Probabilistic MRA Template of the Macaque Putamen for Guiding Convection Enhanced Delivery

Zhan Xu[1], Marina Emborg[2,3], Do Tromp[1], Nagesh Adluru[1], Martin Brady[4], Raghu Raghavan[4], Ken Kubota[5], and Andrew L Alexander[1,6]

[1]Waisman Laboratory for Brain Imaging and Behavior, University of Wisconsin Madison, Madison, WI, United States, [2]Department of Medical Physics, University of Wisconsin Madison, Madison, WI, United States, [3]Wisconsin National Primate Research Center, [4]Therataxis,LLC, Baltimore, MD, [5]Kinetics Foundation, Los Altos, CA, United States, [6]Department of Medical Physics and Psychiatry, University of Wisconsin Madison, Madison, WI, United States

INTRODUCTION: In Contrast Enhanced Delivery (CED), a drug is infused into a region of tissue under pressure through a cannula within the brain. The location of the cannula tip within brain regions will influence the distribution and ultimately the effectiveness of the delivered drug. For the treatment of Parkinson's disease, accurate intraparenchymal delivery of drugs into the posterior putamen is currently being explored in both research studies and clinical trials. A significant loss mechanism for the infused drugs is via the extravascular spaces of blood vessels that are in close proximity to the cannual tip, as shown in fig1. In our work, we aim at generating a probability map of vascular detail in and around the putamen by producing a magnetic resonance angiography (MRA) template of the vessels in the rhesus macaque brain. The macaque is a widely used animal model for CED infusion experiments. The MRA template is then registered to our TW template to aid in better targeting of the optimal infusion region while avoiding the area's with high vessel probability.

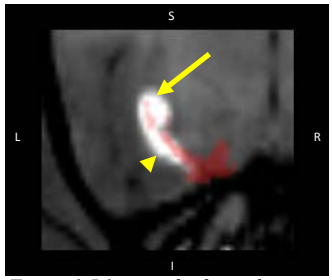

Figure 1:R1 map of infusate loss caused by leakage along a blood vessel. Hyperintense signal is the infused tracer (yellow arrow), and the red area is a blood vessel (arrow head)

METHODS: High-resolution, contrast-enhanced MRA studies were obtained as part of a CED study of 30 rhesus macaque monkeys. All scans utilized a GE 3T scanner with a custom 3-inch diameter, receive only surface coil. MRA scans were obtained before and after intravenous injection of contrast agent, using a 3DSPGR sequence with flow compensation, 15ms TR, 3.7ms TE, 30° flip angle, 140mm FOV with 0,6mm slice thickness, matrix size of 256*256*160, which was resampled to 0.27*0.27*0.3 mm voxels. A single dose of ProHance was administered between the pre- and post- MRA scans. Structural 3D T1W scans were acquired as a anatomical reference with 450ms TI,9.2ms TR, 4.1ms TE, 12° flip angle, 140*105mm FOV, matrix size of 256*224*128, with a 0.8mm slice thickness, which was resampled to 0.27mm*0.27mmin-plane.

To map the vessels, we subtracted pre-contrast from post-contrast MRA for each subject and thresholded the subtraction images to best show the vascular detail in the putamen. A template of blood vessels was generated by spatial normalization of the image volumes. The 3D T1W brain volumes were skull stripped using the brain extraction tool from FSL[1] followed by manual adjustments. The MRA were acquired with finer resolution, so rigid body registration with FLIRT[2] was used to remap the T1W structural image to the subject's MRA image. A highly deformable, diffeomorphic spatial normalization tool, ANTS[3], was used to generate a higher order registration of the T1W data across all subjects to produce a population-averaged template. The transformation from each T1W image to T1W template was applied to co-register the MRA images of all the animals. This normalized the vessel detail maps into the template space. A putamen mask was manually selected on the T1W template, which was applied to each vascular detail map. 17 out of the 30 data sets were selected with usable MRA contrast around the putamen area. The normalized vascular detail map for each study was binarized and summed to generate a vascular spatial probability map of the nonhuman primate putamen.

