Increased “Default Mode” Activity in Adolescents Prenatally Exposed to Cocaine

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Abstract: Prenatal cocaine exposure (PCE) is associated with attention/arousal dysregulation and possible inefficiencies in some cognitive functions. However, the neurobiological bases of these teratogenic effects have not been well characterized. Because activities in the default mode network (DMN) reflect intrinsic brain functions that are closely associated with arousal regulation and cognition, alterations in the DMN could underlie cognitive effects related to PCE. With resting-state and task activation functional magnetic resonance imaging (fMRI), this study investigated the possible PCE related changes in functional brain connectivity and brain activation in the DMN. In the resting state, the PCE group was found to have stronger functional connectivity in the DMN, as compared to the nonexposed controls. During a working memory task with emotional distracters, the PCE group exhibited less deactivation in the DMN and their fMRI signal was more increased by emotional arousal. These data revealed additional neural effects related to PCE, and consistent with previous findings, indicate that PCE may affect behavior and functioning by increasing baseline arousal and altering the excitatory/inhibitory balancing mechanisms involved in cognitive resource allocation. *Hum Brain Mapp* 32:759–770, 2011. © 2010 Wiley-Liss, Inc.

Key words: functional magnetic resonance imaging; prenatal cocaine exposure; default mode network; arousal regulation; deactivation; resting functional connectivity

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INTRODUCTION

Children and adolescents prenatally exposed to cocaine and other psychoactive drugs are at high risk not only for cognitive deficits, but also for problems such as antisocial behavior, substance abuse, academic/occupation failure, and emotional disorders [Bendersky et al., 2006; Coles and Platzman, 1993; Lagasse et al., 2006; Loeber and Farrington, 2000]. Although studies of the exposure effect on specific cognitive abilities like language [Morrow et al., 2004], eye-hand coordination [Arendt et al., 1999], and working memory [Hurt et al., 2008] are undoubtedly important, the complexity of these teratogenic outcomes suggests that there could be neural alterations at a more general level that underlie a variety of the behaviorally observed abnormalities.

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Reviews of the literature on developmental effects of prenatal cocaine exposure (PCE) indicate that while cognitive deficits can be identified, the most consistent and potentially detrimental outcome may be the effects on arousal regulation [Mayes, 2002; Mayes et al., 2006]. These effects can be observed very early in life [Bard et al., 2000; Bendersky and Lewis, 1998; Coles et al., 1999; Dipietro et al., 1995; Karmel and Gardner, 1996; Schuetz and Eiden, 2006] and are reported to be persistent [Bada et al., 2007; Bandstra et al., 2001; Dennis et al., 2006; Kable et al., 2008; Mayes et al., 1998]. Arousal dysregulation (e.g., being distracted more easily by salient but task irrelevant stimuli) also has been seen in animal models of PCE [Gabriel and Taylor, 1998; Garavan et al., 2000; Romano and Harvey, 1998], in which most of the confounding factors (such as nutrition, prenatal care, dose/timing of cocaine exposure) that occur in human studies have been carefully controlled.

Arousal regulation reflects one's ability to adjust and allocate mental resources for distinct yet interactive streams of information processing [Damasio, 1995]. This process regulates ongoing cognition and behavior through an excitatory/inhibitory balancing mechanism. The impact of PCE on arousal regulation could be a neural alteration at a more general level rather than specific cognitive deficits; and this possible alteration needs in depth investigation. With functional MRI, our previous study [Li et al., 2009] showed that PCE adolescents could not efficiently suppress amygdala activation when challenged by emotional arousal, which in turn affected prefrontal working memory activation. This study further investigates the PCE impact on arousal regulation by examining the "default mode" brain activity.

The default mode network (DMN) refers to the brain areas (typically the medial prefrontal and posterior cingulate cortex) that show higher baseline metabolic rate at rest than during a variety of goal-directed or attention demanding behaviors [Gusnard and Raichle, 2001; Raichle et al., 2001]. Besides the reduced activity during cognitive tasks, the DMN can also be identified through connectivity analysis using resting-state (subjects rest without a specific task to perform) functional magnetic resonance imaging (fMRI) [Fox and Raichle, 2007; Fox et al., 2005; Greicius et al., 2003]. Though the physiological/psychological significance of default mode activity still remains to be fully understood, it is generally believed to reflect the intrinsic/spontaneous mental operations that are suspended during goal-oriented behaviors [Gusnard and Raichle, 2001; Raichle and Snyder, 2007; Raichle et al., 2001]. These DMN activities represent mind-wanderings from the current task [Mason et al., 2007], which include stimulus-independent thoughts (or so-called "internal mentation," like reminiscence of past experience) and stimulus-oriented thoughts (or so-called "external monitoring," like attending to the environment) [Gilbert et al., 2007; Gusnard and Raichle, 2001; Gusnard et al., 2001; Hahn et al., 2007; Kelley et al., 2002; Shulman et al., 1997]. Given that PCE alters one's

capability in arousal regulation, which is closely associated with exteroceptive and interoceptive attention [Nagai et al., 2004], we hypothesized that the brain activity in the DMN is altered by PCE.

