4 trials, and the HS infants in 5.2 trials, on average. When a χ^2 analysis was carried out to determine if the groups differed in the number of infants reaching the criterion for habituation to the novelty stimulus (Appendix F, Table F20), the result was marginally significant, $\chi^2(2) = 5.89, p = .053$. Sixteen controls, 13 LS infants, and 10 HS infants reached the criterion for habituation. A one-way ANOVA comparing the groups on the number of trials required to reach the criterion for habituation was non-significant (Appendix F, Table F21). The controls habituated in 9.4 trials, the LS infants in 9.0 trials, and the HS infants in 11.1 trials, on average (Figure 14, Panel b).

In summary, the results of the novelty phase analyses provide further support for a dose-response effect of maternal smoking on newborn information processing. First, because the HS infants made a higher percentage of head turns toward the stimulus in the second block of the familiarization phase, recovery to the novel stimulus was less pronounced for this group relative to the

LS infants and controls. Second, while all three groups made systematic head turns toward the stimulus at the beginning of the novelty phase (1st quartile), only the controls and LS infants turned systematically away from the stimulus during the final trials of the novelty phase (4th quartile); the direction of head turns among the HS infants was random. Third, the LS infants were less likely than the other two groups to reach the criterion for orientation to the novel stimulus, and both the HS and LS infants tended to be less likely to reach the criterion for habituation to the novel stimulus compared to controls.

Dishabituation Phase. Recovery of head-turning to the dishabituation stimulus was assessed by comparing the percentage of head turns toward the stimulus in the last trial block of the novelty phase with the percentage of head turns toward the stimulus in the dishabituation trial block. A 3 (Group) x 2 (Trial Block) repeated measures MANOVA (Appendix F, Table F22) revealed an effect of Trial Block, $F(1, 48) = 39.08$, $p < .001$, qualified by a Group x Trial Block interaction, $F(2, 48) = 6.91$, $p < .01$, and multivariate effect of Group, $F(4, 94) = 4.08$, $p < .01$. Collapsed across groups, the percentage of head turns toward the stimulus increased between the last trial block of the novelty phase ($M = 28.5\%$) and the dishabituation trial block ($M = 56.6\%$). Univariate analyses indicated that the groups differed on the percentage of head turns toward the stimulus during the second block of the novelty phase (previously reported), with a tendency toward group differences during the dishabituation trial block, $F(2, 48) = 2.87$, $p = .067$.

Planned between-group comparisons on the mean percentage of head turns toward the stimulus during the dishabituation trial block indicated that the HS infants made a lower percentage of head turns toward the stimulus relative to the control infants ($p < .05$). The other group comparisons were non-significant. As

shown in Figure 11 (Panel c), the control infants turned toward the stimulus on 67.8% of the dishabituation block trials whereas the HS infants turned toward the stimulus on only 46.6% of the trials; the LS infants turned toward the stimulus on 55.2% of the trials. These group differences were further explored using t tests to determine if the percentage of head turns toward the stimulus in the dishabituation block differed from the percentage of head turns toward the stimulus in the second trial block of the novelty phase (Appendix F, Table F23). The results indicated that both the control infants, $t(16) = -7.34$, $p < .001$, and LS infants, $t(16) = -5.04$, $p < .001$, recovered to the dishabituation stimulus. However, there was no change in responding among the HS infants when the dishabituation stimulus was introduced, $t(16) = -.54$, $p > .50$.

To determine if the group differences in recovery to the dishabituation stimulus were a function of the group differences in habituation to the novelty phase stimulus, recovery to the dishabituation stimulus was re-assessed with the infants who failed to habituate to the novelty phase stimulus excluded (Appendix F, Table F24). Excluding the infants who failed to habituate did not change the results; the LS and control infants still recovered responding to the dishabituation stimulus, whereas the head-turning of the HS infants remained relatively stable. Thus, failure to recover to the dishabituation stimulus among the HS infants was not a function of poor habituation to the novelty phase stimulus.

The direction of head-turning upon introduction of the dishabituation stimulus was assessed by comparing the difference scores for the first three trials of the dishabituation phase with a mean of zero for each group (Appendix F, Table F25). The t test results indicated that only the control infants turned systematically toward the sound source upon introduction of the dishabituation stimulus, $t(16) = 3.70$, $p < .01$. For both the HS and LS infants, the difference

scores were not different from zero, indicating that the direction of head turns was random.

A χ^2 analysis did not reveal between-group differences in the number of infants who reached the criterion for orientation to the dishabituation stimulus (Appendix F, Table F26); 14 infants in each of the control and LS groups oriented, and 13 infants in the HS group oriented. However, a one-way ANOVA for the number of trials required to reach the criterion for orientation indicated between-group differences, $F(2, 38) = 3.86, p < .05$ (Appendix F, Table F27). Planned comparisons of group means indicated that the control infants oriented in fewer trials than both the LS infants ($p < .05$) and the HS infants ($p < .05$), who were not different from each other. As shown in Figure 14 (Panel c) the control infants oriented in 4.4 trials, the LS infants in 6.1 trials, and the HS infants in 6.4 trials, on average.

Together, the results of the dishabituation phase analyses suggest that maternal cigarette smoking has detrimental effects on newborn information processing ability. Relative to infants born to non-smokers, those born to both heavy and light smokers exhibited deficits in recovery to the dishabituation stimulus, failing to turn preferentially toward the stimulus during the initial trials of the dishabituation phase, and requiring more trials to reach criterion for orientation.

Analyses for Sex Differences

Because the male to female ratio differed across the three groups, with the control group consisting of more males than females (65% male, 35% female), the LS group consisting of more females than males (65% female, 35% male), and only the HS groups being nearly balanced (53% female, 47% male), it was important to ensure that the group differences on the information processing

measures were not confounded by sex differences. Analysis of covariance could not be used in this case due to the small sample size. Thus, to determine if sex influenced the results, the relation between sex and each of the variables on which group differences were found was assessed using Pearson product-moment correlations. With all groups combined, there were no significant correlations between sex and any of the information processing measures on which there were effects of tobacco-exposure. To explore the possibility that tobacco-exposure affected male and female infants differently, the correlational analyses were repeated within each group. Again, none of the correlations were significant (Appendix F, Table F28).

Summary

Infants born to heavy smokers and light smokers were different from those born to non-smokers on a number of the information processing measures. In the familiarization phase, HS infants exhibited lower levels of head-turning toward the stimulus in the first quartile and first trial block, followed by higher levels of head-turning toward the stimulus in the second trial block, relative to controls. HS infants also required a greater number of trials to reach the criterion for orientation. Recovery to the novelty phase stimulus was also somewhat impaired among the HS infants relative to controls, as indicated by the near-significant Group x Trial Block interaction and effect of Group. Relative to controls, the HS infants showed higher levels of head-turning in the fourth quartile and second trial block of the novelty phase and they were less likely to habituate to the novel stimulus. In the dishabituation phase, the LS and HS infants exhibited similar decrements in performance on two measures; they displayed random head turning at the beginning of the phase and required a greater number of trials to orient. Throughout the procedure, the HS infants performed more poorly than the

controls and LS infants on all measures on which significant group differences were found, with the exception that the LS infants were less likely to orient to the novelty phase stimulus. Although the ratio of males to females differed across the three groups, sex was not related to any of the information processing measures on which effects of fetal tobacco-exposure were found.

Discussion

The results demonstrate that maternal smoking during pregnancy adversely affects performance on the newborn information processing procedure. Prenatal exposure to two or more cigarettes per day was associated with impairments in orientation and habituation to an auditory familiarization stimulus and lack of recovery to a dishabituation stimulus. Dose-response effects were evident, with infants whose mothers smoked 10 or more cigarettes per day (heavy smokers) showing greater deficits in performance than infants whose mothers smoked less than 10 cigarettes per day (light smokers). In addition to deficits on the familiarization and dishabituation phase measures, infants born to heavy smokers also exhibited deficits in habituation to the novel stimulus. In nearly every case where significant differences were found between groups, the greatest deficits were observed among the infants born to heavy smokers; the performance of infants born to light smokers fell mid-way between that of the infants born to heavy smokers and non-smokers. In cases where the group differences did not reach statistical significance, the group means throughout the three phases of the procedure consistently suggested dose-response effects of smoking on the information processing measures, with infants whose mothers smoked 10 or more cigarettes per day being more adversely affected than infants whose mothers smoked less than 10 cigarettes per day. The only exception was that the infants born to light smokers were less likely to orient to the stimulus in

the novelty phase. Given the consistency of the dose-response effects, it is possible that this finding represents a Type I error. Alternatively, dose-response effects of maternal smoking on recovery to the novel stimulus may exist, but were not as marked as expected in this small sample of infants.

While it is possible that the observed differences between infants born to smokers and non-smokers in Part I of this study were partially mediated by the group differences in birthweight, the dose-response effects in Part II were obtained after careful, individual matching of infants in each group on birthweight and SES. The groups were also similar in terms of weight and age at the time of testing, and maternal age, parity, gravidity, and education level. Although the groups differed on maternal pregnancy weight gain, the mothers who smoked between two and nine cigarettes per day gained the most weight, and the non-smoking mothers gained the least weight. Mothers in all three groups gained more than 10 kilograms during pregnancy implying adequate caloric intake. Moreover, maternal weight gain was not related to infant performance on the information processing measures. The fact that dose-response effects were evident despite control over numerous potentially confounding factors increases the likelihood that the observed effects are due to fetal tobacco-exposure.

Unlike previous studies assessing the effects of maternal smoking on newborn outcome using the NBAS (Brazelton, 1984), this study employed the most valid measure of auditory information processing currently available. The procedure, developed by Zelazo and colleagues, has been extensively researched and shown to consistently elicit a reliable response pattern from normal, healthy newborns (e.g., Brody et al., 1984; Swain et al., 1991; Tarquinio et al., 1990; Tarquinio et al., 1991; Zelazo et al., 1984; Zelazo et al., 1987; Zelazo et al., 1989). Deviation from the expected response pattern in an infant who is in

an alert, testable state implies deficits in the processing of the auditory stimuli. However, deficits in orientation to the familiarization stimulus are unusual and raise the possibility of auditory threshold disturbances.

Relation to Previous Research

Numerous studies conducted by Zelazo and colleagues using the auditory information processing procedure have demonstrated that normal, healthy newborn infants orient and habituate to a familiarization stimulus, recover responding and subsequently habituate to a novel stimulus, and dishabituate to the return of the familiarization stimulus (e.g., Brody et al., 1984; Swain et al., 1991; Tarquinio et al., 1990; Tarquinio et al., 1991; Zelazo et al., 1984; Zelazo et al., 1987; Zelazo et al., 1989). In addition, habituation is marked not only by a lack of head-turning toward the stimulus, but systematic turning away from the stimulus. Turning away from the sound source after repeated presentations of a stimulus is a robust finding that implies that newborns actively process auditory stimuli and that habituation is not simply a result of selective receptor adaptation or effector fatigue (Zelazo et al., 1991). Failure to turn systematically toward the stimulus during the initial trials of a given phase or to turn away from the stimulus in the last trials of a phase implies deficits in information processing.

The hypotheses that tobacco exposure would be associated with deficits in recovery to the novel and dishabituation stimuli, but not on orientation and habituation to the familiarization stimulus, were based on previous research demonstrating the discriminant validity of the information processing procedure with infants at different levels of risk for developmental delay (Zelazo, Weiss, et al., 1989; Zelazo et al., 1991). High risk infants failed to recover responding to the novel stimulus following orientation and habituation to the familiarization stimulus (Zelazo, Weiss, et al., 1989). The results of Study 1 (this dissertation)

corroborated the findings of Zelazo et al.; recovery to novelty discriminated, along with habituation measures, among infants prenatally exposed to cocaine and non-exposed infants.

The tobacco-exposed infants in the present study showed deficits in recovery to novelty, although, unlike previous studies with infants at risk (Zelazo, Weiss, et al., 1989; Study 1, this dissertation), the effects were most pronounced during the dishabituation phase. In addition, the tobacco-exposed infants in the present study showed impairments in both orientation and habituation to the familiarization stimulus. With respect to Zelazo et al.'s findings, these group differences between the tobacco-exposed and non-exposed infants on the familiarization phase measures were both unusual and unexpected. There are, however, at least two possible explanations for the discrepancy between the tobacco-exposed infants' poor performance on the familiarization phase measures in the present study and the lack of group differences among the different risk groups in Zelazo et al.'s (1989) sample and the lack of differences on the orientation measures in the Study 1 sample.

First, in Zelazo et al.'s sample, 14 of the original 167 infants tested on the procedure were excluded prior to data analysis because of failure to reach the criterion for orientation. Unlike the present study, exclusion of the infants who failed to orient in the study by Zelazo et al. was justified on the grounds that these infants had suffered a number of serious perinatal complications that placed them at increased risk for auditory impairments. The infants deemed to be at high risk for developmental delay had suffered such complications as high grade intracranial hemorrhages, asphyxiation requiring ventilation, hydrocephalus, and meningitis; the moderate-risk infants had suffered such complications as low grade intracranial hemorrhage, metabolic acidosis, and meconium aspiration.

Exclusion of the infants who failed to orient would have reduced the variability in performance on the familiarization measures and diminished the likelihood of observing group differences in the familiarization phase.

Second, in Study 1 of this dissertation, 72% of the non-cocaine-exposed infants were born to mothers who smoked cigarettes during pregnancy, and in Zelazo et al.'s (1989) sample, the proportion of infants in each group who were born to smokers was not factored into the data analysis. Given the prevalence of smoking during pregnancy, it is probable that approximately 20 to 30% of the infants in Zelazo et al.'s sample were exposed to tobacco in utero. The tobacco-exposed infants in these two studies may have reduced the scores of the control groups on the familiarization measures from the levels of performance that might have been observed if tobacco-exposed infants had not been included. One could speculate that among Zelazo et al.'s moderate- and high-risk groups that the effects of tobacco-exposure would have been masked by the effects of the other, potentially more serious risk factors, and that the performance of these groups would not have been affected by the inclusion of tobacco-exposed infants. Inclusion of smokers' infants in the control group would thus decrease the likelihood of detecting differences between the control groups and the risk groups on the familiarization phase measures. This argument receives some support from two observations: (a) in the first two quartiles of the familiarization phase, the performance of Zelazo et al.'s low-risk group was approximately mid-way between the level of performance of the tobacco-exposed and non-exposed groups in the present study, and (b) in Study 1 of this dissertation, inspection of the group means reveals that the non-cocaine-exposed group performed similarly to the tobacco-exposed group in the present study. While one could argue that this would be expected since the control group in Study 1 included 18 tobacco-

exposed infants from Study 2, the familiarization phase scores of the Study 1 control group were considerably lower than those obtained in the majority of other studies using the auditory information processing measure (e.g., Brody et al., 1984; Swain et al., 1991; Tarquinio et al., 1990; Tarquinio et al., 1991; Zelazo et al., 1984; Zelazo et al., 1987). However, these comparisons between studies do not explain why the tobacco-exposed infants exhibited impairments on these measures.

The tobacco-associated impairments in orientation and habituation on the familiarization phase measures observed in the present study are strikingly consistent with the findings of previous studies employing the NBAS (Fried & Makin, 1978; Picone et al., 1982; Richardson, Day, & Taylor, 1989; Saxton, 1978). In these studies, infants whose mothers smoked during pregnancy exhibited deficits on the auditory orientation and habituation measures of the NBAS. It has been suggested that such deficits may be secondary to an increased auditory threshold among tobacco-exposed neonates (Fried & Makin, 1978; Picone et al., 1982; Saxton, 1978). Although this is only one of a number of possible interpretations, the possibility that disturbances in auditory threshold were responsible for the impaired performance of the tobacco-exposed infants in the present study is an important issue.

Auditory Threshold Disturbance Versus Information Processing Disturbance

Despite the fact that the results of studies comparing tobacco-exposed infants with non-exposed controls on the NBAS (Brazelton, 1984) have raised the possibility that tobacco-exposure has a detrimental effect on hearing ability, possibly by raising the auditory threshold (Fried & Makin, 1978; Picone et al., 1982; Richardson, Day, & Taylor, 1989; Saxton, 1978), there is little indication in the literature that children whose mothers smoked cigarettes during pregnancy

are at an increased risk for deafness. For example, Trammer, Aust, Koster, and Obladen (1992) examined the auditory evoked potentials of non-drug-exposed infants and infants prenatally exposed to either tobacco only or to tobacco and narcotics. The results indicated that tobacco-exposure alone did not affect the integrity of the neonatal auditory system, although impairments were observed among infants exposed to a combination of tobacco and narcotics. Because the prior studies on prenatal tobacco-exposure employing the NBAS did not assess maternal use of narcotics, it is possible that use of such drugs may have confounded their findings. Similarly, Carzoli et al. (1991) compared the auditory brain-stem responses of 50 control infants with those of 50 infants born to cocaine-users most of whom had also smoked cigarettes during pregnancy, and determined that there was no increased incidence of hearing impairments among drug-exposed infants. While it could be argued that cocaine mitigated the adverse effects of nicotine on the developing auditory receptors, this hypothesis is inconsistent with the findings from other studies. Anderssen, Nicolaisen, and Gabrielsen (1993) observed that both tobacco-exposed and non-exposed newborns responded both autonomically and behaviourally to a sudden 80 decibel noise, although the type of response exhibited differed between groups. Specifically, tobacco-exposed infants were more prone to respond with apnea than non-exposed infants. Finally, a survey of the parents of Kansas public school children who failed the schools' hearing tests indicated that children with hearing impairments were no more likely to have mothers who smoked than children without hearing impairments (Kallail, Rainbolt, & Bruntzel, 1987). However, this study did not specifically assess prenatal tobacco exposure. Although the data from these studies imply that prenatal tobacco-exposure does not have adverse

effects on auditory threshold, the possibility cannot be ruled out on the basis of such a small number of studies.

