

Brain Chemical Concentrations in Autism Spectrum Disorder at 6, 12 and 24 Months as Measured with Magnetic Resonance Spectroscopic Imaging

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INTRODUCTION

The first two years of life constitute the most dynamic phase of post-natal brain development. There is evidence for a temporal link between abnormal brain development in autism spectrum disorder (ASD) and onset of behavioral symptoms during this time period. Behavioral features of ASD are typically present by 12-18 months of age in most children that are subsequently diagnosed with ASD at 2-3 years of age.^{1,2} Head circumference studies of children subsequently diagnosed with ASD suggest normal head size at birth but an accelerated trajectory for head growth compared to typically developing children between 6 and 12 to 18 months of age.^{3,4,5} This enlargement is consistent with MRI studies of children with ASD at 2-5 years of age which report enlarged cerebral volumes.^{3,4,6} However, relatively little is known from structural imaging about the mechanisms that underlie this enlargement. Characterization of the longitudinal pattern of brain chemical changes across brain regions and within tissue types during this crucial stage in early development can provide insight into developmental mechanisms underlying early cerebral enlargement in ASD and may help to elucidate a possible connection between these early brain abnormalities and the emergence of behavioral symptoms. Acquired as part of a multi-site brain imaging consortium Infant Brain Imaging Study (IBIS <http://www.ibisnetwork.org>), we present brain chemical findings from high-resolution 3-D MR spectroscopic imaging of infants at a high genetic risk for developing ASD (HR) scanned at three age-points during this crucial period of brain development. Results are compared to those of infants at lower risk for developing ASD (LR), with no family history of ASD in first or second degree relatives.

METHODS

HR infants and LR infants were scanned at 6, 12 and 24 months. MRI and 3-D MRSI data were acquired for 137 infants (out of 167 total attempts) comprising 62 6mo infants (29HR/33LR), 48 12mo infants (31HR/17LR), and 27 24mo (19HR/8LR). All data were acquired without sedation on sleeping infants. Studies were conducted on a Siemens 3T TIMS Trio scanner using a 12-channel RF head coil. Sagittal 3D T1 MPRAGE and 3-D T2 FSE images were acquired and co-registered with chemical images for partial volume correction and characterization of gray and white matter. Water-suppressed 3D PEPSI metabolite data at two echo times were acquired (TR: 2s; TE: 11/136ms; FOV=256x256x56; 32x32x8 matrix, 8 slabs, slab thickness: 42mm; scan time 4min 50sec), with slabs centered on the midline and extending from below the ACC to above the ventricles. Outer volume saturation bands were used to minimize lipid signal from the scalp. Non-suppressed water 3D PEPSI data (TR:630ms; TE:11ms; FOV=220mm; 32x32x8 matrix; scan time 1min 56sec) were acquired for chemical quantification. A processing pipeline⁷ that utilized all usable acquired spectra along with spectral fitting with LCModel was used to calculate cerebral NAA, choline (Cho), creatine (Cre), myo-inositol (mIns), glutamate (Glu) and Glx concentrations for the entire acquisition volume as well as for the gray matter compartment. Figure 1 shows a characteristic spectrum from the 3D PEPSI acquisition.

RESULTS

Preliminary gray matter findings for data analyzed to date (7HR/8 LR at 6mo, 9HR/6LR at 12mo, 11HR/4LR at 24mo), illustrated in Figure 2, show a relative decrease or no change in NAA levels between 6 and 24 months for the HR group, whereas the LR group shows a steady increase in NAA for that same age period. Cho and Cre show proportionate decreases for both groups over the 6 to 24 month age range. Cross-sectionally, the HR infants show non-significant elevations in NAA at 6 months compared to the LR infants. Thereafter, the HR infants demonstrate lower NAA levels compared to the LR infants at 12 and 24 months.

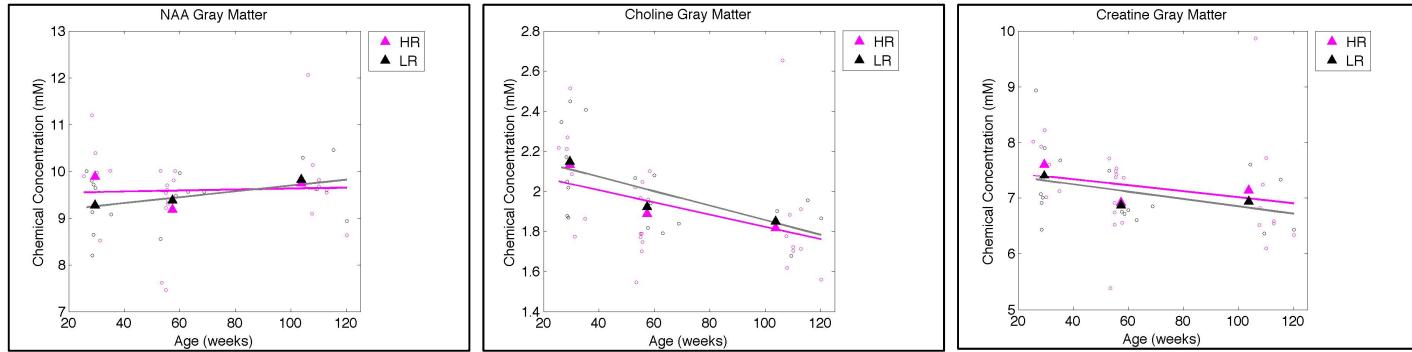


Figure 2. NAA, Cho and Cre concentrations for the gray matter compartment at 6, 12 and 24 months of age, with linear regression fit, for the HR (purple) and LR (black) groups.

CONCLUSIONS

These preliminary findings suggest elevations in gray matter NAA at 6 months for children in the HR group as compared to the LR group. They also suggest a reduction in gray matter NAA between 6 and 12 months in the HR group, whereas gray matter NAA increases in the LR group over this time interval. Choline and creatine decrease for both groups across this time interval. Findings from additional study subjects will also be presented. These results are consistent with our earlier work in 3-4 yo children with ASD^{8,9} who exhibited prolonged chemical T2, interpreted to reflect reduced neuronal cell density at this age.

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