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Prenatal cocaine exposure alters functional activation in the ventral prefrontal cortex and its structural connectivity with the amygdala

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ABSTRACT

Prenatal cocaine exposure (PCE) is associated with arousal dysregulation, and alterations of amygdala activity in response to emotional arousal have previously been reported. However, voluntary regulation of emotional affect, enabling appropriate neural response to different streams of stimuli, must also engage prefrontal regions, yet the impact of PCE on these prefrontal mechanisms has not been investigated. Recent neuroimaging studies have shown the involvement of ventral prefrontal cortex (vPFC) in the modulation of amygdala reactivity and the mediation of effective emotional regulation. Based on these findings, using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), the present study compared functional activations of the vPFC as well as its structural connectivity with the amygdala between groups of PCE and control adolescents. In a working memory task with emotional distracters, the PCE adolescents exhibited less capability of increasing their vPFC activation in response to increased memory load, which corresponded with their less suppressed amygdala activation. Reduced structural connectivity between the vPFC and the amygdala was also observed from DTI measurement in the PCE group. In addition, correlations between amygdala activation and (i) vPFC activation, as well as (ii) amygdala-vPFC structural connectivity, were observed in the control but not in the PCE group. These data complement previous findings of the impact of PCE on the activity of the amygdala and extend our understanding of the neurobiological mechanisms underlying the effect of PCE on arousal dysregulation reported in human and animal studies.

1. Introduction

Arousal dysregulation is one of the major findings of previous investigations of neuro-developmental effects of prenatal cocaine exposure (PCE). This long-term effect has been reported at different stages of postnatal development including neonates (Dipietro et al., 1995; Karmel and Gardner, 1996), infants (Bendersky and Lewis, 1998; Coles et al., 1999; Bard et al., 2000; Schuetze and Eiden, 2006; 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, 2011; Lester et al., 2010). Specifically, children with PCE often exhibit a reduced threshold in response to perceived stress or emotionally salient stimuli, which in turn may affect available attentional resources involved in cognition and behavior (Mayes et al., 1998; Mayes, 2002).

Our previous functional magnetic resonance imaging (fMRI) study (Li et al., 2009) revealed a likely neurobiological mechanism associated with dysregulation of emotional arousal in PCE adolescents. With a working memory task paradigm, which had emotionally arousing pictures as the task-irrelevant distracters, the data of this previous study showed that high memory load suppressed the amygdala response to emotional stimuli in the control but not in the PCE adolescents. In other words, the non-exposed participants exhibited reduced emotional response in a situation of more attentional demand, while this capacity of suppressing emotional distraction was diminished in the PCE adolescents. Although this previous finding is suggestive, it is still incomplete because the amygdala, while playing a key role in emotional processing, does not operate in isolation. Given the extensive neural connections between prefrontal regions and the amygdala (Price, 2003; Stein et al., 2007; Ghashghaei et al., 2007; Cohen et al., 2008; Roy et al., 2009; Bracht et al., 2009), as well as the importance of this circuit in emotion and behavior regulation

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(Davidson et al., 2000; Bachevalier and Loveland, 2006; Quirk and Beer, 2006; Banks et al., 2007), the impact of PCE on emotional arousal is expected to also involve alterations of prefrontal activity and alterations of prefrontal–amygdala neural connectivity.

Previous human and animal studies have reported convergent evidence showing a central role of the ventral prefrontal cortex (vPFC) in emotion regulation and amygdala inhibition (for review, see (Quirk and Beer, 2006) Also termed the orbitomedial, inferior medial,or ventromedial-prefrontal cortex in different studies, the vPFC region usually involves Brodmann areas 10, 11, 32, 46 and 47; and it often shows opposing activity to the amygdala, functionally considered as suppressing or reappraising negative emotion (Ochsner et al., 2002; Rosenkranz et al., 2003; Kim et al., 2003; Hariri et al., 2003; Levesque et al., 2004; Lzquierdo and Murray, 2005; Urry et al., 2006). Neural connections between the vPFC and the amygdala have also been reported repeatedly in human neuroimaging studies examining functional connectivity (Banks et al., 2007; Roy et al., 2009), effective connectivity (Stein et al., 2007), and structural connectivity (Cohen et al., 2008; Bracht et al., 2009). In addition, the strength of these connections is correlated with variations in trait anxiety, which is closely associated with affect regulation and amygdala activity (Kim and Whalen, 2009; Chepenik et al., 2010).

Given that (i) alterations of amygdala activation have been observed in adolescents with PCE, and (ii) there are close functional and structural associations between the amygdala and the vPFC, we hypothesized in the present study that functional activation of the vPFC and its neural connections with the amygdala would also be altered by PCE. Specifically, because high working memory load does not suppress amygdala activation in association with PCE (Li et al., 2009), and the vPFC is assumed to exert an inhibitory influence on the amygdala, it was hypothesized that (1) PCE participants would show a smaller increase of vPFC activation than controls in conditions of high memory load, in which amygdala activations are typically suppressed; (2) PCE participants would exhibit reduced white matter integrity in fiber pathways connecting the amygdala and the vPFC; and (3) measurements of vPFC activation and amygdala-vPFC connection would correlate with amygdala activations in the controls, but these correlations might be diminished in the PCE group.

