

Abnormal age-related changes in diffusion and anisotropy in the thalamus and genu suggest abnormal brain development in infants exposed to stimulants *in utero*

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INTRODUCTION: Children with prenatal methamphetamine (METH)-exposure have shown smaller subcortical brain volumes on MRI¹ and lower diffusion in the frontal white matter on diffusion tensor imaging (DTI)², which suggests METH-exposure may alter brain development. It is unclear whether these changes are related to postnatal environmental influences (e.g. maternal depression, malnutrition, etc.), and studying neonates may minimize these influences. This study aims to evaluate the effects of *in utero* stimulant-exposure (METH and nicotine) on brain white matter microstructures of newborns using DTI. In the white matter of normally developing infants, fractional anisotropy (FA) increases with age while mean diffusion, measured by the apparent diffusion coefficient (ADC), decreases with age³. This may be due to changes in the myelination (radial diffusivity) or axonal growth (axial diffusivity)⁴.

METHODS: Twenty full-term infants (birth age: 39 ± 1.7 weeks) were scanned between the ages of 3 days and <3 months (gestational age: 43.4 ± 3.9 weeks). Eleven infants were exposed to stimulants *in utero* (2 meth-and-nicotine-exposed, 9 nicotine-exposed (for 1.9 ± 0.9 trimesters), and 9 were non-drug exposed. Infants were studied at up to three time-points: one week, one month, or two months. All infants were imaged in 12 directions on the 3 Tesla Siemens TIM Trio scanner. An echo-planar DTI sequence was used with the following parameters: 128x128 resolution in plane, 4mm +1mm gap slices, 3700/88 TR/TE. Infants were asleep and were not sedated. DTI regions of interest were processed with DTIStudio; 14 brain regions were measured (**Figure 1**).

RESULTS: The two groups of infants had similar body length, body weight and head circumference, when these variables were adjusted by gestational age. The left and right hemispheres DTI measurements were not different and were averaged for further analyses. In all infants, normal developmental changes in white matter were observed. The fractional anisotropy values increased with gestational age in all regions of interest ($r > +0.50$, $p < 0.01$) except in the splenium of the corpus callosum, the caudate, and the putamen. The globus pallidus showed a trend toward a significant increase in FA values with age ($r = +0.34$, $p = 0.08$). In addition, ADC values decreased significantly in all regions with age ($r > -0.53$, $p < 0.01$) except for the splenium of the corpus callosum. Finally, the axial and radial diffusivity values decreased with age in all regions ($r > -0.59$, $p < 0.01$) except for axial values of the genu and splenium of the corpus callosum and the radial values of the splenium.

While normal developmental changes in white matter were observed in the two groups as whole, differences were observed between the two groups. A differential age-related increase in FA was observed in the thalamus (ANCOVA $p < 0.05$) with the non-stimulant exposed group showing age-related increases in FA ($r = +0.71$, $p < 0.05$) but not the stimulant exposed group ($r = +0.24$, $p = 0.41$; **Figure 2, left**). While both groups showed age-related declines in ADC in the thalamus, the slope of the decline was steeper (ANCOVA $p < 0.05$) in the non-stimulant ($r = -0.94$, $p < 0.001$) than in the stimulant exposed group ($r = -0.66$, $p < 0.05$) (**Figure 2, middle**). In addition, the radial diffusion in the thalamus also showed a steeper age-related decline in the non-exposed group (**Figure 2, right**). Lastly, age-related changes in axial diffusion in the genu of the corpus callosum showed a trend to decrease with age for the non-stimulant exposed group ($r = -0.50$, $p = 0.07$) but not for the stimulant exposed group ($r = +0.43$, $p = 0.12$; ANCOVA $p < 0.05$).

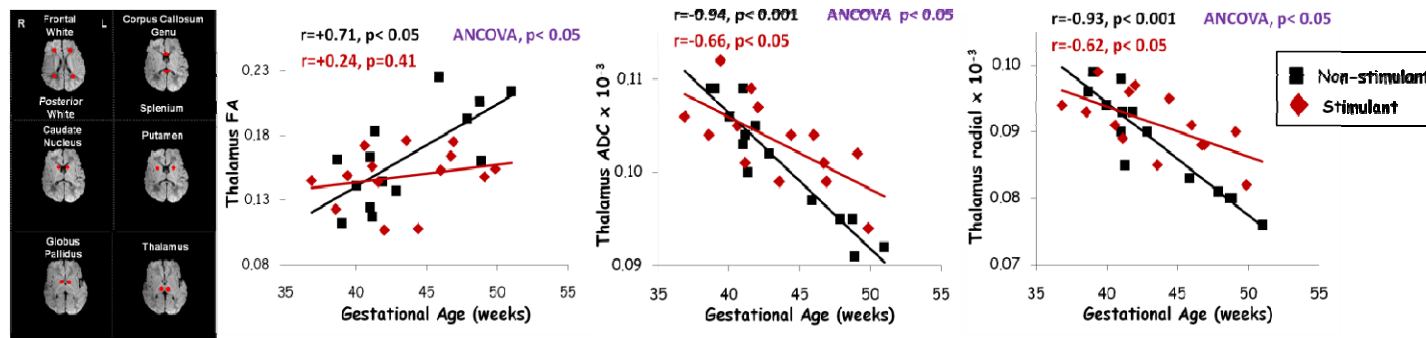


Figure 1: Bilateral regions of interest. **Figure 2: Left:** FA values for the thalamus by gestational age for each group. **Middle:** ADC values for the thalamus by gestational age for each group. **Right:** Radial values for the thalamus by gestational age for each group.

DISCUSSION: FA values increased with age while ADC, radial, and axial values decreased with age in both groups, which indicates that myelination is occurring in the white matter of these infants. Infants exposed to stimulants *in utero*, however, appear to have slower age-related axonal growth (without age-related increase in FA) and age-related myelination (decline in ADC and radial diffusion) in the thalamus than non-stimulant exposed infants. The lack of age-related decline in axial diffusion also suggests slower axonal growth in the genu. Longitudinal evaluations of these infants, as well as a larger sample size are needed to validate these preliminary observations. Further studies are also underway to determine whether prenatal METH-exposure (without concurrent exposure to nicotine) also alters brain development.

ACKNOWLEDGMENTS: Study supported by the NIH [1U54 NS056883 (Specialized Neuroscience Research Program), K24 DA016170; K02 DA016991 and the National Center for Research Resources G12RR003061-21 (RCMI) and 5P20 RR11091-10 (RCMI-CRC)].

REFERENCES: 1) Chang L et al., Psychiatry Res 2004;132(2):95-106, 2) Fujii L et al., 2008; Neurology; 70(S1):A5, 3) Dubois J et al., Neuroimage 2006; 30: 1121-1132, 4) Alexander A et al., Neurotherapeutics 2007; 4(3): 316-329.