Emotional Arousal and Regulation in Adolescents Prenatally Exposed to Cocaine: an fMRI Study

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Introduction Prenatal cocaine exposure (PCE) has been found to lead to disrupted emotional arousal regulation in children [1,2]. Furthermore, attentional control deficits have been reported in infants and children with PCE, including increased frustration and distractibility [2,3]. In the present study, fMRI images in young adolescents with PCE was examined for emotional network activity during a rest period and during a working memory task with that included emotionally neutral and negative distractors.

Methods. fMRI Activation Study: Eleven control (age 13±1, 5M6F) and eleven PCE (age 13±0.9, 8M3F) subjects were scanned with a 3T Siemens Trio scanner (2 EPI-BOLD fMRI scans with 120 volume measurements in each, matrix=64×64, 30 axial slices, thickness/gap=3mm/0mm, TR/TE/FA/FOV=3000ms/30ms/90°/192cm). Participants were asked to perform a working memory task by pressing a button either when "RR" was displayed (0-back condition) or when the displaying letter pair matched with the previous one (1-back condition). Emotionally neutral or negative pictures were placed between the memory stimuli list thus producing 4 different task blocks (neutral 0-back, NEU0; neutral 1-back, NEU1; negative 0-back, NEG0; negative 1-back, NEG1). Figure1 shows an example of stimuli presented in the experiment.

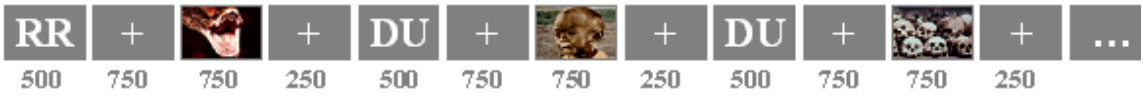

Figure 1. Examples of stimuli. Duration shown in msec. One display cycle is letter-fixation-picture-fixation. Blocks were all "neutral" or "negative" (only negative shown).

AFNI (http://afni.nimh.nih.gov) was used for fMRI data analysis. After preprocessing (slice timing correction, scan concatenation, volume registration, signal normalization to percent change, and 5mm FWHM Gaussian blur), regression coefficients (β-weights), which represent the BOLD signal level for each of the 4 conditions (NEU0, NEU1, NEG0, NEG1), were derived for each subject with a multiple regression analysis. The activation amounts (regression coefficient × activation volume) of bilateral amygdale (only voxels with significant emotion effect) were then submitted into a 2 (PCE vs. control) × 2 (neutral vs. negative) × 2 (0-back vs. 1-back) ANOVA.

Resting State MRI: In the resting state MRI (an EPI-BOLD scan with 210 volume measurements, matrix=64×64, 20 axial slices, thickness/gap=4mm/0mm, TR/TE/FA/FOV=2000ms/30ms/90°/192cm), subjects were instructed to simply gaze at a fixation cross on the screen. The preprocessing included slice timing correction, spatial registration, 0.08-0.01Hz band pass filtering and 5mm FWHM Gaussian blur. The time course from a right amygdala seeding voxel (Talairach coordinates [x,y,z] = [-24,5,-16]) was then used for subsequent whole brain cross-correlation analysis. The correlation coefficients, after being converted to Z-scores, were compared between the control and PCE subjects by group t-test.

Results. Difference maps for baseline emotional arousal in the PCE and control groups are shown in Figure 2. Regions of significantly higher resting functional connectivity with the right amygdala in PCE as compared to control subjects are: anterior cingulate (AC), posterior cingulate (PC), cingulate gyrus (CG), middle frontal gyrus (MFG), and parahippocampal gyrus (ParaHC).

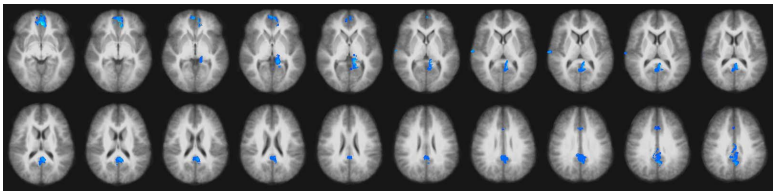

Figure 2. Subtraction map (Control-PCE) of functional connectivity with seeding in the right amygdala. Threshold was p<0.05 with minimum cluster volume of 250 ul.

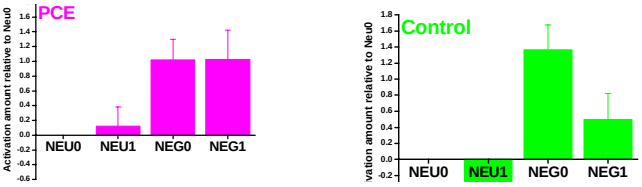

Figure 3. Activation amount comparison between conditions in bilateral amygdala. Data were plotted by putting the "NEU0" value as the baseline (zero). Error bars represent standard error.

Regions of Interest	ROI Talairach coordinate center [x,y,z]	Normalized correlation coefficient		p-value
		PCE	Control	
AC	[±8,-32,7]	6.410	1.959	**0.00042**
PC	[±10,54,14]	7.292	3.878	**0.010**
CG	[±10,11,34]	5.914	3.109	**0.012**
MFG	[±37,-29,26]	6.007	2.371	**0.00004**
ParaHC	[±25,25,-12]	6.539	2.291	**0.0035**

Table 1. Average normalized correlation coefficient (z-score) for functional connectivity with right amygdala seed in regions of interest. P-values were determined from unpaired t-test.

Table 1 indicates the significant difference in correlation z-score between the two groups in these regions of interest. Additionally, for the fMRI data, there was a significant (p=0.03) exposure × memory interaction in the amygdala activation (amount). As shown in Figure 3 higher working memory load reduced the amygdala activity in the controls but not in the PCE subjects.

Discussion. PCE individuals showed more functional connectivity with the right amygdala at rest as compared to controls. Since the regions of higher connectivity are components of an emotional network [3], the results imply that PCE group has higher baseline emotional network activity as compared to the non-exposed group. Furthermore as shown in the fMRI data, when cognitive demand increases, controls subjects can decrease their emotion arousal level, leaving more mental resources available for the ongoing task. In contrast, the PCE subjects exhibit persistent high emotional arousal, as indicated by the high amount of amygdala activation with increased cognitive demand. Taking these observations together, it is possible that the emotional network in PCE subjects is more active in the resting state and this high level of activity continues even during a task involving increased cognitive requirement, leading to more distraction and higher risk for behavioral impairment. Our results support previous findings that PCE individuals are impaired in the modulation of emotional arousal, which may lead to attentional and other cognitive deficits.

References. [1] Bendersky & Lewis. Dev Psychol. 1998 May;34(3):555-64. [2] Mayes, L.C., et al. Ann NY Acad Sci. 1998 Jun 21;846:126-43. [3] Dennis, T. et al. Dev Psychol. 2006 Jul;42(4):688-97. [4] Stein, J.L., et al. Neuroimage. 2007 Jul 1;36(3):736-45. Epub 2007 Mar 28. *Supported by GA Research Alliance, NIH grant RO1 DA17795.*