LATENT GROWTH CURVE ANALYSES OF THE DEVELOPMENT OF EXECUTIVE FUNCTIONS IN A PROSPECTIVE, LONGITUDINAL COHORT OF CHILDREN WITH PRENATAL COCAINE EXPOSURE

By

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To my ever supportive and loving parents
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LATENT GROWTH CURVE ANALYSES OF THE DEVELOPMENT OF EXECUTIVE FUNCTIONS IN A PROSPECTIVE, LONGITUDINAL COHORT OF CHILDREN WITH PRENATAL COCAINE EXPOSURE

By
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Animal studies demonstrate prenatal exposure to cocaine causes disruption of the neurotrophic roles of monoaminergic transmitters during early development, which, in turn, affects the cortical neuronal development of specific brain regions, including prefrontal cortex. In humans, this brain area is implicated in executive function (EF), a set of cognitive processes that are posited to subserve goal-directed behavior. Significant differences in EF between children with prenatal cocaine exposure (PCE) and well-matched comparison groups have not been consistently found. Within a longitudinal context, there have been no studies investigating the potential effect of PCE on the developmental trajectory of EF.

Participants were children of pregnant women who were prospectively enrolled at birth in a longitudinal study of the developmental effects of PCE. At study enrollment, which generally occurred during pregnancy, cocaine-using mothers were matched to non-cocaine using mothers on race, socioeconomic status, parity and location of
prenatal care. Both groups were predominately poor and African American and did not differ by child sex. At birth, PCE group had higher levels of other prenatal drug exposures (alcohol, tobacco, and marijuana), shorter gestational ages, and smaller head circumferences. Measures of EF (inhibition, working memory, and shifting) were obtained by blinded examiners when the children were ages 7, 10½, and 12½ years. There were no group differences between the PCE children ($n = 120$) and non-exposed children ($n = 116$) with regard to cross-sectional performance on measures of EF at any time point.

Univariate latent growth models were used to investigate the effect of amount of PCE as well as pre- and post-natal characteristics of the child and the environment (i.e., birth head circumference, gender, quality of the caregiving environment) on the developmental trajectory of inhibition, working memory, and shifting. Results indicated no direct effect of PCE on the initial performance or the development of EF over time. Smaller birth head circumference negatively predicted the inhibitory and working memory skills at age 7 as well as worse development of inhibitory skills over time. Additionally, a better quality home environment positively predicted working memory ability at age 7 years, though the home environment did not predict the developmental trajectory of any EF over time.
CHAPTER 1
INTRODUCTION

Background

During the 1980s and into the early 1990s, the use of cocaine among pregnant women increased as crack cocaine become more affordable and accessible than previously available forms of cocaine. In response to this increase, the effects of cocaine on human development have received considerable investigation. Animal and prospective longitudinal human studies were undertaken in order to explore the impact of prenatal cocaine exposure (PCE) on the developing fetus. Preclinical findings implicated altered cortical neuronal development of the mesolimbic and prefrontal cortices, brain regions involved in executive functions (EF).

To date, however, studies of cohorts of now school-school age children with PCE have revealed no consistent neurocognitive profile that can be solely attributable to cocaine, and it is likely that confounding factors related to PCE, such as poverty, significantly contribute to the cognitive outcome of children with PCE. The current study sought to investigate the effect of the extent of PCE on the development of EF, specifically, inhibition, working memory, and shifting, in a non-urban sample of children whose mother were enrolled prospectively prior to or at birth. Before exploring these relationships, it is important to understand the construct parameters and development of these subdomains of executive functions.

Inhibition, Working Memory and Shifting in an EF Framework

The construct of executive function (EF) is an umbrella term that is generally associated with various cognitive processes that subserve goal-directed behavior (Miller
There are several models of EF, ranging from those with supported empirically constructs (Miyake et al., 2000; Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003) to those identified using clinical judgment (Denckla, 1996). Three commonly reported subdomains of EF include inhibitory control, working memory, and shifting (Miyake et al., 2000; Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003; Welsh et al., 1991) and will be the focus of the present study. These three functions are also likely to be implicated in the performance of more complex executive tasks and are thought to underlie more complex behavior (Miyake et al., 2000).

Inhibition, more formally referred to as inhibitory control, is a subdomain in many models of EF in both children and adults (Barkley, 1994; 1997; Welsh et al., 1991; Levin et al., 1996; Nigg, 2000; Pennington, 1994). Behavioral inhibition is the core feature of Barkley’s theoretical model of EF and is thought to aid in the development of other executive functions, including working memory (Barkley, 1994; 1997). In Barkley’s model (1994, 1997) inhibition refers to 1) the ability to inhibit the initial prepotent response to a stimulus, 2) stopping an ongoing response or pattern of responses that allows a delay in the decision to response or continue stopping and 3) protecting the delay period and the self-directed responses from interference. Inhibition directly affects subsequent EF processes, including verbal and nonverbal working memory; internalization of self-directed speech; self-regulation of affect, motivation, and arousal; and reconstitution, or the analysis and synthesis of information.

Barkley’s theoretical model is similar to the formulation of EF proposed by Roberts and Pennington (1996). However, the latter model suggests that the interaction between working memory and inhibition is necessary and sufficient to characterize the
cognitive and behavioral development within the executive domain. Working memory is a limited capacity system that provides temporary storage and processing of sensory information for use in guiding behavior (Baddeley, 2007). Working memory is responsible for our ability to temporarily hold, rehearse, and manipulate both verbal and visual information.

Baddeley’s (2007) working memory model is perhaps the most widely empirically supported model, and describes three components of working memory: a domain-general central executive and two subsystems for the temporary storage and rehearsal of modality-specific information. The central executive is an attentional controller responsible for the coordination of the subsidiary systems. Its primary functions are focusing attention, dividing attention among tasks, and providing interference between long-term memory and working memory. The phonological subsystem (phonological loop) is responsible for the temporary storage and rehearsal of verbal material. The visuospatial subsystem (visuospatial sketchpad) provides this function for nonverbal visual and spatial stimuli (Baddeley, 2007).

Roberts and Pennington (1996) hypothesize that working memory and inhibition use the same limited-capacity pool of resources. Therefore, a task that involves active inhibition of prepotent responses requires higher and more consistent working memory activation to avoid committing an error. Both Barkley and Roberts and Pennington argue that there is no distinction between the processes underlying normal and abnormal executive functioning. They posit these processes can be conceptualized on a continuum, with success or failure depending on the interactions between inhibition and working memory. It would follow that the development of executive functioning is
dependent on the development of the two fundamental cognitive processes: inhibition and working memory (Robert and Pennington, 1996).

The third subdomain, shifting, has been consistently demonstrated to represent separate yet related factor in analytic models of EF using exploratory and confirmatory factor models in adults (Miyake et al., 2000) and in children (Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003). Set-shifting has also been referred to as “attention switching” or “task switching,” and henceforth will be referred to as “shifting” for short. Shifting refers to the ability to switch back and forth between mental tasks, operations, or mental sets (Monsell, 1996). The most common explanation of this function is that the shifting process involves the disengagement of attention and/or behavior from an irrelevant task set and the subsequent engagement of a relevant task set (Miyake, 2000).

**Inhibition, Working Memory, and Shifting in a Neuroanatomical Framework**

Substantial evidence suggests that EF in both adults and children are broadly mediated by prefrontal cortical (PFC) regions (for a review, see Stuss & Levine, 2002). Inhibition is often associated with right inferior prefrontal cortex, right dorsolateral prefrontal cortex, and bilateral ventral prefrontal cortex (Rubia, Smith, Brammer, & Taylor, 2003; Bunge et al., 2002; Casey et al., 2001; Durston et al., 2002). In addition to the involvement of these brain regions, several neuroimaging studies using inhibitory paradigms implicate mesial prefrontal cortex and anterior cingulate cortex (MacDonald et al., 2000; Gehring et al., 1993). These regions are thought to be responsible for error detection and performance monitoring (Rubia, Smith, Brammer, & Taylor, 2003).

Neuroimaging studies provide evidence in support of PFC involvement in working memory performance, with additional differentiated brain involvement for the maintenance of domain-specific (i.e., verbal or visuospatial) information in working
memory (Narayanan et al, 2005; Smith & Jonides, 1999). Neuroimaging findings have been consistent with Baddeley’s model, reliably identifying distinct patterns of neural activation associated with the type of information (e.g., verbal or spatial) held in working memory (for a review, see Smith and Jonides, 1998). For the present study, verbal working memory will be the primary focus. The phonological loop is served by a neural circuit in the left hemisphere spanning inferior parietal areas (serving the phonological storage) and more anterior frontal areas, specifically ventrolateral PFC (associated with rehearsal) (Smith & Jones, 1997).

Neuroimaging of both children and adults during tasks requiring shifting (e.g., Trail Making Test Part B, Wisconsin Cart Sorting Task) has consistently demonstrated frontal activation (Moll et al., 2002, Zakzani, Mraz, Graham, 2005). Specifically, the most predominant region of brain activity revealed by fMRI includes left-sided frontal activation including dorsolateral PFC and supplementary motor area/cingulate sulcus (Moll et al., 2002, Weber et al., 2003). These findings are consistent with anatomic and functional neuroimaging data that implicate the dorsolateral and medial prefrontal cortices in tasks requiring cognitive flexibility and inhibition, including go-no go tasks and the Stroop task (Weintraub, 2000).

Development of Inhibition, Working Memory, and Shifting During Childhood

The developmental trajectory of executive functions is related to frontal lobe maturation (Welsh & Pennington, 1988; Diamond, 2002). The frontal lobes are the last brain region to develop. Morphological maturation of the PFC is reached around puberty, but quantitative and qualitative changes may continue into later years (Stuss, 1992). Pathways of the prefrontal lobes are among the last of all brain areas to myelinate fully, continuing up until the age of 20 (Gogtay et al., 2004; Giedd et al., 1999;
The acquisition of abilities mediated by the frontal lobes progresses throughout childhood and into adolescence, serving to condition behavior for the rest of the brain (Romine & Reynolds, 2005; Brocki & Bohlin, 2004; Huizinga et al., 2006). Changes in the structure and function of the PFC occur during the early childhood period (Espy, Kaufmann, Glisky, & McDiamond, 2001) and include the pruning of synaptic connections and the maturation of subcortical prefrontal myelination (Kinney, Brody, Kloman, & Giles, 1988).

The beginnings of self-control and the capacity to regulate and direct goal-oriented behavior in response to the environment can be observed early in development (Welsh & Pennington, 1988). By the age of 10 years, the ability to inhibit attention to irrelevant stimuli and inhibit prepotent responses is observed (Passler, Isaac, & Hynd, 1985; Kenberg, Korkman, & Lahti Nuuttila, 2001) with adult levels of performance reached in late childhood, around the age of 12 (Bunge et al., 2002, Huizinga et al., 2006). Similarly, working memory improves over the course of childhood (Luna et al., 2004; Beveridge, Jarrold, & Pettit, 2002; Gathercole, Pickering, Ambridge, & Wearing, 2004). With regard to the phonological loop, early development before the age of 7 years is mostly related to the increase in memory capacity and the increased rate of rehearsal that enables the child to maintain increasing amounts of verbal material in the phonological store (Humle et al., 1984). Hale, Bronik, and Fry (1997) examined the development of both verbal and visuospatial working memory in two different age groups of children (8-year-olds and 10-year-olds) and one group of adolescents (19-year-olds). Findings suggest a linear relation between age and working memory span,
with the 19-year-olds performing significantly better than the 10-year-olds, who performed significantly better than the 8-year-olds.

Similarly, shifting abilities also improve with frontal lobe development, with adult performance being attained around the age of 12 (Cepeda, Kramer, & Gonzalez de Sather, 2001; Kray, Eber, & Lindenberger, 2004). Studies generally show that the cost of shifting (difference between reaction time and accuracy) between tasks decreases with age (Huizinga, Dolan, and van der Molen, 2006; Cepeda, Kramer, & Gonzalez de Sather, 2001). Age related change in the ability to shift task sets can be interpreted as reflecting the development of executive control (Zelazo, Craik, & Booth, 2004).

To summarize, as children develop, it is generally accepted that their ability to control their thoughts and actions increases (for a review see: Diamond et al., 2002). The development of inhibition, working memory, and shifting are associated with this change, and can be attributed to the protracted and age-related development of the prefrontal cortex and the increasing connectivity to other regions of the brain. With typically developing children, adult levels of performance on tasks of executive functions are reached between the ages of 12 and 21 years.

