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Microstructural changes in locus coeruleus-cortical projections in aged bonnet macaques are independent of myelin loss

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Synopsis

Keywords: Aging, Aging, advanced diffusion, bonnet macaque, locus coeruleus

Motivation: Little is understood about the effects of normal aging on the locus coeruleus and whether quantitative MRI maps are sensitive enough to detect changes.

Goal(s): To understand which MRI maps show sensitivity to LC changes in high resolution *ex vivo* imaging.

Approach: We utilized aged and adult female bonnet macaque specimens. Whole brains underwent an extensive *ex vivo* protocol to generate comprehensive and complimentary sets of quantitative maps.

Results: We found subtle changes in restriction based metrics with age in the LC nucleus itself and alterations in diffusivity metrics but not volume changes or changes in measures of myelin content in LC projections.

Impact: Our study reports subtle changes in the LC and its projections and highlights the benefit of combining multiple quantitative MRI maps. This suggests that incorporating advanced diffusion maps to understand microstructural changes in clinical applications could be beneficial.

Synopsis

Seven fixed aged and adult bonnet macaque brains underwent an extensive *ex vivo* imaging protocol to assess the microstructural environment of the locus coeruleus (LC) and its ascending cortical projections along the central tegmental tract (CTT) with respect to age. Within the LC, we found subtle changes in diffusion-based metrics in aging. In the CTT, we found alterations in diffusivity metrics but not volume changes or changes in measures of myelin content.

Introduction

The locus coeruleus (LC) is a brainstem nucleus best known for being the primary site of noradrenaline production for the forebrain and is involved in the modulation and optimization of behavioral performance. The LC has many targets throughout the cortex, and ascending projections from the LC join the central tegmental tract (CTT), a well-defined white matter brainstem tract in the pons that terminates in the thalamus. Evidence indicates that the LC is one of the first brain regions to show pathological burden in Alzheimer's disease (AD), and AD patients exhibit structural alterations in the LC and its ascending projections. The extent to which changes occur in the LC and its projections in normal aging, however, is less clear. Analysis of LC-forebrain tractography has historically been difficult due to the small size of the LC as well as the abundance of crossing fibers in the brainstem. *Ex vivo* magnetic resonance imaging (MRI) at high resolution enables small tract visualization and measurement. Here, we utilize a cohort of bonnet macaques, an excellent model of normative aging, and analyze the microstructure of the LC and its projections that join the CTT with respect to age.

Methods

All images were acquired on a Bruker 7T pre-clinical MRI scanner with an 86mm quadrature coil. The whole brain imaging protocol included diffusion tensor imaging (DTI) scans at 600µm, multi-spin echo (MSE) T2 scans at 600µm, a high resolution T2 weighted at 200µm, and T1 FLASH and selection inversion recovery (SIR) scan at 200µm resolution. For local imaging a 30mm single channel loop coil was placed on the brainstem as a receive coil. High resolution anatomical (multi-echo T2-weighted) and multi-shell diffusion MRIs at 350µm resolution were collected as described above. Brains were processed individually using software on the University of Arizona's high-performance computing cluster(HPC) . REMMI toolbox[1] and TORTOISE[2] were used to create macromolecular maps such as bound pool fraction (BPF), myelin water fraction (MWF) and diffusivity maps including Fractional Anisotropy, Radial Diffusivity (RD), Axial Diffusivity (AD), and Trace (TR). The local brainstem images were processed to extract mean anisotropic propagator (MAP) metrics such as RTOP, RTAP, RTPP, and PA. All regions of interest were manually drawn, and tractography was performed from the LC to the thalamus along the CTT using MRtrix. Individually generated tracts were converted into ROI maps. The LC and CTT ROIs were then binarized into masks, and voxel values of each map type were extracted and averaged across the mask. Individual relationships between microstructure and age were analyzed in MATLAB.

