

A clinical review of retinotopy

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Abstract

Two observations made 29 years apart are the cornerstones of this review on the contributions of Dr Gordon Plant to understanding pathology affecting the optic nerve. The first observation laid the anatomical basis in 1990 for the interpretation of optical coherence tomography (OCT) findings in 2009. Retinal OCT offers clinicians detailed *in vivo* structural imaging of individual retinal layers. This has led to novel observations which were impossible by direct ophthalmoscopy. The technique also helps to re-introduce the anatomically grounded concept of retinotopy to clinical practise. This review illustrates the anatomical basis for retinotopy through detailed sketches (Plant & Perry 1990). The pre- and post-laminar axons forming the optic nerve and their post-synaptic path from the dorsal lateral geniculate nucleus to the primary visual cortex in humans. With the mapped neuroanatomy in mind we use OCT-MRI pairs to discuss the patterns of neurodegeneration in eye and brain that are a consequence of the hard wired retinotopy: antero- and retrograde axonal degeneration which can, within the visual system, propagate trans-synaptically (Jindahra, Petrie & Plant 2009). The technical advances of OCT and MRI for the first time enable us to trace the signals of axonal degeneration through the visual system entirely at spectacular resolution. In conclusion, the neuroanatomical insights provided by the combination of OCT and MRI allows us to separate incidental findings from sinister pathology and gives us new opportunities to tailor and monitor novel neuroprotective strategies.

Introduction

The Japanese physician Tatsuji Inouye was first to describe the detailed associations between structural damage to the visual pathways in the human brain and the resulting visual deficit [1]. These observations and subsequent work from the Queen Square Neurologist Gordon Holmes introduced the concept of retinotopy to clinical practise [2]. The three key points relevant to this review are:

- *Each point on the retina is represented in the visual occipital cortex*
- *The macula has the greatest area of cortical representation*
- *Damage to any part of this, hard-wired, pathway will cause atrophy of corresponding retinal-cortical areas.*

Over the past century neurologists have, in general, not been very well trained in assessing the macula. The clinical skills of a neurologist included precise localisation of a lesion based on signs and symptoms [3]. With invention of clinically applicable brain imaging, first computed tomography (CT) [4] and then magnetic resonance imaging (MRI) [5] allowed for the visualization of brain lesions. With retinal optical coherence tomography (OCT) it has now also become possible to demonstrate the corresponding lesion in the nervous layers of the retina, including the macula [6]. The anatomical structure of the now easily accessible macula makes it a formidable area to apply retinotopy to routine clinical

practise. In a nutshell patterns of inner retinal layer atrophy observed in the macula substitute for the well described patterns of visual field (VF) loss [7].

This review will first discuss the anatomical basis of retinotopy [8] [9] [10] [11]. This includes novel observations from the OCT literature [12; 13]. The need for a qualitative retinotopic approach to the interpretation of pattern atrophy in the macula will become evident. This will be illustrated in four own clinical cases. The review concludes with opening a window which gives a vision for future neuro-protective treatment trial design and monitoring.

Anatomy

For the past century neurologists were trained to examine the optic disc, why should the focus now be on the macula [14]? There are two anatomical reasons for this:

- *there are no ganglion cells in the optic disc*
- *the peripapillary retinal nerve fibre layer (RNFL) projection pattern is not suitable (or practical) for strict retinotopic research because of intra-individual variation and difficulties to easily match with the visual field [15].*

Figure 1 shows the anatomical relationship of the macula and optic disc [8]. The centre of the macula, called foveola, contains essentially only retinal photoreceptors in order to maximise the resolution of the central part of the visual image. In the OCT terminology, photoreceptors are summarised as the outer nuclear layer (ONL) [16]. Next, Henle fibres are very thin axons which are orientated oblique from the fovea to the perimacular rim. The perimacular rim is also called the parafoveal area and corresponds to an oval of about 0.5 mm in diameter. The thickness of the foveola is about 0.13 mm and total retinal thickness increases to about 0.5 mm in the perimacular rim in humans. Henle fibres are very difficult

to see by direct ophthalmoscopy, but can be easily seen with OCT [17]. A dynamic approach is recommended and shown for teaching by video [18].

In strict hierarchical order the next neuro-axonal retinal layers in OCT terminology are the outer plexiform layer (OPL), inner nuclear layer (INL), inner plexiform layer (IPL), ganglion cell layer (GCL), retinal nerve fibre layer (RNFL) [16].

The INL is where the soma of the main glial cells of the retina, the Müller cells, are located.

The role of Müller cells is to maintain the homeostasis of the retina. In retinal pathology Müller cells proliferate and upregulate glial fibrillary acidic protein (GFAP) expression [19].

Consequently, GFAP levels increase in the adjacent body fluid compartment [20]. A thickening of the INL is thought to be related to Müller cells pathology and an impaired retinal glymphatic system [21; 22]. There are physiological variations of the INL which can be demonstrated with for example a fluid challenge [23]. In contrast, thinning of the INL is not generally observed as part of the atrophy pattern following damage to the optical pathways. It was suggested that the anatomically horizontal, as well as vertical neuronal network of the INL protects the only bipolar cell of the hard wired visual pathway [24].