We tested the above hypothesis with task and resting-state fMRI in this study. Specifically, the negative activations in the DMN were compared between the PCE and nonexposed adolescents during a verbal working memory task. We also added emotionally distracting pictures between the memory stimuli to examine emotional-arousal modulation on the DMN neural activities. With resting-state fMRI, DMN functional connectivity was assessed and compared between groups by approaches of seeding-correlation and independent component analysis. Because the exposed individuals are reported to have a higher arousal level, we anticipated increased default mode activities (reduced negative response during task and increased functional connectivity during rest) in adolescents with PCE.

METHOD

Participants

Participants were adolescents, aged 12–18, recruited from cohorts identified originally as part of two longitudinal studies of PCE on infant development [Brown et al., 1998; Coles et al., 1992]. Both cohorts were drawn from a low income, predominantly African-American population with infants delivered at an urban hospital during 1987–1994. The PCE and control participants in the present study respectively comprised 33 and 23 participants with the adolescents' current demographic and birth information shown in Table I and maternal characteristics at the time of recruitment shown in Table II.

PCE was determined by maternal self-report and/or positive urine screen 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 antabuse, drugs for seizure disorders, warfarin, insulin, benzodiazepines, antipsychotic drugs or any other teratogenic 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 sample 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 periventricular leukomalacia, were diagnosed with genetic disorders or major malformations, were HIV infected, or had major

TABLE I. Characteristics of teen at the time of imaging and at birth

Variable	CON (<i>n</i> = 23) ^a	PCE (<i>n</i> = 33) ^a	<i>P</i> value ^b
Adolescent Variables			
Age, M (SD)	14.61 (2.3)	14.64 (2.0)	0.962
Gender, No. (%)			0.019
Female	15 (65.2)	11 (33.3)	
Male	8 (34.8)	22 (66.7)	
Total monthly household income—\$, M (SD) (<i>n</i> = 53)	1,898 (1,284)	1,221 (922)	0.030
Handedness, No. (%)			0.918
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)	0.497
Verbal IQ—WASI, M (SD)	90.7 (9.5)	86.6 (12.6)	0.182
Performance IQ—WASI, M (SD)	89.3 (9.5)	89.8 (11.2)	0.855
Birth Variables			
Birthweight (g) (M, SD)	2958.7 (783.0)	2882.7 (643.7)	0.693
Gestational Age, No. (%)			0.179
Fullterm	17 (73.9)	29 (87.9)	
Preterm (30–36 weeks of gestational age)	6 (26.1)	4 (12.1)	

CON, control, PCE, prenatal cocaine exposure.

^aIf data for a variable are not available for some participants, the *n* used for the analysis is noted next to the variable name.

^bChi-square analyses completed for categorical variables; Independent sample *t*-tests completed for continuous variables.

surgery. More information regarding the determination of substance use, participants inclusionary criteria, and classification of participants into experimental groups have been described extensively in previous reports [Brown et al., 1998; Coles et al., 1992]. In addition, potential adolescent participants were excluded from imaging if they had contraindications for MRI, or were pregnant, claustrophobic or extremely obese. Adolescent medical status was also evaluated through caregiver responses to a medical history

form. When asked to rate the participants' general health status on a 10-point scale (10 = excellent), the mean rating for this sample was 9.04. Analysis for the effect of group showed no significant difference on this variable. Before the imaging session, urine and blood specimens for 54 of the 56 adolescents were tested to identify metabolites of seven drugs (amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, opiates, and phencyclidine). The majority of these tests showed negative outcomes (only

TABLE II. Maternal characteristics at the time of birth

Variable	CON (<i>n</i> = 23) ^a	PCE (<i>n</i> = 33) ^a	<i>P</i> value ^b
Age, M (SD)	26.3 (5.2)	28.2 (4.3)	0.138
Education, No. (%) (<i>n</i> = 51)			0.006
High school not completed	2 (9.1)	13 (44.8)	
High school graduate or more	20 (90.9)	16 (55.2)	
Monthly income, No. (%) (<i>n</i> = 51)			0.773
≤\$600	20 (90.9)	27 (93.1)	
>\$600	2 (9.1)	2 (6.9)	
Marital status, No. (%)			0.179
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 (<i>n</i> = 52)	9.1 (32.0)	61.1 (50.1)	0.000
Alcohol—oz. of absolute alcohol/week (<i>n</i> = 54)	0.0 (0.1)	1.0 (1.8)	0.004
Marijuana—joints/week (<i>n</i> = 54)	0.0 (0.0)	1.3 (2.9)	0.016

CON, control, PCE, prenatal cocaine exposure.

