In long-term central retinal disease, visual performance is predicted by cortical atrophy with GCL, pRNFL and cortical thickness key biomarkers

Rachel L.W. Hanson[1,2,3,5], Heidi A. Baseler[1,2,3,4], Archana Airody[5], Antony B. Morland[1,2,3] and Richard P. Gale[3,4,5]

[1] Department of Psychology, University of York, UK, [2] York Neuroimaging Centre, University of York, UK, [3] York Biomedical Research Institute, University of York, UK, [4] Hull York Medical School, University of York, UK
[5] Academic Unit of Ophthalmology, York & Scarborough Teaching Hospitals NHS Foundation Trust, UK

Purpose

- Our current understanding of long-term retinal disease is that significant structural changes occur to both the anterior visual pathway (the eye) and the posterior visual pathway (the brain).
- The current study investigated which changes occur to the anterior and posterior visual pathways, potentially identifying biomarkers of disease progression in long-term central retinal disease.
- The second element of this study was to conduct an exploratory analysis of possible relationships between changes in the anterior and posterior visual pathway in the same cohort, attempting to address whether such changes may reflect retrograde or anterograde degeneration, retinal remodelling or adverse anti-VEGF response.

Methodology

- 14 participants diagnosed with long-term central vision loss (CVL): mean age = 78.7 years, 42.9% female
- 33 sighted controls with normal/corrected-to-normal vision: mean age = 71.02 years,42.4% female
- Neither group had any neurological issues

Subject	Gender	Age (y, m)	Bilateral Diagnosis	Worse Eye				Better Eye				Disease Duration (y, m)
				OD / OS	BCVA	# anti-VEGF injections	Retinal lesion size (mm²)	OD / OS	BCVA	# anti-VEGF injections	Retinal lesion size (mm²)	
P01	Male	63, 7	nvAMD	OS	20	6	22.73	OD	29	8	18.95	2, 3
P02	Female	69, 0	nvAMD	OD	HM	0	20.23	OS	34	35	16.75	5, 7
P03	Female	83, 7	nvAMD	OS	HM	0		OD	29	31	16.31	6, 5
P04	Female	75, 10	nvAMD	OD	65	59	6.56	OS	68	17	1.87	5, 10
P05	Male	84, 4	nvAMD	OS	52	55	21.18	OD	67	0	32.29	5, 4
P06	Male	74, 3	nvAMD	OD	46	43	13.5	OS	75	8	11.73	13, 7
P07	Male	77, 5	nvAMD	OD	68	59	13.93	OD	71	1	20.92	6, 1
P08	Female	90, 10	nvAMD	OS	24	0	46.99	OD	31	51	27.6	13, 2
P09	Female	90, 4	nvAMD	OS	HM	3	50.97	OD	48	99	28.51	10, 3
P10	Male	75, 7	nvAMD	OD	85	84	13.59	OS	85	72	28.43	7, 8
P11	Male	87, 11	nvAMD	OS	50	16	8.72	OD	71	49	12.58	6, 6
P12	Male	76, 6	CSCR/nv AMD	OS	3	3	38.79	OD	42	3	19.02	8, 4
P13	Male	73, 2	nvAMD	OS	37	0	35.18	OD	48	15	37.47	11, 11
P14	Female	85, 1	nvAMD	OD	25	17	3.92	OS	68	23	5.41	9, 1

Assessments

- The CVL group completed assessments of the anterior and posterior visual pathway whilst controls completed assessments of the posterior visual pathway only:

  Anterior Visual Pathway: Best corrected Visual Acuity (BCVA)
  Macular Ganglion Cell Layer Thickness (GCL)
  Peripapillary Retinal Nerve Fibre Layer Thickness (pRNFL)

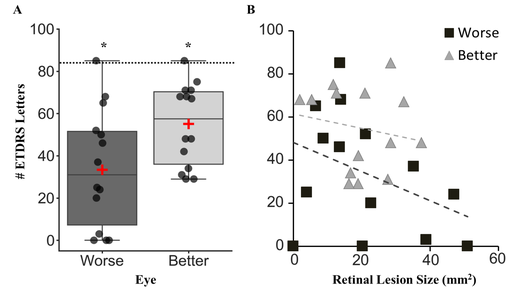
  Posterior Visual Pathway: Cortical volume of entire occipital lobe
  Cortical thickness of the calcarine sulcus (CS) and occipital pole (OP); cortical representations of the peripheral and central retina respectively

