



Introduction

Introduction to “Understanding developmental consequences of prenatal drug exposure: Biological and environmental effects and their interactions”

We are pleased to present this Special Issue to honor the career of Dr. Vincent Smeriglio, developmental psychologist and retired Branch Chief, Behavioral and Brain Development Branch, Division of Clinical Neuroscience and Behavioral Research at the National Institute of Drug Abuse (NIDA). Dr. Smeriglio was an ardent supporter of research on the developmental effects of prenatal substance use and was influential in many investigators' career development, including those represented in this Issue. This Special Issue grew out of a NIDA conference, “Adolescent Development Following Prenatal Drug Exposure”, at which investigators funded by NIDA were invited to discuss research progress, challenges, and opportunities. Subsequently, conference attendees were invited by *Neurotoxicology and Teratology* to submit to the Special Issue, along with other researchers who were part of Dr. Smeriglio's research portfolio.

As Dr. Jag Khalsa has noted in the Preface, concern regarding the possible negative consequences of maternal drug abuse during pregnancy on prenatal and later child development crescendoed to a point of national concern in the 1980s, due to the emergence of the cocaine epidemic in the United States that affected hundreds of thousands of babies. Dr. Khalsa, and other scientists at NIDA such as Dr. Coryl Jones, Dr. Loretta Finnegan, and Dr. Smeriglio, took the lead in countering alarmist media accounts of the “crack-baby” by advocating for the design and funding of scientifically-sound research in this area. The results of these efforts can be seen in the studies reported here, most of which were shepherded by the caring stewardship, inspirational guidance, and insightful knowledge of their Program Officer, Dr. Smeriglio.

A large number of developmental studies of in utero neurotoxic and teratologic exposures have been underway, some for over two decades, and have been seminal in the emergence of behavioral teratology as a distinct area of research. Early comparative models of prenatal exposure have been replaced by more complex models incorporating polydrug exposure and environmental and genetic factors that may moderate risk across a variety of developmental domains. The empirical studies in this Issue represent remarkable advances in methodology related to understanding the role of prenatal exposures in affecting child outcomes. The studies represent large, prospective, well-defined cohorts of mothers and infants enrolled during pregnancy or at infant birth, and with targeted drug exposures (cocaine, marijuana, tobacco, and methamphetamine) ascertained through multiple methods, often with both interview and biologic specimens. Postnatal lead exposure is also measured in some cohorts, as it is a confounding factor in many studies of drug-exposed children living in poor urban environments. These longitudinal cohort studies were designed to address many of the methodological problems inherent in previous studies of children

exposed prenatally to drugs, and have paid special attention to the role of the environment as a moderating factor in understanding the consequences of prenatal exposures (Jacobson and Jacobson, 2005). All have attempted to differentiate biological effects of prenatal exposures from the effects of living with a parent who uses drugs and from the broader social context that often coexists with in utero drug exposure, such as economic hardship, poor parenting, educational disadvantage, and exposure to violence. These studies now extend their follow-ups to the school age and adolescent years and attempt to differentiate the biologic effects of exposure from the environmental effects of continued parental drug use and psychological distress. Moreover, all acknowledge the role of multiple drugs in prenatal exposures, with many studies statistically disaggregating the effects of polydrug exposure.

Consistent with the original impetus of the “crack-cocaine” epidemic in stimulating resurgence in developmental drug studies, the majority of the studies in this Issue focus on prenatal cocaine exposure (PCE). Preclinical studies have demonstrated the multiple mechanisms by which PCE can influence early brain development, including direct effects on neurotransmitter systems, vasoconstriction that decreases placental blood flow and nutrition, and alterations of gene expression (Lester and Padbury, 2009). In her review, Dow-Edwards (2011) (this issue) describes the translational value of preclinical studies of PCE in terms of dosing, timing, and pharmacokinetics of the drug. Research in primate, rabbit, and rodent models has demonstrated that disruption of cortical development and the subcortical dopamine system may explain the effects of PCE on activity, attention, and drug responsiveness. This research is necessary to demonstrate the mechanisms by which prenatal exposures exert their effects. Preclinical studies are also important as most human cohorts were enrolled from low socioeconomic populations, with the many associated confounding sociodemographic, polydrug, and environmental factors. Environmental enrichment, notes Dow-Edwards (2011), can also be evaluated preclinically and, as with the human studies featured in this issue (Lewis et al., 2011), appears to ameliorate some of the negative effects of exposure. Although the focus of Dow-Edwards's paper is on cocaine, the translational methodology described is also generalizable to other drugs.