Because the effects of fetal tobacco-exposure on the integrity of the auditory system have not been widely studied, it was important to address the possibility that the inconsistent performance of the tobacco-exposed infants on the information processing procedure was due to hearing impairments.

There are a number of factors that imply that the group differences on the information processing measures represent problems other than hearing impairments. First, an examination of the frequency of turns toward the stimulus relative to turns away during the first few trials of the familiarization phase for all infants indicated that both the tobacco-exposed and control infants turned systematically toward the stimulus. This pattern of responding was also evident during the first few trials of the novelty phase. Second, both the tobacco-exposed and control neonates turned systematically away from the stimulus during the last few trials of the familiarization and novelty phases. Third, when the novel stimulus was introduced following the familiarization stimulus, the tobacco-exposed group recovered head-turning toward the stimulus. In fact, their performance was indistinguishable from that of the control infants (see Figure 6, Panel b). If the tobacco-exposed infants could not hear the stimuli, these response patterns would not be expected.

To determine whether the poor orientation and habituation scores during the familiarization phase were a case of the scores of the tobacco-exposed infants who were slow to orient to the familiarization stimulus obscuring the better scores of the rest of the group, the data for each infant who was slow to orient (i.e., did not orient within one standard deviation of the mean number of trials required by both groups combined, or 7 trials) was individually examined for

patterns suggestive of adequate hearing ability. In nine of the 11 cases, the infants oriented to either or both of the novelty and dishabituation phase stimuli within the first four trials (6 infants oriented to at least one of these stimuli within the first 3 trials). Another infant made three consecutive head turns away from the stimulus during the last three trials of the familiarization phase immediately after a series of turns toward the stimulus. Only one infant, born to a mother who smoked four cigarettes per day, exhibited questionable evidence of hearing ability. This infant displayed a pattern of random head-turning throughout the familiarization phase, but then oriented to the novelty phase stimulus in six trials (with no turns away, although on two trials the infant did not turn), and habituated in the next three trials. Thus, although these data do not completely rule out the possibility that the auditory threshold is elevated among a number of the tobacco-exposed infants, they do increase the likelihood that the observed deficits on the information processing measures are due to something other than hearing difficulties. In general, these infants tended to respond randomly for the first several trials of the familiarization phase, but at some important point during the procedure, they systematically and appropriately turned toward or away from the stimulus, suggesting that they were listening, hearing, and responding. However, their performance appeared to be very inconsistent across the different phases of the procedure.

In summary, it is unlikely that hearing loss can explain the observed decrements in performance among the tobacco-exposed infants for several reasons. Children whose mothers smoke are no more likely to be hearing-impaired than children whose mothers do not smoke (Anderssen et al., 1991; Carzoli et al., 1993; Kallail et al., 1987; Trammer et al., 1992), inspection of the data for each individual infant who was slow to orient to the familiarization

stimulus revealed consistent, appropriate head-turning at some important point during the procedure, and the preferential direction of head-turning toward and away from the sound source at particular, important points during the procedure strongly suggests that the infants could hear the stimulus.

Implications

While recovery to novelty has been demonstrated to be a sensitive measure for discriminating among infants at different levels of risk for developmental delay (Zelazo et al., 1989), orientation, habituation, and recovery to novelty all depend on intact information processing ability. Thus, while consistent impairments in recovery to novelty discriminated among infants at different levels of risk for developmental delay in Zelazo et al.'s sample, and among cocaine-exposed and non-exposed infants in Study 1 of this dissertation, it is possible that the information processing difficulties associated with prenatal tobacco-exposure may be manifested in a different response pattern. While recovery to the dishabituation stimulus was impaired among the tobacco-exposed infants, along with orientation and habituation to the familiarization stimulus, recovery to the novel stimulus was not impaired.

Information processing interpretations of orientation, habituation and recovery to novelty propose that infants create a mental representations of a repeated stimulus and actively compare incoming information with the existing mental representation (e.g., Bornstein & Sigman, 1986; Zelazo et al., 1991). The initial orienting response is thought to be primarily reflexive (e.g., Kisilevsky & Muir, 1993; Muir & Clifton, 1985; Muir, Clifton, & Clarkson, 1989), which is why failure to orient may signify sensory receptor or motor disturbances. However, the tobacco-exposed infants in the present study turned toward the stimulus more often than they turned away in the first quartile of the familiarization phase, and

59% turned toward the stimulus on the first trial (56% of control infants turned toward the stimulus on the first trial). This initial response implies that whether the mechanism is reflexive or under cortical or subcortical control, it is intact in the majority of tobacco-exposed and control newborns.

Habituation and recovery to novelty are dependent on the creation of a mental representation of the stimulus and the process of actively comparing new information with that mental representation. Failure to create an accurate representation of the stimulus will lead to a breakdown in habituation, and recovery. The amount of familiarization required to form a mental representation of a stimulus varies among infants; however, numerous studies using the auditory information processing procedure developed by Zelazo and colleagues have demonstrated that most normal, healthy infants will orient in six trials or less, on average, when the criterion consists of a head-turn toward the stimulus on three of four consecutive trials, and habituate in 12 or fewer trials when the criterion is three consecutive trials ending in a turn away from the stimulus or no turn (e.g., Brody et al., 1984; Weiss, 1986; Zelazo et al., 1989).

In the clinical sample of high-, moderate-, and low-risk infants tested with the information processing procedure, deficits in performance were evident from the point where the novel stimulus was introduced following habituation to the familiarization study (Zelazo, Weiss, et al., 1989). Moreover, the effects appeared to be cumulative across phases within subjects; that is, the infants who failed to recover responding to the novel stimulus were also less likely to habituate and less likely to recover responding to the dishabituation stimulus. This pattern was also observed in the cocaine-exposed infants in Study 1. However, the effects observed in the familiarization phase among the tobacco-exposed infants did not appear to be cumulative; rather, the performance of these infants was

inconsistent across phases. Although the tobacco-exposed infants did not habituate to the familiarization stimulus to the same degree as the non-exposed infants, they recovered to the novel stimulus. Following recovery to the novel stimulus, those born to the heavy smokers failed to habituate and then did not recover responding to the dishabituation stimulus. Orientation to at least one of the stimuli within four trials was accomplished by 12 of the infants born to heavy smokers, 15 of the infants born to light smokers, and 14 of the infants born to non-smokers (17 infants in each group). Thus, information processing does not appear to be consistently impaired in the tobacco-exposed infants, but is limited to one or two of the three phases.

Inconsistency in performance may not imply primary information processing deficits. Rather, the inconsistent performance of the tobacco-exposed infants may be secondary to deficits in the ability to regulate arousal and sustain attention. In order to create an accurate mental representation of the stimulus, the infant must be at an appropriate level of arousal and attend to the stimulus long enough to process the information (Lécuyer, 1989; Racine & Kairiss, 1987). In many ways this notion is similar to Hebb's concept of the relation between arousal and sensory processing:

In general terms, psychologically, we can now distinguish two quite different effects of a sensory event. One is the *cue function*, guiding behavior; the other, less obvious but no less important, is the *arousal* or *vigilance function*. Without a foundation of arousal, the cue function cannot exist (Hebb, 1955, p. 249, as cited in Strelau, 1994).

A number of investigators have emphasized the importance of arousal level in mediating responsiveness to stimulation on information processing measures (Gardner & Karmel, 1984, 1996; Kaplan and Werner, 1991; Kaplan, Werner, & Rudy, 1990; Karmel, Gardner, and Magnano, 1991; Karmel et al., 1991; Lawson

& Turkewitz, 1980; Lewkowicz & Turkowicz, 1981). For example Kaplan and colleagues propose that infant performance on information processing measures is mediated by two processes: attentional processing and organismal arousal level which they term "sensitization" (Kaplan & Werner, 1991; Kaplan et al., 1990). Whereas attentional processing results in a response decrement, or habituation, sensitization energizes responsiveness and may result in increased responding. Sensitization develops over the course of the initial trials of a stimulus presentation resulting in a gradual increase in responding, similar to that observed among the control infants in Figure 11. Attentional processing and sensitization level interact to determine the level of responding. Thus, in normal infants, after repeated exposure to the stimulus, sensitization wanes and attentional processing prevails and results in response decrement (Kaplan & Werner, 1991; Kaplan et al., 1990).

It is possible that among the tobacco-exposed infants, the sensitization process takes longer to result in increased responding, thereby causing delayed orientation and habituation to the familiarization stimulus. Kaplan and colleagues propose that a novel stimulus, in addition to exciting a different neural network than that excited by the previously habituated stimulus, also generates sensitization (Kaplan & Werner, 1991; Kaplan et al., 1990). Thus, increased responding to novelty is not simply a function of central processing but a result of the interaction between central processing and sensitization. However, an integral part of Kaplan and colleagues' theory is that sensitization responses will result in increased responding to the dishabituation stimulus over and above that observed upon presentation of the stimulus in the familiarization phase. Since the tobacco-exposed infants' response to the dishabituation stimulus was considerably lower than that observed in the familiarization phase, the role of sensitization processes

in explaining the overall performance of the tobacco-exposed infants is questionable. However, it remains likely that arousal level is in some way responsible for the inconsistency in performance of the tobacco-exposed infants.

If an infant is not at an appropriate level of arousal during the information processing procedure, attention to and central processing of the stimulus followed by accurate responding would not be expected. Zelazo et al. (1987; 1991) determined that in neonates, the memory trace for a stimulus decays after a delay of longer than 55 seconds. Thus, if an infant fails to attend for a period of longer than 55 seconds, a well-formed memory trace will dissolve. Presumably, a less-well-formed memory trace would decay over shorter lapses in attention.

The theory that attention and performance on information processing tasks are a function of infant arousal level and the ability of the infant to modulate level of arousal to meet the demands of the situation has been demonstrated in a number of studies. For example, stimulus preference has been shown to vary across different levels of arousal in healthy infants (Gardner & Karmel, 1984; Karmel & Gardner, 1996; Karmel, Gardner, & Freedman, in press; Karmel et al., 1991; Lawson & Turkewitz, 1980; Lewkowicz & Turkowicz, 1981). Karmel and colleagues demonstrated that infants who are swaddled and tested immediately after feeding (low arousal condition) prefer high intensity visual stimuli over low intensity stimuli. Conversely, infants who are tested unswaddled immediately prior to feeding (high arousal condition) prefer low intensity stimuli. Moreover, these effects are not as evident among infants with CNS injury as they are among normal infants (Karmel et al., 1991). Thus, disturbances in arousal modulation may reflect CNS injury (Karmel et al., 1991; Karmel & Gardner, 1996). The inconsistent performance of the tobacco-exposed infants may be a function of changes in arousal level during the procedure. It is possible, therefore, that fetal

tobacco-exposure adversely affects the development of brain structures that play a part in arousal modulation.

Neurodevelopmental Effects of Prenatal Tobacco Exposure

Animal studies have demonstrated that prenatal exposure to nicotine disrupts the development of a number of neural networks involved in the regulation of arousal and attention levels. Prenatal nicotine exposure increases the number of nicotinic cholinergic receptors in several regions of the brain including the hypothalamus, hippocampus, and various other subcortical structures (Slotkin et al., 1987; Van de Kamp & Collins, 1994), and in the inner layers of the neocortex (Lichtensteiger et al., 1988; Slotkin et al., 1987). Nicotinic receptors provide input to catecholaminergic neural pathways both during fetal development, where they play a role in the modulation and organization of neural development (Lauder, 1983, 1988), and postnatally where they are involved in neurobehavioural functioning through their role in autonomic nervous system impulse transmission (Slotkin et al., 1987). Furthermore, prenatal nicotine administration has also been shown to increase CNS levels of norepinephrine and dopamine even before the appearance of nicotinic receptors (Ribary, 1985 as cited in Lichtensteiger et al., 1988). This suggests that normal brain development may be compromised very early in fetal life, with developmental changes at these early stages affecting the course and pattern of future neuronal development. Moreover, disturbances in catecholamine metabolism persist into adulthood among animals treated prenatally with nicotine (Lichtensteiger et al., 1988). This is in contrast to the abnormally high levels of nicotinic receptors observed in the early postnatal period which are normalized in nicotine-exposed rat offspring by the 15th day postnatally (Slotkin et al., 1987).

Disturbances in peripheral sympathetic nervous system development have also been observed in animals exposed prenatally to nicotine (Navarro et al., 1989; Slotkin et al., 1986; Slotkin et al., 1987). This is not surprising since nicotinic receptors are critically involved in postganglionic sympathetic nerve transmission. For example, acetylcholine binds to nicotinic receptors in the hypothalamus and adrenal medulla, stimulating the release of epinephrine and norepinephrine, thereby increasing arousal levels. It is conceivable that an increased number of nicotinic receptors in the sympathetic nervous system pathways could result in increased autonomic reactivity to stimulation.

The results of animal studies raise the possibility that tobacco-exposed infants may have difficulty modulating their level of arousal and attention as a result of disturbances in a number of catecholaminergic neuronal circuits. For example, increased levels of nicotinic receptors in the hypothalamus and disturbances in the peripheral sympathetic neural architecture may adversely affect the functioning of the hypothalamic-pituitary-adrenal axis (HPA) and sympathetic-adrenomedullary (SA) system (Navarro et al., 1989). In general, the SA system mediates attention and vigilance performance and the HPA axis mediates the physiological response to distress in children and adults (Gunnar, 1989; 1994). Disturbances in the neural architecture of the brain substrates mediating HPA and SA activity could translate into poor performance on tasks requiring a sustained level of alertness and attention such as the information processing procedure.

Although all infants tested on the information processing procedure maintained high levels of positive state throughout the procedure (i.e., their eyes were open and they were not fretting) changes in arousal level may not necessarily be reflected in observable changes in behaviour. In the absence of

autonomic measures on these infants, it is difficult to know whether the tobacco-exposed and non-exposed infants were similar in terms of level of arousal throughout the procedure. If feeding and swaddling result in low levels of arousal and hunger and unswaddling and hunger result in high levels of arousal (Karmel et al., 1991), then it is likely that the infants in the present study, tested unswaddled, one hour after feeding, were in a moderate state of arousal. However, the procedure used to obtain an alert state, which included the elicitation of a number of reflexes and other forms of physical stimulation, may have resulted in overarousal of the tobacco-exposed infants.

Hypertonicity and increased nervous system excitation have been observed in response to stimulation among tobacco-exposed infants in the first month of life (Fried, Watkinson et al., 1987). Other studies have found increased irritability (Saxton, 1978), decreased irritability (Fried & Makin, 1987; Jacobson et al., 1984), or general disturbances in state regulation (Picone et al., 1982) among tobacco-exposed newborns, suggesting disturbances in autonomic nervous system functioning. It is possible that the inconsistency in these findings was a result of the time of testing (e.g., in relation to feeding) and other factors (e.g., polydrug exposure) that would converge to either increase or decrease overall arousal level at the time of assessment (e.g., in the two studies reporting decreased irritability, the majority of infants were also exposed prenatally to marijuana).

Increased nervous system excitation might account for the poor performance of the tobacco-exposed infants during the familiarization phase of the information processing procedure. Once the information processing procedure has begun, physical stimulation is only given if the infant shows signs of drowsiness; therefore, the lack of physical stimulation during the procedure

might have resulted in a steady decrease in arousal levels over the course of the procedure among the tobacco-exposed infants. Thus, by the time the novel stimulus was presented, arousal levels may have been normalized allowing the infant to process the stimulus and respond appropriately. However, if arousal levels continued to decline, they may have been too low to allow normal processing by the time the dishabituation stimulus was presented. Thus, one could speculate that while high arousal levels interfered with normal processing of the familiarization stimulus, low levels of arousal interfered with the normal processing of the dishabituation stimulus among the tobacco-exposed infants. Given that, in laboratory animals, nicotine disrupts the development of a number of subcortical structures (Lichtensteiger et al., 1988; Mactutus, 1989; Navarro et al., 1989; Slotkin et al., 1986; Slotkin et al., 1987) involved in the modulation of both arousal and attention, such as the reticular formation, thalamus, hippocampus, and hypothalamus (Mayes et al., 1996; Rothbart, Posner, & Boylan, 1990; Nelson, 1994; Steinmetz, 1994; Strelau, 1994), it is possible that similar neurodevelopmental disturbances occur in human fetuses and result in arousal and attentional impairments in early infancy.

In addition to the previously described effects of nicotine on a number of subcortical structures, it is also possible that the inconsistent performance of the tobacco-exposed infants on the information processing procedure is related to the effects of nicotine on the development of neuronal circuits in the cerebellum. Relative to other cortical and subcortical structures, the cerebellum lags in development (Nelson, 1994; Reinis & Goldman, 1980). For this reason, it may be one area of the developing fetal brain that is particularly vulnerable to nicotine-exposure during the third trimester of pregnancy. A number of studies have shown that the adverse effects of maternal smoking on infant and child outcome

are greatest for third trimester smoking (Olds et al., 1994; Richardson et al., 1989). Animal studies have demonstrated that prenatal nicotine exposure is associated with an increase in the levels and rate of turnover of norepinephrine in the cerebellum and a decrease in cell density (Slotkin et al., 1986; Slotkin et al., 1987). The reason why this may be particularly important in light of the present study is that the cerebellum plays a key role in the organization and coordination of motor responses, such as the head-turning response (Steinmetz, 1994; Racine & Kairiss, 1987; Thompson, 1987). It has also been suggested that sensorimotor engrams may reside in the cerebellum rather than the hippocampus as was formerly believed (Racine & Kairiss, 1987; Thompson, 1987). The cerebellum receives input from all sensory modalities including afferents from the auditory pathways (Gilman & Winans, 1982). The information from the various afferents enters a vast pool of cerebellar neurons where integration takes place and motor output is coordinated. If nicotine disrupts the integrity of cerebellar structure and function as Slotkin and colleagues' (1986, 1987) data imply, then the ability of the tobacco-exposed infants to process the incoming auditory information and organize appropriate motor responses (i.e., head-turning) may be compromised. Moreover, if the motor engram for the response (i.e., the memory trace or mental representation) is stored in some form in the cerebellum, then nicotine-induced disruptions in the neuronal architecture or function may interfere with the accurate formation of this engram. However, it is likely that such a disturbance would interact with the previously discussed issues related to arousal level to produce the pattern of responding observed in these infants.

