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Prenatal cocaine effects on brain structure in early infancy

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ABSTRACT

Prenatal cocaine exposure (PCE) is related to subtle deficits in cognitive and behavioral function in infancy, childhood and adolescence. Very little is known about the effects of *in utero* PCE on early brain development that may contribute to these impairments. The purpose of this study was to examine brain structural differences in infants with and without PCE. We conducted MRI scans of newborns (mean age = 5 weeks) to determine cocaine's impact on early brain structural development. Subjects were three groups of infants: 33 with PCE co-morbid with other drugs, 46 drug-free controls and 40 with prenatal exposure to other drugs (nicotine, alcohol, marijuana, opiates, SSRIs) but without cocaine. Infants with PCE exhibited lesser total gray matter (GM) volume and greater total cerebral spinal fluid (CSF) volume compared with controls and infants with non-cocaine drug exposure. Analysis of regional volumes revealed that whole brain GM differences were driven primarily by lesser GM in prefrontal and frontal brain regions in infants with PCE, while more posterior regions (parietal, occipital) did not differ across groups. Greater CSF volumes in PCE infants were present in prefrontal, frontal and parietal but not occipital regions. Greatest differences (GM reduction, CSF enlargement) in PCE infants were observed in dorsal prefrontal cortex. Results suggest that PCE is associated with structural deficits in neonatal cortical gray matter, specifically in prefrontal and frontal regions involved in executive function and inhibitory control. Longitudinal study is required to determine whether these early differences persist and contribute to deficits in cognitive functions and enhanced risk for drug abuse seen at school age and in later life.

Introduction

Prenatal cocaine exposure (PCE) is related to subtle cognitive, behavioral and physiological differences in infancy, childhood and adolescence. Many well-controlled prospective studies report that infants and toddlers exposed to cocaine *in utero* demonstrate impaired affect (Tronick et al., 2005), arousal (Bendersky and Lewis, 1998), joint attention, visual recognition (Singer et al., 2005), auditory comprehension (Singer et al., 2001) and are at risk for delayed mental development (Noland et al., 2005). At school age, PCE is linked to higher risk for learning disabilities (Morrow et al., 2006) and to subtle deficits in attention, response inhibition (Accornero et al., 2007; Bandstra et al., 2001), impulsivity (Savage et al., 2005), language development (Lewis et al., 2011), working memory (Mayes et al., 2007; Schroder et al., 2004), planning and set shifting (Warner et al., 2006). Adolescents with PCE demonstrate deficits in working memory for words and faces, inhibitory control, and early sensory and higher order processing of language stimuli (Betancourt et al., 2011; Bridgett and Mayes, 2011; Landi et al., 2012). Difficulty with emotional/behavioral and physiological self-regulation is demonstrated in all age groups (Chaplin et al., 2010; Eiden et al., 2009; Minnes et al., 2005; Tronick et al., 2005), and adolescents are more likely to use cocaine and other drugs compared with their non-exposed peers (Delaney-Black et al., 2011). Little is known about the effects of *in utero* exposure to cocaine on human early brain development that may mediate or contribute to such deficits.

Cocaine acts as a powerful central nervous system stimulant by blocking reuptake of the monamines, dopamine, serotonin and norepinephrine, resulting in prolonged, supraphysiologic synaptic and extracellular levels (Meyer and Quenzer, 2005). During critical periods of fetal brain development these neurotransmitters play important roles in growth and organization (Whitaker-Azmitia et al., 1996), exerting widespread effects on neuronal cell proliferation and differentiation (Lauder, 1993; Popolo et al., 2004), migration (Riccio et al., 2012; Vitalis and Parnavelas, 2003), and dendritic growth (Song et al., 2002, 2004). When taken by mothers during pregnancy, cocaine and its active metabolites easily diffuse through the placenta into fetal circulation, where they cross the immature blood–brain barrier (Schenker et al., 1993). Animal research shows that cocaine exerts direct pharmacological effects on

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fetal brain, altering metabolism (Benveniste et al., 2010), cerebral blood supply, cortical neuron volume and functional characteristics (Frankfurt et al., 2011; Ren et al., 2004; Stanwood and Levitt, 2007).

Results from neuroimaging studies conducted in late childhood and adolescence suggest that PCE may be associated with alterations in brain structure and function that persist into adolescence and that may contribute to poorer performance on executive function tasks measured at school age and in later life. Findings in preadolescent children include significant reductions in corpus callosal area, lesser occipital and parietal gray matter (GM) volume, smaller right cerebellar volume (Dow-Edwards et al., 2006) and increased levels of creatine in frontal lobe white matter, indicative of abnormal energy metabolism (Smith et al., 2001). At adolescence, PCE is linked to smaller head circumference, total brain and cortical GM volume (Rivkin et al., 2008), reduced frontal and orbital frontal cortical volume (Roussotte et al., 2010), reduced global cerebral blood flow, greater GM volume in amygdala and reduced GM volume in bilateral caudate (Avants et al., 2007; Rao et al., 2007). Functional MRI studies reveal greater resting state connectivity of the default mode network (DMN), with impaired ability for prefrontal inhibition of limbic circuitry and less deactivation of the DMN during working memory challenge (Li et al., 2009, 2011). A very few imaging studies of infants with PCE have been reported. Delayed brain maturation is suggested by EEG findings of slower auditory brainstem response at birth, and reduced inter-hemispheric connectivity at birth and 1 year (Lester et al., 2003; Scher et al., 2000). Neonatal cranial ultrasounds reveal greater incidence of intracranial hemorrhage in infants with 'heavy' prenatal cocaine exposure; however infants with less exposure do not differ from drug-free infants (Frank et al., 1999). Structural MRI studies of brain development in infants with PCE have been limited to a single case study at 11 months (Gomez-Anson and Ramsey, 1994), and to a group of 8 exposed infants (scanned at .6–12 months) who were then compared with published norms (Link et al., 1991). To date MRI study of neonatal brain structure in infants with PCE compared with drug-free controls and/or non-cocaine drug-exposed infants has not been reported.

