Effects of HIV exposure and gender on VMI scores and neurometabolite levels at 5 and 7 years

Study
Neuropsychological testing was performed and single voxel 1H-MRS (SVS) data were acquired in the midfrontal gray matter (MFGM) and the peritrigonal white matter (PWM) on a Siemens 3T Allegra Head Scanner (Siemens, Erlangen, Germany) in Cape Town, South Africa on a cohort of HIV uninfected children (HUU) at ages 5 and 7. MRS data were acquired with a real-time motion and B0 corrected [1] point resolved spectroscopy (PRESS) sequence (TR 2000 ms, TE 30 ms, 64 averages, Scan Time: 2:16 min). Water reference scans were acquired for eddy current compensation, frequency/phase correction, and to compute absolute metabolite levels. Spectra were analysed with LCModel. Statistical analyses performed in R. A mixed effect linear regression model was used to account for repeated measures.

Subjects: We obtained both neuropsychological and MRS data in the MFGM on nineteen 5-year old (10 female; mean age ± standard deviation = 5.4 ± 0.4 years; 13 Xhosa/6 Cape Coloured; 12 HEU/7 HUU) and twenty-five 7-year old children (8 female; 7.3 ± 0.1 years; 18 Xhosa/7 Cape Coloured; 8 HEU/17 HUU), with eleven children imaged at both ages. In the PWM on twenty-three 5-year old (11 female; 5.5 ± 0.4 years; 14 Xhosa/9 Cape Coloured; 14 HEU/9 HUU) and twenty-eight 7-year old children (9 female; 7.3 ± 0.1 years; 22 Xhosa/6 Cape Coloured; 10 HEU/18 HUU), with ten children imaged at both ages. All HEU children were exposed to treatment for prevention of mother-to-child transmission (PMTCT).

Background
In South Africa, 95% of HIV-positive pregnant women and 68% of HIV-exposed infants have been receiving antiretroviral therapy (ART) [2,3]. Several studies [4,5,6,7] suggest that ART exposure is associated with long-term neurological effects - such as cognitive delay and motor abnormalities - motivating additional study of HIV-exposed uninfected (HEU) children. The increased risks may involve exposure to HIV antibodies, antiretroviral (ARV) drugs and environmental factors [8].

MR spectroscopy (MRS) is used for the non-invasive investigation of neurological development in children. Choline is associated with cellular density [9]. Creatine is related to energy metabolism, and found in neurons and glia [9]. Both metabolites remain constant in childhood [10]. Metabolite levels often correlate with neuropsychological measures [10,11]. The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) provides a measure of the ability to integrate visual perception and motor abilities [12].

We explored perinatal HIV exposure and gender effects on the relationship between metabolite levels and VMI measures over a 2-year period in children.

Results

1. Girls have HIGHER mean VMI scores at age 7

![Graph showing VMI scores by gender at age 7](image)

**Result:** We found increased visual motor integration (VMI) standard scores from age 5 to 7 among girls only (VMI: 89 ± 7 vs 97 ± 5; p = 0.009). At age 7, girls have higher mean VMI scores than boys (p = 0.006). Bars represent confidence intervals.

**Interpretation:** The significant gender differences at age 7 suggest developmental differences in visual perception and motor abilities; at school age, girls may develop these abilities earlier than boys.

2. HEU children have HIGHER mean choline levels in MFGM at age 7

![Graph showing choline levels in HEU and HUU children](image)

**Result:** In MFGM, HEU children have higher mean choline levels at age 7 compared to HUU children (cho (HEU) = 1.07 ± 0.8, cho (HUU) = 0.94 ± 0.13, p = 0.005).

**Interpretation:** The increased mean choline levels among HEU children compared to HUU children suggest developmental differences among HEU children. Increased choline levels may imply glial proliferation/inflammation or increased cellular density.

3. At age 7, VMI scores correlate with choline levels in MFGM in HUU children only

![Graph showing correlation between VMI and choline in HUU children](image)

**Result:** In the MFGM, we found a significant positive correlation between VMI scores and choline levels in HUU children at age 7 (p = 0.01). The relationship is independent of gender, despite observed gender difference in VMI scores (result 1). The positive correlation between VMI scores and choline levels in HUU children at age 7 suggest the relationship is a possible indicator of healthy neurological growth.

4. At age 5 and 7, VMI scores correlate with creatine levels in PWM in boys only

![Graph showing correlation between VMI and creatine in PWM](image)

**Result:** In PWM, we found a negative correlation between VMI scores and creatine levels in boys at ages 5 and 7. Based on gender, the relationship is only significant among male children (p = 0.01) across both ages.

**Interpretation:** Our results suggest metabolite levels may provide additional insight into the evolution of cognitive measures during childhood, as well as possible differences based on gender.

References