Increased creatine and choline in the brains of children exposed to methamphetamine prenatally

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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 [1,2], and postmortem analyses [3]. However, little is known about possible neurotoxic effects in children exposed to METH prenatally. Preliminary studies of METH-exposed children (ages 3-16 years) showed smaller brain volumes on MRI that correlated with poorer cognitive performance [4], and neurochemical changes (specifically elevated total creatine) on *in vivo* proton magnetic resonance spectroscopy (^{1}H MRS) [5]. The current study aims to validate these preliminary findings and to evaluate whether these children's brain development might be altered over a 5-year period. Baseline data in children ages 3-4 years are presented here.

METHODS: Seventy children [33 METH-exposed (aged: 47.7±1.3 months), 37 un-exposed controls (aged: 46.8±1.3 months)] were enrolled; each completed detailed clinical assessments, including neuropsychological tests. 69 of these children had acceptable data for MR spectroscopy (22 of these required 1-4 repeat scans). Localized ^{1}H MRS was performed on a 3 Tesla Siemens Trio MR scanner in four brain regions: medial frontal gray matter (FGM), right frontal white matter (FWM), right basal ganglia (BG), and bilateral thalamus (THAL), using a standard Point RESolved Spectroscopy (PRESS) acquisition sequence (TR/TE=3000/30ms, 64 averages, 3.5 min per location). LCModel analysis in conjunction with additional water T2 measurements allowed for determination of metabolite concentrations [6, 7].

RESULTS: Clinical: The two subject groups had similar age, sex-proportion, height, weight, head circumference, and cognitive performance on the Stanford Binet non-verbal (fluid reasoning) and verbal (vocabulary) tests. The parental education, socioeconomic status, estimated verbal intelligence of the parents and Beck Depression Inventory of the parents, were also similar between subject groups. However, the METH-exposed children had younger gestational age at birth (38.7±0.3 vs. 39.9±0.2 weeks, p=0.0009), and hence lower birth weight and length. **MRS:** Compared to the un-exposed children, METH-exposed children showed higher levels of total creatine (Cr: +4.8%, p=0.036), choline compounds (+7.7%, p=0.02) and a trend for decreased N-acetyl compounds to Cr ratio (-3.5%, p=0.069) in FWM (**Figure 1**), and decreased MI/CR in the thalamus (-6%, p=0.03). No group differences were observed for other metabolites.

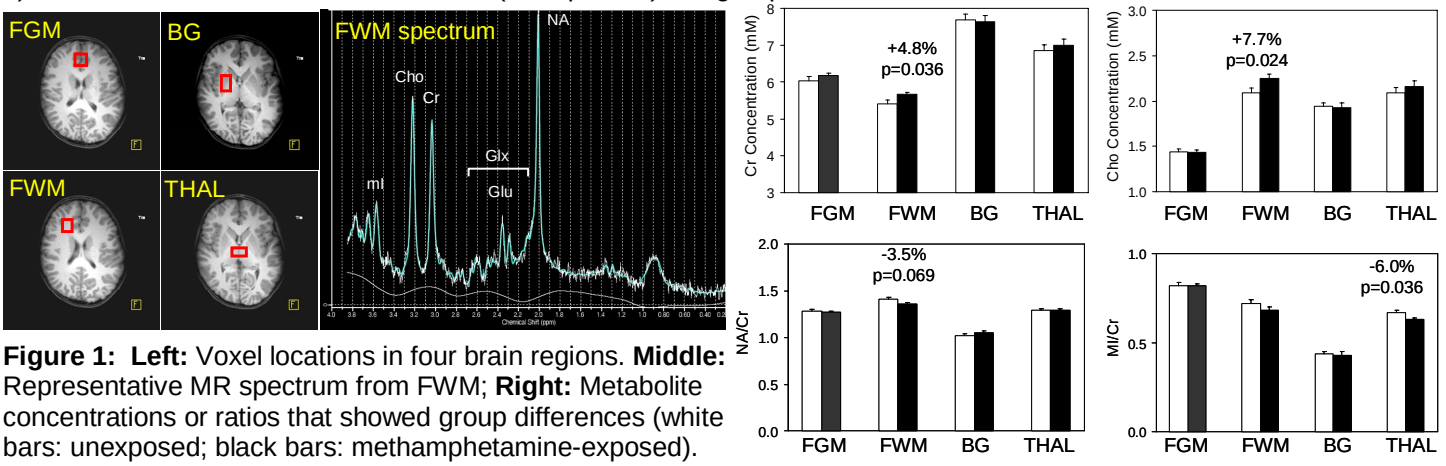

Figure 1: Left: Voxel locations in four brain regions. **Middle:** Representative MR spectrum from FWM; **Right:** Metabolite concentrations or ratios that showed group differences (white bars: unexposed; black bars: methamphetamine-exposed).

DISCUSSION: The prior report of elevated FWM creatine in children exposed to METH prenatally [8] is validated in a much larger group of young children with a narrow age range. The current study also showed elevated frontal white matter choline. Since both creatine and choline are higher in glia than in neurons, the findings suggest higher glial content. Unlike brain disorders in adults, however, the glial marker myoinositol is not elevated. Therefore, in utero exposure to METH may lead to alterations in glial development, although the global cognitive performance is unaffected. Longitudinal follow-up of these children with MRI, MRS and detailed neuropsychological evaluations will determine whether these brain metabolite abnormalities will persist and how they would impact specific aspects of cognition.

ACKNOWLEDGMENTS: Study supported by the NIH (1R01 DA21016; K24-DA16170; K02-DA16991; K01-DA21203; 5P20-RR11091; G12-RR003061). We also thank R. Yakupov, L. Girton, & H. Nakama for data collection, and Dr. C. Derauf for referring some subjects.

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