Abstract

THE EFFECTS OF PRENATAL COCAINE EXPOSURE ON EXECUTIVE FUNCTIONING IN ADOLESCENTS

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Executive functioning refers to higher-order cognitive skills (e.g., inhibition, shifting and sequencing), which improve with frontal lobe maturation from childhood through early adulthood. Research on executive functioning in children with prenatal cocaine exposure (PCE) has yielded inconsistent results, with some studies showing poorer performance for children with PCE compared to typically developing controls and others showing no group differences. To date the literature on the effects of PCE on executive functioning has been limited to early and middle childhood. The frontal lobe and associated brain regions involved in executive functioning undergo extensive development during late childhood and adolescence. Questions remain about whether subtle negative effects of PCE become more evident with specialization of the brain regions involved in executive functioning. The purpose of the current study was to assess the effects of PCE on executive functioning measures in adolescence. Participants (N = 50, 14 - 16 years) are predominantly African American living in rural communities and of lower socio-economic status and at birth were prospectively enrolled in a longitudinal study. Adolescent participants were administered four measures of executive functioning abilities of increasing complexity: the Stroop Color-Word Test (Stroop), Trail Making Test (TMT), Wisconsin Card Sorting Test (WCST), and Iowa Gambling Task (IGT). Group comparisons between PCE and non-PCE adolescents were made using the Wilcoxon Rank Sum test and the ANOVA was used to determine

whether there was a PCE by gender interaction. Multiple regression modeling was used to assess the unique effect of PCE on executive functioning performance while controlling for other drug exposures and gender. Results indicated that there were no group differences between PCE and non-exposed adolescents and no evidence of a PCE by gender interaction on any of the measures of executive functioning. None of the models for predicting Stroop, TMT, WCST, or IGT scores were statistically significant. In this sample of adolescents, there was no evidence indicating that PCE predicts outcomes of executive functioning performance. This study adds to a growing literature base demonstrating that PCE is not related to significant decrements in executive functioning when compared to a well-matched control group.

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CHAPTER 1: INTRODUCTION

Cocaine and other illicit drug use by pregnant women is a significant public health problem in the United States. In a recent National Survey of Drug Use and Health (NSDUH, 2005), 4% of pregnant women reported using illicit drugs (e.g., marijuana, cocaine, opiates), which is an increase from the 2.3% prevalence rate in 1994 (Bhuvaneswar, 2008) and the 2.8% rate in 1996-1998. Of the 2.8% using illicit drugs, 10% reported cocaine use (Ebrahim & Gfroerer, 2003). During the late 1980s and early 1990s, infants born to mothers who abused crack cocaine were written off as a lost generation of "crack babies" who would be severely low-functioning, both academically and socially (NIDA, 2009). Although these claims have proven to be exaggerated, there is some evidence that PCE may have subtle effects on development (Frank, Augustyn, Knight, Pell, & Zuckerman, 2001).

Researchers use the teratogenic model to inform their investigations of the developmental effects of PCE. The basic concepts of teratology were first proposed by Wilson (1973) and later refined by Vorhees (1989). A teratogen is a toxic agent that crosses the placenta and can have deleterious structural or functional effects on the developing fetus. According to the teratogenic model, exposure to a teratogen during fetal development can affect the organism's development in one of four ways: death, physical malformation, growth abnormalities and functional abnormalities (Vorhees, 1989). Studies of animal and human models have been used to investigate whether PCE can result in one or more of these outcomes.

Cocaine can directly affect fetal development by a crossing the placenta, entering blood circulation, and passing through the blood-brain barrier and indirectly via its negative effects on maternal behavior and self-care (Holzman & Paneth, 1994). According to Holzman and Paneth (1994) some studies have reported stillbirth in animal models, perinatal death sudden infant

death syndrome, or spontaneous abortion in humans. However, a review argued that severe effects are exaggerated and after controlling for polydrug use are unlikely attributed specifically to PCE (see references in Frank, Augustyn, Knight, Pell, and Zuckerman, 2001). In human studies, PCE has been associated with reduced head circumferences and lower birth weights as compared to infants in matched control groups (Eyler, Behnke, Conlon, Woods, & Wobie, 1998; Mayes, 2002; Singer et al., 2004; Spear et al., 2002) and these effects have been attributed to heavy and prolonged PCE (Frank et al., 2001). With the exception of a few studies (e.g. Eyler et al., 1998), most did not control for confounding variables, such as polydrug use (e.g., alcohol, tobacco, and marijuana) and maternal characteristics (e.g., nutrition, poverty, prenatal care, postnatal neglect and parenting practices; Holzman & Paneth, 1994; Mayes, 2002).

Teratogenic effects of PCE on the developing fetus are theorized to have lasting implications on postnatal development (Mayes, 2002). Cocaine-induced vasoconstriction in the mother affects blood flow in the fetus causing both hypoxia- and hypoxemia-related effects. These effects can be detrimental to both the development of the cardiovascular system and blood flow to the brain. Thus, depending on the amount and timing of exposure during gestation brain development could be disrupted causing either global or specific damage to different brain regions (Mayes, 2002).

Research with animal models indicates that PCE alters the way the nervous system regulates dopamine (Stanwood and Levitt, 2004). Mayes (2002) proposed a behavioral teratogenic model explaining the mechanisms by which PCE affects the developing nervous system, specifically functional abnormalities in monoaminergic systems involving the regulation of dopamine, norepinephrine, and serotonin. Animal studies supporting this model have shown PCE-associated effects in brain regions strongly innervated by dopamine fibers including the

nucleus accumbens, frontocingulate cortex, mesolimbic, and neostriatal regions (Harvey, 2004). Specifically, PCE causes an uncoupling effect of the D1 dopamine receptor from its G-protein in the caudate nucleus, frontal cortex, and cingulated cortex, which was still present at post natal day 100 in the rabbit model (Harvey, 2000). This can have downstream effects on receptor neurons in the substantia nigra and ventral tegmentum causing dampening or reduced neurobehavioral responses (Dow-Edwards, Mayes, Spear, & Hurd, 1999; Harvey, 2004). Dow-Edwards and colleagues (1999) also found indirect PCE effects using a rat model for which increased D2 receptor activity occurred in the thalamocortical circuit. Results from a meta-analysis show that the strongest effects of PCE are found during adolescence in the striatal tissue where receptor densities for D1 receptors are decreased and D2 receptors are increased and in males who have decreased D1 density (Glatt, Bolanos, Trksak, & Jackson, 2000). These effects may alter functioning of arousal, attention, and regulatory systems, which could manifest into postnatal deficits in cognition and behavior.

CHAPTER 2: REVIEW OF THE LITERATURE

The effects of PCE may have long-lasting implications on brain development, behavior, and cognition, which may not be realized until the child reaches an age at which these abilities are necessary, such as in school-settings and psychosocial functioning. This delay has been termed the "sleeper effect." Sleeper effects are a phenomenon in which one who may receive an insult to the brain early in development (pre- or post- natally) and the effects this has on functioning may not become evident until the age is reached where cognitive abilities subserved by that injured region of the brain are required (Goldman-Rakic, 1987). For instance, an individual with an insult to the brain may perform at an average rate on tests of attention during middle childhood, however during adolescence they may show less than normal performance on assessments involving more complex cognitive processes such as both attentional and inhibitory control. Thus, sleeper effects as a result of PCE may emerge during adolescence resulting in impairments in social and academic functioning that require successful integration of executive functioning for goal-directed behavior.

In summary, the prevalence of cocaine use among pregnant women and the relative uncertainty regarding its effect on fetal development has initiated investigations by researchers to determine the teratogenic effects of PCE. Initial concerns that PCE result in severe effects such as death, gross physical malformations, or mental retardation have proven inaccurate. However, well-designed preclinical studies have shown that PCE effect functional neurocognitive, neurobehavioral development in more subtle ways.

Prior to discussing the potential impact of PCE on executive functioning it is important to understand the development of these abilities in typically developing populations. Over the past decade, multiple disciplines including, cognitive psychology, developmental psychology, and

neuropsychology have made significant advances in research in order to elucidate the construct of executive functions. Currently, researchers and clinicians are trying to operationalize executive functioning as well as understand and demarcate the developmental milestones associated with executive functioning and its subfunctions.

Development of Executive Functions

Many definitions of executive functioning have circulated through the literature. Luria (1973) is perhaps one of the first to describe executive processes as supervisory functions that formulate intentions, plan, and control. Baron (2004) expanded the definition as the processes individuals use to "perceive stimuli from [their] environment, respond adaptively, flexibly change attention, anticipate future goals, consider consequences, and respond in an integrated or common sense way" for the purpose of achieving a goal (p. 135, para 2). Therefore, executive functioning refers to the integration cognitive processes during goal-directed behavior (Miller & Cohen, 2001). Most definitions of executive functioning include goal-directed behavior as the primary construct; however, there remains considerable debate on how to conceptualize and operationalize executive functioning and its subfunctions.