^aIf data for a variable are not available for some participants, the *n* used for the analysis is noted next to the variable name.

^bChi-square analyses completed for categorical variables; Independent sample *t*-tests completed for continuous variables.

Figure 1.

A schematic diagram of the experimental task. Each task block began with an instruction asking subjects to either perform the 0-back or 1-back memory task. The letter pairs were interleaved by fixation crosses and distracter pictures (duration labeled). These pictures were either neutral or negative (only negative

picture shown here) within each fMRI block. The blue/red hands indicate the display on which a button response is required for the 0-back/1-back task. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

three PCE and two control participants were positive for marijuana, one PCE participant was positive for amphetamine) and no group differences were noted.

Children's reported social history was examined for evidence of stable custody arrangements and history of physical or sexual abuse. Of seven items related to stability and trauma (years at current address, changes in house hold composition in the last year, stability in custody, protective services involvement, reported abuse/neglect, school discipline problems and legal problems), two items, the number of changes in care giving and protective service involvement, were higher in PCE youth. For care giving, eight PCE children had more than one caregiver versus 1 in the contrast group (Fisher's Exact Test, 1-sided, $P = 0.01$); for protective service involvement, six PCE children had Division of Family and Children Service record versus one in the contrast group (Fisher's Exact Test, 1-sided, $P = 0.04$).

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

Experimental Task Design

We used a verbal working memory task with two memory loads in the activation fMRI so that the signal difference between the memory loads could be used to identify default mode deactivations. The memory items were lists of letter pairs. In the low memory load condition, adolescents were instructed to press a button on seeing the letter pair "RR" (0-back task). In the high memory load condition, they were to press the button whenever the displaying letter pair exactly matched the last one displayed (1-back task). To introduce emotional distraction, neutral (arousal score 3.2 ± 0.8) and negative (5.7 ± 0.8) pictures selected from the International Affective Picture System

[Lang et al., 1997] were presented between the letter pairs. The fMRI paradigm was a factorial block-design with four different types of blocks (factorial combination of low or high memory loads with neutral or negative distraction) that were pseudo-randomly distributed across two data acquisition scans. Each fMRI scan run contained 12 blocks, each consisting of 12 trials, during which participants were instructed to focus only on the memory task while ignoring the distracting pictures. A schematic diagram of the experimental paradigm is shown in Figure 1.

During the resting-state fMRI scanning, participants did not perform a specific cognitive task but were instructed to simply fixate on a cross shown in the center of the screen. To minimize potential carryover of cognitive activity associated with the memory task or the emotional distracters, resting-state data were always acquired first, prior to the activation fMRI scan.

MRI Data Acquisition

On a 3T MRI scanner (Siemens Medical Solutions, Malvern, PA), the activation and resting-state scans both were performed using a T2*-weighted echo-planar imaging sequence with the following parameters. Activation scan: 120-volumes, matrix = 64×64 , 30 axial slices without gap, thickness = 3 mm, TR/TE = 3,000 ms/30 ms, flip angle = 90° , FOV = 192×192 cm². Resting scan: 210-volumes, matrix = 64×64 , 20 axial slices without gap, thickness = 4 mm, TR/TE = 2,000 ms/30 ms, flip angle = 90° , FOV = 192×192 cm². Corresponding high resolution (256×256) 3D T1-weighted anatomical images were also collected from each subject.

Imaging Data Analysis

AFNI (<http://afni.nimh.nih.gov>) was generally used in the present imaging data analysis. In addition, SPM

(<http://www.fil.ion.ucl.ac.uk/spm/>) and FSL (<http://www.fmrib.ox.ac.uk/fsl/>) were used for brain segmentation and independent component analysis, respectively, in processing the resting-state data.

For the activation fMRI, each subject's data were preprocessed with slice timing correction, volume registration, signal percent change normalization, scan concatenation, and 5 mm FWHM spatial smoothing. A multiple regression analysis was performed thereafter using regressors representing the four experimental conditions (0-back with neutral distracter, 0-back with negative distracter, 1-back with neutral distracter, 1-back with negative distracter) and with head motion parameters included as nuisance covariates. The experimental condition regressors were generated by convolving respective boxcar stimulation functions with a impulse response function [$y = t^b \times \exp(-t/c)$, b and c are constants] [Cohen, 1997]. Once the regression coefficients of the four conditions were obtained, they were transformed into the Talairach space [Talairach and Tournoux, 1988] and fed into a 2 (high vs. low memory load) $\times$ 2 (neutral vs. negative emotion) repeated measures ANOVA for the control and PCE group, respectively; thus the DMN of each group emerged as the resultant maps of negative memory main effect (increased signal in the condition of low memory load than high load). To assess the changes of deactivation in the DMN, the "high load-low load" regression coefficients difference was calculated voxel by voxel for each subject, and this difference, which corresponds to deactivation, was compared between the PCE and control participants using a voxel-wise group t -test.