All but one of the PCE studies in this Issue focus on school age and adolescent outcomes, and provide important new findings on cocaine's longer-term effects on several aspects of development. These studies, many using new longitudinal analytic strategies, document persistent PCE-associated deficits in language, attention, behavior, and offspring drug use.

Three reports in this Issue focus on language development. Previously, the Miami cohort and the Cleveland cohort reported

associations with PCE and language deficits at earlier ages (Bandstra et al., 2004; Lewis et al., 2007). The Miami study (Bandstra et al., 2011) (this issue) showed a dose-dependent relation between PCE level and global language scores at 3, 5, and 12 years of age using longitudinal latent growth curve modeling. Important mediating and moderating relationships were also tested. The Cleveland study found effects of PCE on specific areas of language – syntax, semantics, and phonological processing – at 10 years of age (Lewis et al., 2011) (this issue). Children with PCE in foster/adoptive care, with better home environments and more educated caregivers, had better language skills than exposed children who were in maternal or relative care, demonstrating some compensatory effects of an enriched environment on language outcomes. By contrast to these two reports, Betancourt et al. (2011) (this issue) did not find any effects of PCE on language development.

Four reports in this Issue address attentional and executive processes, which have been identified in multiple studies to be negatively affected by PCE. Bridgett and Mayes (2011) reported that PCE was associated with more commission errors on the Stroop interference task, an indicator of inhibitory control at 7½ and 11½ years of age. Results were qualified, however, by age, gender, and environmental risk status, with boys making more errors, regardless of exposure status. Carmody et al. (2011) (this issue) examined attention and inhibitory control at 6, 9, and 11 years on a Go-NoGo task. PCE was associated with increased attention (omission) errors in boys only, but not with inhibition (commission) errors. In another cohort (Richardson et al., 2011, this issue), PCE was related to greater activity, inattention, and impulsivity at 7 years. Findings were not specific to gender in this cohort, and parent and teacher reports were used rather than experimental or standardized direct child assessments as in the Bridgett and Mayes (2011) and Carmody et al. (2011) studies. By contrast, Betancourt et al.'s (2011) follow-up at 12, 14½, and 17 years did not find attention or inhibitory control deficits related to PCE.

Behavioral and emotional outcomes have been a major focus of interest in developmental teratology studies, with PCE of particular interest because of its hypothesized effects on arousal and regulatory systems (Mayes, 2002). Bada et al. (2011) present results from the large multi-site Maternal Lifestyle Study. Higher levels of PCE were predictive of higher externalizing behavior problems at 7 through 13 years on both the Child Behavior Checklist (CBCL) and the Teacher Report Form (TRF). These findings are consistent with those of Richardson et al. (2011) (this issue), who also reported that PCE predicted more total and externalizing behaviors on both the CBCL and TRF at 7 years. Longitudinal analyses demonstrated that some, but not all, of the 7-year effects were mediated by the effects of PCE on 3-year behavior.

One of the most significant societal questions raised in these developmental studies is whether exposed children will be more likely to initiate substance use at earlier ages than non-exposed children and whether problem use or abuse will result, either due to prenatal sensitization, social modeling, stressful environments, or genetic influences. Three studies in this issue address this question. Warner et al. (2011) (this issue) collected hair samples and analyzed them for cocaine metabolites in 10½- and 12½-year-old children. Fourteen percent of the offspring were positive for current cocaine exposure, with half having a history of PCE. Drug availability in the home was the best predictor of hair positive status. They concluded that there was no support for a direct relationship between PCE and early adolescent cocaine use. By contrast, Frank et al. (2011) (this issue) found PCE was associated with a greater likelihood of initiation of any substance by age 16, and of marijuana and alcohol specifically. Exposure to violence between the ages of 8 and 16 was also a predictor of initiation of drug use. Delaney-Black et al. (2011) (this issue), using structural equation modeling, found that both PCE and caregiver current cocaine use independently predicted adolescent

cocaine use at 14 years. Consistent with Frank et al. (2011) (this issue), community violence exposure also predicted adolescent cocaine use. Although these studies differed in age at assessment and the measures used to define outcome, all document the significant role of environmental context in influencing adolescent substance use.