**Prenatal Cocaine Exposure and Executive Functions**

**Direct Teratogenic Effects on Brain Regions Associated with Inhibition, Working Memory, and Shifting**

The term teratogenic broadly refers to substances or agents that can interfere with normal embryonic development. Within a developmental context, the most frequent manifestation of teratogenic injury to the central nervous system results in behavioral or functional abnormalities that may not be detectable at birth (Vorhees, 1989; Fried, 2002). Cocaine easily crosses the placenta and the blood brain barrier and may directly
or indirectly affect the developing fetus. Preclinical studies of fetal cocaine exposure have demonstrated teratogenic effects of cocaine that potentially extend beyond the neonatal period and infancy (Na & Lidow, 2003; Lidow, 1995; Lidow & Song, 2001). The teratogenic effects of PCE may impact all aspects of the nervous system development, including neurogenesis, neuronal differentiation, arborization, synaptogenesis, and glial migration (Mayes, 2002). In general, findings from preclinical models using several species of animals suggest prenatal cocaine exposure (PCE) causes abnormalities in the neocortical cytoarchitecture of offspring, including: unsuitable positioning of neocortical neurons, loss of typical cortical lamination, reductions in overall neocortical volume, and reduced density of neurons (Lidow, 1995; Lidow & Song, 2001; Lidow et al., 2001; Kosofsky et al., 1994).

Functional alterations in monoaminergically regulated arousal systems is a primary candidate for the mechanism proposed to explain the effect of PCE on the developing neural systems (Mayes, 2002). For instance, PCE causes changes in neural growth factors and alterations of immediate gene expression (Mayes, 2002). More specifically, PCE is likely to affect regulatory control through its disruption of the neurotrophic roles of monoaminergic transmitters during early brain development, which, in turn, affects the cortical neuronal development of specific brain regions, including the mesolimbic and prefrontal cortices (Mayes, 2001; Harbey, 2004).

For instance, a preclinical model in rabbits suggests that PCE during the gestational period of corticogenesis is necessary and sufficient to produce long-term effects on the organization of excitatory and inhibitory neurons in PFC and can cause increased GABA levels in anterior cingulate cortex and other dopamine-rich areas.
(Harvey, 2004; Romano & Harvey, 1996; Stanwood, Washington, Levitt, 2001). As discussed in the proceeding section, these regions have been shown to provide the neuronal substrate in humans for inhibiting prepotent responses, shifting attention, manipulating information in working memory, and completing complex tasks requiring planning (Bendersky et al., 2003; Durston et al., 2003).

The neurobehavioral sequelae of cocaine within the animal literature are congruent with the structural and neurochemical alterations caused by in utero cocaine exposure. For instance, reduction in cingulate activity is associated with an impaired ability to discriminate among salient and relevant stimuli in rats. Additional behavioral outcomes in animals demonstrate effects of learning abilities, such as impairments in classical conditioning, diminished proximal cue learning, increased response perseveration, and impaired habituation (Mayes, 2002; Kosofsky & Wilkins, 1998; Harvey, 2004).

With regard to neurobehavioral outcomes in school-age children with PCE, no overall syndrome has been formulated, in part due to methodological problems (Frank, Augustyn, Pell, Zuckerman, 1998; Lester, LaGasse, & Seifer, 1998). In addition, the widely accepted conceptualization of a interactive and transactional model of development argues that the neurobehavioral outcomes are affected not only by in utero drug exposure, but also by postnatal environmental factors and genetics. Some investigations of infants have demonstrated a neurobehavioral profile of PCE implicating the arousal and regulation system. Within this age range, the effects of PCE on the developing individual include newborn irritability and lability of state, decreased
autonomic and behavioral regulation, and poorer alertness and orientation compared to non-exposed individuals (Eyler & Behnke, 1999).

Studies of PCE in children up to four years of age have yielded inconsistent results. In a systematic review by Frank, Augustyn, Knight, Pell, & Zuckerman (2001), it was reported that “there is no evidence that prenatal cocaine exposure is associated with developmental effects that are different in severity, scope, or kind from the sequelae of multiple risk factors,” (Pages 1-2). This review asserts that the deleterious cognitive outcomes once thought to be solely caused by PCE are, in fact, correlated with other factors, such as prenatal exposure to tobacco and alcohol as well as the quality of child’s home environment. This review revealed little impact of PCE on children’s scores on nationally normed tests of cognitive development. For example, studies of children at age 4 (Singer et al., 2004), age 6 (Richardson, Conroy, & Day, 1999), and age 7 (Morrow et al., 2006) revealed that, after controlling for confounds, PCE was not related to lower full-scale IQ score or summary verbal or performance IQ scores.

Several prospective, longitudinal studies have found that children prenatally exposed to cocaine demonstrate more difficulty with inhibitory control, though results are not consistent across measures or across studies. Performance on computerized continuous performance tasks has revealed impairments in inhibition as assessed by commission error scores (Mayes & Grillon, 1998; Eghbalieh et al., 2000). Bendersky et al. (2003) found that cocaine-exposed children performed worse than unexposed children on the Contrary Tapping task, a measure of inhibitory motor control. Studies using the Stroop task, a common task used to assess the ability to inhibit a prepotent
response have yielded inconsistent results. Using a subsample from a cohort of children followed by the Yale Child Study Center, Mayes et al. (2005) used event-related potentials in a standard Stroop paradigm with a total of 29 exposed and non-exposed children. Findings indicate that PCE may inhibit the specialization of brain region involvement during cognitive processing, and that successful task completion requires more time and more diverse cortical involvement.

Based on a subsample of participants from the cohort from which the present study drew participants, Warner et al. (2006) found a trend towards significant group differences between exposed and non-exposed children with cocaine-exposed children performing more poorly on the Stroop Task. Further, the Trail Making Test, Part B (TMT B), a task assessing shifting ability, has yielded significant group differences within this cohort when compared to non-exposed children with a mean age of 10 years (Warner et al., 2006). Using a novel computer maze-learning task, Mayes et al. (2007) found that a subsample of children who were prenatally exposed to cocaine demonstrated increased reaction time and increased error rates across learning trials, suggesting that despite repeated trials they had difficulty inhibiting responses that they have previously learned to be incorrect. This could represent difficulties with inhibition, as well as with learning across trials. Additionally, the cocaine-exposed group demonstrated increased rule-break and perseverative errors (Mayes et al., 2007), a pattern of performance that is further suggestive of difficulties with shifting (van der Ven, 1998).

More recently, Rose-Jabobs et al. (2009) investigated the effect of PCE on executive functioning in middle school children ages 9½ to 11 years using the Stroop Color-Word Test (Stroop, 1943) and Rey Osterrieth Complex Figure Test (Osterrieth,
1994; translated by Corwin Bylsma, 1993). In covariate-controlled regressions with children who were and were not exposed to cocaine, PCE was not significantly associated with Stroop Interference or Rey Osterrieth Organization scores. However, post-hoc tests comparing the heavier exposed group to the combined non-exposed to lighter exposed group, children with more PCE had significantly poorer Stroop Interference scores, but performed similarly on the Rey Osterrieth. These results suggest that the group of children with heavier PCE may have mild impairment in the ability to inhibit prepotent verbal responses compared to those in a lighter or non-exposed group of school-aged children.

In a study of the entire cohort from which participants for the current were drawn, Eyler et al. (2008) used structural equation modeling at ages 5 and 7 to investigate the complex relationships between frequency of cocaine exposure, other prenatal drug exposures, birth characteristics, quality of the environment, and a latent construct of EF as the outcome variable of interest. At both age five and seven, weeks of PCE had an indirect effect on EF task performance through cocaine’s significant negative effect on adjusted head circumference at birth. Adjusted head circumference at birth has consistently been a significant predictor of cognitive outcomes in this cohort, and may be suggestive of the in utero effects of PCE on brain development.

Although PCE and comparison group were equivalent in terms of head circumference by 6 months of age, others have found significant effects on cognitive outcome related to smaller birth head circumference (Frisk, Amsel, & Whyte, 2002), which has been found to be negatively affected by PCE in humans (Singer, Salvator,
Arendt, Farkas & Kliegman, 2002; Bauer et al., 2005; Behnke et al., 2005; Eyler et al., 1998, etc.) and nonhuman primate studies (Lidow, 2003).

**Environmental Confounds Associated with Cocaine Users**

There are several environmental factors that confound the relationship between potential direct effects of PCE and EF. Many contemporary teratogenic models include possibilities for independent and transactional effects of a toxin in relation to genetics and the rearing environment. Given the inconsistencies in findings across studies of PCE and EF, it is imperative to investigate the other contextual factors known to affect child development, such as the quality of the caregiving environment. Many children with PCE come from low socioeconomic status (SES) households, including those in the current study and in the several large, federally-funded longitudinal research studies of PCE and cognitive development. It is well-documented that children who grow up in low SES environments are less likely to receive cognitive stimulation, have fewer toys and books, and have less exposure to cultural and developmental activities (Farah, Noble, & Hurt, 2005). Powerful effects of environmental stimulation on brain development have been documented, from animal studies of impoverished environments (Cui et al., 2007), to more recent studies using structured assessment methods of a child’s home environment (e.g., Home Observation for Measurement of the Environment (HOME); Caldwell & Bradley, 1984).

The quality of the caregiving environment has been found to be a significant predictor of a range of cognitive and developmental outcomes in both children that have and have not been prenatally exposed to cocaine (Singer et al., 2004; Frank et al., 2001; Behnke et al., 2006; Morrow et al., 2006; Eyler et al., 2008). Specifically, the quality of the home environment of children with PCE has been shown to have
significant direct and indirect effect on preschoolers’ psychomotor development (Behnke et al., 2006) and global intellectual ability (Morrow et al., 2006; Singer et al., 2004). In fact, when preschoolers who were prenatally exposed to cocaine and had been placed in non-relative foster or adoptive care with more stimulating environments as assessed by the HOME, their overall performance on a measure of intellectual functioning appeared similar to non-exposed children and higher than exposed children who remained in biological care (Singer et al., 2004).

In addition to inadequately stimulating home environments, children with PCE from low SES households generally have less exposure to positively reinforcing experiences and much of their exposure could be considered stressful. Animal research has consistently established the powerful effects of both environmental impoverishment and stress on the developing brain, both pre- and postnatally (Gunnar, 1998). In this manner, the effects of infant and childhood stress levels associated with SES may be associated with brain development. Further, lack of access to adequate health care, insufficient nutrition, and exposure to lead, all factors associated with poverty, have been related to poor cognitive development (Center for Children and Poverty, 1997). Similar to the majority of other federally-funded longitudinal studies of PCE, most of the participants in the present study were African American and from impoverished and underserved families. These factors likely further limited their access to prenatal and general health care through pregnancy and into their child’s development. Generally, cocaine users also use other drugs with known teratogenic effects on development, including marijuana, tobacco, and alcohol. It is important to analytically control for these
confounds in order to more accurately assess the potential negative outcomes attributed to PCE.

**Study Purpose and Hypotheses**

The effects of PCE on development have been well-documented in animal models and implicate the monoaminergic system and the prefrontal cortex, the brain region primarily involved with EF. However, these findings have not been consistently demonstrated in investigations of children, as cross-sectional studies have not always demonstrated group differences or a dose-response effect of the amount of exposure on outcome. The purpose of the current study is to investigate the developmental trajectory utilizing latent growth modeling of three frequently postulated executive functions (i.e., inhibition, working memory, and shifting) in a sample of children prenatally exposed to cocaine and other drugs. This methodology will be used to determine whether performance on measures of executive functions in childhood across time is related to PCE, as well as the child’s pre- and postnatal environment and characteristics of the child.

It is hypothesized that 1) inhibition, working memory, and shifting skills will increase (i.e., improve) as children mature as assessed by three measures of EF and 2) that characteristics of the child and the pre- and postnatal environment will impact the development of EF. Specifically, it is hypothesized that a) PCE will negatively impact the development of inhibition, working memory, and shifting such that more prenatal exposure will be more detrimental; b) adjusted birth head circumference will negatively impact the development of EF such that smaller head circumference will be more detrimental; c) child sex will impact the development of inhibition, working memory, and shifting such that being of male gender will be more detrimental; and d) the quality of
the home environment will impact the development of EF such that more a poor home environment will be more detrimental.
CHAPTER 2
METHODS

Participants

The study draws from data collected as part of a larger project funded by the National Institute on Drug Abuse (DA 05854). The primary project, entitled Project C.A.R.E (Cocaine Abuse in the Rural Environment), used a prospective, longitudinal study design to examine the effects of prenatal cocaine exposure on a range of developmental outcomes. The project is based out of the University of Florida’s Department of Pediatrics and the study’s principal investigators are Marylou Behnke, M.D. and Fonda Davis Eyler, Ph.D. In the original study, 154 cocaine-using pregnant women and 154 non-using matched controls were enrolled prospectively during prenatal visits at two public health prenatal clinics whose patients were scheduled to deliver at Shands Hospital at the University of Florida at the hospital’s high risk clinic, and for those without prenatal care, in the postpartum ward after they delivered.