Because the INL acts as a “dam”¹ to propagation of retrograde trans-synaptic atrophy the term, inner retinal layers will only include the next three layers discussed. This interpretation is further strengthened through meta-analysis [25].

In the inner plexiform layer (IPL) the bipolar cells of the INL, amacrine and horizontal cells all synapse with the retinal ganglion cells [26]. The area is relevant for image processing on the retinal level. Simplified, the ONL produces an analogue signal resulting from photo-transduction. Next, the ribbon synapse control of the retinal bipolar cells in the INL [27]

¹The term “dam” comes from the Dutch language to indicate a barrier. Embedded in the name “Amsterdam” the original description was word play “A dam” [24].

convert this analogue signal into digital signal [28]. These ~12 digital streams leaving the INL become ~64 digital streams, containing early visual information, once they pass through the IPL and ganglion cell layer (GCL) to reach the human brain. This is accomplished by only two axons. The first axon leaves the optic disc in a very specific retinal pathway (Figure 1) [8]. Once this non-myelinated axon leaves the retina and passes through the lamina cribrosa it becomes myelinated to contribute to the optic nerve [29] (Figure 1) [12].

Figure 1 clearly shows the horizontal architecture of the RNFL pathways. This is important because any damage occurring at level of the optic disc, as in e.g. glaucoma, will leave a horizontal pattern of RNFL atrophy in the retina and consequently a horizontal pattern of GCL atrophy in the macula. This can be memorised as “the sunset sign” [30].

Likewise, it is relevant to notice the alignment of the different retinal areas within the distal and caudal portion of the optic nerve. Located medially in the distal optic nerve, the perimacular bundle (PMB) relocates centrally in the caudal optic nerve [10]. Axons within the PMB carry the most important part of the visual image which comes from the fovea. Therefore axons of the PMB belong to the most extensively myelinated axons. This explains the selective vulnerability in demyelinating diseases [31]. Selective vulnerability may further be explained on a proteomic level as there is evidence for sectorial variation of neurofilament iso- and phosphoforms [32]. Neurofilaments (Nf) are the scaffold of the axonal cytoskeleton [33] with a wide range of functions [34]. Visualisation of early neurofilament pathology in the retina, which involves protein phosphorylation and aggregation seems tantalising near with emergence of in vivo birifigence techniques [35], but this type of translational research has yet not materialised.

In the retina, axons of the PMB are also the thinnest, rendering them particularly vulnerable to nutritional and toxic pathologies [36] [37].

Once all retinal axons have come together to form the optic nerve, the retinotopic pattern of damage observable by OCT in the macula will be determined by the brain region within which the damage occurs (Figure 2A&B) [12]. This is where MRI becomes important. The classical teaching example is that of damage to the optic chiasm which starts as a superior bi-temporal visual field defect (VFD) [38]. As this review will show there are specific patterns of macular GCL atrophy which correspond to the areas of the brain pathology. As a rule of thumb, lesions to the visual pathways from the chiasm onwards will leave a vertical pattern of macular GCL atrophy (“half moon sign”) [30].

Pathophysiology

Nerve injury has been classified into neuropraxia, axonotmesis and neurotmesis [39].

The latter two leave a permanent deficit, whilst neuropraxia only causes conduction block with a good chance of recovery if there is no more damage. The classical example is again compression at the optic chiasm with excellent visual recovery in most cases if recognised and dealt with promptly [38]. Axonotmesis (= structural injury to axon with preservation of the surrounding connective tissue) and neurotmesis (= complete disruption of the axon and surrounding endoneurium) compromise the axonal compartment which leads to acute release of biomarkers for neurodegeneration such as Nf [33] [40] [32]. Regarding the optic nerve this is followed by development of RNFL atrophy within three months [41] [42].

The contemporary terms for the mechanisms causing this are antero- and retrograde, trans-synaptic, axonal degeneration [12; 13] [43].

Direct anterograde axonal degeneration is also known as Wallerian degeneration.

Wallerian degeneration describes what happens to the distal axonal stump. It is worth noting from August Waller's original publication that during his times there was no

consensus whether this type of degeneration actually existed [44]. Two of the world

experts in the field, Burdach (1837) and Valentin (1839) both stated that there is no

evidence for axonal degeneration after experimental axonal injury. Living in Kent, United Kingdom at the time, Waller examined the two nerves supplying the tongue of the frog, a

practical model because regional atrophy of the tongue muscle can be shown. What is

remarkable is not so much that Waller did excellent in choosing a good model for

experimental demonstration of what came to be known as Wallerian or anterior

degeneration. What is remarkable is that it took neurologists about another century to

recognise that also retrograde axonal degeneration can occur. Initially termed dying back

neuropathy in peripheral nervous injury, the term retrograde axonal degeneration has now

become dominant. Clear experimental evidence for what concerns the very relevant trans-

synaptic aspect, "retrograde trans-synaptic" axonal degeneration was provided by van

Buren [45]. This was 113 years after Waller's initial struggle to convince the medical

community that there is indeed axonal degeneration following axonal injury. The lesson

learned from this historical review is that time matters. There is a risk to overlook an effect

if only examined hastily or in an *ex vivo* system which does not last long enough. Direct

anterograde or Wallerian axonal degeneration is the quickest of all forms of axonal

degeneration. Not surprisingly it was discovered first. Direct retrograde axonal

degeneration takes longer [13] and in the case of trans-synaptic axonal degeneration

within the nervous system of the human brain a time frame of up to three years has been observed [46]. Retrograde degeneration refers to the pattern of destruction that spreads backward along the axon, toward the neuron, and then into the neuron causing apoptosis.

