

Reduced brain volumes and gyrification in 7 year old HIV-infected children compared to controls

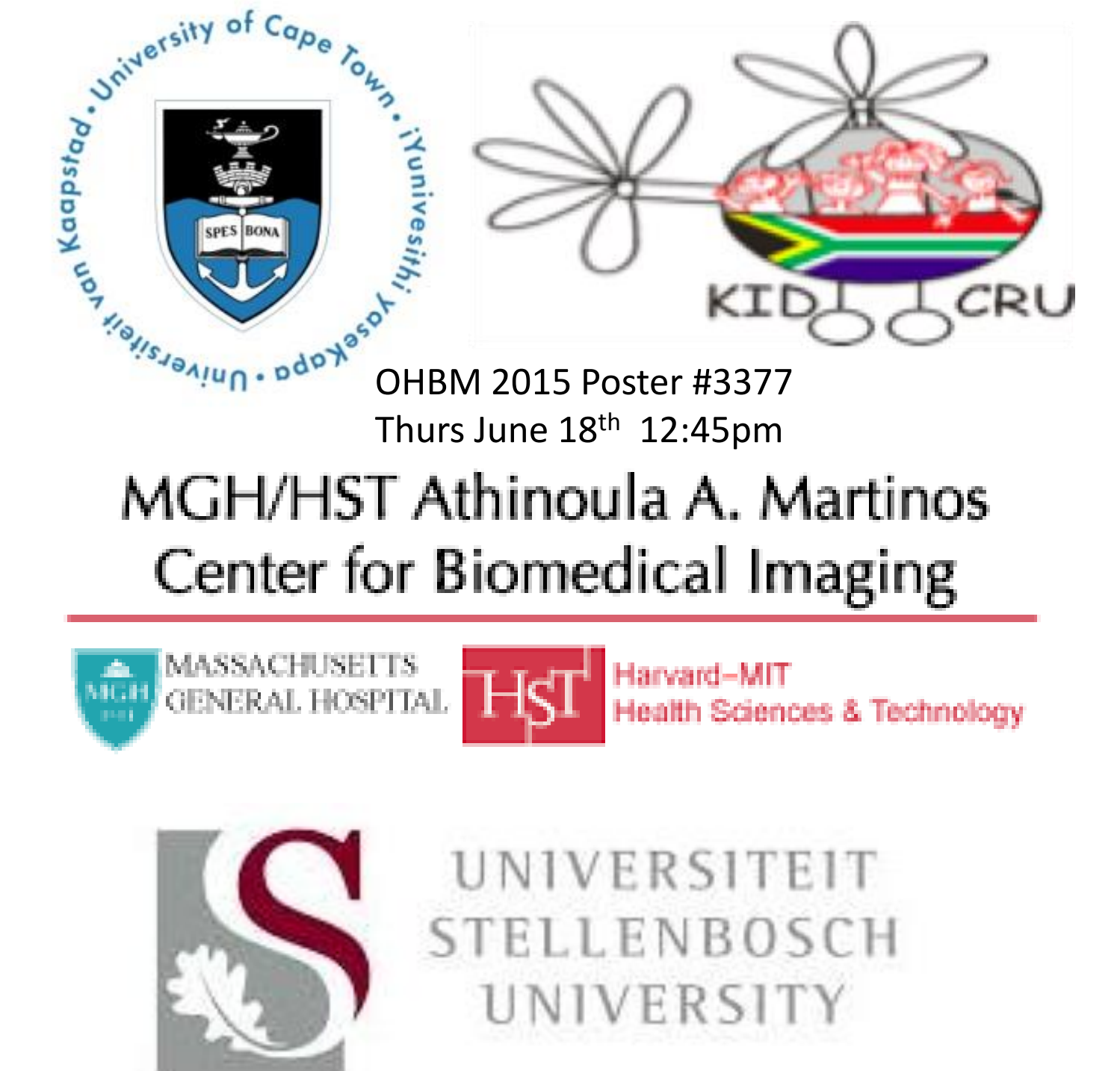
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1. Introduction

By 2013, there were more than 300,000 children living with HIV in South Africa (UNAID, 2013). Early and aggressive treatment has drastically reduced mortality and its progression (Violari et al., 2008). However, not much is known about the long term effects of early antiretroviral therapy (ART) and HIV infection on brain development. This study investigated the effect of HIV and early ART initiation on brain morphometry of HIV-infected children at age 7 compared to uninfected controls.