The areas of the brain subserving executive functioning, the frontal lobe and prefrontal cortex, undergo the most extensive development throughout late childhood and adolescence (Casey, Tottenham, Liston, & Durston, 2005; Paus, 2005). Advances in neuroimaging have enabled researchers to identify structural and functional developmental changes in these areas. Casey and colleagues (2005) explain that frontal lobe development is a dynamic process beginning at the motor cortex during infancy and spreading forward where final maturation occurs in the prefrontal cortex during late adolescence and early adulthood. In a longitudinal study, Gogtay and colleagues (2004) obtained MRI brain scans from typically developing

individuals ages 4 to 21. Differential neurodevelopmental trajectories were reported in this study with regions responsible for motor, sensory, and visual functioning developing during childhood followed by development of the prefrontal dorsolateral and temporal regions responsible for integrating lower order functions during adolescence. This process involves both regressive and progressive changes, which yield more specific and efficient cognitive functioning and eventually result in improved executive functions such as working memory and behavioral inhibition (Paus, 2005; Tsujimoto, 2008).

Researchers have used findings from adolescent brain development research to inform their understanding of typical and atypical development of executive functioning. However, the organization of executive functioning has been a controversial topic. Theoretical considerations began with studies using adult samples and only recently have researchers begun investigating the development of executive functioning. Factor analytic techniques with data from adult neuropsychological measures have been used to identify those cognitive processes that fall under the umbrella term, executive functioning (Duncan, Burgess, & Emslie, 1995; Miyake et al., 2000).

Duncan and colleagues (1995, 1996, 1997) have investigated the validity of the unitary theory of executive functioning. This theory proposes that executive functions, similar to fluid intelligence, are the mental processes employed to devise "effective task plan[s] by activation of appropriate goals or action requirements" (Duncan, Johnson, Swales, & Freer 1997, p. 716). Research supporting this theory has shown that there are cognitive mechanisms shared by functions thought to comprise executive functioning. Moreover, the variance shared across measures is indeed related to an over arching unitary construct. They concluded that although unique aspects of executive functioning were identified, it appears these sub-functions share a

common underlying construct related to goal directed behavior and fluid intelligence (Duncan, Emslie, Williams, Johnson, & Freer, 1996; Duncan, Johnson, Swales, & Freer, 1997).

The diversity theory suggests that executive functioning is comprised of a set of moderately correlated sub-functions operating under distinct cognitive processes (Miyake, 2000). The basic subfunctions studied are assumed to be underlying abilities for more complex executive processes like planning, reasoning, and decision-making. Miyake et al., (2000) proposed a three-factor model of executive functioning: shifting, inhibition, and working memory. Shifting is the ability to flexibly switch perspectives or attention from one mental set to another. Inhibition is the ability to ignore distracting stimuli, resist making a prepotent response in order to make a better or more appropriate response. Working memory is the ability to hold information in mind and manipulate it. Factor analytic and developmental studies have supported both the unity and diversity theories of executive functioning (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Duncan, et al.,1997; Huizenga, Dolon, Van der Molon, 2006; Lehto, Juujarvi, Kooistra, Pulkkinen, 2003; Tsujimoto, 2008).

Recently researchers have examined changes in the cognitive performance from children to adolescence in order to elucidate the neurodevelopmental trajectory of the subfunctions of executive functioning. The validity of Miyake's three-factor model of executive functioning has been investigated in child and adolescent populations. Huizinga and colleagues (2006) investigated age-related changes in executive functions in youth ages 7, 11, 15, and 21 years. Results showed that adult levels of performance were reached at 15 years of age on two measures of working memory and 15 years of age for three measures of shifting performance. Inhibition was assessed using the Stroop task and a measure of complex executive functioning, the Wisconsin Card Sorting Task (WCST), and performance did not mature until young

adulthood (Huizinga et al., 2006). Miyake's three-factor model was also replicated in a study by Lehto et al., (2003), which looked at a sample (N = 108) of typically developing 8- to 13- year old children. Performance on nine of 14 of the executive measures showed a strong positive correlation with age. Measures of working memory and shifting were significantly correlated, but inhibition had only a weak correlation with working memory and shifting (Lehto et al., 2003). These results suggest that working memory and shifting abilities develop by preadolescence, however the cognitive processes required for efficient integration of multiple subfunctions continue to develop in adolescence and into early adulthood. Additionally, using this neuropsychological battery, a three-factor model fit the data significantly better than a one-factor model.

In addition to developmental trends associated with executive functioning, Klenberg, Korkman, and Lahti-Nuuttila (2001) modeled the sequential development of certain abilities in a large sample (N = 400) of Finnish children, ages 3 to 12 years. They showed that inhibitory motor functions and impulse control begin maturing at age 6 with more complex control of inhibition and shifting abilities emerging at the age of 7. Importantly, these researchers found a sex difference in that girls performed better than boys on subtests of inhibition from 3 to 5 years of age. This study provides further evidence that there are distinct developmental trends for the various executive subfunctions and they potentially develop at different rates depending on the sex of the child.

Some researchers suggest that inhibition is a core construct of executive functioning (Logan & Verbruggen, 2009). In order for goal-directed behavior to occur self-regulatory skills, including the ability to inhibit unwanted behaviors, must be well-developed. Therefore, as with executive functioning, researchers have investigated the uni- versus multi-dimensional nature of

the construct of inhibition in order to assess its role in cognitive and behavioral dysfunction. Inhibition had once been considered an intrinsic component to the working memory system (Brocki & Bohlin, 2004). However, Miyake and colleagues (2000) study using factor analytic techniques lends evidence to the idea that inhibition is a distinct subfunction from working memory. Perhaps working memory and inhibition utilize or share the same cognitive resources. For example, Nigg (2000) describes cognitive interference, an element of inhibition, as a form of protection for working memory in which irrelevant information is suppressed.

Nigg (2000) in his literature review describes inhibition as having multiple levels of complexity with clear sequential developmental trends. For instance, during early childhood (e.g., first grade) children have yet to develop cognitive interference, by third grade they begin to show some ability to overcome cognitive interference, by late childhood and early adolescence this ability shows some improvement, and it is not until early adulthood that this ability is mastered. Additionally, neuropsychological measures of inhibition have been used extensively to understand the development of response inhibition. For the purposes of the proposed project, only the developmental trends of inhibition that have been identified by assessing performance in the Stroop task will be discussed. Leon-Carrion, Garcia-Orza, and Perez-Santamaria (2004) assessed age-related trends in performance on the Stroop in Spanish-speaking children and adolescence ages 6 to 17 years ($N = 99$). Results of this study indicated that interference increases in younger age groups but then progressively decreases until 17 years (Leon-Carrion et al., 2004). The researchers concluded that the change in ability can be attributed to the increase in reading abilities, therefore, when children obtain proficient reading skills they then are able to overcome interference which increases their accuracy during the task. These researchers found similar performance and developmental trends of inhibition among boys and girls (Leon-Carrion

et al., 2004). The results of this study strongly suggest that developmental trends exist even within the subfunction inhibition. Thus, inhibitory abilities may not reach maturity until the required cognitive processes are fully developed and integrated.

In summary, the maturation process of executive functioning and its associated brain regions take at least two decades, encompassing the periods of childhood and adolescence. During this time dynamic structural changes in the brain include gray and white matter volume maturation and strengthening of connections (Casey et al, 2005; Gogtay, 2004). Brain development is localized to neuronal pathways (e.g. monoaminergic systems) within and between the prefrontal cortex, frontal lobe, limbic system and other regions associated with executive functioning, attention and arousal (Spear, 2000; Tsujimoto, 2008). Executive dysfunction may not be realized until adolescence when individuals are more responsive to reward and socioemotional contexts (Casey et al., 2008).

Collectively, three factors, working memory, inhibition, and shifting, are considered crucial to normal executive functioning, and they are generally assumed to be underlying abilities for more complex executive processes like planning, reasoning, and decision-making (Miyake, 2000). Impairment in one of these abilities may affect the more complex processes. Distinct structural and functional developmental trends are apparent with increased specialization and efficiency occurring during adolescence (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Huizinga, Dolon, Van der Molon, 2006; Lehto, Juujarvi, Kooistra, Pulkkinen, 2003; Tsujimoto, 2008). This complexity can be appreciated with the example of developmental trends for inhibitory abilities. The current project uses four measures of executive functioning in order to evaluate whether PCE affects the development of dopaminergic pathways and subsequently affects those executive functions subserved by the frontal and prefrontal cortices.

Effects of PCE on Cognitive Development

Research on the cognitive development of children with PCE has been limited to infancy, early, and middle childhood. Based on a systematic review of nine prospective studies of infants and young children with PCE, Frank and colleagues (2001) concluded that there is no consistent effect of PCE on cognitive development. Five studies using nationally normed assessments found no effect of PCE on cognitive development while four studies reported subtle effects of PCE. In the four studies reporting significant PCE effects, the effect disappeared when other drug exposures and confounding factors were controlled or the effects were only found in sub-groups of infants with heavy cocaine exposure (Frank et al., 2001). In summary, studies assessing the development of children with PCE prior to age 4 have not consistently found significant deficits in cognitive functioning.

