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

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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

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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.

Control group difference in behavioral performance, minimizing the possibility of ascribing brain activation differences to task difficulty, rather than group differences.

A block-design fMRI paradigm was used to contrast the brain activity in 4 different types of experimental blocks. In the "Neutral, 0-back" block (NEU0), subjects performed the 0-back task while neutral pictures were presented. Similarly, we had "Neutral, 1-back" (NEU1), "Negative, 0-back" (NEG0) and "Negative, 1-back" (NEG1) blocks. These 4 types of blocks were pseudo-randomly distributed in 2 fMRI scans with an instruction at the beginning of each block instructing the participant which task (0- or 1-back) to perform subsequently.

In each task block, the instruction lasted for 3000 ms, followed by trials each having the following structure: an uppercase letter pair presented for 500 ms, a 750 ms fixation cross, a 750 ms presentation of the distracter picture, and finally another 250 ms fixation cross. A schematic diagram of the trials is shown in Fig. 1. There were 12 trials in each block and 12 blocks in each fMRI scan run. Each subject completed two fMRI scan runs.

2.3. MRI data acquisition

Functional imaging data were collected with a 3T scanner (Siemens Medical Solutions, Malvern, PA) using a T2*-weighted echo-planar imaging sequence (120 volumes per scan, matrix = 64 × 64, 30 axial slices, 3 mm in thickness without gap, TR/TE = 3000 ms/30 ms, flip angle = 90°, FOV = 192 cm). Corresponding high resolution (256 × 256) in-plane spin-echo images (for anatomical overlay) and 3D T1-weighted anatomical images (for stereotaxic transformation) were also collected after the functional scans.

2.4. Behavioral data analysis

Response accuracy and reaction time (only correct responses) were calculated for each subject. For the response accuracy, we calculated an accuracy index (AI), which considered both true "hits" and "false alarms". Specifically,

$$\text{Accuracy Index (AI)} = \text{THF} \times (1 - \text{FAF}), \text{ where}$$

$$\text{THF(True Hit Fraction)} = \frac{\text{number of correctly detected target stimuli}}{\text{total number of target stimuli}}$$

$$\text{FAF(False Alarm Fraction)} = \frac{\text{number of stimuli incorrectly identified as targets}}{\text{total number of nontarget stimuli}}$$

The THF provides a measure of detection sensitivity, and the FAF provides a measure of response specificity [42]. The AI yields an overall measure of performance by combining both sensitivity and specificity factors [37].

2.5. Imaging data analysis

As described above, adolescents were recruited from two different longitudinal cohorts of different ages (older cohort at about 17 and younger cohort at about 13). These two cohorts were separately treated in the initial data analysis with an age factor. However, as young and old subjects showed similar activation patterns in the results with no significant age difference (all the age × exposure related interaction effects had a p value at least higher than 0.7), we collapsed subjects across age.

AFNI (http://afni.nimh.nih.gov) was used for imaging data analysis. After the preprocessing steps (slice timing correction, scan concatenation, volume registration, signal normalization to percent change, and 5 mm FWHM Gaussian blur), regression coefficients for each of the 4 experimental conditions (NEU0, NEU1, NEG0, NEG1) were derived for each subject with a multiple regression analysis. The regressors were generated by convolving the boxcar stimulation functions with a standard impulse response function [$y = t^b \times \exp(-t/c)$, b and c are constants] [13]. In addition, the 6 rigid body head motion parameters (X, Y, Z displacements and roll, pitch, yaw rotations) were also included as regressors to model motion-related signal changes. After transforming into the Talairach space [62], regression coefficients of PCE and control subjects, respectively, were submitted to a 2 (memory effect, 0-back vs. 1-back) × 2 (emotion effect, NEU vs. NEG) repeated measure ANOVA analysis and the emotion and memory effect activation maps were generated ($p < 0.005$/pixel plus 300 voxels cluster, multiple comparison corrected $p < 0.05$) for both groups. In these maps, emotion activation voxels (higher BOLD signal in the negative condition) located in the bilateral amygdala areas (constrained by anatomy and Talairach coordinates) and memory activation voxels (higher BOLD signal in the 1-back condition) located in the left dorsal lateral prefrontal cortex (constrained in BA 9, 46) were selected as the regions of interest (ROIs). For both the amygdala (PCE group, left centroid L23.4, P5.3, I10.7, left volume 1069 mm^3, right centroid R24.5, P4.9, I10.5, right volume 1100 mm^3; control group, left centroid L22.7, P4.3, I10.3, left volume 920 mm^3, right centroid R22.2, P3.8, I10.8, right volume 2025 mm^3) and the frontal (PCE group, centroid L42.2, A21.8, S30.1, volume 730 mm^3, control group, centroid L39.4, A28.1, S30.8, volume 312 mm^3) ROIs in the two groups, degree of activation (regression coefficients × number of ROI voxels) for the 4 conditions were extracted from each subject and subsequently submitted to a 2 (memory effect, 0-back vs. 1-back) × 2 (emotion effect, neutral vs. negative) × 2 (exposure status, PCE vs. control) ANOVA. As the male and female subjects were unevenly distributed in the PCE and control groups, gender was also included in the ANOVA as a "covariate" so that the gender related group differences could be statistically controlled.