To test these hypotheses, the present study further analyzed the neuroimaging data that we previously collected (Li et al., 2009, 2011) in studying the long-term effects of PCE. To test hypothesis (1), the vPFC and amygdala activations were examined by defining regions of interests (ROIs) according to the emotion contrast in the task paradigm (see details described in Section 2). To test the hypothesis (2), the vPFC–amygdala neural connectivity was examined with diffusion tensor imaging (DTI) data by a probabilistic tractography approach (Behrens et al., 2003, 2007). Finally, to test hypothesis (3), individual activations of the amygdala were, respectively, correlated with (i) activations of the vPFC and (ii) vPFC-amygdala neural connectivity.

2. Method

2.1. Participants

Participants were adolescents (12–18 years old) recruited from birth cohorts originally identified as part of two longitudinal studies of the effects of PCE on development (Coles et al., 1992; Brown et al., 1998). Both cohorts were drawn from a low income, predominantly African-American population with infants delivered at an urban hospital during 1987–1994. The present study involved 76 participants from these cohorts with 70% of them providing usable imaging data for both fMRI and DTI. For those who did not provide imaging data in both modalities, the majority of the data losses were on the fMRI side due to excessive head motion, failure to follow task instructions and scanner malfunction (Li et al., 2009). The fMRI and DTI sample used in the present study, respectively, included 56 (23 control vs. 33 PCE) and 73 (31 control vs. 42 PCE) participants.

Information about maternal cocaine and other drug use was obtained both from abstraction of medical records and from the birth mother's self-report at recruitment in the immediate postpartum period using the Addiction Severity Index (McLellan et al., 1985) and the Drug Grid (Coles et al., 1992). The Addiction Severity Index allows assessment of the degree of addiction as well as the social and medical impact of the mother's substance use. The Drug Grid quantifies the use of 16 licit and illicit drugs by quantity/frequency as well as timing of use. Maternal self-report was confirmed using EMIT urine screens taken postpartum from mothers and infants. Participating mothers were free of major medical conditions as well as disulfiram, drugs for seizure disorders, warfarin, insulin, benzodiazepines, antipsychotic drugs or any other teratogenic drugs, or any addictive substances other than cocaine, alcohol and marijuana. Infants were either healthy full term or preterm (30+ weeks) without major medical complications. For neuroimaging, potential adolescent participants were excluded from the source longitudinal cohort if they had contraindications for MRI or were pregnant, claustrophobic or extremely obese. More details regarding PCE determination and participant screening were reported in our previous publications (Coles et al., 1992; Brown et al., 1998; Li et al., 2011). The adolescents' demographic

Table 1
Characteristics of adolescents at the time of imaging and at birth.

Variable	fMRI sample			DTI sample		
	CON (N=23)[a]	PCE (N=33)[a]	p value[b]	CON (N=31)[a]	PCE (N=42)[a]	p value[b]
Adolescent variables						
Age, M (S.D.)	14.61 (2.3)	14.64 (2.0)	0.962	14.3 (2.5)	14.4 (2.0)	0.782
Gender, No. (%)			0.019			0.174
Female	15 (65.2)	11 (33.3)		16 (51.6)	15 (35.7)	
Male	8 (34.8)	22 (66.7)		15 (48.4)	27 (64.3)	
Total monthly household income—$, M (S.D.) ($N_{fMRI}$=53, N_{DTI}=70)	1898 (1284)	1221 (922)	0.030	2042 (1239)	1349 (1123)	0.017
Handedness, No. (%)			0.918			0.500
Right	20 (87.0)	29 (87.9)		26 (83.9)	36 (85.7)	
Left	3 (13.0)	4 (12.1)		5 (16.1)	6 (14.3)	
Full-Scale IQ—WASI, M (S.D.)	88.8 (8.4)	87.0 (11.4)	0.497	85.7 (9.9)	86.3 (12.6)	0.831
Verbal IQ—WASI, M (S.D.)	90.7 (9.5)	86.6 (12.6)	0.182	87.3 (10.2)	85.8 (13.0)	0.588
Performance IQ—WASI, M (S.D.)	89.3 (9.5)	89.8 (11.2)	0.855	87.0 (11.7)	89.1 (12.5)	0.483
Birth variables						
Birthweight (g) (M, S.D.)	2959 (783)	2883 (644)	0.693	3060 (694)	2796 (652)	0.100
Gestational age, No. (%)			0.179			0.554
Fullterm	17 (73.9)	29 (87.9)		28 (90.3)	36 (85.7)	
Preterm (30–36 weeks of gestational age)	6 (26.1)	4 (12.1)		3 (9.7)	6 (14.3)	

CON: control, PCE: prenatal cocaine exposure.

[a] If data for a variable are not available for some participants, the N used for the analysis is noted next to the variable name.

[b] Chi-square analyses completed for categorical variables; independent sample t-tests completed for continuous variables.