Studies assessing global intelligence among school-age children with PCE and non-exposed children have found, at most, subtle differences. With the exception of one study, researchers assessing global IQ and overall academic performance have found no significant group differences between exposed and non-exposed children (Delaney-Black et al., 2000; Hurt, Brodsky, Roth, Malmud, & Gianetta, 2005; Pulsifer, Butz, O'Reilly, Foran, & Belcher 2008; Singer et al., 2004; Singer, Nelson, Short, Min, Lewis, Russ, 2008; Wasserman et al., 1998). Arendt and colleagues (2004) found difference in global and verbal IQ between PCE and non-PCE groups at age 7; these differences were attenuated after controlling for environmental and other prenatal factors. However, subtle differences have been found in specific areas of cognitive functioning, in which children with PCE show poorer performance than non-exposed children on tests of perceptual reasoning (Singer et al., 2008), abstract reasoning and working memory (Bennett, Bendersky, & Lewis, 2002), language ability (Delaney-Black et al., 2000), and visual-

spatial and mathematic skills (Singer et al., 2004). Notably, most studies report that both groups, exposed and non-exposed, performed below average on tests of intelligence (e.g., Pulsifer et al., 2004) for which scores are between 0.5 and 1 standard deviation below the mean (Ackerman, Riggins, Black, 2010). Deficits in these areas of cognitive functioning have largely been attributed to adverse developmental outcomes associated with being raised in poor care-giving and high-risk environments (Arendt et al., 2004; Bendersky, Gambini, Lastella, Bennett, & Lewis, 2003; Singer et al., 2004).

Additionally, some research has suggested that an interaction between cocaine exposure and sex, such that boys are at greater risk for developing impairments in cognitive functioning and arousal. Singer and colleagues (2004) evaluated a sub-sample of their original cohort and found, at four years of age, boys with PCE exhibited poorer arithmetic scores than non-exposed boys. In another cohort boys with PCE at four years of age had lower IQ scores and at five years of age made more errors on a test of inhibitory control than girls with PCE and non-exposed children (Bendersky et al., 2003; Bennett et al., 2002). Further, boys with PCE are consistently rated throughout childhood as having more by more hyperactivity, increased arousal and demonstrated more externalizing behaviors teacher and parent reports (Bada, 2010; Delaney-Black, Covington, Bailey, Ager, Janisse, Hannigan, 2004; Dennis, Bendersky, Ramsey, & Lewis, 2006; Minnes, Singer, Richardson, 2010). Moreover, Delaney-Black and colleagues (2004) reported that when they moderated for quantity of PCE, boys with persistent exposure exhibited increased behavior problems due to hyperactivity. Whether these differences persist or diminish in adolescence has yet to be determined.

In summary, the global functioning of cohorts of children with PCE is similar to that of their socio-demographically matched control groups. However, some subtle deficits have been

found in specific areas of cognitive functioning. Youngsters with PCE, particularly boys, may exhibit greater deficiencies as cognitive and psychosocial demands increase in adolescence. In conclusion, more research is warranted to identify whether these subtle differences become more pronounced in the later stages of life when the brain is more fully developed.

Effects of PCE on Executive Functioning

Due to the effects PCE has on the development of the dopaminergic pathways in animals and the subtle effect it has on in human cognitive development, it has been hypothesized that these children are at risk for developing more severe deficits in attention and other subfunctions of executive functioning. Thus, it is necessary to continue assessing for potential sleeper effects as relevant brain regions are becoming increasingly specialized during middle childhood and adolescence in this population.

Attention is one area in which researchers have consistently found subtle differences between children with PCE and controls. Computerized continuous performance tasks (CPTs) have been used across cohorts and other prenatal substance exposure groups to measure both sustained attention and response inhibition as indicated by errors of omission and commission and response time variability. Whether children with PCE performance are different from that of non-exposed children has yet to be determined based on conflicting findings. Some studies show that children with PCE and the non-exposed control groups do not differ on rates of omission (Accornero et al., 2007; Richardson, Conroy & Day, 1996), while Bandstra, Morrow, Anthony, Accornero, & Fried (2001), found that PCE had a unique effect, independent of other substance exposures, for which had more errors of commission at 5 and 7 years of age. These results suggest that PCE may negatively influence attentional processes.

Pulsifer and colleagues (2008) used the Gordon Diagnostic System (GDS), which assesses attention and impulse control, in 5 years-olds who were prenatally exposed to both cocaine and opiates. Comparisons of the cocaine-only and opiate-only groups revealed no significant differences in performance. Further, both exposed and non-exposed groups performed equally poorly on measures of sustained attention. The group exposed to both cocaine and opiates performed well below the mean on the measure of impulsivity. Additionally, Savage, Brodsky, Malmud, Giannetta, and Hurt (2005) used the GDS and reported, that at age 10, when compared to the non-exposed group, the PCE group made more commission errors on the Distractibility task which is the most difficult of all three tasks since it requires both greater sustained attention and impulse control. Finally, the Miami Prenatal Cocaine Study is currently evaluating the effects of PCE on development in a longitudinal study using Connor's CPT (Accornero et al., 2007). Results from their studies have shown at ages 5 and 7 years children with PCE make more omission errors on the CPT than the control group. This is consistent with previous research assessing children at 4 and 5 years of age (Dow-Edwards, Mayes, Spear, Hurd, 1999), for which CPT performance was moderated by level of cocaine exposure; children with heavy exposure performed significantly worse than children with moderate to light exposure. In summary, studies with CPTs have shown that PCE-associated effects in children include increased impulsivity and difficulty sustaining attention, which is perhaps moderated by level of cocaine exposure.

To date, three published studies have used the Stroop Color-Word task to investigate executive functioning in children with PCE (Mayes, Molfese, Key, & Hunter, 2005; Rose-Jacobs et al., 2008; Warner et al., 2006). The Stroop Color-Word task (Stroop, 1935) has been used in a wide variety of studies examining both typical and atypical development of executive

functioning. Participants are required to name the color of the ink that the word is printed in, thus inhibiting the initial desire to read the color word. Specifically, it is a timed task that measures cognitive flexibility and requires inhibition, selective focus of attention, and set-shifting. The Stroop task measures interference resolution and behavioral conflict resolution with better performance associated with greater maturation of prefrontal and frontal cortices in healthy children and adolescents (Adleman et al., 2002). Performance on the Stroop task requires attention, mental flexibility, and the application of rule governed behavior in the presence of conflicting cues (Rose-Jacobs et al., 2009). Mayes et al., (2005) reported that 7 – 9 year old children with PCE took significantly longer to respond during the Color-Word task. At 10 years of age, group differences in response time were not significant in a sub-sample of a children participating in a longitudinal study (Warner et al., 2006). According to Warner and her research team, the cocaine-exposed children performed more poorly on the Color-Word task than the non-exposed children. Furthermore, Rose-Jacobs and colleagues (2009) found that performance among youngsters 9 – 11 years of age was mediated by the amount of cocaine exposure, where the heavier exposed group had worse performance (i.e., greater interference) with age than the lighter to moderately exposed group. The analysis by age revealed that the heavy exposed group's performance, and to a lesser degree the lighter exposed group, worsened from age 9.5 to age 11. Although performance across exposed groups when they were assessed at age 11 were significantly different revealed a large effect size (eta-squared = 0.68; Rose-Jacobs et al., 2009). According to Mayes and colleagues,. (2005), slower reaction times exhibited by children with PCE indicate that the frontal lobe is not as specialized in functioning thereby inefficiently using diffuse brain regions to accomplish the interference task. Results from these studies suggest the

emergence of sleeper effects from PCE for which functional efficiency and inhibitory control is negatively affected as well as moderated by the amount of cocaine exposure.

Another test used to assess executive functioning in longitudinal cohorts of children with PCE is the Trail Making Test (TMT; Reitan, 1971) a timed visual-spatial subtest of the Halstead-Reitan Neuropsychological Test Battery that is employed to assess shifting between two cognitive sets, sequencing, and processing speed. Researchers have assessed cohorts ranging from middle childhood to early adolescence and have found no difference in time scores (Savage, Brodsky, Malmud, Giannetta, & Hurt, 2005). The cohort from which the current sample was drawn for the proposed project was assessed for their executive functioning abilities at ages 5 and 7 years on the TMT. Using the TMT part A, they concluded "the weeks of prenatal cocaine exposure to cocaine had an indirect effect on the performance on executive functioning tasks through cocaine's negative effect on [the infants head circumference at birth]" (Eyler et al., 2009, p. 11). Additionally, Warner and colleagues (2006) showed that children with PCE not only took significantly longer to complete TMT Part B but also the differences in time-to-completion were associated with the level of white matter integrity in the frontal lobe. Diffusion tensor imaging results from Warner's study indicate that faster completion time on the TMT Part B is associated with greater of diffusion in the frontal lobe, thus greater efficiency. In the same study, Warner suggests that the TMT Part B taps into language demands of interpreting letters and numbers. Similarly, children with PCE have shown poor performance on the Stroop task, which Adleman and associates (2001) have found includes elements of language including word reading and production. Delaney-Black and colleagues (2000) reported that children with PCE at 6 years of age were 2.4 times more likely to exhibit expressive language deficits than the non-exposed group. Collectively, these results suggest that PCE affects development in regions of the

brain (e.g., frontal lobe) associated with language, however more research is needed using these neuropsychological measures and neuroimaging techniques to elucidate the brain-behavior relationships.

