Factor Analysis of Proton MR Spectroscopic Imaging data in HIV infection: Regional patterns of involvement and relationship to cognitive status

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Introduction: Previous MRS studies have revealed significant alterations in white matter early in the course of HIV-associated dementia (HAD), before it is visible on structural MRI [1], but most HIV studies have focused on single-voxel MRS at short TE. While single-voxel MRS provides good spectral quality, it is limited by the number of regions that can be sampled within a typical clinical visit. In contrast, MRSI provides data from many regions both quickly and simultaneously. However, a complication in using MRSI lies in the large number of variables generated in its analysis and the need for statistical correction. Multislice MRSI data necessitates the exploration of non-traditional forms of analysis such as factor analysis [2, 3]. In this study, factor analysis was applied to 1H MRSI data from a large cohort of HIV+ and seronegative control subjects, with the aims of: 1) determining regional metabolism changes induced by HIV infection, 2) comparing these changes to individual neuropsychological evaluations, and 3) comparing these changes to clinical and immunologic markers for HIV dementia.

Methods: Seventy-four chronically infected HIV+ (34 with cognitive impairment and 40 without) and 20 seronegative healthy control subjects underwent high resolution multi-slice 2D-MRSI of the brain using a 1.5 Tesla MRI scanner at long echo time (280 ms). N-acetyl aspartate (NAA), choline (Cho) and creatine (Cr) concentrations were estimated using the phantom replacement technique in 7 brain regions (Figure 1, *left*): thalamus, basal ganglia, frontal white matter (WM), centrum semiovale, parietal white matter, frontal gray matter (GM), and parietal gray matter, yielding 21 variables in total. Subjects also underwent neurocognitive, blood and cerebrospinal fluid (CSF) testing. Factor analysis was performed on the 21 variables and generated three main significant factors related to cognitive dysfunction and HIV status. Each subject was assigned a score for each rotated factor based on the loadings of the subject's original 21 variable levels. ANOVA and two-tailed least squares means (LSM) t-tests were performed to identify significant differences between cohorts based on HIV and cognitive status. Nonparametric Spearman rank correlation coefficients were used to determine if viral loads, immunologic markers, or neurocognitive tests were related to the three factors.

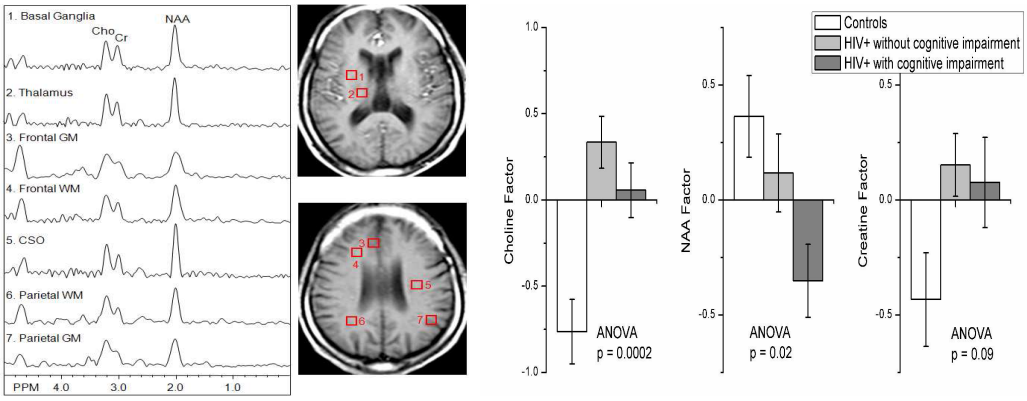

Figure 1: *Left:* Sample spectra and voxel locations of 7 brain regions. *Right:* Choline factor scores were elevated from controls for HIV+ subjects without cognitive impairment ($p = 0.00003$) and those with cognitive impairment ($p = 0.002$). NAA factor scores were lower in those with cognitive impairment when compared to controls ($p=0.01$) or HIV+ subjects without cognitive impairment ($p=0.02$).

Results: Examination of the loadings in each factor indicated major contributions due to specific metabolites in each. Thus, one was named a "choline factor" (dependent on WM and deep GM Cho levels), one an "NAA factor", (frontal and parietal WM, parietal GM), and a "creatine factor" (parietal and frontal WM). Choline factor scores differentiated between HIV- and HIV+ subjects, with higher scores in HIV+ subjects (Figure 1, *Right*). The choline factor weightings were strongest in WM and deep GM regions. The NAA factor differentiated between subjects with and without cognitive impairment (ANOVA, $p=0.02$). Specifically, NAA concentrations in WM regions (and to a lesser degree parietal GM) were most affected by cognitive impairment, with lower NAA scores in subjects with cognitive impairment. A factor correlating to creatine levels across the white matter regions was also observed, but was not significantly associated with HIV status or cognitive impairment ($p = 0.09$). Scores on tests of psychomotor ($Rs =0.41$, $p<0.0005$) and executive function ($Rs =0.32$, $p<0.007$) correlated with subjects NAA factor scores. MCP-1 in the CSF correlated with subjects "Cr factor" scores ($Rs = 0.45$, $P = 0.0008$), while CD4+ T-cell levels in the plasma correlated best with Cho factor scores ($Rs = -0.44$, $P = 0.0002$). Neither CSF nor plasma viral loads correlated with any MRSI factor.

Conclusions: This is the first extensive report of regional variations in brain metabolism using absolute concentrations from HIV+ subjects. These results indicate the importance of early white matter involvement in HAD, and (although not a longitudinal study) support the model of early glial cell proliferation (Cho and possible Cr elevations) in HIV infection, and later neuronal dysfunction (NAA decrease) associated with dementia. Choline scores were more elevated in subjects whose health was worse (as indicated by CD4 T cell levels). Through factor analysis, metabolite patterns can reveal differences between HIV status and severity of HIV-associated cognitive impairment, and provide information on the spatial distribution of metabolic changes within these subjects.

References:

1. Navia BA, et al., Neuroimaging Clin N Am 1997; 7(3): 431-45.
2. Griffin JL, Philos Trans R Soc Lond B Biol Sci 2004; 359(1446): 857-71.
3. Yiannoutsos CT, et al., Neuroimage 2004; 23(3): 928-35.

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