Developmental Cognitive Neuroscience 16 (2015) 155–165

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

Executive function and cortical thickness in youths prenatally exposed to cocaine, alcohol and tobacco

Prapti Gautam[a], Tamara D. Warner[b], Eric C. Kan[a], Elizabeth R. Sowell[a,c,*]

[a] Department of Pediatrics, Keck School of Medicine, University of Southern California, Children's Hospital of Los Angeles, Los Angeles, CA, United States
[b] Department of Pediatrics, University of Florida, Gainesville, FL, United States
[c] Department of Neurology, University of California at Los Angeles, Los Angeles, CA, United States

ARTICLE INFO

Article history:
Received 24 July 2014
Received in revised form 19 January 2015
Accepted 23 January 2015
Available online 2 February 2015

Keywords:
Prenatal alcohol exposure
Adolescent brain development
Socio-economic status (SES)
Cortical thickness
Executive functions
Brain-behaviour relationships

ABSTRACT

Small and detrimental, albeit inconsistent, effects of prenatal cocaine exposure (PCE) during early childhood have been reported. The teratogenic effects of prenatal alcohol (PAE) and tobacco exposure (PTE) on neurobehavior are more firmly established than PCE. We tested if co-exposure to all three drugs could be related to greater differences in brain structure than exposure to cocaine alone. Participants ($n = 42$, PCE = 27; age range = 14–16 years) received an executive function battery prior to a T1-weighted 3 T structural MRI scan. Cortical thickness was measured using FreeSurfer (v5.1). Fetal drug exposure was quantified through maternal self-reports usage during pregnancy. Using general linear modeling, we found no main effects of PCE on cortical thickness, but significant main effects of PAE and PTE in superior and medial frontal regions, after co-varying for the effects of age, sex, and each drug of exposure. Significant alcohol-by-tobacco interactions, and significant cocaine-by-alcohol interactions on cortical thickness in medial parietal and temporal regions were also observed. Poly-drug exposure and cognitive function also showed significant interactions with cortical thickness: lower cortical thickness was associated with better performance in PCE-exposed adolescents. Results suggest that although children with PCE have subtle but persistent brain cortical differences until mid-to-late adolescence.

1. Introduction

1.1. Prevalence of substance use during pregnancy

Substance use during pregnancy is highly prevalent in the US and internationally.

As prenatal substance use is associated with poorer developmental outcomes during infancy and also during adolescence and into adulthood, it is an important public health issue based on disability (Bandstra et al., 2010; Lupton et al., 2004; Spohr, 2007). Based on combined data from 2011 to 2012, it is estimated that 5.9% of pregnant women are illicit substance users in the U.S. out of which 0.2% of all pregnant women reported using cocaine (SAMHSA, 2012). In the same report, 8.5% of women reported drinking alcohol while pregnant, with 2.7% reporting binge drinking; and almost 16% of women reported tobacco use when pregnant. Women who use drugs during pregnancy are typically poly-substance users (Havens et al., 2009; Muhuri and Gfroerer, 2009; Keegan

* Corresponding author at: Department of Pediatrics, Keck School of Medicine, University of Southern California, Division of Research on Children, Youth and Families, Children's Hospital Los Angeles, 4650 Sunset Blvd., Mailstop #130, Los Angeles, CA 90027, United States.
Tel.: +1 323 361 7347; fax: +1 323 361 7836.
E-mail address: esowell@chla.usc.edu (E.R. Sowell).

http://dx.doi.org/10.1016/j.dcn.2015.01.010

et al., 2010). Given that exposure to one drug is known to cause harm to the developing fetus, (Valenzuela et al., 2012; Williams et al., 2012; Zugno et al., 2013) exposure to more than one substance, combined with their potential interactive effects could elevate the risks to the developing fetal brain and cause changes to the developing brain.

1.2. Prenatal cocaine exposure

Several studies in children have shown a small, but consistent detrimental effects of prenatal cocaine exposure (PCE) during infancy and early childhood. Smaller head circumferences, preterm birth, and increased subependymal hemorrhages (Singer et al., 2002; Frank et al., 1999; Buckingham-Howes et al., 2013; Ackerman et al., 2010) are more common in children with PCE. However, meta-analyses suggest reduced effect sizes of cocaine exposure with age (Held et al., 1999), such that effects of PCE exposure are smaller in childhood compared to the effects seen at birth (Ackerman et al., 2010), and are much harder to detect by adolescence (Buckingham-Howes et al., 2013; Hurt et al., 2008). For instance, extensive behavioral and neurocognitive batteries have found no effects of PCE on executive functions, language, memory, or behavior (Singer et al., 2002; Hurt et al., 2009) in adolescents with PCE. Nonetheless, despite smaller than expected behavioral differences, differences in brain structures of the deep gray matter (Roussotte et al., 2010; Avants et al., 2007) and white matter (Lebel et al., 2013; Li et al., 2009) have been reported in children and adolescents. Therefore, it is possible that subtle brain structural differences might persist during adolescence in those with PCE.

