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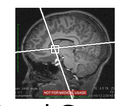
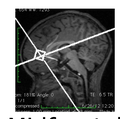
Effects of HIV exposure on MRS metabolite levels in children: at 5 and 7 years

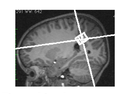
Study

Single voxel ^{1}H-MRS (SVS) data were acquired in twenty-five 5-year old (16 Xhosa and 9 Cape Coloured; 16 HIV-exposed and 9 HIV-unexposed) and twenty-three 7-year old children (16 Xhosa and 7 Cape Coloured; 12 HIV-exposed and 11 HIV-unexposed) on a Siemens 3T Allegra Head Scanner (Siemens, Erlangen, Germany) in Cape Town, South Africa. Eleven children were imaged at both ages. MRS data were acquired using a real-time motion and B_0 corrected [1] point resolved spectroscopy (PRESS) sequence (TR 2000 ms, TE 30 ms, 64 averages, Scan Time: 2.16 min).

We collected spectra in the left peritrigonal white matter (PWM), midfrontal gray matter (MFGM) and basal ganglia (BG). Water reference scans were acquired in each voxel for eddy current compensation, frequency/phase correction, and to compute absolute metabolite levels (AMLs). Spectra were analysed using the linear combination model software LCModel, exclusion criteria included FWHM > 0.075 ppm, SNR < 7 and LCModel standard deviation > 20%. R was used for all statistical analyses. For regions where we expected to see a metabolite level increase/decrease with age, a mixed effect linear regression model was used to account for repeated measures for some children.


Basal Ganglia


Midfrontal gray matter


Peritrigonal white matter

Background

Successful programs preventing mother to child HIV transmission have created a new population of HIV-exposed, uninfected children. These children have an increased risk of mortality, morbidity, slower early growth [2,3] and neurological symptoms such as cognitive delay, behavioral disorders, and motor abnormalities[4,5]. Exposure to antiretroviral (ARV) drugs and environmental factors may account for the increased risk [2].

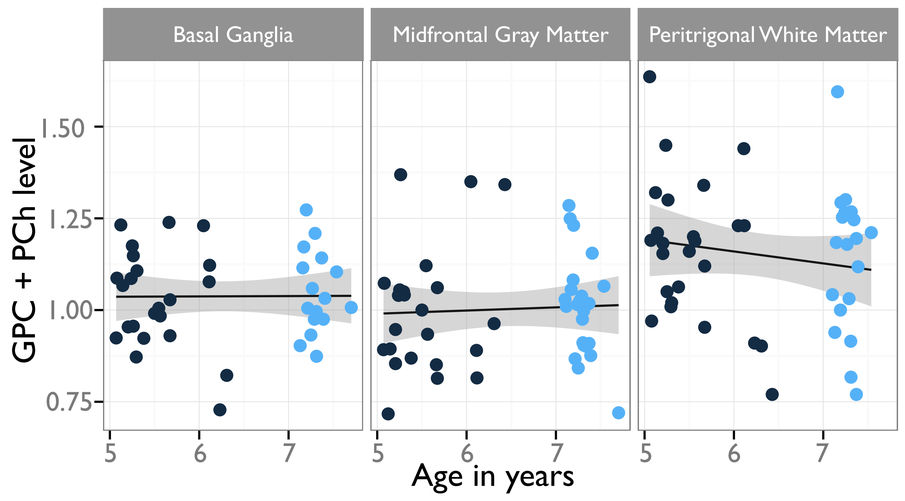
MR spectroscopy (MRS) is used for the non-invasive investigation of neurological development in children. Many childhood neurological processes are accompanied by metabolite changes that sometimes correlate with demographic variables such as age and neuropsychological measures throughout childhood [6,7,8,9]. Few studies have examined metabolite levels through childhood among healthy children. NAA is associated with neurogenesis and increases with age; the steepest rate of increase is observed in gray matter in early childhood [9]. Choline is highest among infants, and remains relatively constant throughout childhood; however, the choline concentration in white matter among older children (age 5 - 18) is about 15% lower than that of infants and younger children (age 0 - 5 years) [9].

Our goal was to investigate the relationship between age and metabolite level in healthy children at ages 5 and 7, focussed on the possible effects of HIV-exposure.