As some prior studies found that PCE-exposed infants are more difficult to care for, less responsive, and their caregivers who use drugs are less sensitive (LaGasse et al., 2003; Minnes et al., 2005), Eiden et al. (2011) (this issue) addressed whether maternal distress or infant reactivity at 7 months mediated or moderated the relationships between PCE and maternal sensitivity and infant responsivity at 13 months. Mothers who used cocaine during pregnancy who rated their infants as more reactive at 1 month were less sensitive to them at 13 months, compared to women who used cocaine and rated their infants as less reactive. Of interest, since later follow-up studies show that caregiver negativity predicted adolescent drug use (Delaney-Black et al., 2011) (this issue), the Eiden study highlights the important role of infancy and the proximal caregiving environment in affecting emotional and behavioral outcomes.

In addition to cocaine, several other drugs are addressed in this Issue. Marijuana is the most widely used illicit drug during pregnancy (National Institute on Drug Abuse, 1996). Cannabinoids may directly affect dopaminergic neurotransmission in the fetal brain, affecting multiple aspects of central nervous system development. The Pittsburgh group (Day et al., 2011, this issue) is one of only two large longitudinal cohorts addressing the outcomes of prenatal marijuana exposure (PME), the other being Fried's study in a Canadian middle-class sample. Fried and Smith (2001) postulated that PME results in selective, rather than global, deficits in components of executive functioning. In Day et al.'s (2011) study, 14-year-old children who were heavily exposed to marijuana prenatally were more likely to have self- or parent-reported delinquent behaviors. Interesting mediating analyses were also explored between PME, attention and depressive symptoms at age 10, and delinquency at 14 years.

Tobacco remains by far the most commonly used drug during pregnancy with 10 to 16% of women in the United States reporting smoking during pregnancy (Substance Abuse and Mental Health Services Administration, 2000). Exposure to nicotine, the primary psychoactive component of tobacco, is disruptive to prenatal brain development and related to poor growth outcomes and prematurity. Two studies in this issue address behavioral outcomes of prenatal tobacco exposure (PTE). More parent-reported delinquent, aggressive, and externalizing behaviors at 10 years were seen in the Pittsburgh group's cohort of PTE-children of adolescent mothers (Cornelius et al., 2011, this issue). PTE-associated deficits in selective attention and response inhibition were also observed. Similarly, in an adolescent sample, Wakschlag et al. (2011) (this issue) found that physical aggression and non-compliance with authority were predicted by PTE, but were moderated by paternal responsiveness, again demonstrating the modifying effect of the parenting environment. A third study validated a new statistical method of integrating data from multiple biologic and self-report indices of tobacco use, fuzzy clustering, to better reflect the complexity of PTE (Fang et al., 2011, this issue). Three groups were validated (non-, lighter-, and heavier-exposed) that predicted birth weight and neonatal irritable reactivity, known sequelae of PTE.

Finally, two studies present emerging data on the developmental effects of prenatal methamphetamine exposure. Methamphetamine (MA) and other stimulants, such as MDMA, have become increasingly used world-wide (Moore et al., 2009) and, like cocaine, are conceptualized as altering brain circuitry in multiple brain areas. In addition to direct neurotoxic mechanisms, vasoconstriction and maternal anorexia may also be implicated. MA-exposed cohorts in the United States and New Zealand were assessed in the neonatal

period at 5 days of age (LaGasse et al., 2011, this issue) and prenatal MA exposure was related to low tone, under-arousal, poorer quality of movement, and increased stress/abstinence in both cohorts. In a later follow-up of MA exposure in the United States IDEAL cohort, Smith et al. (2011) (this issue) did not find any effects of prenatal MA exposure on global motor or cognitive development at 1, 2, or 3 years of age. However, the study found modest effects of prenatal MA exposure on fine motor skills (poorer grasping) at 1 year that were no longer significant by 3 years.

This Special Issue highlights the methodologic and statistical advancements that have occurred in this field. All of the studies took into consideration the multiple factors that are correlated with prenatal substance use, a statement that could not have been made a decade ago. There is a range of factors represented in these studies, including racial composition (many samples are predominantly African American, but others have both White and African American participants); socioeconomic characteristics; urban versus rural samples; time of enrollment (during pregnancy or at delivery); domains of assessment; amount and characteristics of attrition; information about and differences in dose and timing of exposure; and the differing polydrug exposures accompanying the targeted exposure. As noted in the studies reported in this Issue, environmental context may vary widely, exerting additional influences that may moderate or minimize biologic effects. Foster or adoptive care has also been shown to be a factor. Depending on the outcome, the characteristics of the foster, adoptive, or kinship home may be protective (Lewis et al. (Lewis et al., 2011), this issue,) (Singer et al., 2004) or may increase risk (Frank et al., 2002).