Detailed information regarding recruitment and enrollment of participants is provided in the Procedures section. There has been a relatively low attrition rate (approximately 15%) since initiation of the longitudinal study. Children who participated in follow-up assessments at ages 7, 10 ½, and 12 ½, and who had at least two time points of completed data for each target measure were included in the present study.

Of the 154 users, 70% reported primarily using crack, 16% primarily used powder cocaine, and 14% denied any cocaine use but had a positive urine screen. Users and non-users were matched on race, socioeconomic status (SES) category (Hollingshead, 1995), and parity. Overall, the project sample was predominately African American (n = 250), within the lowest Hollingshead SES category, and had more than one child. As a
group, cocaine-using mothers used more tobacco, alcohol, and marijuana compared to their matched controls.

Previous analyses of the original project sample have yielded a variety of findings regarding developmental outcomes (Behnke, Eyler, Conlon, Wobie, Woods, & Cumming, 1998; Behnke, Eyler, Woods, Wobie, & Conlon, 1997; Eyler, Behnke, Conlon, Woods & Wobie, 1998a, 1998b, Eyler, Behnke, Garvan, Woods, Wobie, & Conlon, 2001; Woods, Behnke, Eyler, Conlon, & Wobie, 1995). There were no significant differences between groups in perinatal deaths, but prenatal cocaine exposed neonates were generally born at an earlier gestational age, had lower birthweights, and had smaller head circumference even when head circumferences was adjusted for gestational age. After controlling for concurrent use of tobacco, alcohol, and marijuana, there were no longer cocaine-related differences on gestational age or birth weight. However, the mean daily amount of reported cocaine use was significantly related to birth head circumference and to infant regulation of behavioral state, which is generally hypothesized to be an infant precursor to the development of executive functions (Diamond & Aspinwall, 2003). More detailed descriptions of these relationships and of other birth outcome measures within this cohort have been previously published (Eyler, Behnke, Conlon, Woods & Wobie, 1998a, 1998b; Eyler, Behnke, Garvan, Woods, Wobie, & Conlon, 2001).

**Measures**

Three cognitive measures representing executive functions (collected at ages 7, 10½, and 12½) and four sets of predictor variables (e.g., prenatal drug exposure variables, adjusted birth head circumference, child sex, and a cumulative score of the caregiving environment) were included to investigate the development of inhibition,
working memory, and shifting. The predictor variables are considered to be time invariant variables as each variable is represented by a single score for each child. The cognitive measures representing executive functions are considered time variant variables, as they were collected at three separate time points throughout development and each individual will have three scores for each measure.

**Time Invariant Predictor Variables**

**Prenatal drug exposure**

Maternal use of cocaine, alcohol, tobacco, and marijuana was obtained using a drug history interview adapted from that of Day, Wagener, and Taylor (1985). More detailed information about the drug history interview procedure can be found in the Procedures section. Prenatal cocaine exposure was quantified as a ratio of the number of weeks of reported cocaine use divided by the total number of weeks of each gestation plus 3 months prior to gestation. Prenatal alcohol exposure was quantified using the average number of ounces of absolute alcohol consumed per day throughout pregnancy. The average number of tobacco cigarettes smoked per day and the average number of marijuana joints smoked per day throughout the pregnancy were used to measure prenatal tobacco and prenatal marijuana exposure, respectively. These quantitative measures of exposure to cigarettes, alcohol and marijuana were used to create a latent factor that was allowed to covary with PCE.

**Adjusted birth head circumference**

Head circumference at birth was measured by pediatric nurse practitioners masked to drug exposure of the newborns. Including both gestational age and head circumference in the same model would likely result in the statistical problem of multicollinearity due to their shared variance, and adjustment was made that maintained
the distributional form of the head circumference variables while controlling for the effect of gestational age on infant size. Infants born at 40 weeks or later were assigned the head circumference measured just after birth; however, if an infant was born before term, the infant’s head circumference at full term was projected to the anticipated circumference at 40 weeks from their positions on the Centers for Disease Control’s normative newborn size/growth charts.

**Child sex**

Sex differences on several domains of executive functions have been found (Brocki & Bohlin, 2004). Further, within this cohort, child sex has been found to independently predict executive functioning at age 7 with females performing better on tasks (Eyler et al., 2008). Therefore, child sex was also used as a predictor of the development of inhibition, working memory, and shifting.

**Quality of the caregiving environment**

The quality of the home environment is represented by a cumulative score for each child from data collected at ages 5, 7, 10 ½, and 12 ½ years using the Home Observation for Measurement of the Environment (HOME, Bradley & Caldwell, 1981). Across these specified ages, several age-appropriate versions of the HOME were used to measure the stimulation potential of a child’s developmental environment. The total score from each version at the identified time points for each child was used to represent a cumulative score representing the quality of the environment.

All versions of the HOME have been found to have sound psychometric properties (Bradley & Caldwell, 1981; Bradly, Mundfrom et al., 1994). Test-retest reliability, as measured by coefficient alpha, is above .90 for the total scores and is generally higher for the longer subscales. Interobserver agreement is reported at 90% or higher for all
versions. Concurrent and predictive validity studies have shown that the HOME is significantly correlated with IQ, sometimes as high as $r = .58$. As expected, HOME scores have low to modest correlations with a wide variety of demographic variables including race, family structure, and maternal age. However, two studies have shown that no single demographic factor accounts for a significant amount of the variance in HOME scores and that all the demographic factors taken together account for only about 50% of the variance.

Three forms of the HOME were used to create a cumulative score: the Early Childhood version (EC; ages 3 to 6 years), the Middle Childhood version (MC; ages 6 to 10 years), and the Early Adolescent version (EA; ages 10 to 14 years). The EC HOME contains 55 items clustered into 8 subscales: 1) Learning Materials, 2) Language Stimulation, 3) Physical Environment, 4) Parental Responsivity, 5) Learning Stimulation, 6) Modeling of Social Maturity, 7) Variety in Experience, and 8) Acceptance of Child. The MC HOME contains 59 items clustered into eight subscales: 1) Parental Responsivity, 2) Physical Environment, 3) Learning Materials, 4) Active Stimulation, 5) Encouraging Maturity, 6) Emotional Climate, 7) Parental Involvement, and 8) Family Participation. Finally, the EA HOME contains 60 items clustered into seven subscales: 1) Physical Environment, 2) Learning Materials, 3) Modeling, 4) Fostering Self-Sufficiency, 5) Regulatory Activities, 6) Variety of Experiences, and 7) Acceptance and Responsivity.

**Time-Variant Measures**

Three measures of EF were assessed at ages 7, 10 ½, and 12 ½ years, and represent the time-variant variables within the present study. Aspects of inhibition were assessed using the Integrated Visual and Auditory Continuous Performance Test (IVA
Aspects of working memory were assessed using the raw total score from the Digit Span subtest of the Wechsler Intelligence Scale for Children, 3rd or 4th Edition. Finally, shifting was assessed using a ratio score from the Trail Making Test (Part B/Part A times to completion).

**Inhibition**

Inhibition of prepotent responses was assessed using the visual prudence score from the Integrated Visual and Auditory Continuous Performance Test (IVA CPT; Sandford & Turner, 1994; Sandford, 1995). The IVA CPT is a 13-minute test of attention for children and adults that measures responses to 500 intermixed visual and auditory stimuli spaced 1.5 seconds apart. The task requires responding by clicking a computer mouse when the stimulus is a visual or auditory 1 and inhibiting responses when the stimulus is a visual or auditory 2. Prudence is a measure of impulsivity and response inhibition as evidenced by three different types of errors of commission.

The stimuli from the IVA CPT are presented in pseudo-random order in five sets of 100 trials with each set consisting of two 50-trial blocks. The blocks are counterbalanced between visual and auditory stimuli and between frequent and infrequent presentation of target stimuli. The IVA CPT yields six composite quotient scores for two factors (Response Control and Attention), 22 raw scores which comprise a Fine Motor Regulation scale, three Attribute scales, and six Validity scales (Sandford, 1995).

Information about the IVA CPT suggests that it has adequate reliability and validity (Sandford, 1995). The IVA CPT’s test-retest reliability was studied using 70 normal volunteers (43 females, 27 males) between 5 and 70 years of age (mean age = 21.8 years). Correlation for a one- to four-week interval between test administrations for
the Visual Attention Quotients was very strong at .75. Validity studies on the IVA CPT were conducted in a small sample of 26 children (ages 7 to 12) diagnosed by a physician or psychological as having ADHD and a comparison group of 31 children with no known learning, emotional, neurological, or ADHD related problems. Results of this comparison indicated that IVA CPT shows strong sensitivity, specificity, positive predictive power, and negative predictive power: 92%, 90%, 89%, and 93%, respectively. Concurrent validity was established by comparing the IVA CPT to two other continuous performance tests and two rating scales. The IVA CPT showed 90% to 100% agreement with these other measures and had the lowest false positive rate at 7.7%.

**Verbal working memory**

Verbal working memory was assessed using the total raw score from the Digit Span subtest from either the Third for Fourth edition of the Wechsler Intelligence Scale for Children (WISC-III, Wechsler, 1991; WISC-IV, Wechsler, 2003). The WISC is a well-validated test of general cognitive functioning for children ages 6 years to 16 years, 11 months. The test was standardized on a national sample of 2,220 children stratified by age, sex, race/ethnicity, geographic region and parent education according to the 1988 (WISC-III) and 2000 (WISC-IV) U.S. Census data. The Digit Span subtest has a forward component where the child is required to repeat an increasing span of numbers, and a backward component, in which the child is required to repeat in reverse order an increasing span of numbers.

**Shifting**

Shifting was assessed using the Trail Making Test (TMT; Reitan & Wolfson, 1985). The TMT is one subtest in the Halstead-Reitan Neuropsychological Test Battery and
consists of Part A and Part B. The TMT Part A is generally thought to measure visual attention and scanning ability, while Part B is sensitive to the executive function subdomain of shift (Lezak, Howieson, & Loring, 2004; Kelly, 2000). The TMT is a timed paper-and-pencil test. Part A requires the child to draw a line in sequence between numbered circles scattered across the page. Part B is considered more complex and requires the child to draw a line alternating between circled numbers and letters in sequence.

In order to successfully complete the task, the child is required to inhibit a prepotent response to serially connect numerically or alphabetically, and must instead shift sets to the next appropriate alternate target circle. If an error is made, the examinee’s error is pointed out and a correction is required. This process adds to the time-to-completion score. For the current study, a ratio score was derived using the completions times from Part B/Part A, such that visual scanning and motor speed is extracted from the overall ability to inhibit and flexibly shift sets, thus providing a clearer measure of executive ability (Lamberty, Putnam, & Chatel, 1994; Drane et al., 2002).

**Procedure**

Comprehensive information regarding participant recruitment and assessment of birth outcome measures used in the larger study is provided in Eyler et al., (1998a, 1998b) and will be summarized briefly here. Recruitment of participants took place between July 1991 and July 1993. Institutional Review Board (IRB) approval was obtained for all study procedures (IRB Protocol # 391-2001). At the time of study enrollment, informed written consent was obtained for all participants, which included an explanation of child, maternal, and family measures, drug tests and interviews, the Federal Certificate of Confidentiality, and the distinction between the researchers and
clinical providers to assure the strictest confidentiality. Child assent was obtained once
the child was old enough to demonstrate understanding of the study.

Maternal factors that might confound the effects of cocaine on pregnancy
outcome or child development were reduced using a priori exclusion criteria. These
exclusion criteria included: illicit drug use beyond cocaine and marijuana, chronic use or
abuse of prescription or other medications, and any major illness present prior to
pregnancy (i.e., diabetes, sickle cell disease, and mental retardation). Only mothers
who spoke English and were equal to or greater than 18 years of age were consented
for enrollment in the study. A priori participant matching criteria to a non-using control
group were used in the original longitudinal study to minimize the effect of possibly
confounding variables on pregnancy or child outcomes.

