

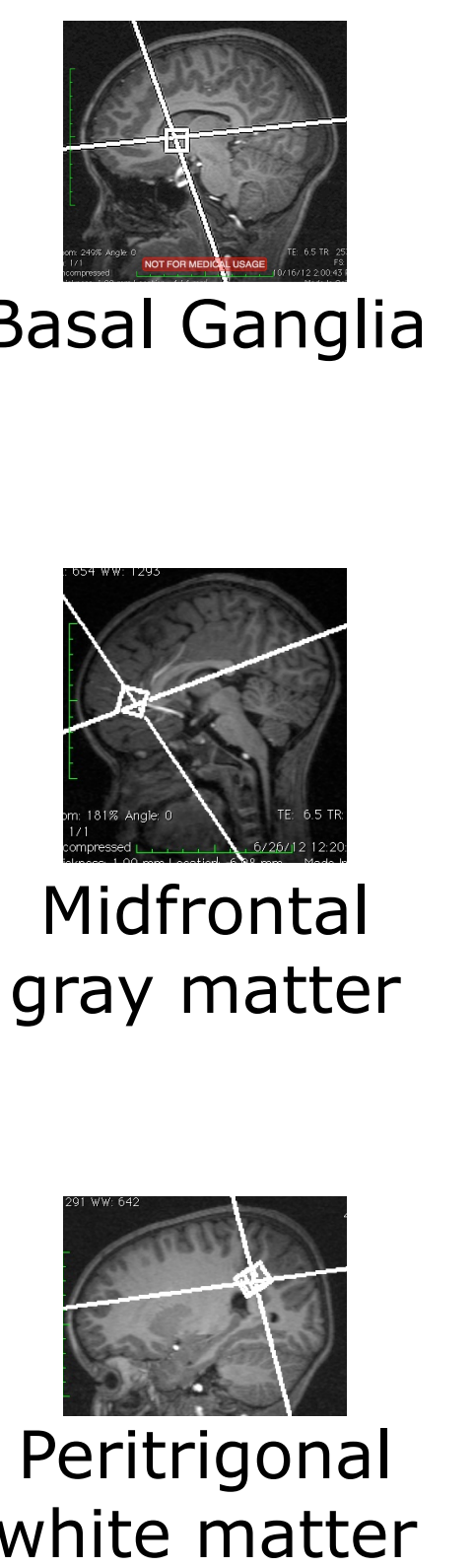
Effects of ART on neurometabolite and neurocognitive measures in HIV-infected children

Study

Single voxel ¹H-MRS (SVS) data were acquired for 37 HIV-infected (mean age: 5.5 ± 0.3) and 17 HIV-uninfected Xhosa children (mean age: 5.6 ± 0.5) on a Siemens 3T Allegra Head Scanner (Siemens, Erlangen, Germany) in Cape Town, South Africa. MRS data were acquired using 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). We collected spectra in the left peritrigonal white matter (PWM), midfrontal gray matter (MFGM) and basal ganglia (BG). Water reference scans were acquired in each voxel for eddy current compensation, frequency/phase correction, and to compute absolute metabolite levels (AMs). Spectra were analysed using the linear combination model software LCModel; exclusion criteria included FWHM > 0.075 ppm, SNR < 7 and LCModel standard deviation > 20%. All statistical analyses were performed in R; linear regression models were used and pairwise comparisons performed in regions where plotted confidence intervals suggested significant differences.

The children (36 HIV-infected and 15 HIV-uninfected) were assessed on the Griffiths Mental Developmental Scales-Extended Revised Version (GMDS-ER) [2] and (35 HIV-infected and 13 HIV-uninfected) with the Beery-Buktenica Developmental test for Visual-Motor Integration (6th Edition), including visual perception [3].

HIV-infected children were participants on the Children with HIV Early Antiretroviral Therapy (CHER) trial [4], in which children with a median age of 7 weeks and baseline CD4% ≥ 25% were randomly assigned to either one of two early antiretroviral therapy (ART) arms or a deferred ART arm. The ART regimes are defined as: Arm 1 - deferred until immunological or clinical criteria met (13 children), Arm 2 - ART initiated before 12 weeks of age with planned interruption at 40 weeks (13 children) and Arm 3 - ART initiated before 12 weeks of age with planned interruption at 96 weeks (11 children).



Background

The use of ART in young children limits HIV damage to the brain. However, little is known about the optimal ART for children born HIV-infected or how/if ART affects neurological development during childhood. MR spectroscopy (MRS) is used to investigate neurological development in children, as many neurological processes that occur during childhood are accompanied by metabolite level changes. Previous studies used metabolite levels to identify potential biomarkers in healthy and diseased populations [5,6,7,8]. Few studies have examined metabolite levels through childhood among healthy children, making it difficult to detect metabolite abnormalities among diseased children.