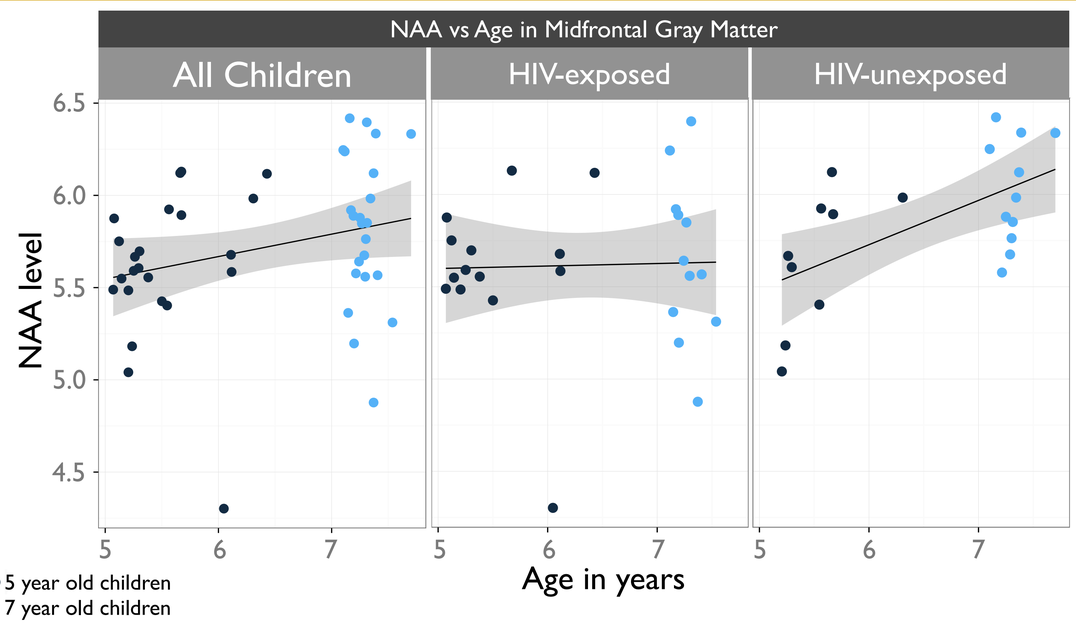
Hypothesis - From age 5 to age 7 we expect to observe an increase in NAA levels in gray matter and constant choline levels in all regions. We do not expect HIV-exposure to affect these changes with time.

Results

1. Constant choline levels in all three regions. Small negative slope in Peritrigonal White Matter (PWM).



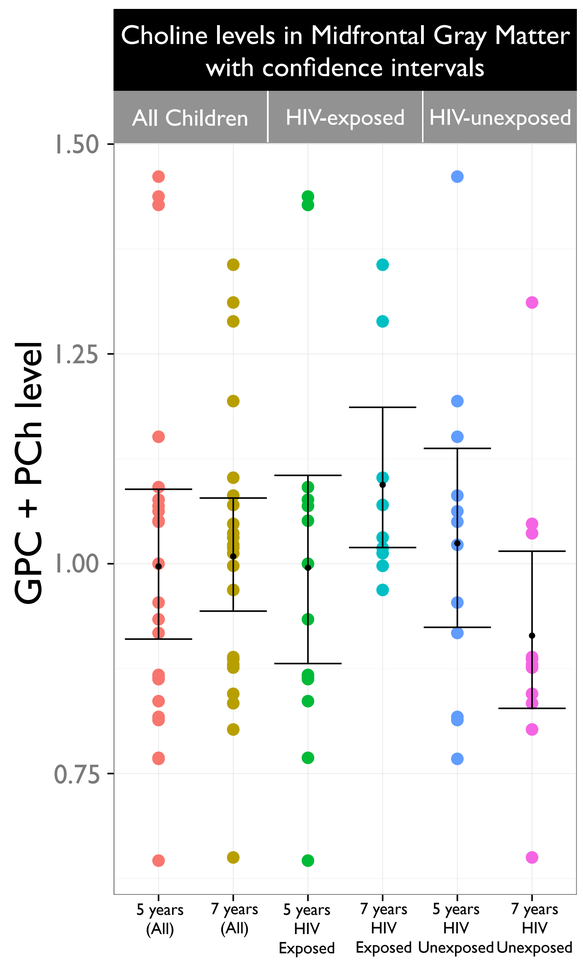
2. We found a significant increase in NAA with age in Midfrontal Gray Matter (MFGM) (p = 0.01) - driven by HIV-unexposed children.