It is tempting to draw a parallel between the inconsistent performance of the tobacco-exposed infants on the information processing procedure and the inconsistent performance on cognitive tasks often noted among children with

ADHD. A number of studies have indicated that prenatal tobacco-exposure is related to later symptoms of ADHD (Denson et al., 1975; Dunn et al., 1977; Kristjansson et al., 1989; Naeye & Peters, 1984; Weitzman et al., 1992). While newborn behaviour is obviously qualitatively very different from that observed in childhood, and environmental experiences no doubt interact with constitutional factors to determine childhood behaviour, and neocortical structures which are not developed in neonates (Bronson, 1982; Capone, 1996; Goldman-Rakic, 1987; Nelson, 1994; Nowakowski, 1987; Reinis & Goldman, 1980; Schore, 1996) are often implicated in attention deficit disorder in childhood (e.g., Chelune, Ferguson, Koon, & Dickey, 1986), it is possible that tobacco-related disturbances in fetal CNS development are the early precursors of such later attentional difficulties.

A number of studies have documented small but measurable decrements in IQ and achievement test scores among children whose mothers smoked during pregnancy (Butler & Goldstein, 1973; Dunn et al., 1977; Fried & Watkinson, 1990; Gusella & Fried, 1984; Makin et al., 1991; Naeye & Peters, 1984; Olds et al., 1994; Sexton et al., 1990). However, it is extremely difficult, if not impossible, to separate the effects of the postnatal environment from the effects of prenatal tobacco-exposure when studying older children. The neonatal period offers a rare opportunity to study the impact of exposure to potentially teratogenic agents, before any effects become inextricably inter-twined with the effects of the postnatal environment. Thus, it is interesting to note that the small, but measurable decrements in IQ and achievement test scores seen among tobacco-exposed children may be evident in the form of auditory information processing difficulties in very early infancy. A number of studies have shown that verbal ability is more adversely affected in tobacco-exposed children than nonverbal ability (Fried & Watkinson, 1990; Gusella & Fried, 1984; Makin et al., 1991;

Naeye & Peters, 1984; Sexton et al., 1990). This suggests that if the deficits in verbal ability are related to the effects of fetal exposure to tobacco, then tobacco may selectively affect the development of the auditory system. Thus, by using an auditory information processing procedure to assess the effects of tobacco-exposure during the neonatal period, it is possible that the functioning of neural structures that are ultimately involved in the development of verbal skills are assessed.

Although animal studies imply that fetal nicotine exposure disrupts the development of a number of nervous system structures, it remains possible that the observed deficits on the information processing procedure among the tobacco-exposed infants are due to an increased auditory threshold. While there is no evidence that children born to smokers are at an increased risk for deafness, it is possible that the auditory threshold in infancy is raised just enough to interfere with hearing ability and limit the auditory experiences of tobacco-exposed infants. Examination of the performance of individual infants in the present study generated evidence suggestive of normal hearing, but if the auditory threshold is slightly increased, then the processing of the auditory stimuli may require more attentional resources among the tobacco-exposed infants than the control infants.

As this is the first study to examine information processing among tobacco-exposed infants, and the sample size was small, it is impossible to determine the exact nature of the tobacco-associated problems in performance. However, the data are intriguing and highlight the importance of controlling for prenatal tobacco-exposure in studies assessing the cognitive development of infants.

Summary

The results of the present study imply that maternal smoking during pregnancy has an adverse impact on newborn information processing ability and that whether the mother smoked 10 or more cigarettes per day, or less than 10 cigarettes per day, during pregnancy is related to the degree of decrement in performance on the information processing measures. However, it is not clear whether the observed deficits in performance are due to information processing impairments per se or to other factors such as disturbances in attention and arousal levels or increased auditory threshold. Although orientation and habituation to the familiarization stimulus were impaired, as was recovery to the dishabituation stimulus, recovery to the novel stimulus was not impaired. Since recovery to novelty has been previously demonstrated to be the best discriminator among infants at different levels of risk for developmental delay, the fact that the tobacco-exposed infants recovered to the novel stimulus suggests that this stimulus was actively processed and recognized as being different from the familiarization stimulus. However, the results are inconclusive since recovery to the dishabituation stimulus was impaired. The preferred interpretation of the inconsistent performance of the tobacco-exposed infants is that difficulties in the ability to modulate their arousal levels to meet the task demands interfered with their performance. However, it is also possible that the ability to encode the stimulus characteristics into memory and co-ordinate the head-turning response were impaired due to nicotine's disruptive effects on the architecture and functioning of the neural networks in the hippocampus, cerebellum, and/or other brain structures. In this case, recovery to the novel stimulus could have been due to the sensitization process rather than to central processing of the stimulus characteristics.

In summary, the response pattern of the tobacco-exposed infants on the information processing procedure was both unusual and unexpected. As this is the first known study in which tobacco-exposed and non-exposed newborns were compared on an information processing procedure, a more concrete explanation of the performance pattern awaits further research. Furthermore, it is possible that the group differences are attributable to something other than prenatal tobacco exposure. Although attempts were made to control for potential covariates, this study is not without its limitations both in terms of potential confounding factors and other issues such as subject identification procedures and sample size.

Confounding and Intervening Variables

In Part I, the offspring of smokers were compared with the offspring of non-smokers on the information processing measures and a number of potential confounding infant and maternal variables were examined. The two groups were found to be similar in terms of infant gestational age, age at the time of testing, maternal weight gain during pregnancy, gravidity, parity, and level of education. However, the tobacco-exposed infants weighed less at birth and at the time of testing, and were born to younger mothers from lower-income households. Because the majority of mothers were not clear about their occupational status or that of their partners, occupational indices of SES could not be used (for example, one mother said she was a "journalist" although she had less than a high school education and another mother with a grade nine education claimed to be an "accounting executive"). Thus, household income was used as an index of SES rather than indices based on occupation.

Although statistical control of covariates is often regarded as necessary to rule out the possibility that variations between groups on the target measures are

a result of factors other than maternal smoking, a number of investigators have warned against 'over-control' of covariates on the basis of purely statistical arguments in studies assessing risks associated with maternal smoking (Baghurst et al., 1992; Kiely, 1991; Tong & McMichael, 1992). Researchers must be careful to distinguish between "intervening (or mediating) variables" and "confounding variables". For example, according to Kiely (1991), "... in a study of the effect of maternal cigarette smoking on perinatal mortality, birthweight is an intervening variable and it makes no sense to control for it" (p. 247). Statistical adjustment for group differences on birthweight, in studies examining the impact of maternal prenatal smoking on infant development, would result in partial control of the smoking variable itself (Baghurst et al., 1992; Tong & McMichael, 1992). On the basis of these arguments, group differences on birthweight were not statistically controlled in the data analyses in Part I. In addition, since SES and maternal age were not associated with the outcome measures, the group differences on these measures were also not statistically controlled.

Matched pair designs are generally superior to statistical control procedures (Briere & Elliot, 1993); by using subject matching procedures, in addition to controlling for group differences on the matching variables, a host of other factors associated with the chosen matching variables are also controlled. Thus, by matching the subjects on birthweight and SES in Part II, the group differences on maternal age observed in Part I were not evident among the three matched groups. However, by separating the smokers into two groups, differences between the light and heavy smokers on maternal pregnancy weight gain became evident; the light smokers gained significantly more weight than the non-smokers, with the weight gain of the heavy smokers falling midway between the two groups. Because both the light and heavy smokers gained more weight

on average than the non-smokers, and maternal weight gain was not related to the information processing measures, this variable was not treated as a covariate. One could speculate that the light smokers had reduced their prior cigarette consumption because of pregnancy, and had gained more weight as a result of eating in place of smoking the cigarettes they would normally have smoked had they not been pregnant.

Despite subject matching on birthweight and SES in Part II, and the lack of group differences on gestational age, and maternal parity, gravidity, age, and level of education, it is possible that there were other covariates which were not assessed. For example, some researchers have reported that in follow-up studies of children whose mothers smoked during pregnancy, maternal intelligence was related to child outcome (e.g., Baghurst et al., 1992; Olds et al., 1994). Maternal intelligence could conceivably affect performance on the newborn information processing measures through genetic influences, although the chances of this variable selectively affecting the tobacco-exposed infants is low since there is no indication that maternal smoking is generally associated with lower intelligence (Baghurst et al., 1992). While Olds and colleagues (1994) did find an association between maternal PPVT (Dunn, 1965) scores and smoking, the PPVT is a measure of receptive vocabulary and is not a valid measure of overall intelligence (Sattler, 1982). Despite the relation between maternal PPVT scores and cigarette smoking, maternal PPVT scores were not related to child intellectual development scores until the age of three years. Nevertheless, maternal intelligence was not assessed in the present study and the possibility that the mothers who smoked were of lower intelligence than control mothers and that this influenced infant performance, although unlikely, cannot be ruled out.

One potential confounding factor that was not assessed in this study is maternal caffeine intake. Jacobson and colleagues (1984) found that maternal consumption of caffeine prior to pregnancy was associated with reduced orientation scores among newborns assessed with the NBAS (Brazelton, 1984), and caffeine consumption during pregnancy was associated with poor neuromuscular development and reflex functioning. Furthermore, while prenatal tobacco exposure was associated with reduced orientation scores, this effect disappeared once caffeine consumption prior to pregnancy and maternal SES were added to the model. These findings raise the possibility that maternal caffeine consumption prior to pregnancy could confound the information processing results. Jacobson and colleagues speculate that caffeine may alter biological processes in the mother's body prior to pregnancy, resulting in adverse effects on the developing fetus, or that caffeine may interfere with the early stages of embryonic development before the mother is aware that she is pregnant. However, these findings have not been replicated in published studies. Nevertheless, the possibility that the mothers who smoked also consumed more caffeinated beverages than the non-smokers, and that this influenced the performance of the infants on the information processing measures cannot be ruled out.

In summary, a number of potential confounding variables were assessed in the present study, and SES and birthweight were controlled in Part II through subject matching. As recommended by Kiely (1991), birthweight was treated as an intervening variable in the causal pathway between maternal smoking and infant outcome, rather than a confounding factor in Part I, and was therefore not statistically controlled. Although attempts were made to identify numerous potential confounds, maternal intelligence and caffeine consumption were not

assessed, and it is possible that they, along with other unidentified factors, influenced the results.

Identification of Smokers

Although in the original design of this study, it was planned that analysis of meconium for cotinine would be used to confirm maternal self-reports of smoking or not smoking during pregnancy, the presence of cotinine in newborn meconium proved to be unreliable as a marker of prenatal tobacco-exposure. Infants born to both smokers and non-smokers were equally likely to have or not have cotinine in their meconium. D. Lewis of the United States Drug Testing Laboratories where the meconium analyses were carried out has recently confirmed that meconium analysis for cotinine is indeed unreliable for identifying prenatal tobacco exposure (D. Lewis, personal communication, June 17, 1996). Although Ostrea et al. (1994) reported a relation between cotinine levels in meconium and maternal active and passive smoking, only those cases in which the mother had smoked more than one pack of cigarettes per day were distinguishable from those cases where the mothers were exposed to passive smoke. This is the only report in the literature of a relation between cotinine levels in newborn meconium and maternal smoking. According to D. Lewis (personal communication, June 17, 1996), no researcher has been able to replicate Ostrea et al.'s findings. In addition, during a recent informal discussion at the biennial conference of the International Society for the Study of Behavioral Development, researchers from two independent laboratories indicated that they also were finding no relation between cotinine in meconium and maternal smoking (L. Singer & J. Gardner, personal communication, August 14, 1996).

The use of meconium analysis for cotinine, as a marker of maternal prenatal smoking, was a new procedure when the present study began, and

although toxicologists were optimistic about its potential for identifying tobacco-exposed neonates, the method has now generally been accepted to be unreliable (D. Lewis, personal communication, June 17, 1996). Since levels of cotinine in maternal and fetal cord blood and hair are highly correlated (Bardy et al., 1994; Donnenfeld, Pulkinnen, Palomaki, Knight, & Haddow, 1993; Eliopoulos et al., 1994; Luck, Nau, Hansen, & Steldinger, 1985; Schulte-Hobein, Schwartz-Bickenbach, Abt, Plum, & Nau, 1992) it was generally assumed that meconium levels of cotinine would also be related to maternal levels of cotinine, which are directly related to nicotine ingestion. However, for some reason, cotinine does not accumulate in meconium in a dose-response manner. One possible explanation is that the fetal digestive tract contains enzymes that metabolize cotinine into a variety of other compounds. Conversely it is also possible that molecules that mimic cotinine are created in the digestive tract of some infants and thus yield positive meconium analysis results in infants who were not prenatally exposed to nicotine (D. Lewis, personal communication, June 17, 1996). At this point such explanations are purely speculative. However, on the basis of the results of research such as the present study, toxicology laboratories are no longer recommending the use of meconium analysis for cotinine as a marker of fetal nicotine exposure (D. Lewis, personal communication, June 17, 1996).

Despite its lack of reliability for determining prenatal tobacco-exposure, meconium analysis for the detection of other illicit substances remains a valid procedure. The present study improved on previous research by analyzing newborn meconium for cocaine, BE, cannabinoids, and opiates to rule out drug exposure. The issue of prenatal exposure to illicit drugs has not previously been addressed in studies assessing the outcome of tobacco-exposed infants and a number of researchers have included infants exposed prenatally to marijuana in

their samples (e.g., Fried & Makin, 1987; Richardson et al., 1989). This is unsatisfactory for assessing the effects of prenatal tobacco-exposure on infant outcome because, despite statistical control techniques, the constituents of tobacco may interact with other drugs to produce different developmental outcomes than exposure to each drug individually.

Unfortunately, as stated previously, a lack of funds prevented the analysis of all meconium specimens. Thus, prenatal drug-exposure could not be ruled out for all infants. However, a bogus-pipeline method was employed to increase the reliability of self-reported substance use (Lowe et al., 1986; Werch et al., 1987; Murray, O'Connell, & Schmid, 1987; Murray & Perry, 1987). Because the mothers were informed prior to their giving informed consent that meconium samples would be collected from their infants and analyzed for any drugs ingested during pregnancy, it was expected that drug-using mothers would be likely to either admit to prenatal drug use or refuse to participate in the study. Lowe et al. (1986) found that the bogus pipeline method improved the validity of self-reported alcohol use among a group of pregnant women.

Despite the use of meconium analysis and the bogus pipeline procedure, it is possible that infants exposed to illicit drugs during the first trimester were not detected. It is also possible that a number of mothers whose infants' meconium was not analyzed concealed their use of illicit drugs. Thus, while steps were taken to reduce the likelihood of including drug-exposed infants in the sample, it is possible that the methods employed were not entirely successful.

The lack of validity of meconium analysis for cotinine is of particular concern since the objective of the study was to assess the impact of prenatal tobacco-exposure on newborn information processing ability. Although a number of reviews of the self-report literature suggest that self-reports of cigarette

smoking are generally as accurate as the commonly employed toxicological assays such as analysis of saliva, plasma and urine for cotinine (e.g., Gilpin et al., 1994; Koslowski & Heatherington, 1990; Patrick et al., 1994), it is doubtful that these findings are generalizable to pregnant women. Because cigarette smoking during pregnancy is relatively common (i.e., approximately 20 to 30% of women smoke during pregnancy) and smoking during pregnancy has become socially unacceptable, it is possible that a number of tobacco-exposed infants were misclassified as non-exposed based on misleading maternal self-reports. This would have the effect of reducing the differences between groups on the information processing measures. Since this issue could not be addressed experimentally in the present study, it must be recognized as a limitation in the interpretation of the results.

It is recommended that future studies examining the effects of maternal cigarette smoking on infant outcome use a reliable marker of fetal nicotine-exposure. Recently analysis of maternal and newborn hair has shown promise as a method for identifying maternal prenatal cigarette smoking (Eliopoulos et al., 1994; Kintz, Lieffer, Messer, & Mangin, 1992; Kintz & Mangin, 1993; Klein, Chitayat, & Koren, 1993; Klein, Forman, Eliopoulos, & Koren, 1994; Koren, 1995a, 1995b). Although the use of hair analysis for detecting exposure to illicit drugs is controversial because of the problems related to external contamination of hair with drugs and the differential rate at which drugs are incorporated into hair of different colours (Holden, 1990; Kidwell, 1992), it is unlikely that the same issues would be as sensitive when screening hair for tobacco use. Unfortunately, hair analysis is costly and could, therefore, not be used in the present study.

Conclusion

Infants born to mothers who smoked cigarettes during pregnancy exhibited deficits in performance on an auditory information processing task relative to infants whose mothers did not smoke. Fetal exposure to more than 10 cigarettes per day had a greater adverse effect than exposure to less than 10 cigarettes per day. However, the response pattern exhibited by the tobacco-exposed neonates had not been observed previously on this task, and suggested inconsistency in the processing of the stimuli rather than a lack of ability to process the stimuli. Specifically, tobacco-exposed infants showed deficits in orientation and habituation to a familiarization stimulus, but recovered responding to a novel stimulus. The infants whose mothers were heavy smokers did not habituate to the novel stimulus to the same degree as the other groups, and both infants born to light smokers and those born to heavy smokers showed deficits in recovery to the dishabituation stimulus. The control over numerous potentially confounding factors, in addition to the use of meconium analysis and the bogus pipeline procedure to identify tobacco-exposed infants and exclude those exposed to illicit drugs, increased the likelihood that the observed deficits were related to fetal tobacco-exposure rather than to other factors. It is hypothesized that prenatal tobacco exposure disrupts the normal development of the CNS structures involved in the modulation of arousal and attentional processes, and possibly those involved in the processing of auditory stimulation. Deficits in arousal and attention would impact negatively on learning ability, eventually resulting in reduced scores on standardized tests in later childhood. However, the possibility that fetal tobacco-exposure is associated with an increased auditory threshold cannot be ruled out. Whatever the mechanism, it is possible that the disturbances observed in the processing of auditory information by tobacco-

exposed neonates are related to the subsequent decrements in cognitive ability, achievement test scores, and to the ADHD-like behavioural problems observed by a number of researchers in later childhood.