As almost all PCE children are poly-drug (typically tobacco, alcohol and marijuana) exposed, the cocaine effect in human studies is usually contaminated by the non-cocaine drugs. In addition, due to

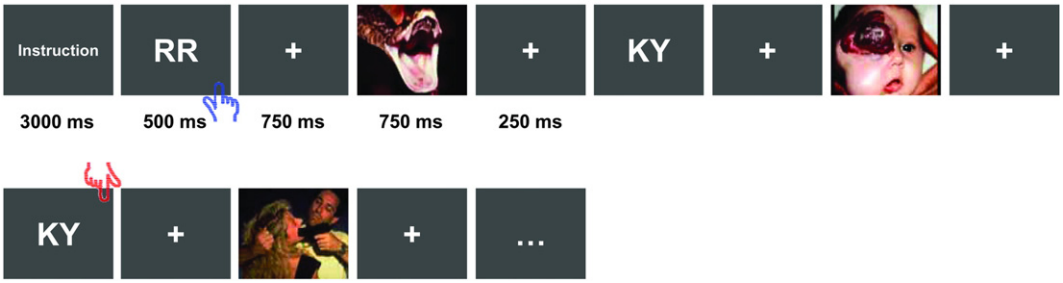

Fig. 1. A schematic diagram of the experimental task. Each task block began with an instruction asking subjects to either perform the "letter RR" or the "Same as 1-back" task. Memory letter pairs were interleaved by fixation crosses and distracter pictures (duration labeled). These pictures were either 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.

the complexity of the exposure background, there are also many other confounding factors in human study, such as gestational age or birth weight, social economic status, mother's education and foster care. Previous behavior studies usually control all these confounding factors by including them as covariates in the statistical model. However, with a relatively small sample size, functional neuroimaging study cannot statistically control all of them. To examine the confounding situation in the present study, we only included 3 more representative covariates in the ANOVA model: (i) amount of alcohol exposure, (ii) amount of marijuana/tobacco exposure and (iii) the birth weight. The marijuana/tobacco was a joint variable derived by principle component factor reduction because their uses were highly correlated (Pearson correlation, $p=0.04$) in our sample.

3. Results

3.1. Sample characteristics

Twenty-eight of 84 participants had data that could not be included in the analysis due to movement artifacts or other problems; therefore, we compared members of the group who were eliminated and those who were included on the following measures: birth weight, head circumference, gestational age, Apgar scores, birth-mother's age, amount of prenatal drug and alcohol use, child's age at time of imaging, current family monthly income level, verbal performance, and full scale IQ. With the exception of current family monthly income, there were no differences between those who were included and those who were not and no interactions were found between task inclusion and drug group. For current family monthly income, those who were excluded had a mean income of $2252 versus $1502 for those who completed ($p=0.02$), but there was no interaction ($p=0.37$) with prenatal exposure group.

Because the present task paradigm involves emotionally negative pictures as the distracters, which could affect subjects with different traumatic histories differently, we examined children's reported social history for evidence of stable custody arrangements and a 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, number of changes in care giving and protective service involvement, were higher in PCE youth. For care giving, 8 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, 6 PCE children had Division of Family and Children Service record versus 1 in the contrast group (Fisher's Exact Test, 1-sided, $p=0.04$).

