Low nadir CD4+ counts and disrupted MRS brain metabolite levels are associated with reduced brain volume in HIV/AIDS

The HIV Neuroimaging Consortium Cohort Study
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An emerging body of data suggests that brain injury and cognitive impairment are common events in the aging, chronically infected and treated population.

The HIV Neuroimaging Consortium was formed to:

- Prospectively map the course of functional and structural injury and its relation to cognitive impairment in the setting of cART and chronic disease.
- Identify host and disease-related factors contributing to brain injury and cognitive impairment in the setting of cART and chronic disease.
- Identify biomarkers predictive of risk for brain injury and cognitive impairment, its progression and response to treatment.
The HIV Neuroimaging Consortium Cohort Study: Multimodal Imaging Strategy

Benefits

- An integrated multimodal imaging strategy (MRS, DTI, MRI) provides a robust and quantitative in vivo approach to identify patterns and trajectories of cerebral injury over the course of the disease:
  - Interrogate the HIV brain across multiple levels
    - Cellular injury and response - MRS
    - Fiber tract morphology and connectivity - DTI/DT/PT
    - Cortical thickness maps, volumes - MRI
  - Examine the HIV-infected brain as a distributed network of interrelated pathological processes in relationship to cognitive and functional outcomes
  - Uncover useful diagnostic and prognostic markers for both clinical practice and clinical trials
Design and Methods

- Prospective study of ~300 HIV-infected subjects across 7 centers
  - Brain bank centers at UCLA, UCSD and Harbor-UCLA
  - ACTG and primary HIV clinics at Colorado, Pittsburgh, Harbor, Stanford

- Inclusion criteria:
  - Nadir CD4+ T-cell counts ≤200 cells/μl
  - ART for at least 12 weeks

- Exclusion criteria:
  - Confounding neurological, psychiatric and medical disorders (hepatic, renal, diabetes)
  - Active drug use
Subjects:
- N=210 patients with HIV/AIDS
- Age: 48.6±8.4 years
- Sex: 175 men (83%) and 35 women (17%)
- Race: 148 Caucasian (70%), 54 African-American (26%), 6 Native American and American Indian (3%), and 2 Asian (1%)

MRI: T1-weighted MPRAGE sequence
- TE = 3.57 ms, TR = 2730 ms, flip angle = 7, FOV = 256×256 mm, 1×1×1 mm resolution

MRS: Single-voxel ¹H spectra
- Customized PRESS sequence
- Voxels: 6 cc in volume in midline frontal gray matter, right or left frontal white matter in the centrum semiovale, and right or left basal ganglia
- Water suppressed spectra: TE/TR = 35/3000 ms, bandwidth =2500 Hz, 128 averages, NEX = 8
- The metabolite ratios NAA/Cr, Cho/Cr, MI/Cr, and Glx (=Glu + Gln)/Cr were determined using the LC Model spectral analysis software and an unsuppressed water FID at TE = 30 ms for eddy-current correction
- Inter-individual variations: 10% to 15%
- Intra-subject variability: 3% to 8%
A high-resolution average brain template was created to represent common anatomical features for the study group. Individual brain images were non-linearly aligned to the brain template, using an inverse-consistent registration algorithm. Maps were created to show regions of volume deficit or excess relative to the brain template, reflecting, in part, profiles of neurodegeneration.
Methods

- At each voxel in the brain, multiple regression was used to assess associations between regional brain volumes and
  - demographic variables: age, sex, and race
  - immune system measures: current and nadir CD4+ T-cell counts (cells/μl)
  - brain metabolite levels: 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

- Maps of associations were declared significant if they controlled the false discovery rate at 5%
Results

- 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; a greater amount of brain atrophy was shown in women vs. men, and African-American vs. Caucasian.

- After controlling for age, sex and race, lower nadir CD$_4$+ count, but not current CD$_4$+ count, was associated with reduced brain volumes (critical $P=0.02$).

Lower nadir CD$_4$+ count was associated with greater atrophy, in a broad region encompassing the frontal/parietal white matter bilaterally; for each 25-point reduction in nadir CD$_4$+, there was a 1-2% greater deficit in frontal white matter volumes (beta values range from 0.04-0.08%).
Brain metabolite levels were associated with brain volumes

- **Lower levels of NAA** in the frontal white matter (critical $P=0.01$)
- **Lower levels of NAA** in the basal ganglia (critical $P=0.01$)
- **Increased level of Glx** in basal ganglia (critical $P=0.02$)

were associated with lower brain volumes.
Results

- Regional brain volumes were associated with the ratios of brain metabolites
  - 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 $P = 0.003$)
  - 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.

The result on nadir CD4+ expands on recent cross sectional studies linking nadir CD4+ to cognitive impairment (Heation et al., 2011; Valcour et al., 2011).

TBM analysis of brain MRI provides a sensitive and noninvasive measure of HIV-associated brain atrophy, potentially useful to aid early detection as well as early intervention.

**Future studies** will use longitudinal TBM to measure regional brain change over time.
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