Regional Brain Alterations in Children with Prenatal Alcohol Exposure: A Preliminary 3D Multi-Voxel ^{31}P Spectroscopy Study at 4 Tesla

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Introduction: Maternal alcohol consumption during pregnancy can harm the fetus, particularly the vulnerable central nervous system, making prenatal alcohol exposure (PAE) a leading cause of mental retardation and developmental disorders that include deficits in behavior and cognition, especially focused attention, arithmetic and working memory problems in children. Despite well-documented risk for Fetal Alcohol Spectrum Disorders (FASDs) like Fetal Alcohol Syndrome (FAS), and an estimated incidence of the various FASDs in the United States at about 0.9% of live births, PAE continues to be a widespread public health concern. Identification of reliable neural and behavioral effects characteristic of PAE remain important areas of study for diagnosis and for determining effective treatments for FASDs.

In vivo phosphorus (^{31}P) spectroscopy may assist in profiling neurodevelopmental alterations in FASDs by measuring neurochemicals that are part of the metabolic pathways of membrane phospholipids (MPLs), including precursors (e.g., phosphoethanolamine [PE] & phosphocholine [PC]) and breakdown products (e.g., glycerophosphoethanolamine [GPE] & and glycerophosphocholine [GPC]). MPL precursor level measurements have been shown to be sensitive to critical early neurodevelopmental changes involving synapse formation on dendritic spines and shafts, and on cell bodies. We hypothesized that PAE would be associated with greater alterations in the synthesis activity of MPLs, reflecting underdevelopment in brain areas associated with focused attention, arithmetic and working memory, specifically, dorsolateral prefrontal cortex (DLPFC), striatum, thalamus and parietal regions.

Methods: Twenty African American children (11 PAE, 5 females and 6 males, 6.7±0.6 mean age, 6.0-7.6 age range; 9 non-PAE, 6 females and 3 males, 7.0±0.7 mean age, 6.0-8.0 age range) who are part of a larger ongoing study of children born to inner-city mothers investigating interactive effects of gestational nutrition and prenatal alcohol exposure on child development, participated in this study.

A 3D whole-brain, multi-voxel ^{31}P spectroscopy measurement was collected in each subject on a 4-Tesla Bruker MedSpec scanner using a dual-tuned ^{31}P-^{1}H head coil (Bruker BioSpin MRI Inc.). An 80-cm thick axial slab was placed parallel to the AC-PC line to cover the whole-brain. The acquisition parameters of the ^{31}P spectroscopy included: FOV= 280x280x160mm, phase encoding steps= 14x14x8, zero-filled to 16x16x8 (nominal voxel dimension= 1.75x1.75x2.0cm^3 and estimated effective voxel size= 12.2cm^3), TR= 0.54sec, flip-angle= 33^0, complex data points= 2,048, spectral bandwidth= 4.0kHz, 24 averages (weighted-average and elliptical k-space sampling, pre-acquisition delay time of 1.4ms and acquisition time 23 minutes. For each bilateral region of interest (DLPFC, striatum, thalamus and parietal), the 16x16x8 grid was shifted in all three directions relative to the MRI images accordingly to ensure optimal voxel placements using 3DiCSI (Hatch MR Research Center, Columbia University). The MR signals of those voxels were then extracted, apodized (5Hz Gaussian), and modeled in the time domain with 15 Gaussian-damped sinusoids [i.e., PE, PC, Pi, GPE, GPC, *broad*-PDE, phosphocreatine (PCr), dinucleotides (DN) and ATP (two doublets and a triplet)]. A generalized linear regression model (PROC GENMOD; SAS Institute Inc.) with subject group, gender and side (right vs. left side) as the main effects, was used as well as with additional terms for group-by-side and group-by-age interactions.

Results: Levels of PE were significantly lower bilaterally in the thalamus of PAE children compared to non-PAE children (p=0.0095). PE levels were higher in the right parietal region of PAE children compared to non-PAE children (main term: p=0.012; *post-hoc*: p=0.034). The group-by-age interaction was also significant in the right parietal region for PE (p=0.029), with non-PAE (r=-0.84, p=0.0090) but not PAE subjects (r=-0.09, =0.80) showing decreasing PE levels with age. There were other age-by-group interactions for both GPC and β-ATP in the DLPFC and striatum (p<0.045) with greater contrasts occurring in the older subjects. Specifically, in non-PAE subjects GPC decreased significantly with age and β-ATP increased significantly with age in both the DLPFC and striatum (p<0.038), but these relations were all not significant in PAE children. There were no significant groups differences in PC, GPE, PCr or DN levels in any of the 4 brain regions.

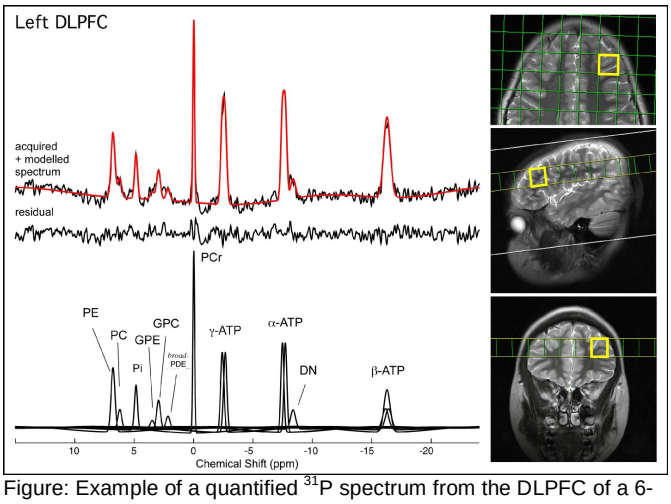

Figure: Example of a quantified ^{31}P spectrum from the DLPFC of a 6-year child. A 5 Hz Gaussian filter was applied.

Discussion and Conclusion: The lower MPL precursor levels in the thalamus of PAE children suggest an underdevelopment of dendritic branching and/or synaptic formation. Also, though based on cross-sectional data, the lack of both decreasing levels of MPL breakdown products and increasing levels of high-energy phosphate ATP with age in the DLPFC and striatum, and the lack of decreasing levels of MPL precursors in the right parietal region of PAE children compared to non-PAE children, suggests an absence of the normal progressive neurodevelopmental changes in brain regions that play a role in attention, motor behavior and working memory. In all, these alterations suggest that maternal alcohol consumption during pregnancy may alter the time course of developmental changes from that seen in healthy children.

Continuing study with increased sample size will help clarify the effects of PAE on MPL and high-energy phosphate metabolism, as well as potential impact on other brain regions.

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