- Structural assessments of the anterior visual pathway were completed using Heidelberg spectral domain optical coherence tomography (SD-OCT)
- Assessments of the posterior visual pathway were performed using structural magnetic resonance imaging (MRI) on a 3T Siemens MAGNETOM scanner

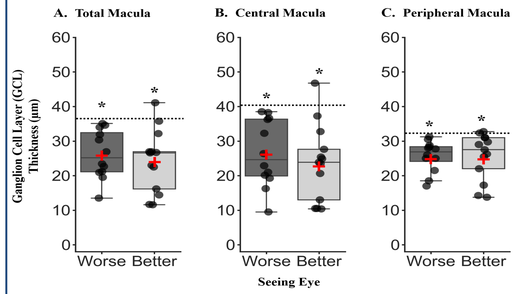
Exploratory Analyses

- 3 x sets of analyses explored the relationship between changes to the anterior and posterior visual pathways

Results – Anterior Visual Pathway

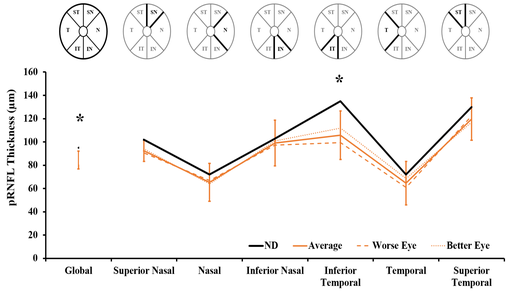


- One-sample t-test revealed that BCVA was significantly reduced from normal for the worse seeing (mean = 33.9 ETDRS letters, t(13) = -6.670, p = .000015, 2-tailed) and better seeing eye (mean = 54.7 ETDRS letters, t(13) = -5.628, p = .000082, 2-tailed)
- BCVA was not related to retinal lesion size, assessed via a Pearson correlation, for the worse seeing (R = -.387, p = .172) or better seeing eye (R = -.176, p = .546)



Compared against normative means of 36.8, 40.2 and 32.5µm respectively, both the worse and better seeing eyes were significantly thinner in each macular location:

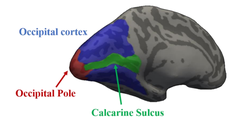
- **Total Macular GCL Thickness:** Worse seeing eye: mean = 26.2µm, t(11) = -5.257, p = .000269, 2-tailed; Better seeing eye: mean = 24.3µm, t(12) = -4.977, p = .000321, 2-tailed
- **Central Macular GCL Thickness:** Worse seeing eye: mean = 26.4µm, t(11) = -4.895, p = .000475, 2-tailed; Better seeing eye: mean = 23.6µm, t(12) = -5.409, p = .000158, 2-tailed
- **Peripheral Macular GCL Thickness:** Worse seeing eye: mean = 25.6µm, t(11) = -5.262, p = .000268, 2-tailed; Better seeing eye: mean = 25.6µm, t(12) = -3.728, p = .003, 2-tailed

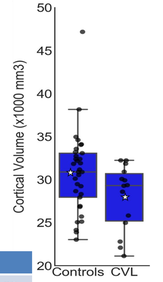


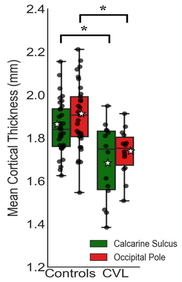
- Mean **Global pRNFL Thickness** was significantly thinner in the worse (mean = 82.8µm; t(11) = -3.229, p = .008) and better seeing eye (mean = 86.2µm; t(12) = -2.357, p = .036) compared to a normative mean of 95.0µm
- pRNFL thickness in the **Inferior Temporal quadrant** was significantly thinner in both the worse (mean = 99.5µm; t(11) = -5.531, p = .000178) and better seeing eye (mean = 111.8µm; t(12) = -3.716, p = .003) compared against a normative mean of 135.0µm
- pRNFL thickness at all other locations were not significantly different