Emotional impact on deactivations in the DMN was further examined by regions of interest (ROI) analyses. Specifically, regression coefficients of the four experiment conditions were extracted from the ROIs and fed into "ANOVA" statistics seeking potential group by emotion interactions. Based on the task related deactivations, we defined four ROIs in the DMN: two "group-difference" regions, where the deactivation was significantly different between the groups, and two "group-common" regions, where fMRI signal was generally decreased in all the participants with group difference not considered. More details about the ROIs are described in the Results section along with the deactivation results.

Both cross-correlation analysis (CCA) and independent component analysis (ICA) have been used in assessing resting brain networks, each with its own advantages and shortcomings [Ma et al., 2007; Uddin et al., 2008]. To avoid biasing the results by the specific method used, the resting-state fMRI data were analyzed with both approaches in this study.

In the CCA, we defined a seeding region in the posterior cingulate area based on the deactivations during the working memory task. Specifically, using the four conditions' regression coefficients of 46 participants (23 PCE and 23 control) as inputs, a 2 (high vs. low memory load) $\times$ 2 (neutral vs. negative emotion) repeated measures ANOVA

revealed a posterior cingulate voxel cluster (centroid coordinate = 3.6, 54.9, 16.9 mm, volume = 175 mm³) that showed a highly significant ($P < 10^{-8}$) negative memory main effect, and this cluster was selected as the seeding region. We used equal number of participants (23 PCE and 23 controls, 10 PCE participants randomly dropped) in this ANOVA so that the resultant seeding region would not be biased by deactivation of either group. The other steps of the data processing were similar to those used by Fox et al. [2005] for characterizing the intrinsic resting functional networks. After image preprocessing (slice timing correction, rigid body registration, 0.009 Hz $< f <$ 0.08 Hz band-pass filtering, and 5 mm FWHM Gaussian smoothing), cross-correlation between the time courses of the posterior cingulate seeding area and every brain voxel was calculated for each subject. The time course of the seeding area was obtained by simple average over all the voxels in the area. Spurious contributions from the white matter and cerebrospinal fluid as well as the head motion parameters were removed in this cross-correlation analysis through multiple linear regression. Another variable often included in this regression as a nuisance effects is the global brain signal. However, Murphy et al. [2009] have recently demonstrated that using global signal regression can bias connectivity measures by introducing anti-correlations. As it is unclear whether using global signal regression would significantly affect connectivity group differences, we performed the analysis with and without removing the global signal regression. To combine/compare correlation results within/between groups, correlation coefficients (r) for each subject were converted to standardized z -scores and Fisher's z -scores, respectively, and then transformed into the Talairach space. For standardized z -scores, correlation coefficients were converted to t values first (for null hypothesis of $r = 0$) by $t = r \times \sqrt{DF/(1 - r^2)}$ (DF = degrees of freedom), and corresponding p values were found for those t values, and were then converted to standardized z -scores. The Fisher's z -scores were derived using $z = 0.5 \times \ln[(1 + r)/(1 - r)]$. The standardized z -scores were used for thresholding in the group-mean correlation maps and the Fisher's z -scores were used for group comparison of the correlation strength with a voxel-wise group t -test.

The independent component analysis followed the steps used by Greicius et al. in their aging [Greicius et al., 2004] and depression [Greicius et al., 2007] studies. After slice timing correction, rigid body image registration, 0.01 Hz high-pass filtering (to reduce very slow signal artifact like scanner drift) and 5 mm FWHM spatial smoothing, individual's resting-state fMRI data were fed into the "MELODIC ICA" module of FSL for independent component decomposition, where 35 components (1/6 the TR points in the scan) were assumed. In the outputs, individual spatial component maps were converted into z -score maps by dividing the raw IC estimates by the voxel-wise noise standard deviation [Beckmann and Smith, 2004]. To select the component of DMN, a "two-step, best fit" process was

used. First, because resting functional networks are so far only detected based on low-frequency signal fluctuations, components with high-frequency (>0.1 Hz) signal constituting 50% or more of the total power were discarded. Then, the remaining low-frequency components of each participant were sorted according to its “goodness of fit” with a DMN template and the one with the “best fit” was selected as the DMN component for subsequent group comparison. The DMN template was derived by the same memory $\times$ emotion ANOVA described above in the CCA for finding correlation seed. Specifically, it was a 3D mask in the brain covering voxels with a significant ($P < 0.01$) negative memory main effect. The “goodness of fit” was calculated by subtracting the mean z -score of the outside-template voxels from the mean z -score of the inside-template voxels. The higher this z -score difference, the better the component map fits the DMN template. Once the DMN component was selected for each participant, they were transformed into the Talairach space and compared between groups by a group t -test. To obtain the DMN maps of each group, the selected z -score component maps of the control and PCE groups were also compared with zero, respectively, through one-sample t -test.

