

CASL Perfusion fMRI Revealed Altered Resting Brain Function in Prenatally Cocaine Exposed Teenagers

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Introduction Theories and models from animal experiments have focused on interference of cocaine with corticogenesis and clearly indicated the alternations and deficits of cortical development caused by prenatal cocaine exposure (PCE), especially in the dopamine-rich areas of cerebral cortex (1). Recent studies in nonhuman primates and humans have suggested that cocaine-exposed children may have altered neurobehavioral regulation patterns and the effects of PCE might not be manifested until the adulthood (2-3). However, little is known regarding the neurobiological mechanism mediating longitudinal effects of PCE on the neurocognitive development of human brain. Arterial spin labeling (ASL) perfusion MRI provides a promising means to non-invasively assess cerebral blood flow (CBF) and associated brain function, and is particularly advantageous for pediatric neuroimaging (4). In the present study, we used continuous ASL (CASL) perfusion fMRI as well as optimized voxel-based morphometry (VBM) to compare resting CBF and brain structure in prenatally cocaine exposed teenagers and socioeconomically matched controls.

Methods Twenty-five prenatally cocaine-exposed teenagers (11 females, mean age 14.8 ± 1.1 years) and 24 socioeconomically matched controls (13 females, mean age 14.3 ± 1.2 years) were scanned on a Siemens 3.0T Trio scanner. An amplitude-modulated CASL technique (5) [16 slices, 6mm thk/ 1.5mm sp, TR=4s, Labeling time=2s, Delay time=1.2s, TE=17 ms, FOV=22x22cm², matrix=64x64, gradient echo EPI] was used for functional scans. Each resting state CASL scan (80 acquisitions) took 320s. Functional image processing and analysis were carried out with SPM. For each subject, raw EPI images were corrected for head motion, followed by pair-wise subtraction of label and control acquisitions. Absolute CBF images were generated based on the single-compartment perfusion model (5). First, Global CBF was calculated and compared between the two groups. Voxel-wise population comparisons (AnCova, 1scan/subject) were then conducted on CBF images with additional covariates to account for the age and gender variability. Comparisons were conducted on both absolute CBF (without global CBF correction) and relative CBF (with global CBF correction). Areas of significant activation associated with the contrast (PCE – Control) were identified for the false discovery rate (FDR) corrected P value smaller than 0.05 and cluster size larger than 100 voxels (voxel size $2 \times 2 \times 2$ mm³). Optimized VBM analysis (6) was also performed on the high resolution MR structure images (MPRAGE, TR=1620ms, TI=950ms, TE=3ms, flip angle=15°, 160 contiguous slices of 1.0 mm thickness, FOV=192x256mm², matrix =192x256) to explore the difference of gray matter volume (GMV) between PCE groups and controls.

Results The global mean CBF was significantly lower for cocaine-exposed children than controls (60.2 ml/100g/min vs. 68.0 ml/100g/min, $t=2.04$, $p<0.05$). Without global CBF correction, reduced absolute CBF was found in multiple posterior brain regions for PCE including bilateral occipital, inferior temporal, cerebellum and thalamus (Fig1a). After global CBF correction, greater relative CBF was found in multiple frontal and superior brain regions for PCE including bilateral insula, medial frontal, cingulate and parietal cortex (Fig1b). The VBM results showed no difference between two groups using the FDR corrected threshold. When decreasing the threshold to uncorrected $p<0.005$ and cluster size larger than 800 voxels (voxel size $1 \times 1 \times 1$ mm³), greater GMV was found in bilateral insula/amygdala/superior temporal complex for PCE (Fig1c).

Discussion The overall decrease in global CBF in PCE subjects supports the view that chronic exposure may alter cerebrovascular reactivity and permanently decrease CBF (7), and suggests that chronic exposure in utero may have had similar effects on the fetus and persisting into childhood. In the face of this reduced global CBF, the apparent increase in distribution of relative CBF to frontal cortex in PCE subjects suggests that compensatory mechanisms may be involved. The optimized VBM results suggest that the effect of PCE may even alter structural development of brain. The overlay of greater relative CBF and greater GMV in the insula-amygdala areas, which known to be involved in processing negative emotion and arousal (8), is consistent with the view (9-10) that PCE may affect the emotional and arousal regulation. These results suggest ASL perfusion MRI may provide a valuable tool for investigating long-term effects of long-term effects of intrauterine drug exposure.

References

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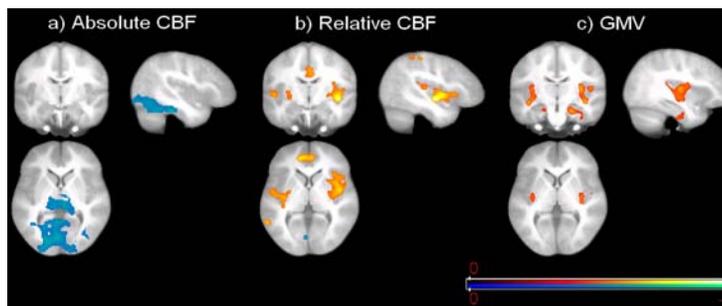


Fig2. Absolute CBF, relative CBF and GMV differences between PCE and socioeconomically matched controls (PCE-control).