Exploring quantitative MRI contrast in posterior cortical atrophy using ex vivo imaging

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Introduction:

Posterior cortical atrophy (PCA) is a rare variant of Alzheimer's disease (AD) where degeneration begins in the occipital lobe rather than the hippocampus/temporal lobe [Crutch2016]. Recent work has found MRI-visible breakdown of cortical lamination in AD neurodegeneration [Kenkuis2019]. We scanned post mortem samples of PCA, AD, and control tissue with quantitative MRI metrics (R1, R2*, mean diffusivity (MD), mean kurtosis (MK), and fractional anisotropy (FA)) sensitive to cortical microstructure [Edwards2018] to investigate whether similar cortical changes occur in PCA and whether these changes qualitatively differ from those in AD. With this we aim to inform in vivo applications.

Methods:

We used formalin-fixed tissue blocks containing primary visual cortex (V) and superior temporal gyrus (T) from a donor with PCA (PCA1, 75y m) provided by the Queen Square Brain Bank, UCL London (QSBB); a healthy control donor (CTRL) and 2 donors with AD (Braak V–VI; AD1 77y f, AD2 81y m) provided by the Brain Banking Centre Leipzig, Leipzig University; and a V-block from another donor with PCA (PCA2 71y m; QSBB). Before MRI, remnant fixative was washed out with PBS and blocks were placed in 20 mm syringes in Fomblin.

Multiparameter mapping (MPM) data [Weiskopf2013] was recorded on a 7T Siemens Magnetom scanner with custom CP transceive coil (220 µm isotropic resolution (iso.), 12 equispaced echoes TE 4–41 ms, TR 95 ms, PDw flip angle 12°, T1w 60°). B1 maps (1.5 mm iso.) were measured as per [Sacolick2010]. R2* was computed as per [Weiskopf2014], and R1 using an analytical solution of the Ernst equation (Eq. 17 in [Dathe2010]). A 50 µm iso. T2*w image (TE 19 ms, TR 200 ms, flip angle 50°) was also recorded.

Diffusion weighted imaging (DWI) data was recorded on a Bruker BioSpec 94/20 9.4T preclinical scanner with cryocoil (spin echo segmented EPI DWI sequence, 200 µm iso., 16 averages, b [0.3,2,4,8,12] ms/µm², 60 directions per b, TR 4 s, TE 25 ms). Kurtosis tensors fits using MDT (https://github.com/robbert-harms/MDT) gave MD, MK and FA.

MPMs were registered to DWI space. Initial GM/WM masks were estimated by thresholding and k-means clustering of the PDw echoes. Gross errors in the masks were manually corrected (by LJE).

Cortex was segmented into 20 equivolume layers in Nighres (https://github.com/nighres/nighres). Visual inspection of the V images showed the stria of Gennari (layer IVb) was mostly found in layers 8–13. We thus binned each parameter into layers 2–7 (lower), 8–13 (mid), and 14–19 (upper) so "mid" approximates layer IV. Areas showing artefacts were manually masked out (by LJE) before binning.

For histology, tissue blocks were paraffin-embedded, cut into 8 µm sections, and processed, alternating Nissl stain and immunohistochemistry for myelin basic protein (MBP) and Aβ deposits. Microscope images were recorded on a Zeiss Axioscan Z1. Layers I–III (upper), IV (mid), and V–VI (lower) were manually segmented (by CJ) on Nissl sections, projected onto the nearest MBP and Aβ sections, and used to bin the average optical density.

Box plots for all metrics were plotted in Matlab.

Results:

Fig. 1 shows cortical lamination degradation relative to CTRL in MRI contrasts, in line with previous R2*

observations in post mortem AD tissue [Nabuurs2013,Kenkuis2019].

Fig. 2 suggests that multimodal combination of regional differences in R2*, MD, and FA profiles could differentiate between AD and PCA. This differentiation could reflect differences in Aβ, myelin, or iron distribution, but could also reflect minor differences in tissue preparation. Quantitative iron measurements and in vivo experiments will allow further investigation.