Four matching criteria for the non-using control group were chosen, three of which
were based on characteristics that typically differ between prenatal cocaine users and
the general obstetric population and have been shown to relate to pregnancy outcome
or child developmental outcome. These criteria were: 1) self-reported racial/ethnic group
membership (African American versus other racial/ethnic categories), 2) parity (first
versus subsequent births), and 3) level of Hollingshead Index of Socioeconomic Status
(SES). The fourth matching criterion, location of prenatal care, was chosen in order to
control for risk factors of complications that developed during, but not before,
pregnancy. This variable included the local public health unit, outlying clinics, or no
prenatal care.

**Subject Enrollment**

Of the 2,526 potential subjects approached, 85% consented to participate. One
hundred seventy-nine of the total were approached for consent at delivery and 89% of
these women consented to be potential subjects. The 372 refusals included 13 women who gave consent to participate in the study but were unable or unwilling to complete procedures necessary for enrollment, such as provide a urine sample. Further, after the first interview, 22 of the consented women (11 cocaine-users and their potential non-user matches) were eliminated from the study due to illicit drugs that met exclusion criteria \((n=16)\). Further, three reported using prescription medications that met exclusion criteria and another three were no longer able to deliver at the specified hospital.

Of those women who were consented and were not excluded, 154 were identified as cocaine users, and therefore continued in the longitudinal study. Of the women whose urine specimens and interviews indicated no evidence of cocaine use during pregnancy, a group of participants was selected from the consenting, non-excluded women on each matching criteria. As each target was identified, the oldest matched control was selected from the appropriate category (Eyler et al., 1998a).

**Identification and Documentation of Drug Use**

All women underwent a drug use interview, adapted from Day, Wagener, and Taylor (1985). This interview was administered by one of several well-trained interviewers who sought to establish rapport with the consenting maternal participant. Interviewers carefully read and explained all portions of a detailed drug history due to the presumed low literacy level some of the mothers enrolled in the study. Whenever possible, interviews were conducted at the end of each pregnancy trimester and details about drug use during the previous three months were obtained. Women with very late or no prenatal care were interviewed after birth about drug use throughout their
pregnancy. Individualized pregnancy calendars were used to help each woman with recall of drug use history. In addition to cocaine, participants were queried about their use of other drugs, including marijuana, alcohol, tobacco, and other illicit drugs (used for exclusion purposes) using street or slang drug names as appropriate. Each woman’s typical use of each drug was recorded per trimester, noting any increases and decreases in usage patterns were noted.

Urine specimens were obtained for drug screening on two unanticipated occasions during the study. The first specimen was collected on the day of enrollment into the study and the second specimen was obtained from the mother on the day of the baby’s birth if an infant specimen was unavailable. Fluorescence polarization immunoassay was used to conduct full toxicology screens of the urine. Positive cocaine screens were then confirmed with gas chromatography/mass spectroscopy.

**Assessment Procedures**

Throughout the longitudinal study, all measures were administered by trained, certified, or licensed professionals blinded to the study group membership of the child. Physical examination, including orbitofrontal head circumference measurements, were obtained at birth by one of a team of neonatal nurse practitioners blinded to the drug history of the mother. Frequent assessments were made of the children, their primary caregivers, and the home environment from birth to 36 months.

At ages 5, 7, 10 ½, and 12 ½ years, the children underwent comprehensive, standardized neuropsychological assessments by examiners masked to drug histories. All but the age 5 time point were used for the current study. A licensed neuropsychologist provided training and oversight of all neuropsychological evaluations.
and a senior level school psychologist administered or supervised all developmental and psychological testing.

With consent from families and schools, the psychological tests were administered in a mobile evaluation unit outside each child’s school during class hours or outside the child’s home during non-school hours. At the end of each assessment, children were offered their choice of toy or game and received certificates noting their participation. Each of the school age assessment time points also included an evaluation of the home environment using the age-appropriate version of the Home Observation for Measurement of the Environment (HOME). This measure was completed during an interview conducted with the primary caregivers in the child’s home.

After assessment protocols were reviewed for scoring accuracy, the scores for each participant were entered into a Microsoft Access database. Data were entered a second time and checked against the original input to minimize errors. Discrepancies between the two set of entries were reconciled by checking the hard copy assessment protocols (at ages 5 and 7) or by utilizing validation ranges for specific database items (at age 10 ½ and 12 ½).

Three variables representing EF were included. First, age-corrected standard scores for the visual Prudence Quotient score, synonymous with a commission error score, from the IVA-CPT were used to represent inhibition. Second, verbal working memory was measured using the total raw score from Digit Span task from either the WISC-III or WISC-IV. Third, a variable representing shifting abilities was derived from the completion time of TMT Part A and B by computing a ratio score of B/A. The ratio score provides a clearer measure of shifting and cognitive flexibility as it factors out the
motor component of the tasks (Lamberty, Putnam, & Chatel, 1994; Drane et al., 2002). For structural equation modeling, it is not necessary for all variables to be in the same metric as the solution can be standardized by setting factor variances to one.

Four potential predictors for cognitive outcome were included to determine whether they were associated with the variability in change of development of executive functions. The identified risk factors were prenatal drug exposure, adjusted birth head circumference, child sex, and quality of caregiving environment (measured by the HOME). These risk factors are well-established as making significant impacts on a variety of outcomes and are likely to provide insight into the nature of the causal mechanism(s) underlying the development of EF.

**Aims and Hypotheses**

Based on a review of the relevant literature, four a priori hypotheses were developed to examine the relationship between prenatal cocaine exposure and the development of EF control in children:

**Aim 1:** Do inhibition, working memory, and shifting skills as assessed by three measures of EF improve as children mature?

**Hypothesis 1:** Inhibition, working memory, and shifting skills as assessed by three measures of EF will improve as children mature.

**Aim 2:** Do characteristics of the child and the pre- and postnatal environment impact the development of EF?

**Hypothesis 2:**

a. Prenatal cocaine exposure will negatively impact the development of inhibition, working memory, and shifting such that more prenatal exposure will be more detrimental.
b. Adjusted birth head circumference will negatively impact the development of inhibition, working memory, and shifting such that smaller head circumference will be more detrimental.

c. Child sex will impact the development of inhibition, working memory, and shifting such that being of male gender will be more detrimental.

d. The quality of the home environment will impact the development of inhibition, working memory, and shifting such that a poorer home environment will be more detrimental.

Data Inspection and Analyses

Data Screening and Participant Missing Data at Each Timepoint

The first step in the data analysis involved screening the data for violations of normality and for missing data. Data screening was conducted using SPSS 17.0. With the exception of the four drug variables, data with significant skewness, kurtosis, or both were transformed into approximately normal scores using log or square root transformations. The drug variables were not transformed as it was expected that these data would not have a normal distribution. The Trail Making ratio variable was further transformed by multiplying each child’s ratio score by -1 so that a larger ratio reflected better shifting skills.

Missing Data

Participants were included in the present study based on an a priori rule. Specifically, all participants had to have been assessed at the first time point (age 7 years) and at least one other time point (either 10½ or 12½ years). This rule was established given the importance of the first time point in creating a valid and reliable intercept, or baseline performance level, for each participant.
Missingness at Time 1

A total of 35 participants (n = 17 for PCE group, n = 18 for non-exposed group) had missing data for all three measures at age 7 years. Further, four participants did not have data for the Digit Span task (n = 2 for PCE group, n = 2 for non-exposed group) and 24 participants did not have data for the IVA task (n = 11 for PCE group, n = 13 for non-exposed group). Therefore, a total of 63 participants (21% of initial sample) were excluded from the present study given missing data points at age 7 years. Mann-Whitley U tests were conducted between the groups of children with missing data at age 7 and the rest of the sample at age 7. Results indicated significant differences between the groups missing data and the rest of the sample with data on the child’s gestational age (Mann-Whitley U = 5622.5, n₁ = 61, n₂ = 246, p < .05) and a cumulative HOME score (Mann-Whitley U = 2118.5, n₁ = 15, n₂ = 235, p < .05), with those included having higher gestational age and a lower cumulative HOME score. No significant differences were demonstrated on measures of adjusted birth head circumference, prenatal drug exposures, or ethnicity (Table 2-1).

At age 7, missing scores for the Trail Making Test were generally the result of the child not being able to count to 15 or not being able to complete the practice items. A total of 12 participants could not complete Trails A (n = 5 for the PCE group, n = 7 for the non-exposed group) and a total of 36 participants could not complete Trails B (including the 12 who could not do Trails A) (n = 15 for the PCE group, n = 21 for the non-exposed group). To avoid the bias of eliminating children with delayed cognitive skills, these children were assigned a score of 301 seconds, one second above the worst score possible for a child completing the task within the 5-minute time limit. Another child from the PCE group was excluded because of a medical condition (i.e.,
deafness). The total sample size at this point was 246 (n = 124 for the PCE group, n = 122 for the non-exposed group).

**Missingness at Time 2**

Twelve participants were missing data for all three measures at age 10 ½ years. Of these participants, three had data for all measures at age 12 ½ years, and could be kept in the present study. Therefore, 9 (n = 4 for PCE group, n = 5 for non-exposed group) participants with missing data at both age 10 ½ and 12 ½ were excluded from the study.

**Missingness at Time 3**

Of the 236 remaining participants, seven were missing data for all three measures at age 12 ½ (n = 4 for PCE group, n = 3 for non-exposed group). Two of the four remaining participants from the exposed group were missing data for the Trail Making Test. However, all of these participants were kept in the present study, as they had data for all measures at the other two time points, thus meeting the criteria of the pre-established rule for missing data described above. A total of 236 participants (76.9% of the initial sample, n = 120 for PCE group, n = 116 for non-exposed group) remained.

**Data Validity Considerations**

The IVA CPT includes three validity scales associated with the Visual Prudence Quotient. The validity scales attempt to identify random responding (i.e., Visual Comprehension), measure fatigue and motivation (i.e., Persistence), and detect abnormally slow reaction time (i.e., Sensory/Motor). A child’s IVA CPT Visual Prudence score was determined to be invalid if two or more validity scales were elevated. Of the children that met the a priori inclusion criteria of having data at age 7 and at least one other time point, it was noted that 11 children at age 10 ½ years and 25 children at age
12 ½ years had elevations of two or more validity scales. These invalid performance scores for that respective time point were not included in the analyses. However, none of these children needed to be excluded from the study given the presence of valid performance scores age 7 scores and at least one other valid score at a separate time point (i.e., either age 10 ½ or 12 ½ years).

**Statistical Analysis**

Use of maximum likelihood statistical methods is now standard treatment for participant loss and infrequent missing data (Cheung, 2007). These methods provide more consistent and efficient estimates of population parameters than methods relying on complete cases, available pairwise, mean imputation, or single-imputation regression methods (Graham, Hofer, & MacKinnon, 1996; Schafer & Graham, 2002). In all analyses conducted, the estimation method of full information maximum likelihood (FIML) available in Amos 17.0 (Arbuckle & Wothke, 1999) was used for missing variables. By maximizing casewise likelihood, this method uses data from participants with less than three but greater than one time point and therefore utilizes all possible available information (see Enders, 2001).

**Latent Growth Curve Models**

Latent growth curve analysis is a method of longitudinal data analysis that emphasizes individual change and initial status. Latent growth curve analysis involves estimating within-individual regressions of performance on time. Therefore, individual level data (intercept), the rate of change (slope), and error (residual) parameters for each domain of EF were summarized in a structural equation model format. Growth curve analysis was used to model initial level and rate of change using three measures of EF at three time points per measure.
All univariate models were fit using a linear growth curve. Two parameters determine the straight line. First, the intercept represents the value at the start of the process, and is often called the “initial level”. The estimation factor loading (i.e., regression weights) for the intercept at each time point were constrained to 1, which makes this parameter the initial status level. Second, the slope represents how much the linear curve grows or declines at each time point. The regression weights for each time point were set to represent the time between each testing point starting at baseline (i.e., seven years of age). Therefore, the factor loadings from the latent slope to each measured time point were set to (1, 4.5, and 6.5) to represent linear change with unequal spacing reflecting the ages at each assessment point.

There are two parameters associated with both the intercept and the slope – the mean and the variance. The mean of the intercept is the average value for the first time point for the total sample, while the variance of the intercept reflects the variation of individual intercepts. The mean of the slope is the average slope for the total sample. The variance of the slope reflects the extent to which individuals have different slopes. Finally, the covariance between two variances is depicted by a double-headed arrow, and represent how two variables change together.

Figure 2-1 shows the proposed structural model of the longitudinal relationship for each variable representing a domain of EF. Three models of latent growth, each with a level and slope, were fitted for three measures of EF (IVA, DS, and TMT). Prenatal drug exposure other than cocaine was included as a latent factor that was allowed to covary with PCE. Next, the predictor variables (gender, PCE, adjusted birth head circumference, quality of caregiving environment) were incorporated into each model as
predictors of the level and slope of each domain of EF. Figures 2-2 to 2-4 represent the proposed structural models with the predictor variables included.