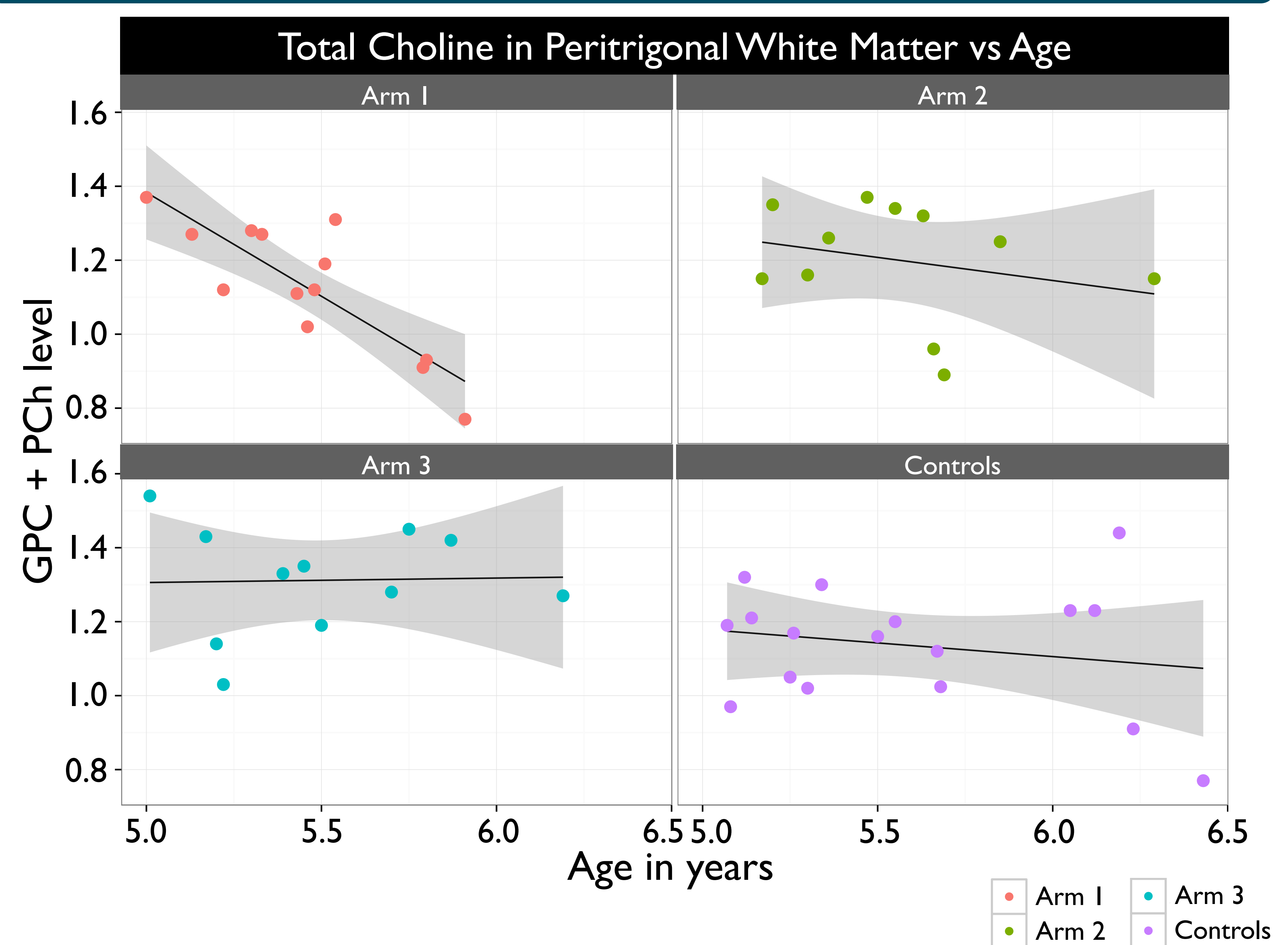
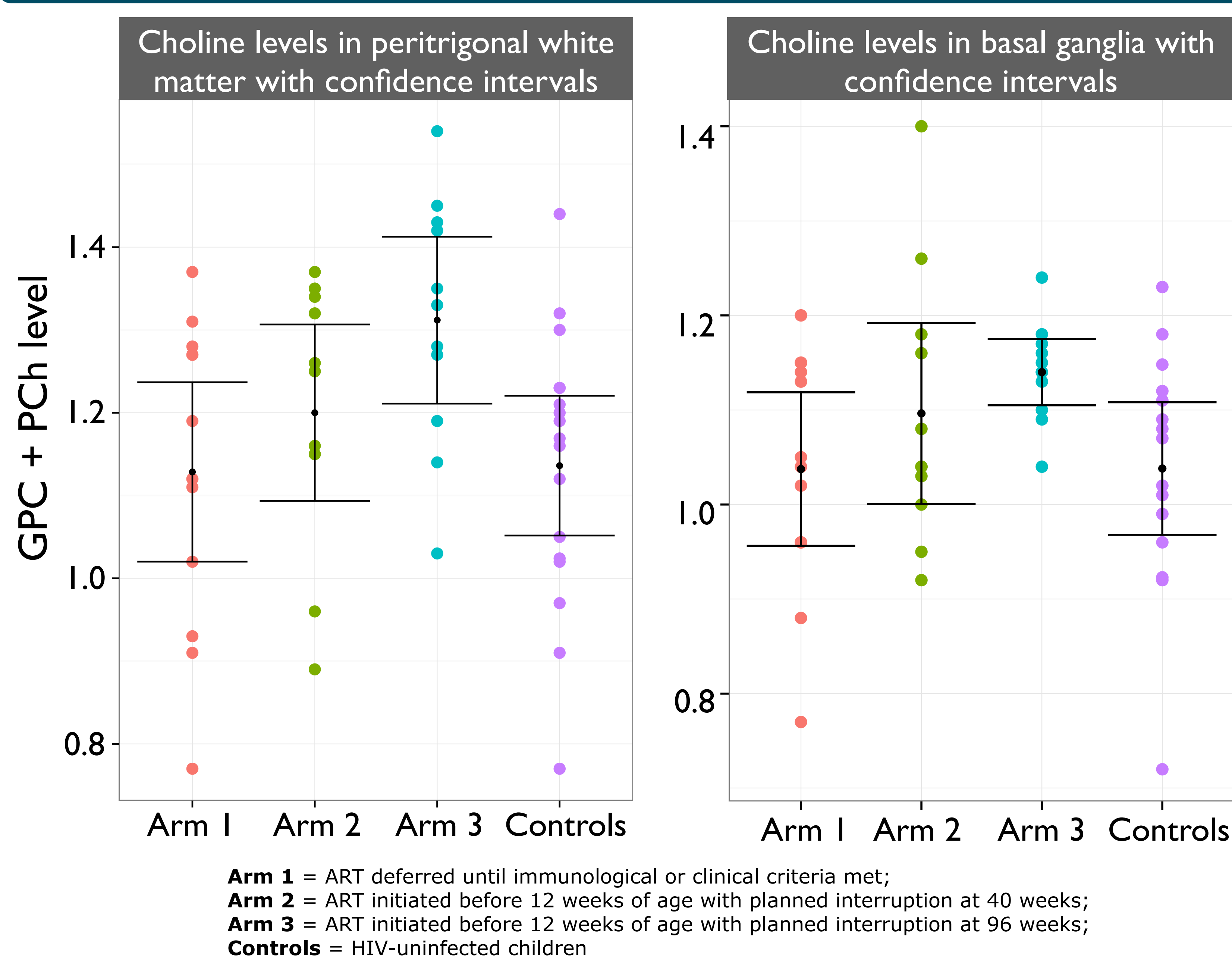
Neurocognitive measures are also used to monitor neurological development in children [5,7,10]. By combining neurocognitive and MRS measures, we hope to gain additional insight into the efficacy of different ART regimes as well as the influence of HIV on neurological development in children. The goal of this study is to examine metabolite levels and cognitive abilities between HIV-infected children receiving different ART regimes, and between HIV-infected and HIV-uninfected children.