Chapter 6: Study 3

A Case of Maternal Cocaine Use With No Evidence of Fetal Exposure

Despite numerous studies documenting the adverse effects of fetal cocaine exposure, including Study 1 of this dissertation, the fact remains that a number of infants whose mothers used cocaine during pregnancy show no adverse effects of exposure to the drug. Individual differences are nearly always apparent in studies examining pre- and perinatal risk factors on infant outcome, with some resilient children developing very well despite pre- and perinatal complications and other postnatal risk factors (Basic Behavioral Science Task Force of the National Advisory Mental Health Council, 1996; Bradley et al., 1994; Cowen & Work, 1988; Garmezy, Masten, & Tellegen, 1984; Garmezy, 1993; Wolin & Wolin, 1995). The few studies examining the antecedents of resilience among children born to drug-users have focused on postnatal environmental factors, particularly mother-infant interaction (e.g., Beckwith et al., 1994; Beeghly et al., 1994; Johnson et al., 1992). However, differences among drug-exposed infants in the neonatal period cannot be attributed to postnatal environmental influences; i.e., the variation in outcome among neonates must be the result of pre- and perinatal factors. One factor which may influence infant outcome is the degree of fetal drug exposure. While it has been assumed that the degree of fetal exposure to a drug is directly related to the quantity ingested by the mother, degree of fetal exposure may be mediated by individual differences on a number of variables including drug metabolism.

It has been well-documented that when cocaine is ingested by a pregnant woman, the drug crosses the placenta (Krishna, Levitz, & Dancis, 1993; Malek, Ivy, Blann, & Mattison, 1995; Szeto, 1993; Wiggins et al., 1989), and this

phenomenon has rarely been questioned. Cocaine and its metabolites can be found in neonatal urine (Bateman et al., 1993; Callahan et al., 1992; Casanova et al., 1994; Osterloh & Lee, 1989), meconium (Lewis et al., 1994; Mirochnick et al., 1995; Ostrea et al., 1989; Ostrea et al., 1992; Rosengren et al., 1993; Ryan et al., 1994), and hair (Bailey, 1989; Forman et al., 1992; Graham et al., 1989; Katikeneni et al., 1992; Klein et al., 1994; Koren et al., 1992; Marques et al., 1993; Nakahara et al., 1992; Selavka & Reiders, 1995). However, not all infants whose mothers admit to gestational cocaine use test positive for the drug, even with sensitive screening measures such as hair and meconium analysis. In the majority of such cases, the toxicology results are dismissed as false negatives and the results are not explored further (D. Lewis, Personal communication, June 5, 1995); i.e., it is assumed that the infant was prenatally exposed to the drug ingested by the mother, but that the toxicology assay failed to detect the drug.

While it is likely that many cases where negative toxicology results are obtained from the urine, meconium, or hair specimens of an infant whose mother used cocaine during pregnancy are false-negatives, this may not always be the case. It has recently been hypothesized that cocaine adversely affects some fetuses while sparing others due to a large variability in the way different placentae handle the drug. This hypothesis is supported by *in vitro* perfusion studies with human placentae showing large variability in the ability to bind, metabolize, and transfer cocaine (Simone, Derewlany, Oskamp, & Koren, 1993; Simone et al., 1994).

The following case report supports the hypothesis that in some cases, the placenta may protect the fetus from exposure to cocaine. The theory is supported by both toxicological assays for maternal and infant drug exposure and the performance of the infant on the auditory information processing procedure

described in the previous chapters. This case further exemplifies the discriminant validity of the information processing procedure and highlights the importance of exploring individual differences in infant outcome and toxicology results from infants whose mother used illicit drugs during pregnancy.

Case Report

In February, 1993, a 26-year-old caucasian woman gave birth in a Montreal hospital, at 32 weeks gestation, to a baby girl weighing 1750 g. The mother voluntarily admitted to once-daily use of 2 to 5 grams of cocaine throughout pregnancy by the intravenous route, with the exception of the last three weeks of pregnancy when she was hospitalized without access to drugs. The mother also reported drinking 12 beers per month and smoking between 0.5 and 1 gram of hash weekly during the first three months of pregnancy, and smoking between 20 and 40 cigarettes per day throughout pregnancy. Physical and neurological examinations of the infant were normal. Following discharge, the mother, who wished to raise her infant, was enrolled in a drug rehabilitation program and the infant was placed in a foster home.

The infant was tested for Study 1 of this dissertation and was the tenth infant born to a cocaine-using mother to be tested. At the time of testing, the toxicology assays for prenatal drug exposure had not been completed and the infant was assessed under the assumption that she was a cocaine-exposed newborn. Based on the poor performance of the previous nine cocaine-exposed infants on the information processing procedure, it was expected that this infant would also display deficits in information processing ability. It was also expected that toxicology assays would reveal evidence of fetal exposure to high levels of cocaine and nicotine. Since the mother used cannabis only in the first trimester of pregnancy, meconium was not expected to test positive for cannabinoids.

Method

Toxicology Assays

Meconium was collected from the infant from the first excretion until the appearance of milk stool (i.e., all meconium excreted by the infant was available for analysis). The samples were kept in a freezer in a locked room at the Sir Mortimer B. Davis General Hospital for approximately three weeks before being sent to the United States Drug Testing Laboratory in Chicago, Illinois for analysis. The meconium samples were pooled, homogenized, and analyzed for the presence of cocaine, benzoylecgonine, opiates, cannabinoids, amphetamines and cotinine by GC/MS. Meconium analysis was carried out twice on different allocots from the homogenate.

Urine samples were collected from the mother and infant shortly after delivery. Urine was analyzed for the presence of cocaine, benzoylecgonine, and opiates by commercial radioimmunoassay at the laboratory of the Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec.

Seven weeks after delivery, hair samples were collected from the mother and infant and sent to the Hospital for Sick Children in Toronto, Ontario for drug analysis. Maternal and neonatal hair were analyzed for benzoylecgonine, cotinine, and nicotine by radioimmunoassay, and the results were confirmed by thermal desorption mass spectrometry. Assuming hair growth at a rate of 1 cm per month, the maternal hair sample was sectioned to reflect cocaine and cigarette use in the first, second, and third trimester (period of low cocaine use due to hospitalization of the mother for 3 weeks) of pregnancy, as well as after pregnancy (drug-free period).

Newborn Information Processing

The infant was tested twice on the information processing procedure described in the previous chapters. The first testing took place when the infant was 2½ weeks of age (34½ weeks corrected gestational age) and still in the hospital, and the second testing took place at 11½ weeks of age (43½ weeks corrected gestational age) by which time she had been discharged. At the time of the first testing, the meconium had not been analyzed, and at the time of both the first and second testing, the hair analysis results were not known. However, the experimenters were aware that the infant was born to a mother who used cocaine during pregnancy.

Results

Toxicology Assays

The results of the toxicology assays are shown in Table 16. Neither cocaine, benzoylecgonine, nor cannabinoids were detected in the infant's meconium on either of the two assays that were carried out. Cotinine was detected by both of the meconium assays and the second assay also revealed trace amounts of amphetamine. The results of the neonatal hair analysis were consistent with the results of meconium analysis. The infant's hair contained both nicotine and cotinine, but did not contain benzoylecgonine. These data imply that while the infant was exposed to nicotine in utero, she was not exposed to cocaine.

Conversely, analysis of maternal hair sections confirmed the mothers' self-report of cocaine and cigarette use. Maternal hair concentrations of benzoylecgonine were consistent with the maternal self-report of cocaine use and with a previously published dose-response curve in women (Forman et al.,

Table 16

Results of Toxicological Assays of Infant and Maternal Hair: Concentrations of Benzoyllecgonine, Nicotine, and Cotinine by Mass Spectrometry

Period of Exposure	Benzoyllecgonine (ng/mg)	Nicotine (ng/mg)	Cotinine (ng/mg)
<u>Mother</u>			
2 months postpartum	0.8	6.5	0.4
3rd trimester	0.9	11.8	0.2
2nd trimester	3.1	14.5	0.3
1st trimester	2.3	23.4	0.3
<u>Infant</u>	Undetectable	3.0	0.1

1992). Each segment of the mother's hair also contained high levels of nicotine and cotinine, consistent with the self-report of continuous smoking throughout pregnancy.

Newborn Information Processing

The data for the familiarization, novelty and dishabituation phases of the information processing procedure were scored as described in Chapters 4 and 5. The infant's scores were compared with those of two other groups: (a) all cocaine-exposed infants whose mothers smoked 10 or more cigarettes per day ($n=15$), and (b) all non-drug-exposed infants whose mothers smoked 10 or more cigarettes per day (i.e., the HS group from Study 2, Part II; $n=17$). The data from each of the two testing sessions with the case study infant ("infant A") and the cocaine/tobacco-exposed and tobacco-exposed only groups are presented in Figure 16.

The infant's performance was fairly consistent from test 1 to test 2. On the first testing, she oriented to the familiarization stimulus in the first three trials, and although the percentage of head turns toward the stimulus declined and two of the last three head turns were away from the stimulus, she did not meet the criterion for habituation. In the novelty phase, the infant recovered responding and oriented within six trials. She also reached the criterion for habituation in 11 trials, turning away from the stimulus on the last three trials. During the dishabituation phase, she did not reach the criterion for orientation.

On the second testing, the infant oriented to the familiarization stimulus in four trials and habituated by the tenth trial. As in the first testing, she recovered responding to the novel stimulus, orienting in four trials, and although she did not reach the criterion for habituation to the novel stimulus, she turned

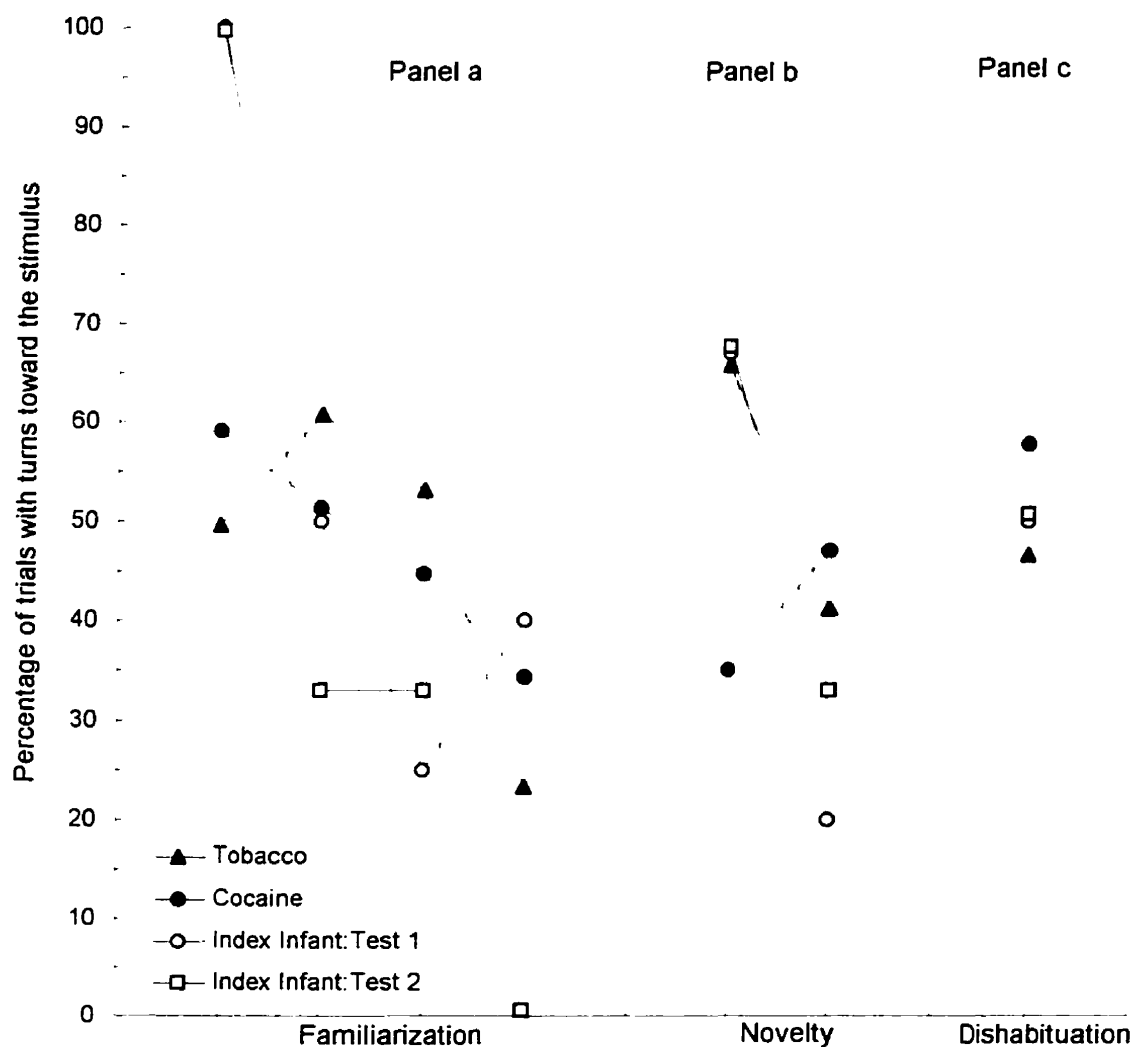


Figure 16. Mean percentages of head turns toward the sound source for the cocaine/tobacco-exposed infants, tobacco-exposed-only infants, and the two tests of the index infant during: familiarization phase quartiles (Panel a); novelty phase trial blocks (Panel b); and the dishabituation trial block (Panel c).

toward the stimulus on only one of the last four trials. In the dishabituation phase, the criterion for orientation was achieved in eight trials.

Overall, as Figure 16 shows, this infant's performance during the novelty phase was very different from that of the cocaine-exposed infants. Unlike the cocaine-exposed infants, she showed good orientation to the familiarization stimulus and, although she did not always reach criterion for habituation, she decreased responding and turned away from the sound source more often than toward it after repeated presentations. Most importantly, she recovered responding to the novel and dishabituation stimuli. Although her performance in the novelty phase was more like that of the infants born to heavy smokers than to cocaine-users, orientation and habituation to the familiarization stimulus and habituation to the novel stimulus were better than the average scores of the smokers' infants as a group.

Discussion

This mother voluntarily admitted to intravenous cocaine use throughout her pregnancy, and her report was confirmed by analysis of her hair samples. Nonetheless, it appears that her infant was not exposed in utero to cocaine, at least not after 16 weeks gestation, when meconium accumulation of the drug begins (Ostrea et al., 1993). The agreement between the infant's meconium and hair tests, along with her relatively good performance on the information processing procedure, lends credibility to this observation. These findings indicate that negative toxicological test results are not necessarily a result of the limited sensitivities of the screening assays.

The positive results on hair and meconium tests for nicotine and cotinine and the trace amounts of amphetamine present in the meconium suggest that, although these xenobiotics crossed the placenta, cocaine did not. For decades

the placenta was perceived as a barrier that protects the fetus from xenobiotics circulating in the maternal system. As analytic methods have improved, it has been shown that the placenta has metabolizing capacity (Simone et al., 1993), an observation which may explain why even the known teratogens affect only a percentage of fetuses while sparing others (Koren, 1994).

Cocaine has a mean distribution volume of 2 L/kg and an elimination half-life between 40 and 60 minutes when taken via the intranasal route and a more rapid rate of clearance from the body when taken intravenously; the rate of clearance of cocaine from plasma is related to the rate of uptake (Hutchings & Dow-Edwards, 1991). If the pregnant woman had injected the drug intravenously once daily, the rapid elimination would have exposed the placenta to decreasing levels of cocaine over time, with many hours without circulating levels. It has recently been shown that the in vitro perfused human placenta may bind and retain up to 35% of continuously circulated doses of cocaine (Simone et al., 1994). Data from the current case imply that rapid elimination of cocaine from the mother's body, potentially coupled with the ability of this particular placenta to bind large amounts of the drug arriving at the placental vessels, could have protected the fetus from exposure.

The toxicology results are also supported by the behavioural data on this infant. Relative to the cocaine-exposed infants whose mothers smoked 10 or more cigarettes per day, the information processing ability of this particular infant was relatively intact. On both testing occasions she responded immediately to the onset of the familiarization stimulus and recovered responding to the novel stimulus. This finding was remarkable given that only one cocaine-exposed infant showed a similar level of performance: a full-term infant with normal birthweight born to a mother who did not smoke cigarettes.

The performance of the case study infant is further evidence for the validity of the auditory information processing procedure developed by Zelazo and colleagues (Brody et al., 1984; Weiss, 1986; Zelazo et al., 1989).

Conclusion

This case study provides evidence that cocaine does not always cross the placenta and accumulate in the fetus. Despite documented maternal cocaine use, there was no evidence that the fetus was exposed to the drug. Both toxicological data and the auditory information processing ability of the neonate indicate that the infant was not exposed to the drug. This case highlights the need to address interpatient variability in maternal and placental handling of cocaine as a possible explanation for the variability seen in pregnancy outcome, and raises the possibility that discordant maternal/neonatal toxicology results in which the infant tests negative for a drug when the mother tests positive may be an indication that the fetus was not exposed to detectable levels of the drug.

