Reduced executive function & default mode network connectivity in HIV+ children at age 7 years

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Introduction

- Resting state fMRI[1] (RS-fMRI) is not yet used to study network connectivity in HIV infected (HIV+) children
- Although early antiretroviral therapy (ART) in infants protects the brain against HIV, little is known on the long-term effects of early ART on neurological development
- We use RS-fMRI[1] to explore differences in resting state functional connectivity (RSFC) in HIV+ children who started ART early and HIV-uninfected (HIV-) children. Independent Component Analysis (ICA) and Seed-based Correlation Analysis (SCA) were used, followed by a combination of voxel probability and minimum cluster size thresholding

Methods

Participants

- After exclusion criteria (e.g. excess motion during scanning), we report data for 45 isiXhosa children recruited from either the neurodevelopmental sub-study of the 'Children with HIV early antiretroviral therapy' (CHER) [2] trial or a linked vaccine trial
- The sample comprised:
  - 27 HIV+ children (mean age ± sd = 7.2 ± 0.1 years, 9 males) who were all receiving ART at time of scan
  - 18 HIV- children (mean age ± sd =7.2 ± 0.2 years, 7 males), some born to uninfected mothers (unexposed) and some to HIV+ mothers (exposed to HIV and ART in utero)

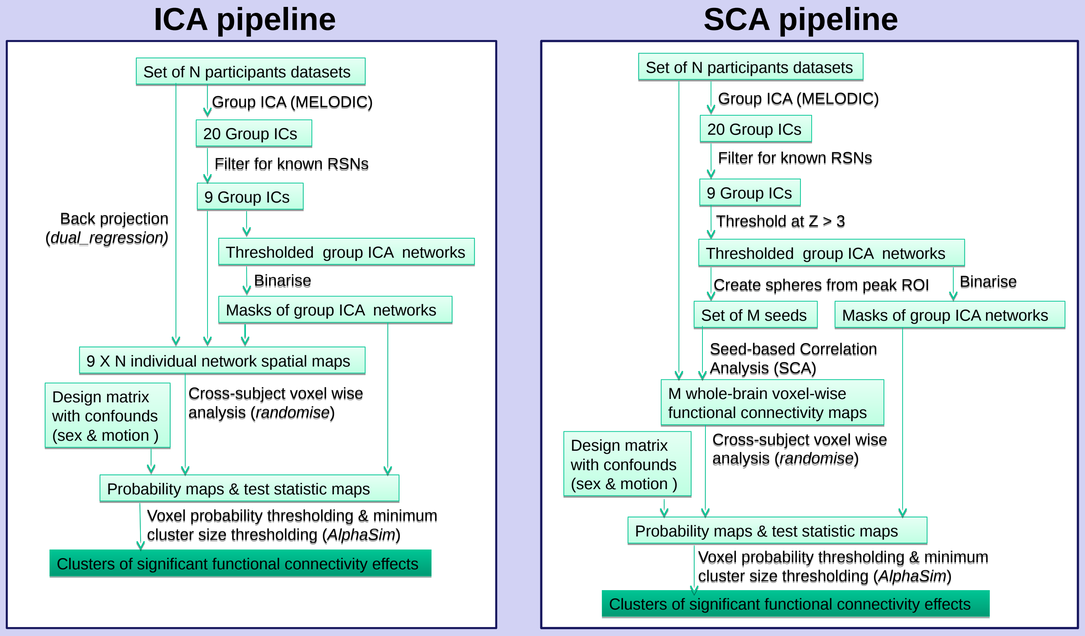
Image acquisition

- Scanning was performed on a 3T Siemens Allegra in Cape Town, South Africa, in accordance with protocols approved by the Human Research Ethics Committees of Stellenbosch and Cape Town Universities
- T1-weighted images were acquired using a motion navigated[3] MEMPRAGE sequence[4] (1.3x1x1 mm^3 resolution)
- RS-FMRI data were acquired using an EPI sequence (3.4x3.4x4 mm^3, 180 time points, TR=2000 ms, TE=30 ms)

Image processing and analysis

Preprocessing pipeline (using AFNI[5]): removal of first 5 volumes, despiking, slice timing correction, structural alignment, warping to standard space, volume registration, spatial smoothing, regression of motion (CSF/WM), and bandpass filtering (0.01-0.1 Hz).

Processing pipelines for ICA and SCA (using AFNI[5] and FSL[6]):



Group differences: HIV+ on ART vs. uninfected children
A) within functional RSN maps (using ICA pipeline)
B) across whole-brain (using SCA pipeline)

HIV+ vs. HIV-

Results

Resting state networks from ICA

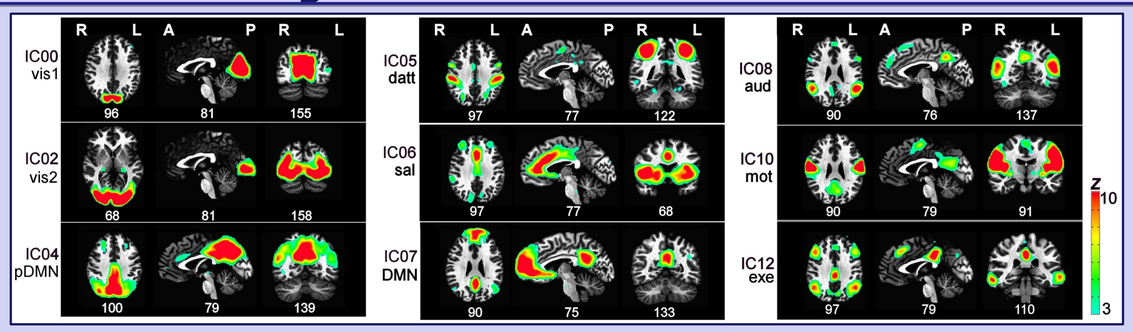


Fig. 1: *Z*-score maps (*Z*>3) extracted from group-ICA, representing the nine resting state networks (RSNs) of interest: visual lingual gyrus (vis1); visual occipital lobe (vis2); posterior default mode network (pDMN); default mode network (DMN); dorsal attention (datt); salience (sal); auditory (aud); motor (mot); and the executive function (exe) networks.