**Evaluation of fit**

For all analyses, the criterion for significance was set at alpha < .05. Several indices were used to assess the goodness-of-fit. One index used was the ratio between the chi-square and the degrees of freedom for the model. Generally, a model is considered to fit well if the chi-square statistic is less than twice the degrees of freedom (χ² < 2 df) and is non-significant. A significant chi-square would mean that the model does not adequately reproduce the relationships within the data. Other indices used to assess fit in the current study include Bentler's (1990) normed comparative fit (CFI) and Bentler and Bonett's (1980) nonnormed fit (NNFI) indices. For each of these indices, better fit is associated with higher values, and .90 is considered a minimum acceptable level (Bentler and Bonett, 1980). The root mean square error of approximation (RMSEA) takes into the account the error of approximation in the population, and a value of ≤ .05 is considered an indicator of good fit (Browne and Cudeck, 1993).
Table 2-1. Comparisons Between Participants With and Without Executive Function Scores at Age 7

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>Included&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Excluded&lt;sup&gt;b&lt;/sup&gt;</th>
<th>M</th>
<th>SD</th>
<th>M</th>
<th>SD</th>
<th>p-value</th>
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<td></td>
<td>Prenatal cocaine exposure</td>
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<td>.31</td>
<td>.31</td>
<td>.39</td>
<td>.25</td>
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<td></td>
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<tr>
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<td>Prenatal alcohol exposure</td>
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<td>.31</td>
<td>.13</td>
<td>.33</td>
<td>.94</td>
<td></td>
<td></td>
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<td></td>
<td>Prenatal tobacco exposure</td>
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<td>7.98</td>
<td>5.33</td>
<td>8.29</td>
<td>.68</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Prenatal marijuana exposure</td>
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<td>.28</td>
<td>.22</td>
<td>1.52</td>
<td>.97</td>
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<td>Adjusted Head Circumference (cm)</td>
<td>34.16</td>
<td>1.49</td>
<td>33.91</td>
<td>1.58</td>
<td>.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gestational age</td>
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<td>1.95</td>
<td>36.16</td>
<td>5.81</td>
<td>.02&lt;sup&gt;*&lt;/sup&gt;</td>
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</tr>
<tr>
<td></td>
<td>Ethnicity&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>.82</td>
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<td></td>
<td>HOME Total Score</td>
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<td>134.0</td>
<td>15.01</td>
<td>.02&lt;sup&gt;*&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>Note.</sup>
<sup>a</sup> n = 235-246
<sup>b</sup> n = 24-62
<sup>d</sup> Ethnicity was coded that African American = 1, others = 0. The numbers in this row indicate the proportion of the group that was African American.
<sup>*</sup> p < .05, two-tailed using the independent samples Man-Whitley U Test.

Figure 2-1. Representation of Three Latent Growth Curve Models of Executive Functions. IVA= Intermediate Visual and Auditory Continuous Performance Test, Visual Prudence Score. DS = WISC-III Digit Span backward, raw score. TMT = Trail Making Test, Part B / Part A in time.
Figure 2-2. Representation Inhibition with Predictor Variables. IVA = IVA-CPT Visual Prudence Quotient Score, PCE = Prenatal cocaine exposure, ABHC = Adjusted birth head circumference, HOME = Cumulative score from the Home Observation for Measurement of the Environment.

Figure 2-3. Representation Working Memory with Predictor Variables. DS = WISC Digit Span Raw Total Score, PCE = Prenatal cocaine exposure, ABHC = Adjusted birth head circumference, HOME = Cumulative score from the Home Observation for Measurement of the Environment.
Figure 2-4. Representation Shifting with Predictor Variables. TMT = Trail Making Test Ratio Score, PCE = Prenatal cocaine exposure, ABHC=Adjusted birth head circumference, HOME = Cumulative score from the Home Observation for Measurement of the Environment.
CHAPTER 3
RESULTS

Sample Characteristics

A total of 236 participants (76.9% of the initial sample; PCE \( n = 120 \), non-exposed \( n = 116 \)) were included in the present study. Group differences within the original study sample were also present within the current study sample (Table 2-3). Tables 3-1 and 3-2 depict group differences derived from the original study sample for reference. As in the original sample, the current study group with PCE had significantly greater mean amounts of prenatal cocaine exposure \([t(235) = -17.42, p < .001]\), prenatal alcohol exposure \([t(235) = -5.74, p < .001]\), prenatal tobacco exposure \([t(235) = -6.79, p < .001]\), and prenatal marijuana exposure \([t(235) = -2.17, p < .01]\) than the non-exposed group. Additionally, the group with PCE had a significantly smaller mean head circumference as compared to the non-exposed group \([t(235) = -2.58, p < .05]\). Finally, statistically similar proportions of females and African Americans were found in the current and original samples. Table 3-3 depicts demographic variable comparisons by group in the current study.

Although the analyses used to assess the hypotheses combined the groups (i.e., prenatally cocaine-exposed and non-exposed), the two groups were first compared on the three cognitive variables at each time point in order to characterize the sample and to determine if any group differences existed. Table 3-4 summarizes mean scores for each of the cognitive assessments by group at 7, 10½, and 12½ years and presents results from a MANOVA comparing the two groups. There were no significant differences in executive functioning abilities at any age between cocaine-exposed and non-exposed children (all \( p \)’s > .05).
Figures 3-1 through 3-3 show mean values for each measure by time point. Figure 3-1 shows that inhibition declined with age. Because age-adjusted standard scores from the IVA-CPT were used to assess inhibition, the negative slope could be interpreted as a failure on the part of the participants in the present study to make normative gains as they aged compared to the normative sample. Figure 3-2 and Figure 3-3 show that working memory shifting abilities increased with age, as expected.

Latent Growth Curve Models

Hypothesis 1

To test the first hypotheses – that inhibition, working memory, and shifting skills will improve as children mature – individual, univariate LGM’s were created for each cognitive measure at three time points using a linear time structure. The means and variances for each intercept and slope as well as the chi-square fit index for each univariate model are reported in Table 3-5.

Inhibition. The univariate LGM for inhibition showed a respectable fit with the data. The overall model had a non-significant chi-square value [χ2 (df = 1, N = 236 = 1.80, p = .18], and all other indices demonstrated adequate fit (CFI = .98, NNFI = .96, and RMSEA = .05). The intercept of inhibition was estimated to have a significant mean (M = 89.27, p ≤ .001), indicating that the sample’s initial starting level was significantly greater than zero. The variance was not significant (D = 58.32, p = .45), suggesting there was not significant variation between individual intercepts.

The mean for the slope was significant (M = -1.37, p ≤ .001), indicating that group’s performance on the task did not follow the normative developmental trajectory, as the trend demonstrated a decrease in ability compared to same-age children from the normative sample at each time point. The variance of the slope was not significant.
$(D_s = 8.66, p = .06)$, suggesting that the individual developmental trajectory of inhibition did not differ significantly between children. Finally, the covariance between the intercept and slope was not significant, which indicates no relationship between the initial level of performance and the development of inhibitory control.

**Working memory.** The univariate LGM for Digit Span fit the data very well and yielded a non-significant chi-square $[\chi^2 (df = 2, N = 236) = 1.01, p = .60]$ and acceptable goodness-of-fit values (CFI = .99, NFI = .99, RMSEA = .01). The intercept of working memory was estimated to have a significant mean ($M_i = 9.15, p < .001$). The variance of the intercept was also significant ($D_i = 3.36, p < .001$), suggesting there was a significant variation of individual intercepts, i.e., not all individual began at the same initial level at age 7.

The mean for the slope was significant ($M_s = 3.83, p < .001$), an indication that children’s performance on the task increased over time. The variance of the slope was also significant ($D_s = .82, p < .05$), suggesting that significant individual variation existed in the development of working memory. Finally, the covariance between the intercept and the slope was significant and positive, which suggests that children who have better initial performance (i.e., longer digit span length at age 7 years) showed more growth over time of working memory ability.

**Shifting.** The univariate LGM for shifting fit the data well and yielded a non-significant chi-square $[\chi^2 (df = 1, N = 236) = 0.30, p = .49]$. Other fit indices demonstrated good fit (CFI = 1.00, NNFI = .96, RMSEA = .01). The intercept of the shifting variable was estimated to have a significant mean ($M_i = .49, p < .001$). The variance of the intercept was not significant ($D_i = .02, p = .09$), suggesting there was not
significant variation of individual shifting ability at the initial level of performance. The mean for the slope was significant ($M_s = .04, p < .001$), indicating that children’s mean performance on the task improved over time. The variance of the slope was not significant ($D_i = .01, p = .06$), which suggests that the individual developmental trajectory of shifting abilities did not significantly differ between children. Finally, the covariance between the intercept and slope is not significant, which indicates no significant relationship between the initial performance and the development of shifting skills.

Therefore, the results partially supported the first hypothesis, as performance on measures of working memory and set-shifting increased over time. However, inhibitory control did not improve at a rate similar to same-age children from the normative sample.

**Hypothesis 2**

Variables representing PCE, adjusted birth head circumference, gender, and quality of the home environment were added to each separate univariate model of EF in order to determine the impact of these variables on the development of EF.

**Relationship of predictor variables.** Extent of cocaine exposure was represented as a ratio of the number of weeks of reported cocaine use divided by the total number of weeks of each gestation plus 3 months prior to gestation. A latent variable, named “other drugs”, was created to analytically control for the potential impact of the mother’s use of alcohol, tobacco, and marijuana on the development of EF. Consistent with previous findings, the presence of “other drugs” was positively and significantly related to the extent of PCE ($\beta = .69, p < .001$).

Head circumference and PCE were significantly related, in that more frequent PCE was associated with a smaller head circumference ($\beta = -.16, p < .05$). Gender and
adjusted head circumference were also significantly related, with girls having smaller heads at birth than boys (β = .23, p ≤ .001). The means for each predictor variable (PCE, adjusted head circumference, gender, and the home environment) were significant, as were the variances for each of these variables. See Table 3-6 for estimates and alpha levels for each variable. No other significant relationships were found between the predictor variables. The following sections describe the relationship of the predictor variables with each univariate model of EF separately. Unstandardized estimates, standard errors, and t-values are summarized in Tables 3-7 to 3-9. Standardized beta coefficients for the relationships of the predictors variables and the intercepts and slopes for each univariate model are depicted in Table 3-10.

**Inhibition.** The overall fit of the model with all four predictor variables was acceptable [χ² (df = 25, N= 236) = 37.56, p =.05, CFI = .92, NNFI = .81, RMSEA = .04]. Adjusted head circumference significantly predicted the initial performance and the developmental trajectory of inhibition. Specifically, smaller head circumference was related to lower inhibitory skills at age 7 (β = .60, p < .05) and a less normative development of inhibitory skills over time (β = -.47, p < .01).

**Working memory.** The overall fit of the model was good and yielded the following fit indices: χ² (df = 25, N = 236) = 34.70, p =.12, CFI = .97, NNFI = .91, RMSEA = .04. The quality of the caregiving environment positively predicted the initial level of working memory (β = .22, p < .01). Adjusted head circumference also significantly predicted the initial level of working memory performance (β = .22, p < 01), such that a smaller head circumference was related to lower working memory abilities at age 7. No other
predictor variables were significantly related to the initial level or the developmental trajectory of working memory abilities.

**Shifting.** The overall fit of the model with the predictor variables was acceptable and yielded the following fit indices: $\chi^2(df = 25, N = 236) = 25.72, p = .42, CFI = .99, NNFI = .81, RMSEA = .02$. No significant relationships were found between predictor variables and the initial level or developmental trajectory of shifting abilities.

In summary, results indicated no direct effect of PCE on the initial performance or the development of EF over time. Smaller birth head circumference negatively predicted the inhibitory and working memory skills at age 7 as well as less normative development of inhibitory skills over time. Additionally, a better quality home environment positively predicted working memory ability at age 7 years, though the home environment did not predict the developmental trajectory of any EF over time.
### Table 3-1. Variables that Differed Significantly Between Mothers in the Original Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cocaine Users</th>
<th>Matched Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>27.61</td>
<td>4.82</td>
<td>23.81</td>
</tr>
<tr>
<td>Week entered prenatal care</td>
<td>14.82</td>
<td>7.67</td>
<td>12.10</td>
</tr>
<tr>
<td>Cocaine use (average ratio of weeks of cocaine use)</td>
<td>.48</td>
<td>.30</td>
<td>----</td>
</tr>
<tr>
<td>Tobacco use (average number of cigarettes smoke per day)</td>
<td>8.30</td>
<td>7.70</td>
<td>2.14</td>
</tr>
<tr>
<td>Alcohol use (average ounces of absolute alcohol consumed per day)</td>
<td>.23</td>
<td>.41</td>
<td>.01</td>
</tr>
<tr>
<td>Marijuana use (average number of joints smoked per day)</td>
<td>.16</td>
<td>1.10</td>
<td>.01</td>
</tr>
</tbody>
</table>

a

n = 154 for each group.