Chapter 7: General Discussion

Effects of Fetal Cocaine and Tobacco Exposure on
Neonatal Information Processing

The preceding studies demonstrated that maternal use of cocaine and/or tobacco during pregnancy has adverse effects on the ability of the neonate to process auditory information. Cocaine and tobacco appear to have differential effects on newborn auditory information processing. In the present studies, fetal cocaine-exposure was associated with deficits in habituation and recovery to novelty, but not orientation to an auditory familiarization stimulus relative to controls matched on a number of variables, including maternal cigarette smoking. Conversely, tobacco exposure appeared to exert a dose-response effect on orientation to a familiarization stimulus, and recovery to the return of the familiarization (dishabituation) stimulus; at the higher doses (10 or more cigarettes per day), habituation to both the familiarization and novel stimuli was also adversely affected. However, most importantly, recovery to novelty was not consistently affected by fetal tobacco-exposure, at either high (10 or more cigarettes per day) or low (less than 10 cigarettes per day) doses. Although the tobacco-exposed infants failed to recover responding to the dishabituation stimulus, they recovered responding to the novel stimulus. This was surprising since recovery to novelty has been shown to be the information processing measure with the best discriminant validity for identifying infants at risk for developmental delay (Zelazo et al., 1989). The results imply that fetal cocaine exposure directly disrupts auditory information processing, whereas the inconsistent performance of the tobacco-exposed infants may be secondary to difficulties in modulating arousal levels.

Animal studies have demonstrated that cocaine and nicotine have similar adverse effects on the developing fetal brain. Both drugs have been shown to disrupt the processes of neuronal proliferation, migration and differentiation, and alter CNS levels of monoaminergic neurotransmitters, in addition to reducing the blood supply to the fetus through their vasoconstrictive actions (e.g., Akbari & Azmitia, 1992; Akbari, Kramer, et al., 1992; Beeker et al., 1992; Kaufmann, 1990, as cited in Lidow, 1995; Kosofsky et al., 1994; Lichtensteiger et al., 1988; Navarro et al., 1989; Slotkin et al., 1986; 1987). Nicotine has the additional effect of increasing the number of cholinergic nicotinic receptors, prompting one researcher, T. Slotkin of Duke University School of Medicine, to advise that smoking cigarettes may be more harmful to the developing fetus than ingesting cocaine (Cotton, 1994). Because nicotinic receptors are involved in the functioning of the autonomic nervous system, it is plausible that nicotine exerts its detrimental effects on newborn arousal regulation through its effects on nicotinic receptor development.

Interestingly, although no longitudinal study has systematically compared the development of cocaine-exposed and tobacco-exposed infants, the results of follow-up studies of infants prenatally exposed to tobacco have been very similar to those of studies in which infants prenatally exposed to cocaine have been followed into childhood. Many studies suggest that fetal exposure to tobacco results in a similar outcome as fetal exposure to cocaine; specifically, both drugs appear to be associated with verbal deficits (Angelilli et al., 1994; Bruce & Wallace, 1994; Fried & Watkinson, 1990; Gusella & Fried, 1984; Johnson et al., 1994; Lewis et al., 1994; Makin et al., 1991; Malakoff et al., 1995; Naeye & Peters, 1984; Nulman et al., 1994; Sexton et al., 1990). However, unlike cocaine, prenatal tobacco exposure has also been shown to

result in decreased IQ and achievement test scores, particularly in middle childhood, and at doses of more than 10 cigarettes per day (Butler & Goldstein, 1973; Dunn et al., 1977; Fried & Watkinson, 1990; Gusella & Fried, 1984; Makin et al., 1991; Naeye & Peters, 1984; Olds et al., 1994; Sexton et al., 1990). Although the majority of studies have indicated that fetal cocaine-exposure is not associated with reductions in IQ when confounding factors are controlled (e.g., Azuma & Chasnoff, 1993; Chasnoff, Griffith et al., 1992; Graham et al., 1992; Hurt et al., 1992; Kaiser et al., 1992; Mayes et al., 1995), it is possible that the cocaine-exposed infants of the late 1980's were too young for the effects to be detected and the results reported. In addition, it is also possible that the failure to detect differences between cocaine-exposed and non-exposed infants was due to the use of poor subject identification methods, which resulted in the inclusion of cocaine-exposed infants in the control groups.

The fact that verbal deficits are the most frequently reported adverse, long-term outcome of exposure to cocaine and/or tobacco suggests that auditory processing may be selectively affected by exposure to either of these drugs. The findings of the current studies support this hypothesis. Visual information processing ability has not reliably discriminated between cocaine-exposed infants and controls in prior studies (Mayes et al., 1993; Struthers & Hansen, 1992), and the only newborn behavioural measure employed in studies of fetal-tobacco exposure, the NBAS, also failed to demonstrate tobacco-associated impairments on the visual orientation and habituation measures (Fried & Makin, 1978; Picone et al., 1982; Richardson, Day, & Taylor, 1989; Saxton, 1978); thus, the results of the current studies imply that the assessment of auditory information processing may be more relevant for infants at risk for subsequent impairments in language development. By the time cognitive

impairments become evident in drug-exposed children, it is usually impossible to extricate the relative contributions of postnatal environment and prenatal drug-exposure to the developmental problems. However, the preceding studies provide evidence that fetal exposure to cocaine and/or tobacco has detrimental effects on infant information processing ability before the postnatal environment has chance to impact on child development.

These studies provide further evidence for the validity of the auditory information processing procedure developed by Zelazo and colleagues (Brody et al., 1984; Swain et al., 1993; Tarquinio et al., 1990, 1991; Weiss, 1986; Weiss et al., 1988; Zelazo et al., 1989; Zelazo et al., 1987; Zelazo et al., 1991). In study 2, infants who were not prenatally exposed to tobacco or illicit drugs oriented and habituated to the familiarization stimulus, recovered responding and subsequently habituated to the novel stimulus, and dishabituated (recovered responding) to the return of the familiarization stimulus. Furthermore, the previously observed pattern of systematic head-turning toward the sound source during the initial presentations of a stimulus, followed by systematic turning away from the stimulus after repeated exposure, was clearly demonstrated by these non-drug-exposed infants. Conversely, both cocaine- and tobacco-exposure were associated with impairments on a number of these measures.

Despite the evidence that fetal cocaine and tobacco exposure impair newborn information processing, because the majority of infants in the present studies were tested within 72 hours of birth, it is possible that the observed effects were due to nicotine and/or cocaine withdrawal, and, therefore, the effects may be transient. While withdrawal from cocaine and/or nicotine does not appear to result in neonatal abstinence syndromes (Besunder & Blumer,

1994), the effects of drug withdrawal on arousal and attention may be sufficient to impair performance on the information processing procedure without producing gross physiological symptoms. However, the evidence from animal studies that cocaine and nicotine disrupt fetal brain development, along with the reports of verbal deficits among children exposed to cocaine and/or nicotine in utero, suggest that the information processing deficits may be the result of disturbances in CNS development. In order to address this issue, short-term follow-up studies with cocaine- and tobacco-exposed neonates are needed.

As illustrated by the case report presented in Chapter 6, individual differences in drug transfer to the fetus may be a source of individual variability in outcome. Despite maternal consumption of large doses of cocaine on a daily basis, all available evidence implied that this particular fetus was not exposed to measurable quantities of the drug. Not only did toxicology reports support this interpretation, but the performance of the infant on the information processing procedure was far superior to all but one of the cocaine-exposed infants, despite having the additional risk factor of being born eight weeks premature and weighing less than four pounds. This case challenges the current thinking on the gestational pharmacodynamics of cocaine; researchers have rarely questioned the widely held assumption that if a pregnant woman ingests cocaine, it crosses the placenta and enters fetal circulation. Negative toxicology reports on the neonates of confirmed drug users are typically dismissed as false negative results and the possibility that the fetus was not exposed is not even considered. This case report suggests that not all fetuses are exposed to detectable quantities of the substances their mothers ingest and highlights the need for researchers to pursue false negative results, possibly by performing

further toxicological drug assays on media other than the one originally employed.

Meconium analysis proved to be a reliable technique for detecting second and third trimester fetal cocaine-exposure, although first trimester exposure was not detected. In addition, while no relationship was found between maternal smoking and the presence or quantity of cotinine in newborn meconium, this finding is important in its own right; the information will no doubt be valuable to researchers who are considering using, or are already using, meconium analysis for cotinine to detect fetal tobacco-exposure. Moreover, this is the first study on the effects of prenatal tobacco-exposure to employ an objective biological measure of fetal exposure to other commonly used illicit substances. Although first trimester exposure to illicit substances cannot be ruled out, it is likely that the majority of tobacco-exposed infants in Study 2 were not exposed to other drugs. Moreover, unlike many other studies, infants with documented or suspected exposure to illicit substances were excluded from the tobacco-exposed sample, increasing the likelihood that the information processing results are due to fetal tobacco-exposure and not to other substances.

Previous studies on the effects of fetal cocaine- and tobacco-exposure have been plagued by difficulties which render the findings virtually uninterpretable and of questionable validity. Unreliable subject identification procedures, poor control over confounding factors, and assessment procedures with virtually no predictive validity are just a few of the shortcomings that were addressed in the current studies. It is noteworthy that researchers studying the effects of cocaine on infant outcome rarely control for maternal cigarette smoking, and researchers studying the effects of maternal smoking on infant outcome rarely control for other substance use. The present studies highlight

the need for researchers to address these issues simultaneously, since both cigarette smoking and illicit substance use are relatively common occurrences.

Overall Summary and Conclusion

The studies presented in this dissertation imply that fetal exposure to cocaine and/or tobacco has detrimental effects on the ability of the newborn infant to process auditory stimulation. It is not known if the disturbances observed in the neonatal period are transient or will persist into later childhood, but it is possible that the disturbances in newborn auditory information processing may be an early manifestation of verbal deficits observed in both cocaine-exposed and tobacco-exposed children at follow-up evaluations. The results imply that even small amounts of cocaine taken at irregular intervals during pregnancy can have detrimental effects on information processing ability. Mothers who smoke cigarettes during pregnancy are also placing their infants at risk for auditory information processing deficits. However, the data imply that smoking fewer than 10 cigarettes per day is less harmful than smoking 10 or more cigarettes per day. The case report of an infant who appears to have escaped exposure to cocaine in utero despite the ingestion of large quantities of cocaine by her mother raises the possibility of individual differences in the placental handling of cocaine and highlights the need for researchers to consider this issue as a potential mechanism underlying individual differences in infant outcome. Finally, the current studies highlight the importance of controlling for maternal cigarette smoking in studies assessing the outcome of cocaine-exposed newborns.

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Appendix A

Statement of Informed Consent

Parent Consent Form -
Newborn Information Processing Study

Purpose and Procedure

The purpose of this study is to gain an understanding of how newborn babies respond to sounds. Babies whose mothers took cocaine during pregnancy and babies born to mothers who did not take drugs during pregnancy will be studied in order to determine if exposure to cocaine is associated with any developmental difficulties. You may be asked to fill out a questionnaire concerning drug use during your pregnancy. A stool sample may be taken from your baby's diapers for drug analysis. If you took cocaine during this pregnancy, Social Services must be notified and a social worker will contact you for an interview.

Babies will be tested at the Jewish General Hospital in a room across from the main nursery. The baby will listen to words played through speakers at a normal speaking volume and head turns in response to the words will be noted.

For further information concerning this study you may contact Dr. Philip Zelazo or Susan Potter, Department of Psychology, Montreal Children's Hospital at 934-4449, ext. 2154. For general information on patient participation in research you may call the Jewish General Hospital Patient Representative, Roslyn Davidson, at 340-8222, ext. 5833.

Statement of Informed Consent

I have read and understand the description of this study. Both my baby's identity and my identity will be kept confidential in all published reports of the study. I give permission for my baby to participate in this study and for the results to be used in publications. I am willing to allow my baby's birth and medical records to be examined, so that information relevant to this study may be used. I recognize that if I took cocaine during my pregnancy, it is mandatory that a social worker contact me.

I have been given an opportunity to write in below any limitations or restrictions concerning my baby's participation. _____

If for any reason I wish to discontinue my baby's participation, I am free to do so. I have received a copy of this consent form.

Date: _____ Signed: _____
Parent or Guardian

Signed: _____ Signed: _____
Investigator Witness

Appendix B

Demographic Questionnaire

Code Number: _____

Date: _____

General Information

1) Your age: _____

2) Language spoken at home: _____

3) Other languages spoken: _____

4) Marital Status: _____

5) Occupation: _____

6) Occupation of baby's father: _____

7) Income scale: (circle one that best describes the total income of the household, i.e., combined annual incomes of mother and father):

a) less than \$10,000	b) \$10,000 - \$20,000	c) \$20,001 - \$30,000
d) \$30,001 - \$40,000	e) \$40,001 - \$50,000	f) \$50,001 - \$60,000
g) \$60,001 - \$70,000	h) more than \$70,000	

8) Last year of education completed: _____

9) Number of persons in household: _____

10) Number of dependents (including this baby): _____

Maternal Health History

Please enter the appropriate number (all questions include this baby):

11) Number of pregnancies: _____ 12) Miscarriages: _____

13) Induced abortions: _____ 14) Stillbirths: _____

15) Multiple births: _____ 16) Full-term births (>38 wks): _____

17) Preterm births: _____

18) Babies with abnormalities: _____ Describe: _____

19) Babies with birthweight < 2500 grams (5 lbs, 9 oz): _____

20) Babies with birthweight > 4100 grams (9 lbs, 2 oz): _____

The following questions concern your present newborn infant and pregnancy:

21) Sex of infant: _____

22) Date of birth of infant: _____

23) Time of birth: _____ 24) Number of hours in labour: _____

25) Type of delivery: a) spontaneous vaginal b) forceps
 c) cesarean section d) induced labour

26) If cesarean section or induced labour, what was the reason? _____

27) How much weight did you gain during your pregnancy? _____

28) Were you examined by a doctor during your pregnancy? _____

29) If yes, how often did you see a doctor? _____

30) Did you suffer any illnesses during your pregnancy? _____

31) If yes, please describe: _____

32) What was the estimated date of delivery calculated from the first day of last menstrual period? _____
calculated by ultrasound? _____

33) At what stage of the pregnancy did you find out you were pregnant?
_____ weeks

The following questions concern medication, drug, and alcohol use during your pregnancy. It is important that you answer these questions honestly. All answers will be kept strictly confidential, with the exception that cocaine use must be reported to Social Services. You and your baby will be assigned code numbers and your names will not appear anywhere on this questionnaire. The aim of this study is to assess the mental functioning of babies who may have been exposed to certain drugs in the womb, in order that we may help these babies in the future. Drug use during pregnancy is common. For example, in many urban hospitals, one out of every ten newborns tests positive for cocaine. In order to properly assess these babies, those who were not exposed to drugs in the uterus must also be tested. Therefore, accurate information concerning any drugs you may have taken during your pregnancy is very important. Again, it is stressed that all information will be kept strictly confidential, with the exception that cocaine use must be reported to Social Services. Your cooperation is greatly appreciated.

34) Are you offended by questions concerning the use of alcohol and drugs? yes no

35) Did you take any prescription medications during your pregnancy? If yes, please describe: _____

36) List any "over-the-counter" medications taken during your pregnancy (e.g., painkillers, cold remedies, etc.): _____

37) Did you smoke cigarettes at any time during your pregnancy? _____

How many per day on average? _____

Which brand did you usually smoke? _____

If you quit smoking, how many weeks pregnant were you at the time? _____

38) Were you exposed to second-hand smoke during your pregnancy? _____

If yes, how often? _____

39) During your pregnancy did you ever use any of the following substances (please circle yes or no -- if "no" to all, go to question 46):

marijuana or hashish	yes	no
amphetamines	yes	no
cocaine	yes	no
"crack" cocaine	yes	no
tranquilizers (type: _____)	yes	no
acid (LSD)	yes	no
heroin	yes	no
other drugs (list):		

1) _____

2) _____

3) _____

40) During the first 3 months of your pregnancy, which of the following substances did you use (pleas put an "X" (where appropriate) and enter the amount consumed and the frequency you used it, e.g., X cocaine, 1 gram, 3 time/week)?

☐ marijuana/hashish	amount: _____	how often: _____
☐ amphetamines	amount: _____	how often: _____
☐ cocaine	amount: _____	how often: _____
☐ "crack" cocaine	amount: _____	how often: _____
☐ tranquilizers	amount: _____	how often: _____
☐ acid (LSD)	amount: _____	how often: _____
☐ heroin	amount: _____	how often: _____
☐ other drugs (list):		
1) _____	amount: _____	how often: _____
2) _____	amount: _____	how often: _____

41) During the second 3 months of your pregnancy, (i.e., months 4, 5, and 6) which of the following substances did you use?

☐ marijuana/hashish	amount: _____	how often: _____
☐ amphetamines	amount: _____	how often: _____
☐ cocaine	amount: _____	how often: _____
☐ "crack" cocaine	amount: _____	how often: _____
☐ tranquilizers	amount: _____	how often: _____
☐ acid (LSD)	amount: _____	how often: _____
☐ heroin	amount: _____	how often: _____
☐ other drugs (list):		
1) _____	amount: _____	how often: _____
2) _____	amount: _____	how often: _____

42) During the last 3 months of your pregnancy (i.e., months 7, 8, and 9) which of the following substances did you use?

☐ marijuana/hashish	amount: _____	how often: _____
☐ amphetamines	amount: _____	how often: _____
☐ cocaine	amount: _____	how often: _____
☐ "crack" cocaine	amount: _____	how often: _____
☐ tranquilizers	amount: _____	how often: _____
☐ acid (LSD)	amount: _____	how often: _____
☐ heroin	amount: _____	how often: _____
☐ other drugs (list):		
1) _____	amount: _____	how often: _____
2) _____	amount: _____	how often: _____

43) Which of the following substances did you take just before delivery (i.e., within 24 hours of the onset of labour or during labour)?

