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Effects of HIV infection and gender on metabolite level changes in the basal ganglia in children from 5 to 7 years

Introduction

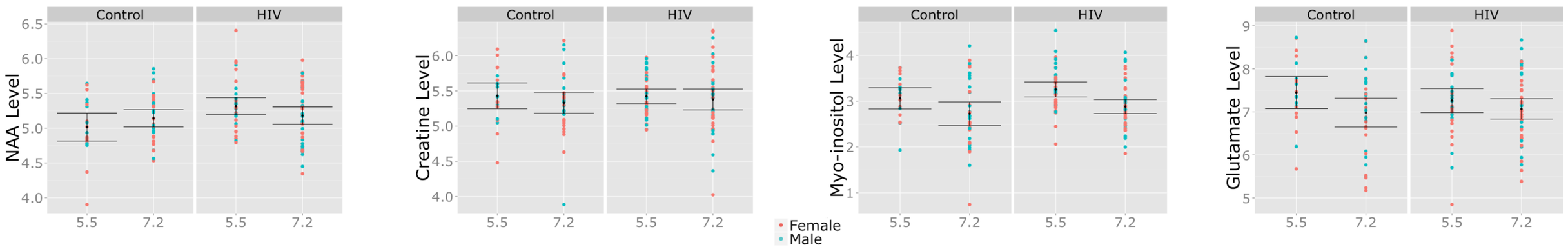
- **What is magnetic resonance spectroscopy (MRS)?** MRS is a non-invasive technique measuring metabolite levels in localized brain tissue.
- **What metabolites are measured?** Metabolites measure different aspects of brain health. Choline (GPCPCh) is associated with cellular density. Creatine (CrPCr) is related to energy metabolism. NAA (N-acetyl-aspartate) represents neuronal density and integrity. Glutamate is a neurotransmitter. Myo-inositol is considered a glial marker [1].
- **Why look at HIV-infected children stable on ART?** Early initiation of antiretroviral therapy (ART) has been shown to be particularly beneficial to children born HIV-infected [2,3], however the long-term impact of ART usage and HIV infection on child brain development is unknown. A deeper understanding of neurodevelopment of children stable on ART will allow for better overall health care and management of ART to ensure ideal development.
- **Why look at gender?** Gender-specific maturational changes occur in the developing brain [4]. MRS studies focused on age dependent changes in healthy children have not observed any gender differences [5,6]. Metabolites may shed light on the underlying mechanisms of gender related brain maturation.
- **Why look at the basal ganglia?** The basal ganglia (BG) play an important role in motor control as well as executive and limbic functions [7]. The basal ganglia is vulnerable to damage from HIV infection in children [8,9], and previous MRS studies in HIV-infected children have found altered neurometabolism in the BG [8,10].
- **Why look at metabolite level trajectories?** Metabolite levels are expected to remain relatively constant in childhood [5,6]. Metabolite level increases or decreases in childhood represent neurodevelopmental delay, possible damage/recovery or gender-specific maturation differences.

Study

Single voxel ^{1}H-MRS (SVS) data were acquired in the right BG on a Siemens 3T Allegra Head Scanner (Siemens, Erlangen, Germany) in Cape Town, South Africa on a cohort of HIV-infected and HIV-uninfected children at ages 5 and 7. MRS data were acquired with a real-time motion and B_0 corrected [11] point resolved spectroscopy (PRESS) sequence (TR 2000 ms, TE 30 ms, 64 averages, Scan time: 2:16 min). Absolute metabolite levels were determined with LCModel [12]. R was used for statistical analysis [13].

Subjects: We obtained MRS data in the BG on fifty-six 5-year old (30 female; mean age ± standard deviation = 5.5 ± 0.4 years; 36 HIV-infected/20 HIV-uninfected) and eighty-one 7-year old children (44 female; 7.2 ± 0.3 years; 46 HIV-infected/35 HIV-uninfected), with thirty-two children imaged at both ages. HIV-infected children were a subset of the children with HIV early ART (CHER) trial [2,3], and all initiated ART between 6 weeks and 1 year of age (except two children who started by 18 months).