A Monte Carlo simulation was used in the present study for false positive control (<http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>) in the voxel-wise statistics. With combination of individual voxel thresholding and minimum cluster size thresholding, the probability of a “true” positive detection was estimated. For the within-group maps, statistics were performed in the whole brain and a threshold of $P < 0.01/\text{voxel}$ plus 648 mm^3 cluster was used (corrected $P < 0.05$). For the group-difference maps, because the comparison was restricted to regions of DMN only (voxels with positive correlation—for resting data, or negative activation—in task data, in all the participants), voxels involved in the multiple comparison were much less; therefore, the threshold was set to $P < 0.01/\text{voxel}$ plus 243 mm^3 cluster (corrected $P < 0.05$).

For each significant cluster revealed by the voxel-wise group t -test described above, group comparison was performed again at ROI level (using mean voxel values in the whole cluster) with several potentially confounding factors statistically controlled. This is because that the effects of PCE in humans are often confounded by other factors that are difficult to match between groups. For example, besides cocaine, PCE participants are usually poly-drug (commonly tobacco, alcohol and marijuana) exposed. Statistically controlling these confounding effects could ensure that the final results are more specifically associated with the cocaine exposure. In the present analysis, we considered three major confounding variables (in addition to exposure, which was the independent/interested variable): (i) gender (males and females may have different default mode and emotional responses and they are not evenly distributed in the two groups), (ii) alcohol use (ounces of absolute alcohol used weekly during pregnancy), and (iii) marijuana~tobacco use (amount used during pregnancy in

units of joints/cigarette per week). The marijuana~tobacco use was a combined variable derived by principle component factor reduction because their uses were highly correlated (Pearson correlation, $P = 0.04$) in our sample. These controlling factors were determined by our preliminary analysis (data shown in Supporting Information) that revealed confounding effect on voxels in the DMN. Other factors (e.g. race, other drug use, preterm birth) that are known to be related to cocaine effects were controlled via experimental design [Brown et al., 1998; Coles et al., 1992].

RESULTS

The behavioral measures of the working memory task were described in detail in our previous report [Li et al., 2009]. Briefly, the overall memory performance was decreased with higher memory load (as compared to low load) and negative emotional distraction (as compared to neutral). However, because the task paradigm was deliberately designed to minimize behavioral group difference [Li et al., 2009], there were no significant group differences in task performance related to cocaine exposure.

The results of group comparison of resting-state data are shown in representative mid-sagittal slices in Figure 2. Consistent with the reports of Murphy et al. [2009], using global signal regression introduced more negative correlation in the results. However, significant positive correlations in the DMN could be observed in both cases regardless of whether the global signal regression was used. Global signal (or part of it) could also be separated as independent component(s) in ICA, and there were negative areas in the group maps derived from ICA as well. Though the group difference maps obtained by CCA with and without global signal regression and by ICA are not exactly the same, Figure 2 shows that the DMN functional connectivity of the PCE group was generally higher in all the cases. Significant clusters revealed by the voxel-wise group comparison are listed as the first three sections (CCA with global regression, CCA without global regression and ICA) in Table III. In these clusters, the PCE participants exhibited higher resting connectivity in DMN than the controls and no significant group difference in the reverse direction (control higher than PCE) was observed. Most of these regions, including the medial prefrontal cortex, the parahippocampal gyrus, the anterior and posterior cingulate regions, as well as the lateral parietal areas, are prominent nodes in DMN. With gender and multi-drug confounding factors statistically controlled, the group differences remained significant in most of these regions with only one exception—the right medial frontal gyrus identified by ICA, where the group difference was marginal (see the P values in Table III).

Group differences of default mode activity were also observed in the working memory fMRI data (Fig. 3, top portion). Compared with the 0-back condition, both the PCE and control participants exhibited a decreased BOLD

Figure 2.