3.2. Behavioral performance

The accuracy indices (AI) and reaction times (RT) for the two groups are shown in Table 3. For both measures, a 2 (emotion effect, neutral vs. negative)×2 (memory effect, 0-back vs. 1-back)×2 (exposure, PCE vs. control) ANOVA revealed significant emotion ($p_{AI}<0.001$, $p_{RT}<0.001$), memory ($p_{IA}<0.001$, $p_{RT}=0.01$) and emotion×memory ($p_{AI}<0.001$, $p_{RT}<0.001$) interaction effects. These results replicated the expected pattern of performance, poorer (i.e., lower accuracy and longer reaction time) with higher memory load or with negative emotion. The differences in accuracy and reaction time between memory load conditions were significantly larger with negative distracters, indicating the predicted interaction between the emotion and memory processes. There were no other significant effects or interactions in behavioral performance (all $p>0.2$). Therefore, participants' exposure status was not significantly distinguished in behavior.

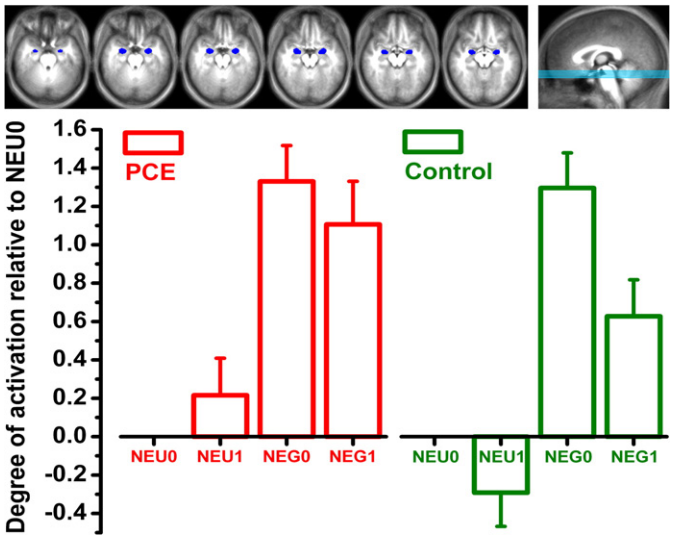

Fig. 2. Top: averaged brain images with bilateral amygdalae highlighted (images shown are axial consecutive slices of 2 mm thick). Bottom: a comparison of degree of activation (regression coefficient × activation volume) between condition and groups. They were plotted by putting the "NEU0" value as the baseline (zero). The error bars represent standard error of the mean.

3.3. Regional brain activity

The regional activation level comparisons across groups and conditions are shown in Fig. 2 (for the bilateral amygdalae) and Fig. 3 (for the left DLPFC).

The bilateral amygdalae, areas typically associated with emotional processing, exhibited a significantly higher fMRI signal when negative pictures were presented as compared to neutral (emotion effect, $p<0.001$). Furthermore, the modulation of amygdala response by increased memory load differed significantly between groups. Specifically, compared to the 0-back condition, the higher memory load (1-back) decreased the amygdala activation in the controls but not in the PCEs (memory×exposure effect, $p=0.05$). In the controls, this result is consistent with the predicted cognitive inhibition of emotional arousal but this inhibitory effect is markedly attenuated in the PCE group.

Table 3
Memory task behavioral performance and statistic.

Group	Accuracy index ±Standard deviation				Reaction time (ms) ±Standard deviation			
	Neutral 0-back	Neutral 1-back	Negative 0-back	Negative 1-back	Neutral 0-back	Neutral 1-back	Negative 0-back	Negative 1-back
Control($n=23$)	0.93 ±0.05	0.93 ±0.07	0.95 ±0.05	0.87 ±0.08	431 ±51	423 ±50	430 ±50	466 ±65
PCE($n=33$)	0.93 ±0.06	0.91 ±0.09	0.93 ±0.08	0.84 0.12	419 ±46	414 ±65	423 ±62	449 ±80