Functional connectivity deficits (HIV+ vs. HIV-) from SCA

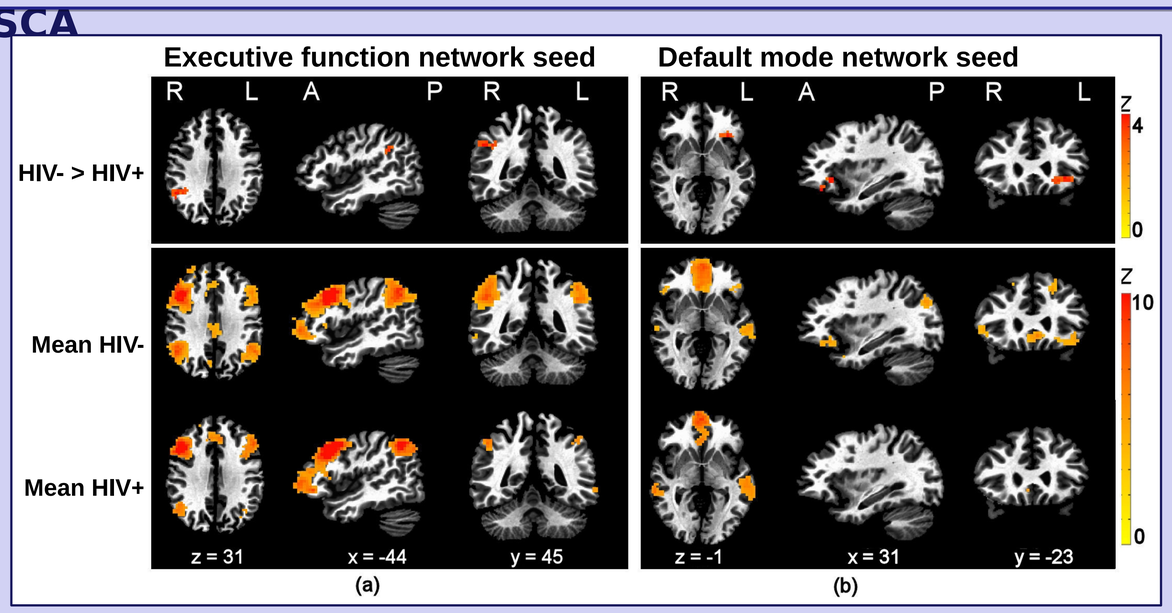


Fig. 2: (Top panel) Regions showing reduced connectivity in HIV+ children than HIV- children. In (a) the right supramarginal gyrus shows reduced connectivity to the right middle frontal gyrus in the executive control network, and in (b) the left middle frontal gyrus shows reduced connectivity to the left cingulate gyrus in the default mode network. The middle and lower panels show the mean connectivity maps of the HIV- and HIV+ respectively. The Talairach coordinates of the slice are at the base of each column.

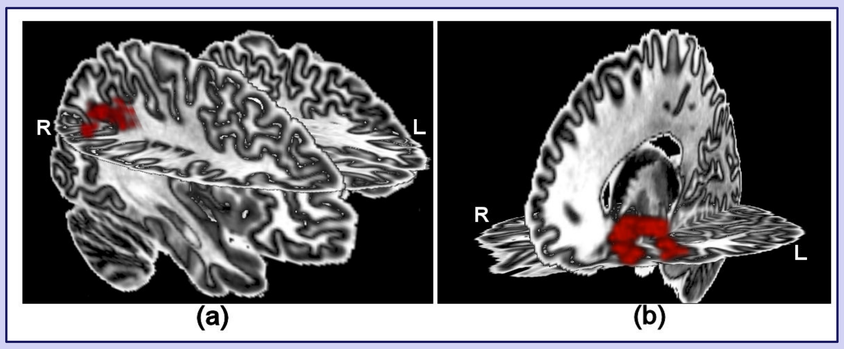


Fig. 3: Regions showing reduced connectivity in infected children to a seed in the (a) executive control and (b) default mode networks, respectively.

Conclusion

SCA revealed decreased functional connectivity in two RSNs in HIV+ compared to HIV- children: executive function (exe) and DMN. RS-fMRI and fMRI studies in HIV+ adults have also reported reduced FC compared to HIV- adults in numerous DMN regions[7,8] and in the exe network[9]. However, in contrast to the adults where a number of areas within the networks have been implicated, we only observed a focal effect in these two specific RSNs.

From ages 7 to 9, the DMN and exe are both still maturing into an interconnected network[10], therefore reduced connectivity among the HIV+ children may represent delayed network maturation. Specifically, memory improvement processing (within the DMN) along with cognitive flexibility, goal setting and information processing (within the exe network) are undergoing development during this age and may be delayed in HIV+ children[10,11]. These reductions in functional network strength during a critical time in development require further investigation with neuropsychological tests and follow up scans at age 9.

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