Group comparisons of resting-state DMN activity based on different data analysis approaches. Top: CCA approach with global regression; middle: CCA approach without global regression; bottom: ICA approach. Results are shown in a representative sagittal slice near the median fissure with the slice position marked. In the group maps, positive (red/yellow) and negative (blue/azury) correlations, or component contributions, are displayed at a threshold level of $P < 0.01/\text{voxel}$ plus 648 mm³ cluster (multiple comparison corrected $P < 0.05$). In the group difference maps, the displaying threshold is $P < 0.01/\text{voxel}$ plus 243 mm³ cluster (multiple comparison corrected $P < 0.05$). CON, control; PCE, prenatal cocaine exposure. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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TABLE III. Brain regions with significant^a group difference in DMN activity

Approach	Brain region	Volume	X	Y	Z	P value ^b
Resting data CCA with global regression	Left medial frontal gyrus (BA 10/32)	1,246	8.9	-54.7	17.7	0.006
	Left posterior cingulate (BA 23)	835	2.2	58.7	14.8	0.005
	Right parahippocampal gyrus (BA 30)	721	-8.5	44.4	3.8	0.017
	Left middle temporal gyrus (BA 21)	623	56.5	5.6	-10.9	0.015
	Left precuneus, cingulate gyrus (BA 7/31)	586	5.1	51.1	40.5	0.018
	Left parahippocampal gyrus (BA 30)	403	8.7	39.9	1.4	<0.001
Resting data CCA without global regression	Left superior frontal gyrus (BA 8)	585	2.9	-37.9	47.0	0.008
	Left superior frontal gyrus (BA 6)	539	23.3	-12.2	48.9	0.021
	Left middle temporal gyrus (BA 21)	324	57.3	7.2	-11.2	0.044
	Left medial frontal gyrus (BA 9/10/32)	324	9.9	-46.7	20.6	0.002
	Left precuneus (BA 7)	302	4.4	51.6	43.9	0.047
	Left medial/superior frontal gyrus (BA 10)	276	14.9	-60.9	20.8	0.007
Resting data ICA	Right posterior cingulate (BA 23)	261	-1.0	55.9	16.1	0.014
	Right precuneus, cingulate gyrus (BA 7/31)	2,036	-2.1	38.6	42.9	0.006
	Right parahippocampal gyrus, posterior cingulate (BA 29/30)	1,751	-13.0	43.9	5.2	0.003
	Right superior frontal gyrus (BA 8)	512	-21.9	-22.8	49.6	0.027
	Left parahippocampal gyrus (BA 36)	460	29.5	25	-11.5	0.010
	Right medial frontal gyrus (BA 6)	310	-7.5	-41.7	35.9	0.131
Task data deactivation	Left parahippocampal gyrus (BA 27/30)	303	10.5	37.2	-0.4	0.010
	Right medial frontal gyrus (BA 10)	295	-6.5	-64.1	9.4	0.008
	Right anterior cingulate (BA 24)	277	-0.6	-28.2	18.7	0.026
	Right precuneus, angular gyrus (BA 19/40)	251	-34.7	69.7	34.6	0.004
	Right posterior cingulate (BA 23)	245	-4.7	55.1	16.3	0.003
	Left posterior cingulate (BA 29, 30)	776	10.7	49.8	9.8	0.085
	Left cingulate gyrus (BA 31)	754	4.8	44.5	39.7	0.017
	Left medial/superior frontal gyrus (BA 9/10)	255	11.0	-55.6	24.1	0.023

^a $P < 0.01/\text{voxel}$ plus 243 mm³ cluster in voxel-wise group *t*-test.

^bCluster value compared between groups with confounding factors statistically controlled.

Figure 3.

Voxel-wise (top) and ROI level (bottom) group comparisons of task related deactivations in the DMN. The voxel-wise comparisons are shown in a representative sagittal slice that have exactly the same threshold as those in Figure 2. The shallow to deep signal decreases are coded by the blue to cyan color gradient. In the ROI comparisons, the “group-difference” (red) and “group-common” (green) ROIs are linked to the corresponding bar-graphs of regression coefficients with lines of the same color. The regression coefficient plots use the “Neutral, 0-back”

condition as the baseline and all bars are plotted by the same scale. For easy visualization purpose, the group comparisons of the memory and emotion effects are put at the right end of the bar-graphs. CON, control; PCE, prenatal cocaine exposure; AC, anterior cingulate; PC, posterior cingulate; Neu, neutral; Neg, negative; 0, 0-back; 1, 1-back; Mem, memory effect ($(\text{Neu1} + \text{Neg1} - \text{Neu0} - \text{Neg0})/2$); Emo, emotion effect ($(\text{Neg0} + \text{Neg1} - \text{Neu0} - \text{Neu1})/2$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

signal in the DMN during the 1-back condition. However, the magnitude of these signal reductions was significantly higher in the controls; in other words, the signal of PCE subjects did not decrease as much as that of the controls. As shown in the last section of Table III, this group difference was observed in three DMN areas including medial prefrontal cortex, and cingulate areas.