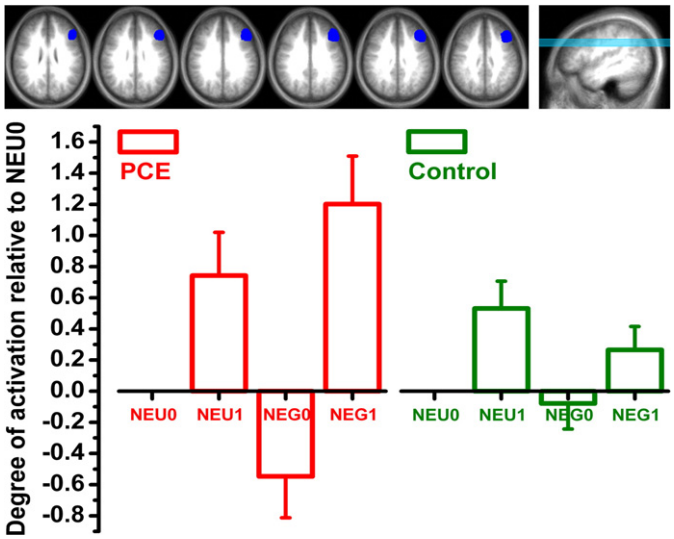

Fig. 3. Top: averaged brain images with left dorsal lateral prefrontal area highlighted. Bottom: a comparison of degree of activation between condition and groups. The figure layout is the same as that of Fig. 2.

As a major working memory area, left DLPFC showed a significantly higher overall activation in the 1-back condition than the 0-back ($p<0.001$). In this region, the group difference appeared first on the memory main effect [(NEU1–NEU0)+(NEG1–NEG0)] with memory-related response being higher in the PCE group than in the controls (memory×exposure, $p=0.01$). Consistent with our hypothesis, this group difference is much greater in the negative (NEG1–NEG0) condition than in the neutral (NEU1–NEU0) condition (memory×exposure×emotion interaction, $p=0.002$). Namely, response to cognitive challenge in the PCE group differed from that of the controls primarily under the condition of negative emotional arousal.

The exposure effect here varied with level of cognitive demand. In the NEG0 condition, prefrontal activation was decreased (relative to NEU0) more in the PCE subjects than the controls ($p=0.08$). This means PCE subjects' prefrontal activity was suppressed (by negative emotion) more in the low cognitive demand. However, in the NEG1 condition, while this emotional inhibition was still apparent (NEG1 lower than NEU1) in the control group, PCE participants showed much increased prefrontal activity ($p=0.01$). Frontal activations in negative and neutral condition reflect emotional modulation of cognitive function; thus both differing effects in low and high cognitive demand conditions reflect a PCE associated alteration of this bottom-up effect.

With the 3 covariates (alcohol, marijuana/tobacco and birth weight) added in the ANOVA model, the prefrontal group difference still remained significant (emotion×memory×exposure interaction, $p=0.005$), but the amygdala PCE effect was changed. It turned out that the amygdala data variance is largely explained by the marijuana/tobacco effect (memory×marijuana/tobacco interaction, $=0.02$). This result reflects 3 possibilities: (1) the amygdala group difference is not associated with cocaine but marijuana/tobacco; (2) the group difference is still associated to cocaine but the exposure amount of marijuana/tobacco and cocaine are highly correlated; (3) the group difference has contribution from both the cocaine and marijuana/tobacco. These possibilities can be assessed by only looking at the subjects that were not exposed to marijuana ($N=14$) or tobacco ($N=7$). When excluding marijuana or tobacco exposed subjects, similar group difference pattern still exist as that included the entire exposed group (BOLD response memory effect, 1-back minus 0-back, Control $=-0.96$, $\text{Exposed}_{\text{no-marijuana}}=-0.16$, $\text{Exposed}_{\text{no-tobacco}}=-0.39$). These data still indicate that higher memory load could not suppress the amygdala response in the exposed subject as much as that of the controls, therefore, the group difference at least could not be explained solely by marijuana or tobacco.

