A macaque brain white matter atlas based on averaged high resolution DTI

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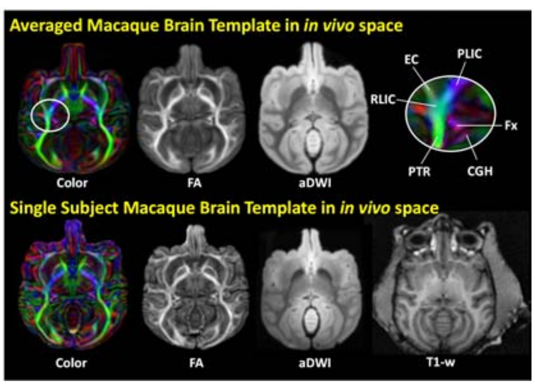
Target audience: MR physicists and neuroscientists who are interested in using the high resolution probabilistic macaque brain DTI atlas.

Purpose: Characterizing white matter (WM) anatomy based on DTI has greatly enhanced our knowledge on human brain anatomy (e.g. 1-4). A comprehensive characterization of WM anatomy of macaque brain with DTI can not only provide neuroanatomical atlases for neuroscientific studies using macaque model (e.g. 5-6), but also aid the study of the WM evolution (e.g. 7). Currently available macaque atlases based on histology, conventional T1 weighted MRI (e.g. 8-9) and chemical tracing (10) are playing important roles as anatomical references. Recently, a macaque brain DTI template (11) from a larger cohort of *in vivo* macaques has been established. However, there has been no high resolution digital WM atlas providing the detailed WM tract labels. WM tracts underlie the connectivity of brain regions which play essential roles for understanding brain functions and evolution of brain functions. Such a WM atlas based on high resolution averaged DTI data and in *in vivo* space and digital format is needed. In this study, we aimed to generate a probabilistic and comprehensive digital atlas including labeling of WM tracts with ultra-high resolution DTI data (0.35x0.4x0.45mm^3) of a population of macaque brains

Methods: *Macaques:* Ten young adult macaques (age: 5.3±2.8 year; body weight=5.7±2.3kg; 6 M and 4 F) were obtained from the macaque colony. All studies were done with great care to ensure the well-being of the monkeys. After *in-vivo* MRI/DTI, 8 macaque brains were fixed by perfusion fixation with 4% paraformaldehyde. *In-vivo acquisition of T1 weighted image:* A Philips 3T Achieva MR system was used. Anesthesia was maintained by either sodium pentobarbital (25mg/kg IV) or a mixture of ketamine (7mg/kg) and xylazine (0.5-2mg/kg). T1 weighted (MPRAGE) image at resolution of 0.75x0.75x0.75mm was acquired. *Ex-vivo high resolution DTI acquisition:* 3D multiple spin echo DTI was performed in 4.7T Bruker scanner. Multiple echo (number of echoes = 8) DTI sequence was adopted to improve the SNR. The nominal resolution was 0.3x0.43x0.45 mm. *Macaque brain template:* Single subject macaque brain template was obtained by transforming the *ex vivo* high resolution DTI data into *in vivo* space with LDDMM transformation (12) based on contrasts of *ex vivo* averaged diffusion weighted image (aDWI) and *in vivo* T1-weighted image. Affine and LDDMM transformations to the single subject template in *in vivo* space were applied to high resolution *ex vivo* DTI data of other 7 macaque brains to generate averaged macaque brain template. These inter-subject matrixes were saved for transformation of the tractography results below. *Probabilistic tracts:* Totally 20 different tracts (see legend of Fig. 2 for abbreviations and names of the tracts) were traced with the tracotography protocol (13) from the ultra-high resolution *ex vivo* DTI in their native space. The inter-subject transformation matrices above were applied to transfer the tracts into the averaged brain template in *in vivo* space. *WM atlas with the tract labels:* Based on the anatomical information from probabilistic tracts derived from tractography, contrasts of DTI color-encoded map and literature (8-10), the common WM structures were manually delineated by a neuroanatomist.

Results: *Macaque brain template:* Fig. 1 shows both averaged and single subject template of macaque brain in *in vivo* space. High resolution and high signal-to-noise ratio (SNR) of both templates are clear. Sharp contrasts of averaged macaque brain template (upper panels of Fig. 1) suggest high quality of inter-subject registration. Due to these factors, detailed WM anatomical information including that of small WM fibers can be readily appreciated from averaged macaque template, especially with the enlarged color-encoded map. *Probabilistic tracts:* Probabilistic tracts of some of 20 tracts in *in vivo* averaged brain template space are shown in Fig. 2. Individual differences around the boundaries of WM bundles, indicated by cold color with low probability, and consistency at the core of the WM bundles, indicated by warm color with high probability, can be observed. *WM atlas:* The macaque brain atlas in its axial, parasagittal and coronal orientation with clear labels of all major WM tracts is shown in Fig. 3.