To date the literature on the effects of PCE on executive functioning has been limited to early and middle childhood. It is unclear whether the subtle negative effects of PCE on executive functioning are exacerbated as cognitive demands increase during adolescence. Researchers are challenged with issues of identifying whether these sleeper effects can be attributed to prenatal cocaine exposure, postnatal environmental factors, or a result of an interaction between factors. Researcher of the proposed project will investigate the effects of PCE and other drug exposures (alcohol, tobacco, and marijuana) on executive functioning during adolescence using the Iowa Gambling Task, Wisconsin Card Sorting Task, and Trail Making Task, and the Stroop Task. Further, the current project will investigate whether there is a sex and PCE interaction that influences performance on each measure. It was hypothesized that:

1) Adolescents with PCE will perform worse than controls on each measure of executive functioning.
2) There will be a PCE by sex interaction in which boys with PCE will perform worse on measures of executive functioning than both girls with PCE and non-exposed boys and girls.
3) PCE, measured as a quantitative variable, will predict performance on measures of executive functioning; PCE will be associated with poorer performance. Potential confounders (sex and quantitative measures of prenatal exposure to tobacco, alcohol and marijuana) will be included in the model in order to determine the unique effect of PCE on executive functioning.

CHAPTER 3: METHODOLOGY AND RESULTS

Participants for the proposed project were a sub-sample of adolescents (19 boys, 26 girls) 13 to 16 years of age enrolled in a longitudinal study. The cohort of adolescents and their families was enrolled at birth in a NIH-funded study investigating the developmental effects of PCE, called Project CARE (Cocaine Abuse in the Rural Environment). Enrollment of participants in Project CARE, which is housed at the University of Florida, has been described in detail elsewhere (Eyler et al., 1998). Briefly, mothers of the adolescents were enrolled during pregnancy over a two year period (1991-1993) from two public health clinics when they presented for prenatal care and from the tertiary hospital when they presented for delivery. Mothers were predominantly Black, residing in rural communities, and in the lowest socioeconomic status. At enrollment, pregnant women identified as cocaine users were matched to socio-demographically similar pregnant women with no evidence of cocaine use. Compared to nonusers, mothers who identified as cocaine users presented to health clinics later and consumed higher amounts of alcohol, tobacco, and marijuana. Cocaine users were identified using a structured interview adapted from Day, Wagener, and Taylor (1985) as well as urine screens collected at two unanticipated times. Identification of illicit drug use was determined by self-report and urine toxicology screens. Amounts of cocaine consumption varied during pregnancy with 29% of mothers reporting use during their first trimester, 15% during the first and second trimester, and 32% throughout pregnancy. The remaining mothers reported variable use during pregnancy.

Children and families of Project CARE have participated in follow-up interviews and assessments at multiple time-points through age 16. The data included in the proposed project are a sample of 48 adolescents (18 being boys and 30 being girls), ages 14 -16, from Project

Care. The adolescents were assigned to one of two groups; the first group was comprised of participants who have a history of prenatal cocaine exposure (PCE+) and the second group was comprised of participants who have no history of prenatal cocaine exposure (PCE-). Participants were identified as PCE+ based on a positive result of maternal urine analysis during pregnancy. The current study sample was divided into two study groups as follows: 32 PCE+ (21 being girls and 11 being boys) and 16 PCE- (9 being girls and 7 being boys). Exclusion criteria included 1) presence of any serious physical illness or chronic condition, 2) left-handedness, and 3) presence of irremovable metal objects in the body. Inclusion criterion for participants was willingness to undergo all study procedures including collection of hair and urine samples for drug and/or pregnancy screening.

Neuropsychological Measures

Current literature suggests that PCE may negatively affect areas of executive functioning subserved by the monaminergic dopamine pathways and frontal lobe. Researcher of the proposed project will assess different constructs of executive functioning using four validated, standardized neuropsychological tests: the Stroop Color Word Test (Stroop; Golden, Freshwater, & Golden, 2003), the Trail Making Test (TMT; Reitan, 1971), the computerized Wisconsin Card Sorting Test version II (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993), and the Iowa Gambling Task (IGT; Bechara et al., 1994).

The Stroop task (Stroop, 1935) is a brief measure of cognitive flexibility, which requires inhibition, selective focus of attention, and set-shifting abilities. The timed task requires participants to name the color of the ink that the word is printed in, thus inhibiting the initial desire to read the color word. The Stroop has a long history of employment as a well-validated assessment of inhibition in both normal and clinical populations (e.g., ADHD, learning

disabilities; MacLeod, 1991; Nigg, 2000). Performance on the Stroop has been shown to improve steadily during adolescence thus reflecting the development of attentional processes throughout this period (Leon-Carrion et al., 2000). Additionally, the Stroop color and word task has been associated with activation in left lateral prefrontal cortex in pediatric neuroimaging studies (Adleman et al., 2002; Shroder, Snyder, Sielski, & Mayes, 2004). Multiple studies have used the Stroop to assess children with prenatal cocaine exposure (Mayes et al., 2005; Rose-Jacobs et al., 2008; Warner et al., 2006). The test-retest reliability for the Stroop task ranges from .71 to .91 (Golden, Freshwater, & Golden, 2000). Each participant was asked to read stimuli from the sheet as quickly as possible without making a mistake, with a 45 second time limit. Response inhibition is determined based on the interference score which is the number of items correctly read in the 45 second time limit as well as calculating the standardized Interference T-score based on published norms. Scores on the Color-Word task are also used as a reliable measure of interference (Stroop, 1935).

The TMT is a timed visual-spatial task from the Halstead-Reitan Neuropsychological Test Battery that is employed to assess shifting between two cognitive sets, sequencing, and processing speed (Reitan, 1971). Part A involves sequencing a set of numbers ranging from 1-15 which are randomly scattered across the paper. The TMT part A has been used to asses visuo-motor attention and sequencing abilities in individuals who have acquired damage to the frontal lobe (Reitan & Wolfson, 2004). Part B requires one to sequence numbers and letters in alternating form (e.g., 1 to A to 2 to B to 3 and so on). Part B is thought to rely heavily on executive functions because one is expected to inhibit the previously established number-to-number sequence rule and switch to a new set that requires number-to-letter sequencing. The TMT Part B has been used to assess neuropsychological and academic functioning in typically

developing children ages 9-14 (Demakis, 2004). Importantly, evidence from developmental studies in children ages 7 to 13 years have shown that performance on the TMT Part B improves as development of inhibition and sustained attention progresses (Kelly, 2000). The TMT has been used in a cross-sectional study to assess children with PCE (Savage et al., 2005). Notably, this measure has been used to assess the cohort the current sub-sample was drawn from at previous time points (Eyler et al., 2009; Warner et al., 2006). The reliability coefficients have been reported as 0.98 for the TMT part A and 0.67 for the TMT Part B. For the proposed project, shifting abilities will be assessed based on the time to completion on the TMT Part B.

The WCST requires matching cards to categories in response to feedback and is designed to assess mental flexibility, inhibition, self-monitoring, hypothesis-testing and problem-solving with adult-level performance reached by age 10 in typically developing children (Baron, 2004). The WCST involves matching one card to a series of four cards. The correct choice is determined by the category of shapes, color, design, and quantity, that the cards are sorted. The category for matching cards changes throughout the task, thus requiring the subject to overcome the tendency of sorting according to a previous rule and switch to sorting cards according to a to-be-discovered correct category (Aron, 2008). Heaton and colleagues (1993) reported that the internal reliability coefficients of the standard WCST for children and adolescents range from 0.37 - 0.72. The computerized method increases the reliability of results with its increased scoring accuracy. In the proposed project, four outcome variables from the WCST will be used for analysis of performance: number of categories completed, failure to maintain set, nonperseverative errors, and perseverative errors. The number of categories completed is a measure of overall performance based on the number of sequences of 10 consecutive correct matches, for which the maximum is 6. Perseverative errors are a measure of shifting ability

based on the number of times an individual makes a choice based on an incorrect category (Heaton et al., 2003). Nonperseverative errors are a measure of hypothesis testing based on the number of response one makes that is essentially random choosing of cards as opposed to persistently choosing cards based on a category (Heaton et al., 1993). Failure to maintain set is a measure of sustained attention based on the making an error in a category after previously making at least five consecutive correct choices in the same category.