The invention of OCT made it possible to observe retinal axons longitudinally in patients who suffered from injury to their brain [12; 13]. One model chosen to investigate this was stroke, because in these cases the onset is known [12]. The landmark paper on OCT in stroke comes from the Queen Square neurologist, Gordon Terence Plant who recognized very early the potential of OCT in establishing the concept of *trans*-synaptic axonal degeneration [12]. Having just moved from Bangkok (Thailand) to London (UK) around the time of the bomb attacks at 9:47 on 7 July 2005 [47], Panitha Jindahra accomplished the formidable task to prospectively collect and follow up OCTs from a cohort of deep phenotyped patients who had suffered a stroke. The thorough cross-sectional description at baseline [12] was duly followed up by presentation of longitudinal data of up to 917 days post-stroke [13]. An important co-variate recognized was age. This was considered in an equation to determine the mean peripapillary Retinal Nerve Fiber Layer thickness (pRNFL) as follows:

$$\text{mean pRNFL } (\mu\text{m}) = 110.3 - (9.08) * (\text{elapsed time in log years}) - (0.4) * (\text{age at time of measurement})$$

One criticism of this work is that there can be no absolute certainty about timing of onset of the stroke, pre-existing strokes, relevance of vascular comorbidities and direct ischaemic insults to the LGN. The latter likely was the reason for the much faster progression of pRNFL atrophy in their patient #11 (Figure 4 in reference [13]). In order to

circumvent these obstacles a surgical model was chosen. Figure 2 B shows that following synapsing in the LGN some of the axons entering Meyers loop are located more anterior, close to the hippocampus which is the target of epilepsy surgery. A well know iatrogenic issue with surgery is neurotmesis of Meyer's loop axons [48]. Because of the inter-individual variation of the exact location of these axons it is presently impossible to completely prevent this complication. For this reason visual function in individuals undergoing surgery is tested before and after surgery [49]. This can of course be elegantly combined with OCT thereby circumventing the inherent problems with stroke studies and retrograde trans-synaptic axonal degeneration [50]. Because the time point of surgery is known precisely it is much easier to review the time course of axonal degeneration. The findings are consistent with experimental data. Direct anterograde axonal degeneration is quickest and also most severe and stops at level of the INL². Trans-synaptic retrograde axonal degeneration is slower and also stops at level of the INL. A new observation is that the size of the injury matters. A smaller brain lesion affecting less axons in Meyer's loop causes self-terminating retrograde trans-synaptic axonal degeneration within one year. A larger brain lesion causes for yet unknown reasons prolonged propagation of retrograde trans-synaptic axonal degeneration which also affects a larger area of GCL in the retina.

The differences described here may at first glance seem small, even if statistically significant. Conceptually, they may however be important because they may lead to a better understanding of the neurodegenerative death cascade. The time delay of the trans-synaptic part in this death cascade could open opportunities for neuroprotection.

2 This is, of course, for the case of anterior axonal degeneration originating in the outer retinal layers[43].

Clinico-structural paradox

The clinico-radiological paradox describes a discrepancy between the extent of abnormal signal changes on MRI and the severity of clinical symptoms [51] [52]. In analogy to the clinico-radiological paradox there appears also to be an clinico-structural paradox in the retina [53]. There are data on individuals with myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOGAD) [54] that showed well preserved high contrast visual acuities (VA) even in the context of severe macular GCL and pRNFL atrophy [55] [56]. Figure 3 illustrates the clinico-structural paradox in a patient with newly diagnosed MOGAD. The retina showed rapid (4 week interval) development of severe GCL atrophy (lost 50% of layer thickness) with excellent recovery of VAs from right eye (RE) 6/60-3 to 6/6. On the left VAs were 6/5. Likewise, colour vision recovered from severe dyschromatopsia judging a red target or reading Ishihara charts (0/17) on the right to hardly perceptible red desaturation only and reading of all 17 Ishihara charts. There was persistence of the strong relative afferent pupillary deficit (RAPD) on the right. The MRI showed enhancement of the intracranial, posterior portion of the right optic nerve as it approaches the optic chiasm.

Pitfalls with OCT

One needs always to carefully review the raw data for the possibility of imaging artefacts [57] [58] [59]. Furthermore it is crucial to be aware of the blind spots in our understanding of the clinical relevance of several OCT image abnormalities.

