

Primate brain template image and reference atlas creation for voxel-based functional analysis of PET in *Macaca fascicularis*

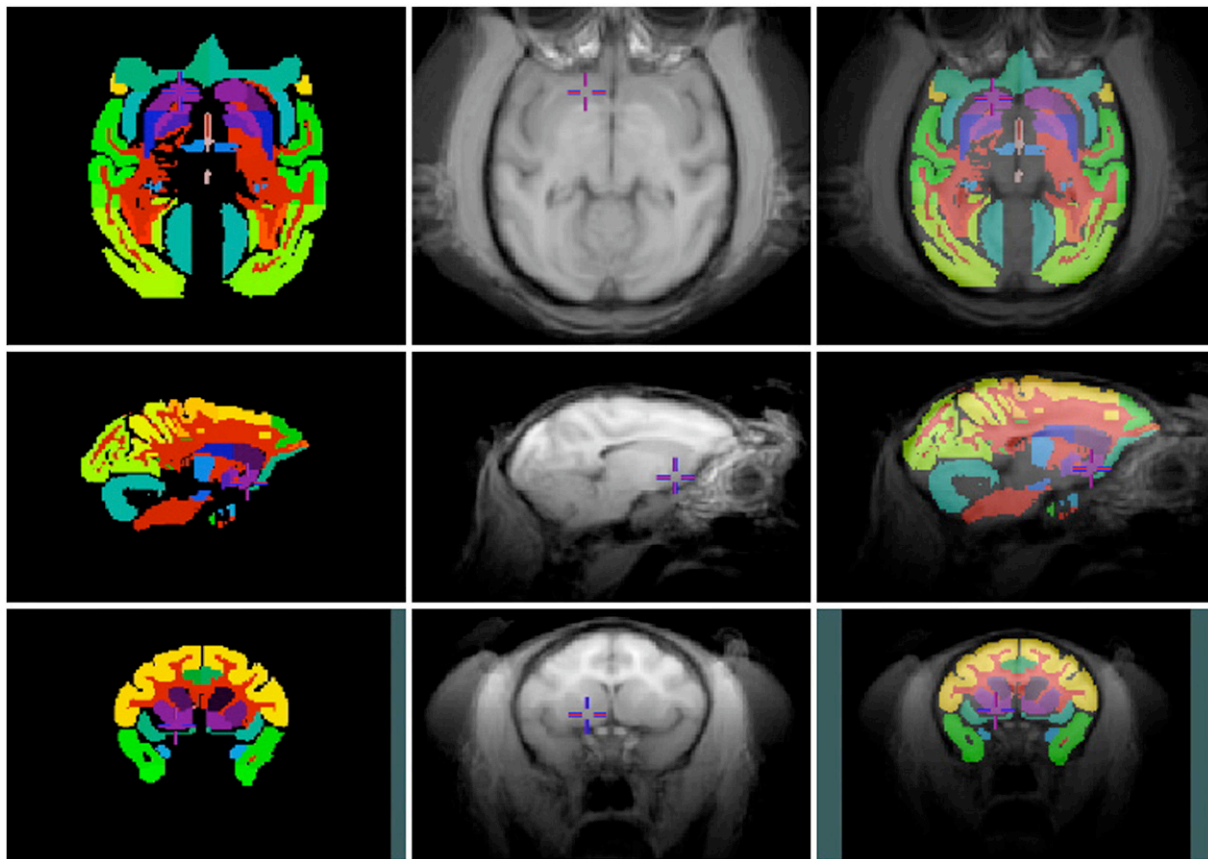
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Neuroimaging studies are increasingly performed on non-human primates, including *Macaca fascicularis*. The analysis of functional imaging studies requires a corresponding anatomical image in order to identify brain structures. In the specific case of positron emission tomography (PET), anatomical correspondence is also required for quantification and modeling of interactions between the PET ligand and its pharmacological receptors. For voxel-based statistical parametric mapping, a reference frame (template) is needed to perform spatial normalization of individual brains. In this work we introduce a specific brain template and its associated atlas, with the purpose of enabling accurate, robust and reliable normalization and anatomical labeling of *Macaca fascicularis* brain images.



Methods: Seven animals were included for template creation. For each, three high-resolution (0.6 mm^3) 3D T1 MRI scans were acquired and averaged for noise reduction. The atlas was created from the MRI of one subject by labeling 38 brain structures in three dimensions, following a precise manual delineation protocol. Regions included cortex, sub-cortical nuclei, brainstem, white matter and cerebrospinal fluid. The chosen MRI was then used as the target for an automatic iterative procedure of template creation: each MRI was subjected to automatic brain extraction, coregistered to the target with rigid-body transformations and resampled. Coredgistered MRIs were averaged. The average brain was then coregistered to the original brain target to compensate for misalignment bias. The resulting image constituted the first template, and was used as the target for the next iteration. Iterations continued until each parameter of the coregistration of the i th template to the original target was below 0.3 mm and 1 arc degree. The final template was tested for accuracy, robustness and reproducibility as follows: accuracy was assessed by visually inspecting the normalized brain on the template, with positioning inspection of the brain structures of the atlas projected on individual MRI with the reverse normalization transform. Robustness was tested by normalizing a new set of MRIs coming from other individuals to the template.

Reproducibility was tested on four of the seven monkeys which were also submitted to PET acquisitions with various tracers ($[^{11}\text{C}]$ raclopride, $[^{18}\text{F}]$ -dopa, $[^{18}\text{F}]$ MPPF, $[^{11}\text{C}]$ pe2i, and $[^{11}\text{C}]$ DASB), with test-retest scans. Time-activity curves were extracted from manually delineated regions of interest (ROI), from automated delineated ROIs of the atlas on normalized data, and from atlases propagated to

individual MRIs. By comparison of ROI volumes, ROI tracer distribution volumes and modeled binding parameters were established, and bias, standard error and intra-class coefficients (ICC) computed.

Results: Fig. 1 shows the atlas, template and fusion on three orthogonal slices centered on the striatum. Visual inspections were in good agreement with the anatomy. Robustness tests were passed with success for every individual. Reproducibility was high, with bias between methods smaller than the test–retest standard error, and ICCs were over 0.7.

Conclusion: A brain *Macaca fascicularis* template and a reference atlas were obtained and validated. These references are suitable for future voxel-based, longitudinal and multi-tracer analyses. They are also useful for quantification, for post-hoc corrections such as partial volume effect recovery, and for inter-individual comparisons.

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