Identification of the Teratologic Effect of Prenatal Exposure of Cocaine using Voxel Based Morphometry

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INTRODUCTION : Cocaine crosses the placental and fetal brain barriers and has a direct effect on the fetal neurodevelopment. Studies have demonstrated a relationship between prenatal cocaine exposure (PCE) and reduced cognitive and language functioning in infancy and early childhood[1-3], as well as deficits in visual-spatial skills, general knowledge and arithmetic skills [4,5]. Little is known about the teratologic damage to the brain underlying these deficits. This study was designed to determine if the combination of high spatial resolution MR imaging of PCE and non cocaine-exposed (NCE) children and Voxel Based Morphometry (VBM) could identify local differences in gray and white matter volumes between the two populations and thereby elucidate the neuronal substrates underlying the neurobehavioral findings.

METHODS : *Subjects:* MRI was completed on 35 (21 cocaine-exposed and 14 non-exposed) children at ages 7-8 years selected from a cohort of 415 participating in a longitudinal investigation of the effects of prenatal cocaine exposure[4]. Inclusion criteria for the longitudinal study controlled for weeks of gestation, IQ, primary caregiver since birth, known genetic abnormalities, postnatal growth problems, and medical illnesses. PCE children were matched to NCE children on age, race, gender, handedness, and the presence of heavy alcohol-exposure during pregnancy. The children were assessed at regular intervals from 1 month to 9 years of age on a variety of standardized, normative, or experimental neurodevelopmental tests. *Imaging:* Volumetric MPRAGE T1 – weighted structural MRIs were performed on a Siemens Symphony 1.5T (Siemens Medical Systems, Erlangen, Germany) : TR = 1710 ms, TE = 2.09 ms, Tl = 1100ms, flip angle = 15; voxel size 1mmx1mmx1mm. *Image Analysis:* The VBM analysis was obtained using SPM5 and the VBM5 toolbox by C. Gaser (http://dbm.neuro.uni-jena.de/vbm/)[6] . A pediatric atlas (courtesy of CCHMC)) was used for spatial normalization in combination with 6mm FWHM Gaussian smoothing. Two types of design matrices were employed with the general linear model (GLM): one with PCE and NCE as covariates, and the second with perceptual reasoning index (PRI) or block design (BD) scores, the two WISC-IV measures for which the PCE children scored significantly ($p< 0.001$) below their NCE counterparts. Family Wise Error (FWE) was applied to correct for multiple comparisons.

RESULTS AND DISCUSSION : A statistically significant (FWE corrected p-value = 0.007) decrease in white matter (WM) for the PCE population located in the Brodmann's area 19 (BA19; which was correlated with the BD ($r=0.73$) and PRI ($r=0.77$, Figure 1) scores taken at 9 years of age (origin of the decrease depicted in Figure 2). Gray matter (GM) tissue concentration was noted to be reduced in Brodmann's Area 37 (BA37) ($p<0.001$ uncorr); and showed correlation with BD ($r=0.74$) and PIQ ($r=0.80$). BD and PRI are WISC-IV measures that strongly reflect visual spatial processing skills. Notably, the identified regions appeared in the left cerebrum of the inferior occipital lobe, or the visual association cortex. BA 19 is involved in feature-extracting, shape recognition, attentional, and multimodal integrating functions while BA37 is involved in mental image generation. The recruitment of these regions during visual spatial task performance is further supported by the findings of an FMRI study of mental imagery that demonstrated that it was the visual association cortex (specifically, BA37 and BA19) as opposed to the primary visual cortex that was engaged during image generation and that the activation was asymmetrically localized to the left [7].

CONCLUSIONS: The results the present study demonstrate that high spatial resolution MR imaging in combination with the use VBM employing age appropriate parameters is a powerful tool for identifying tissue volume differences between pediatric populations in cortical regions consistent with the neurobehavioral observations. The results of this study will be used to guide the design of more specific neuroimaging studies as well as to aid in the development of targeted behavioral and pharmacologic interventions for PCE children.

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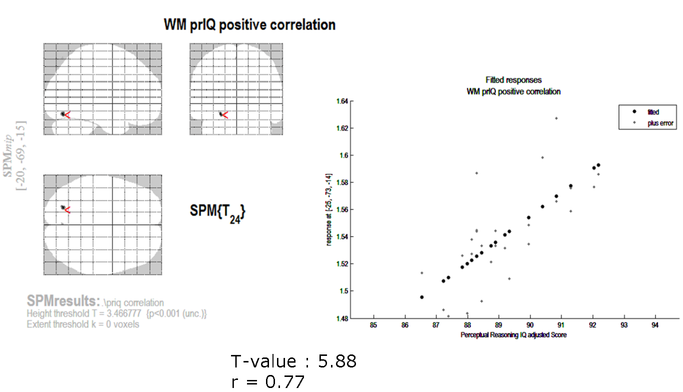

Figure 1. VBM analysis of WM concentration using PRI score as covariate in GLM model

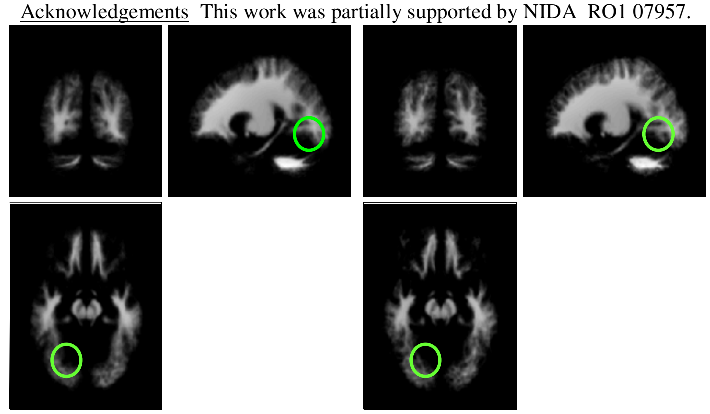

Figure 2. PCE (left) showed significantly less WM concentration in left inferior Brodmann area 19 than NCE (right)

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