Diminished Resting-State Functional Connectivity in Lateral Occipital Cortex in Early HIV Infection

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Introduction: Human Immunodeficiency Virus (HIV) infection is associated with considerable risk of brain injury and deterioration in cognitive function that may progress to dementia in the most severe cases. While brain viral invasion occurs soon after initial exposure, limited information is available concerning early HIV-induced changes in the Central Nervous System. Resting-state functional connectivity MRI, based on temporal correlations in spontaneous blood oxygen level–dependent (BOLD) signal oscillations, has been used to evaluate connectivity between brain networks[1]. This study, which was part of a larger multiparametric quantitative imaging investigation of early HIV infection, examined differences in resting state functional connectivity in seropositive (HIV+) subjects within the first year of infection and in age-matched controls.

Methods:

Subjects: Fifteen HIV+ (median age 29.5.5±6.36) and fifteen healthy control (median age 29.5±6.50) subjects were enrolled. Study exclusion criteria included history of neurological disorder, stroke, head trauma, opportunistic CNS infection, and psychosis or MR contraindication. Seropositivity was confirmed by ELISA and Western blot. Recent infection (within one year of seroconversion) was determined on the basis of low sensitivity Ortho Vitros LS-Eci testing and/or an available prior negative HIV test result. During resting scan period, subjects were instructed to rest and with eyes open, not to think systematically and stay awake.

MR Image Acquisition: Subjects were scanned on a 3.0 T whole body scanner (Siemens TrioTim B15 software, Elangen, Germany) with a 12 channel head coil. The imaging protocol included a T1 anatomic volume sequence (MPRAGE with TR/TI/TE=2300/900/2.91 ms, 9 degree flip angle, 1mm isotropic resolution) and 225 resting-state fMRI volumes acquired using a gradient echo EPI sequence (TR/TE=2500ms/20ms, matrix 128x128, FOV 220 mm, forty 3mm slices using GRAPPA).

Image Analysis: Resting-state fMRI analysis was carried out using MELODIC (part of FSL tools, www.fmrib.ox.ac.uk/fsl)[2]. Preprocessing consisted of motion correction, brain extraction, spatial smoothing using a 6mm Gaussian kernel, and high-pass temporal filtering equivalent to 100s (0.01 Hz). fMRI volumes were registered to the individual's structural scan and MNI152 standard space images using FLIRT (part of FSL tools). Preprocessed functional data containing 225 time points for each subject were concatenated in time across subjects to create a single 4D data set and decomposed into 36 ICA components[3]. ICA components were back-reconstructed for each subject's 4D data to estimate subject-specific spatial maps using the dual-regression technique[4], which were subject to statistical analyses looking for significant resting-state functional connectivity differences between controls and patients.

Statistical analyses: The two groups (HIV and CONTROL) were included in our statistical design and hypothesis tested included (1) HIV>0, (2) CONTROL>0, (3) CONTROL>HIV and (4) HIV>CONTROL. Nonparametric permutation testing (500 permutations) corrected for multiple comparisons using threshold-free cluster enhancement (TFCE).

Results: Out of 36 ICA components, one component involved with the visual network shows patients have diminished connectivity within the lateral occipital cortex (LOC) network, one of the main resting state networks[3], which includes the occipital pole extending laterally towards the occipito-temporal junction and more dorsally in superior parietal regions This set of regions is related to visual attention or visuospatial attention. HIV positive patients have diminished connectivity within the LOC network in the left lateral occipital cortex region (X=33, Y=15, Z=25, $p<0.05$ TFCE FWE corrected) (Figure 1: top) ($P<0.1$ FWE-corrected). Group main effect for patients (ie. HIV>0) (Figure 1: middle) and controls (ie. Control>0) (Figure 1: bottom) are also shown ($p<0.05$ TFCE FWE corrected).

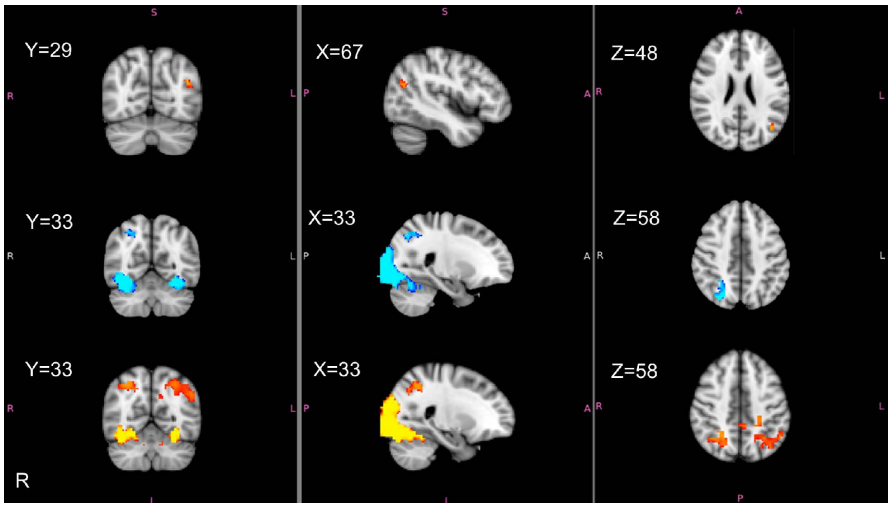

Figure 1: Results

Conclusion: Ongoing brain injury in early HIV infection may be clinically silent and not detected by neurologic examination or by neuropsychological tests for prolonged periods in the clinical course. By the time symptoms such as cognitive deficits present, injury to the brain may be irreversible. Rational neuroprotection requires a clearer understanding of the evolution of neuropathological changes early in the clinical course of infection. This in vivo imaging investigation, which was based on a comparison of a small sample of seropositive and control subjects, finds prominent changes in functional connectivity of the lateral occipital cortex networks early in the course of HIV infection. The findings suggest that this network may be affected due to the dramatic burst of viremia (Acute HIV) that is known to occur before host cellular immune defenses can contain the massive viral replication associated with initial exposure to the virus[5]. Further studies aimed at clarifying factors associated with HIV neurological vulnerability will replicate these methods in a larger sample and examine the brain functional connectivity at a follow-up evaluation, two years later in the clinical course.

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Acknowledgement: This study was funded by NIH MH080636.