1.3. Prenatal alcohol and tobacco exposure

The effects of prenatal alcohol exposure (PAE) on neurobehavioral outcomes are more firmly established than cocaine. Neurobehaviorally, poorer working memory and executive functioning (Mattson et al., 2012; Astley et al., 2009), as well as high rates of conduct disorders cause lifelong disability (Lupton et al., 2004). A dose-response relationship has also been found in IQ with increasing maternal alcohol-intake (Goldschmidt et al., 1996). Effects on brain structure due to PAE include smaller and reduced gray matter (Archibald et al., 2001; Lebel et al., 2012); and reduced white matter volumes (Gautam et al., 2014) in children and adolescents. Abnormalities in cortical thickness (Zhou et al., 2011; Sowell et al., 2008) as well differential longitudinal trajectories of brain activation (Gautam, in press) of the frontal, temporal, and parietal regions have also been documented in those with Fetal Alcohol Spectrum Disorders (FASD).

Similar to PAE, prenatal tobacco exposure (PTE) is associated with increased risk for developing behavioral and psychiatric problems in adolescence (Ekblad et al., 2010). Higher risks of spontaneous abortions in smokers (Blanco-Munoz et al., 2009), lower birth weights and smaller head circumferences in children born to smokers (Kallen, 2000), and differences in cortical thickness in those with PTE (Toro et al., 2008; Liu et al., 2013) have been reported. A meta-analysis has also found lower academic achievement in children of mothers who smoked while pregnant (Clifford et al., 2012).

1.4. Co-exposure to prenatal substances

Co-exposure to poly-drugs might have interactive effects in the fetus, over and beyond the effects of each drug taken alone. Rivkin et al. (2008) found that while PCE, PAE, and PTE were each related to smaller brain volumes, newborns with the most co-exposure had the smallest brain regions. A potential mechanism for detrimental effects in metabolism is production of cocaethylene, which could have a higher potential for toxicity than the ingestion of each of these drugs alone (McCance-Katz et al., 1998). Poly-substance use is also related to highest overall incidences of lowered fetal birth weights compared to individual substances in human studies (Janisse et al., 2013; Singer et al., 2002) while animal studies suggest that the effects of prenatal exposure might cause heritable changes in the genetic makeup (Vassoler et al., 2014), with synergistic effects of ethanol and cocaine also being reported by others (Tallarida et al., 2014). Finally, while a previous study has also suggested that co-exposure to cocaine and tobacco are related to differences in brain microstructural properties and poorer behavioral outcomes in children (Warner et al., 2006), the effects of poly-drug exposure and their interactions on cortical surfaces are not fully known.

1.5. Effects of socio-economic status and maternal health/education

The use of substances during pregnancy is related to additional health risks for children, above and beyond the direct risks of drug exposure. Previous studies have shown that mothers of children with PCE tend to be of lower socioeconomic status (SES) and have lower levels of education – factors that have been associated with poorer visuo-motor co-ordination and poorer intellectual functioning in the offspring (Singer et al., 2002; Arendt et al., 2004; Bandstra et al., 2002). Similar results have been found for children with PAE and PTE: mothers who drink while pregnant are significantly more likely to be of lower SES and have poorer health behaviors (May et al., 2011; Connor and McIntyre, 1999). In contrast, better health behaviors by mothers and higher family income have been previously associated with better health outcomes in typically developing children (Adler and Rehkopf, 2008; Hackman et al., 2010). For instance, mothers with higher education levels were also more likely to stop smoking while pregnant compared to mothers with lower education levels (Connor and McIntyre, 1999; Yu et al., 2002). Therefore, studies of prenatal drug exposure effects on children need to consider the socio-economic status, maternal education, and income levels to rule out confounding effects of these variables on brain and behavior.

The aim of the current study was to investigate the effects of PCE on cortical thickness in adolescents and how this is affected by co-exposure to alcohol and tobacco in children with PCE. A secondary aim was to test the effects of exposure to cocaine and other drugs on cognitive function in relation to cortical thickness. Given the well-known