* p < .05, ** p < .01, *** p < .001, two-tailed using the independent samples t-test.

### Table 3-2. Neonatal Variables that Differed Significantly in the Original Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cocaine-Exposed</th>
<th>Non-exposed</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>2985</td>
<td>668</td>
<td>3179</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>48.7</td>
<td>3.2</td>
<td>49.7</td>
</tr>
<tr>
<td>Adjusted Head Circumference (cm)</td>
<td>33.8</td>
<td>1.4</td>
<td>34.4</td>
</tr>
</tbody>
</table>

a

n = 154 for each group.

* p < .05, ** p < .01, *** p < .001, two-tailed using the independent samples t-test.
Table 3-3. Demographic Variables Comparing Groups in Current Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>PCE a</th>
<th>Non-exposed b</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>.46</td>
<td>.28</td>
<td>.00</td>
<td>.00</td>
</tr>
<tr>
<td></td>
<td>.24</td>
<td>.42</td>
<td>.02</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>8.85</td>
<td>9.28</td>
<td>2.05</td>
<td>5.66</td>
</tr>
<tr>
<td></td>
<td>.10</td>
<td>.37</td>
<td>.02</td>
<td>.13</td>
</tr>
<tr>
<td></td>
<td>33.87</td>
<td>1.42</td>
<td>34.36</td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td>Sex c</td>
<td>.49</td>
<td>.50</td>
<td>.45</td>
</tr>
<tr>
<td></td>
<td>Ethnicity d</td>
<td>.81</td>
<td>.39</td>
<td>.84</td>
</tr>
</tbody>
</table>

*Note. PCE = prenatal cocaine exposure

a n = 120
b n = 116
c Sex was coded so that female = 1, male = 0. The numbers in this row indicate the proportion of the group that was female.
d Ethnicity was coded that African American = 1, others = 0. The numbers in this row indicate the proportion of the group that was African American.

* p < .05, ** p < .01, *** p < .001, two-tailed using the independent samples t-test.

Table 3-4. Groups Means and Standard Deviations for Executive Function Variables

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>PCE a</th>
<th>Non-exposed b</th>
<th>Variable Ranges</th>
<th>p-value c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>87.87</td>
<td>23.89</td>
<td>89.4</td>
<td>19.90</td>
<td>40-120</td>
</tr>
<tr>
<td></td>
<td>8.95</td>
<td>2.67</td>
<td>9.26</td>
<td>2.30</td>
<td>1-15</td>
</tr>
<tr>
<td></td>
<td>3.68</td>
<td>2.12</td>
<td>3.64</td>
<td>2.22</td>
<td>.00-.16</td>
</tr>
<tr>
<td></td>
<td>84.59</td>
<td>21.28</td>
<td>86.59</td>
<td>19.91</td>
<td>40-117</td>
</tr>
<tr>
<td></td>
<td>12.32</td>
<td>2.80</td>
<td>13.23</td>
<td>3.08</td>
<td>6-24</td>
</tr>
<tr>
<td></td>
<td>2.64</td>
<td>1.12</td>
<td>2.50</td>
<td>1.35</td>
<td>-.09-.95</td>
</tr>
<tr>
<td></td>
<td>87.01</td>
<td>19.52</td>
<td>83.56</td>
<td>20.81</td>
<td>44-118</td>
</tr>
<tr>
<td></td>
<td>16.80</td>
<td>3.38</td>
<td>16.84</td>
<td>3.63</td>
<td>9-27</td>
</tr>
<tr>
<td></td>
<td>2.06</td>
<td>.85</td>
<td>2.02</td>
<td>.91</td>
<td>-.11-.77</td>
</tr>
</tbody>
</table>

*Note. PCE = prenatal cocaine exposure, IVA-CPT VPQ = Intermediate Visual and Auditory Continuous Performance Test Visual Prudence Quotient

a n = 106
b n = 107
c Two-tailed using the independent samples t-test
d Log transformed ratio scores (Trails B/Trails A)
Table 3-5. Estimates for Univariate Latent Growth Curve Models of Executive Functions

<table>
<thead>
<tr>
<th>Model</th>
<th>Intercept Mean</th>
<th>Variance</th>
<th>Slope Mean</th>
<th>Variance</th>
<th>(\chi^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition</td>
<td>89.27***</td>
<td>58.32*</td>
<td>-1.37***</td>
<td>8.66*</td>
<td>1.80</td>
</tr>
<tr>
<td>Working Memory</td>
<td>9.15***</td>
<td>3.36***</td>
<td>3.83***</td>
<td>.82**</td>
<td>1.01</td>
</tr>
<tr>
<td>Shifting</td>
<td>.49***</td>
<td>.02</td>
<td>.04***</td>
<td>.01</td>
<td>.30</td>
</tr>
</tbody>
</table>

Note. \(N = 236, ** p < .01, *** p < .001\)

Table 3-6. Estimates for Pre- and Postnatal Child Characteristics and the Environment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>.53***</td>
<td>.25***</td>
</tr>
<tr>
<td>Cocaine Exposure</td>
<td>.23***</td>
<td>.09***</td>
</tr>
<tr>
<td>Home Environment</td>
<td>41.99***</td>
<td>41.84***</td>
</tr>
<tr>
<td>Head Circumference</td>
<td>34.19***</td>
<td>2.32***</td>
</tr>
</tbody>
</table>

Note. \(N = 236, *** p < .001\)

Table 3-7. Estimates of Predictors on Inhibition Growth Curve Intercepts and Slopes

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Effect(^a)</th>
<th>Standard Error (SE)</th>
<th>t-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercept</td>
<td>Slope</td>
<td>Intercept</td>
</tr>
<tr>
<td>Gender</td>
<td>.12</td>
<td>.05</td>
<td>.03</td>
</tr>
<tr>
<td>PCE</td>
<td>-1.83</td>
<td>-.39</td>
<td>5.31</td>
</tr>
<tr>
<td>Home</td>
<td>-.19</td>
<td>.10</td>
<td>.25</td>
</tr>
<tr>
<td>Head Circumference</td>
<td>2.63*</td>
<td>-.79*</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Note. \(^a\) = unstandardized estimates, * \(p < .05\), ** \(p < .01\)

Table 3-8. Estimates of Predictors on Working Memory Growth Curve Intercepts and Slopes

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Effect(^a)</th>
<th>Standard Error (SE)</th>
<th>t-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercept</td>
<td>Slope</td>
<td>Intercept</td>
</tr>
<tr>
<td>Gender</td>
<td>-.31</td>
<td>.01</td>
<td>.31</td>
</tr>
<tr>
<td>PCE</td>
<td>-.09</td>
<td>.23</td>
<td>.51</td>
</tr>
<tr>
<td>Home</td>
<td>.06**</td>
<td>-.01</td>
<td>.02</td>
</tr>
<tr>
<td>Head Circumference</td>
<td>.26*</td>
<td>.07</td>
<td>.11</td>
</tr>
</tbody>
</table>

Note. \(^a\) = unstandardized estimates, * \(p < .05\), ** \(p < .01\)
Table 3-9. Estimates of Predictors on Shifting Growth Curve Intercepts and Slopes

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Effect</th>
<th>Standard Error (SE)</th>
<th>t-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercept</td>
<td>Slope</td>
<td>Intercept</td>
</tr>
<tr>
<td>Gender</td>
<td>-.04</td>
<td>.01</td>
<td>.02</td>
</tr>
<tr>
<td>PCE</td>
<td>-.04</td>
<td>-.00</td>
<td>.06</td>
</tr>
<tr>
<td>Home</td>
<td>.00</td>
<td>.00</td>
<td>.01</td>
</tr>
<tr>
<td>Head</td>
<td>.01</td>
<td>-.01</td>
<td>.01</td>
</tr>
<tr>
<td>Circumference</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* a = unstandardized estimates, * p < .05, ** p < .01

Table 3-10. Standardized Betas of Predictors on Growth Curve Intercepts and Slopes

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Inhibition Intercept</th>
<th>Inhibition Slope</th>
<th>Working Memory Intercept</th>
<th>Working Memory Slope</th>
<th>Shifting Intercept</th>
<th>Shifting Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>.21</td>
<td>.17</td>
<td>-.11</td>
<td>.19</td>
<td>-.07</td>
<td>-.06</td>
</tr>
<tr>
<td>PCE</td>
<td>-.09</td>
<td>-.04</td>
<td>-.02</td>
<td>.08</td>
<td>-.08</td>
<td>-.03</td>
</tr>
<tr>
<td>Head</td>
<td>-.16</td>
<td>.18</td>
<td>.22**</td>
<td>-.01</td>
<td>-.01</td>
<td>-.03</td>
</tr>
<tr>
<td>Circumference</td>
<td>.60*</td>
<td>-.47**</td>
<td>.22*</td>
<td>.12</td>
<td>.081</td>
<td>.06</td>
</tr>
</tbody>
</table>

*Note.* * p < .05, ** p < .01

Figure 3-1. Mean Changes in Inhibition. IVA-CPT = Intermediate Visual and Auditory Continuous Performance Test, VPQ = Visual Prudence Quotient (M=100, SD = 15).
Figure 3-2. Mean Changes in Working Memory. Scores represent WISC Digit Span total raw score.

Figure 3-3. Mean Changes in Shifting. TMT = Trail Making Test Ratio = (Trails B time/Trails A time), Y axis has been reversed to represent a smaller ratio reflecting better shifting performance.
Figure 3-4. Conditional Latent Growth Model of Inhibition. IVA = Intermediate Visual and Auditory Continuous Performance Task Visual Prudence Quotient Score, PCE = Prenatal cocaine exposure, ABHC=Adjusted birth head circumference, HOME = Cumulative score from the Home Observation for Measurement of the Environment.
Figure 3-5. Conditional Latent Growth Model of Working Memory. DS = WISC Digit Span Total Raw Score, PCE = Prenatal cocaine exposure, ABHC=Adjusted birth head circumference, HOME = Cumulative score from the Home Observation for Measurement of the Environment.
Figure 3-6. Conditional Latent Growth Model of Shifting. Trails = Trail Making Test ratio score (Part B/Part A), PCE = Prenatal cocaine exposure, ABHC=Adjusted birth head circumference, HOME = Cumulative score from the Home Observation for Measurement of the Environment.
CHAPTER 4
DISCUSSION

Study Summary

The current study sample (n = 236) was comprised of 120 children who were
prenatally exposed to cocaine (along with marijuana, alcohol, and/or tobacco) and 116
matched controls, none of who were exposed to cocaine and most of whom (i.e., 64)
were exposed to tobacco, alcohol, and/or marijuana. Among the controls, 42 children
had no drug exposure at all. The children with prenatal cocaine exposure (PCE) had
significantly higher levels of exposure to alcohol, tobacco, and marijuana than non-
exposed children. The children with PCE also had significantly smaller mean head
circumference and gestational age at birth than the non-exposed children. All children
were predominately African American and were almost equally divided between boys
and girls.

Main Findings

Longitudinal latent growth curve analyses were used to examine the relationship
between prenatal cocaine exposure and the development of executive functions across
a developmental span from age 7 to 12 ½ years. The first hypothesis, that inhibition,
working memory, and shifting skills would improve as children mature, was partially
supported. Inhibition as measured by age-corrected scores on a computerized
continuous performance test demonstrated a linear decrease in skills compared to
same-age peers from the normative sample. In contrast, both working memory (Digit
Span) and shifting abilities (Trail Making Test) significantly improved as children
matured.
The relationship of the predictor variables deserves comment. Prenatal drug exposures other than cocaine were combined into a single latent variable that was used as a covariate with PCE. This decision was based on the significant multicollinearity of the four drug exposure variables and the confounding effects on explaining the relationship of each individual drug on the variables representing cognitive outcome. For instance, the individual contribution of each independent variable on cognitive development would be difficult to measure because the independent effects are confounded due to the shared variance of the drugs. Head circumference and PCE were significantly related, in that more PCE was associated with a smaller head circumference. Gender was also a strong predictor of head circumference, with girls having smaller heads at birth than boys.