2. Methods

- Participants were 99 isiXhosa children (56 infected, 43 uninfected; 50 boys; mean age: 7.21 ± 0.14 years).
- From the neuroimaging follow-on study of the Children with HIV early Anti-retroviral (CHER) trial. Infected children were enrolled before 12 weeks of age and all were stable on ART at age 7.
- All children received T1 structural magnetic resonance imaging (MRI) scan within 6 months of their 7th birthday.
- MRI scans were analyzed with FreeSurfer automated processing stream (<http://freesurfer.net/>) to generate measures of:
 - ❖ cortical thickness
 - ❖ local gyrification index (LGI)
 - ❖ volumes of global grey and white matter
 - ❖ volumes of the corpus callosum, caudate, hippocampus, putamen, thalamus and lateral ventricles
- Vertex-wise and region of interest (ROI) comparisons were performed to investigate:
 - ❖ morphometric differences between HIV-infected and uninfected children
 - ❖ linear relationships between morphometric and CD4 count at time of enrolment in the HIV-infected children

3. Results

❖ Uninfected vs. Infected

- There was no significant difference in cortical thickness.
- Uninfected children had greater (8223mm^3) LGI in a left lateral and medial parietal region (MNI coordinates -6.2, -25.5, 51.3) that remained significant after controlling for sex.

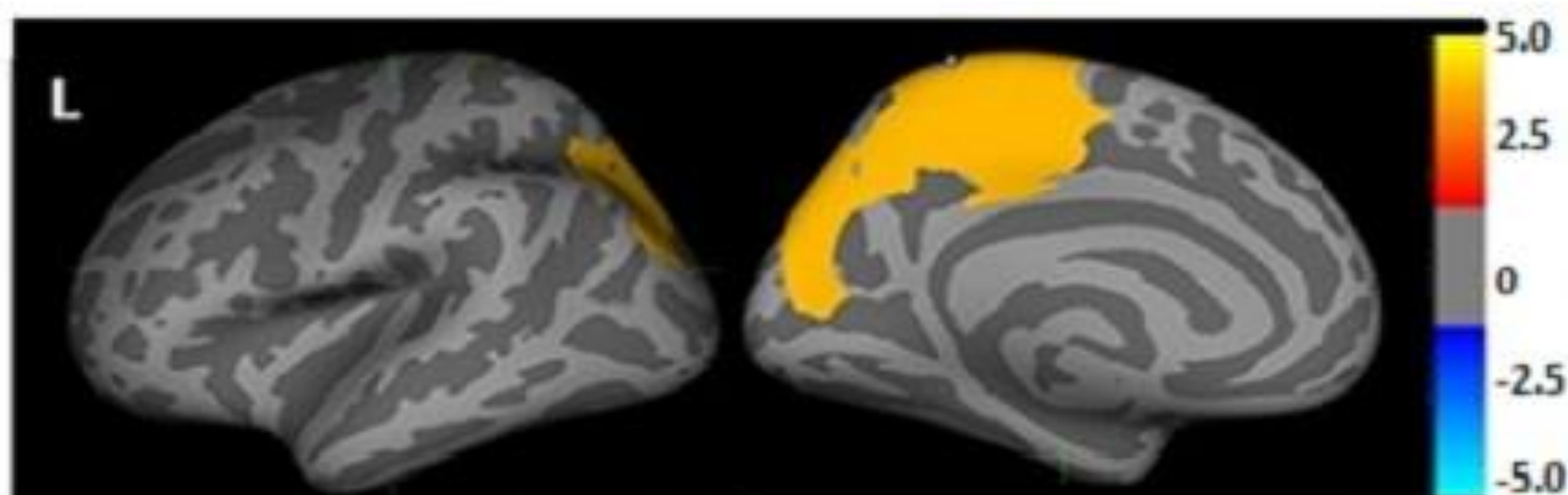


Figure 1: Left lateral and medial parietal region where uninfected children showed significantly greater LGIs than HIV infected children (threshold at $p < 0.05$, cluster size threshold $p < 0.05$)

- Uninfected children had significantly greater total grey ($p=0.02$) and white ($p=0.03$) matter volumes than HIV-infected children, after controlling for sex and intracranial volume which is consistent with previous findings.
- Uninfected children had significantly greater regional volumes only in the bilateral putamen (both p 's = 0.002) and right hippocampus ($p=0.01$) than infected children unlike previous HIV-infected children studies that had more regions.

