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Thalamocortical functional connectivity and behavioral disruptions in neonates with prenatal cocaine exposure

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ABSTRACT

Prenatal cocaine exposure (PCE) affects neurobehavioral development, however, disentangling direct drug-related mechanisms from contextual effects (e.g., socioeconomic status) has proven challenging in humans. The effects of environmental confounds are minimal immediately after birth thus we aimed to delineate neurobehavioral correlates of PCE in a large cohort of neonates (2–6 weeks of age, N = 152) with and without drug exposure using resting state functional magnetic resonance imaging (rsfMRI) and developmental assessments at 3 months with the Bayley Scales of Infant & Toddler Development, 3rd edition. The cohort included healthy controls and neonates with similar poly-drug exposure ± cocaine. We focused on the thalamus given its critical importance in early brain development and its unique positioning in the dopamine system. Our results revealed PCE-related hyper-connectivity between the thalamus and frontal regions and a drug-common hypo-connective signature between the thalamus and motor-related regions. PCE-specific neonatal thalamo-frontal connectivity was inversely related to cognitive and fine motor scores and thalamo-motor connectivity showed a positive relationship with composite (gross plus fine) motor scores. Finally, cocaine by selective-serotonin-reuptake-inhibitor (SSRI) interactions were detected, suggesting the combined use of these drugs during pregnancy could have additional consequences on fetal development. Overall, our findings provide the first delineation of PCE-related disruptions of thalamocortical functional connectivity, neurobehavioral correlations, and drug-drug interactions during infancy.

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1. Introduction

Prenatal cocaine exposure (PCE) is a serious public health concern commonly associated with a number of adverse behavioral consequences throughout development (Lambert and Bauer, 2012; Ross et al., 2015). The pathophysiology of the effects of PCE are thought to operate over three different axes (Lester and Padbury, 2009); 1) neurochemical, i.e. monoaminergic interactions [dopamine (DA), norepinephrine (NE), and serotonin (5-HT)], 2) vasoconstrictive mechanisms, and 3) fetal programming. Disentangling these effects from postnatal environmental adversities, which are often co-morbid with PCE, has proven challenging in studies of later childhood and adolescence (Eiden et al., 2014; Yumoto et al., 2008). However, recent neuroimaging efforts in neonates have shown great promise, effectively allowing for more direct delineation of drug-related effects by minimizing exposures to postnatal risk factors (Grewen et al., 2014; Grewen et al., 2015; Salzwedel et al., 2015). These studies have opened a new window and thus enabled more specific investigations of PCE-related brain-behavior mechanisms starting from birth.

PCE is typified by abnormal arousal and attention regulation/reactivity to stressful conditions, as well as deficits to sustained focus, salience processing, and working memory (Mayes, 2002; Mayes et al., 1998). Imbalanced gating between different processing streams, particularly between limbic and executive regions, has been put forth as a potential mechanism (Harvey, 2004; Mayes, 2002). Indeed, neuroimaging efforts have lent credence to this theory (Grewen et al., 2014; Li et al., 2009; Li et al., 2016; Li et al., 2013; Liu et al., 2013; Rando et al., 2013; Rao et al., 2007; Roussotte et al., 2010; Salzwedel et al., 2015; Sheinkopf et al., 2009) and shown PCE-related structural and functional alterations associated with the amygdalo-frontal pathway. However the thalamus, another region that is reportedly critical for this set of PCE-affected functions, has received relatively little attention. Numerous reports support a role for the thalamus and thalamocortical connectivity in 1) arousal regulation (Paus et al., 1997) that is closely related to the performance of sustained attention (Paus et al., 1997; Sarter et al., 2001), 2)

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saliency detection and processing (Ding et al., 2010), especially in terms of salient error monitoring (Harsay et al., 2012; Li et al., 2008; Zhang et al., 2014), and 3) working memory through the contribution from the mediodorsal nucleus (Watanabe and Funahashi, 2012). Therefore, abnormal thalamocortical connectivity could also contribute to the reported PCE-related functional deficits and deserves further attention as a novel target for better understanding of the neural correlates of PCE. Notably, explorations of thalamocortical connectivity in infants have successfully demonstrated that both structural and functional connectivity between thalamus and limbic/frontal regions predict later cognitive abilities (Alcauter et al., 2014a; Ball et al., 2015), supporting the behavioral significance of thalamocortical connectivity during infancy. More importantly, the human thalamus, unlike other species, is richly innervated with DA-afferents (Garcia-Cabezas et al., 2007; Sanchez-Gonzalez et al., 2005) making it potentially highly susceptible to PCE-induced disruptions during in utero development (Crandall et al., 2007; Frankfurt et al., 2011; Ohtani et al., 2003; Song et al., 2002). Therefore, a systematic study of the thalamus and its functional connections may provide new insights into PCE effects and behavioral associations in infants. Lastly, poly-drug use is relatively common in women who abuse drugs during pregnancy therefore other drugs may also affect the hypothesized thalamocortical connectivity, and thus exploration of potential drug-drug interactions is also of high importance and interest (Meyer and Quenzer, 2005; Ross et al., 2015).

