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HIV exposure and gender effects on the relationship between cognitive scores and ^{1}H-MRS measures in the basal ganglia at 7 years

Study

Neuropsychological testing and single voxel ^{1}H-MRS (SVS) data acquired in the Basal Ganglia (BG) on a Siemens 3T Allegra Head Scanner (Siemens, Erlangen, Germany) in Cape Town, South Africa were performed as part of an ongoing longitudinal study. MRS data were acquired with 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). 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.

Twenty-five 7-year old HIV-uninfected children, 16 HIV-unexposed (HUU) and 9 HIV-exposed (HEU), (8 girls; mean age ± standard deviation: 7.3 ± 0.1; 6 Cape Coloured/19 Xhosa) were analysed. HEU children were exposed to treatment for prevention of mother-to-child transmission (PMTCT). The Kaufmann Assessment Battery for children 2nd edition (KABC-II) [2] was performed and standard scores for the KABC-II subtests and global Non Verbal Index (NVI) were calculated using USA norms. We performed regression analyses of metabolites with a select number of KABC-II scales/subtests (Sequential Processing, Learning Ability, Simultaneous Processing, and Hand Movements (HM)).

Background

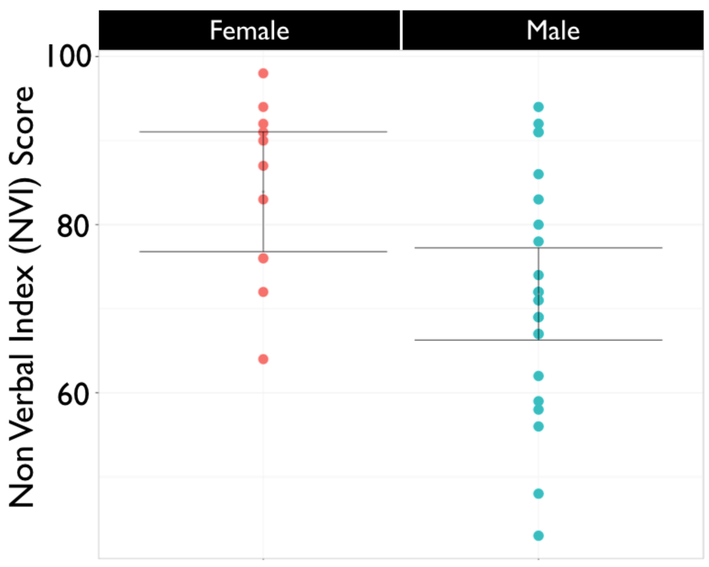
In South Africa, 95% of HIV-positive pregnant women and 68% of HIV-exposed infants have been receiving antiretroviral therapy (ART) [3,4]. Studies [5,6,7,8] suggest long-term effects associated with perinatal ART exposure - including an increased risk of neurological symptoms such as cognitive delay 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 [9].

MR spectroscopy (MRS) is a non-invasive tool used to measure metabolite levels in the brain. Metabolite levels often correlate with neuropsychological measures [10,11]. Choline is a marker of cellular density [12]. The metabolite creatine is found in neurons and glia, and is associated with energy metabolism [12].

We explored the relationship between metabolite levels in the right basal ganglia (BG) and neuropsychological measures at age 7, focusing on the potential effects of gender and HIV exposure.

Results

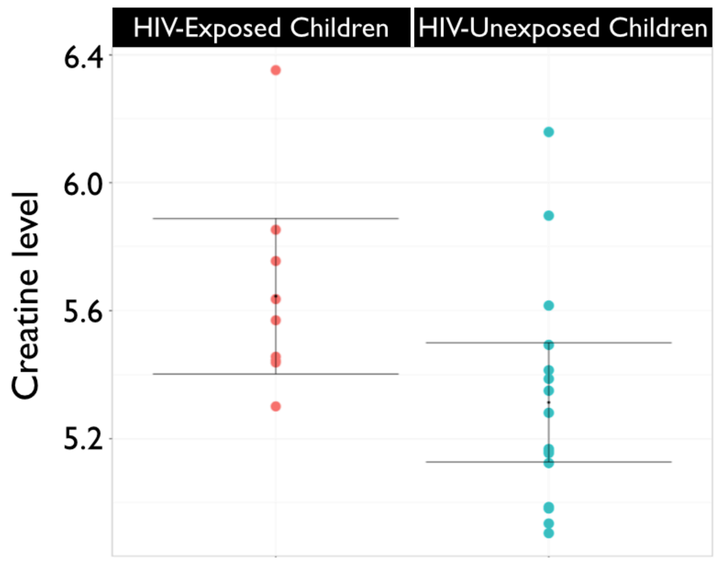
1 Girls have HIGHER mean Non Verbal Index scores



Result: Girls have higher global NVI test scores than male children (Male = 72 ± 13, Female = 84 ± 11; p = 0.008). Bars represent confidence intervals.

Interpretation: The NVI measures the ability to recognise spatial relationships and patterns. The higher mean NVI scores among girls at age 7 may represent developmental differences at school age, suggesting girls may develop these abilities earlier than boys.