- The age of the lesion and degree of axonal injury, neuropraxia/axonotomesis/neurotmesis, might influence the image.
- Gliosis can affect the retinal OCT and influence the reliability of automatic retinal layer segmentation or signal intensities.
- Rare anatomical variations may not have been described.
- The GCL could be affected by remote lesions via a retrograde downstream effect. This may for example give the false impression of a progressive optic neuropathy in patients with MS and a high MS lesion load in the posterior visual pathways.
- The OCT image could be influenced by systemic factors, e.g. metabolic, electric, enzymatic or other diffuse, transient, physiological changes.
- The likelihood for discovery of novel pathologies based on OCT findings. Two recent examples were microcystic macular oedema³ (MMO) and PHOMS [61] [62] [63] [64-66].

Our incomplete understanding of retinal OCT stresses the need for image sharing in an open access data repository, just like it was done for MRI [52].

3 We acknowledge that about in 20% of patients these microcysts are chronic, there is severe atrophy of retinal ganglion cells and the term “retrograde maculopathy” has merit [60].

OCT helps to interpret MRI signal changes

There is a great level of confidence interpreting a contrast enhancing optic nerve on MRI as was shown in Figure 3, in the context of a clear clinical picture. A diagnosis of acute optic neuritis (ON) can readily be made. It is much more complex to interpret a diffuse increase of signal MRI which is non-enhancing as shown in Figure 4. In this patient the increased signal comes from an optic nerve which is reduced in diameter indicating optic atrophy. The corresponding OCT shows severe atrophy of the pRNFL, mildly cupped discs and severe atrophy of the macular GCL which did not progress over a one year observation period. His best corrected visual acuities were RE 6/9, LE 6/6 and there was no dyschromatopsia or RAPD. Intraocular pressures were high in childhood, but normalised following bilateral trabeculectomy for juvenile onset angle glaucoma. The signal increase on MRI is due to Wallerian or antero-grade axonal degeneration in an individual who has a glaucomatous optic neuropathy.

Another example is shown in Figure 5. This 29-year old patient had experienced visual difficulties especially at the end of the days for over 10 years before he presented with

subnormal central vision of 20/30 and 20/25 and small paracentral scotomas. The OCT shows selective atrophy of the PMB. These axons are, as Figure 2A&B illustrated, located in the optic nerve exactly so to match the MRI signal changes shown in Figure 5. A toxic cause of the chronic optic neuropathy was suspected, possibly caused by illicit drug use

(amphetamin, GHB) or medication (SSRIs which have been described as rare causative agents), as the B vitamin tests were all normal. The loss of ganglion cells in this case could either be due to direct toxicity, or to retrograde atrophy caused by loss of optic nerve fibers.

Another situation where OCT can contribute to interpreting MRI findings is in the context of non-specific observations such as an empty sella. The historical origin of the term comes from cadaver observations showing a flattened pituitary gland with an empty appearance of the sella turcica. Rapidly adapted by radiologists with the invention of CT and MRI this term has been associated with a diagnosis of idiopathic intracranial hypertension (IIH). The finding is however non-specific and can lead to overdiagnosis of IIH. A number of other MRI signs for IIH have been discussed and the most specific one appears to be flattening of the posterior wall of the orbit. What the MRI does not permit to distinguish in this context is however true optic disc swelling from pseudopapilloedema. In IIH the optic discs frequently shows presence of peripapillary hyperrefractive mass like structures (PHOMS) [65] [66] .

PHOMS are a novel OCT finding which was only proposed to the medical community as a term in 2018 [64]. The original description was intended to be an exclusion from true optic disc drusen (ODD) and it required a large international validation effort to agree on a distinct, feature based definition [67]. Based on this reproducible definition the presence of PHOMS was found to be frequent (62%) in individuals with IIH [65]. The three key OCT features of PHOMS are [67]:

- i. *location*: strictly peripapillary and sitting on top of Bruch's membrane in the OCT B-scan. Frequently; a gap can be observed in the B-scan scans of PHOMS aligned through the centre of the optic disc;
- ii. *effect on adjacent retinal layers*: there is typically an upward deflection (like a ski slope) of at least two of the other retinal layers;
- iii. *signal* appearance which is similar to the reflectivity to the retinal nerve fiber and ganglion cell layers because there is evidence that they may represent axonal stasis, and because the normal egress of axons at the optic disc can resemble PHOMS. The latter is can be observed in tilted discs, discs with an elevated border and myopia. This downward slope of essentially normal axons can easily be mistaken for PHOMS.

Because it can be challenging at first to recognise these features the consortium has made 100 teaching and testing slides available as free downloadable supplementary data to the original report [67]. In clinical practise it is however much easier to scroll through a OCT volume scan and review the impression of a complete or partial torus [66]. It is suspected that the histology of PHOMS, which to date still remain to be matched to pre-enucleation OCT, will be similar to already described appearance of impaired axonal flow in a large number of species [66] [29] [66]. Of note, PHOMS are not disease specific and can be observed with a large group of pathologies or be of no further clinical significance [65; 66].

The observation of the dynamic nature of PHOMS, which can develop de novo, increase or diminish in size [65; 66] coincides in time with the discovery of a retinal glymphatic system [22]. Based on several lines of evidence the experimental description of a retinal glymphatic system had been anticipated for a number of years [21; 68] [69] [70] [71].