As the PCE and control adolescents were different on some indices associated with traumatic history, and amygdala signal is sensitive to impact of negative arousal, we also examined whether the impact of negative arousal varies according to the early trauma history. With the amygdala activation value (negative minus neutral condition) as the dependent variable, group×trauma-index ANOVA was performed, respectively, for the 7 trauma history associated factors mentioned above in "Sample Characteristics". The result showed neither trauma effect nor group × trauma interaction for all the 7 indices (all $p>0.2$).

4. Discussion

Cocaine use by pregnant women and the possibility of its long-term effects on offspring have been a major public health concern since the 1980's. Previous studies of behavioral outcomes have suggested that long-term behavioral PCE effects are subtle [1,5,28,31,33,49,57,58] and there are limited neuroimaging studies that examine the functional neural basis of this teratological effect. In the present fMRI study, we found evidence that PCE is associated with altered arousal regulation between two systems that have been characterized as the dorsal cognitive and ventral emotion systems [23,25,45,66]. The two groups of adolescents did not differ in ability level at the time of neuroimaging and exhibited similar behavioral performance in the current experiment. Thus, brain activation differences were ascertained without the confounding factor of task difficulty. This approach provides a means to examine compensatory neural mechanisms that may be required for clinical groups to function behaviorally as well as typically developing peers. As our results demonstrate, absence of group differences in behavior does not necessarily imply an absence of neurobiological differences, and similar patterns are seen in other recent prenatal substance exposure studies [9,56].

Reciprocal inhibition between the dorsal cognitive network and the ventral emotional network has been reported frequently in brain imaging studies of healthy individuals [23,25,45,66]. Emotional arousal can inhibit cognitive performance by diverting resources from and disrupting the cognitive network. Conversely, cognitive activity can actively inhibit emotional arousal as well. These interactions are critical for the maintenance of socially appropriate behavior and for the capacity to perform demanding cognitive tasks in the presence of distraction. In this study, fMRI data provided neurobiological evidence of PCE-related alterations of these interactions. In bilateral amygdalae, increased cognitive demands suppressed neural activity in the controls but not in those who had been prenatally exposed to cocaine. This observation extends the previous behavioral research findings in neonates [21], infants [7,14], and school-aged children [34], which suggest that PCE is associated with alterations in psychophysiological arousal. For the exposed subjects, it is possible to speculate that their reduced ability in suppressing task-irrelevant arousal (top-down regulation) might reduce the effective attentional resources available for cognitive functions.

The present prefrontal data showed that decreased ability to inhibit emotional arousal did affect cognitive brain activities. When memory load was low, DLPFC activity was suppressed more in the PCE group, suggesting that exposed adolescents were more affected by emotional arousal than their non-exposed peers. When memory load increased, the expected suppression of frontal memory-associated activation was still observed in the controls; in contrast, the negative stimuli increased DLPFC activation in exposed individuals. In the controls, the decreased DLPFC activation is consistent with the observed drop in behavioral performance. However, in the PCE

group, even though a similar drop in behavioral performance was also observed, it is likely that they had to recruit additional executive/storage resources for working memory (or additional regulation resources for emotional arousal control), which resulted in the increased DLPFC activation. This additional resource recruitment may represent a compensatory mechanism for PCEs to achieve a comparable behavioral performance as that of the controls in the condition of high emotional arousal.

An fMRI study of PCE effect on working memory function was published recently [32]. In contrast to the present findings, Hurt and colleagues found similar brain activations between the groups with no significant PCE effect observed. Similar to this pure (no specific distraction) working memory study, the PCE and control groups showed comparable prefrontal activation in the present neutral condition. However, once the emotional distraction became high (negative condition), a significant prefrontal activation difference could be seen between the present groups. The effect of PCE on one specific cognitive function (e.g. working memory) may be "subtle", but it may be more significant on one's capability in regulating multiple streams of information processing.

The prefrontal cortex is the neocortical region that coordinates a wide range of neural processes. Besides the well known working memory function, previous investigations also suggest the involvement of prefrontal cortex in regulating attention, sorting salient from irrelevant stimuli and inhibiting distractions [41,65]. As a region generally playing an important role in cognitive control [43], prefrontal differences must underlie arousal alterations associated with PCE. However, because we defined the left DLPFC ROI on the basis of memory activation (see Methods), this region may only overlap partially with the prefrontal areas mediating arousal regulation. Given that different prefrontal regions are activated differently even across different stages of working memory processing [18] and that regions previously implicated in coping with distraction are situated inferiorly in the ventral frontal cortex [22,63], the present results reported for the prefrontal cortex may capture only a subset of the prefrontal changes that are directly associated with arousal regulation.