The IGT is a computerized, decision-making task that involves affective decision-making skills which involves choices that have an immediate award versus one with delayed, long-term value (Anderson, Jacobs, & Anderson, 2008; Bechara, 1994). The IGT involves four decks of cards (A, B, C, and D) which have a positive or negative monetary value. Participants are asked to choose one card at time for 100 trials with the goal of winning money and avoid losing as much money as possible. Individuals are expected to discover, through trial and error, that certain decks are more advantageous in terms of money won and frequency of punishment (money lost). Evidence of the validity of the IGT has been presented in research with normal and clinical populations. Bechara et al., (2007) reports that the IGT is sensitive in detecting decision making impairments in clinical populations including; patients with neurological impairments, substance abusers, chronic pain patients, and those with impulsive aggressive disorders, however these studies have yet to be replicated. Performance on the latter portion of the IGT has also been shown to correlate with other measures of executive functioning like the WCST (Bechara, 2007; $r = 0.294 – 0.330$). Two studies have shown that the IGT is sensitive to developmental changes in the frontal cortex of the brain in healthy adolescents ages 9 to 17 years (Hooper et al., 2004) and boys with behavioral disorders, ages 9 to 16 years (Blair, Colledge, & Mitchell, 2001). Performance on the IGT also differed between healthy adolescents and those

with behavioral disorders (Ernst et al., 2003). Although adaptations of the IGT have been used with children and adolescence (Crone, Vendel, & van der Molan, 2003), this task's equivalence to the IGT has yet to be reported. The proposed project plans to analyze the groups based on six outcome variables obtained from performance on the IGT. One score is the net total, which is the difference between the total number of advantageous choices and the total number of disadvantageous choices across the 100 trials. This difference was calculated for each block of 20 trials (i.e., 5 blocks) as measure of performance over time.

Procedure

As in Project CARE, a Federal Certificate of Confidentiality was obtained to protect the data from disclosure. Study approval for data collection was approved from the University of Florida Institutional Review Board (IRB). Permission for data analysis was obtained from the East Carolina University IRB. Potential participants were sent a letter informing them of the opportunity to participate in a new research protocol related to the ongoing longitudinal study. Letters were followed by a telephone call by research staff to assess interest in study participation and answer any questions. During telephone contact, the study requirements and procedures will be explained to both the adolescent participant and his/her primary caregiver. Transportation to the study site was provided, if needed. A brief series of questions was used to screen interested participants to ensure that they meet participation criteria (e.g., medical history).

Prior to study participation, study requirements and procedures were reviewed, and signed informed consent from the primary caregiver and signed assent from the adolescent was obtained. Adolescents underwent standardized neuropsychological assessments by a licensed psychologist blinded to PCE status. Urine samples were collected, and girls were screened for

pregnancy. A 15-minute interview to establish rapport and obtain demographic information and medical history was followed by a 30-minute neuropsychological battery (five tests) designed to assess executive functioning. Hair samples were collected after all study measures had been completed. Breaks and snacks were provided as needed. Adolescents were received a $50 gift card to a nationwide retail chain for their participation.

Finally, the participants of the current study were drawn from a sample of adolescents recruited for a study designed to investigate brain development and behavior in adolescents with PCE. Specifically, researchers recruited adolescents from the original Project CARE sample to participate in a study investigating brain development and behavior. Thus, the data used in the current study is drawn from the sample of adolescents that participated in the brain development and behavior study.

Statistical Analyses

SAS 9.2 statistical software package (SAS, Inc., Cary, NC) was used to conduct data screening and all statistical analyses. The criterion for significance was set at an alpha level of .05, two-tailed. The data analysis took place in three stages. The first stage involved data inspection and treatment of missing data for each of the outcome variables. Data were inspected for non-normality based on measures of skewness and kurtosis to determine whether the normality assumption for parametric procedures was met. If normality assumptions were violated, then attempts were made to transform the data or the appropriate non-parametric procedures were applied. Next, data for the outcome variables were inspected for patterns of missingness. If the data appeared to be missing mostly at random and the amount of missing data was less than 5% of the total observations, then imputation methods were used to replace missing data.

In the second step, group comparisons were made between participants in the current study ($N = 47$) and the rest of the surviving cohort ($N = 249$) to evaluate if the current sample was an accurate representation of the surviving cohort. Specifically, the PCE and non-PCE groups in the current sample and in the remaining cohort were compared on the three matching variables used to enroll the original cohort of mothers (race, parity and socioeconomic status) as well as three birth outcome measures for the child (gestational age, birth weight and adjusted birth head circumference).

In the third step, each of the hypotheses was tested using the appropriate parametric or non-parametric tests. For the first hypothesis, the Wilcoxon Rank Sum Test were used to test the hypothesis that adolescents with PCE would have significantly poorer scores than non-exposed adolescents on each measure of executive functioning. The groups were compared based on the previously mentioned 13 outcome variables (i.e., four from the Stroop, one from the TMT, four from the WCST, and six from the IGT).

For the second hypothesis, 2 x 2 analysis of variance (ANOVAs) was used to test for a PCE by sex interaction for each measures of EF. For each ANOVA, one outcome variable for each test was used: the number of items read correctly during Stroop Color-Word task, the time to completion from the TMT Part B task, the total number of errors made during the WCST, and the net total score from the IGT. It was predicted that boys with PCE would perform worse on outcome variables and have poorer scores for each outcome variable as compared to girls with PCE, non-exposed boys and non-exposed girls. Confidence intervals and effect size estimates using Cohen's guidelines were also calculated.

Finally, for the third hypothesis, multiple regressions were conducted. Two models were tested. In the first model, only PCE and adjusted birth head circumference were entered as

predictors for each of the four primary measures of executive functioning. A second model included the effects of other drug exposures (tobacco, alcohol, and marijuana,) in order to evaluate the unique effect of PCE on executive functioning performance. The regression coefficients (i.e., beta weights) for PCE and adjusted birth head circumference were compared for the two models as well as the change in the total amount of variance explained (ΔR^2). The four dependent variables for the regression analyses were the same as those in the ANOVAs.

Results

Statistical analyses were conducted using SAS 9.2 statistical software package (SAS, Inc., Cary, NC). Initially, raw data were inspected for missing data and normality. Data from one subject were deleted since over half of the data were missing, and four subjects were not included in the IGT analysis due to the software program malfunctioning at time of testing. In cases of significant nonnormality, where skewness was greater than or equal to 2.0 and kurtosis was greater than or equal to 3.0, the appropriate nonparametric statistic was employed. A power analysis assuming a moderate effect size was completed using the G*Power statistical software program which revealed for tests of group means, ANOVAs, and multiple regressions our sample had 39%, 41%, and 48% power, respectively. This indicates that with the current sample of 50 subjects we had small to medium power to detect significant differences between groups and account for the variance in performance on executive functioning tasks.

Descriptive Statistics

First, analysis was conducted to compare the current sample to the original cohort (N = 308) as well as assess for potential attrition bias. Table 1 provides descriptive statistics for the current sample. There were no significant differences by cocaine exposure status for subject characteristics with the exception of birth weight and mother's age.

Table 1.
Sample Characteristics for Mother and Child (N = 50)

Characteristics	Exposed (n = 32)	Nonexposed (n = 18)	p
Biological Mother			
Race, n (% African American)[a]	26(52%)	16(32%)	.69
Parity, n (% multiparous) [a]	29(58%)	18(36%)	.54
Socio-economic status at birth[a,b]	4.7 ± 0.5	4.9 ± 0.3	.17
Age at delivery (years)	27.4 ± 4.6	23.3 ± 6.2	.0029*
Education (years)	11.5 ± 1.4	11.1 ± 1.1	.40
Cigarettes during pregnancy (no./day)	7.4 ± 7.6	0.4 ± 1.3	.0001*
Alcohol during pregnancy (oz. absolute/day)	0.2 ± 0.4	0.0 ± 0.1	.0192*
Marijuana during pregnancy (joints/day)	0.1 ± 0.3	0.0 ± 0.0	.0139*
Cocaine during pregnancy (% weeks used)	0.4 ± 0.3	0 ± 0	<.0001*
Child			
Sex, n (% female)	20(40%)	10(20%)	.64
Gestational age (wks)	38.7 ± 2.0	39.1 ± 1.4	.94
Birth weight (g)	3080.7 ± 460.6	3392.2 ± 561.5	.03*
Adjusted birth head circumference (cm)	34.0 ± 1.3	34.3 ± 1.4	.32

Fisher's Exact Test was used for categorical variables
Wilcoxon Rank Sum Test was used for continuous variables
* $p < 0.05$
[a] Race, parity and socio-economic status were match variables for the PCE and non-exposed participants at student enrollment.
[b] Based on Hollingshead scale where 1 = highest, 5 = lowest category.

Attrition analyses were conducted comparing the 246 study participants with the 50 surviving participants on the three study enrollment match variables (race, parity, sex, and SES), prenatal drug exposures (tobacco, alcohol, marijuana, and cocaine) and three child birth characteristics (gestational age, birth weight, and head circumference). Results revealed the sex distribution was significantly different between groups (p = 0.04). The current sample consists of 40% boys and 60% girls, which differed significantly from the original sample, which consisted

of 56% boys and 44% girls. Since sex has previously been found to influence outcomes of executive functioning it was entered as a covariate in each model. Additionally the current sample had significantly higher levels of prenatal alcohol exposure than the original cohort (p = 0.03). There were no significant group differences on the remaining variables.