As hypothesized, adjusted head circumference was significantly associated with the mean level of initial inhibitory and working memory abilities and the developmental trajectory of inhibition such that smaller head circumference was related to worse development. The quality of the home environment was also significantly associated with initial working memory abilities such that a better quality home environment was related to better performance. However, no predictors were significantly associated with initial shifting ability or development in this domain. Contrary to the second hypothesis, gender and prenatal cocaine exposure did not significantly directly predict the initial level or the development of any EF.

**Study Findings in the Context of the Literature**

**Preliminary Group Comparisons**

The lack of significant group differences on executive function measures at each cross-sectional time point between children with PCE and non-exposed children in the
current study is generally consistent with previous studies within this cohort (Warner, et al., 2006; Eyler et al., 2009) and is partially consistent with the majority of the literature in this area. A review by Frank, Augustyn, Knight, Pell and Zuckerman (2001) concluded that after controlling for confounding factors (i.e., prenatal drug exposure other than cocaine), PCE had no consistent negative association with physical growth, cognitive ability as assessed by developmental tests, or language skills in children under 3 years of age. Other studies investigating cognitive functioning in children up to age 7 years that were prenatally exposed to cocaine have typically found similar findings, particularly on measures of more global functioning, such as on index scores on tests of intellectual functioning (Singer et al., 2004; Morrow et al., 2006; Richardson, Conroy, and Day, 1996).

Recent studies using children 7 years of age or older have demonstrated inconsistent direct effects of PCE on the development of cognitive abilities (Arendt et al., 2004; Rose-Jacobs et al., 2009). In fact, it may be more accurate to conceptualize PCE as a risk factor for negative cognitive outcome, with associated variables such as the caregiving environment representing additional risk or protective factors in the child’s development. For instance, children with PCE who were placed in foster or adoptive care have been found to perform similarly to non-exposed children on measures of cognitive functioning, and better than children with PCE who remained in their biological mother’s care (Singer et al., 2004, 2008). Additional studies support the associated PCE factors as the strongest predictors of developmental outcome (Adrendt et al., 2004; Behnke et al., 2006; Eyler et al., 2009), suggesting that the behavioral teratogenic
model of PCE may not thoroughly and accurately describe the relationships between PCE and cognitive outcomes in humans.

A few studies have demonstrated an effect of varying levels of cocaine exposure. When children were classified into heavier and lighter cocaine exposure groups, poorer outcomes were associated with heavier prenatal cocaine exposure (Bandstra et al., 2001; Singer et al., 2008; Rose-Jabobs et al., 2009). Within these studies, the effects were mediated by smaller birth head circumference, which has been found to be affected by PCE in humans (Singer, Salvator, Arendt, Farkas & Kliegman, 2002; Bauer et al., 2005; Behnke et al., 2005; Eyler et al., 1998, etc.) and nonhuman primate studies (Lidow, 2003).

Consistent with the current study findings, previous group comparisons of children from the original cohort found no differences between children with PCE and non-exposed children on measures of attention (IVA CPT), inhibition (Stroop test), visuomotor attention and sequencing (Trail Making Test A), or shifting (Trail Making Test Part B) at ages 5, 7, and 10 ½ years of age (Eyler et al., 2009). It is important to note that, overall, prenatally cocaine exposed and non-exposed children combined in the current study generally performed below the published test norms. This finding is consistent with previous studies of this cohort (Eyler et al., 2009); as well as other cohorts (Pulsifer, Butz, Foran, & Belcher, 2008; Morrow et al., 2006), and suggests that factors generally associated with PCE (i.e., poverty, other drug exposures) may have a more detrimental effect on cognitive outcome than PCE, per se.

Pulsifer, Butz, Foran, & Belcher (2008) found that, at age 5 years, their total combined sample (PCE and non-exposed children) performed significantly lower than
the normative mean on standardized measures of intelligence, language, school readiness, visual-motor skills, and impulse control, and 40% of the total sample performed at least one standard deviation below the mean on a measure of intelligence. Similarly, Morrow et al. (2006) found that between 19% and 20% of the children in each group (PCE and non-exposed children) had IQ scores that fell in the intellectually disabled range (standard score < 70) at age 7 years. It is possible that the developmental outcome of children raised in impoverished families may have other associated environmental disparities, including parental neglect or abuse, severe mental health issues, family instability, and exposure to violence, which may or may not be unique to PCE, and represent significant risk factors that negatively impact a child’s outcome.

**Hypothesis 1**

The findings that working memory and shifting demonstrated a positive developmental trajectory over time are consonant with previous studies of executive functions in typically developing children (Brocki & Bohlin, 2004; Huizinga, Dolan, & van der Molen, 2006; Hale, Bronik, & Fry, 1994; Beveridge, Jarrold, & Pettit, 2002). These changes are thought to be related to normal neuroanatomical, neurophysical, and neurochemical changes involved in the continued development of the frontal lobes throughout childhood, adolescents, and adulthood (Romine & Reynolds, 2005; Eslinger, 1996).

It is not wholly surprising that inhibition in the study sample, as measured by an age-adjusted normative score from the IVA CPT, did not demonstrate a developmental trajectory similar to the normative sample of same-age peers. There are several factors
related to the measure itself and the clinical nature of the current sample that may help explain this finding.

First, several measurement issues are apparent with the use of the IVA CPT in the current sample. For instance, many children received quotient scores (i.e., standard score, $M = 100$, $SD = 15$) four or more standard deviations below the mean (i.e., $\leq 40$). At age 7, 5% of the study sample (10 children) had scores of 40 or less and this number increased with age (9% of the study sample at 10½, 20 children; and 16% of the study sample at 12½ years, 34 children). Therefore, an increasing amount of children over time performed in a severely impaired range on this measure compared to the normative sample, suggesting a non-normal distribution of data at each time point. In fact, even after analytic transformation (i.e., Log transformation), the data remained statistically non-normal.

Unlike most other CPTs (e.g., Conners’ CPT, Test of Variables of Attention), the IVA CPT yields validity scales, providing guidance as to whether a child’s performance can be interpreted in a meaningful way. The Visual Prudence Quotient score has three associated scales to attempt to identify random responding (i.e., Visual Comprehension), measure fatigue and motivation (i.e., Persistence), and detect abnormally slow reaction time (i.e., Sensory/Motor). In an effort to maintain ecological validity, the current study included children despite elevations on a validity scale. The number of children at any age with elevations on one or more validity scales ranged from 88 (41%) at age 7 years, 91 (43%) at age 10½ years, and 60 (28%) at age 12½ years.
It is important to note that the participants at each time point with IVA CPT validity problems did not necessarily represent significantly impaired performance scores (i.e., less than 2 SDs below the mean), and many children with performance scores of 70 or below did not have elevations on any validity scale. In fact, approximately half (57%) of the children who had elevations on one or more validity scales performed within normal limits (i.e., ± 1 SD). This suggests that a low score on the Visual Prudence scale of the task could be due to: a) impaired inhibitory control, b) another factor not detected and represented by a validity scale elevation, or c) a factor detected and represented by a validity scale elevation (i.e., random responding).

Second, the validity of age-adjusted scores in the analyses is limited by the nature of the IVA-CPT normative sample. The manual for the IVA CPT indicates that the normative data are derived from 781 subjects (423 female, 358 male), at 10 different age groupings between ages 5 and 90 years. There is no breakdown by age category available, there is no evidence that the norms are stratified, and very little demographic information is provided about the subjects. Specifically, there is no information provided regarding socioeconomic levels, geographic regions, educational levels, or race. Comparing the sample of children in the current study to the normative sample could potentially be misleading, as the current sample is primarily African American and of low socioeconomic status. It has been well-documented that there is often a significant association of low SES and poorer performance on measures assessing neurocognitive functioning in both young and school-aged children as compared to higher SES youth (Noble, Norman, & Farah, 2005; Noble, McCandliss, & Farah, 2007).
Furthermore, the model of inhibition in the current study had a negative slope, and demonstrates a decrease in ability to inhibit prepotent responses compared to same-age children from the normative sample at each time point. Raw scores (which were not available for the current study analyses) would enable the examination of the developmental trajectory of inhibition without the reliance of making the additional age-adjustment, and thereby eliminating the potential confounds of a non-representative normative group. This could be the focus of a future study.

**Hypothesis 2**

**Relationship of predictor variables**

The relationship between predictor variables is consistent with previous studies with this cohort (Eyler et al., 2008, Eyler et al., 1998; Behnke et al., 2006) as well as with published literature from other longitudinal cohorts (Chasnoff et al., 2002; Singer et al., 2002; Singer et al., 2008; Bauer et al., 2005; Bandstra et al., 2004). The current study further supports the relationship between birth head circumference and characteristics of the child (i.e., gender) and the child’s prenatal history (i.e., prenatal exposure to other drugs). The relationship between head circumference and gender is consistent with many studies of neonatal anthropomorphic gender differences of humans (for a review, see Ellis et al., 2008) in both exposed and non-exposed infants.

Additionally, it has been documented that prenatal cocaine exposure negatively affects birth head circumference in published studies using the current cohort (Eyler et al., 1998) as well as in other human (Chasnoff et al., 2002; Singer et al., 2008) and animal (Lidow, 2003) studies. Although the direct mechanism of this relationship is not known, it is generally agreed that head circumference at birth may serve as an early
marker of brain growth impairment and act as a proxy for detecting the teratogenic effects of PCE (and other drug exposures) on in utero brain development.

**Relationship of predictor variables and the development of executive functions**

Though somewhat surprising that PCE did not directly predict the development of any EF as hypothesized, several issues help provide potential explanations. Although there have been no published studies using latent growth modeling methodology to investigate these relationships, the current literature using cross-sectional analyses suggests little, if any, consistent significant effect of PCE on the cognitive functioning in children. Generally, the effects of PCE are indirect and are associated with birth head circumference or other variables that are often commonly associated with prenatal drug exposure (i.e., the quality of the home environment).

Although the current study did not examine mediation effects of head circumference on the development of cognitive functioning, as head circumference was used as a separate and unique predictor variable in each model, several published studies have demonstrated indirect influences of cocaine on cognitive and neurobehavioral functioning via head circumference in children. Chasnoff et al. (1992) and Singer et al. (2002) demonstrated significant correlations between head circumferences at various ages up to 24 months and Mental and Psychomotor indices of the Bayley Scales of Infant Development (BSID, Bayley, 1969) in children prenatally exposed to cocaine, alcohol, tobacco, and/or marijuana.

Previous reports from this same cohort of children as well as studies using other cohorts have found indirect effects of cocaine via head circumference in children three years of age and older. Using structural equation modeling with the original cohort from which current study participants were drawn, it was found that, at three years of age,
developmental outcome as measured by a factor comprised of BSID scores and four subtests of the Vineland Adaptive Behavior Scales (Sparrow, Balla, Cicchetti, 1984) was predicted by birth head circumference, which itself was predicted by cocaine exposure after controlling for alcohol and tobacco exposure (Eyler, Behnke, Garvan, Wobie, & Hou, 2002).

Azuma and Chasnoff (1993) used path analyses to examine the relationships between prenatal and birth characteristics and developmental outcome of children at age 3 years who were exposed prenatally to cocaine and other drugs. Findings suggested that, while PCE was not a direct predictor of the Stanford-Binet Intelligence Scale-Fourth Edition (Thorndike, Hagen, & Sattler, 1986), it did have an indirect effect on composite IQ and was mediated indirectly through head circumference and home environment. More recently, Singer et al. (2008) found an indirect effect of PCE on perceptual reasoning abilities through its effect on birth head circumference in a group of exposed and non-exposed children at age 9 years. Therefore, head circumference may represent in utero teratogenic effects on brain development and appears to play a role in cognitive development. Specifically, intrauterine cocaine exposure has been hypothesized to impair fetal brain growth through direct effects of cocaine on cell division, cell migration, and neurotransmitter function within the developing brain (Bateman & Chiriboga, 2000; Zachor, Moore, Jin, Theibert, & Percy, 1998).

With regard to performance on EF outcome measures, structural equation modeling with the present study’s original cohort at age 5 and 7 years demonstrated that a smaller head circumference at birth was significantly associated with worse performance on a factor score comprised of measures of executive functions. Further,
PCE was indirectly associated with executive functioning through a direct negative effect on birth head circumference (Eyler et al., 2009).

The results of the current study demonstrated that birth head circumference, when adjusted for gestational age, significantly predicted inhibition and working memory ability at age 7 and the development of inhibitory control in a combined group of non-exposed and exposed children, with smaller head circumference predicting worse performance and development. Children who were prenatally exposed to cocaine in the current study did have a significantly smaller head circumference at birth compared to non-exposed children. However, the mean difference between groups was less than one centimeter and disappeared by six months of age, suggesting that even a subtle initial size difference may be clinically meaningful with regard to cognitive outcome.

