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Longitudinal changes of amygdala and default mode activation in adolescents prenatally exposed to cocaine

Zhihao Li [a,b,*], Claire D. Coles [c], Mary Ellen Lynch [c], Yuejia Luo [a], Xiaoping Hu [b,**]

[a] Institute of Affective and Social Neuroscience, Shenzhen University, Shenzhen 518060, Guangdong, PR China
[b] Biomedical Imaging Technology Center, Department of Biomedical Engineering, Emory University & Georgia Institute of Technology, Atlanta 30322, GA, USA
[c] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta 30322, GA, USA

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ABSTRACT

Prenatal cocaine exposure (PCE) is associated with long-term and negative effect on arousal regulation. Recent neuroimaging studies have examined brain mechanisms related to arousal dysregulation with cross-sectional experimental designs; but longitudinal changes in the brain, reflecting group differences in neurodevelopment, have never been directly examined. To directly assess the interaction of PCE and neurodevelopment, the present study used a longitudinal design to analyze functional magnetic resonance imaging (fMRI) data collected from 33 adolescents (21 with PCE and 12 non-exposed controls) while they performed the same working memory task with emotional distracters at two points in time. The mean age of participants was 14.3 years at time_1 and 16.7 years at time_2. With confounding factors statistically controlled, the fMRI data revealed significant exposure-by-time interaction in the activations of the amygdala and default mode network (DMN). For the control adolescents, brain activations associated with emotional arousal (amygdala) and cognitive effort (DMN) were both reduced at time_2 as compared to that at time_1. However, these activation reductions were not observed in the PCE group, indicating persistently high levels of emotional arousal and cognitive effort. In addition, correlations between longitudinal changes in the brain and in behavior have shown that adolescents with persistently high emotional arousal were more likely in need of high cognitive effort; and their cognitive performance was more likely to be affected by distractive challenges. The present results complement and extend previous findings from cross-sectional studies with further evidence supporting the view of PCE associated long-term teratogenic effects on arousal regulation.

1. Introduction

Prenatal cocaine exposure (PCE) has long-term effect on arousal regulation with ample evidence reported in animal (Johns et al., 1992, Romano and Harvey, 1998, Campbell et al., 2000, Salas-Ramireza et al., 2010) as well as in human studies of neonates (Dipietro et al., 1995, Regalado et al., 1995, Karmel and Gardner, 1996), infants (Bendersky and Lewis, 1998, Coles et al., 1999, Bard et al., 2000, Schuetze and Eiden, 2006, Schuetze et al., 2007, Eiden et al., 2009a, 2009b), young children (Bandstra et al., 2001, Dennis et al., 2006, Bada et al., 2007, Kable et al., 2008, Chaplin et al., 2009), and adolescents (Li et al., 2009, Chaplin et al., 2010, Lester et al., 2010, Li et al., 2011, Li et al., 2013a). Specifically, individuals with PCE often exhibit a reduced threshold in response to perceived distractions, or salient but task-irrelevant stimuli, which in turn may compromise the availability of their attention resource for on-going cognition and behavior (Mayes et al., 1998, Mayes, 2002, Harvey, 2004). Arousal regulation refers to how different stimuli are gated to different cortical regions and reflects one's capability to adjust and allocate mental resources for distinct yet interactive streams of information processing (Damasio, 1995). The behavioral manifestations in children with PCE thus suggest an imbalanced gating of stimulation to limbic and cognitive regions such that allocation of processing resource is inappropriately biased towards salient but task-irrelevant information (Mayes, 2002).