☐ marijuana/hashish	amount: _____	how often: _____
☐ amphetamines	amount: _____	how often: _____
☐ cocaine	amount: _____	how often: _____
☐ "crack" cocaine	amount: _____	how often: _____
☐ tranquilizers	amount: _____	how often: _____
☐ acid (LSD)	amount: _____	how often: _____
☐ heroin	amount: _____	how often: _____
☐ other drugs (list):		
1) _____	amount: _____	how often: _____
2) _____	amount: _____	how often: _____

44) Do you feel that you may have a problem controlling your intake of certain drugs?
yes no

If yes, please specify which drugs: _____

45) Comments? _____

46) Do you drink? yes no

47) At what age did you start drinking? _____

48) Has there been any change in your drinking patter during the last year? yes no

49) If yes, please describe: _____

50) What type of alcoholic beverage do you usually drink? _____

51) Do you ever drink in the morning? yes no
How many occasions per week, on average? _____
How many occasions per month, on average? _____

52) During the first 3 months of your pregnancy, on average:
How many occasions per week did you drink? _____
How many occasions per month did you drink? _____
How many drinks per occasion? _____

53) During the second 3 months of your pregnancy (i.e., months 4, 5, & 6), on average:

How many occasions per week did you drink? _____

How many occasions per month did you drink? _____

How many drinks per occasion? _____

54) During the last 3 months of your pregnancy (i.e., months 7, 8, & 9), on average:

How many occasions per week did you drink? _____

How many occasions per month did you drink? _____

How many drinks per occasion? _____

55) Did you drink any alcoholic beverages within 24 hours of the onset of labour, or during labour? yes no

If yes, how many drinks? _____ Over how many hours? _____

56) Do you feel that you may have a problem controlling your intake of alcohol? yes no

57) Comments? _____

Thank you for your cooperation.

Appendix C
Sample Data Scoring Sheet

Infant Information Processing (Auditory)
Montreal Children's, St. Mary's, & Jewish General Hospitals

Infant # Example
 Name _____
 D.O.B. _____
 T.O.B. _____
 Age (Hrs) _____
 Gest. Age _____

Group Normal Control
 Sex _____
 Sound # _____
 Direction _____
 Weight _____
 Birth _____

Date _____
 Time _____
 Holder _____
 Coder _____
 Presenter _____
 Apgar _____

Tr #	Stim	Dir	Turn	Critern	Length	Fret	Eyes	Comments
1	1	L	T					
2		R	N					Q1 - Fa =
3		R	T	Orientation				
4		L	A			67% = B1 - Fa		Q2 - Fa = 67%
5		L	T					
6		R	T					
7		R	N					Q3 - Fa = 50%
8		L	T					
9		L	A	Habituation		20% = B2 - Fa		Q4 - Fa = 0%
10		R	A					
11		R	A					
12	2	L	T					Q1 - Nv = 50%
13		L	N	Orientation				
14		R	T			75% = B1 - Nv		Q2 - Nv = 100%
15		R	T					
16		L	T					Q3 - Nv = 50%
17		L	N	Habituation				
18		R	A			25% = B2 - Nv		Q4 - Nv = 0%
19		R	A					
20	1	L	N					
21		L	T	Orientation				Ds = 75%
22		R	T					
23		R	T					



T = head turn toward sound
 A = head turn away from sound
 N = no turn

Q = Quartile
 B = Block
 Fa = Familiarization
 Nv = Novelty
 Ds = Dishabituation

Familiarization

Novelty

Dishabituation

Appendix D

Data Analysis Tables for Study 1

Table D1

MANOVA for Between Group Differences on the Subject Matching Variables for Cocaine-Exposed and Control Infants

Multivariate Repeated Measures Analysis of Variance				
Source	Wilks' Lambda	df	F	p
Matching Variables x Group	.96	3, 46	.707	.553
Group	.96	4, 45	.520	.721

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Birth weight	380530.12	1, 48	.72	.399
Cigarettes per day	89.73	1, 48	1.31	.258
SES	254.54	1, 48	.65	.425
Pregnancy weight gain	16.44	1, 48	.27	.607

Table D2

MANOVA for Between Group Differences on the Demographic Control Variables for Cocaine-Exposed and Control Infants

Multivariate Repeated Measures Analysis of Variance				
Source	Wilks' Lambda	df	F	p
Control Variables x Group	.68	3, 46	7.216	.000
Group	.59	4, 45	7.965	.000
Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Corrected gestational age at testing	5.12	1, 48	1.97	.167
Five minute APGAR	.31	1, 48	2.83	.099
Age of mother	26.45	1, 48	.02	.892
Prenatal Care	.15	1, 48	22.79	.000

Table D3

One-way ANOVA for Overall Occurrence of Head-turning for the Cocaine-exposed and Control Infants

Source	MS Error	df	F	p
Group	227.61	1, 48	.76	.389

Table D4

Repeated Measures MANOVA for Positive State Across Phases for Cocaine-exposed and Control Infants

Multivariate Repeated Measures Analysis of Variance				
Source	Wilks' Lambda	df	F	p
Positive State	.92	2, 47	2.09	.135
Positive State x Group	.98	2, 47	.43	.655
Group	.98	3, 46	.29	.836

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Familiarization Positive State	186.87	1, 48	.16	.691
Novelty Positive State	229.26	1, 48	.00	.955
Dishabituation Positive State	375.50	1, 48	.53	.532

Table D5

Familiarization Phase: Repeated Measures MANOVA and Univariate F Tests of Quartiles for Cocaine-exposed and Control Infants

Multivariate Repeated Measures Analyses				
Source	Wilks' Lambda	df	F	p
Familiarization Quartiles	.50	3, 46	15.52	.000
Familiarization Quartiles x Group	.96	3, 46	.67	.574
Group	.93	4, 45	.82	.518
Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
First Quartile	718.92	1, 48	.06	.802
Second Quartile	899.62	1, 48	.02	.886
Third Quartile	958.42	1, 48	.00	.964
Fourth Quartile	644.91	1, 48	3.19	.080

Table D6

Familiarization Phase: One-sample t Tests for Difference Scores of Cocaine-exposed and Control Infants for the First and Last Quartiles

Quartile	Group	Mean (SD)	t	df	p
First Quartile of Familiarization Phase	Cocaine	1.43 (1.38)	5.17	24	.000
	Control	.99 (1.37)	3.62	24	.001
Last Quartile of Familiarization Phase	Cocaine	.09 (1.46)	.29	24	.772
	Control	-.93 (1.24)	-3.73	24	.001

Table D7

Familiarization Phase: χ^2 Analysis for the Frequency of Orientation Among Cocaine-exposed and Control Infants

Group*	Frequencies	
	Orientation	No Orientation
Cocaine-exposed	20	5
Controls	22	3
Total	42	8

* $\chi^2 (1) = .60, p = .44$

Table D8

Familiarization Phase: One-way ANOVA for Number of Trials to Orient
Between Cocaine-exposed and Control Infants

Source	MS Error	df	F	p
Group ^a	13.01	1, 40	.33	.568

^a Infants who failed to orient were excluded from this analysis.

Table D9

Familiarization Phase: χ^2 Analysis for the Frequency of Habituation Among Cocaine-exposed and Control Infants

Group*	Frequencies	
	Habituation	No Habituation
Cocaine-exposed	11	14
Controls	19	6
Total	30	20

* $\chi^2 (1) = 5.33, p = .021$

Table D10

Familiarization Phase: One-way ANOVA for Number of Trials to Habituate
Between Cocaine-exposed and Control Infants

Source	MS Error	df	F	p
Group ^a	15.48	1, 28	1.38	.250

^a Infants who failed to habituate were excluded from this analysis.

Table D11

Novelty Phase: Repeated Measures MANOVA and Univariate F Tests of Quartiles, for Cocaine-exposed and Control Infants

Multivariate Repeated Measures Analyses				
Source	Wilks' Lambda	df	F	p
Novelty Quartiles	.66	3, 46	8.03	.000
Novelty Quartiles x Group	.42	3, 46	21.06	.000
Group	.42	4, 45	15.77	.000

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
First Quartile	688.27	1, 48	11.39	.001
Second Quartile	940.40	1, 48	19.35	.000
Third Quartile	753.87	1, 48	1.15	.288
Fourth Quartile	571.67	1, 48	34.82	.000

Table D12

Novelty Phase: One-sample *t* Tests for Difference Scores of Cocaine-exposed and Control Infants for the First and Last Quartiles

Quartile	Group	Mean (SD)	<i>t</i>	<i>df</i>	<i>p</i>
First Quartile of Novelty Phase	Cocaine	.28 (1.09)	1.30	24	.208
	Control	1.40 (1.12)	6.26	24	.000
Last Quartile of Novelty Phase	Cocaine	.92 (1.24)	3.73	24	.001
	Control	-1.02 (1.25)	-4.06	24	.000

Table D13

Novelty Phase: Repeated Measures ANOVA for Recovery^a to the Novel Stimulus Among Cocaine-exposed and Control Infants

Univariate Repeated Measures Analysis			
Source	df	F	p
Between subjects			
Group	1	7.14	.010
<u>S</u> within-group error	48	(549.14)	
Within subjects			
Trial Blocks	1	13.75	.001
Trial Blocks x group	1	21.07	.000
Trial Blocks x <u>S</u> within-group error	48	(406.94)	

Note. Values enclosed in parentheses represent mean square errors. S = Subjects.

Table D14

Novelty Phase: Between Group MANOVA for Recovery^a to Novelty Among Cocaine-exposed and Control Infants

Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.65	2, 47	12.65	.000

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Familiarization Block 2	426.58	1, 48	1.06	.310
Novelty Block 1	529.50	1, 48	22.75	.000

^a Recovery to novelty was assessed by comparing the last trial block of the familiarization phase with the first trial block of the novelty phase.

Table D15

Novelty Phase: One-way ANOVA Comparing Response in the First Block of the Novelty Phase Among Cocaine-exposed and Control Infants who Habituated to the Familiarization Stimulus

Source	MS Error	df	F	p
Group ^a	649.19	1, 28	9.07	.005

^a Infants who did not reach the criterion for habituation to the familiarization stimulus were excluded prior to analysis.

Table D16

Novelty Phase: χ^2 Analysis for the Frequency of Orientation Among Cocaine-exposed and Control Infants

Group*	Frequencies	
	Orientation	No Orientation
Cocaine-exposed	12	13
Controls	23	2
Total	35	15

* $\chi^2 (1) = 11.52, p = .001$

Table D17

Novelty Phase: One-way ANOVA for Number of Trials to Orient Comparing Cocaine-exposed and Control Infants

Source	MS Error	df	F	p
Group ^a	9.09	1, 33	6.72	.014

^a Infants who failed to orient were excluded from this analysis.

Table D18

Novelty Phase: χ^2 Analysis for the Frequency of Habituation Among Cocaine-exposed and Control Infants

Group*	Frequencies	
	Habituation	No Habituation
Cocaine-exposed	3	22
Controls	18	7
Total	21	29

* $\chi^2 (1) = 18.47, p = .000$

Table D19

Dishabituation Phase: Repeated Measures ANOVA for Recovery^a to the Dishabituation Stimulus Among Cocaine-exposed and Control Infants

Univariate Repeated Measures Analysis			
Source	df	F	p
Between subjects			
Group	1	6.35	.015
<u>S</u> within-group error	48	(532.97)	
Within subjects			
Trial Blocks	1	8.119	.006
Trial Blocks x group	1	.869	.356
Trial Blocks x <u>S</u> within-group error	48	(539.09)	

Note. Values enclosed in parentheses represent mean square errors. S = Subjects.

^a Recovery was assessed by comparing head turns toward the stimulus during the last trial block of the novelty phase and the dishabituation trial block.

Table D20

Dishabituation Phase: Between Group MANOVA for Recovery^a to Novelty
Among Cocaine-exposed and Control Infants

Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.84	2, 47	4.481	.017

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Novelty Block 2	391.18	1, 48	8.140	.006
Dishabituation trial block	680.88	1, 48	.979	.327

^a Recovery was assessed by comparing head turns toward the stimulus during the last trial block of the novelty phase and the dishabituation trial block.

Table D21

Dishabituation Phase: Paired Comparison *t* Tests for Turns Toward the Stimulus in the Second Novelty Phase Trial Block and in the Dishabituation Trial Block for Cocaine-exposed and Control Infants.

Group	Mean Difference (SD)	<i>t</i>	<i>df</i>	<i>p</i>
Cocaine	-8.90 (27.22)	-1.63	24	.115
Control	-17.56 (37.62)	-2.33	24	.028

Table D22

Dishabituation Phase: Comparison of Difference Scores for the First Three Trials With a Mean of Zero Among Cocaine-exposed and Control Infants

Group	Mean Difference (SD)	<i>t</i>	df	<i>p</i>
Cocaine	.42 (1.41)	1.45	23	.162
Control	.45 (1.53)	1.48	24	.151

Table D23

Dishabituation Phase: χ^2 Analysis for the Frequency of Orientation Among Cocaine-exposed and Control Infants

Group*	Frequencies	
	Orientation	No Orientation
Cocaine-exposed	16	7
Controls	19	6
Total	35	13

* $\chi^2 (1) = 0.25$, $p = .616$

Table D24

Dishabituation Phase: One-way ANOVA for Number of Trials to Orient
Between Cocaine-exposed and Control Infants

Source	MS Error	df	F	p
Group ^a	4.33	1, 33	.83	.368

^a Infants who failed to orient were excluded from this analysis.

Table D25

Post Hoc Analysis for Sex Differences in the Frequency of Habituation to the Familiarization Stimulus Among Cocaine-exposed Neonates

Group*	Frequencies (row percentage)	
	Habituation	No Habituation
Females (<u>n</u> =15)	8 (53.3)	7 (46.7)
Males (<u>n</u> =10)	3 (30.0)	7 (70.0)

* $\chi^2 (1) = 1.33$, $p = .250$

Table D26

Post Hoc Analysis for Sex Differences in the Frequency of Habituation to the Novel Stimulus Among Cocaine-exposed Neonates

Group*	Frequencies (row percentage)	
	Habituation	No Habituation
Females ($n=15$)	2 (13.3)	13 (86.7)
Males ($n=10$)	1 (10.0)	9 (90.0)

* $\chi^2 (1) = .06, p = .802$

Table D27

Post Hoc Analyses Comparing Difference Scores in the Last Quartile of the Familiarization Phase with a Mean of Zero for the Male and Female Cocaine-exposed Neonates

Group	Mean Difference (SD)	<i>t</i>	<i>df</i>	<i>p</i>
Females	.08 (1.47)	.20	14	.844
Males	.10 (1.52)	.21	9	.840

Table D28

Post Hoc Analyses Comparing Difference Scores in the Last Quartile of the Novelty Phase with a Mean of Zero for the Male and Female Cocaine-exposed Neonates

Group	Mean Difference (SD)	<i>t</i>	<i>df</i>	<i>p</i>
Females	.54 (1.28)	1.64	14	.123
Males	1.50 (.97)	4.88	9	.001

Table D29

Post Hoc ANOVA for Sex Differences on the Percentage of Head Turns
Toward the Stimulus During the Second Trial Block of the Familiarization Phase
Among Cocaine-exposed Infants

Source	MS Error	df	F	p
Sex <u>Infants</u>	431.59	1, 23	1.26	.274

Table D30

Post Hoc ANOVA for Sex Differences on the Percentage of Head Turns
Toward the Stimulus During the Second Trial Block of the Novelty Phase
Among Cocaine-exposed Infants

Source	MS Error	df	F	p
Sex <u>Infants</u>	372.39	1, 23	.2622	.614

Table D31

Post Hoc Repeated Measures ANOVA for the Effect of Sex on Recovery^a to the Novel Stimulus Among Cocaine-exposed Infants

Univariate Repeated Measures Analysis			
Source	df	E	p
Between subjects			
Sex	1	.05	.823
<u>S</u> within-group error	23	(560.80)	
Within subjects			
Trial Blocks	1	.74	.398
Trial Blocks x Sex	1	1.77	.197
Trial Blocks x <u>S</u> within-group error	23	(429.38)	

Note. Values enclosed in parentheses represent mean square errors. S = Subjects.

^a Recovery to Novelty was assessed by comparing the percentage of turns toward the stimulus in the last block of the familiarization phase with the first block of the novelty phase.

Table D32

Post Hoc Repeated Measures ANOVA for the Effect of Sex on Recovery^a to the Dishabituation Stimulus Among Cocaine-exposed Infants

Univariate Repeated Measures Analysis			
Source	df	F	p
Between subjects			
Sex	1	1.06	.313
<u>S</u> within-group error	23	(528.47)	
Within subjects			
Trial Blocks	1	2.811	.107
Trial Blocks x Sex	1	.248	.623
Trial Blocks x <u>S</u> within-group error	23	(382.45)	

^a Recovery to the dishabituation stimulus was assessed by comparing the second trial block of the novelty phase with the dishabituation trial block.

Table D33

Post Hoc Analyses for Recovery to the Dishabituation Stimulus Among Male and Female Cocaine-exposed Neonates: Paired Comparison t Tests for Turns Toward the Stimulus in the Second Novelty Phase Trial Block and in the Dishabituation Trial Block

Group	Mean Difference (SD)	t	df	p
Females	-6.65 (31.18)	- .83	14	.423
Males	-12.28 (21.03)	-1.85	9	.100

Table D34

Post Hoc Analysis for the Effect of Prenatal Care: Differences in the Frequency of Habituation to the Familiarization Stimulus Among Cocaine-exposed "Care" and "No Care" Groups

Group*	Frequencies (row percentage)	
	Habituation	No Habituation
No Care ($n=11$)	6 (54.6)	5 (45.4)
Care ($n=14$)	5 (35.7)	9 (64.3)

* $\chi^2 (1) = .89, p = .346$

Table D35

Post Hoc Analysis for the Effect of Prenatal Care: Differences in the Frequency of Habituation to the Novel Stimulus Among Cocaine-exposed "Care" and "No Care" Groups

Group*	Frequencies (row percentage)	
	Habituation	No Habituation
No Care ($n=11$)	1 (9.1)	10 (90.9)
Care ($n=14$)	2 (14.3)	12 (85.7)

* $\chi^2 (1) = .16, p = .692$

Table D36

Post Hoc Analyses Comparing Difference Scores in the Last Quartile of the Familiarization Phase with a Mean of Zero for the "Care" and "No Care" Cocaine-exposed Neonates

Group	Mean Difference (SD)	t	df	p
No Care	-.35 (1.34)	-.87	10	.404
Care	.43 (1.51)	1.07	13	.306

Table D37

Post Hoc Analyses Comparing Difference Scores in the Last Quartile of the Novelty Phase with a Mean of Zero for the "Care" and "No Care" Cocaine-exposed Neonates

Group	Mean Difference (SD)	t	df	p ^a
No Care	1.11 (1.41)	2.59	10	.027
Care	.79 (1.12)	2.63	13	.021

^a The significant p-values indicate preferential turning toward the stimulus at a point in the procedure where turning away would be expected.