There was a need to explain the physiological variation of individual retinal layers [72] [73] [23]; the dynamic nature of MMO in the majority of cases [63] [74] [75] [76]; the potential for local accumulation of neurotoxic products driving compartmentalised neurodegeneration [77]. Now that it is possible to design quantitative longitudinal studies with composite imaging modalities including OCT and MRI neuroprotective treatment strategies can be tested not only with regard to the principal action, but more importantly probably, with regard to their timing.

MRI helps to interpret OCT atrophy patterns

Unilateral brain lesions if involving the posterior visual pathway cause a contra-lateral hemianopia or quadrantanopia [12; 13] [78] [79]. The visual fields can be directly matched with the retinal OCT because by convention, and different to anything else done in clinical medicine, the right visual field is shown on the right and the left on the left. So it is as if the patient (rather than the doctor) looks down at his own fields. In contrast, in radiology everything which appears on the right of the image is truly on the left of the patient's body. This is shown for a right cerebral metastasis in Figure 6.

The pattern of a hemimacular atrophy can also be memorised as “the half moon sign” and should always at first observation lead to imaging of the brain [30].

In our experience, a lesion which only affects the posterior visual pathways does not lead to MMO. This observation is consistent with the pioneering experimental work by van Buren [45]. Whilst atrophy continues trans-synaptically causing severe inner retinal layer atrophy, MMO cannot be observed. In contrast, axonotmesis or neuropraxia affecting the

anterior visual pathway is in a proportion of affected subjects associated with MMO [61] [63] [80] [74] [81].

A vision through an open window for neuroprotective treatment strategies

There is proverb stating that “When God closes a door, he opens a window”.

By definition, axonotmesis and neurotmesis are like a closed door leaving a neurological deficit behind. But at the time axonotmesis and neurotmesis occur there may still be a chance to salvage the post-synaptic downstream effects. This time interval may be substantial because of the slow propagation of trans-synaptic degeneration which can take over one year as reviewed here.

This observation may be particular relevant in the context of larger lesions to the human brain because in addition to a trans-synaptically ruled pathway of neurodegeneration [12; 13] there is evidence for special spatial stoichiometric relationship of the axon–oligodendrocyte interface [82]. Axons are electrically and metabolically isolated [83] which renders them vulnerable to a failing support line. The prolonged and spreading retinal atrophy after substantial damage to Meyer’s loop in epilepsy surgery opens up a window of opportunity to halt the trans-synaptic part of neurodegeneration [49], in which case OCT imaging will be the ideal modality to monitor treatment effects. The aim of such future neuroprotective treatment strategies would not be to reverse what nature has taken, but to help the human body in what it is good: healing what is damaged.

Figure legends

Figure 1: “The anatomical basis of the caecocentral scotoma.” **(A)** The photomicrograph shows the axons projecting from the retinal ganglion cells of the foveola to the optic disc in a flat mounted retina of *M. mulatta*. **(B)** A sketch of individual retinal ganglion cells and their axons. This illustrates that all axons

tend to avoid the horizontal meridian. Once these axons reach the lamina cribrosa they become myelinated and form the optic nerve which projects to the dorsal lateral geniculate nucleus (DGN) of the thalamus.

This anatomical relationships are relevant for interpretation of the OCT findings because damage anywhere in this pathway will cause axonal degeneration in both directions (antero- and retrograde) resulting

in characteristic OCT atrophy patterns, which if attitudinal indicate pathology involving the optic disc (Figures reprinted with permission from [8]).

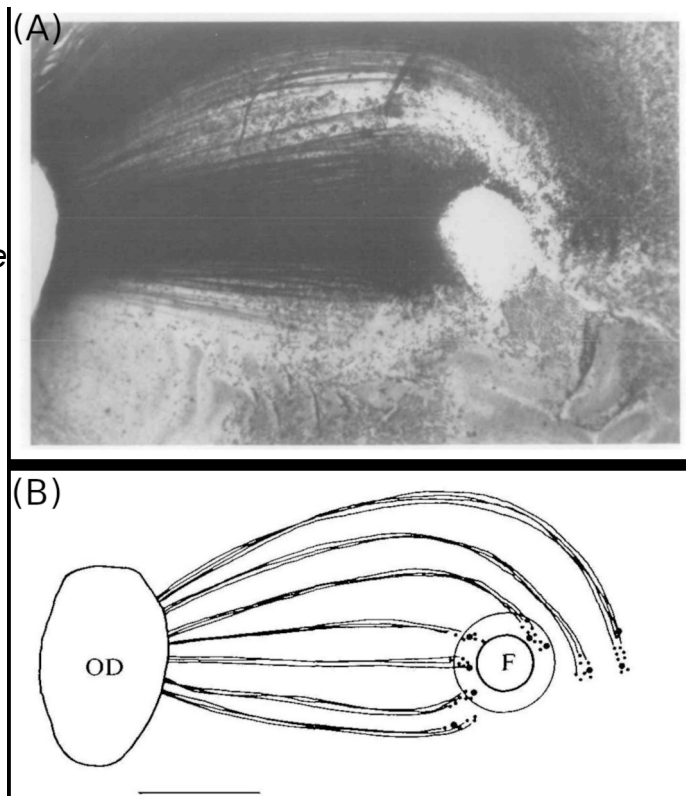
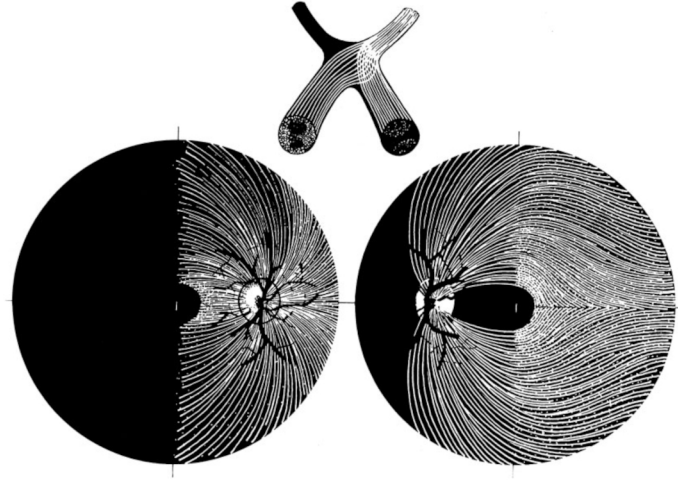