In examining the neurobiological mechanisms of this PCE effect, our previous neuroimaging studies have shown that adolescents with PCE have reduced capacity to suppress brain activations in the amygdala (Li et al., 2009, Li et al., 2013a) and in the default mode network (DMN) (Li et al., 2011), which is assumed to be involved in mediating task-irrelevant arousal. Neuroimaging studies from other groups also reported PCE-related morphological alterations in caudate (Avants et al., 2007, Roussotte et al., 2012), amygdala (Rao et al., 2007, Rando et al., 2013), and prefrontal cortex (Roussotte et al., 2012, Liu et al., 2013, Rando et al., 2013), as well as activation alterations in frontal and striatal regions (Sheinkopf et al., 2009). These observations also may contribute to the anatomical and functional underpinnings of

* Correspondence to: Z. Li, Institute of Affective and Social Neuroscience, Shenzhen University, 3688 Nanhai Ave, Shenzhen 518060, PR China.
** Correspondence to: X. Hu, Department of Biomedical Engineering, Emory University & Georgia Institute of Technology, 1760 Haygood Drive, Atlanta, GA 30322, USA.
E-mail addresses: zli8@emory.edu (Z. Li), xhu3@emory.edu (X. Hu).

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arousal dysregulation. However, as a newly emerging research field of PCE, neuroimaging studies to date have only been cross-sectional in design with brain changes over time in the same individuals not directly examined.

Adolescence is the period during which developmental and social problems become acute for children of substance abusing parents (Loeber and Farrington, 2000). For example, recent studies have shown in teens with PCE problems of social interaction (Greenwald et al., 2011) and adolescent substance use (Delaney-Black et al., 2011, Chaplin et al., 2014). Although these problems may also be influenced by prenatal exposure of other drugs and environmental factors (Lambert and Bauer, 2012), may mainly occur in an emotional context (Mayes, 2002), or may simply reflect delayed maturation (Bennett et al., 2015), these findings still suggest the importance of a deeper understanding of the impact of PCE on the developing brain, particularly on the interplay of cognitive and limbic systems. In typically developing adolescents, the ability to regulate emotion and attention increases substantially (Crone and Dahl, 2012) with children demonstrating decreasing emotional arousal (Guyer et al., 2008) and increasing executive functioning (Giedd, 2008). However, while adolescents with PCE are known to be generally over-sensitive to salient but task-irrelevant distractions (Mayes, 2002), there is still a lack of direct evidence as to whether this teratogenic effect can be offset by neurodevelopmental changes associated with maturity.

To examine these questions, the present study analyzed fMRI data acquired from the same group of adolescents, with or without PCE, when they were performing the same working memory task with emotional distracters at two different times about 2.4 years apart. These adolescents were recruited from a larger sample designed to assess developmental effect of PCE (Kable et al., 2008, Li et al., 2009, Deshpande et al., 2010, Li et al., 2011, Li et al., 2013a, 2013b) and neuroimaging data was obtained twice from the same individuals. At both time points, the fMRI experiments used identical paradigm and stimuli that required participants to perform a working memory task while suppressing distraction from emotional pictures. The memory and emotion stimuli in this task were two streams of information competing for processing resources thus challenging individual's capacity for arousal regulation.

During the time_2 test, given that (i) brains are more mature, (ii) subjects are more familiar with the task and the imaging environment, and (iii) emotional stimuli are believed to be less salient/distractive with repeated viewing, it was hypothesized that the non-exposed participants would improve their memory performance with increasing age; and their brain activations would reflect reduced emotional arousal and less cognitive effort. For the exposed participants, based on aforementioned long-term effect of arousal dysregulation, brain activation changes related to PCE were expected to reflect either a delayed development or a deviant development. If the activation changes over time follow the same trend in the two groups but are only reduced for the PCEs, a delayed development would be noted; but if the activation changes exhibit a different trend in the two groups, a deviance interpretation would be supported.

