Neurotoxicology and Teratology 31 (2009) 342–348

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Prenatal cocaine exposure alters emotional arousal regulation and its effects on working memory

Zhihao Li [a], Claire D. Coles [b], Mary Ellen Lynch [b], Stephan Hamann [c], Scott Peltier [a], Stephen LaConte [a], Xiaoping Hu [a,*]

[a] Biomedical Imaging Technology Center, Department of Biomedical Engineering, Emory University & Georgia Institute of Technology, Atlanta 30322, Georgia, USA
[b] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta 30322, Georgia, USA
[c] Department of Psychology, Emory University, Atlanta 30322, Georgia, USA

ARTICLE INFO

Article history:
Received 5 October 2008
Received in revised form 17 July 2009
Accepted 11 August 2009
Available online 21 August 2009

Keywords:
Prenatal cocaine exposure
fMRI
Working memory
Emotional arousal
Amygdala
Prefrontal cortex

ABSTRACT

While prenatal cocaine exposure (PCE) has been associated with arousal dysregulation and attentional impairments in both human and animal studies, the neurobiological bases of these teratogenic effects have not been well characterized. In the current study, we report functional neuroimaging observations of these effects in exposed youth. Using functional magnetic resonance imaging (fMRI), we embedded task-irrelevant emotional distracters in a working memory task to examine the interaction of emotional arousal and memory in 33 PCE and 23 non-exposed adolescents. Though with similar behavioral performance, the two groups exhibited different activation patterns associated with emotion–memory interactions. On the one hand, higher memory load attenuated emotion-related amygdala activation in controls but not in the exposed adolescents; on the other hand, prefrontal activation associated with memory load decreased in the presence of emotional distraction in the controls but increased in the exposed group. These group interaction differences suggest neurobiological substrates for arousal-associated neuronal alterations related to prenatal cocaine exposure. Consistent with previous findings in behavioral and physiological studies, the present neuroimaging data provided more in-depth evidence supporting the view that PCE has significant long-term teratogenic effect on arousal regulation system.

1. Introduction

Children prenatally exposed to cocaine attracted a great deal of public attention as a result of the epidemic of cocaine use [10,27]. Although exposed children were initially portrayed by the popular media as highly impaired "crack babies" with bleak prospects for normal development, subsequent research showed that the effects of exposure on cognition and growth are limited and inconsistent [2,3,6,8,29,38,39,51,58]. However, despite these inconsistencies in cognitive ability, effects on stress responses and arousal regulation and associated impairments in attention and memory have been reported more often [1,20,26,34,40,41,55]. Such effects are apparent very early in life and appear to persist [5,14,21,54]. They cannot be accounted for by the poly-drug exposure and lifestyle differences that usually accompany maternal cocaine use [34].

Understanding the impact on arousal regulation and attention in affected individuals might provide an explanation for how such prenatal exposure can account for reported behavior problems [35]. Arousal regulation is a central concept for understanding how stimulation is gated to different cortical regions [19]. It reflects one's capability to adjust and allocate mental resources for distinct yet interactive streams of information processing. Therefore, the arousal regulation system provides an excitatory/inhibitory balancing mechanism that protects the central executive brain system from excessive stimulation and also facilitates coordination among multiple cortical systems involved in an ongoing task [41]. For example, Drevets and Raichle reported excitatory/inhibitory balancing between brain regions mediating emotional arousal and cognitive activity [25]. Alterations in arousal regulation may affect the balance between different functional brain networks and have the potential to impact both cognition and emotion.

To date, the underlying neurobiological bases of functional brain alterations related to prenatal cocaine exposure (PCE) are not well characterized. Because behavioral problems related to arousal regulation increase at adolescence [35], this is a particularly important period during which to evaluate the impact of PCE on arousal and behavior. Given that PCE has been found to have persistent effects on autonomic arousal as well as reactivity in response to emotionally salient stimuli, it is very likely that functional neural activity associated with the above mentioned emotion-cognition balance can be altered by prenatal cocaine exposure.

Neuroimaging provides a means to investigate the neurobiological basis of teratological effects of PCE [24]. While neuroimaging has been employed in several previous studies of cocaine and poly-drug exposure [4,32,50,52,61,64], none of them are directly relevant to the question of

* Corresponding author. Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Woodruff Memorial Building, 101 Woodruff Circle, Suite 2001, Atlanta Georgia 30322. Tel.: +1 404 712 2615; fax: +1 404 712 2707.
E-mail address: xhu@bme.gatech.edu (X. Hu).

0892-0362/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.ntt.2009.08.005

arousal regulation between different information processing streams. The aim of the current functional MRI (fMRI) study was to examine the hypothesis that PCE is associated with neuronal alterations in arousal regulation between emotion and working memory. Because the dorsal lateral prefrontal cortex (DLPFC) and the amygdala are respectively the typical brain regions involved in the dorsal cognitive [17,60] and ventral emotional [47,48] neural network, this hypothesis can then be examined specifically by group comparison of functional activation patterns in these two regions.

In the present study, we adopted a well characterized N-back working memory task [46,59] with task-irrelevant emotionally-arousing pictures embedded in the stimuli list. With this paradigm design, we could first identify brain activity associated with memory and emotion respectively, and then examine the interaction between these two factors. Specifically, to examine the effect of cognition on emotional processing, it is possible to examine whether variations in memory load modulate amygdala activity differently in the two groups. Similarly, to evaluate the impact of emotional arousal on cognition, it is possible to examine whether emotional arousal modulates prefrontal activity differently in these two groups. Based on literature reporting interactions between the dorsal cognitive network and ventral emotional network in normal adults [23,25,45,66], we expected to observe reciprocal inhibition between activations of the left DLPFC and amygdala in the control group. However, because of previous reports of arousal dysregulation in prenatally exposed individuals, we hypothesized that there would be alterations in this dorsal–ventral interaction in the PCE group.