A more conservative nonparametric test, the Wilcoxon Rank Sum Test, was used to compare groups on each of the measures of executive functioning due to instances of non-normality where kurtosis was greater than 3.0. There were no significant group differences found on any executive functioning variables. The groups did not differ in overall performance on the Stroop Color-Word Test ($W = 505.0, p = 0.36$), the TMT Part B ($W = 405.0, p = 0.28$), or the IGT ($W = 352.5, p = 0.63$). Further they did not differ in performance on the WCST as indicated by the following variables; perseverative errors ($W = 374.5, p = 0.92$), nonperseverative errors ($W = 381.5, p = 0.67$), failure to maintain set ($W = 390.5, p = 0.80$), or number of categories completed ($W = 399.5, p = 0.96$). Table 2 provides means and standard deviation for scores on each measure for each group.

Table 2.
Average Scores on Measures of Executive Functioning

	PCE		Control		
Measure	Mean	*SD*	Mean	*SD*	*p*
Stroop Color-Word Test (raw score)	40.22	9.22	42.50	10.37	.36
TMT Part B (seconds)	29.56	10.81	28.00	14.34	.28
IGT (raw score)	-3.13	23.68	-4.88	19.09	.63
WCST Perseverative Errors (standard score)	99.44	14.15	92.29	15.23	.92
WCST Nonperseverative Errors (standard score)	94.13	12.46	96.24	13.93	.67
WCST Failure to Maintain Set (raw score)	1.16	1.35	1.11	1.40	.80
WCST Categories Completed (raw score)	5.25	1.14	5.28	1.07	.96

Analysis of Variance (ANOVA)

Fourth, 2 x 2 ANOVAs were used to investigate evidence for a PCE by sex interaction for each executive function outcome variable. Therefore the main effects of target, alcohol, sex,

and the target by sex interaction were tested in each ANOVA. Results revealed that were no significant interactions in the models of executive functioning. Table 3 provides the results of this analysis.

Table 3.
ANOVA Source Summary for Measures of Executive Functioning

Source	*SS*	*df*	*MS*	*F*	*p*	η^2
Stroop Color-Word task						
Sex	151.10	1	152.10	1.63	0.21	0.03
PCE	0.13	1	0.13	0.00	0.97	0.00
Sex*PCE	45.40	1	45.40	0.49	0.49	0.01
Error	4289.12	46	93.24			
Total	4525.92	49				
Model				0.85	0.48	
TMT Part B						
Sex	260.10	1	260.10	1.77	0.19	0.04
PCE	0.30	1	0.30	0.00	0.97	0.00
Sex*PCE	39.24	1	39.24	0.27	0.61	0.01
Error	6741.70	46	146.57			
Total	7144.00	49				
Model				0.91	0.44	
IGT						
Sex	258.04	1	258.04	0.57	0.46	0.05
PCE	1317.36	1	1317.36	2.90	0.10	0.07
Sex*PCE	1770.46	1	1770.46	3.90	0.06	0.09
Error	4289.12	46	93.24			
Total	21756.87	45				
Model				1.98	0.13	
WCST Perseverative Errors						
Sex	247.14	1	247.14	1.15	0.29	0.03
PCE	140.83	1	140.83	0.66	0.42	0.01
Sex*PCE	173.47	1	173.47	0.81	0.37	0.02
Error	9667.26	45	214.83			
Total	9929.92	48				
Model				0.41	0.75	
WCST Nonperseverative Errors						
Sex	240.00	1	240.00	1.41	0.24	0.03

PCE	19.20	1	19.20	0.11	0.74	0.00
Sex*PCE	161.64	1	161.64	0.95	0.34	0.02
Error	7672.26	45	170.49			
Total	7962.00	48				
Model				0.57	0.64	
WCST Failure to Maintain Set						
Sex	0.28	1	0.28	0.14	0.71	0.02
PCE	0.03	1	0.03	0.02	0.90	0.00
Sex*PCE	0.00	1	0.00	0.00	0.97	0.00
Error	89.12	46	1.94			
Total	90.02	49				
Model				0.16	0.93	
WCST Categories Completed						
Sex	2.34	1	2.34	1.88	0.18	0.04
PCE	1.01	1	1.01	0.81	0.37	0.02
Sex*PCE	2.06	1	2.06	1.66	0.20	0.04
Error	57.14	46	1.24			
Total	59.62	49				
Model				0.67	0.58	

Results for the Stroop Color-Word Test indicated no significant main effects were present of sex, $F(1, 46) = 1.63, p = 0.21, \eta^2 = 0.03, CI_{.95}$ [0, 0.15]; PCE, $F(1, 46) = 0.00, p = 0.97, \eta^2 = 0, CI_{.95}$ [0, 0]; or the PCE by sex interaction $F(1, 46) = 0.49, p = 0.49, \eta^2 = 0.01, CI_{.95}$ [0, 0.10]. Results for the TMT Part B indicated no significant main effects were present of sex, $F(1, 46) = 1.77, p = 0.19, \eta^2 = 0.04, CI_{.95}$ [0, 0.16]; PCE, $F(1, 46) = 0, p = 0.96, \eta^2 = 0, CI_{.95}$ [0, 0]; or the PCE by sex interaction, $F(1, 46) = 0.27, p = 0.61, \eta^2 = 0.01, CI_{.95}$ [0, 0.09]. For the IGT, no significant main effects were found of sex, $F(1, 42) = 0.57, p = 0.46, \eta^2 = 0.05, CI_{.95}$ [0, 0.18]; PCE, $F(1, 42) = 2.90, p = 0.10, \eta^2 = 0.07, CI_{.95}$ [0, 0.21]; or the PCE by sex interaction, $F(1, 42) = 3.90, p = 0.055, \eta^2 = 0.09, CI_{.95}$ [0, 0.23]. Four variables were investigated from the WCST data. Results for perseverative errors indicated that there were no significant main effects of sex, $F(1, 45) = 1.15, p = 0.29, \eta^2 = 0.03, CI_{.95}$ [0, 0.14]; PCE, $F(1, 45) = 0.66, p = 0.42, \eta^2 = 0.01,$

$CI_{.95}$ [0, 0.11]; or the PCE by sex interaction, $F(1, 45) = 0.81$, $p = 0.37$, $\eta^2 = 0.02$, $CI_{.95}$ [0, 0.12]. Additionally, for nonperseverative errors results indicated that there were no significant main effects of sex, $F(1, 45) = 1.41$, $p = 0.24$, $\eta^2 = 0.03$, $CI_{.95}$ [0, 0.15], PCE, $F(1, 45) = 0.11$, $p = 0.74$, $\eta^2 = 0.00$, $CI_{.95}$ [0, 0.07]; or the PCE by sex interaction, $F(1, 45) = 0.95$, $p = 0.34$, $\eta^2 = 0.02$, $CI_{.95}$ [0, 0.13]. For the WCST variable, failure to maintain set, there were no significant main effects of sex, $F(1, 46) = 0.14$, $p = 0.71$, $\eta^2 = 0.02$, $CI_{.95}$ [0, 0.13]; PCE, $F(1, 46) = 0.02$, $p = 0.90$, $\eta^2 = 0.00$, $CI_{.95}$ [0, 0.07], or for the PCE by sex interaction, $F(1, 46) = 0$, $p = 0.97$, $\eta^2 = 0$, $CI_{.95}$ [0, 0]. Results for the last variable, number of categories completed, indicated there were no significant effect of sex, $F(1, 46) = 1.88$, $p = 0.18$, $\eta^2 = 0.04$, $CI_{.95}$ [0, 0.16], PCE, $F(1, 46) = 0.81$, $p = 0.37$, $\eta^2 = 0.02$, $CI_{.95}$ [0, 0.12]; or for the PCE by sex interaction, $F(1, 46) = 1.66$, $p = 0.21$, $\eta^2 = 0.04$, $CI_{.95}$ [0, 0.15]. These results indicate that neither sex, PCE, nor the interaction was significantly related to performance on these four measures of executive functioning.

Multiple Regression Models

To test the third hypothesis, multiple regression modeling was conducted for each measure of executive functioning. Seven regression models were tested to determine the unique effect of PCE on each measure of executive functioning while controlling for the covariate. For each model, PCE, sex, and the other drug exposures (tobacco, alcohol, and marijuana) were entered into the model. In each model PCE was entered as a continuous variable measured as the percentage of weeks cocaine was used during pregnancy plus the three months prior to pregnancy. Sex was included in all models because this variable differed significantly between groups and has been previously shown to influence performance on certain executive functioning tasks.