It is surprising that shifting ability was not significantly related to birth head circumference, or other predictor variables, as hypothesized. There are several reasons that could account for this. For instance, with regard to the specific measures of executive function, the variables representing working memory and inhibition may be more sensitive representations of cognitive ability, thereby representing better measures of potential cognitive effects of small head circumference. The use of a transformed ratio score to represent shifting ability may have restricted the range of scores derived from performance. For instance, the range of shifting ratio scores at age 12½ years was .88, while the range of scores for the other measures was much larger, thereby increasing the possibility for individual performance variance within the respective domain. For the value ranges of the outcome variables at each time point, refer to Table 3-4.
Predictor variables in latent growth models essentially account for variability in the dependent variable (i.e., in this case, the three measures of executive function). The more variability among individuals on an outcome score, the more likely a predictor variable will be able to account for this variability should a relationship exist. Significant variability between individuals was demonstrated on measures of working memory and inhibition, while the variable representing shifting ability lacked significant variability (both for the intercept and the slope). Thus, lack of performance variability on the shifting task in the current sample may have contributed to failure to find a relationship with head circumference (or other predictor variables), either at baseline or across developmental time points.

Contrary to previous studies of this cohort (Eyler et al., 2009), being female did not significantly predict better executive functioning at age 7 years. Previous studies on the development of executive functioning in typically developing, non-exposed children do not provide any consistent data on sex effects. Welsh, Pennington, and Grossier (1991) found no significant main effects of gender on any measures of executive function and no interactions between age and gender. In contrast, Berlin and Bohlin (2002) found preschool boys to have a lower level of inhibitory control than girls. Similarly, Carlson and Moses (2001) found 3- and 4-year-old girls to significantly perform better than boys on measures of inhibitory control. Thus, although gender effects were previously demonstrated within this cohort at age 7, these findings were not replicated and gender did not predict the development of executive functions. This finding is partially consistent with previous literature in typically developing children.
The quality of the home environment represented a significant predictor of working memory abilities, though no effect was found with regard to inhibition or shifting abilities. Previous studies with the original cohort have found the quality of the home environment to be a significant predictor of executive functioning as represented by a factor score as opposed to individual measures (Eyler et al., 2009). Using structural equation modeling at age 5 and 7 years, Eyler et al. found the path coefficient between quality of the home environment and executive functioning latent factors to be larger than that between birth head circumference and executive functions.

In the current study, the quality of the home environment significantly predicted the initial level of performance of working memory at age 7 years; though the effect appears to attenuate over time, as the home environment did not significantly predict the developmental trajectory of working memory. Thus, the current study revealed that the effects of the home environment on working memory may be “short-lived” and not have a lasting impact over time on development.

The home environment did not significantly predict the initial level or the development of inhibition or shifting ability. This may be due to measurement issues, such as the lack of significant individual variability found within these measures. The predictive effects of the quality of the home environment on working memory are generally consistent with the literature, in that a negative, distressed home environment may serve as a risk factor in the development of cognitive abilities (Farah, Noble, & Hurt, 2005; Behnke et al., 2006; Morrow et al., 2006; Singer et al., 2004). However, current study findings suggest that this relationship is not necessarily universal for all executive functions.
Taken together, the results of the current study suggest that the effects of PCE, if any, on executive functions in school-age children are subtle. In fact, it appears that there is no direct effect of PCE on the developmental trajectory of executive function. The effects of PCE on childhood development may be better accounted for by the multiple risk factors for poor outcome generally associated with PCE, such as exposure to multiple substances in utero, poverty, and poor caregiving environments. These findings support the importance of taking into account complex pre- and postnatal factors when attempting to explain the developmental outcome of children with PCE. This line of research will not only help explain the cognitive outcome in children with PCE, but also help provide targets for intervention and identify areas for prevention.

**Study Strengths**

The strengths of the present study primarily lie in the strong methodology used in the original study from which current participants were drawn and in the use of latent growth curve modeling. First, the original study utilized several sound methodological practices, including the use of *a priori* matching criteria for the comparison group and blinded examiners. The original study groups were matched for demographic variables. The similarities between the two groups were maintained in the current study, and therefore, these variables are controlled for by design.

The original study also used examiners blinded to the children’s cocaine exposure status. Examiner bias can lead to significant distortions in data (Kazdin, 1980). Frank et al. (2001) excluded 20 studies in their review because they did not protect against examiner bias by masking cocaine exposure status. The specific negative examiner bias with children labeled as prenatally cocaine exposed has been well-documented,
and its control represents a major strength of the study (Thurman, Brobeil, & Ducette, 1994; Woods, Eyler, Conlon, Behnke, & Wobie, 1998).

Another strength of the current study lies in the high retention rate of the participants that remained in the study. Fewer than 10% of the surviving children were completely loss to follow-up or declined continual participation. After eliminating participants with missed data, the current study sample represented 77% of the original sample, and thorough analysis of the characteristics of the sample revealed similar pre- and post-natal child characteristics. Because these similarities were maintained, it can be assumed that any attrition over the course of the study period was not significantly related to differential cocaine exposure, or other factors (i.e., other prenatal drug exposures, gestational age, or ethnicity).

In addition to controlling for confounding variables by design, the current study also controlled confounds through the use of analytic methodology. The potential impact of prenatal drug exposures other than cocaine was controlled analytically by creating a latent variable representing a cumulative score of substances that was allowed to covary with PCE. Failing to control for confounding variables, especially other drug exposures, is perhaps the one of the most common flaws in the literature on children with PCE that potentially creates spurious assumptions about outcomes.

The use of latent growth curve modeling has never been used to investigate cognitive outcome in children with PCE and represents a significant contribution to the literature. Latent growth modeling is the most powerful statistical tool to investigate longitudinal change and allows for more precise exploration of potential cocaine associated deficits. Structural equation modeling allows researchers to examine
relationships between multiple variables that cannot be adequately investigated using traditional methods. The use of structural equation modeling also allows for the utilization of all possible data through the use of full information maximum likelihood (FIML). As such, this technique allows for more powerful and representative analyses of potential relationships.

Finally, using a structural approach to latent growth models, each variable is allowed to contain some measurement error. For instance, most studies report the reliability of cognitive measures should be approximately .80 (Lezak, Howieson, & Loring, 1994). Conventional statistical procedures assume that there is no error, while structural modeling accounts for the variance by incorporating time-specific measurement error into the model. Thus, including predictors in latent growth modeling allows researchers to ask if change in one variable leads to change in another variable in a more dynamic way than in traditional analyses. The impact of a predictor on development can be investigated at the level of the relatively stable, starting off point of an attribute (i.e., the intercept), the rate of change of the attribute (i.e., the slope), and the amount of individual variation of the attribute within and between each child.

Study Limitations

Measurement Issues

One of the primary limitations of the current study is the use of single measures to represent each of the three domains of executive functioning. Inhibition, working memory, and shifting represent complex domains of executive functioning and involve utilization of a number of overlapping and disparate structures of the brain. The use of a score from a single measure may not adequately represent each respective domain, and significantly reduces the likelihood that the score reliably and validly represents the
cognitive construct in question. The problem of task impurity hinders interpretation of results. Task impurity refers to the assumption that a single measure of a given construct (i.e., working memory) can rarely be viewed as a pure measure of that construct.

For instance, working memory, as represented by the total raw score from the Digit Span subtest, included performance on the digits forward and backward component of the task. It is generally accepted that the digits forward component is more of a measure of attention, while the digits backward component requires manipulation of information, and is generally considered a better representation of working memory. Therefore, this measure of working memory may not adequately represent the domain within a developmental context, as children who obtained the same score could have considerable differential performance on the different components of the task, which represent two unique cognitive abilities with differential developmental trajectories.

Furthermore, the trail making ratio score was derived from two components (completion time of Part A and Part B) of a speeded task. Although the use of the ratio attempted to partial out processing speed and general visual scanning abilities, good performance on this task requires intact abilities other than shifting, such as visual attention, working memory, and graphomotor efficiency.

Finally, the use of scaled scores to examine the development of inhibitory control was discussed previously, though no doubt represents a limitation of the study. The use of raw scores would enable a better representation of development within the study
sample, as opposed to relying on the published normative sample that may or may not be appropriately representative of the study participants.

**Generalizability Issues**

The majority of prospective, longitudinal studies on outcomes of children prenatally exposed to cocaine funded by the National Institute on Drug Abuse (NIDA) are based in urban cities, including Baltimore, Boston, Chicago, Cleveland, Detroit, Miami, and Pittsburgh. In contrast, participants in the current study reside in rural, north central Florida. Although the majority of participants in all NIDA-funded studies are from poor and/or impoverished environments, whether from urban cities or rural Florida, significant geographical differences could influence a number of factors that are related to developmental outcome. It is likely that the quality of drugs varied, and although mothers from different geographical regions could report the same amount of cocaine usage while pregnant, the impact on the fetus could be significantly different based on the differential potencies of the drug.

Other region-specific varying environmental factors have been documented to significantly affect developmental outcome (i.e., lead exposure) and may represent a transactional relationship between the family environment and brain development. Further, there are a number of potential post-natal protective factors that likely vary between regions, such as the availability of community, school, or family support. Thus child development could be differentially impacted by effects mediated through environmental variables.

**Future Directions**

The current study represents the first attempt to utilize latent growth modeling to elucidate the relationship between PCE and the development of executive functions.
The majority of suggestions for future studies relate to measurement issues. First, future studies should utilize an approach that minimizes the difficulties inherent in measuring domains of executive functioning (i.e., task impurity). This can be done by using multiple tasks to represent a single EF domain and create a latent factor, which statistically extracts the variance common in the tasks. The latent variable could then be used to represent a domain of executive functioning within a structural model, thereby representing a more “pure” (i.e., representative) measure of a specific domain. This issue is especially important in studies measuring the same domain over time, as statistically it is assumed that the same construct is being assessed at each time point. Using a time variant latent variable, or deriving a factor score from several measures of EF at each time point, would increase the reliability that the respective domain was accurately being represented over time.

Second, future studies should attempt to tease apart potential differences in children with PCE, as it is possible there are subgroups of children that may vary in their cognitive trajectory. Previous studies have documented dose-response and timing effects of PCE on cognitive outcome (Bandstra et al., 2001; Rose-Jacobs et al., 2009) and it may be that significant relationships between PCE and outcome were not demonstrated because subgroups of children were combined in the current study. Exposure to multiple teratogens also potentially represents an important subgroup difference, and cocaine-using mothers rarely use cocaine in isolation. It is reasonable to hypothesize that interactions among different drugs may produce potentially neurotoxic metabolites and may create further, more detrimental, effects on cognitive development (Mayes, 2001; Randall, Cook, Thomas, & White, 1999).
Finally, given the results of the current study and the failure to find a direct PCE effect on cognitive development, it is imperative that future studies include variables to take into account the transactional effects across the course of development. As demonstrated in the current study, as well as in the majority of previous studies, there are many interrelated factors that may impact developmental outcome above and beyond that of PCE. Examples of salient factors include caregiver attitudes, caregiver intellectual and reading abilities, changing and multiple caregivers or out of home placements, family functioning, and acquisition of intervention and support. It is likely that the interactions of these factors affect the long-term multidimensional outcome of children with PCE. Continued use of more advanced statistical modeling methodology will enable future researchers to incorporate multiple factors of the child and child’s environment to better represent the potential teratogenic impact of PCE and the transactional relationships of multiple risk factors and cognitive development. By elucidating a pattern of relationships, potentially efficacious and cost-effective interventions that target the specific area of need can be implemented.
LIST OF REFERENCES


BIOGRAPHICAL SKETCH

Sarah Jean McCann was born in Corvallis, OR and was raised by her parents, Martha and Joseph McCann. Sarah earned her Bachelor of Science degree in psychology with a concentration in biology and philosophy from the University of Tampa in 2003. Sarah enrolled in the University of Florida’s doctoral program in clinical psychology in 2005. Her primary area of study was neuropsychology with a focus on pediatric populations. Following completion of graduate studies at the University of Florida, she completed a predoctoral internship at the Kennedy Krieger Institute, Johns Hopkins University School of Medicine. Sarah completed rotations in pediatric neuropsychology and pediatric psychology consultation. She is currently pursuing a clinical postdoctoral residency in pediatric neuropsychology at Emory University School of Medicine and Children’s Healthcare of Atlanta.