Notably, the aforementioned cognitive, neurobehavioral and neuroimaging findings are by no means unequivocal across a large, decades-long body of research (Coyle, 2013; Dow-Edwards, 2011; Roussotte et al., 2010). Study is complicated by the fact that prenatal cocaine exposure is often comorbid with maternal use of other licit and illicit drugs. To address this, most investigations have compared children with *in utero* exposure to cocaine plus tobacco, alcohol and/or marijuana, to children with prenatal exposure to these same drugs but without cocaine. Nevertheless some studies report no observable PCE effects (Frank et al., 2001). Others reveal independent or interactive effects with nicotine, alcohol, or contextual factors (prematurity, gender, maternal care, environmental characteristics Bandstra et al., 2010; Eiden et al., 2011a, 2011b; Irner, 2012; Liu et al., 2013). The purpose of the current study was to examine the effects of prenatal cocaine exposure on infant brain structure during early infancy, at a time more proximal to *in utero* exposure, and less influenced by the postnatal environment. We used structural MRI to examine total and regional gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) brain volumes in 2–6 week old cocaine-exposed infants with or without other drug exposures, comparing them to drug-naive infants, and also to infants with similar patterns of polydrug exposure without cocaine.

Materials and methods

Participants

Infants were part of an ongoing study of the effects of prenatal cocaine exposure on biological mechanisms underlying mother–infant interaction and attachment characteristics. Here we report results from the first 119 infants to complete the infant MRI protocol. Mothers were recruited during pregnancy from local obstetric clinics, health departments, and programs for substance abuse treatment of pregnant and postpartum mothers. Infants were medically healthy singletons, born at ≥36 weeks gestation. The study sample ($N = 119$) consisted of 33 cocaine-exposed infants with or without *in utero* exposure to marijuana, alcohol, nicotine, opiates and/or SSRIs (PCE), 40 infants with *in utero* exposure to these same drugs but without cocaine (NCOC), and 46 drug-free controls (CTL). The sample included 61 males and 58 females, and maternal report of ethnic composition was 59 White, 33 African American, 25 multi-racial, 2 other. Drug use status was based on self-report on Time Line Follow Back Interview (Sobell and Sobell, 1995) conducted at 1 month postpartum, response to a questionnaire about maternal substance use done at 3 months, and medical record queries of prenatal urine toxicology. If maternal self-report or urine toxicology was positive for cocaine use at any time during pregnancy, that mother–infant dyad was classified as PCE. This study was approved by the Biomedical Institutional Review Board of the University of North Carolina.

MR image acquisition

Infants were scanned during sleep without sedation. Infants were first fed and then swaddled. Sleeping infants were each fitted with ear protection. A vacuum-fixation device was used to secure head position in the scanner. A nurse monitored each infant by sight, touch and by pulse oximetry for heart rate and % oxygen saturation throughout the scan. All images were acquired using a 3 T MRI scanner. An unavoidable scanner replacement occurred during the study, resulting in 94 infants scanned on a 3T head only Siemens Allegra and 25 infants scanned on a 3T Siemens Tim Trio (Siemens Medical Solutions, Erlangen, Germany). Both scanners are Food and Drug Administration approved for use in all age groups. Adjustment for scanner type was added to all statistical models.

T1-weighted structural pulse sequences were obtained with a 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence (repetition time (TR) = 1820 ms, echo time (TE) = 3.75 ms, inversion time (TI) = 1100 ms, flip angle = 7°, 144 slices, voxel size: 1 × 1 × 1 mm). Proton density and T2-weighted images were acquired with turbo spin echo sequence (TR = 6200 ms, TE1 = 17 ms, TE2 = 116 ms, flip angle = 150°, 58 slices, voxel size = 1.3 × 1.3 × 1.5 mm).

Image analysis

Brain tissue and cerebral spinal fluid (CSF) were segmented with an automatic segmentation tool specifically designed for the neonatal brain, described previously (Prastawa et al., 2005). The segmentation method makes use of dual contrast MRI (T1w, T2w) for optimal separation of GM, WM and CSF space and uses a co-registered probabilistic neonatal atlas, developed by our group, as a spatial prior (Figs. 1A–C). The neonatal population atlas includes a lobar parcellation into 16 boxes aligned along the brain hemisphere symmetry plane and the AC–PC line (Fig. 1D). The choice for a box parcellation versus more detailed anatomical lobe parcellation as often applied in adult neuroimaging was motivated by the fact that the very dense and compact cortical geometry of the neonatal brain presents a challenge for a reproducible and reliable subdivision based on sulcal features. The neonatal segmentation tool integrates multimodal T1w/T2w MRI registration, intensity bias inhomogeneity correction, tissue segmentation, brain stripping and lobe parcellation into one integrated platform, and represents a key instrument that has led to a series of publications on neonatal brain growth (Gilmore et al., 2007, 2010; Knickmeyer et al., 2008, 2011). Fig. 1 displays representative 3D visualizations of segmented WM (1E, red) and GM (1F, green), and of CSF shown on the brain cavity surface (1G, blue).