Neurotoxicology and Teratology 45 (2014) 1–17

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Level of intrauterine cocaine exposure and neuropsychological test scores in preadolescence: subtle effects on auditory attention and narrative memory

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ARTICLE INFO

Article history:
Received 21 January 2013
Received in revised form 13 June 2014
Accepted 18 June 2014
Available online 28 June 2014

Keywords:
Intrauterine cocaine exposure
Preadolescents
Neuropsychological functioning
Auditory attention
Narrative memory
NEPSY – A Developmental Neuropsychological Assessment

ABSTRACT

Neuropsychological processes such as attention and memory contribute to children's higher-level cognitive and language functioning and predict academic achievement. The goal of this analysis was to evaluate whether level of intrauterine cocaine exposure (IUCE) alters multiple aspects of preadolescents' neuropsychological functioning assessed using a single age-referenced instrument, the *NEPSY: A Developmental Neuropsychological Assessment* (NEPSY) (Korkman et al., 1998), after controlling for relevant covariates. Participants included 137 term 9.5-year-old children from low-income urban backgrounds (51% male, 90% African American/Caribbean) from an ongoing prospective longitudinal study. Level of IUCE was assessed in the newborn period using infant meconium and maternal report. 52% of the children had IUCE (65% with lighter IUCE, and 35% with heavier IUCE), and 48% were unexposed. Infants with Fetal Alcohol Syndrome, HIV seropositivity, or intrauterine exposure to illicit substances other than cocaine and marijuana were excluded. At the 9.5-year follow-up visit, trained examiners masked to IUCE and background variables evaluated children's neuropsychological functioning using the NEPSY. The association between level of IUCE and NEPSY outcomes was evaluated in a series of linear regressions controlling for intrauterine exposure to other substances and relevant child, caregiver, and demographic variables. Results indicated that level of IUCE was associated with lower scores on the *Auditory Attention* and *Narrative Memory* tasks, both of which require auditory information processing and sustained attention for successful performance. However, results did not follow the expected ordinal, dose-dependent pattern. Children's neuropsychological test scores were also altered by a variety of other biological and psychosocial factors.

1. Introduction

In both animal and human studies, intrauterine cocaine exposure (IUCE) has been shown to alter monoaminergic neurotransmitter systems during gestation (Bhide, 2009; Mayes, 1999), which may influence developing mechanisms underlying the regulation of attention and affect, executive functions, and motor control (Lester and Padbury, 2009; Li et al., 2009; Mayes, 1999). These alterations are concerning because they have potential implications for the development of higher cognitive processes, such as language, memory, and learning (Adams and Gathercole, 2000; Bailey and Snowling, 2002; Duinmeijer et al., 2012; Marton, 2008; Paul, 2001), as well as academic achievement (Bull et al., 2008a; Rogers et al., 2011).

Although the effects of IUCE on fetal growth and newborn neurobehavior are fairly robust (Frank et al., 2001; Held et al., 1999; Lester et al., 2002; Tronick et al., 1996), reports of IUCE effects on

Abbreviations: IUCE, Intrauterine cocaine exposure; NEPSY, NEPSY – A Developmental Neuropsychological Assessment.

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http://dx.doi.org/10.1016/j.ntt.2014.06.007
0892-0362/

neuropsychological functioning beyond early childhood are not consistent. Many large well-controlled studies find no significant effects of IUCE on general intelligence or academic achievement at school age (Ackerman et al., 2010; Hurt et al., 2005; Nair et al., 2008; Richardson et al., 1996; Rose-Jacobs et al., 2012; Wasserman et al., 1998). In one study, IUCE was associated with poorer performance on the Perceptual Reasoning composite from the *Wechsler Intelligence Scale for Children* (WISC-IV) (Wechsler, 1991a) but not the Verbal Comprehension, Working Memory, or Processing Speed composites, or scores on a standardized achievement test (Singer et al., 2008).

When significant IUCE effects on specific neuropsychological functions are reported in this literature, results often vary from sample to sample and tend to be subtle rather than global or devastating (Ackerman et al., 2010; Lester et al., 1998; Rose-Jacobs et al., 2009). Moreover, the magnitude of IUCE effects is often attenuated when the effects of biological and environmental risk and protective factors on neuropsychological functioning are covaried (Ackerman et al., 2010; Arendt et al., 2004; Dow-Edwards, 2011; Marques et al., 2007). In recent reviews, the most consistent IUCE effects on children's neuropsychological functioning after covariate control have been reported for language, attention, memory, and associated executive control processes (e.g., arousal, impulsivity, inhibition) (Ackerman et al., 2010; Buckingham-Howes et al., 2013).

