Brain Metabolite Changes in Infants Exposed in Utero to Methamphetamine and/or Nicotine

S. Buchthal[1], T. Ernst[2], L. M. Anderson[1], C. Cloak[1], R. Kitamura[1], and L. Chang[1]
[1]Medicine, University of Hawaii, Honolulu, HI, United States, [2]University of Hawaii

INTRODUCTION: Smaller subcortical brain volumes on MRI and elevated total creatine, assessed with brain MR spectroscopy (MRS), were observed in children with prenatal METH exposure, which suggest METH may alter brain development.[1,2] It is unclear whether these changes are related to postnatal environmental influences (e.g. maternal depression, malnutrition, etc.). Studying neonates may minimize these influences. In normal infant brain development, the metabolite NAA, a marker of neuronal function, increases with age. On the other hand, choline, a marker of cell membrane synthesis, creatine, a marker of energy metabolism, and myoinositol, a marker of glial cell function, all decrease with age.[3] Therefore, elevated brain creatine in a prior small study of prenatally METH-exposed children[2] may reflect abnormal brain development. A larger study at earlier ages is needed to further evaluate possible abnormalities in brain metabolite development in these children.

METHODS: A total of 26, full term infants (age at birth: 39±2 weeks) between the ages of 3 days and 3 months were enrolled (gestational age at first visit: 42.9±3.2 weeks). There were 13 unexposed and 13 infants with prenatal exposure to a stimulant–METH and/or nicotine. Exclusion criteria for the infants included: <35 weeks gestation, >1 week intensive care known TORCH infection, congenital heart disease or anomaly, chromosomal anomaly or gross structural abnormalities on MRI. Infants were also excluded if their mothers were <18 years, could not understand English, polydrug or alcohol use (>3 drinks/month). Localized ^{1}H MRS was performed on unsedated sleeping infants using a 3 Tesla Siemens Tim Trio MR scanner in five brain regions: medial frontal gray matter, right frontal white matter, right basal ganglia , medial thalamus , and left periatal along the developing motor track as identified by hyperintensity . In each region, the concentrations of Creatine (tCr), Glutamate (GLU), Choline (CHO), Myo-Inositol, N-Acetyl-Aspartate (NAA), and Glutamine+Glutamate (GLX) concentrations was measured using a standard Point RESolved Spectroscopy (PRESS) acquisition sequence (TR/TE=3000/30ms, 48 averages, 2.6 min per location). LCModel analysis in conjunction with voxel water T2 measurements allowed for determination of metabolite concentrations.[3,4]

RESULTS: High quality MR spectra were obtain from all infants, as shown by the representative frontal gray matter spectrum from a 1-month old infant is shown in Figure 1. A higher myoinositol concentration was observed in the motor tracks of the exposed compared to the unexposed infants (+21%, p<0.0001); no other group differences in brain metabolite concentrations were observed after adjusting for gestational age. All infants showed age-dependent increases for tCr, NAA and GLX in all regions, as well as age-related increase in CHO in the basal ganglia (r=0.68 , p= 0.017). However, stimulant-exposed infants showed a slower age-related increase in NAA than control infants (**Figure 2a**, ANCOVA interaction-p=0.02). Furthermore, stimulant-exposed infants had slower age–related decline in the myoinositol in the left motor track (ANCOVA interaction-p=0.06, **Figure 2b**).

Figure 1

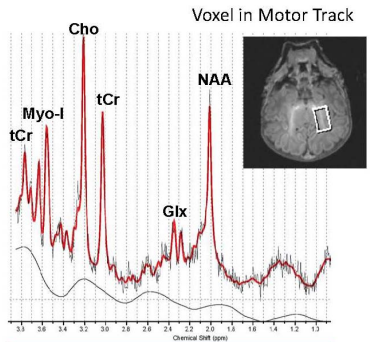
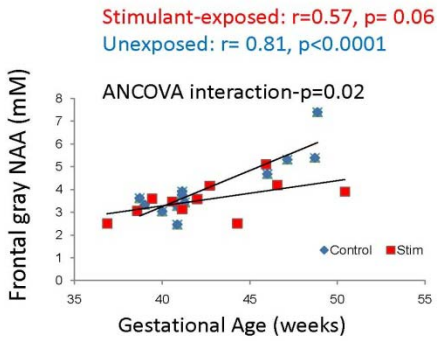
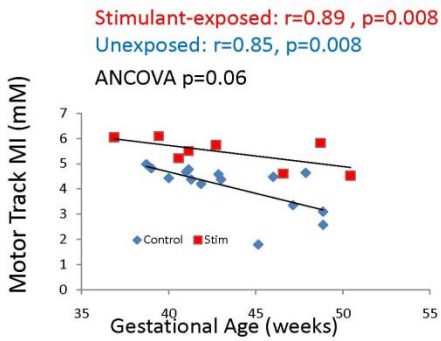


Figure 2a



2b



DISCUSSION: These stimulant-exposed infants showed abnormal age-dependent changes in NAA and myoinositol. While the unexposed infants showed a healthy age-related increase in NAA, indicative of neuronal maturation axonal growth, and synatpogenisis, the stimulant exposed subjects showed only a modest increase in NAA at this early months of age. Similarly, myoinositol decline with age in the unexposed infants, as is typical of brain maturation during the first year of life,[5] and likely reflects the decrease in astroglial developmental scaffolding. However, the stimulant-exposed infants show a less steep age-related decline in the glial marker myoinositol. Taken together these data suggest slower or abnormal brain development in infants exposed to stimulants in utero. Longitudinal studies are needed to evaluate whether these abnormalities will normalize with continued development in these infants.

References:

1) Chang L, et al. Psychiatry Res: Neuroimaging 2004; 95-106.;2) Smith L et a. Neurology 2001;255-260. 3) Ernst et al, J Magn Reson 1993;B102:1-8. 4) Kreis, R, et al. J Magn Reson 1993;B102:9-19. 5) Kreis R, et al MRM Magn Res Med 1993;30:424-437

ACKNOWLEDGMENTS: Supported by the National Institutes of Neurological Disorders and Strokes, and co-sponsors (1U54 NS056883-01, the National Institutes on Drug Abuse (1R01 K24 DA016170; K02DA016991) and the National Center for Research Resources G12RR003061-21 (RCMI) and 5P20 RR11091-10 (RCMI-CRC).