The current imaging results are consistent with several animal behavioral studies that controlled the factors (such as nutrition, prenatal care, dose/timing of cocaine exposure) that can make it difficult to interpret human studies. In those studies, cocaine-exposed animals were less able to inhibit attention to distracting stimuli, perhaps demonstrating a distorted excitatory/inhibitory balance. For example, Romano and Harvey observed that PCE rabbits preferentially attended to salient but task irrelevant stimuli and that these effects persisted into adulthood [53]. Garavan and colleagues also found that the attentional focus of PCE rats was heavily influenced by the relative salience of environmental cues [30]. The present findings have more in common with those of Romano and Harvey's in terms of the long-term effect. As the present participants are from a longitudinally followed cohort with altered arousal responses already shown at 8 years of age [34], both animal and human studies have revealed a relatively persistent PCE effect on neural development.

We used high arousal pictures across a variety of specific emotions (e.g. snake can elicit fear and disfigured infant can elicit disgust) in the present study. According to previous report that fear may elicit amygdala activation while disgust tends to activate the insula more than amygdala [44], one may suggest simply using pictures that are more pertinent to fear and amygdala. However, we chose to use stimuli of general arousal rather than specific emotion based on 3 considerations. First, the goal of the present study was to examine differences in general arousal regulation between the prenatal cocaine-exposed and non-exposed adolescents and this goal motivated our selection of high arousal negative valence pictures across a variety of specific emotions. In addition, we are not aware of any previous imaging data suggesting that arousal regulation effects are associated only with a specific type of negative, high emotion stimulus, or that a specific type of negative emotion interacts with PCE effects. Second, a recent meta-analysis of 385 imaging studies [16] has shown that amygdala can be activated by many types of emotionally arousing stimuli including both fear and disgust. Third, for many emotional arousing pictures, it is actually difficult to strictly categorize them into either fearful or disgusting; in such cases, the amygdala activation should reflect the effect of both. For example, a snake could elicit fear, but also likely to elicit other related emotions such as disgust (thinking of mucus discharge). Likewise, a picture of a disfigured infant could induce disgust, but it could also elicit fear of disease.

There are some limitations in the present study that should be considered in interpreting results. While the study is characterized as a comparison between a group who were prenatally exposed to cocaine and a non-exposed group, the drug group was in fact really a poly-drug exposure group. Thus, observed group differences could also be due to impacts of other drugs or the complex interaction of these drugs. In addition, there are many other social factors that may also contribute to the observed results and potential gender × exposure interaction was not directly examined. Nonetheless, prenatal cocaine exposure is likely a major contributor to the results observed in this study based on the following considerations. First, the present neuroimaging study was conceptualized as a result of our previous behavior [7,11,14] and psychophysiology [34] findings on the same longitudinally followed individuals, in whom the poly-drug and social factors were statistically controlled. These previous studies all found a specific PCE association with arousal dysregulation when other factors were controlled. The present imaging study was conducted to ascertain the neurobiological basis. Second, though the present sample size is limited as compared to behavioral studies, when we examined other drug exposures and birthweight, the prefrontal PCE effect still remained significant and the amygdala PCE effect could not be excluded. Thus, while there may be contributions on these outcomes from a number of factors, it is clear that prenatal exposure to cocaine and other drugs does lead to alterations in brain arousal responses.

In summary, by showing different amygdala-DLPFC activation patterns in exposed and control subjects, the present fMRI study suggests the neurobiological substrates for arousal-associated neuronal alterations related to prenatal cocaine exposure. Though the precise mechanisms by which cocaine and other drugs affect the brain's function associated with arousal regulation remain far from clear, the present study provides one step toward understanding these effects. Such studies can provide a greater understanding of the teratogenic effects of PCE and how the brain responds to such challenges.

Conflict of interest statement

We have no conflict of interest relevant to this article to disclose.

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