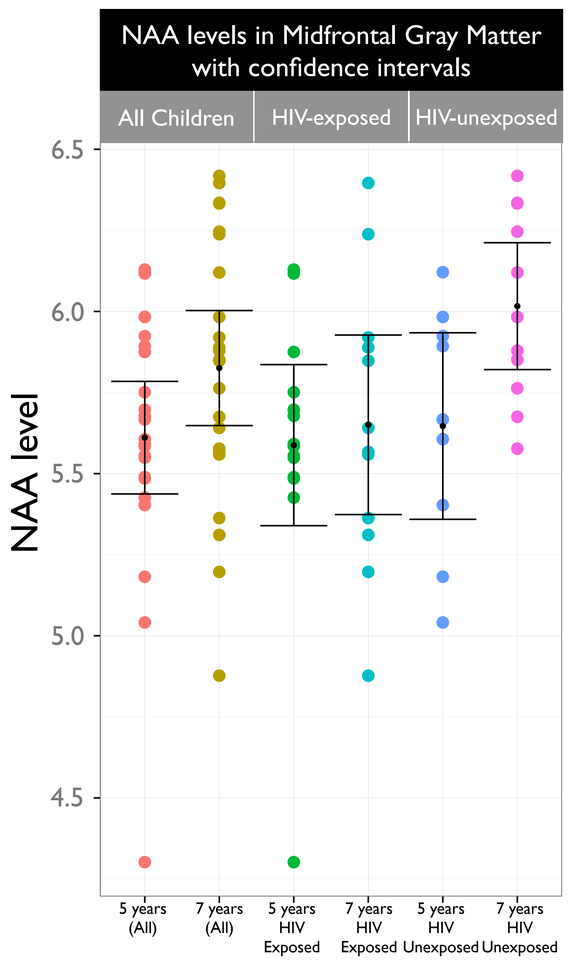


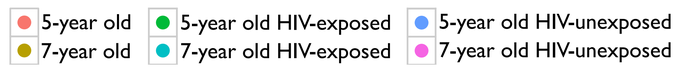
3. At 7 years, HIV exposure significantly affects mean value of NAA and Choline in the MFGM.

HIV-exposed children have significantly HIGHER choline levels at 7 years (*t-test: exposed vs unexposed - p = 0.009*).

HIV-exposed children have significantly LOWER NAA levels at 7 years (*t-test: exposed vs unexposed - p = 0.03*).







Interpretation

A detailed understanding of the normal age-dependent neurological metabolite changes is critical to interpreting MRS results across pediatric populations. The average NAA value at 7 years is higher than at 5 years in all three regions. The increase is significant only in the MFGM (slope = 0.16, p = 0.01), and may be due to an increase in neuron populations and increased synaptic connections with age [8]. HIV-exposure alters the relationship between age and NAA in the MFGM: we find NAA increases with age among HIV-unexposed children (slope = 0.23, p = 0.01), but the metabolite level increase with age disappears (slope = 0.07, p = 0.4) among the HIV-exposed group. In addition, the HIV-exposed children have significantly lower NAA levels at 7 years than HIV-unexposed children. The reduced NAA growth, as well as the lower NAA level at 7 years, suggests a possible long-term effect of HIV exposure/ARV treatment on neuron populations, axons, dendrites and synaptic terminals in gray matter.

The observed constant choline levels in the BG and MFGM, as well as the small decline in the PWM, are consistent with previous MRS studies of healthy children [6,8]. Our finding of significantly higher choline among HIV-exposed children at 7 years in the MFGM implies a possible effect of HIV exposure. Increased choline levels imply glial proliferation/inflammation in the MFGM, since glial cells have higher choline levels than neurons; increased choline levels are reported in the MFGM in HIV-infected children [7].

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Acknowledgements

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