Microstructural Brain Abnormalities in Neonates with Prenatal Stimulant Exposure

Linda Chang[1], Kenichi Oishi[2], Jon Skranes[3], Steve Buchthal[1], Caroline Jiang[1], Dan Alicata[4], Antonette Hernandez[1], Heather Johansen[1], Christine Cloak[1], Tricia Wright[5], Lillian Fujimoto[6], Susumu Mori[2], and Thomas Ernst[1]

[1]Dept of Medicine, University of Hawaii, Honolulu, Hawaii, United States, [2]Dept of Radiology, Johns Hopkins University, Baltimore, Maryland, United States, [3]Dept of Laboratory Medicine, Children's & Women's Health, Norwegian University of Science and Technology, Tronheim, Oslo, Norway, [4]Dept of Psychiatry, University of Hawaii, Honolulu, Hawaii, United States, [5]Dept of Obstetric & Gynecology, University of Hawaii, Honolulu, Hawaii, United States, [6]Straub Mililani Clinic, Mililani, Hawaii, United States

INTRODUCTION: Prenatal stimulant exposure with nicotine (NIC) and methamphetamine (METH) may be associated with abnormal brain development,[1] although imaging data in humans are limited.[2-5] This study aims to evaluate whether microscopic brain structures assessed with DTI are altered in neonates with prenatal exposure to NIC or METH+NIC, whose brains would have less environmental influences compared to those of older children studied in the past.

METHODS: 63 healthy term-born neonates [45 unexposed to drugs (age: 18.5±2.5 days, postconceptional age: 41.8±0.4 weeks, 16 boys and 29 girls) and 18 stimulant-exposed (13 NIC, 5 METH+NIC, ages: 23.2±5.8 days, post-conceptional age: 42.3±0.9 weeks, 12 boys and 6 girls)] were studied with DTI. Each infant was evaluated clinically with the Amiel-Tison neurological assessment[6] to ensure normal neurological development. DTI was performed at 3T (Siemens TIM Trio) in these unsedated infants [12 diffusion directions, 28 slices, 2.0 or 2.5 mm, 0.46 mm gap, TR/TE=3700/88ms, 128x128 matrix, b=[0,1000s/mm^2]. An automated atlas-based technique with large deformation diffeomorphic metric mapping (LDDMM) was performed using MRIStudio[7,8] (**Fig 1**). Fractional anisotropy (FA), radial, axial and mean diffusivity (ADC) were calculated for 25 ROIs (major white matter tracts and subcortical gray matter). ANCOVAs were performed on the DTI measures to compare group effects, co-varied for postconceptional age at time of scan and matrix size.

Figure 1. Automated Atlas-Based DTI Analyses

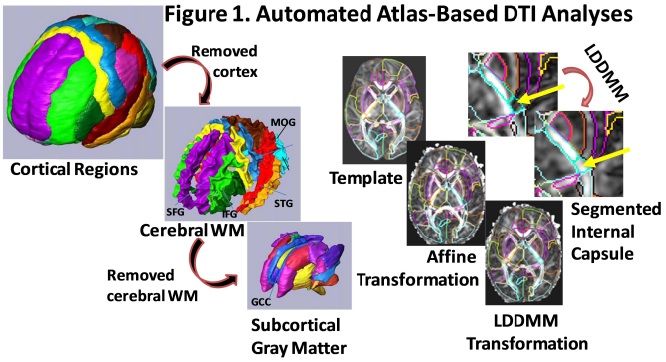
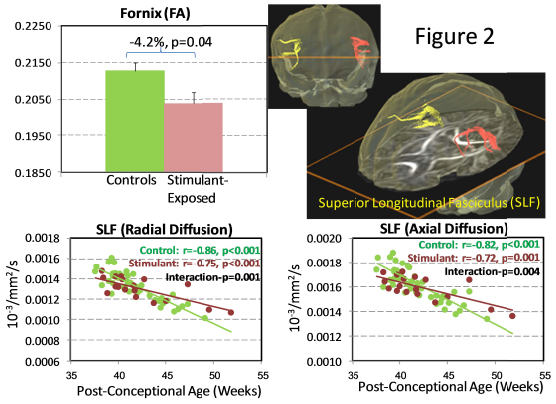


Figure 2



RESULTS: Clinical: Mothers using NIC or METH+NIC during pregnancy were slightly younger (stimulant: 27.9±1.1 vs. control: 31.0±0.9 years, p=0.06), had lower education (12.8±0.3 vs. 14.1±0.4 years, p=0.04), more depressive symptoms (Beck Depression Inventory: 11.3±2.0 vs. 6.0±0.9, p=0.01), and poorer socioeconomic status (Index of Social Position: 52.2±5.2 vs. 40.2±2.8, p=0.05) compared to the control mothers. Stimulant mothers smoked 984±444 nicotine cigarettes during their pregnancies, while those who additionally smoked METH used 22.1±9.6 grams, primarily during the first two trimesters. The two neonatal groups were born at similar gestational age (39.0±0.3 vs. 39.2±0.2 weeks), and hence had similar birth weight (3.2±0.1 vs 3.4±0.1 kilograms) but the stimulant exposed neonates were shorter at birth (49.4±0.7 vs. 51.2±0.3 cm, p=0.01). However, the two neonatal groups had similar head circumference, body length (51.7±1.0 vs. 52.9±0.5 cm, p=0.24) and weight (3.9±0.1 vs. 4.0±0.1 kilograms, p=0.56) at the time of their MR scans.

DTI: The stimulant-exposed infants had lower FA in the Fornix (-4.2%. p=0.04, **Fig 2, top left**) and a trend for lower FA in the thalamus. Additionally, stimulant-exposed neonates showed less steep age-related decline in both radial and axial directions of the Superior Longitudinal Fasciculus (SLF) compared to unexposed neonates (interaction-p=0.001 and 0.004, **Fig 2, bottom graphs).**

DISCUSSION: Lower FA and less steep age-related decline of brain diffusion in the stimulant exposed neonates suggest slower brain development. FA typically increases with age and brain diffusion rapidly declines with age during early weeks of life due to myelination and brain growth.[9,10] The apparent delay in myelination along the SLF, indicated by the less steep age-related decline in radial diffusion, and is consistent with the lower glial metabolites seen in young children with prenatal nicotine exposure[5] or the reduced myelin in the optic nerves of rats treated with METH prenatally.[11] Lower FA in the fornix also suggests less axonal fiber coherence. These microstructural differences were found despite the well-matched subject characteristics between the two groups at time of scans. Ongoing data collection including longitudinal assessments will provide further validation.

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