To further examine the emotion effect on fMRI signal in DMN, we defined two regions of interest (ROIs) based on the group difference of the deactivation. They are one medial prefrontal (centroid coordinate = 11.0, -55.6, 24.1 mm, volume = 255 mm³) and one posterior cingulate (centroid coordinate = 10.7, 49.8, 9.8 mm, volume = 776 mm³) clusters that showed a significant group difference on fMRI deactivation (Fig. 3, bottom panel, the red

regions). Examining the four condition regression coefficients of these two ROIs, a 2 (PCE vs. control group) $\times$ 2 (negative vs. neutral emotion) $\times$ 2 (1-back vs. 0-back memory load) $\times$ 2 (medial prefrontal vs. posterior cingulate location) ANOVA (with gender and multi-drug exposure as nuisance factors) showed a significant memory $\times$ exposure ($P = 0.02$) and emotion $\times$ exposure ($P = 0.05$) effect. With the signal regression coefficients shown in Figure 3 (the red frame), the memory $\times$ exposure effect was evident as these ROIs were defined on the group difference map of default mode deactivation. The ROI data simply replicated the results of voxel-wise group comparison that PCE adolescents could not decrease the signal as much as the controls during the high memory load task. However, the emotion $\times$ exposure effect in these two ROIs was a

new observation. Compared to the neutral distracters, the negative distracters generally increased the DMN signal level and this increase was greater in the PCE group as compared to the controls.

To examine whether these results could represent the group differences in a larger extent of the DMN, we defined two alternative ROIs also in the medial prefrontal (centroid coordinate = 0.9, -49.8, 10.8 mm, volume = 7,356 mm³) and posterior cingulate (centroid coordinate = 2.9, 49.9, 23.7 mm, volume = 9,082 mm³) cortices (Fig. 3, bottom panel, the green regions). Instead of group difference, these two ROIs were defined based on the common deactivation map of both groups. They were derived by the same memory × emotion ANOVA used to define the seed region in CCA and the DMN template in ICA. The regression coefficients of these group-common ROIs are presented in Figure 3 (the green frame) and were analyzed by the same emotion × memory × group × location ANOVA mentioned above. The results of these group-common ROIs were generally the same as those of the group-difference ROIs. Specifically, the PCE group exhibited reduced deactivation magnitude and increased response to emotional arousal. However, while the group × emotion effect was still statistically significant ($P = 0.02$), the group × memory effect, because many more “group-common” voxels were involved, did not reach statistical significance ($P = 0.43$).

The potentially confounding effect of gender was statistically controlled in results described above. Another way of assessing gender effect is to randomly drop 4 female and 14 male participants from the control and PCE group, respectively, and perform exactly the same group comparison as above (thus 11 females and 8 males in each group). This was done with deactivation and resting data (CCA approach with global regression) with the results shown in the Supporting Information. Though clusters showing significant group differences were reduced because of the reduced sample size (thus less statistic power), the general conclusion that PCEs have a higher DMN activity (less deactivation during task and stronger functional connectivity during rest) still remains.

DISCUSSION

The DMN, which is believed to be active during the internal mode of cognition, is a converging finding of various neuroimaging studies. Alterations of activity and connectivity in the DMN have already been reported to be associated with many brain disorders including autism, schizophrenia, Alzheimer's disease, depression, obsession disorders, attention-deficit/hyperactivity disorder, and post-traumatic stress disorder [Buckner et al., 2008]. With the observation of increased default mode activity in the adolescents prenatally exposed to cocaine, namely increased functional connectivity during rest and less suppressed activation during task, the present study extends

the scope of reported alterations in default mode functionality to the domain of prenatal influences of drug exposure on cognition. The importance of studying PCE effect on default mode functioning should be no less than those focused on specific cognitive functions, because this intrinsic brain activity reflects a fundamental property of neuronal functional organization, which consumes the majority of the regular brain energy budget [Raichle, 2006; Raichle and Mintun, 2006; Raichle and Snyder, 2007].

