MRI Evidence of Brain Structure Alterations in Adolescence Prenatally Exposed to Cocaine

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Introduction

Children prenatally exposed to cocaine have demonstrated performance deficits in various behavioral assessments including sustained attention, self regulation and visuo-spatial tasks during their development[1,2]. The structural effects of prenatal cocaine exposure (PCE) on the developing brain are not well studied, particularly with the potential confounds of the environment as well as other prenatal drug exposure. In this study, we investigated the structural gray and white matter (GM & WM) alterations in PCE adolescence after controlling for various critical confounds in an attempt to isolate the effect predominantly attributed to PCE.

Methods

Participants: Eighteen PCE participants and 14 non-cocaine exposed controls (NCE) matched on gender (Male: 8/18 vs. 5/14, p=.62), age (mean±SD: 14.05±0.48 vs. 14.27±0.51yrs), race (African American 16/18 vs. 13/14, p=0.70) , maternal socioeconomic status (low SES: 18/18 vs. 14/14) were recruited from an ongoing longitudinal PCE study in Case Western Reserve University[2]. Prenatal drug exposure and a measurement of the home environment (HOME score at 12 yrs) are summarized in Table 1.

Table 1. Summary of prenatal drug exposure and HOME score

	PCE (n=18)		NCE (n=14)		p-value
	Mean	SD	Mean	SD	
Cocaine /week	20.66	25.88	0	0	<.0001
Drinks /week	8.45	11.82	1.06	2.52	.007
Marijuana/week	1.04	1.98	0.04	0.13	.02
HOME score (12yrs)	48.61	7.00	51.43	5.94	.24

Data Acquisition: All participants underwent identical structural MRI and diffusion-tensor imaging (DTI) protocols on a 4T Siemens-Bruker using an eight channel head coil. A 3D MPRAGE sequence was employed to acquire the T_1-weighted structural image with: TR/TE = 2500/3.52ms, TI = 1.1s, flip angle = 12°, FOV= 256 ×192 × 176mm and a voxel size of 1 × 1 × 1 mm. For DTI, diffusion-weighted images were collected using 2D SE-EPI(TR/TE = 6000/100ms, BW=1562Hz/pixel, FOV = 22 cm, matrix = 128x128, 37 contiguous 3mm-thick AC-PC parallel slices) in 12 directions at a b-value of 1000s/mm^2, together with a b_0 image.

Data Analysis: (1) Voxel-based morphometry (VBM) analysis[3] was applied to the T_1 structural data to investigate the GM alterations. After extraction and tissue-type segmentation of the brain, the resulting GM images were aligned to the MNI152 template and then averaged across 28 participants (14 per group) to create a study-specific template, towards which all 32 native GM images were then non-linearly re-registered. The registered GM images were subsequently modulated by the Jacobian of the registration warp field, and smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxelwise GLM was applied to contrast the GM between PCE and NCE groups. (2) Tract-based spatial statistics (TBSS)[4] was employed for voxelwise statistical analysis of the fractal anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) maps that were generated from the DTI data corrected for eddy current distortion in order to contrast the WM between groups. For both analysis, the dosage of alcohol, marijuana and HOME score were used as covariates while the threshold free cluster enhancement (TFCE)[5] technique was used for multiple comparison correction. Both analysis were carried out with tools in FMRIB Software Library.

Results & Discussion

Reduced GM density was revealed by VBM analysis in the PCE cohort in the right precuneus and the ventralateral prefrontal cortex (VLPFC) extending to the frontal pole. TBSS analysis revealed a widespread, but slightly right lateralized WM alteration characterized by highly significant MD and RD elevation (p_c< .01) in PCE. No FA difference was detected even with a more lenient p_c of 0.1. There was good correspondence between the reduced GM and the WM exhibiting increased MD and RD found in the right VLPFC and the right anterior corona radiata /forceps minor of the PCE cohort (**Fig. 1A &C**). Similar concordance was also found in the parietal lobe (**Fig. 1B &D**). Considering there is a convergence of evidence that the right VLPFC plays an important role in self- control[6] while the precuneus is closely implicated in visuo-spatial processes[7], the distribution of the GM changes was consistent with the behavioral test features of the PCE in that the GM and WM alterations in the right prefrontal lobe (/ right parietal lobe) are likely related to functional impairments of sustained attention and self regulation (/ visuo-spatial process) in PCE individuals.

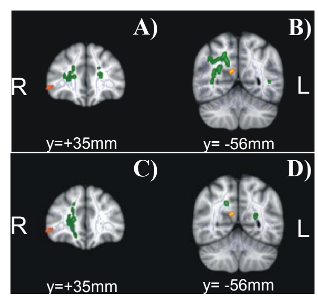

Fig. 1 Concordance between WM with higher MD (p_c< .01, green) and reduced GM (p< .007,yellow-red) was found for PCE in both the frontal lobe (**A**) and the right parietal lobe (**B**). Similar finding for WM RD (p_c< .01, green) vs. GM density (yellow-red) (**C&D**). The skeletonized results for WM have been thickened for better visibility.

References

[1] Ackerman et al., Pediatric 2010; [2] Singer et al., J Pediatr 2008; [3] Ashburner et al., NeuroImage 2000; [4] Smith et al., NeuroImage 2006; [5] Smith et al., NeuroImage 2009; [6] Cohen et al., Ch. 8, Self Control in Society, Mind & Brain, Oxford, 2010; [7] Cavanna et al., Brain 2006.