Table D38

Post Hoc ANOVA for Differences on the Percentage of Head Turns Toward the Stimulus During the Second Trial Block of the Familiarization Phase Among the "Care" and "No Care" Cocaine-exposed Infants

Source	MS Error	df	F	p
Prenatal Care	81.46	1, 23	.180	.675

Table D39

Post Hoc ANOVA for Differences on the Percentage of Head Turns Toward the Stimulus During the Second Trial Block of the Novelty Phase Among the "Care" and "No Care" Cocaine-exposed Infants

Source	MS Error	df	F	p
Prenatal Care	17.29	1, 23	.046	.832

Table D40

Post Hoc Repeated Measures ANOVA for the Effect of Prenatal Care on Recovery^a to the Novel Stimulus Among Cocaine-exposed Infants

Univariate Repeated Measures Analysis			
Source	df	F	p
Between subjects			
Prenatal Care	1	.979	.333
<u>S</u> within-group error	23	(539.12)	
Within subjects			
Trial Blocks	1	.411	.528
Trial Blocks x Prenatal Care	1	.228	.638
Trial Blocks x <u>S</u> within-group error	23	(457.82)	

Note. Values enclosed in parentheses represent mean square errors. S = Subjects.

^a Recovery to Novelty was assessed by comparing the percentage of turns toward the stimulus in the last block of the familiarization phase with the first block of the novelty phase.

Table D41

Post Hoc Repeated Measures ANOVA for the Effect of Prenatal Care on Recovery^a to the Dishabituation Stimulus Among Cocaine-exposed Infants

Univariate Repeated Measures Analysis			
Source	df	F	p
Between subjects			
Prenatal Care	1	.023	.881
<u>S</u> within-group error	23	(552.37)	
Within subjects			
Trial Blocks	1	2.483	.129
Trial Blocks x Prenatal Care	1	.014	.907
Trial Blocks x <u>S</u> within-group error	23	(386.34)	

Note. Values enclosed in parentheses represent mean square errors. S = Subjects.

^a Recovery to Novelty was assessed by comparing the percentage of turns toward the stimulus in the last block of the familiarization phase with the first block of the novelty phase.

Table D42

Post Hoc Analyses for Recovery to the Dishabituation Stimulus Among "Care" and "No Care" Cocaine-exposed Neonates: Paired Comparison *t* Tests for Turns Toward the Stimulus in the Second Novelty Phase Trial Block and in the Dishabituation Trial Block

Group	Mean Difference (SD)	<i>t</i>	<i>df</i>	<i>p</i>
No Care	-8.16 (35.11)	- .77	10	.459
Care	-9.49 (20.47)	-1.73	13	.107

Appendix E

Data Analysis Tables for Study 2. Part I

Table E1

MANOVA for Between Group Differences on the Demographic Control Variables for Tobacco-Exposed and Control Infants

Multivariate Repeated Measures Analysis of Variance				
Source	Wilks' Lambda	df	F	p
Control Variables x Group	.77	7, 78	3.36	.004
Group	.77	8, 77	2.91	.007

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Birth weight	200667.85	1, 84	7.02	.010
Gestational Age	3.93	1, 84	2.18	.143
SES	504.46	1, 84	4.18	.044
Pregnancy Weight Gain	28.35	1, 84	1.18	.280
Age of Mother	23.62	1, 84	7.89	.006
Parity	.88	1, 84	1.51	.223
Gravidity	2.00	1, 84	.11	.746
Education	1.90	1, 84	.32	.575

Table E2

One-way ANOVA for Overall Occurrence of Head-turning for the Tobacco-exposed and Control Infants

Source	MS Error	df	F	p
Group	121.38	1, 84	1.76	.189

Table E3

Repeated Measures MANOVA for Positive State Across Phases for Tobacco-exposed and Control Infants

Multivariate Repeated Measures Analysis of Variance				
Source	Wilks' Lambda	df	F	p
Positive State	.80	2, 83	10.33	.000
Positive State x Group	.99	2, 83	.54	.584
Group	.95	3, 82	1.31	.278

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Familiarization Positive State	123.31	1, 84	2.35	.129
Novelty Positive State	179.27	1, 84	2.71	.104
Dishabituation Positive State	299.00	1, 84	3.57	.062

Table E4

Familiarization Phase: Repeated Measures MANOVA and Univariate F Tests of Quartiles for Tobacco-exposed and Control Infants

Multivariate Repeated Measures Analyses				
Source	Wilks' Lambda	df	F	p
Familiarization Quartiles	.19	3, 82	116.53	.000
Familiarization Quartiles x Group	.82	3, 82	6.21	.001
Group	.81	4, 81	4.69	.002

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
First Quartile	697.10	1, 84	3.20	.077
Second Quartile	549.51	1, 84	11.08	.001
Third Quartile	881.69	1, 84	.41	.524
Fourth Quartile	342.08	1, 84	9.18	.003

Table E5

Repeated Measures Manova for Head-Turning Toward the Stimulus Across the Two Trial Blocks of the Familiarization Phase Among Tobacco-exposed and Control Neonates

Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.86	2, 83	6.68	.002
Univariate F Tests for the Effect of Group				
Source	MS Error	df	F	p
Trial Blocks	461.49	1, 84	126.53	.000
Trial Blocks x Group	461.49	1, 84	12.86	.001
Familiarization Block 1	338.41	1, 84	11.57	.001
Familiarization Block 2	346.04	1, 84	6.21	.015

Table E6

Familiarization Phase: One-sample t Tests for Difference Scores of Tobacco-exposed and Control Infants for the First and Last Quartiles

Quartile	Group	Mean (SD)	t	df	p
First Quartile of Familiarization Phase	Tobacco	1.27 (1.48)	5.01	33	.000
	Control	1.40 (1.19)	8.44	51	.000
Last Quartile of Familiarization Phase	Tobacco	-.85 (1.35)	-3.67	33	.001
	Control	-1.06	-6.34	51	.000

Table E7

Familiarization Phase: χ^2 Analysis for the Frequency of Orientation Among Tobacco-exposed and Control Infants

Group*	Frequencies (Row Percent)	
	Orientation	No Orientation
Tobacco-exposed	31 (91.2)	3 (8.8)
Controls	52 (100)	0 (0)

* $\chi^2 (1) = 4.75, p = .029$

Table E8

Familiarization Phase: χ^2 Analysis for the Frequency of Habituation Among Tobacco-exposed and Control Infants

Group*	Frequencies (Row Percent)	
	Habituation	No Habituation
Tobacco-exposed	23 (67.7)	11 (32.3)
Controls	47 (90.4)	5 (9.6)

* χ^2 (1) = 7.02, **p = .008**

Table E9

Familiarization Phase: One-way ANOVA for Number of Trials to Orient
Between Tobacco-exposed and Control Infants

Source	MS Error	df	F	p
Group ^a	4.99	1, 81	14.711	.000

^a Infants who failed to orient were excluded from this analysis.

Table E10

Familiarization Phase: One-way ANOVA for Number of Trials to Habituate
Between Tobacco-exposed and Control Infants

Source	MS Error	<u>df</u>	<u>F</u>	<u>p</u>
Group ^a	10.09	1, 68	5.06	.028

^a Infants who failed to habituate were excluded from this analysis.

Table E11

Novelty Phase: Repeated Measures MANOVA and Univariate F Tests of Quartiles, for Tobacco-exposed and Control Infants

Multivariate Repeated Measures Analyses				
Source	Wilks' Lambda	df	F	p
Novelty Quartiles	.20	3, 82	109.09	.000
Novelty Quartiles x Group	.98	3, 82	.58	.631
Group	.98	4, 81	.48	.744

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
First Quartile	900.82	1, 84	.53	.470
Second Quartile	871.25	1, 84	.04	.851
Third Quartile	892.66	1, 84	.03	.854
Fourth Quartile	331.30	1, 84	1.38	.244

Table E12

Repeated Measures Manova for Head-Turning Toward the Stimulus Across the Two Trial Blocks of the Novelty Phase Among Tobacco-exposed and Control Neonates

Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.99	2, 83	.08	.928
Univariate F Tests for the Effect of Group				
Source	MS Error	df	F	p
Trial Blocks	643.85	1, 84	80.23	.000
Trial Blocks x Group	643.85	1, 84	.11	.738
Familiarization Block 1	503.93	1, 84	.04	.840
Familiarization Block 2	370.08	1, 84	.15	.698

Table E13

Novelty Phase: One-sample t Tests for Difference Scores of Tobacco-exposed and Control Infants for the First and Last Quartiles

Quartile	Group	Mean (SD)	t	df	p
First Quartile of Novelty Phase	Tobacco	1.12 (1.26)	5.56	33	.000
	Control	1.21 (1.12)	7.77	51	.000
Last Quartile of Novelty Phase	Tobacco	-.91 (1.32)	-4.01	33	.000
	Control	-7.01 (1.19)	-7.01	51	.000

Table E14

Novelty Phase: Repeated Measures ANOVA for Recovery^a to the Novel Stimulus Among Tobacco-exposed and Control Infants

Univariate Repeated Measures Analysis			
Source	df	F	p
Between subjects			
Group	1	2.18	.143
<u>S</u> within-group error	84	(400.31)	
Within subjects			
Trial Blocks	1	111.07	.000
Trial Blocks x group	1	2.88	.093
Trial Blocks x <u>S</u> within-group error	48	(449.67)	

Note. Values enclosed in parentheses represent mean square errors. S = Subjects.

Table E15

Novelty Phase: Between Group MANOVA and Univariate Tests of Trial Blocks for Recovery^a to Novelty Among Tobacco-exposed and Control Infants

Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.93	2, 83	3.07	.052

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Familiarization Block 2	346.04	1, 84	6.21	.015
Novelty Block 1	503.93	1, 84	.04	.840

^a Recovery to novelty was assessed by comparing the last trial block of the familiarization phase with the first trial block of the novelty phase.

Table E16

Novelty Phase: Repeated Measures ANOVA for Recovery^a to the Novel Stimulus Among Tobacco-exposed and Control Infants, with Infants Who Failed to Habituate to the Familiarization Stimulus Excluded

Univariate Repeated Measures Analysis				
Source	df	F	p	
Between subjects				
Group	1	.829	.366	
<u>S</u> within-group error ^b	68	(365.25)		
Within subjects				
Trial Blocks	1	122.113	.000	
Trial Blocks x group	1	1.28	.263	
Trial Blocks x <u>S</u> within-group error ^b	68	(407.80)		
Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.95	2, 67	1.62	.206
Univariate <u>F</u> Tests for the Effect of Group				
Variable	MS Error	df	F	p
Familiarization Block 2	246.74	1, 68	3.28	.075
Novelty Block 1	526.30	1, 68	.02	.868

^a Recovery was assessed by comparing head turns toward the stimulus during the last trial block of the familiarization phase and the first trial block of the novelty phase.

^b Values enclosed in parentheses represent mean square errors. S = Subjects.

Table E17

Novelty Phase: χ^2 Analysis for the Frequency of Orientation Among Tobacco-exposed and Control Infants

Group*	Frequency (Row Percent)	
	Orientation	No Orientation
Tobacco-exposed	30 (88.2)	4 (11.8)
Controls	50 (96.2)	2 (3.8)

* χ^2 (1) = 1.99, p = .159

Table E18

Novelty Phase: χ^2 Analysis for the Frequency of Habituation Among Tobacco-exposed and Control Infants

Group*	Frequency (Row Percent)	
	Habituation	No Habituation
Tobacco-exposed	23 (67.7)	11 (32.3)
Controls	41 (78.9)	11 (21.1)

* $\chi^2 (1) = 1.35$, $p = .245$

Table E19

Novelty Phase: One-way ANOVA for Number of Trials to Orient Comparing Tobacco-exposed and Control Infants

Source	MS Error	df	F	p
Group ^a	5.92	1, 78	1.89	.173

^a Infants who failed to orient were excluded from this analysis.

Table E20

Novelty Phase: One-way ANOVA for Number of Trials to Habituate Comparing Tobacco-exposed and Control Infants

Source	MS Error	df	F	p
Group ^a	6.16	1, 62	.22	.641

^a Infants who failed to habituate were excluded from this analysis.

Table E21

Repeated Measures ANOVA for Recovery^a to the Dishabituation Stimulus
Among Tobacco-exposed and Control Infants

Univariate Repeated Measures Analysis				
Source	df	F	p	
Between subjects				
Group	1	3.48	.066	
<u>S</u> within-group error ^b	84	(449.48)		
Within subjects				
Trial Blocks	1	58.89	.000	
Trial Blocks x group	1	4.63	.034	
^b Trial Blocks x <u>S</u> within-group error	84	(543.44)		
Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.93	2, 83	3.20	.046
Univariate <u>F</u> Tests for the Effect of Group				
Variable	MS Error	df	F	p
Novelty Block 2	370.08	1, 84	.15	.698
Dishabituation trial block	622.84	1, 84	6.46	.013

^a Recovery was assessed by comparing head turns toward the stimulus during the last trial block of the novelty phase and the dishabituation trial block.

^b Values enclosed in parentheses represent mean square errors. S = Subjects.

Table E22

Dishabituation Phase: Comparison of Difference Scores for the First Three Trials With a Mean of Zero Among Tobacco-exposed and Control Infants

Group	Mean Difference (SD)	t	df	p
Tobacco	.42 (1.58)	1.54	33	.133
Control	1.12 (1.39)	5.83	51	.000

Table E23

Dishabituation Phase: χ^2 Analysis for the Frequency of Orientation Among Tobacco-exposed and Control Infants

Group*	Frequencies	
	Orientation	No Orientation
Tobacco-exposed	27 (79.4)	7 (20.6)
Controls	48 (92.3)	4 (7.7)

* $\chi^2 (1) = 3.07, p = .080$

Table E24

Dishabituation Phase: One-way ANOVA for Number of Trials to Orient
Between Tobacco-exposed and Control Infants

Source	MS Error	df	F	p
Group ^a	4.20	1, 73	4.56	.036

^a Infants who failed to orient were excluded from this analysis.

Appendix F

Data Analysis Tables for Study 2, Part II

Table F1

Repeated Measures ANOVA for Between Group Differences on Birthweight and SES Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Repeated Measures Analysis of Variance				
Source	MS Error	df	F	p
Group	109152.55	2, 48	.59	.561
Variable x Group	108187.24	2, 48	.56	.574

Multivariate Statistics for the Effect of Group				
Source	Wilk's Lambda	df	F	p
Group	.98	4, 94	.30	.880

Univariate F - Tests for the Effect of Group				
Variable	MS Error	df	F	p
Birth weight	216872.96	2, 48	.57	.567
SES	467.98	2, 48	.05	.954

Table F2

MANOVA for Between Group Differences on the Demographic Control Variables for Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Multivariate Repeated Measures Analysis of Variance				
Source	Wilks' Lambda	df	F	p
Control Variables x Group	.67	10, 88	1.93	.051
Group	.62	12, 86	1.90	.045
Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Weight at Testing	180814.91	2, 48	.74	.481
Pregnancy Weight Gain	20.84	2, 48	7.42	.002
Age of Mother	25.49	2, 48	.27	.764
Parity	.82	2, 48	.31	.733
Gravidity	1.59	2, 48	1.05	.359
Education	1.24	2, 48	.62	.544

Table F3

One-way ANOVA for Overall Occurrence of Head-turning for Infants With
Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Source	MS Error	df	F	p
Group	126.29	2, 48	.30	.739

Table F4

Repeated Measures MANOVA for Positive State Across Phases for Infants
With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Multivariate Repeated Measures Analysis of Variance				
Source	Wilks' Lambda	df	F	p
Positive State	.83	2, 47	4.89	.012
Positive State x Group	.86	4, 94	1.88	.121
Group	.79	6, 92	1.88	.093

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Familiarization Positive State	157.89	2, 48	.89	.419
Novelty Positive State	172.75	2, 48	3.68	.033
Dishabituation Positive State	319.271	2, 48	3.85	.028

Matrix of Pairwise Comparisons for Novelty Phase:
Mean Difference Between Groups

	Heavy Exposure	Light Exposure
Light Exposure	-9.88 (p=.083)	--
Controls	1.30 (p=.955)	11.18 (p=.043)

Matrix of Pairwise Comparisons for Dishabituation Phase:
Mean Difference Between Groups

	Heavy Exposure	Light Exposure
Light Exposure	-9.00 (p=.315)	--
Controls	7.99 (p=.400)	16.99 (p=.021)

Table F5

Familiarization Phase: Repeated Measures MANOVA and Univariate F Tests of Quartiles for Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Multivariate Repeated Measures Analyses				
Source	Wilks' Lambda	df	F	p
Familiarization Quartiles	.26	3, 46	44.05	.000
Familiarization Quartiles x Group	.74	6, 92	2.45	.031
Group	.74	8, 90	1.80	.088

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
First Quartile	693.32	2, 48	4.44	.017
Second Quartile	613.54	2, 48	1.90	.160
Third Quartile	625.38	2, 48	.78	.464
Fourth Quartile	468.47	2, 48	2.08	.136

Matrix of Pairwise Comparisons for the First Quartile:
Mean Difference Between Groups

	Heavy Exposure	Light Exposure
Light Exposure	24.41 (p=.009)	—
Controls	22.00 (p=.019)	-2.41 (p=.791)

Table F6

Repeated Measures Manova for Head-Turning Toward the Stimulus Across the Two Trial Blocks of the Familiarization Phase Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Repeated Measures Analysis of Variance				
Source	MS Error	df	F	p
Group	238.05	2, 48	.17	.849
Trial Blocks	425.02	1, 48	67.87	.000
Trial Blocks x Group	425.02	2, 48	5.61	.006
Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.80	4, 94	2.70	.035
Univariate F Tests for the Effect of Group				
Source	MS Error	df	F	p
Familiarization Block 1	380.23	2, 48	3.48	.039
Familiarization Block 2	282.84	2, 48	3.90	.027
Matrix of Pairwise Comparisons for First Trial Block: Mean Difference Between Groups				
	Heavy Exposure	Light Exposure		
Light Exposure	11.32 (p=.097)	--		
Controls	17.38 (p=.012)	6.06 (p=.370)		
Matrix of Pairwise Comparisons for Second Trial Block: Mean Difference Between Groups				
	Heavy Exposure	Light Exposure		
Light Exposure	-7.12 (p=.223)	--		
Controls	-16.07 (p=.008)	-8.95 (p=.127)		

Table F7

Familiarization Phase: One-sample t Tests for Difference Scores of Infants
With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None) for the
First and Last Quartiles

Quartile	Group	Mean Difference (SD)	t	df	p
First Quartile of Familiarization Phase	Heavy Exposure	.80 (1.32)	2.48	16	.024
	Light Exposure	1.71 (1.53)	4.59	16	.000
	Controls	1.53 (1.22)	5.18	16	.000
Last Quartile of Familiarization Phase	Heavy Exposure	-.85 (1.60)	-2.19	16	.043
	Light Exposure	-.82 (1.19)	-2.87	16	.011
	Controls	-.77 (1.15)	-2.75	16	.014

Table F8

Familiarization Phase: χ^2 Analysis for the Frequency of Orientation Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group*	Frequencies (Row Percent)	
	Orientation	No Orientation
Heavy Exposure	15 (88.2)	2 (11.8)
Light Exposure	16 (94.1)	1 (5.9)
Controls	17 (100)	0 (0)

* $\chi^2 (2) = 2.13, p = .346$

Table F9

Familiarization Phase: One-way ANOVA for Number of Trials to Orient Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Source	MS Error	df	F	p
Group ^a	6.92	2, 45	4.99	.011

^a Infants who failed to orient were excluded from this analysis.