This overview of this Special Issue suggests that while there are a number of apparent convergences to date, there are also a number of gaps to be addressed in research on drugs of abuse and child development. The majority of studies have focused on growth, cognitive, behavioral, and adolescent risk as outcomes and much more information is needed on health, hormonal, and reproductive outcomes. Further, there is little data on fathers' influence on outcomes in behavioral teratology studies, although, as seen in this issue (Wakschlag et al., 2011), paternal responsiveness was an important contributor to outcome in their study. Environmental context may also have a greater impact for male versus female offspring and needs to be further investigated. There is also a need for studies on a number of drugs not represented here, such as heroin, MDMA ("Ecstasy"), the benzodiazepines, and methadone. Although not addressed in this Issue, many of the current studies are using neuroimaging techniques that are beginning to illuminate the neurobiological underpinnings of the cognitive and behavioral differences delineated in these studies. Genetic studies will also be needed as some discrepancies in findings may be explained by genetic influences. As Dr. Khalsa stated, there is a need to continue to follow these cohorts into adulthood in order to examine the full range of outcomes that might be affected by prenatal exposures. As these cohorts progress into adulthood, continued research will enhance the potential to develop better prediction of those infants most at-risk for later negative effects and lead to earlier intervention with improved outcomes.

Acknowledgements

We wish to thank our colleagues who responded with overwhelming enthusiasm to the concept of this Special Issue by submitting their work for consideration, a clear reflection of the respect that we all have for Dr. Smeriglio. All submissions were subject to the usual *Neurotoxicology and Teratology* peer-review process. We also wish to thank the numerous individuals who served as reviewers. There were 27 submissions in response to the Special Issue invitation, 18 of which were selected for this issue. Selection was based first on the results of the peer-review, and then on additional considerations such as space and timing. We also wish to thank

Kristen Sonon, M.H.A., Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, for helping to summarize the findings of the submitted manuscripts.

