MEMRI based NOD/scid-IL-2Rγ $_c^{null}$ mouse brain atlas for HIV pathobiology studies

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Introduction: Magnetic resonance imaging (MRI)-based mouse brain atlases allow longitudinal quantitation of brain structure during aging and disease progression. However, accurate assessments require evaluations of specific mouse strains and image enhancements. Thus, manganese enhanced (MEMRI) was applied to NOD/scid-IL-2Rγ_c^{null} (NSG) mice to create brain atlases. NSG mice were chosen based on their abilities to accept human cell transplants and reflect human disease [1]. Thus, a MEMRI based NSG brain atlas was created to track structure-wise alterations following HIV-1 infection in NSG mice transplanted with human immune cells [2].

Methods: Animal preparation: Nineteen NSG male mice, weight = 28.5 ± 2.4 grams, age = 1 year from a breeding colony in our institution were used. MRI Acquisition: MRI data were acquired 24 hours after $MnCl_2$ administration using Bruker Bioscan 7 Tesla/21 cm small animal scanner (Bruker, Billerica, MA) with a 72 mm volume resonator and a laboratory built surface coil. Mice were anesthetized by inhalation of isoflurane in 100% oxygen and maintained 40-80 breaths/minute. 3D T1 weighted data were acquired using a spin echo sequence with parameters: TR/TE = 600/8 ms, averages = 4, image matrix = 176 × 128 × 128 with 100 μm isotropic pixel size. Average mouse brain: All MR brain images were manually sub-imaged by separating brain from non-brain tissue using Analyze 10.0v software (www.analyzedirect.com). All images were corrected for intensity inhomogeneity using an N3 method [3]. Brains (18 total) were registered to median volume using rigid body registration. Individual brain volumes were averaged. Then all individual brain volumes were iteratively (4 times) affine registered and updated. Finally, nonlinear registration of individual brain images to the average based on Large Deformation Diffeomorphic Metric Mapping (LDDMM) aligned differences. To minimize the interpolation errors, transformation matrices from individual iterations were combined and applied in one step to each brain to generate the final average. All the registration procedures were performed using Diffeomap 1.6v as implemented in DTIStudio software (www.mristudio.org). Enhanced average brain: The final step was to sharpen the boundaries between anatomic features (enhanced brain) by applying the Laplacian as: $g(x, y) = f(x, y) - \nabla^2 f(x, y)$, where g(x, y) and f(x, y) represent enhanced and input images respectively, and ∇^2 represents the Laplacian operator. Amira® 5.21v VSG software (www.amira.com) was used for labeling brain regions.

Results: Representative coronal and axial slices of average brain from 19 mice are shown in first column of figure 1. Result of image enhancement is shown in the middle column. Improvement in sharpness due to enhancement of boundaries improved identification of brain structure boundaries not visible on standard MRI. To date, 22 brain structures have been labeled.

Discussion: These preliminary results demonstrate our ability to successfully label major structures on *in vivo* averaged MEMRI. This project will be extended to label all possible substructures and used to determine morphological changes in brain due to HIV-1 infection.

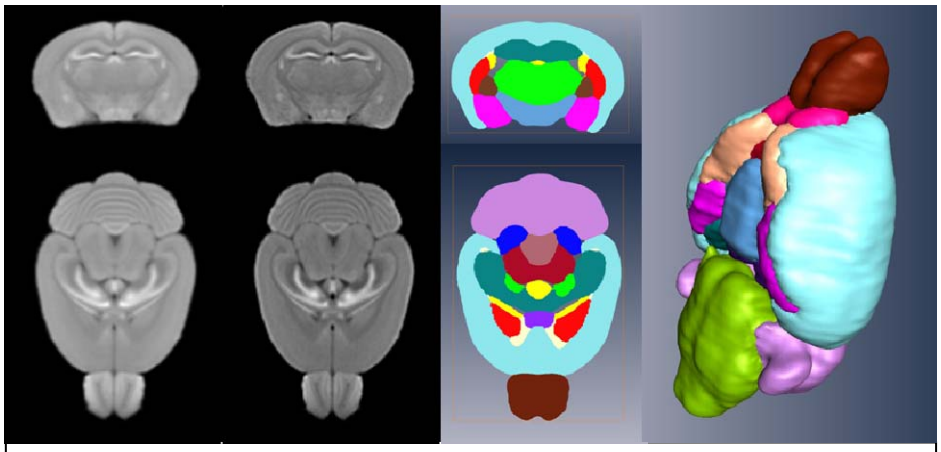

Figure 1: *Columns: First: representative images of average brain generated from brain MEMRI of 19 mice. Second: Enhanced images with Laplacian operator. Third: Labeled images of corresponding slices. Fourth: A 3D rendering of labeled brain atlas.*

References: 1. Watanabe S. et al. *Blood* 109:212-218, 2007. 2. Gorantla S, Poluektova L and Gendelman HE, Trends *Neurosci.* 35:197-208, 2012. 3. Sled JG, Zijdenbos AP and Evans AC, *IEEE Trans Med Imaging*. 17:87-97,1998.