2. Methods

2.1. Participants

Participants (see Table 1) were recruited from cohorts identified as part of two longitudinal studies of PCE on development [12,15]. Both cohorts were drawn from a low income, predominantly African–American population that was delivered at an urban hospital in 1987–1994. From 2005 to 2007, we scanned 84 subjects but functional imaging data from only 56 subjects were finally used. The loss of data was due to 3 reasons: (i) subjects with severe head motion (more than one voxel movement; 4 controls and 6 PCEs), (ii) subjects failed to follow task instructions (quitting or falling asleep during scans, or fleetly pressing the response button in every trial regardless stimuli; 6 controls and 5 PCEs) and (iii) scanner malfunction (3 controls and 4 PCEs). These 56 analyzed subjects included 33 adolescents prenatally exposed to cocaine (17 subjects from the older cohort, age 17 ± 0.9, 10M7F; 16 subjects from the younger cohort, age 13 ± 0.9, 12M4F) and 23 non-exposed controls (11 subjects from the older cohort, age 17 ± 1, 3M8F; 12 subjects from the younger cohort, age 13 ± 1, 5M7F).

Prenatal cocaine exposure was determined by maternal self report at recruitment post-partum and/or by a positive urine screen at that time (See Table 2 for maternal characteristics). Urine specimens for 54 of the 56 adolescent participants were also tested for the presence of metabolites of 7 drugs: amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, opiates, and phencyclidine. Of the 378 drug tests completed, only 6 were positive. Five were positive for marijuana (3 from the PCE and 2 from the control group) and 1 positive for amphetamines (from the PCE group). In addition, Chi-square analyses showed no group difference on Self-reports of smoking ($p = 0.69$) and drinking ($p = 0.77$) behavior.

Participating families were recontacted by study personnel and consented for the imaging study using a protocol approved by the Emory University Medical School's Institutional Review Board. Adolescents provided written assent and adults, including both teens and caregivers, provided informed consent to participate.

2.2. Experimental and task design

The visual stimuli for the verbal working memory were lists of letter pairs. In the 0-back condition (low memory load), subjects were instructed to press a button immediately whenever the letter pair "RR" was displayed on the screen and it was therefore called "letter RR task". In the 1-back condition (high memory load), they were asked to press the button whenever the current letter pair matched the last one displayed ("same as 1-back task"). To provide emotionally arousing distracters, pictures selected from the international affective picture system (IAPS) [36] were inserted between the letter pairs. They were either negative (e.g., aggressive behavior, disgusting scenes, disaster) or neutral pictures (e.g., outdoor plants, housewares) with the mean IAPS arousal scores being 5.7 (SD = 0.8) and 3.2 (SD = 0.8), respectively. Because the participants were teenagers, we selected pictures that were emotionally arousing but still judged suitable for viewing by young adolescents (similar to those that might be seen on television or in a news magazine). During the fMRI scan, subjects were told to focus only on the memory task and ignore the distracting pictures.

The use of letter pairs, instead of single letters, was based on results of pilot testing. Participants' performance tended to be perfect in the single letter 1-back task but dropped dramatically in the single letter 2-back task. The letter pair 1-back task was then used to ensure a relatively high behavioral performance without a "ceiling effect". In addition, this letter pair task design led to no significant PCE vs.

Table 1
Characteristics of teen at follow-up.

Variable	Control ($n = 23$)[a]	PCE ($n = 33$)[a]	P value[b]
Age, M (SD)	14.61 (2.3)	14.64 (2.0)	.962
Gender, No. (%)			.019
Female	15 (65.2)	11 (33.3)	
Male	8 (34.8)	22 (66.7)	
Total monthly household income – $, M (SD) $n = 53$	1898 (1284)	1221 (922)	.030
Handedness, No. (%)			.918
Right	20 (87.0)	29 (87.9)	
Left	3 (13.0)	4 (12.1)	
Full scale IQ – WASI, M (SD)	88.8 (8.4)	87.0 (11.4)	.497
Verbal IQ – WASI, M (SD)	90.7 (9.5)	86.6 (12.6)	.182
Performance IQ – WASI, M (SD)	89.3 (9.5)	89.8 (11.2)	.855

[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.

Table 2
Maternal Characteristics.

Variable	Control ($n = 23$)[a]	PCE ($n = 33$)[a]	P value[b]
Age, M (SD)	26.3 (5.2)	28.2 (4.3)	.138
Education, No. (%) $n = 51$			.006
High school not completed	2 (9.1)	13 (44.8)	
High school graduate or more	20 (90.9)	16 (55.2)	
Monthly income, No. (%) $n = 51$			.773
≤$600	20 (90.9)	27 (93.1)	
>$600	2 (9.1)	2 (6.9)	
Marital status, No. (%)			.179
Married	6 (26.1)	4 (12.1)	
Single, divorced, separated, widowed	17 (73.9)	29 (87.9)	
Other substance use in pregnancy, M (SD)			
Tobacco – cigarettes/week $n = 52$	9.1 (32.0)	61.1 (50.1)	<.001
Alcohol – oz. of absolute alcohol/week $n = 54$	0.0 (0.1)	1.0 (1.8)	.004
Marijuana – joints/week $n = 54$	0.0 (0.0)	1.3 (2.9)	.016

[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.