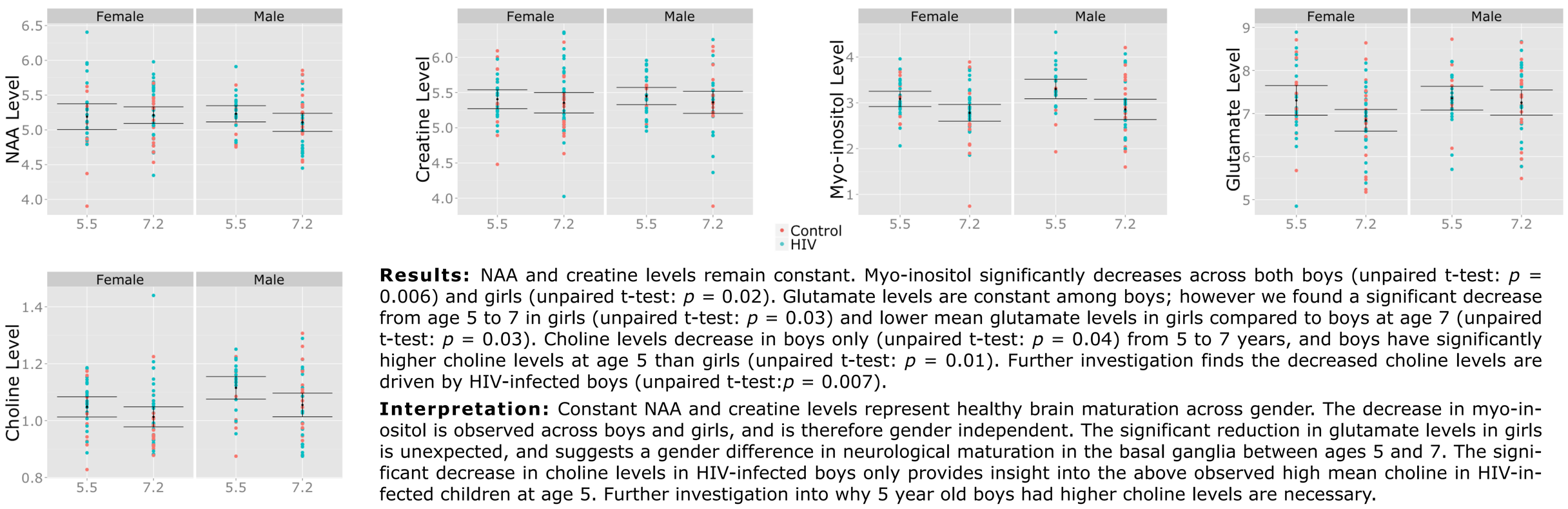
Results: HIV-infected and HIV-uninfected



Results: Mean NAA, creatine and glutamate metabolite levels remained constant from age 5 to 7 years among all children. Choline levels remained constant among control children, however we observed a significant decrease (unpaired t-test: p = 0.01) among HIV-infected children. We observed a significant decrease in myo-inositol across all children (unpaired t-test: p = 0.0003), that is more significant among the HIV-infected children (unpaired t-test: p = 0.001) compared to the HIV-uninfected children (unpaired t-test: p = 0.08).

Interpretation: Constant NAA, creatine and glutamate levels indicate healthy development among HIV-infected children. Decreased myo-inositol levels are unexpected, and may indicate normal development between 5 and 7 years. The fact that the difference is more significant among the HIV-infected children may be due to the larger sample size (82 HIV-infected children/55 HIV-uninfected children). Previous studies may not have observed decreases in myo-inositol because of the wide age ranges used [5,6]. The high mean choline levels at age 5 in infected children suggest possible regional inflammation, followed by recovery at age 7.

Results: Girls and Boys



Results: NAA and creatine levels remain constant. Myo-inositol significantly decreases across both boys (unpaired t-test: p = 0.006) and girls (unpaired t-test: p = 0.02). Glutamate levels are constant among boys; however we found a significant decrease from age 5 to 7 in girls (unpaired t-test: p = 0.03) and lower mean glutamate levels in girls compared to boys at age 7 (unpaired t-test: p = 0.03). Choline levels decrease in boys only (unpaired t-test: p = 0.04) from 5 to 7 years, and boys have significantly higher choline levels at age 5 than girls (unpaired t-test: p = 0.01). Further investigation finds the decreased choline levels are driven by HIV-infected boys (unpaired t-test:p = 0.007).

Interpretation: Constant NAA and creatine levels represent healthy brain maturation across gender. The decrease in myo-inositol is observed across boys and girls, and is therefore gender independent. The significant reduction in glutamate levels in girls is unexpected, and suggests a gender difference in neurological maturation in the basal ganglia between ages 5 and 7. The significant decrease in choline levels in HIV-infected boys only provides insight into the above observed high mean choline in HIV-infected children at age 5. Further investigation into why 5 year old boys had higher choline levels are necessary.

Summary

1. NAA and creatine levels remain constant across ages 5 and 7, independent of HIV status and gender;
2. HIV-infected children show a significant decrease in mean choline levels at age 7, driven by boys;
3. All children exhibit a significant decrease in myo-inositol levels from age 5 to 7 years;
4. Glutamate levels decreased significantly from age 5 to 7 among girls only.

References

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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 Maroof, our research staff Thandiwe Hamana and Rosy Khethelo, and Shabir A Madhi for access to control participants on the CIPRA-SA04 trial.