References

- Bada HS, Bann C, Bauer CR, Shankaran S, Lester BM, LaGasse LL, et al. Preadolescent behavior problems after prenatal cocaine exposure: Relationship between teacher and caregiver ratings (Maternal Lifestyle Study). *Neurotoxicol Teratol* 2011;33:79–88.
- Bandstra ES, Vogel AL, Morrow CE, Xue L, Anthony JC. Severity of prenatal cocaine exposure and child language functioning through age seven years: a longitudinal latent growth curve analysis. *Subst Use Misuse* 2004;39:25–59.
- Bandstra ES, Morrow CE, Accornero VH, Mansoor E, Xue L, Anthony JC. Estimated effects of in utero cocaine exposure on language development through early adolescence. *Neurotoxicol Teratol* 2011;33:25–35.
- Betancourt LM, Yang W, Brodsky NL, Gallagher PR, Malmud EK, Giannetta JM, et al. Adolescents with and without gestational cocaine exposure: longitudinal analysis of inhibitory control, memory, and receptive language. *Neurotoxicol Teratol* 2011.
- Bridgett DJ, Mayes LC. Development of inhibitory control among prenatally cocaine exposed and non-cocaine exposed youths from late childhood to early adolescence: the effects of gender and risk and subsequent aggressive behavior. *Neurotoxicol Teratol* 2011;33:47–60.
- Carmody DP, Bennett DS, Lewis M. The effects of prenatal cocaine exposure and gender on inhibitory control and attention. *Neurotoxicol Teratol* 2011;33:61–8.
- Cornelius MD, DeGenna NM, Leech SL, Willford JA, Goldschmidt L, Day NL. Effects of prenatal cigarette smoke exposure on neurobehavioral outcomes in 10-year-old children of teenage mothers. *Neurotoxicol Teratol* 2011;33:137–44.
- Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. *Neurotoxicol Teratol* 2011;33:129–36.
- Delaney-Black V, Chiodo LM, Hannigan JH, Greenwald MK, Janisse J, Patterson G, et al. Prenatal and postnatal cocaine exposure predict teen cocaine use. *Neurotoxicol Teratol* 2011;33:110–9.
- Dow-Edwards D. Translational issues for prenatal cocaine studies and the role of environment. *Neurotoxicol Teratol* 2011;33:9–16.
- Eiden RD, Schuetz P, Coles CD. Maternal cocaine use and mother-infant interactions: Direct and moderated associations. *Neurotoxicol Teratol* 2011;33:120–8.
- Fang H, Johnson C, Christian S, Espy KA. A new look at quantifying tobacco exposure during pregnancy using fuzzy clustering. *Neurotoxicol Teratol* 2011;33:155–65.
- Frank DA, Jacobs RR, Beeghly M, Augustyn M, Bellinger D, Cabral H, et al. Level of prenatal cocaine exposure and scores on the Bayley Scales of Infant Development: modifying effects of caregiver, early intervention, and birth weight. *Pediatrics* 2002;100:1143–52.
- Frank DA, Rose-Jacobs R, Crooks D, Cabral HJ, Gerteis J, Hacker KA, et al. Adolescent initiation of licit and illicit substance use: Impact of intrauterine exposures and postnatal exposure to violence. *Neurotoxicol Teratol* 2011;33:100–9.
- Fried PA, Smith AM. A literature review of the consequences of prenatal marijuana exposure: an emerging theme of a deficiency in aspects of executive function. *Neurotoxicol Teratol* 2001;23:1–11.
- Jacobson JL, Jacobson S. Methodological issues in research on developmental exposure to neurotoxic agents. *Neurotoxicol Teratol* 2005;27:395–406.
- LaGasse LL, Messinger D, Lester BM, Seifer R, Tronick EZ, Bauer CR, et al. Prenatal drug exposure and maternal and infant feeding behavior. *Arch Dis Child Fetal Neonatal* 2003;F-391–9 Ed 88.
- LaGasse LL, Woules T, Newman E, Smith AM, Shah RZ, Derauf C, et al. Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. *Neurotoxicol Teratol* 2011;33:166–75.
- Lester BM, Padbury JF. Third pathophysiology of prenatal cocaine exposure. *Dev Neurosci* 2009;31:23–35.
- Lewis BA, Kirchner HL, Short EJ, Minnes S, Weishampel P, Satayathum S, et al. Prenatal cocaine and tobacco effects on children's language trajectories. *Pediatrics* 2007;120:e78–85.
- Lewis BA, Minnes S, Short E, Weishampel P, Satayathum S, Min MO, et al. The effects of prenatal cocaine on language development at 10 years of age. *Neurotoxicol Teratol* 2011;33:17–24.
- Mayes LC. A behavioral teratogenic model of the impact of prenatal cocaine exposure on arousal regulatory systems. *Neurotoxicol Teratol* 2002;24:385–95.
- Minnes S, Singer LT, Arendt R, Satayathum S. Effects of cocaine/polydrug use on maternal-infant feeding interactions over the first year of life. *J Dev Beh Pediatr* 2005;26:194–200.
- Moore DG, Turner JJT, Parrott AC, Goodwin JE, Fulton SE, Min MO, et al. During pregnancy, recreational drug-using women stop taking ecstasy (MDMA) and reduce alcohol consumption but continue to smoke tobacco and cannabis: initial findings from the DAISY study. *J Psychopharmacol* 2009;24:1403–10.
- National Institute on Drug Abuse. National Pregnancy and Health Survey: drug use among women delivering livebirths: 1992. Rockville, MD: NIDA; 1996.
- Richardson GA, Goldschmidt L, Leech S, Willford J. Prenatal cocaine exposure: Effects on mother-and teacher-rated behavior problems and growth in school-age children. *Neurotoxicol Teratol* 2011;33:69–77.
- Singer LT, Minnes S, Short E, Arendt R, Farkas K, Lewis BA, et al. Cognitive outcomes of preschool children with prenatal cocaine exposure. *JAMA* 2004;291:2448–56.
- Smith LM, LaGasse LL, Derauf C, Newman E, Shah RZ, Haning W, et al. Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. *Neurotoxicol Teratol* 2011;33:176–84.

Substance Abuse and Mental Health Services Administration. Summary of findings from the 1999 National Household Survey on Drug Abuse. Rockville, MD: SAMHSA; 2000.

Wakschlag L, Henry DB, Blair JR, Burns J, Pickett KE, Dukic V. Unpacking the association: Individual differences in the relation of prenatal exposure to cigarettes and disruptive behavior phenotypes. *Neurotoxicol Teratol* 2011;33:145–54.

Warner TD, Behnke M, Eyler DF, Szabo NJ. Early adolescent cocaine use as determined by hair analysis in a prenatal cocaine exposure cohort. *Neurotoxicol Teratol* 2011;33:88–99.

E-mail address: Lynn.Singer@case.edu.

Gale A. Richardson

University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, United States

Lynn T. Singer

Case Western Reserve University, School of Medicine, Adelbert Hall, 216, Cleveland, Ohio 44106, United States

Corresponding author. Lynn Singer Case Western Reserve University, Adelbert Hall, 216, 10900 Euclid Avenue, Cleveland, Ohio 44106, United States. Tel.: +1 216 368 4389; fax: +1 216 368 4325.