

## Longitudinal evaluation of lactate in children with autism disorder using MR spectroscopic imaging

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**Purpose:** Autism is a clinically-defined developmental disorder with unknown origin that manifests in early childhood. Recently, cerebral mitochondrial dysfunction has been suggested as a possible etiologic factor<sup>1</sup>. Although mitochondrial disorders can be difficult to diagnose, abnormal elevation of cerebral lactate as measured with MR spectroscopy has been suggested as the gold standard biomarker for subtle mitochondrial dysfunction in the brain. Brain lactate, however, can be challenging to measure, as it is present in relatively small quantities and shares a chemical shift frequency with lipids and other macromolecules that are abundant in the scalp and can bleed into the imaging volume. We have developed an improvement in magnetic spectroscopic imaging (MRSI) data analysis that provides increased accuracy in measurement of metabolite levels than conventional techniques by averaging high quality spectra in the fourier domain prior to evaluating chemical concentrations. In unpublished work [ISMRM 2009 abstract submission] this method is demonstrated to significantly decrease the Cramer-Rao bounds for chemical estimation and is especially useful for providing more accurate measurement of metabolites at low concentrations in the brain, such as lactate. The aim of this study is to use this analytic method to characterize cerebral lactate levels of children with autism disorder and age-matched typically developing children at three different age points (3-4, 6-7 and 9-10 years of age) to determine whether there is any evidence of mitochondrial disorder in autism during these periods of childhood development.

**Methods:** Structural and MRSI data were collected on a 1.5T Signa Horizon GE scanner for 29 children diagnosed with autism disorder (AD) and 10 typically developing (TD) children that were part of a larger study to longitudinally evaluate brain chemistry at 3-4, 6-7, and 9-10 years of age. The AD children were sedated with propofol due to clinical status. High-resolution axial proton density and T2-weighted images covering the whole brain were acquired for all subjects, with TE=13/91 ms, TR=2000 ms, FOV=22 cm, matrix=256x160, and 2.5 mm slice thickness. A proton echo-planar spectroscopic imaging (PEPSI) sequence with standard parameters (TR 2,000 msec, 32 X 32 spatial matrix, nominal voxel size 1 cm<sup>3</sup>, 22 cm FOV, 20 mm slice thickness) was acquired from axial sections through the basal ganglia and the temporal lobes. The T2 weighted images were segmented using a k-means algorithm to produce volumes representing grey matter, white matter and cerebral spinal fluid. Spectra were reconstructed with software developed in the laboratory and shifted and phased corrected using LCModel. An automated algorithm was used to identify and remove spectra that were of poor quality, mostly due to scalp lipid signal bleed into the PEPSI volume or susceptibility artifacts. The spectroscopy data were then averaged across the entire slab for each subject. Lactate and NAA levels were calculated by integrating the areas under the respective peaks of the average spectra, and the ratio of Lactate/NAA for each child was calculated.

**Results:** Lac/NAA was not found to be elevated in the AD group as compared to the TD group at 3-4 years of age. On the contrary, the TD lactate levels were found to be higher in both gray and white matter than in the AD group, with gray matter lactate differences more significant (P=0.131) than white matter (P=0.187) at the trend level, as evaluated with a two-tailed t-test.

**Conclusion:** This work follows up and extends longitudinally prior work by our group that reported a similar finding, which also found not elevation of lactate in children with autism in the 3-4 year age range. The results for the 3-4 year old age range indicate that brain lactate is not elevated in children with autism at this age. These findings, coupled with our previous work, does not support a mitochondrial defect in the brain of children with autism at 3-4 years of age. Longitudinal findings from the children at 6-7 and 9-10 years of age will additionally be presented

<sup>1</sup> [http://www.ninds.nih.gov/news\\_and\\_events/proceedings/20090629\\_mitochondrial.htm](http://www.ninds.nih.gov/news_and_events/proceedings/20090629_mitochondrial.htm)

<sup>2</sup> Friedman, et al. Regional brain chemical alterations in young children with autism spectrum disorder. *Neurology* 2003; 60; 100-107