Three-dimensional Multivoxel Proton MR Spectroscopy Distinguishes Regional Gray Matter Metabolic Abnormalities in SIV-Infected Rhesus Macaques at 3T: Initial Findings

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Introduction: Although HIV is known to variably affect different brain regions in chronic HIV patients (1-2), its effects during the acute (‹1 month) and subacute (1-3 months) stages of infection remain poorly understood. Because of its similar pathogenesis to HIV-infection, the simian immunodeficiency virus (SIV)-infected rhesus macaque is often used as an animal model to study brain abnormalities using MRI and proton spectroscopy (^{1}H-MRS).. Although previous ^{1}H-MRS studies have identified region-specific metabolic responses to SIV-infection, these have been limited by use of low 1-3 cm^3 (relative to the ~80 cm^3 macaque brain) spatial resolution single voxels, which invariably suffer low brain coverage and partial volume contamination. To mitigate the prohibitive effects of these limitations, we performed three-dimensional (3D) multivoxel ^{1}H-MRS imaging (MRSI) over extensive, 28 cm^3 (~35%) of the macaque brain at 0.125 cm^3 spatial resolution and compared the absolute *N*-acetylaspartate (NAA), creatine (Cr), choline (Cho), and myo-inositol (mI) concentrations in the basal ganglia of gray matter and centrum semiovale of white matter in three rhesus macaques at baseline and 6 weeks post-infection. We hypothesize that metabolic changes can be detected that may be related to disease activity.

Methods: All experiments were done in a 3-T MR imager (Magnetom TIM Trio, Siemens AG, Erlangen, Germany) with a circularly-polarized transmit-receive human knee coil. To guide placement of the ^{1}H-MRS volume-of-interest (VOI), sagittal and axial turbo spin echo MRIs (TE/TR=16/7430 ms, 140×140 mm^2 field-of-view (FOV), 512×512 matrix, 2.0 mm sagittal and 1.2 mm axial slice thickness) were acquired. A 4.0 cm anterior-posterior (AP) × 3.5 cm left-right (LR) × 2.0 cm inferior-superior (IS) =28 cm^3 ^{1}H-MRSI VOI was then centered on the corpus callosum. The VOI was excited using PRESS (TE/TR=33/1440 ms) with two 2nd-order Hadamard encoded slabs (4 slices) interleaved within every TR. These slices' planes were encoded with 16×16 2D-CSI over an 8×8 cm^2 (LR×AP) FOV to yield nominal (0.5 cm)^3 voxels, 224 of which fell in the VOI. These 224 VOI spectra were each frequency-aligned and zero-order phased in reference to the NAA peak, then zero-filled to 256×256 in the time and chemical shift directions. Although zero-filling does not add new content to the raw data, it has been shown to increase spatial resolution by adding overlapping interpolated voxels, thereby reducing partial volume effects (3, 4). Relative levels of the i^{th} (NAA, Cr, Cho, *m*I) metabolite in the j^{th} animal were estimated from their peak areas, S_{ij}, using parametric spectral modeling and least-squares optimization software by Soher *et al.* (5). The S_{ij} were then scaled into absolute concentrations by phantom replacement as described previously (6). Three (2 females, 1 male; 5.0–5.6 kg weight) healthy adult rhesus macaques, all 3 years old, were scanned at baseline, then infected by intravenous injection with SIV, and rescanned 6 weeks later. Animals were under constant veterinary supervision. The protocol was approved by both the Harvard Medical School and Massachusetts General Hospital IACUCs. Regional metabolite concentrations were estimated in three gray matter and one white matter brain regions shown in **Fig. 1**. Each region was outlined (bilaterally) on axial MRI and overlaid on their corresponding spectral model functions using in-house software (IDL, Research Systems Inc., Boulder, CO). The software averaged all voxels that fell entirely or partially within the outlined areas.

