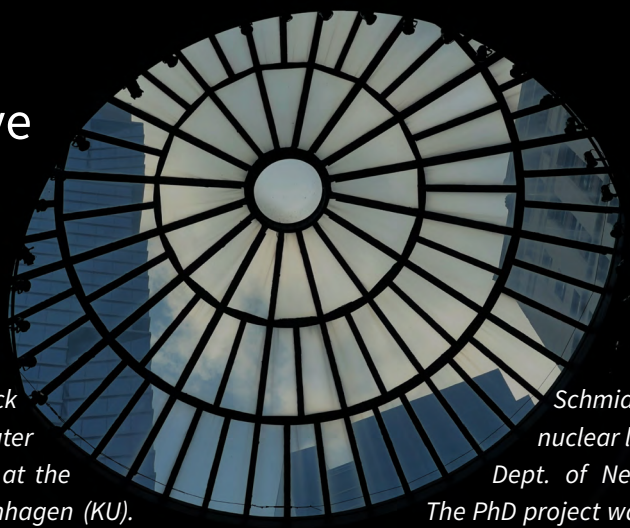
The retina as a window to the brain:
Retinal hyperreflective foci in multiple sclerosis and optic neuritis



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On June 14, 2024, Mathias Falck Schmidt defended his thesis "Hyperreflective foci in the avascular outer nuclear layer of the retina in multiple sclerosis with and without optic neuritis" at the Dept. of Neurology, Faculty of Health and Medical Sciences, University of Copenhagen (KU). The PhD project was conducted at the Dept. of Neurology, Rigshopitalet. The main supervisor was Prof. Jette Lautrup Frederiksen, Dept. of Neurology, Clinic of Optic Neuritis, Danish Multiple Sclerosis Center (DMSC), KU; with co-supervisors Prof. Michael Larsen, Dept. of Ophthalmology and Dr. Gorm Pihl-Jensen, Dept. of Neurology, Clinic of Optic Neuritis, DMSC; both at Rigshospitalet and KU, Denmark.

The retina is considered an extension of the central nervous system (CNS), sharing anatomy, function, and immune activity with the brain. Major neurodegenerative diseases, including multiple sclerosis (MS), manifest in the retina, underscoring its role as a mirror of CNS pathology. Approximately 20% of patients present with optic neuritis as the first clinical sign of MS. Among the available imaging methods, optical coherence tomography (OCT) offers a non-invasive way to visualize retinal pathology in both MS and optic neuritis (ON). One of the more recently recognized OCT findings is hyperreflective foci (HF) (**Figure 1**). The exact nature of HF remains unclear, but they are thought to represent activated microglia, the resident immune cells of the CNS and key players in neuroinflammation.

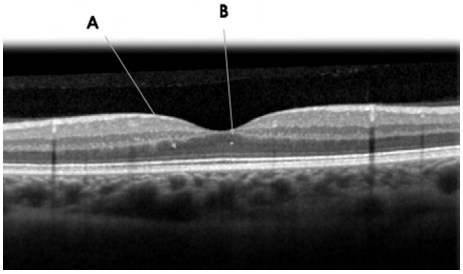

Figure 1. Cross-sectional OCT image shows a hyperreflective focus (B) in the outer nuclear layer of the retina (A). Figure republished from the PhD thesis "Hyperreflective foci in the avascular outer nuclear layer of the retina in multiple sclerosis with and without optic neuritis," Graduate School of Health and Medical Sciences, University of Copenhagen, April 28, 2024.

The outer nuclear layer (ONL) is an avascular retinal zone containing the nuclei of photoreceptor cells. In healthy eyes, it appears hyporeflective on OCT and normally lacks fixed elements. Although one study found an increased number of HF in the inner nuclear layer (INL) of patients with early-onset relapsing-remitting MS (RRMS), HF numbers have not been shown to be elevated in the ONL. Differentiating HF from retinal vessels, particularly in the INL, remains a major challenge. This PhD therefore focused specifically on HF in the ONL. The first article of this thesis investigated HF in the ONL of the retina in 44 patients with RRMS and 53 healthy controls. HF were nearly absent in controls but present in 70.5% of patients, establishing HF in the ONL as a potential MS-related finding. The second article followed a smaller MS cohort longitudinally for up to three years. HF recurred over time, with higher infiltration rates observed in patients with a history of ON. The third article developed and validated an automated method for HF detection in the ONL. Using convolutional neural networks, the model achieved high accuracy (AUC 0.989).

In summary, this PhD was the first to demonstrate that HF occur more frequently in the avascular ONL of patients with RRMS, particularly in those with prior ON, while remaining rare in healthy controls. Further studies should be performed to validate these findings, as HF may represent a novel marker of immune activity in an unmyelinated part of the CNS. Automated machine learning tools enable reliable identification and quantification of HF, thereby supporting future OCT protocols designed to monitor the precise dynamics of HF within the ONL of the retina.

Key points:

- Hyperreflective foci (HF) observed in the outer retina of patients with multiple sclerosis
- Non-invasive in vivo detection can be performed using OCT
- HF in the outer retina may serve as a marker of immune cell activity in the unmyelinated CNS

Future directions:

- Examine the diagnostic potential of hyperreflective foci (HF)in optic neuritis and MS
- Explore the potential correlation with MS severity and progression, which may elucidate the utility of HF detection in MS patients

References

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