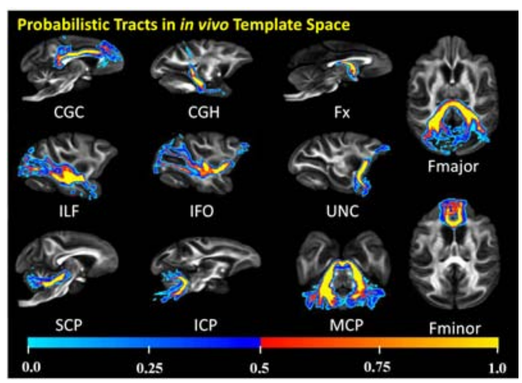


Fig. 1 (left): High resolution color-encoded map, FA map and aDWI of averaged macaque brain template (upper panel) and single subject macaque brain template (lower panel) *in vivo* space. *In vivo* T1 weighted image with anatomical information of head is also shown in lower panel.

Fig. 2 (right): Probabilistic tracts in *in vivo* template space. The underlying FA map is from the averaged macaque brain template in *in vivo* space. Abbreviations: ACR: anterior coronal radiation; ALIC/PLIC/RLIC: anterior/posterior/retrolenticular limb of internal capsule; ATR/PTR/STR: anterior/posterior/superior thalamic radiation; BCC/GCC/SCC: Body/genu/splenium of corpus callosum; CGC: cingulum in the cingulate cortex; CGH: cingulum in the hippocampal area; CP: cerebral peduncle; CST: corticospinal tract; EC: external capsule; Fmajor/Fminor: forceps major/minor; Fx: fornix; ICP: inferior cerebellar peduncle; IFO: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; MCP: middle cerebellar peduncle; ML: medial lemniscus; SCP: superior cerebellar peduncle; SS: sagittal striatum; TAP: tapetum of CC; UNC: uncinate fasciculus.

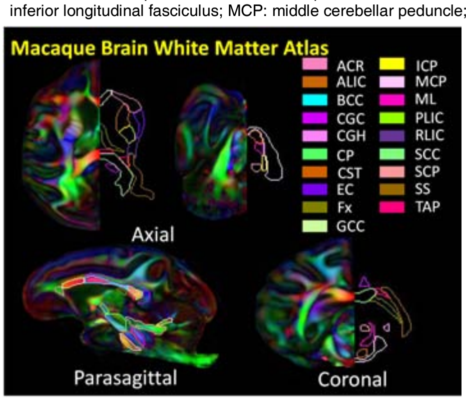


Fig. 3 (lower): Averaged macaque brain WM atlas. The underlying color-encoded map is from the averaged macaque brain template in *in vivo* space.

Discussion and conclusion: A probabilistic atlas of macaque brain white matter has been established based on high resolution DTI data from a population of macaques. Fig. 1 demonstrates the high quality of the high resolution DTI data and inter-subject registration. The probabilistic tracts in Fig. 2 not only show the reproducible core of major bundles among different macaque brains, but also provide convincing anatomical reference for atlas making. Based on the anatomical information from probabilistic tracts derived from tractography, contrasts of DTI color-encoded map and literature, the WM tracts were parcellated and labeled comprehensively on the average macaque brain template. With its digital and probabilistic nature, it will be a complementary resource of current T1- and histology-based atlas for neuroscientific researches. The anatomical information from this atlas may be not only used for anatomical guidance for neurobiological research but also for evolution studies. Anatomical information about cerebral cortex and subcortical nuclei will be integrated to yield an atlas with comprehensive anatomical information in future.

References: [1] Markis et al (1997) Ann Neurol 42:951. [2] Catani et al (2002) Neuroimage 17:77. [3] Wakana et al. (2004) Radiology 230:77. [4] Mori et al (2005) Elsevier. [5] Hendry and Yoshioka (1994) Science 264: 575 [6] Steinmetz et al (2000) Nature 404: 187. [7] Rilling et al (2008) Nat Neurosci 11: 426. [8] Martin R and Bowden DM (1996) Neuroimage 4:119. [9] Saleem KS and Logothetis NK (2007) Elsevier. [10] Schmahmann JD and Pandya DN (2006) Oxford Univ. Press. [11] Adluru et al. (2012) Neuroimage 59: 306. [12] Miller et al (2002) Annu Rev Biomed Eng 4: 375. [13] Wakana et al. (2007) Neuroimage 36: 630. **Acknowledgement**: This study is sponsored by NIH MH092535 and NIH EB009545.