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Effects of HIV exposure on metabolite levels in midfrontal gray matter in children: at 5 and 7 years

P_45

Introduction

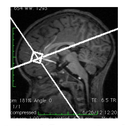
Magnetic resonance spectroscopy (MRS) is a non-invasive neuroimaging technique used to investigate neurological development in children. Many childhood neurological processes include metabolite changes that may correlate with age [1,2]. This study is motivated by the burgeoning population of HIV-exposed, uninfected (HEU) children in South Africa - 95% of HIV-positive pregnant women and 68% of HIV-exposed infants have been receiving antiretroviral therapy (ART) [3,4] - and evidence suggesting possible long-term neurological effects in HEU children, such as an increased risk of cognitive delay and motor abnormalities [5-8]. The increased risks may involve exposure to HIV antibodies, antiretroviral (ARV) drugs and environmental factors [9].

MRS measures metabolite levels in a small region of interest in the brain. Our study focused on two metabolites - NAA (N-acetylaspartate) and choline (glycerophosphocholine (GPC) + phosphorylcholine (PCh)). NAA is associated with neuronal density and integrity, and increases with age in childhood [1,2]. Choline is related to cellular density and glial integrity, and remains constant throughout childhood [2].

We investigate the possible effects of HIV exposure on metabolite levels in midfrontal gray matter in healthy children at ages 5 and 7.

Study

Single voxel spectroscopy ^{1}H-MRS data were acquired in the midfrontal gray matter (MFGM) in twenty-one 5-year old (median age (age range): 5 years 4 months (5 years 1 month - 6 years 5 months); 15 Xhosa/6 Cape Coloured; 13 HEU/8 HIV-unexposed, uninfected (HUU)) and thirty-one 7-year old children (7 years 3 months (7 years - 7 years 8 months); 24 Xhosa/7 Cape Coloured; 9 HEU/22 HUU) on a Siemens 3T Scanner (Siemens, Erlangen, Germany) in Cape Town, South Africa. Nine children imaged at both ages.

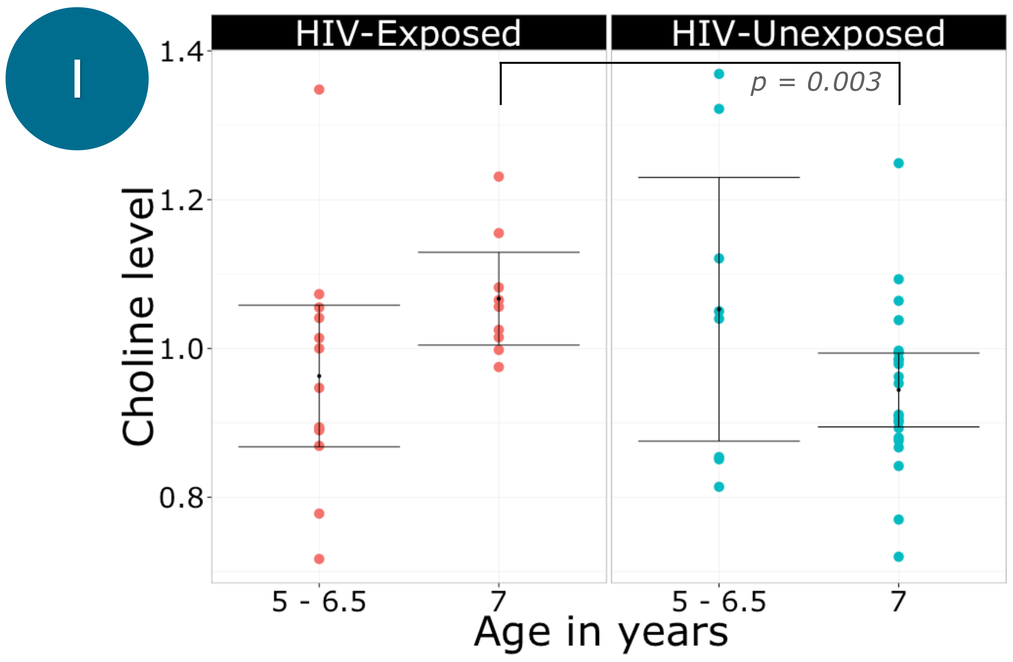

Midfrontal gray matter

HEU children were exposed to treatment for prevention of mother-to-child transmission, mostly zidovudine antenatally from 28 to 34 weeks and single dose nevirapine (sd NVP) to the mother and zidovudine for a week and a sd NVP to the infant.