Hypothesis - We hypothesize that Arm 3 - the group of HIV-infected children receiving ART at a young age, for the longest time period prior to planned interruption - will show metabolite and neurocognitive measures similar to HIV-uninfected children.

Results

1. Significantly higher choline in Arm 3 compared to Arm 1 and HIV-uninfected controls in both the Peritrigonal White Matter (PWM) and Basal Ganglia (BG).

2. Significant difference in the linear relationship between age and choline in the PWM in Arm 1 as compared to Arm 3 and HIV-uninfected controls.



3. No significant differences in neuropsychological measures between Arms or between HIV-infected and HIV-uninfected children.

Interpretation

All children are of the same ethnicity, from the same socioeconomic background, and of similar age. A pairwise comparison of total choline levels in the BG found significant differences between: Arm 1 and Arm 3, and Arm 3 and the HIV-uninfected group ($p < 0.05$). A pairwise comparison of the total choline levels in the PWM also found significant differences between Arm 3 and both Arm 1 and the HIV-uninfected group ($p < 0.01$). We observed no additional significant differences between groups in NAA, GPC+PCh or cognitive measures.

In addition, we observed a significant difference in the linear relationship between age and choline in the PWM among the following groups: Arm 1 and Arm 3 ($p = 0.009$) and Arm 1 and Controls ($p = 0.01$). Arm 1 displays a significant negative correlation with age ($p = 0.009$). Choline levels are expected to remain constant throughout childhood. However, there is evidence that in white matter choline levels are about 15% lower among older children (ages 5-18) than younger children (ages 0 - 5) [9].

Our results suggest ART has mitigated neurological damage related to HIV-infection observed in other studies [6,8]. Overall, we found very few differences between the HIV-infected and HIV-uninfected children. The association of choline with age is very different in the deferred treatment arm compared to the other arms and controls. These findings support early treatment as protecting against possible neurological and cognitive deficits associated with HIV in young children. Longitudinal studies of HIV-infected and HIV-uninfected children will provide data of normal development patterns over this age range; these results will aid in interpreting the effects of HIV and different treatment strategies on the developing brain.

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