Characterization of Structural Connectivity of the Default Mode Network in Dogs using Diffusion Tensor Imaging

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Purpose: In the evolutionary hierarchy, dogs occupy an intermediate stage between primitive species (e.g., rodents) and highly advanced species (e.g., primates). This makes them an interesting species worth studying as animal models in translational research to investigate human diseases that affect white matter integrity such as neurological demyelinating conditions (e.g., Multiple Sclerosis) [1] and Rabies, a virtually incurable disease [2]. Thus non-invasive imaging of neural white matter tracts in the dog brain by using diffusion tensor imaging (DTI) could prove to be very useful. In this study, diffusion-weighted images (DWI) were acquired in anesthetized dogs to develop a DTI-based atlas of the dog brain for use in future studies investigating healthy and diseased structural connectivity patterns. Specifically, we use the dog DTI atlas to test the following hypothesis: In a study recently conducted on dog brains using resting state fMRI [3], it was observed that the anterior and posterior parts of the Default Mode Network (DMN) seem to be dissociated unlike in primate brains. Therefore, we investigated whether DTI tractography provided a structural basis for this dissociation in the form of weaker structural connection between these regions in dogs as compared to humans.

Methods: Diffusion Weighted Images were obtained using a 3T MAGNETOM Verio (Siemens Healthcare, Erlangen, Germany) MRI scanner from 23 anaesthetized dogs using a human knee coil (serving as a dog head coil) and an EPI (Echo Planar Imaging) based diffusion sequence with the following parameters: TR=3.6 s, TE=95 ms, flip angle=90˚, 128×128 acquisition matrix, 30 diffusion directions, b=0 and 1000, voxel size=3×3×3 mm^3. Data were preprocessed using the standard FMRIB's Diffusion Toolbox (FDT, which is part of the FMRIB software library (FSL)). Data were first brain extracted, and then eddy current corrected. Following this, diffusion tensors were fit to the corrected data, creating tensor and fractional anisotropy (FA) maps. FA maps for each subject were registered to the high-resolution canine ex-vivo template created previously [4] using FMRIB's linear registration tool (FLIRT). The resulting transformation matrix computed while registering FA maps to the template was applied to the tensor maps for each subject, thus obtaining the vector data of each subject in the same standard space. By averaging all the FA maps and the vector data in the template space, an average FA map and average color-coded tensor map were computed. Diffusion parameters were modelled using the BEDPOSTX tool in FSL and then probabilistic tractography was implemented using the PROBTRACKX tool in FSL to estimate the likely connections between two regions of interest (ROIs). The ROIs were defined as 4mm radius spheres in the posterior cingulate cortex (PCC) and in the anterior cingulate cortex (ACC), which were registered to each subject using the previously defined transformation matrix. In this way, fiber tracts were calculated in the subject space, and then transformed to the template space. A group-wise mean FA value was extracted from the ACC-PCC tracts. ACC-PCC tracts of each subject were then binarized and compiled to create a group level probability map of the tracts for dogs with a subject count threshold in which value of each voxel represents the number of subjects that had a tract passing though that voxel.

Results and Discussion: Average FA weighted first principal direction color map and average FA map were computed (Fig 1) to provide a robust atlas void of disproportionate influence from any one subject. This average color map gives a fair idea about the neural tracts in the white matter of a dog brain. Group mean FA was extracted from the ACC-PCC tract which was found to be 0.32 which is much lower compared to the mean FA previously calculated for humans (young adults) [5] which was 0.57. Additionally, the group level probability map of the tracts obtained for dogs (Fig 2), indicates significant individual variability in the ACC-PCC tracts as a maximum of only 9 out of 23 dogs were found to have the same tract.. As previously reported [6] in a study conducted with humans as subjects, tracts connecting Medial Prefrontal Cortex (mPFC) to PCC were detected in 22 of 23 subjects. Low FA values in the cingulate cortex (along the ACC-PCC axis) in dogs leading to probable less number of fibers might have contributed to increased individual variability. This supports our hypothesis that the weaker resting state functional connectivity found between ACC and PCC in dogs compared to humans [3] may have a structural basis. This might also suggest that the evolution of higher cognitive functions in humans was supported by stronger functional and structural connectivity between anterior (ACC) and posterior regions (PCC) of the DMN.

Limitations: Direct comparison of FA values between dogs and humans involves certain caveats - (i) The size of the brain in dogs is smaller than in humans, but the resolution of diffusion data acquired was not proportionally higher in dogs, (ii) The exact placement of seed ROIs in humans is likely to be more accurate than in dogs given that labeled atlases are available in humans, (iii) the anatomy of dog and human brains, especially the frontal cortex, may not be exactly comparable.

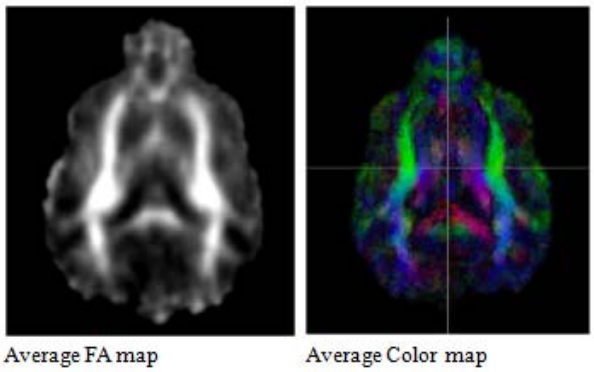

Figure 1. *Average FA map and color map atlas using a group of 23 dogs. Color map represents left-right tracts in Red, anterior-posterior in Green and superior-inferior in Blue.*

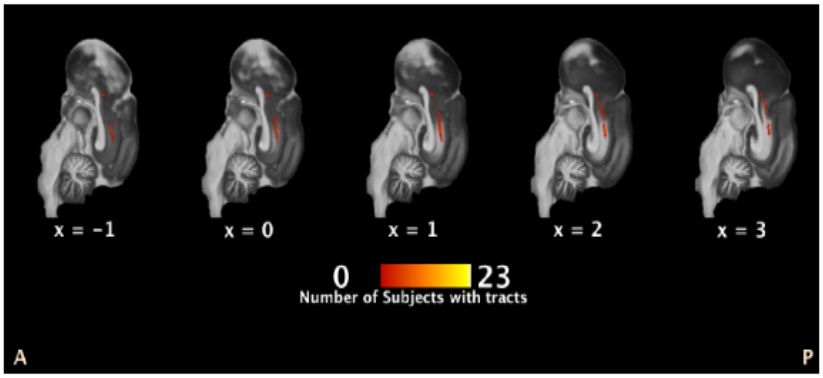

Figure 2. *Group level probabilistic map of ACC-PCC tracts. The color scale indicates number of subjects that had a tract in a given voxel.*

References: **1.** Yu et al. NeuroImage 2011 **2.** Laothamatas et al. Adv. in Virus Research, 2011 **3.** Kyathanahally et al. Brain Structure & Function. 2014 (in press) **4.** Datta et al. PLoS ONE, 2012 **5.** Supekar et al. NeuroImage, 2010 **6.** Greicius et al. Cereb. Cortex, 2009. **Acknowledgment**: Funding from Auburn University's Intramural Grant and from the Defense Advanced Research Projects Agency (government contract/grant number W911QX-13-C-0123) is gratefully acknowledged