1.1. IUCE and neuropsychological functioning

1.1.1. Language

A growing body of results from several large well-designed, covariate-controlled prospective studies suggests that IUCE may be linked to mild but persistent language delays in preschool, school-aged, and early adolescent children, although specific findings vary (Bandstra et al., 2004, 2011; Beeghly et al., 2006; Lewis et al., 2007, 2011). Bandstra and colleagues (Bandstra et al., 2011) evaluated the developing language skills of a large urban sample of cocaine-exposed and unexposed children at 3, 5, and 12 years of age using an age-appropriate version of a single standardized assessment, the *Clinical Evaluation of Language Fundamentals* (CELF) (Semel et al., 2003). Results of latent growth curve modeling revealed that a dichotomous measure of IUCE (exposed/unexposed) was associated with lower expressive and total language scores after controlling for prenatal exposure to tobacco, alcohol, and marijuana, and other medical and socio-demographic covariates. In a second analysis, a latent variable reflecting level of IUCE had a linear, dose-dependent relationship with receptive, expressive, and total language scores, controlling for child age, sex, and other prenatal exposures. However, the associations for receptive and expressive language scores were attenuated when other covariates were added to the model.

Contrasting findings were reported in other covariate-controlled prospective studies of children with and without IUCE. In a longitudinal analysis of children's standardized receptive, expressive, and total language scores during the first six years of life, Lewis et al. (2007) reported a stable negative effect of IUCE on all language measures; however, prenatal tobacco exposure and environmental measures also accounted for significant, unique variance in language outcomes. In a follow-up of this cohort at age 10, Lewis et al. (2011) found that IUCE was associated with mild compromise on specific rather than general measures of language, including syntax, semantics, and phonological processing.

In a longitudinal analysis of language data collected in the present cohort at ages 6 and 9.5 years, Beeghly et al. (2006) reported no significant main effects of IUCE on standardized language scores; however, significant interactions of IUCE with child age, sex, and birth weight on language outcomes were found. Specifically, children with IUCE had lower receptive language scores than unexposed children at age 6, but not at age 9.5 years, and girls with IUCE had lower expressive and total language scores at both ages, compared to girls without IUCE and boys regardless of exposure status. Moreover, children with IUCE with a lower birth weight had lower expressive language scores than children with IUCE with a higher birth weight.

1.1.2. Attention and associated executive control processes

Recent reviews of IUCE studies with school-aged and adolescent children suggest that IUCE is linked to subtle alterations in attention and associated executive control processes, such as arousal, impulsivity, task persistence, and response inhibition, as assessed using performance-based neuropsychological measures (Ackerman et al., 2010; Buckingham-Howes et al., 2013). These findings are concerning because these regulatory processes underlie children's ability to engage in independent goal-directed behavior and complex learning tasks (Lezak et al., 2004), which are increasingly required in higher education. Deficits in attention and other executive functions may undermine children's academic performance and social emotional competence in the elementary school years and beyond (Sroufe, 2013).

To date, most studies on the effects of IUCE on attentional processes have evaluated visual attention and related executive functions, and the results of this literature are not entirely consistent. In several analyses based on data collected in a large covariate-controlled prospective study, children with IUCE had significantly lower scores on measures of sustained visual attention assessed at ages 3, 5, and 7 years, as well as greater variability in performance, slower response time, and more omission (but not commission) errors at age seven (Accornero et al., 2007; Bandstra et al., 2001). A similar IUCE-related increase in omission errors on a continuous performance task was reported after covariate control in two independent cohorts; one at age 6 (Richardson et al., 1996) and the other at age 7 (Ackerman et al., 2008). In contrast, in two other studies, IUCE was associated with higher rate of commission (but not omission) errors on a continuous performance tasks at age 4 (Noland et al., 2005) and on a distractibility task with high performance demands at age 10 (Savage et al., 2005).

Moreover, in one prospective longitudinal study, no direct IUCE effects on visual attention and other dimensions of executive functioning were observed ages 5 or 7 (Eyler et al., 2009). However, IUCE was indirectly associated with attention and other dimensions of executive functioning via its effect on head circumference at birth. The quality of children's caregiving environment and caregivers' functioning also accounted for a significant proportion of the variance.

Although understudied, there is increasing evidence suggesting that IUCE may also alter auditory attention processes, which may contribute to the language impairments reported for this population. In the animal literature, IUCE has been shown to accelerate aspects of the cochlear sensorineural maturation process, which may desynchronize development of the auditory pathway and lead to auditory dysfunction, and may in turn be associated with altered auditory brainstem response identified in experimental animals postnatally (Trigueiros-Cunha et al., 2006). Similarly, using a protocol designed to capture primary features of human recreational cocaine usage, Mactutus et al. showed that IUCE in rats was associated with persistent alterations in auditory information processing and with dysfunction in the central noradrenergic circuitry modulating these responses (Mactutus et al., 2011). In human studies, IUCE has been linked to alterations in newborns' auditory brainstem responses (Tan-Laxa et al., 2004) and to slowed auditory information processing during an habituation paradigm (Potter et al., 2000), each of which could interfere with language development and general learning in later childhood. Beyond the newborn period, IUCE has been linked to deficits in auditory processing at one year of age (Singer et al., 2001), altered auditory threshold at age 7 (Chawla et al., 2007), and altered speech processing ability among adolescents as assessed using event-related potentials (Landi et al., 2012).

1.1.3. Memory

Recent reviews suggest that IUCE is associated to alterations in verbal and non-verbal memory (Ackerman et al., 2010; Buckingham-Howes