Figure 2: Anatomical sketch of the retinal ganglion cell axonal pathway pattern from the retina through the chiasm. This anatomical relationship is relevant for interpretation of the

OCT atrophy findings resulting from retrograde trans-synaptic axonal degeneration. The MRI shows in most cases the site of pathology. In a very small proportion the lesion can be below the resolution of the MRI or are missed because of a number of other



reasons known as the clinico-radiological paradox (Figures reprinted with permission from [12]).

Figure 3: OCT and MRI from an individual with MOG-ON. Inner retinal layer atrophy is due to direct, retrograde axonal degeneration. This is severe and rapid. MRI in the acute phase shows a contrast enhancing optic nerve.

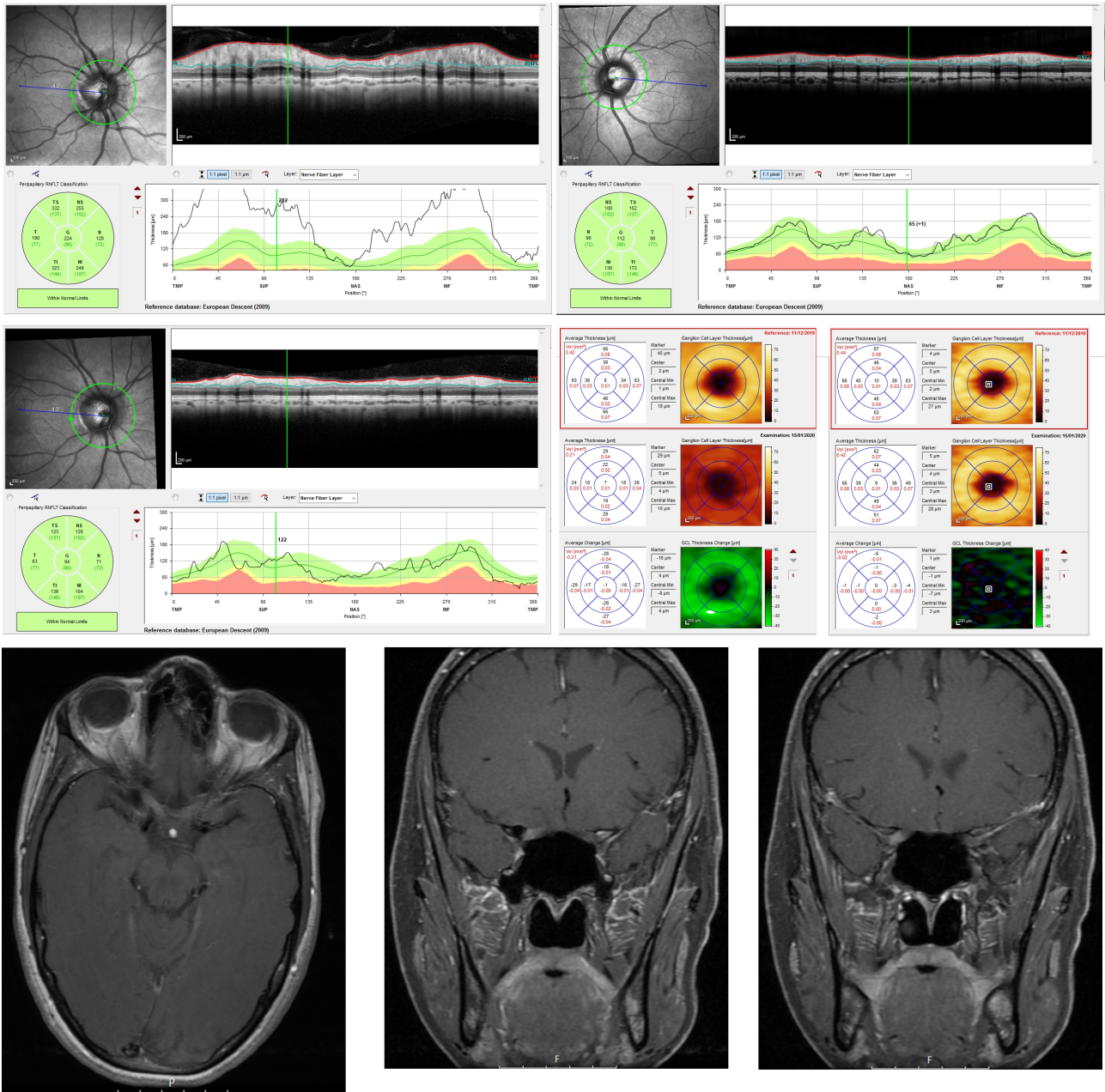


Figure 4: OCT and MRI from an individual with bilateral glaucoma. Bilateral inner retinal layer atrophy is severe and the cause of anterograde axonal degeneration. This results in an increased signal of the optic nerve on MRI which is not contrast enhancing.

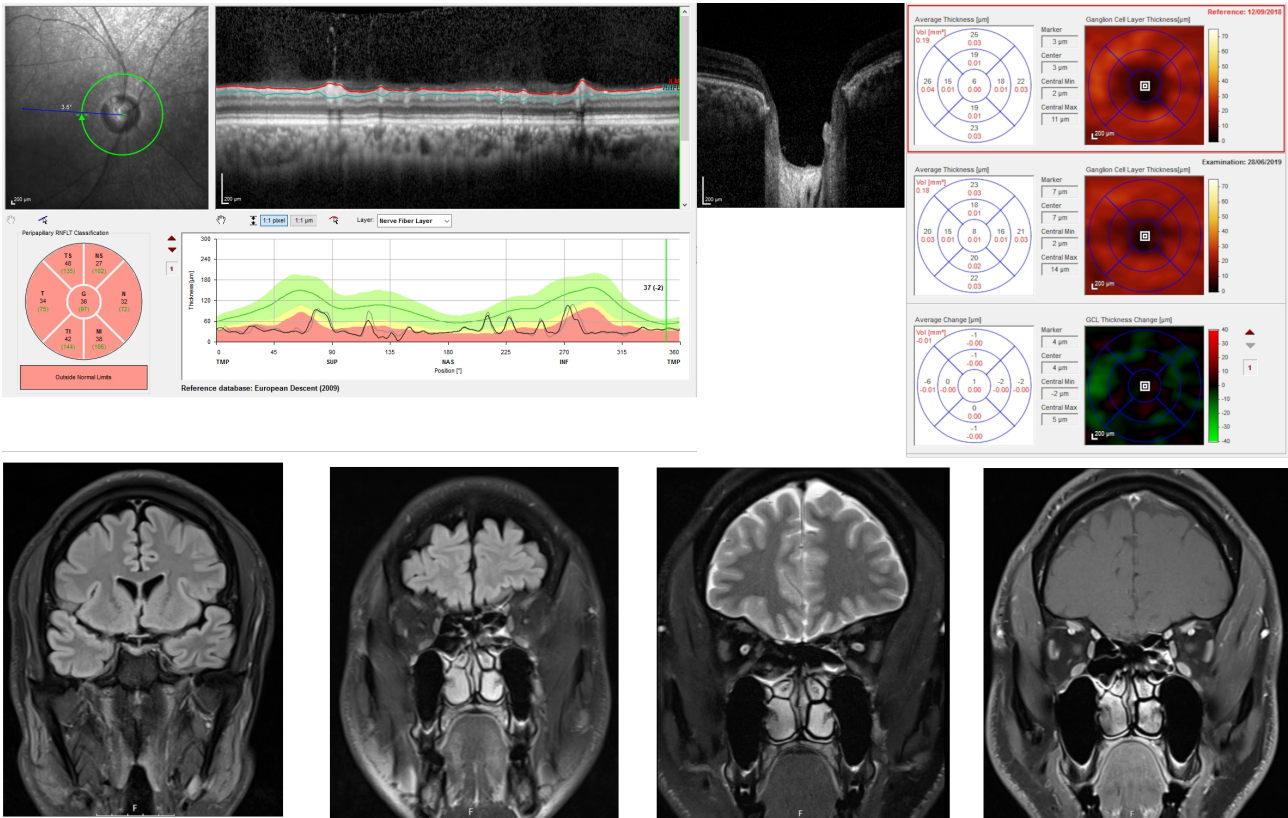


Figure 5: OCT and MRI from an 29-year old individual with a suspected toxic optic neuropathy which shows selective atrophy of the PMB on OCT. The resulting anterograde axonal degeneration gives bright (white dot inside the optic nerve in this image) signal changes on the MRI (coronal STIR) along the course of the PMB in both optic nerves. The atrophy of the caeco-central projections as beautifully demonstrated in Figure 2A&B are visible on the heat map of the RNFL. The OCT composite image shows the loss of these axons as a dark area between the optic disc and fovea. Superiorly and inferiorly to the optic disc there are still axons left showing in the heat map as a bright, yellowish area. The 6 mm EDTRS grid (blue) demonstrates that this loss of axons encompasses almost the entire macula. The superimposed (green coloured) heat map of the macular ganglion cell layer reveals more profound ganglion cell loss in the more severely denervated area of the macula (similar to the scattered dots in the sketch in Figure 2B). The B-scans demonstrate the lines of retinal layer segmentation for the RNFL (red and green lines) through the foveola and at the optic disc; and for the ganglion cell layer (green and purple lines) through the foveola. The findings of the composite volume scans are consistent with those of the ringscan demonstrating visually and in numbers the isolated atrophy of the papillomacular bundle (PMB).

