Neuroimaging Biomarkers in HIV Infection: Report of Working Group 4

J.T. Becker (Pittsburgh, USA)
L.G. Epstein (Chicago, USA)

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Objectives for Neuroimaging Markers

• Specificity for diagnoses of CNS injury that underlies HIV associated dementia and cognitive impairment.
• Ability to detect CNS injury or inflammation at pre-symptomatic phase.
• Ability to monitor HIV disease stage and treatment efficacy in the CNS. (Non-invasive means to quantify changes in injury/inflammation.)
• NB: These markers are not likely to be useful in resource limited settings.
Neuroimaging in the Pre-HAART Era

- Loss of brain volume in late stages of disease
- Consistent findings of structural and metabolic abnormalities in the subcortical regions (basal ganglia) and cerebral white matter. (Tucker et al. *J Neuroimmunol* 2004).
- Ability to identify mass lesions associated with opportunistic or reactivated CNS infections or lymphomas.
MRI Morphometric Studies

• Whole brain studies including voxel- and tensor-based morphometry, 3-D surface mapping, automated labeling pathway and similar techniques reveal widespread alterations in brain structure.

• Alterations in sub-cortical regions (esp. basal ganglia) and the white matter are related to disease stage and to degree of cognitive impairment. (Paul et al. Neuroscience & Biobehavioral Reviews, 2002)
The Corpus Callosum is abnormally thin in AIDS suggesting altered Cortical Structure.
Diffusion Tensor Imaging (DTI)


• DTI measures for whole brain are significantly associated with dementia severity (Ragin et al. *Neurology*. 2004)

• Diffusion abnormalities in centrum semiovale are associated with higher plasma viral load (Filippi et al. *Am J Neuroradiol* 2001; Pomara et al. *Psychiatry Res* 2001)
Figure 1. This axial slice through intraventricular foramen shows the largest portion of putamen and caudate nuclei. Color-coded, uniform sized ROIs were placed on anatomical T2 weighted image and then automatically projected on FA and ADC maps.

Figure 2. ROIs for centrum semiovale were placed on an axial slice above the bilateral ventricles and aligned with the central sulcus for consistency. (Ragin et al, J. Neurovirology, in press, 2005)
Diffusion Tensor Imaging (DTI)

- Measures for centrum semiovale were significantly correlated with visual memory deficits (apparent diffusion coefficient/ADC), visuoconstruction (fractional anisotropy/FA).
- Anisotropy measures for caudate were significantly correlated with deficits in visual memory. (Ragin et al. J Neurvirol. In press, 2005)
Diffusion Tensor Imaging (DTI)

- FA values for splenium were significantly reduced and correlated with measures of dementia severity.
- ADC values for splenium and genu were increased and correlated with the degree of cognitive impairment determined by neuro-psychological evaluation. (Ragin et al., *ISMRM*, 2005).
- Experiments in non-human primates found changes in DTI measures in corpus callosum 11 days following inoculation with SIV (He et al., *Prog Intl Mag Reson Med*, 2003).
Magnetization Transfer Imaging (MTI)

- MTR (magnetization transfer ratio) is sensitive to neuro-pathological changes in patients with HIV (Dousset et al. *Neuroimaging Clin N Am*, 1997).
- MTR can distinguish white matter lesions associated with HIV encephalitis from those of PML (Ernst et al. *Radiology* 1999).
Magnetization Transfer Imaging (MTI)

- Reduced MTR was observed in neurologically asymptomatic individuals preceding measurable losses in brain volume. (Ge et al. *Am J Neuroradiol* 2003)
- Reductions in whole brain MTR measures correspond to the cognitive status of HIV patients (Ragin et al. *Neurology* 2004)
Magnetic Resonance Spectroscopy

- MRS is most widely available of the neuro-imaging techniques to show metabolic changes in CNS due to HIV.
- 1H-MRS reveals reductions in the neuronal marker N-acetyl-aspartate (NAA) and increases in the choline (cho) and myo-inositol (MI) to creatinine (Cr) ratios consistent with glial activation related to dementia severity. (Harrison et al. *J Neurol Neurosurg Psychiatry* 1998)
Magnetic Resonance Spectroscopy

MRS abnormalities:

- localize to frontal white matter (glial markers) and basal ganglia (neuronal loss). (Ernst et al. AIDS 2004)
- may be present in neurologically asymptomatic patients (Tarasow et al. Acta Radiol, 2003)
- do not recover with HAART (Chang et al. Antivir Ther, 2004)
Functional MRI

- fMRI studies report consistent evidence of a compensatory hyperactivation in mildly impaired patients, and this appears to precede clinical signs or abnormal neuropsychological test performance.
- fMRI more valuable as a research tool than for clinical assessment.
Conclusions/Future Directions

• Additional research is needed to correlate neuro-imaging methods with new clinical syndromes in the HAART era.
• Improvements and deterioration in clinical status associated with HAART may present an important opportunity to conduct this research.
Conclusions/Future Directions

• We need non-invasive measures of CNS integrity that can be implemented on a large scale (appropriate for epidemiological studies) and that can be applied to longitudinal cohort studies.
Conclusions/Future Directions

- Quantitative structural MRI (including DTI and MTI) and MRS are the most promising and available neuroimaging techniques.
- We need to correlate neuroimaging findings with other biomarkers in blood and CSF.