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Development of inhibitory control among prenatally cocaine exposed and non-cocaine exposed youths from late childhood to early adolescence: The effects of gender and risk and subsequent aggressive behavior

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ABSTRACT

The goal of the present investigation was to characterize the development of inhibitory control, an aspect of executive functions, in a sample of prenatally cocaine exposed (CE; $n=165$) children compared to an at risk, but prenatally cocaine unexposed (NCE; $n=119$) sample across time (i.e. 7.5 to 11.5 years of age). Gender and cumulative risk, a combination of postnatal medical (i.e. low birth weight and APGAR scores) and demographic risk, indexed by maternal educational attainment, were examined as predictors of change in inhibitory control across time and aggression was modeled as an outcome when children reached 14 years of age. Multiple group latent growth models indicated that CE children made more errors at 7.5 years of age during a standard Stroop interference task, however, over time CE children had greater age-related improvements, narrowing the initial gap, with NCE children in the ability to inhibit errors. Gender effects at 7.5 years within the NCE group were identified with NCE boys making initially more errors than NCE girls; both NCE and CE girls improved faster across development compared to NCE and CE boys, respectively. Greater cumulative risk was associated with more errors at 7.5 years in the CE and NCE groups. No differences were observed between CE and NCE children on time to complete the Stroop task at 7.5 years. However, NCE children had greater age-related improvements in their time to complete the Stroop interference task relative to their CE counterparts. NCE girls improved the fastest over time relative to NCE boys; a similar trend emerged ($p<0.10$) with CE girls improving faster over time than CE boys. Although all participants improved across development, higher cumulative risk in both groups was associated with slower age-related improvements (i.e. higher slopes) in the time to complete the Stroop task across development. After accounting for gender and cumulative risk, findings in both groups indicated that those who made more errors at 7.5 years of age and/or who had slower age-related changes (i.e. higher slopes) of time to complete the Stroop task across development were more aggressive as rated by caregivers at 14 years of age. Although qualified by gender and cumulative risk, these findings are consistent with reduced cognitive processing efficiency and executive function difficulties in CE children relative to NCE children. Findings suggest that executive function difficulties in CE children may be subtle as development continues to unfold over time. Furthermore, these findings indicate that development of inhibitory control may be an important mechanism linking prenatal cocaine exposure, gender, and cumulative risk to later adverse outcomes.

1. Introduction

The frontal lobes are critical for diverse cognitive functions, such as planning, working memory, prepotent response inhibition, and set shifting as well as other cognitive processes that fall under the rubric of executive functions (Kimberg et al., 1997; Mesulam, 2002; Wagner et al., 2006). One aspect of executive functions that is particularly important over the course of development is inhibitory control. Inhibitory control refers to the ability to inhibit a prepotent (i.e. over learned) dominant response in favor of activating a subdominant response (Diamond, 2002; Kochanska et al., 2000; Rothbart and Posner, 1985). While effective inhibitory control has been implicated in better emotion regulation, reasoning, and one's ability to maintain efforts toward attainment of goals (Carlson and Wang, 2007; Fox and Calkins, 2003; Hadley et al., 2004; Silverman and Ippolito, 1997), ineffective inhibitory control has been implicated in the development of psychopathology (e.g., ADHD) and externalizing and internalizing

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difficulties in general (Barkley, 1997, 1998; Eisenberg et al., 1996; Huijbregts et al., 2008; Muris et al., 2007; Zhou et al., 2009).

Under typical prenatal conditions, the development of inhibitory processes has been studied in a variety of age groups, from infancy to adulthood, using various tasks. For example, Diamond (Diamond, 1985) found improvements during performance on the A not B task in infants from the ages of 7 to 12 months. Kochanska et al. (Kochanska et al., 2000) identified improvements in toddlers' ability to delay gratification in two paradigms, "Gift in a Bag" and "Wrapped Gift," from 22 to 33 months of age, indicating continued improvements during performance of inhibitory control tasks prior to the preschool age period. In older age groups, others' have observed improvements during performance of inhibitory control tasks from early childhood to late adolescence (e.g., Leon-Carrion et al., 2004) and into adulthood (Williams et al., 1999).

Imaging (e.g., Bunge et al., 2002; Rubia et al., 2000; Rubia et al., 2007; Velanova et al., 2008) and electrophysiological (e.g., Jonkman et al., 2003; Mayes et al., 2005; West, 2003) studies have demonstrated the importance of the frontal lobes during performance of inhibitory control tasks as well as developmental changes in frontal activation during such tasks. In regard to the latter, changes in white matter in the frontal regions appear to underlie changes in performance during tasks that recruit frontal areas for successful completion (for a review, see Casey et al., 2000 or Lenroot and Giedd, 2006). In sum, evidence from behavioral inhibitory control tasks, neuroimaging (e.g., fMRI), and electrophysiological (e.g., ERP) studies support the role of the frontal lobes during inhibition of prepotent responses and suggest improvements in inhibitory task performance and changes in brain activation from early in life through adulthood (For a more thorough overview see Diamond, 2002). Furthermore, the studies reviewed above provide evidence of how the development of inhibitory control unfolds across the life span in low risk, typically developing individuals.