None of the multiple regression models were significant in explaining the variance in performance on each executive functioning task. As shown in the Table 4, all of the predictors had non-significant zero-order correlation with each measure of executive functioning. The four drug exposures were entered in simultaneously into each model. The Stroop Color-Word model was non-significant, $F(5, 49) = .53, p = 0.75, R^2 = .05$, CI [.00, .08]. The TMT Part B model was also non-significant, $F(5, 49) = 1.00, p = 0.43, R^2 = .09$, CI [.00, .15]. The model predicting IGT net total was non-significant, $F(5, 45) = 1.09, p = 0.38, R^2 = .12$, CI [.00, .20]. The model for perseverative errors on the WCST was non-significant, $F(5, 48) = 1.34, p = 0.27, R^2 = .13$, CI [.00, .20], non-perseverative errors on the WCST was also non-significant, $F(5, 48) = 1.56, p = 0.19, R^2 = .15$, CI [.00, .15]. For failure to maintain set on the WCST, the model was nonsignificant, $F(5, 49) = .57, p = 0.73, R^2 = .06$, CI [.00, .09]. Finally, the model for the number of categories completed on the WCST the model was nonsignificant, $F(5, 49) = 0.95, p = 0.46, R^2 = .10$, CI [.00, 0.15].

Table 4.
Multiple Regression Model Summary for Measures of Executive Functioning

Source	β	sr^2	*b*	*F*	*p*	R^2
Stroop Color-Word Test						
Cocaine	-0.08	0.00	-2.55			
Tobacco	-0.00	0.00	-0.01			
Alcohol	-0.14	0.01	-4.34			
Marijuana	0.07	0.00	2.33			
Sex	0.18	0.03	2.99			
Model				0.53	0.75	0.06
TMT Part B	0.04	0.00	2.08			
Cocaine	-0.09	0.01	-0.15			
Tobacco	0.23	0.03	9.27			
Alcohol	0.00	0.00	-0.16			
Marijuana	0.05	0.05	-5.70			
Sex	0.04	0.00	2.08			
Model				1.00	0.43	0.10
IGT						
Cocaine	-0.10	.01	-7.52			
Tobacco	0.27	.06	0.84			

Alcohol	-0.15	.01	-10.62			
Marijuana	-0.02	.00	-1.84			
Sex	-0.14	.02	-6.34			
Model				1.09	0.38	0.12
WSCT Perseverative Errors						
Cocaine	0.26	0.04	13.25			
Tobacco	0.16	0.02	0.34			
Alcohol	-0.20	0.03	-9.53			
Marijuana	-0.19	0.31	-9.79			
Sex	0.06	0.00	1.67			
Model				1.34	0.27	0.13
WSCT Nonperseverative Errors						
Cocaine	0.11	0.11	4.97			
Tobacco	0.16	0.16	0.29			
Alcohol	0.05	0.05	1.97			
Marijuana	-0.35	-0.35	-15.90			
Sex	0.08	0.01	2.17			
Model				1.56	0.19	0.15
WSCT Failure to Maintain Set						
Cocaine	-0.09	0.01	-0.43			
Tobacco	0.19	0.05	0.04			
Alcohol	0.12	0.01	0.52			
Marijuana	0.05	0.00	0.23			
Sex	-0.05	0.00	0.42			
Model				0.57	0.73	0.06
WSCT Categories Completed						
Cocaine	0.18	0.02	0.69			
Tobacco	0.10	0.01	0.02			
Alcohol	0.01	0.00	0.05			
Marijuana	-0.25	0.05	-0.98			
Sex	0.06	0.00	0.13			
Model				0.95	0.46	0.10

CHAPTER 4: DISCUSSION AND CONCLUSIONS

The current project focused on identifying whether PCE affects adolescent performance on executive functioning tasks of varying complexity. During the 1980s and early 1990s the level of crack-cocaine use reached epidemic proportions. This led researchers to investigate the relationship between drug use during pregnancy and its pre-natal effects on development. Original claims that PCE would have severe effects on general cognitive development have proven to be exaggerated. Recently, researchers have begun to examine the relationship between PCE and development of executive functioning. Most published studies have focused on childhood with only a few examining PCE effects as these children approach adolescence.

Discussion of Results

The current sample of 50 adolescents ages 14 to 16 years was drawn from a larger sample, which was prospectively enrolled at birth in a longitudinal study of the effects of PCE (*N* = 308). The current sample had significantly more girls and higher levels of prenatal alcohol exposure than the original cohort. As expected, the PCE group was exposed to significantly more alcohol, tobacco, and marijuana than the comparison group. The groups did not differ on maternal characteristics and growth measures at birth.

For the first hypothesis, it was predicted that adolescents with PCE would perform worse than controls on four measures of executive functioning. This hypothesis was not supported. Adolescents with PCE and the control group demonstrated similar levels of performance on the Stroop, TMT, WCST, and IGT. Results from other cohorts have been mixed. The lack of between-group differences on the Stroop and TMT Part B is consistent with results from another cohort, which used the TMT at age 10 and the Stroop at age 12 (Hurt et al., 2009; Savage et al., 2005). Conversely, one study found poorer performance on the Stroop among PCE children

(mean age = 8.3; Mayes et al., 2005) and another reported poorer performance on the TMT with a trend toward poorer performance on the Stroop (mean age = 10.6; Warner et al., 2006). The results of the current study demonstrate that individuals with PCE have similar inhibitory control, set-shifting, and sequencing abilities as the matched control group by the time they reach middle adolescence. The current study appears to be the first in the PCE literature to investigate executive functioning abilities as measured by the WCST and IGT. The PCE and control groups performed similarly, suggesting that adolescents with PCE are similar to the matched control group on tasks that involve integration of complex cognitive abilities. However, based on the inconsistent results for TMT and Stroop performance in the available literature and because this is the first study using the WCST and IGT, more research is necessary to draw definitive conclusions for PCE-associated effects in executive functioning in an adolescent population.

For the second hypothesis, a PCE by sex interaction was predicted in which boys with PCE would perform worse than girls with PCE and the boys and girls in the control group on all four measures of executive functioning. Analyses indicated that neither PCE, sex, nor the interaction significantly accounted for variance in performance on the Stroop, TMT Part B, WCST, or IGT. Therefore we failed to reject the null hypothesis for the PCE by sex interactions. These results are inconsistent with previous research, which found that at 5 years of age boys with PCE performed poorly on inhibitory control tasks when compared to girls with PCE and the boys and girls in the control groups (Bendersky et al., 2003). Other studies have also reported a gender effect in which boys have poorer general cognitive intelligence from 4 to 9 years (Bennett, 2008) and exhibit more externalizing behaviors from 6 to 7 years (Delaney-Black et al., 2004). Results from the current study suggest that by adolescence, boys with PCE have not

only similar inhibitory control, but also have similar executive functioning abilities as same ages peers.

Multiple regression analyses were used to test the last hypothesis that PCE would be a significant predictor of performance on executive functioning measures after controlling for other prenatal drug exposures (alcohol, tobacco, and marijuana) as well as sex. This hypothesis was not supported. The results of the current analysis indicated that PCE does not have a direct unique effect on the measures of executive functioning used in this study. Additionally, other drug exposures did not significantly explain variance in any model of executive functioning. Previous research from the full cohort from which the current study sample was drawn (N's > 250) found indirect effects of PCE through adjusted birth head circumference on executive functioning at ages 5 and 7 (Eyler et al., 2009). One other study using regression analyses detected a PCE effect on executive functioning among children, age 9 to 11, such that those with heavy PCE performed worse on the Stroop than the group of unexposed and lightly exposed children ($N = 143$, Rose-Jacobs et al., 2009). Although the current study found no PCE-associated effects on performance, studies with larger sample sizes may elucidate effects, direct or indirect, on executive functioning.

The current sample is underrepresented in PCE literature and research on executive functioning performance in typically developing adolescence, as it is comprised of youth from rural communities, of lower SES, and is predominantly African American. When compared to typically developing children, the scores for the PCE and control groups were within the average range for the Stroop, TMT, and WCST (Baron, 2004). Thus, despite the mixed results reported in the PCE literature, the youth in the current study performed do not demonstrate clinically significant deficits in areas of inhibitory control, sustained attention, set-switching, sequencing,

and hypothesis testing as measured by these three tests. According to the normative data for adults ages 18 to 39, the current sample (14 to 17 years) ranks in the 27th to 31st percentile for their net total scores. In conclusion, the current sample performed within the average levels for all tasks as compared to their same age peers or, in the case of the IGT, similar to adult level performance.

Compared to the available data from a recent study of IGT performance among adolescents, participants in the current study may perform more poorly than their same-age peers. Cauffman and colleagues (2010) used a modified version of the IGT in multi-site study with a large sample of 10 to 30 years old ($N = 901$). They reported that adolescent net total score (percentage of advantageous choices minus the percentage of disadvantageous choices) indicated they made more advantageous choices than disadvantageous choices and performance improved over the course of the task. In contrast, both the PCE group (mean net total = -2.33) and control group (mean net total = -4.88) made more disadvantageous choices than advantageous choices and did not improve their performance over the course of the task (data not shown). When compared to overall performance on the original IGT task in adults, the current sample, regardless of exposure status, performs within the average range, however they appear to have poorer performance as compared to their same ages peers.