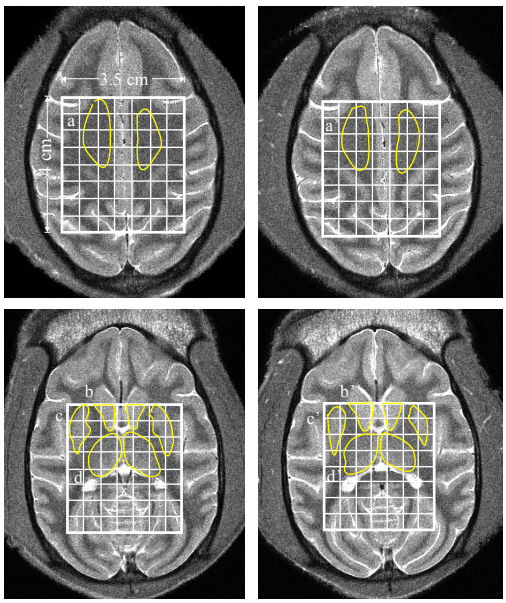

Fig. 1. Axial MRI pre- (left) and post-SIV infection, showing the 3.5 × 4 cm^2 VOI (thick white frame), CSI grid (thin white lines) and selected brain regions where the voxels' metabolite signals were averaged: (**a, a'**) centrum semiovale in the WM, (**b, b'**) caudate head, (**c, c'**) putamen, and (**d, d'**) thalamus in the GM.

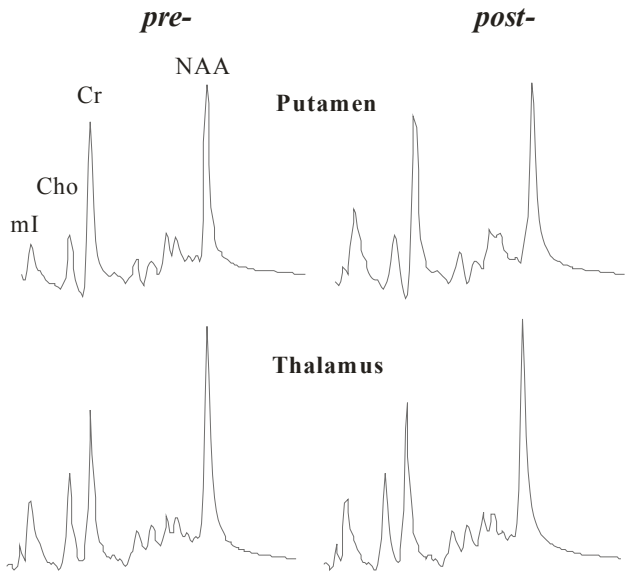

Fig. 2. Average fitted model functions of the aligned ^{1}H-spectra from the voxels containing putamen (top) and thalamus (bottom), from a single macaque pre- (left) and post-SIV infection. All are on common intensity and chemical shift scales. Note the significant (› 45%) elevation in putamen mI, and (›15%) elevation in thalamus Cr.

Results: Averaged fitted model functions of the aligned ^{1}H spectra from the putamen and thalamus for a typical animal pre- and post-infection, are shown in **Fig. 2**. For three animals, there was a significant mean 15% increase in thalamus Cr concentration (6.8±0.4 millimoles/g (mM) wet weight to 7.8±1.0 mM; p‹0.02), and 45% increase in putamen mI (4.3±1.4 to 6.3±0.5 mM; p‹0.02) , after SIV-infection compared to baseline. We found no significant change in any other region for any metabolite.

Discussion: Based on the preliminary results and **Fig. 2**, we provisionally confirm our hypothesis that metabolic changes are detectable in specific GM subregions using 3D ^{1}H -MRSI. This may be useful in pinpointing areas which are selectively more vulnerable to SIV, and in determining areas for therapeutic intervention during early stages of the disease.

References: (1) Moore e*t al, AIDS* 2006 (2) Lee *et al,J MRI 2003* (3) Du *et al, J MRI 1994* (4) Bernstein *et al, J MRI* 2001 (5) Soher BJ *et al, MRM* 1998 (6) Inglese M *et al, MRM* 2003