Results

In the LC nucleus itself, RTPP was significantly correlated with age such that older animals had higher restriction values. There was no association with age and volume of the LC and no significant associations between age and FA, AD, RD, TR, RTOP, RTAP or PA. In the LC-CTT, there was a significant correlation between age and FA and AD values such that older age was associated with lower FA values and lower AD values. There were no age-related associations with tract volume, RD, TR, MWF or BPF.

Discussion

Alterations in diffusivity metrics within the LC nucleus itself are consistent with reports of higher neuronal density in the LC in old age due to subtle volume but not cell population losses[3]. Lower FA and AD values were reported in the LC-CTT with age, but these changes were not associated with volumetric or myelin content metrics. This suggests that the LC-CTT does not experience loss of myelin or axons during normal aging processes. The lower FA and AD values may be due to inflammation, which can impact the microstructural environment.

Conclusion

Using high quality, high resolution microstructural MRI we found age-related restriction in the LC itself and decreased anisotropy in the CTT in the absence of volumetric or relaxometry changes. Therefore, subtle cellular alterations are detectable using diffusion MRI during normative aging in the LC and its projections.

Acknowledgements

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References

Figures

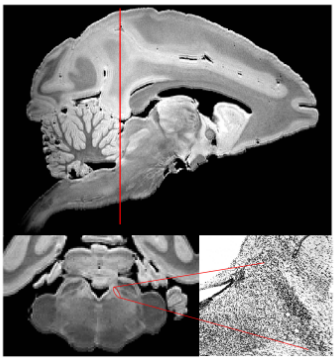

Figure 1: A whole brain high resolution anatomical image and Nissl-stained brainstem section from the same animal. The LC is visible from sagittal and coronal sections and the location has been validated with histology.

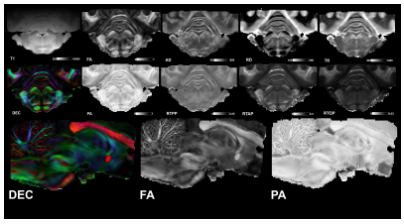

Figure 2: Local imaging of brainstem anatomical and diffusion weighted maps from a representative animal. Top row: coronal cross section of brainstem T1 inversion recovery, FA, AD, RD, and TR maps. Middle row: DEC, PA, RTPP, RTAP, and RTOP maps. Bottom row: sagittal cross section of DEC, FA, and PA maps.

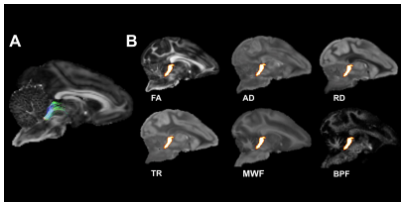

Figure 3: LC CTT Tractography. Tractography for the LC – CTT was first generated for each animal in native space; **A)** shows a representative example. **B)** The individual tracts were then binarized and overlaid onto different quantitative maps to determine microstructural values of FA, AD, RD, TR, MWF, and BPF within the LC-CTT.

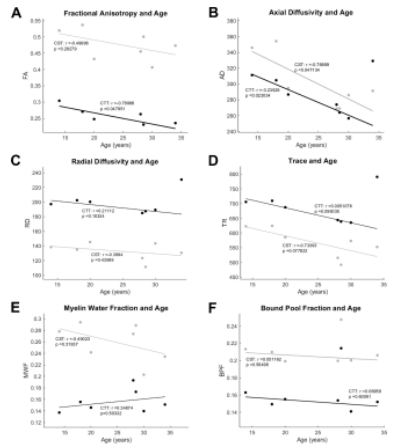

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Figure 4: Analysis of age and MR metrics in the LC- central tegmental tract and corticospinal tract. **A)** Fractional anisotropy was negatively correlated with age in the CTT, but was not associated with age in the CST. **B)** Axial diffusivity was negatively correlated with age in both the CTT and the CST. Neither tract showed significant associations with age and **C)** radial diffusivity, **D)** trace, **E)** myelin water fraction, or **F)** bound pool fraction.