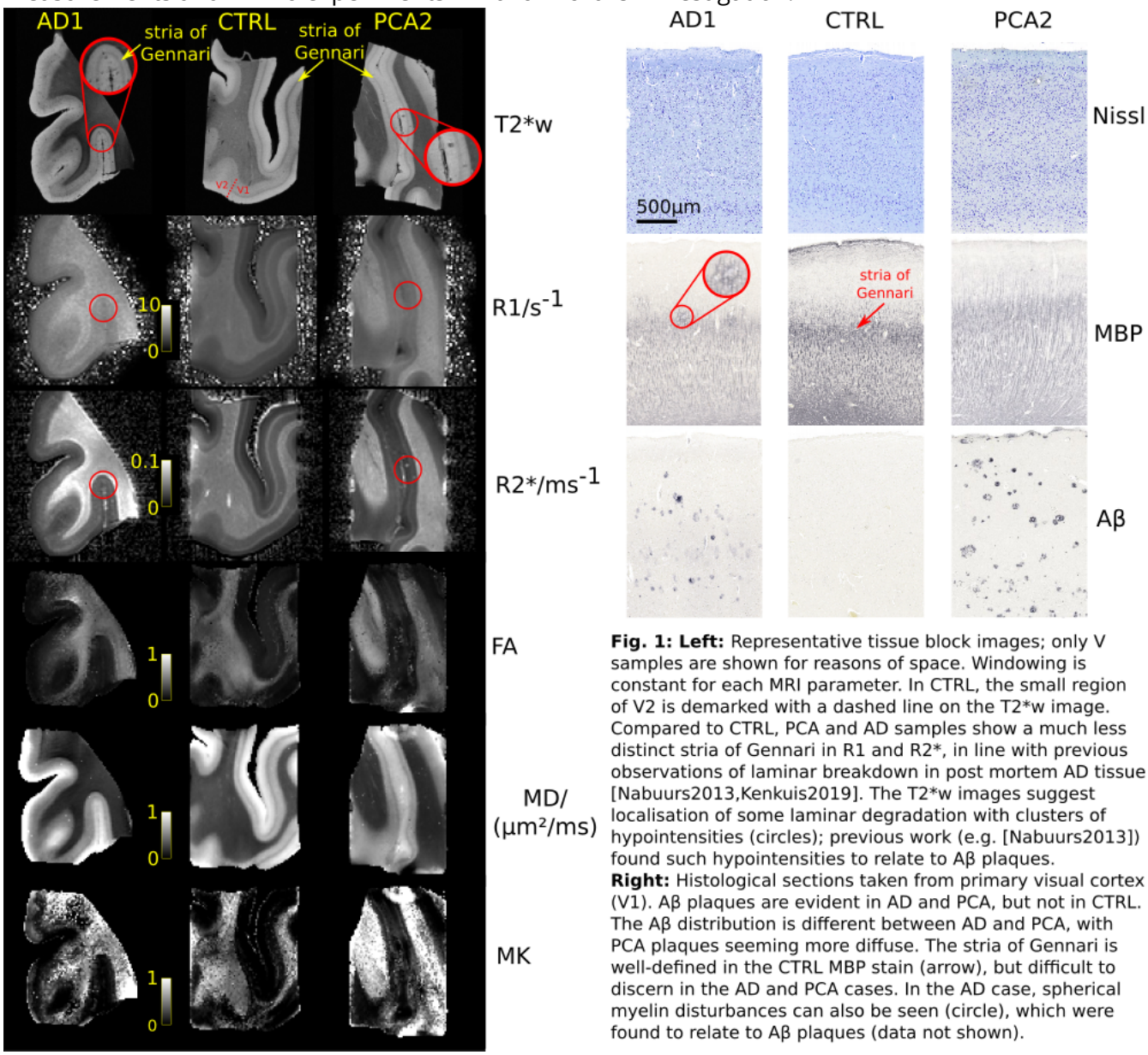

Fig. 1: Left: Representative tissue block images; only V samples are shown for reasons of space. Windowing is constant for each MRI parameter. In CTRL, the small region of V2 is demarked with a dashed line on the T2*w image. Compared to CTRL, PCA and AD samples show a much less distinct stria of Gennari in R1 and R2*, in line with previous observations of laminar breakdown in post mortem AD tissue [Nabuurs2013,Kenkuis2019]. The T2*w images suggest localisation of some laminar degradation with clusters of hypointensities (circles); previous work (e.g. [Nabuurs2013]) found such hypointensities to relate to Aβ plaques.
Right: Histological sections taken from primary visual cortex (V1). Aβ plaques are evident in AD and PCA, but not in CTRL. The Aβ distribution is different between AD and PCA, with PCA plaques seeming more diffuse. The stria of Gennari is well-defined in the CTRL MBP stain (arrow), but difficult to discern in the AD and PCA cases. In the AD case, spherical myelin disturbances can also be seen (circle), which were found to relate to Aβ plaques (data not shown).