Matrix of Pairwise Comparisons for Number of Trials to Orient:
Mean Difference Between Groups

	Heavy Exposure	Light Exposure
Light Exposure	-1.82 (p=.061)	--
Controls	-2.93 (p= .003)	-1.11 (p=.232)

Table F10

Familiarization Phase: χ^2 Analysis for the Frequency of Habituation Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group*	Frequencies (Row Percent)	
	Habituation	No Habituation
Heavy exposure	11 (64.7)	6 (35.3)
Light Exposure	12 (70.6)	5 (29.4)
Controls	16 (94.1)	1 (5.9)

* $\chi^2 (2) = 4.58$, $p = .101$

Table F11

Familiarization Phase: One-way ANOVA for Number of Trials to Habituate Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Source	MS Error	df	F	p
Group ^a	11.14	2, 36	1.94	.159

^a Infants who failed to habituate were excluded from this analysis.

Table F12

Novelty Phase: Repeated Measures MANOVA and Univariate F Tests for Quartiles Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Multivariate Repeated Measures Analyses				
Source	Wilks' Lambda	df	F	p
Novelty Quartiles	.20	3, 46	63.17	.000
Novelty Quartiles x Group	.87	6, 92	1.09	.372
Group	.73	8, 90	1.96	.061

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
First Quartile	1016.27	2, 48	.52	.598
Second Quartile	903.04	2, 48	.63	.536
Third Quartile	744.51	2, 48	2.06	.139
Fourth Quartile	412.51	2, 48	6.23	.004

Matrix of Pairwise Comparisons for the Fourth Quartile: Mean Difference Between Groups		
	Heavy Exposure	Light Exposure
Light Exposure	-20.04 (p=.006)	--
Controls	-22.37 (p=.002)	-2.33 (p=.739)

Table F13

Repeated Measures Manova for Head-Turning Toward the Stimulus Across the Two Trial Blocks of the Novelty Phase Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Repeated Measures Analysis of Variance				
Source	MS Error	df	F	p
Group	240.25	2, 48	3.90	.027
Trial Blocks	688.49	1, 48	57.71	.000
Trial Blocks x Group	688.49	2, 48	2.28	.113

Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.75	4, 94	3.62	.009

Univariate F Tests for the Effect of Group				
Source	MS Error	df	F	p
Novelty Block 1	569.72	2, 48	.77	.470
Novelty Block 2	359.02	2, 48	5.77	.006

Matrix of Pairwise Comparisons for the Second Trial Block: Mean Difference Between Groups		
	Heavy Exposure	Light Exposure
Light Exposure	-19.65 (p=.004)	--
Controls	-18.53 (p=.006)	1.12 (p=.864)

Table F14

Novelty Phase: Repeated Measures ANOVA for Recovery^a to the Novel Stimulus Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Univariate Repeated Measures Analysis			
Source	df	F	p
<u>Between subjects</u>			
Group	2	.50	.611
<u>S</u> within-group error ^B	48	(388.27)	
<u>Within subjects</u>			
Trial Blocks	1	72.65	.000
Trial Blocks x group	1	2.90	.065
Trial Blocks x <u>S</u> within-group error ^B	48	(464.29)	

Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.84	4, 94	2.10	.088

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Familiarization Block 2	282.84	2, 48	3.90	.027
Novelty Block 1	569.72	2, 48	.77	.470

^a Recovery to novelty was assessed by comparing the last trial block of the familiarization phase with the first trial block of the novelty phase.

^B Values enclosed in parentheses represent mean square errors. S = Subjects.

Table F15

Novelty Phase: Repeated Measures ANOVA for Recovery^a to the Novel Stimulus Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None), with Infants Who Failed to Habituate to the Familiarization Stimulus Excluded

Univariate Repeated Measures Analysis			
Source	df	F	p
<u>Between subjects</u>			
Group	2	.25	.784
<u>S</u> within-group error ^b	36	(354.35)	
<u>Within subjects</u>			
Trial Blocks	1	75.16	.000
Trial Blocks x group	2	1.59	.219
Trial Blocks x <u>S</u> within-group error ^b	36	(437.67)	

Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.87	4, 70	1.24	.301

Univariate F Tests for the Effect of Group				
Variable	MS Error	df	F	p
Familiarization Block 2	190.14	2, 36	2.19	.126
Novelty Block 1	601.88	2, 36	.60	.552

^a Recovery was assessed by comparing head turns toward the stimulus during the last trial block of the familiarization phase and the first trial block of the novelty phase.

^b Values enclosed in parentheses represent mean square errors. S = Subjects.

Table F16

Recovery to Novelty: One-sample t Tests Comparing the Percentage of Head-Turning Toward the Stimulus During the Last Trial Block of the Familiarization Phase and the First Trial Block of the Novelty Phase Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group	Mean (SD)	t	df	p
Heavy Tobacco Exposure	-26.41 (27.65)	-3.94	16	.001
Light Tobacco Exposure	-32.19 (35.41)	-3.75	16	.002
Controls	-50.51 (27.69)	-7.52	16	.000

Table F17

Novelty Phase: One-sample t Tests for Difference Scores for the First and Last Quartiles Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Quartile	Group	Mean (SD)	t	df	p
First Quartile of Novelty Phase	Heavy Exposure	1.47 (1.46)	4.15	16	.001
	Light Exposure	.94 (1.03)	3.77	16	.002
	Controls	1.25 (1.20)	4.31	16	.001
Last Quartile of Novelty Phase	Heavy Exposure	-.47 (1.81)	-1.07	16	.299
	Light Exposure	-1.24 (.90)	-5.64	16	.000
	Controls	-1.43 (1.03)	-5.74	16	.000

Table F18

Novelty Phase: χ^2 Analysis for the Frequency of Orientation Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group*	Frequency (Row Percent)	
	Orientation	No Orientation
Heavy Exposure	17 (100)	0 (0)
Light Exposure	13 (76.5)	4 (23.5)
Controls	17 (100)	0 (0)

* χ^2 (2) = 8.68, $p = .013$

Table F19

Novelty Phase: One-way ANOVA for Number of Trials to Orient Among Infants
With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Source	MS Error	df	F	p
Group ^a	4.16	2, 44	.66	.522

^a Infants who failed to orient were excluded from this analysis.

Table F20

Novelty Phase: χ^2 Analysis for the Frequency of Habituation Among Infants
With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group*	Frequency (Row Percent)	
	Habituation	No Habituation
Heavy Exposure	10 (58.8)	7 (41.2)
Light Exposure	13 (76.5)	4 (23.5)
Controls	16 (94.1)	1 (5.9)

* χ^2 (2) = 5.89, **p = .053**

Table F21

Novelty Phase: One-way ANOVA for Number of Trials to Habituate Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Source	MS Error	df	F	p
Group ^a	6.34	2, 36	2.23	.122

^a Infants who failed to habituate were excluded from this analysis.

Table F22

Repeated Measures ANOVA for Recovery^a to the Dishabituation Stimulus Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Univariate Repeated Measures Analysis				
Source	df	F	p	
<u>Between subjects</u>				
Group	2	.87	.426	
<u>S</u> within-group error ^b	48	(516.76)		
<u>Within subjects</u>				
Trial Blocks	1	39.08	.000	
Trial Blocks x group	2	6.91	.002	
Trial Blocks x <u>S</u> within-group error ^b	48	(513.44)		
Multivariate Analysis for Effect of Group				
Source	Wilks' Lambda	df	F	p
Group	.73	4, 94	4.03	.005
Univariate <u>F</u> Tests for the Effect of Group				
Variable	MS Error	df	F	p
Novelty Block 2	359.02	2, 48	5.77	.006
Dishabituation trial block	671.19	2, 48	2.87	.067
Matrix of Pairwise Comparisons for the Dishabituation Trial Block: Mean Difference Between Groups				
	Heavy Exposure	Light Exposure		
Light Exposure	8.59 (p=.339)	--		
Controls	21.16 (p=.021)	12.57 (p=.164)		

^a Recovery was assessed by comparing head turns toward the stimulus during the last trial block of the novelty phase and the dishabituation trial block.

^b Values enclosed in parentheses represent mean square errors. S = Subjects.

Table F23

Recovery to the Dishabituation Stimulus: One-sample t Tests Comparing the Last Trial Block of the Novelty Phase with the Dishabituation Trial Block Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group	Mean (SD)	t	df	p
Heavy Tobacco Exposure	-5.41 (41.02)	-.54	16	.594
Light Tobacco Exposure	-33.65 (27.51)	-5.04	16	.000
Controls	-45.10 (25.33)	-7.34	16	.000

Table F24

Recovery to the Dishabituation Stimulus With Infants Who Failed to Habituate to the Novel Stimulus Excluded: One-sample t Tests Comparing the Last Trial Block of the Novelty Phase with the Dishabituation Trial Block Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group	Mean (SD)	t	df	p
Heavy Tobacco Exposure	-18.30 (38.26)	-1.51	9	.165
Light Tobacco Exposure	-33.00 (26.09)	-4.56	12	.001
Controls	-48.35 (22.19)	-8.72	15	.000

Table F25

Dishabituation Phase: Comparison of Difference Scores for the First Three Trials With a Mean of Zero Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group	Mean Difference (SD)	t	df	p
Heavy Exposure	.41 (1.70)	1.00	16	.331
Light Exposure	.41 (1.54)	1.10	16	.288
Controls	1.24 (1.38)	3.70	16	.002

Table F26

Dishabituation Phase: χ^2 Analysis for the Frequency of Orientation Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Group*	Frequencies	
	Orientation	No Orientation
Heavy Exposure	13 (76.5)	4 (23.5)
Light Exposure	14 (82.4)	3 (17.6)
Controls	14 (82.4)	3 (17.6)

* $\chi^2 (2) = .25, p = .883$

Table F27

Dishabituation Phase: One-way ANOVA for Number of Trials to Orient Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Source	MS Error	df	F	p
Group ^a	4.21	2, 38	3.86	.030

^a Infants who failed to orient were excluded from this analysis.

Matrix of Pairwise Comparisons for the Number of Trials to Orient to the Dishabituation Stimulus: Mean Difference Between Groups

	Heavy Exposure	Light Exposure
Light Exposure	-.31 (p=.694)	--
Controls	-2.02 (p=.015)	-1.71 (p=.034)

^a Recovery was assessed by comparing head turns toward the stimulus during the last

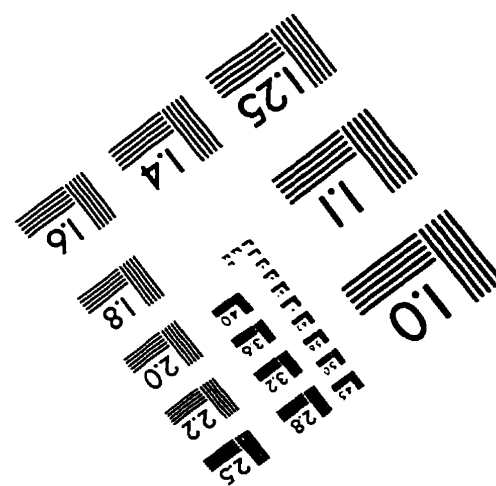
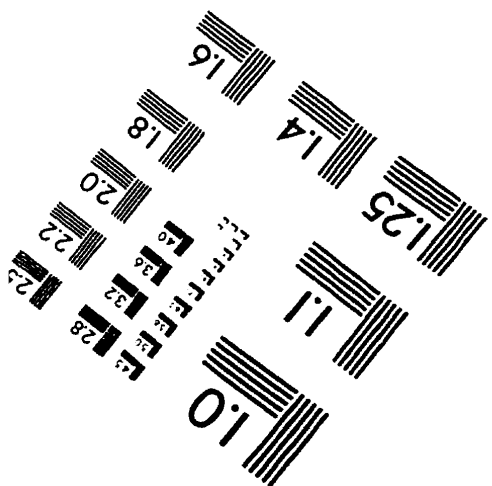
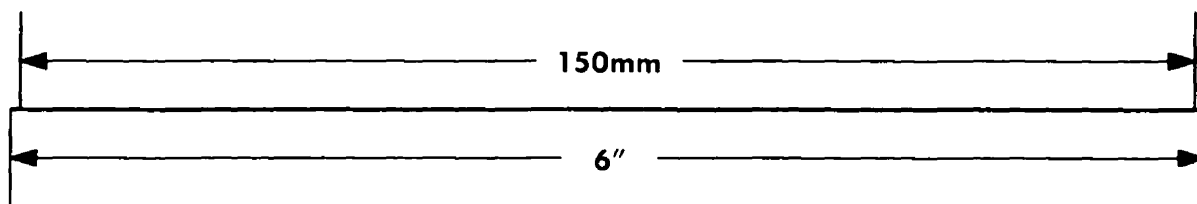
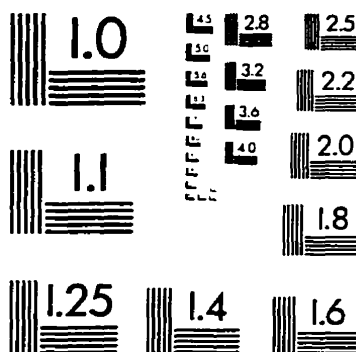
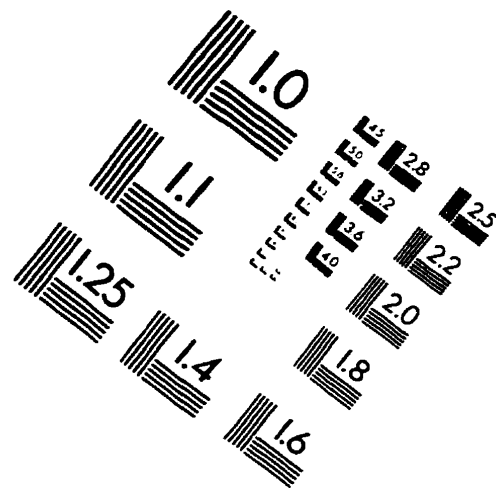
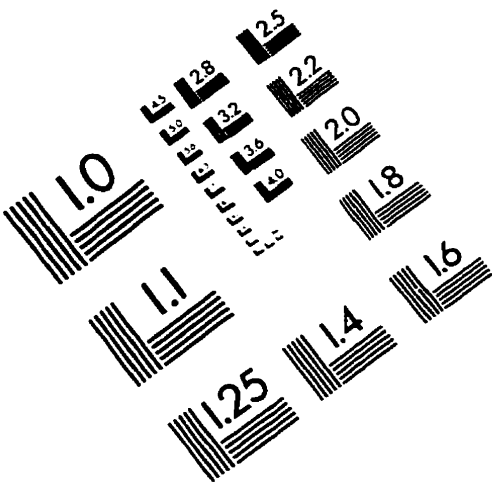
Table F28

Correlational Analyses for Sex Differences Among Infants With Three Levels of Prenatal Tobacco-Exposure (Heavy, Light, None)

Variable	Variable x Sex: Correlation Coefficient (r)			
	All	HS	LS	CTRL
Familiarization, 1st Quartile	.09	-.06	.02	.33
Familiarization, 1st Trial Block	.21	.09	.27	.22
Familiarization, 2nd Trial Block	.08	.13	.43*	-.08
Familiarization, # Trials to Orient	-.21	.04	-.41	-.28
Novelty, 4th Quartile	-.15	-.30	.11	.19
Novelty, 2nd Trial Block	-.08	-.17	-.10	.03
Novelty, 4th Quartile Difference Score	-.03	-.15	-.08	.30
Novelty, Orientation	-.01	--	.17	--
Novelty, Habituation	-.08	-.31	.17	.19
Dishabituation Trial Block	-.04	-.12	-.07	-.12
Dishabituation Difference Scores	-.00	.05	.04	-.33
Dishabituation, # Trials to Orient	-.23	-.12	-.25	-.12

* $p = .085$

IMAGE EVALUATION TEST TARGET (QA-3)



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