While the studies outlined above are important for understanding typical development of inhibitory control, there are two notable limitations across these studies. First, most studies use cross-sectional designs (e.g., Leon-Carrion et al., 2004; Velanova et al., 2008; Williams et al., 1999) rather than following a single sample of participants over time. While cross-sectional research designs are useful and can identify age group and interindividual differences, information regarding individual differences within intraindividual change and age changes is not obtained when using a cross-sectional design (Miller, 1998; Robinson et al., 2005). A further limitation of most existing studies of inhibitory control development is the use of low-risk populations (For a recent exception in young children, see Moilanen et al., 2010). While low risk samples define what might be expected under ideal circumstances, such samples do not identify potentially important patterns of development in individuals who have experienced serious challenges to normative developmental trajectories. These challenges encompass prenatal factors such as substance exposure as well as postnatal economic adversity and serious psychopathology among caregivers.

Cocaine exposure in particular has been linked to difficulties with behavior, attention, and executive functions and longitudinal studies of children exposed prenatally to cocaine have identified negative effects of prenatal exposure during performance on various measures of cognitive and emotional functioning, including behavioral measures of executive functions. Early in life, infants exposed to cocaine in utero have been identified as having a "difficult temperament" (i.e. fussy, harder to soothe), which has been linked with later behavioral difficulties, and lower performance during the Bayley Scales of Infant Development motor scales (Richardson et al., 2008). Similarly, Mayes, Cicchetti, Acharyya, and Zhang (Mayes et al., 2003) found that infants exposed to cocaine obtained lower scores on the Bayley Scales of Infant Development, 2nd Ed., compared to non-exposed infants and infants who were exposed in utero to non-cocaine substances (e.g., alcohol). In addition to reduced performance on broad based cognitive measures relative to controls, infants and toddlers exposed to cocaine prenatally have been identified as performing lower on specific measures of cognitive ability, such as visual attention (e.g., Heffelfinger et al., 1997), spatial working memory (Mayes et al., 2007; Schroder et al., 2004), and inhibitory control and executive functions (e.g., Espy et al., 1999) relative to their non-exposed, same age peers. These findings are consistent with theoretical work, which has drawn on animal and human studies, indicating that prenatal cocaine exposure affects arousal regulatory systems, which then effects prefrontal lobe function (See Mayes, 2002 for additional discussion).

While early work examining the effects of prenatal cocaine exposure has typically covered the developmental periods of infancy through toddlerhood, more recent follow-up studies have been carried out that suggest that individuals exposed to cocaine in utero continue to have difficulties in domains potentially affected by ineffective inhibitory control (e.g., behavioral problems; Muris et al., 2007; Zhou et al., 2009). For example, during the preschool period, children exposed in utero to cocaine were identified as experiencing more frustration and difficulties regulating problem solving behaviors relative to non-exposed children (Dennis et al., 2006). Similarly, Richardson Goldschmidt, and Willford (Richardson et al., 2009) found that preschoolers exposed to cocaine in utero were rated as having more behavioral difficulties and as being more fussy/difficult than children who were not exposed to cocaine in utero. School-aged children prenatally exposed to cocaine have also displayed greater levels of behavioral difficulties relative to their non-exposed peers (Bada et al., 2007).

In addition to accumulating evidence of inhibitory control difficulties in the prenatally cocaine exposed population, there is growing recognition that some characteristics of prenatally exposed children, such as gender and sociodemographic and medical risk factors, may influence broad cognitive ability, inhibitory control, and/or outcomes associated with inhibitory control difficulties. For example, several studies examining animal models of cocaine exposure have identified greater performance difficulties in male rats relative to female rats (Markowski et al., 1998; Spear et al., 2002). Gender effects, with males prenatally exposed to cocaine performing more poorly than prenatally exposed females on measures of cognitive function (Bennett et al., 2008) and inhibitory control (Bendersky et al., 2003), in human participants have also been reported. Greater behavioral difficulties, potentially linked to poor inhibitory control, have also been reported in males compared to females prenatally exposed to cocaine (Bailey et al., 2005; Delaney-Black et al., 2004). Likewise, in later childhood (i.e. between 10 and 11 years), in utero exposure to cocaine has been associated with increased risky behavior in males (Bennett et al., 2007). Other studies have identified low birth weight and sociodemographic risk as contributing to inhibitory control difficulties in children. For instance, a recent meta-analysis identified early gestational age as a risk factor for executive function difficulties (Mulder et al., 2009); similarly, Li-Girning (Li-Grining, 2007) noted that low birth weight was a particular risk factor for difficulties with inhibition and executive attention. Residing in a low income household (e.g. Moilanen et al., 2010) and/or low maternal education (Hughes and Ensor, 2009) have also been noted as potential sociodemographic characteristics that can contribute to poor executive functions in children.

While the findings reported above are important, there are some noted limitations. For example, most studies reviewed reflect comparisons of cocaine exposed and non-cocaine exposed children at single time points, although all were identified and followed since birth. Only three studies were identified (Bandstra et al., 2004; Bennett et al., 2008; Mayes et al., 2003) that have reported on repeated measures data to understand differential development of cognitive ability over time in cocaine exposed compared to non-cocaine exposed participants. However, these studies use either measures of broad cognitive ability or language, typically report on data from the preschool through the