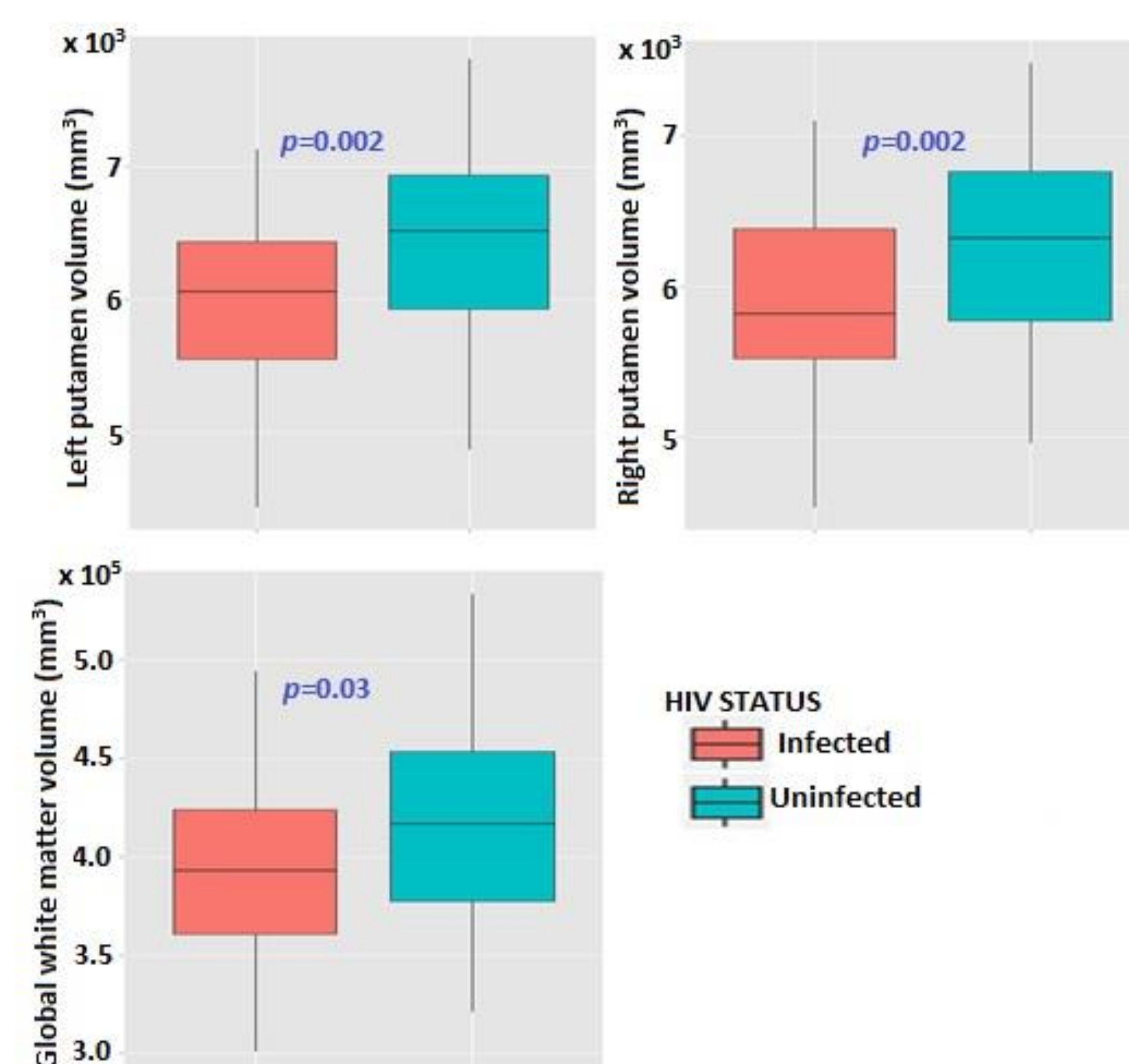


Figure 2: Box plot showing significantly larger brain volume in uninfected children than HIV-infected children in bilateral putamen and global white matter volume