Absolute metabolite levels calculated with LCModel. R was used for statistical analysis. A mixed effect linear regression model was used for repeated measures.

Results

1

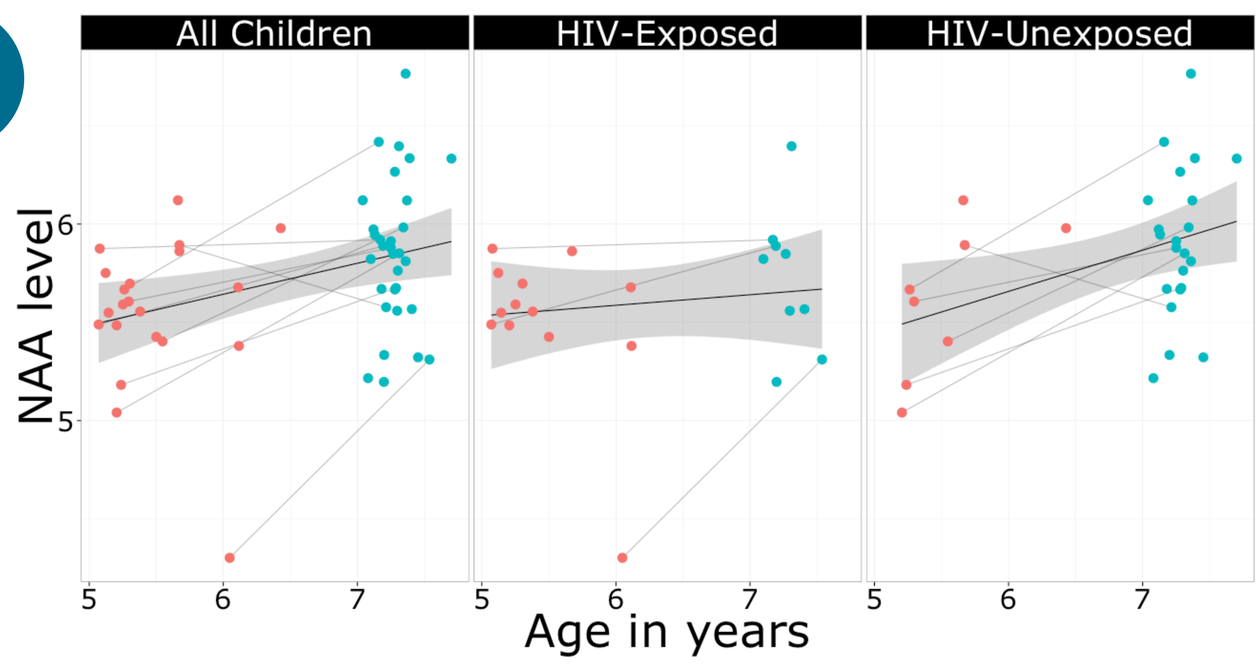


HEU children have HIGHER mean choline levels at age 7

Result: HEU children have HIGHER choline levels at 7 years compared to HUU children (*t-test at age 7: HEU vs HUU - p = 0.003)*. Bars represent 95% confidence intervals.

Interpretation: The higher mean choline level at age 7 in HEU children (compared to HUU children) suggests a developmental difference among HEU children at age 7. Increased choline levels may imply glial proliferation/ inflammation or increased cellular density.

2



Mean NAA levels increase from age 5 to 7 in HUU children *only*

Result: We found an increase in NAA with age - from age 5 to 7 (slope = 0.15; p = 0.02) across all children. The relationship is driven by HIV-unexposed children (slope = 0.21, p = 0.02). Gray lines connect repeated measurements.

Interpretation: The increased NAA levels may be due to increased neuronal populations and synaptic connections with age [1]. The increase is driven by HUU children; NAA increases with age among HUU children, however the metabolite level increase with age disappears (slope = 0.05, p = 0.5) in HEU children. The lack of age related NAA growth suggests a long-term effect of HIV exposure and/or ARV treatment on neuron populations, axons, dendrites and synaptic terminals.

Summary

1. In the MFGM, we observe higher choline levels in HEU children *only* at age 7.
2. In the MFGM, we observe increasing NAA levels across all children from age 5 to 7, *driven* by HUU children.

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