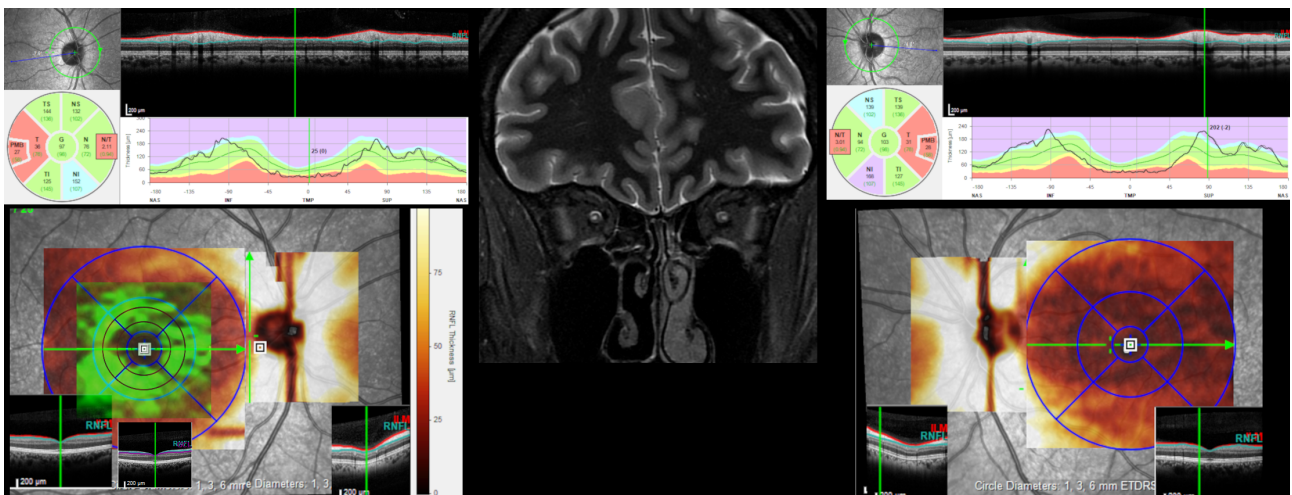
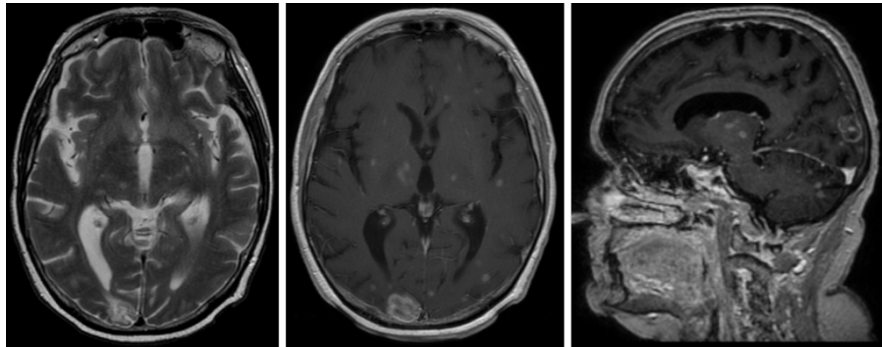
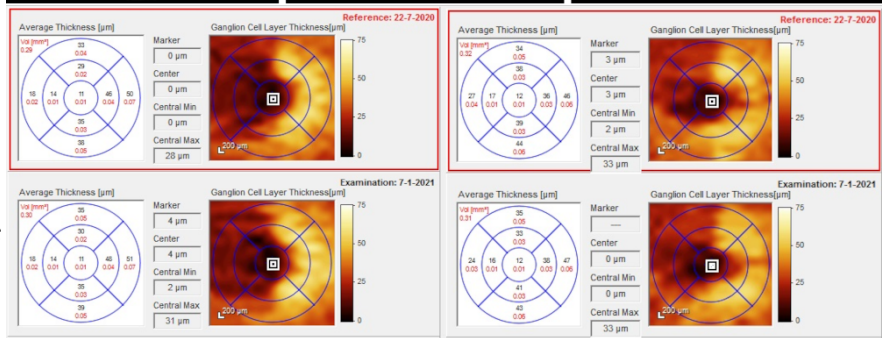


Figure 6: OCT and MRI from an individual with brain metastases of a non-small cell lung

adenocarcinoma and a large occipital lesion on the right side, which causes anatomically corresponding (see sketch in Figure 2) inner macular GCL atrophy



in both eyes. If observed in clinic this pattern of atrophy, which can be memorised as “the half moon sign” should



always trigger imaging of the brain. In this 72-year old patient the central vision was 20/30 in both eyes, but the visual field test showed a deep but incomplete homonymous hemianopsy of the left visual field.

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