❖ Relationship between CD4 count and morphometric measures in HIV-infected children

- There was no significant association between cortical thickness and CD4 count at enrolment in any of the regions.
- Greater LGIs in the left Pars orbitalis ($r=0.42$, $p=0.001$) and caudal middle frontal ($r=0.33$, $p=0.01$) regions were associated with higher CD4 count at enrollment which remained after accounting for sex.

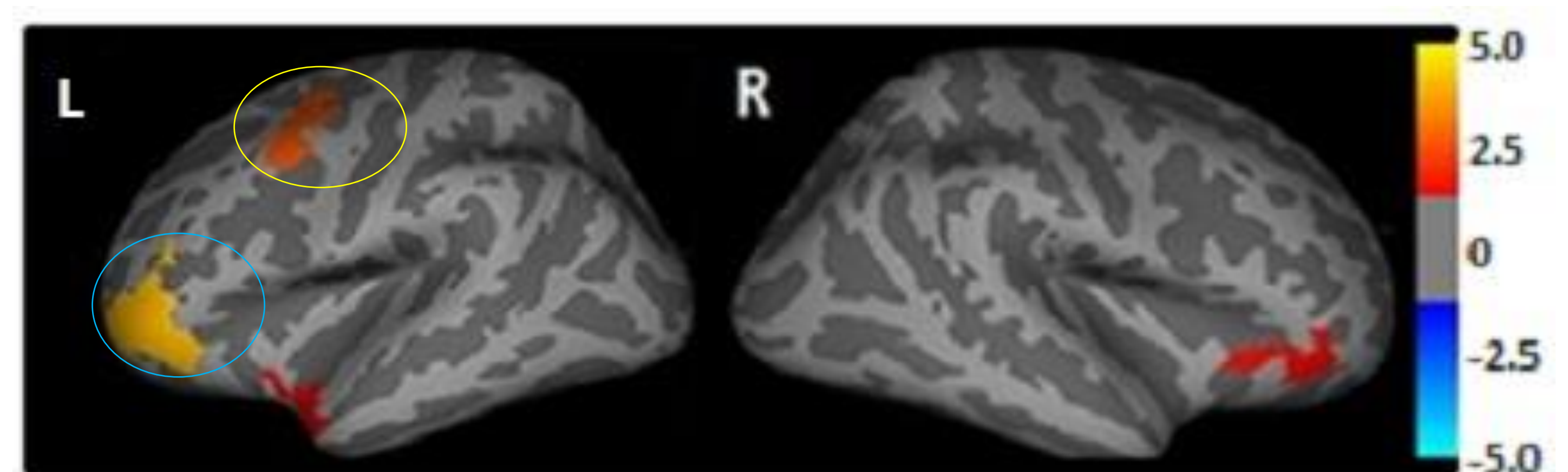


Figure 3: Lateral views of regions with significant relationship between CD4 count at enrollment and LGI ($N=58$) (threshold at $p < 0.05$, cluster size threshold $p < 0.05$)

4. Conclusions

- Despite early ART treatment, 7-year old HIV-infected children had reduced LGI in the parietal region. Reduced LGI represents enlarged sulci which has previously been associated with lower psychomotor score and IQ (Treble et al, 2012; Kallianpur et al, 2012). Cortical thickness and LGI to our knowledge have not been investigated in early pediatric HAART initiation previously.
- HIV-infected children had smaller volumes of global grey and white matter, right hippocampus and bilateral putamen compared to uninfected children. This may affect neurodevelopment
- Poorer immune health at enrollment as reflected by low CD4 count is associated with a regional decrease in LGIs that suggests disruption of normal cortical development that persists into early childhood.

References

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Acknowledgement of financial support

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). The Departments of Health of the Western Cape and Gauteng, South Africa and ViiV Healthcare/GlaxoSmithKline plc provided additional support for the CHER study.