In this study, we systematically examined thalamocortical connectivity, its behavioral correlations, and drug-drug interactions to gain novel insights into the effects of PCE. Specifically, resting state functional magnetic resonance imaging (rsfMRI) was employed to evaluate functional connectivity in naturally sleeping neonates (2–6 weeks old at time of scan). The study cohort included neonates with in utero exposure to cocaine plus some combination of other non-cocaine drugs (PCE), exposure to similar a combination of non-cocaine drugs (NCOC), and drug-free controls (CTR). The inclusion of the NCOC drug-exposed subgroup allowed for more rigorous control of the effects due to other drugs as well as common drug-related environmental conditions. In addition, the NCOC group enabled a more thorough exploration of potential drug-drug interaction effects. We hypothesized that thalamic connectivity would show significant PCE related disruptions, particularly with frontal areas. Moreover, these neural correlates would predict later behavioral outcomes. Finally, we also expected significant interaction effects between different drug types.

2. Subjects and methods

2.1. Subjects

The study cohort (N = 152) consisted of three groups: 45 cocaine exposed infants with or without in utero exposure to marijuana, alcohol, nicotine, SSRIs, and opiates including heroin, oxycodone, oxycontin, methadone and the mixed agonist/antagonist, suboxone (PCE); 43 infants with in utero exposure to similar combination of the aforementioned drugs minus cocaine (NCOC); and 64 drug free controls (CTR). Pregnant women were recruited in the third trimester of pregnancy. Primary recruitment sites for PCE and NCOC participants were local residential and outpatient treatment programs for women with perinatal substance abuse and their children. In addition, we recruited CTR and drug-exposed mothers from Chatham, Orange, Durham, Alamance, and Wake County Health Department obstetric clinics, the University of North Carolina hospital low-income obstetrics clinic, and flyers, local advertisements, and Craigslist. At enrollment, mothers were required to be between 18–44 years of age and free from; 1) chronic medical or psychiatric disease, 2) untreated current clinical depression or anxiety disorder, and 3) language barrier that might prevent informed consent. A number of subjects with opiate abuse were treated with methadone or suboxone maintenance treatment for part of their pregnancies. The infants took part in the imaging experiment during the neonatal period (2–6 weeks of age) and participated in behavioral assays at approximately 3 months of age. All infants were required to be living with biological mother at time of testing. Infants were excluded for multiple reasons, including; gestational birth weight < 2500 g, delivered at <32 weeks or >42 weeks gestation, history of mechanical ventilation or surgery of any kind, >24 h in NICU, or chronic illness of any kind. Mother-infant dyads were characterized and compared on the following criteria: gestational age at birth, gestational age at scan, birth weight, pre/postnatal drug exposure, infant cognitive and motor functions, maternal education and depression at the time of scan. All participants were tested for prenatal drug use using interviews, medical record review, and postnatal urine toxicology at study visits. Prenatal drug exposure status was based on three criteria: (1) maternal self-report with Time Line Follow Back interview (Robinson et al., 2014) conducted in 3rd trimester and again at neonatal MRI visit; (2) response to a questionnaire about maternal substance use done at 3 months; and (3) medical record queries of prenatal urine toxicology. Maternal self-report or positive urine toxicology for cocaine qualified the mother–infant dyad for PCE status. Postnatal drug exposure was characterized using maternal self-reports of drug use and infant feeding method. Maternal education was determined by rank scores (Table 1). Maternal depression was indexed by score on the Edinburgh Postnatal Depression Scale at time of scan (Murray and Carothers, 1990). Infant behavior was assessed using the Bayley III Scales of Infant and Toddler Development (Bayley, 2006). Please see the supporting material for a detailed description of the Bayley III and the assessment procedures for the following three domains: Cognitive development; language development which includes both receptive and expressive communication as separate but combinable subtests; and motor development which also includes both fine and gross motor development as separate but combinable subtests. Research staff that conducted the Bayley assessments was blinded to specific drug-exposure status. Group means for each characteristic were compared using the analyses of variance (ANOVA) and group proportions were tested using the chi-square statistic. This study was approved by the University of North Carolina at Chapel Hill's Biomedical Institutional Review Board.

2.2. Image acquisition and image preprocessing

Data were collected for all neonates at 2–6 weeks of postnatal age, adjusted for prematurity, using two scanners: 1) 3 T Siemens Allegra (n = 89; 14 for PCE, 34 for NCOC, and 41 for CTR) with circular polarization head coil and 2) 3 T Siemens Tim Trio (n = 63; 31 for PCE, 9 for NCOC, and 23 for CTR) with 32-channel head coil. Time of day for scan was determined by infant nap schedule with the majority done between 10 am and 2 pm but was not systematically controlled. T1-weighted structural images were collected using a 3D magnetization prepared rapid gradient echo pulse 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 mm^3). rsfMRI images were acquired using a $T2^*$-weighted echo planar imaging (EPI) pulse sequence (TR = 2 s, TE = 32 ms, 33 slices, voxel size = 4 mm^3, number of volumes = 150). Data were preprocessed using the FMRIB's Software Libraries (Jenkinson et al., 2012) and AFNI (Cox, 1996). Functional preprocessing included discarding the first 10 volumes, slice-timing correction, motion correction, spatial smoothing (Gaussian kernel FWHM = 6 mm), band-pass filtering (0.01–0.08 Hz), data scrubbing, and regression of whole brain, white matter, cerebrospinal fluid signals and the six motion parameters. Given the higher likelihood of fine motion from naturally sleeping infants, data scrubbing was performed as an added motion correction step in addition to the standard rigid-body motion correction procedures. Specifically, volumes with global signal changes >0.5% and/or frame-wise displacements (FD) > 0.5 mm (Power et al., 2012) were excluded (plus one before and two after). Post-scrubbing, subjects with less than 90 volumes were excluded