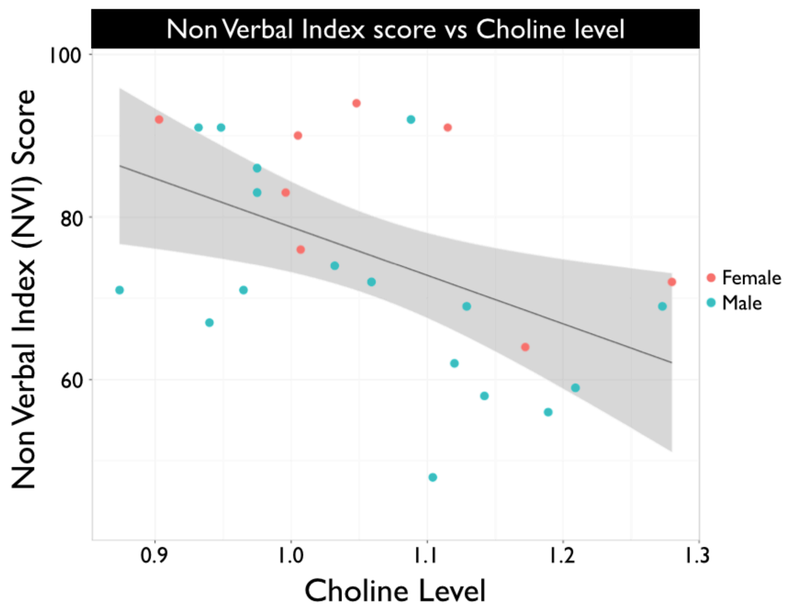
2 HEU children have HIGHER mean creatine levels



Result: We found HEU children have significantly higher mean creatine levels ((HEU) 5.6 ± 0.3 vs (HUU) 5.3 ± 0.3 ; p = 0.03). Result remains significant with the exclusion of the highest creatine value. Bars represent confidence intervals.

Interpretation: Increased creatine levels among HEU children suggest abnormal energy metabolism in the BG, and may indicate a possible compensatory mechanism.

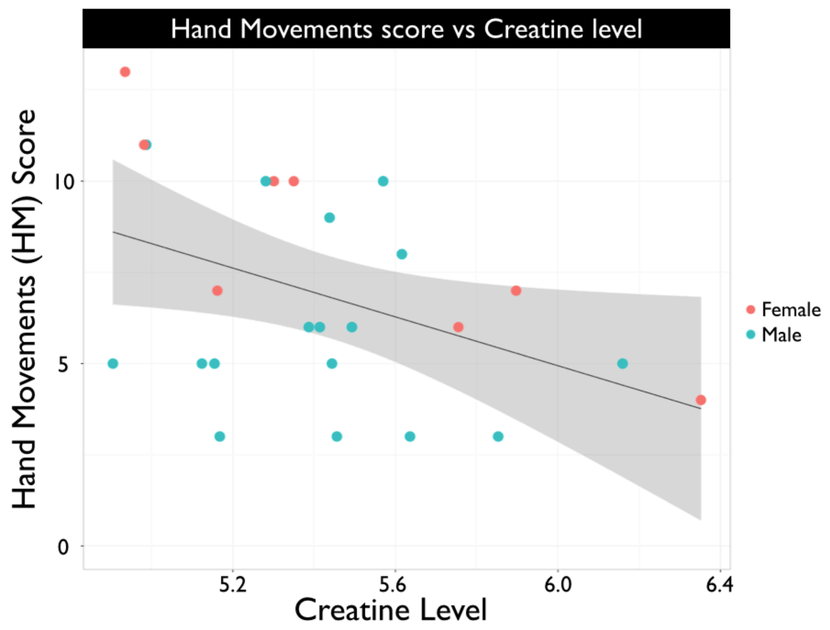
3 Non Verbal Index scores correlate with choline levels across all children



Result: Higher choline levels in the BG are associated with lower Non Verbal Index (NVI) test scores among all children (slope = -61,p = 0.007).

Interpretation: Gender differences in NVI scores (result 1) do not influence the relationship between choline and NVI scores; the correlation is independent of gender. The negative correlation between NVI and choline levels has not been previously reported, however it is not completely unexpected. Previous studies [12] find significant negative correlations between choline levels and measures of intelligence. NVI scores correlate strongly with achievement and intelligence tests [2].

4 Hand Movement scores correlate with creatine levels across all children



Result: We find an inverse relationship between HM scores and creatine levels (slope = -3.4, p = 0.04) in all children, driven by girls (slope = -5.2, p = 0.01).

Interpretation: The relationship between HM scores (visual spatial memory or motor function) and creatine levels is driven by girls. The gender difference may explain the absence of HIV exposure effects despite the differences in creatine levels (result 2). Creatine is expected to be constant across populations, and has rarely been examined in relation to pathology, demographics, or cognitive measures; this result suggests that further exploration of how creatine levels correlate with other variables is warranted.

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Acknowledgements

Support for this study was provided by NRF/DST South African Research Chairs Initiative; US National Institute of Allergy and Infectious Diseases (NIAID) through the CIPRA network, Grant U19 AI53217; NIH grants R01HD071664 and R21MH096559; NRF grant CPR20110614000019421, and the Medical Research Council (MRC). We thank the CUBIC radiographers Marie-Louise de Villiers and Nailah Marood, our research staff Thandiwe Hamana and Rosy Khethelo, and Shabir A Madhi for access to control participants on the CIPRA-SA04 trial.

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