

Low Nadir CD4+ Counts and disrupted MRS Brain Metabolite Levels are associated with reduced brain volume in HIV/AIDS

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Around 40% of HIV/AIDS patients experience minor to severe cognitive impairments, but the brain changes underlying this cognitive decline are still poorly understood. We used tensor-based morphometry to map 3D patterns of relative brain volume reduction in 210 patients with HIV, enrolled into the HIV Neuroimaging Consortium study (mean age: 48.6±8.4 years; 175 men/35 women). We hypothesized that regional brain volumes would be associated with nadir CD4+ counts and with brain metabolite levels measured by proton magnetic resonance spectroscopy.

Individual scans were non-linearly aligned to a high-resolution average brain template, using an inverse-consistent registration algorithm. Maps were created to show regions of volume deficit or excess relative to the template, reflecting, in part, profiles of neurodegeneration. Voxel-wise multiple regression was used to assess associations between regional brain volumes and (1) demographic variables, (2) immune system measures, and (3) brain metabolite levels including absolute concentrations of *N*-acetyl aspartate (NAA), Creatine (Cr), Choline (Cho), *myo-inositol* (MI), glutamate and glutamine (Glx), and ratios of NAA/Cr, Cho/Cr, MI/Cr, Glx/Cr in the frontal white matter, basal ganglia, and medial frontal cortex.

We did not detect an age effect in this cohort, but both sex (FDR $q=0.05$, critical $P=0.006$) and race (critical $P=0.03$) were significantly associated with regional brain volumes. After controlling for age, sex and race, lower nadir CD4+ count, but not current CD4+ count, was associated with reduced brain volumes (critical $P=0.02$). Lower levels of NAA in the frontal white matter or the basal ganglia, and increased level of Glx in basal ganglia, were associated with lower brain volumes (critical $P=0.01$ for NAA in frontal white matter; critical $P=0.01$ for NAA in basal ganglia; critical $P=0.02$ for Glx in basal ganglia). Additionally, regional brain volumes were associated with the ratios of Cho/Cr in frontal white matter (critical $P=0.002$), MI/Cr in frontal white matter (critical $P=0.01$), NAA/Cr in basal ganglia (critical $P=0.003$), and Glx/Cr in basal ganglia (critical $P=0.01$).

Brain atrophy was associated with immunosuppression and alterations in brain metabolites that reflect neuronal integrity. Disruption in these metabolites may lead to

subsequent structural loss. This supports a model of brain injury that implicates frontal/striatal pathways in the pathogenesis of HIV-associated cognitive impairment.