The default mode function has often been interpreted as representing either internal self-reflective thoughts [Gusnard et al., 2001; Kelley et al., 2002] or external environment monitoring [Hahn et al., 2007; Shulman et al., 1997]. The increased default mode activity observed in our PCE adolescents could represent contributions from both of these aspects of nontask oriented thought. With respect to the external monitoring, PCE subjects are reported to be more sensitive to salient stimuli in the environment [Gabriel and Taylor, 1998; Garavan et al., 2000; Romano and Harvey, 1998], and their sleep was found to be more easily disturbed [Platzman et al., 2001; Regalado et al., 1995]. Related to the internal thoughts, PCE children were found to have a higher daydreaming score, which was deemed problematic behavior by their teachers [Delaney-Black et al., 1998]. With DMN activities also observed in animals, unconscious humans and very young children [Buckner et al., 2008], recent studies on the default mode function speculate that the intrinsic brain activity of DMN may represent a “balance” between the excitatory and inhibitory neural responses [Raichle, 2006; Raichle and Mintun, 2006; Raichle and Snyder, 2007]; namely, a neural mechanism that controls brain responsiveness to various inputs. This view is in line with the concept of arousal regulation function, which is frequently reported to be altered by PCE [Mayes, 2002]. Under a stressful condition, such as either being in the unfamiliar MRI environment or seeing negative pictures, a relatively low arousal threshold may put the PCE subjects on a higher level of alertness that may interfere with their concurrent cognition/behavior processes as a result of insufficient attention resource. Our previous report showed that PCE alters the excitatory and inhibitory “balance” between the emotion and working memory systems [Li et al., 2009]. Here, a similar PCE effect is demonstrated from the view point of default mode function. A notable common outcome of these two studies is that PCE adolescents are more vulnerable to task irrelevant emotional arousal challenge (as indicated by their stronger emotion responses in both the amygdala and DMN). Group differences in balancing different streams of information processing suggest that PCE may affect the brain in a fundamental level that could underlie a variety of cognitive functions.

The present findings based on blood oxygen level dependent (BOLD) signals are also consistent with previous neuroimaging observations based on cerebral blood flow (CBF) measurements [Rao et al., 2007]. Rao et al. recently reported that PCE could increase the relative cerebral

blood flow in the cingulate, insular and parietal cortices as well as in the amygdala area. These brain regions are largely the important nodes in the DMN, and higher proportion of blood supply to these regions could underlie the increased default mode activity in the PCEs. Rao et al. also observed that PCE was associated with a higher gray matter volume in the amygdala area (we replicated this result using structural images of the present participants with data shown in the Supporting Information). As amygdala is responsible for emotional processing, this result is also in accordance with both our present and previous [Li et al., 2009] findings that showed an increased emotional arousal level in the PCE subjects.

Cocaine inhibits the reuptake of monoamines at the pre-synaptic junction thus could affect neural development not only in the monoaminergic system itself but also several other neurotransmitter systems such as the GABAergic system [Mayes, 1994; Mayes, 2002; Olsen, 1995]. Though the detailed biochemical basis of the default mode function is still unclear, these neurotransmitter associated alterations may contribute to the increased default mode activity observed in our PCE adolescents. The monoamines are generally excitatory neurotransmitters that regulate various aspects of arousal, like motivation, alertness or sleep cycle. Less synaptic reuptake of the monoamines elevates their excitatory effects in arousal regulation. In contrast, GABA is the most abundant inhibitory neurotransmitter in the central nervous system. More importantly, Northoff et al. [2007] have reported that GABA concentration is positively correlated with the default mode deactivation amplitude (more suppressed default mode activation with more GABA) in the anterior cingulate area. As there are animal studies showing that GABAergic functions are decreased by PCE [Crandall et al., 2004; Morrow et al., 2003], the increased default mode activity in the PCEs may also be due to reduced GABA inhibition.

Limitations of the present study need to be considered in interpreting results. Studies of PCE in human subjects often have confounding factors that are very difficult to match between groups. The present study controlled factors of gender and poly-drug exposure in the analysis so that the observed group differences are more ascribed to cocaine exposure. The report from Bluhm et al. [2008] that default mode activity is generally higher in women than men also provided additional evidence supporting our view that the presently observed group difference is unlikely to be due to the unmatched gender distribution (we have more females and fewer males in the control group). However, the simplified statistical model could not exclude the possibility that besides cocaine, other factors could also contribute to the observed group difference because their interactions with cocaine and development still remain unclear and their contributions may not be linear. Social factors that were not statistically controlled (e.g. household income and mother's education) may indirectly affect BOLD signals in DMN as well. We interpreted the observed group differences based on general understand-

ings we have so far about the DMN function, such as inward mentation and environment monitoring; however, the precise function of DMN is still not fully understood, and it may interact with PCE more generally beyond these cognitive processes. It is still well possible that PCE may also disrupt the normal development of DMN and even alter the overall functional connectivity at rest (i.e. the other resting state networks).

The interaction between PCE and neural development is a complicated process. To achieve a more comprehensive understanding of the teratogenic effects of PCE, studies of behavior, psychophysiology and neuroimaging are all important as they each provide complementary pieces of information. Following our previous research line on the same cohort of subjects [Bard et al., 2000; Brown et al., 2004; Coles et al., 1999; Kable et al., 2008; Li et al., 2009], the present study provides more insights into the neural alterations associated with PCE and arousal regulation. Future studies that combine multi-modal neuroimaging approaches like functional, structural, and diffusion tensor imaging could lead us to a greater understanding of the teratogenic effects of PCE and of ways in which the brain responds to such challenges.

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