Results – Posterior Visual Pathway

- There was a non-significant reduction in **Cortical Volume** between groups, despite a medium effect size: F(1, 44) = 3.339, p = .074,
- Representing the central retina, **Occipital Pole Thickness** was significantly reduced with a large effect size, F(1, 46) = 13.086, p = .001, η^2 = .225
- Representing the peripheral retina, **Calcarine Sulcus Thickness** was significantly reduced with a large effect size, F(1, 46) = 12.122, p = .001, η^2 = .212







	Worse Seeing Eye				Better Seeing Eye			
	R	R^2	p	BCp	R	R^2	p	BCp
BCVA v Retinal lesion size	-.387	-.150	.172	.172	-.176	-.031	.546	.546
Can retinal structure predict cortical structure?								
Total macular GCL thickness v cortical volume (N = 13)	.324	.105	.304	.608	.003	.000	.992	.999
Global pRNFL thickness v cortical volume (N = 13)	.148	.022	.647	.999	.450	.202	.123	.246
Central macular GCL thickness v mean cortical thickness OP (N = 13)	-.134	-.018	.677	.999	.274	.075	.364	.999
Peripheral macular GCL thickness v mean cortical thickness OP (N = 13)	-.141	-.019	.663	.999	-.059	-.003	.847	.999
Average Temporal pRNFL thickness v mean cortical thickness OP (N = 13)	.049	.002	.880	.999	-.135	-.018	.660	.999
Average Nasal pRNFL thickness v mean cortical thickness CS (N = 13)	-.165	-.027	.609	.609	.202	.041	.509	.509
Can changes in cortical structure predict visual function?								
Mean cortical thickness OP v BCVA (N = 14)	.576	.331	.031	.062	.513	.263	.061	.122
Mean cortical thickness CS v BCVA (N = 14)	.332	.110	.246	.492	.142	.020	.629	.999
Can bilateral disease duration and number of anti-VEGF injections predict retinal structure, visual function or cortical structure?								
Bilateral disease duration v								
Total Macular GCL Thickness (N = 13)	-.140	-.019	.665	.999	-.804*	-.646	.001	.002
Global pRNFL Thickness (N = 13)	.367	.135	.240	.480	.003	.000	.992	.999
BCVA (N = 14)	-.083	-.007	.777	.777	.073	.005	.805	.805
Cortical volume (N = 14)	-.168	-.028	.566	.999				
Mean cortical thickness OP (N = 14)	.223	.049	.444	.999				
Mean cortical thickness CS (N = 14)	-.027	-.000	.927	.999				
Number of Anti-VEGF injections v								
Total macular GCL thickness (N = 13)	-.266	-.071	.403	.806	-.084	-.007	.785	.999
Global pRNFL thickness (N = 13)	.036	.001	.913	.999	-.195	-.038	.524	.999

Results – Exploratory Analyses

Exploratory analyses assessed the following questions:

- **Can retinal structure predict cortical structure?**

The relationship between total GCL thickness and Global pRNFL thickness and cortical volume require further investigation due to small effect sizes

- **Can cortical structure predict visual function?**

There was a medium effect size when correlating BCVA and cortical thickness in the occipital pole requiring further investigation

- **Can bilateral disease duration predict retinal structure, visual function or cortical structure?**

A large effect size was shown when correlating bilateral disease duration and total macular GCL thickness requiring further investigation

Conclusion

- Long-term central vision loss is associated with significant structural changes to both the retina and the brain
- Exploratory analysis suggests that monitoring GCL thickness may be a sensitive biomarker of disease progression and reductions in visual cortical thickness may be associated with reduced visual acuity
- Whilst this study is limited by its heterogeneous population, larger cohort studies would be needed to better establish some of the relationships detected between disease dependent structural properties of the anterior and posterior visual pathway given the effect sizes reported in our exploratory analysi

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