It is difficult to draw conclusions about the effect of PCE on executive functioning due to mixed results found across studies and the varying ages at which assessments were conducted. Significant between group differences on the Stroop have been reported for children at the average age of 8.1 ± 1.14 ($N = 29$; Mayes, et al, 2005) and 10.5 ± 0.56 ($N = 141$; Rose-Jacobs et al., 2009), but not at 10.6 ± 0.2, ($N = 53$; Warner et al., 2006). One factor that could explain this inconsistency is that development of executive functioning is a rapidly evolving process with

significant improvements in performance between early childhood and mid-adolescence in typically developing children. For instance, interference scores on the Stroop, a measure of inhibitory control, increases during childhood and progressively declines during adolescence indicating improvement with age (Leon-Carrion et al., 2004). Perhaps group differences are demonstrable at younger ages when abilities are evolving, but then levels off as adolescents approach maturity, as evidenced by the results of the current study. However, two different studies using the TMT conducted when participants were age 10, yielded opposite results (Warner et al., 2006; Savage et al., 2005). More studies reporting on outcomes of executive functioning in adolescents with PCE would allow for comparisons across cohorts as well as elucidate whether PCE-associated differences persist into adolescence.

Differences in executive functioning in PCE children have also been found within cohorts. Warner's study (2006) found that children with PCE, ages 9 to 11, performed worse than controls on the TMT Part B, while no differences were found between PCE and unexposed adolescents ages 14 to 16. Performance on the TMT Part B has been shown to improve as development of inhibition and sustained attention progress in children ages 7 to 16 years (Kelly, 2000). Perhaps, these within cohort differences indicate that youth with PCE experience a developmental lag such that they demonstrate poor performance in childhood, but upon re-assessment during adolescence their abilities have caught up with those of the matched control group. This illustrates potential resilience in cocaine-exposed youth, which highlights the importance of identifying both factors of resiliency and areas of developmental deficits in these samples. Similarly, other researchers have suggested that cocaine exposed youth demonstrate resiliency particularly those raised in enriching environments (Bennett et al., 2002; Brown,

Bakerman, Coles, Platzman, & Lynch, 2004; Dennis, Bendersky, Ramsay, & Lewis; 2006; Pulsifer et al., 2004; Singer et al., 2004).

Limitations and Methodological Issues

Determining the unique effect that PCE has on development has proven difficult as multiple factors can confound results including the use of other drugs in conjunction with cocaine, maternal characteristics and postnatal environment. In prospectively-enrolled cohorts, researchers have attempted to control for the effects of drugs other than cocaine by enrolling a control group in which mothers used the other drugs but did not use cocaine. This design strategy is of limited utility, however, because the amounts of the other drugs used by cocaine-using women are significantly larger than the amounts used in the control groups. Thus, statistical procedures are used to try to partial out of the effects of the other drugs, but this strategy cannot account for the possible interactive effects of cocaine with other drugs. Notably, maternal characteristics such as general cognitive intelligence and levels of depression, as well as postnatal environment such as caregivers changes and environmental attributes associated with low SES can also confound investigations of the unique effect that PCE has on developmental outcomes (Bennett, 2008; Singer et al., 2008). One strength of this study includes using a matched control sample, some confounding maternal and environmental characteristics factors were controlled for including, maternal education, race, parity, and SES. Moreover, the current sample of adolescents is predominantly African American from low-income families living in rural communities. Thus the results of this study provide unique and valuable insight into a typically underrepresented group in the literature.

There are methodological limitations to the study of cocaine use and PCE literature in general. Assessment of cocaine use during pregnancy is particularly difficult primarily due to the

nature of cocaine use. Unlike other drugs of abuse, which have more "standardized" units of measure (e.g., ounces of beer, wine or hard liquor for alcohol; number of cigarettes for tobacco), mode of cocaine use can vary by intravenous injections, snorting lines of powder, and smoking crack cocaine "rocks" of varying shapes and sizes. In addition, there is no way to measure the purity or concentration of cocaine, which can fluctuate across time as well as regionally. Thus, various methods have been employed to assess cocaine use among pregnant women including, maternal self-report, maternal and infant urine and hair assays, and infant meconium assays. Use of biological tests is recommended as pregnant women and substance users in general typically under-report substance use, particularly illicit drug use (Ostrea, Brady, Gause, Raymundo, Stevens, 1992). However, a review of previous research has shown that urine, meconium, and hair tests can fail to detect prenatal drug use (Eyler, Behnke, Wobie, Garvan, & Tebbett, 2005). Eyler and colleagues (2005) reported that toxicological analysis failed to identify drug use occurring three months prior to delivery. Of all drug tests examined, urine analysis identified the most number of users who reported no drug use, and structured interviews identified drug use when biological tests were negative. Therefore the most reliable method to assess drug use during pregnancy appears to be a detailed structured interview and urine analysis test given throughout pregnancy. For the current cohort, assessment of maternal drug use during pregnancy is a significant strength to this study, specifically use of self-report as assessed by an in-depth interview procedure adapted from Day and colleagues (1985) to obtain a quantitative measure of cocaine exposure as well as urine samples collected at two unanticipated times, study enrollment and delivery of the baby.

Additionally, researchers have yet to establish a well-defined system that differentiates heavy, moderate, and light cocaine exposure. For instance, Rose-Jacobs and colleagues (2009)

determined level of use, *a priori,* by assessing of days of mother's self-reported use and the concentration of cocaine metabolites in infant meconium assays. In another study, mothers who self-reported cocaine use greater than 61 days during pregnancy were categorized as heavy users, while all others were classified as light users (Rivkin et al., 2007). Another group of researchers classified heavy users as those who used cocaine at least twice a week during pregnancy (Jacobson, Bihun, & Chiodo, 1999). While this does not directly relate to the current study, inconsistent criteria for heavy, moderate, and light exposure make it difficult to make cross-cohort comparisons.

Finally, there are challenges when assessing executive functioning because it is difficult to fully assess this multi-faceted construct. Ideally, researchers choose a variety of tests that encompass multiple subfunctions, such as attention, response inhibition, and visuo-motor control in order to assess general executive functioning abilities. Therefore studies using a limited test battery may inadvertently miss subtle effects of PCE on executive functioning. For example Rose-Jacobs and colleagues (2008) measured executive functioning using two assessments, the Stroop and Rey Osterrieth Complex Figures tests. A strength of the current study is that it uses four measures of varying complexity to assess executive functioning, which is more than any other study investigating PCE effects on executive functioning. However, studies evaluating PCE effects in executive functioning may find group differences using measures aimed at assessing other factors of executive functioning.

A significant limitation to the current study is its small sample size ($N = 50$), which resulted in low power ranging from 39% to 48%. With insufficient power it is unlikely that the current study could detect a small or medium effect of PCE if it does in fact exist. Research with

larger sample sizes would help elucidate the potential effect of PCE on executive functioning in adolescence.

Another limitation to this current study is that the participants were drawn from a sample of adolescents recruited for participation in a study designed to investigate brain development and behavior in adolescents with PCE. Specifically, researchers recruited adolescents from the original Project CARE sample to participate in a study investigating brain development and behavior. Thus, the data used in the current study is drawn from the sample of adolescents that participated in the brain development and behavior study. Therefore the current sample is a sample of convenience for which the data was collected to answer a different set of research questions.

Conclusions and Future Directions

Although it appears that PCE does not directly affect executive functioning abilities in the current sample these results need to be taken in considerations of its low power. The current sample, regardless of drug exposure, performed within the average range as compared normative data available for the Stroop, TMT Part B, and WCST. Additionally, the potential deficits discussed for IGT performance may not necessarily reflect PCE-associated impairment or clinically significant impairment. Between group performances on the TMT Part B is different from a previous report of group differences on the same cohort. This highlights potential resiliency in this unique sample. The current study is one of the first to report on the effects of PCE on executive functioning in an adolescent sample, thus further study with larger sample sizes is necessary to make any definitive conclusions.

Future research involving adolescents with PCE should investigate executive functioning, decision-making abilities, and emotion and behavior regulation. Previous studies using teacher

and parent reports suggest that children with PCE exhibit higher levels of externalizing behavior problems (for review see Ackerman et al., 2010; Bada et al., 2007). However, there are little to no reports on whether behavior problems persist into adolescence. Warner and colleagues (2010) reported that PCE was not associated with adolescent drug experimentation. Studies beginning to look at whether adolescents with PCE are at a greater risk for high impulsivity, poor decision-making, and externalizing behaviors would aid in development of treatment and intervention techniques.

It is difficult to attribute the subtle impairments reported in these populations as direct effects of PCE. Moreover, cognitive and behavioral impairments reported in this population are often been better explained by the postnatal environment and interactions of PCE with other drug exposures (Ackerman et al., 2010; Singer et al., 2008). Risk factors in the environment related to maternal psychopathology, caregiver changes, and low SES during development have also been associated with poor outcomes in children with PCE (Arendt et al., 2004; Bennett et al., 2002). Therefore studies investing whether the direct or indirect PCE effects persist or diminish in adolescents would help in planning prevention and treatment programs for the disadvantaged youth in this population.

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