Longitudinal DTI in Young Children with Prenatal Methamphetamine Exposure: A 3 Year Follow-Up Study

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INTRODUCTION: Methamphetamine (METH) is an addictive stimulant drug that is abused with increased frequency among pregnant women who abuse drugs. METH may be neurotoxic, as shown in animal models and adult METH users, using neuropsychological tests, neuroimaging studies and postmortem analyses [see Review[1]]. Only a few studies evaluated children with prenatal METH-exposure, and found smaller subcortical brain volumes on MRI that correlated with poorer cognitive performance[2] or intelligence,[3] and elevated total creatine on magnetic resonance spectroscopy,[4,5] and lower diffusion on diffusion tensor imaging (DTI).[6,7] The current study aims to validate the lower diffusion findings in young children with prenatal METH-exposure and to evaluate whether the lower diffusion persists over a 3-year period.

METHODS: 118 children [50 METH-exposed (ages 4.1±1.3 years, 37 boys and 31 girls), 68 un-exposed controls (ages: 4.2±0.9 years, 31 boys and 19 girls)] were studied with DTI. Follow-up DTI were obtained in 62% exposed and 53% unexposed children at year 1, 44% and 38% at year 2, and 24% and 21% at year 3. Each child completed detailed clinical assessments, including neuropsychological tests. DTI scans were performed on a 3 Tesla Siemens Trio TIM MR scanner with 12 diffusion directions, 28 slices, 4.6 mm slices, 0.46 mm gap, TR/TE=3700/88ms, 128x128, b-factor [0,1000s/mm2]. An automated atlas-based technique, based on large deformation diffeomorphic metric mapping (LDDMM), was performed using MRIStudio[7,8] (**Figure 1**). Fractional anisotropy (FA), radial, axial and mean diffusivity (ADC) were measured from 176 ROIs. However, ROI values from right and left hemispheres were averaged if not different which resulted in 97 brain regions for ADC and 99 regions for FA. Repeated-measures ANCOVAs were performed to compare group effects, with nicotine usage and scanner upgrade effects as covariates. Simes corrections for multiple comparisons were performed.

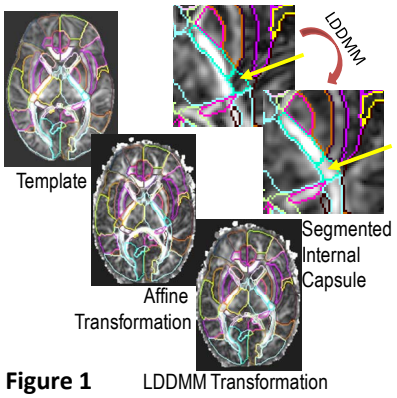
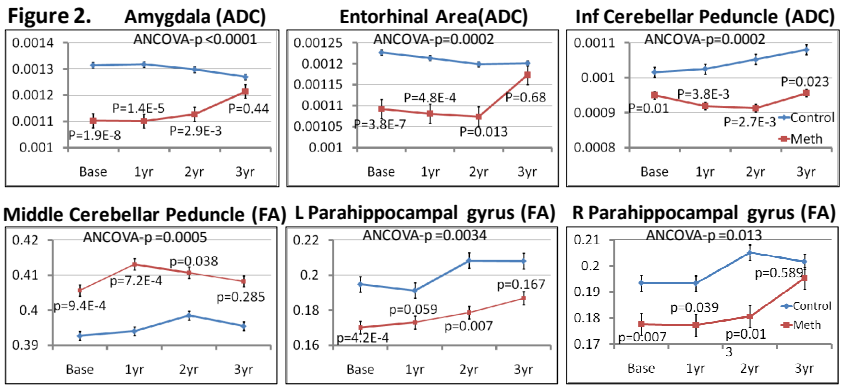


Figure 1

RESULTS: Clinical: The two subject groups had similar maternal age at birth, parental education, socioeconomic status, estimated verbal intelligence and Beck Depression Inventory of the parents. However, the METH-exposed children had a younger gestational age at birth (38.5±1.64 vs. 39.2±1.42 weeks, p=0.013), and hence lower birth weight (p=0.008) and length (p=0.018). The mothers of the exposed group used METH 2.41±0.83 trimesters. At baseline, the two groups had similar head circumference and weight, but METH-exposed were shorter (98.3±5.9 vs. 100.8±6.0cm, p=0.026). The two groups performed similarly on Stanford Binet non-verbal (fluid reasoning) and verbal (vocabulary) tests but poorer on visual motor integration (-9.7%, p=0.003).

DTI: Compared to the un-exposed children, METH-exposed children showed lower ADC in 23/97 (23.7%) brain regions throughout the frontal, temporal and occipital lobes, but also higher FA in the cerebellar peduncle but lower FA in left and right parahippocampal gyri (see selected regions in **Figure 2**). Across all subjects, ADC changed in 25 brain regions and FA changed in 16 brain regions over the 3 year period. No significant time-by-prenatal METH-exposure status was observed.

Figure 2.



DISCUSSION: Lower brain diffusion in children with prenatal METH-exposure is validated in the current larger sample. We extended the prior findings by showing abnormalities in FA, and persistence of the lower diffusion and altered FA throughout the brain over a three-year follow-up period in these children (between 3-7 years of age). The lower ADC suggests greater compactness and lower FA suggests less coherence of the axons. Further correlations with detailed neuropsychological evaluations and the amounts of METH-exposure in these children are ongoing and will determine whether these brain diffusion and FA abnormalities would impact specific aspects of cognition.

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