2. Methods

2.1. Participants

Thirty-three adolescents (21 with PCE and 12 non-exposed) were included in the analysis for the present study. They were a sub-sample from our previous fMRI study of PCE (N = 56) (Li et al., 2009). In that study (when time_1 imaging data acquisition occurred), PCE associated arousal dysregulation was examined with cross-sectional group comparisons. In this study, which includes imaging data acquisition at time_2, we scanned the same group of participants again with identical experiment settings for longitudinal comparison. However, the present sample size was reduced from N = 56 to N = 33 due to attrition at time_2 (11 were not located, 3 were not scanned for imaging-related concerns such as installation of teeth braces, 3 had excessive head motion, 2 had scheduling issues, 2 quit imaging before completion, 1 dropped for scanner malfunction, and 1 refused to re-participate). The present 33 adolescents are individuals with fMRI data available at both time points. They were not significantly ($p > 0.3$) different from the time_1 sample of N = 55 on any one of the following variables: birth weight, head circumference, gestational age, Apgar scores, birthmother's age, amount of prenatal drug and alcohol use, child's age at time_1 imaging, family monthly income level, verbal performance, and full scale IQ.

In the present sample, adolescents were on average 14.3 (SD = 1.9) years of age at time_1 and 16.7 (SD = 2.1) at time_2. The participants, predominantly African-American with low income and born during 1989–1994, were recruited from birth cohorts originally identified as part of two longitudinal studies of PCE effects on development (Coles et al., 1992, Brown et al., 1998). Their detailed demographic characteristics are shown in Table 1. Sources of information used to determine maternal cocaine and other substance use in pregnancy included medical records, maternal self-report following delivery (Coles et al., 1992), the Addiction Severity Index carried out at 6 weeks postpartum (McLellan et al., 1980) and postpartum maternal and infant urine screens. These measures also provided information about maternal use of cigarettes, alcohol and other drugs.

PCE group status was determined by maternal self-report and/or positive urine screens at recruitment postpartum. Positive maternal urine screens at labor and delivery and during pregnancy noted in the medical record were also accepted as evidence of use. Mothers were excluded if they used other drugs with teratogenic properties (e.g. Antabuse, seizure medications, warfarin, and insulin), benzodiazepines, antipsychotic drugs, or any addictive substances other than cocaine and marijuana. Mothers had to be 19 years of age or older, English speaking and free of major medical conditions. Additionally, their infants needed to be singletons or firstborns of multiple births and either healthy full term or preterm without major medical complications. Preterms who were less than 30 weeks of gestational age were excluded. Preterm infants and their mothers were subsequently dropped from the recruiting cohort if the infants developed the following complications during their neonatal course: received oxygen for more than 28 days, developed major infection, had seizures, were diagnosed with intraventricular hemorrhage grade III or IV, or with

Table 1
Characteristics of teens.

Variable	Control (n = 12)[a]	PCE (n = 21)[a]	p-value[b]
Age — time_1 (M,SD)	14.4 (2.2)	14.3 (1.8)	0.86
Age — time_2 (M,SD)	16.8 (2.3)	16.6 (2.0)	0.87
Duration between time_1 and time_2 (Month, SD)	25.4 (3.3)	27.2 (4.2)	0.22
Gender, No. (%)			0.51
Male	6 (50.0)	13 (61.9)	
Female	6 (50.0)	8 (38.1)	
Ethnic Background, No. (%)			0.44
African-American	12 (100.0)	20 (95.2)	
White	0 (0.0)	1 (4.8)	
Total monthly household income, $(M, SD) (n = 32)	2132 (1421)	1116 (834)	0.016
Handedness, No. (%)			0.91
Right	11 (91.7)	19 (90.5)	
Left	1 (8.3)	2 (9.5)	
Birth Weight, g (SD)	2853 (770)	2750 (662)	0.69
Full scale IQ — WASI, M (SD)	89.3 (6.7)	86.8 (12.1)	0.45
Verbal IQ — WASI, M (SD)	89.3 (7.7)	87.0 (11.9)	0.54
Performance IQ — WASI, M (SD)	91.8 (9.9)	89.1 (12.5)	0.53

[a] If data are not available for all participants, the n used for the analysis is stated next to the variable name.
[b] Independent sample t-tests were completed for the continuous variables; chi square analyses were completed for categorical variables.