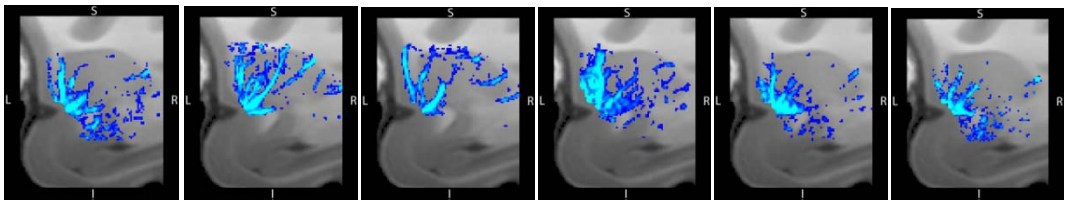

Figure 2: Normalized MRA MIPs of 6 subjects with threshold to zero out non-vessel background, overlaying on T1W template in sagittal view.

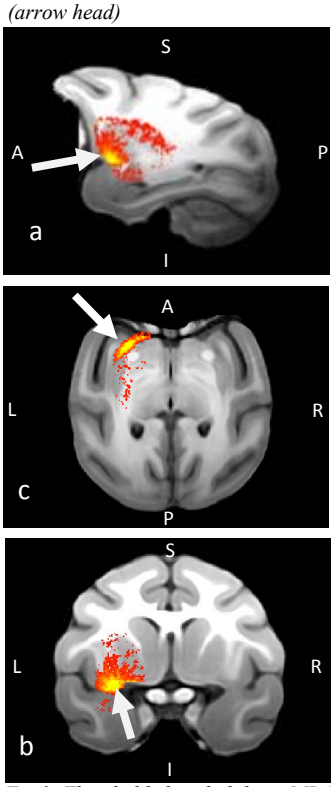

Fig 3: Thresholded probabilistic MRA putamen template MIP overlaid with T1W template in (a) sagittal view, (b) coronal view, (c)axial view. Yellow demonstrated high SI pixels, red for low SI pixels

RESULTS: Fig2 shows MIPs of 6 subjects with good vascular contrast in putamen. In general the vessels appear to originate in the same region but there is considerable variability in both density and location of the finer vessel details.

Fig 3 is a maximum intensity projection (MIP) of the probabilistic MRA putamen template overlaid on theT1 template in the3 orthogonal planes. The minimum MIP threshold was set at 3 subjects. The yellow hot spot is the blood vessels region with highest probability, which corresponds to a maximum of 17 subjects. This region is in the rostral ventral lateral region of the putamen. The probability is much lower over much of the rest of putamen. In our experience with CED infusions, much of the infusion loss occurs from vessels in this yellow area.

DISCUSSION: It is important to minimize the loss of infused drugs from the target area. This study presents a novel approach for mapping the density and location of blood vessels for a population of subjects. This atlas reflects the probability of vessels detected as a function of anatomical location. In the monkey putamen, the highest probability of vessels is in a ventral lateral region of the putamen. The vessel likelihood is much lower across the rest of the structure. This knowledge will be useful for planning future infusion studies in the putamen to avoid vascular shunting of the therapeutic agent. Though the study used contrast enhanced MRA techniques, the framework would work equally as well for other MRA methods like time-of-flight or phase contrast. These methods may be applied to human infusion studies by creating templates of vascular probability by applying the same strategies outlined here. This would be of potential value for surgical planning as well as infusion targeting in clinical studies

REFERENCE: [1] M.W. Woolrich, et.al. NeuroImage, 2009. [2] M. Jenkinson and S.M. Smith. Medical Image Analysis, 5(2):143-156, June 2001.[3] Avants, B. & Gee, J. C. Neuroimage, University of Pennsylvania, Philadelphia, PA 19104, USA., 2004, 23 Suppl 1, S139-S150