(https://files.aievolution.com/prd/hbm2101/abstracts/abs_1421/Fig1.png)

·Fig. 1

Fig. 2: Box plots showing the distribution of the MRI (left) and histological (right) parameters in upper, mid and lower layers. The central red line is the median, the bottom and top edges of the blue box are the 25 and 75% percentiles, the black whiskers the most extreme values (excluding outliers), and the red crosses the outliers. To guide the eye, we plot the median mid-CTRL value as a red line across each plot. **Right:** The AD and PCA MBP layer distributions showed large decreases relative to CTRL, as well as a relative decrease in the prominence of the laminar profile. This could imply that the MRI-visible degradation of cortical lamination is partly associated with myelin changes. In line with AD progression, Aβ was higher than CTRL in T but not V. Interestingly, Aβ was elevated in all PCA samples, but the distribution within each bin was much broader. This is in line with the more diffuse spatial distribution of Aβ for PCA2 seen in Fig. 1. Aβ values were non-zero in CTRL because Aβ is found in all elderly brains; formation into senile plaques defines the pathology [Nabuurs2013]. **Left:** The stria of Gennari in CTRL/V manifested as a broadening of the mid layer distribution in R2* relative to CTRL/T, rather than a distinct peak (cf. MBP CTRL/V), likely due to imperfections in the layer definitions. R1 showed increases for AD1 and PCA2, but other samples had either a small decrease or were similar to CTRL. This may reflect differences in iron distribution in the different cases, as it is consistent neither with the Aβ nor the MBP observations. For the AD samples, R2* followed the same pattern as Aβ, with little difference relative to CTRL for V, but an increase for T. PCA R2* was similar to CTRL for all samples, except for a slight decrease for PCA1/V; this could reflect the more diffuse distribution of Aβ. In both AD and PCA (with the exception of the AD1/V upper layer), MD showed a decrease compared to CTRL; this contradicts in vivo observations of an MD increase in AD, but the in vivo increase may be confounded by partial volume effects [Henf2018]. MK showed a small increase compared to CTRL, but the maps are noisy (Fig. 1). For AD, FA showed a general increase in the T samples compared to CTRL, whereas in V the upper and lower layers moved in opposite directions. For PCA, the only clear FA difference was an increase in the lower layers of PCA1/T. FA is expected to reflect changes in myelin, as myelinated axons anisotropically hinder water diffusion [Edwards2018]. However, the FA changes here do not seem to correlate with the MBP patterns and thus likely reflect myelin reorganisation.

(https://files.aievolution.com/prd/hbm2101/abstracts/abs_1421/Fig2.png)

·Fig. 2

Conclusions:

We have shown that AD cortical lamination disturbances previously seen in R2* [Nabuurs2013] can be seen in other quantitative maps and in PCA. Observed differences in MRI contrast between PCA and AD may reflect their different progression, but the small number of samples calls for caution when extrapolating the results.

Disorders of the Nervous System:

Neurodegenerative/ Late Life (eg. Parkinson's, Alzheimer's) [1]

Neuroanatomy, Physiology, Metabolism and Neurotransmission:

Cortical Anatomy and Brain Mapping [2]

Novel Imaging Acquisition Methods:

Anatomical MRI
Diffusion MRI

Keywords:

ADULTS
Cortex
Cortical Layers

Degenerative Disease
DISORDERS
HIGH FIELD MR
MRI
Neurological
STRUCTURAL MRI

[1|2]Indicates the priority used for review

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No

Please indicate below if your study was a "resting state" or "task-activation" study.

Other

Healthy subjects only or patients (note that patient studies may also involve healthy subjects):

Patients

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Yes

Was any animal research approved by the relevant IACUC or other animal research panel? NOTE: Any animal studies without IACUC approval will be automatically rejected.

Not applicable

Please indicate which methods were used in your research:

Structural MRI
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Diffusion MRI
Postmortem anatomy

For human MRI, what field strength scanner do you use?

7T
If Other, please list - 9.4T

Which processing packages did you use for your study?

SPM
FSL
Other, Please list - Advanced Normalization Tools (ANTs), Microstructure Diffusion Toolbox (MDT), Nighres

Provide references using author date format

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