ESCOLA SUPERIOR DE TECNOLOGIA DA SAÚDE DE LISBOA
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Characterization of the structural findings obtained through Optical Coherence Tomography and Magnetic Resonance in Glaucomatous Optic Neuropathy: Systematic Review

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Mestrado em Radiações Aplicadas às Tecnologias da Saúde – Ramo de Ressonância Magnética

Lisboa, 2023

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Master's degree in radiation applied to health technologies - field of magnetic resonance imaging

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ABSTRACT

Glaucomatous optic neuropathy is structurally characterized by chronic and progressive damage to retinal ganglion cells and their axons, which form the retinal nerve fiber layer (RNFL). However, these structural alterations, which cause irreversible visual field loss, are initially asymptomatic and an earlier diagnosis becomes essential.

A systematic review protocol was initially developed (ID PROSPERO= CRD42021284152) that supported the development of the systematic review (under review in Optometry and Vision Science (OVS)) to study the importance and pertinence of the potential role of magnetic resonance imaging (MRI) in the early diagnosis of glaucoma and compare with the SD-OCT structural gold standard.

For this search were selected 28 studies. The results showed that several OCT and MRI findings may provide valuable insights for an earlier glaucoma diagnosis in clinical practice. It also showed that structural MRI findings appear to be mostly related to RNFL and visual field changes, while metabolic findings appear to be more closely related to ganglion cell layer (GCL) changes. These changes demonstrated a strong relationship not only with the clinical findings of the OCT but also with the severity of the pathology. This systematic review may contribute to a better understanding of which MRI parameters may play an important role in the early diagnosis of glaucoma alongside OCT due to their relationship with the stage of the pathology.

So, we can conclude that MRI may be useful not only in the diagnosis, but also to follow up some patients alongside with OCT and the visual field.

KEYWORDS: Glaucoma, Magnetic Resonance Imaging, Optical coherence Tomography, Systematic Review.

ABSTRACT (PT)

A neuropatia ótica glaucomatosa é caracterizada estruturalmente pelo dano progressivo das células ganglionares da retina e respetivos axónios, que formam a camada de fibras nervosas da retina (RNFL). No entanto, essas alterações estruturais que causam perda irreversível do campo visual, são inicialmente assintomáticas e por essa razão, o diagnóstico precoce torna-se fundamental.

O protocolo de revisão sistemática foi inicialmente desenvolvido (ID PROSPERO = CRD42021284152), e guiou o desenvolvimento desta revisão sistemática (em revisão na revista Optometry and Vision Science (OVS)), cujo objetivo é estudar a importância e pertinência do potencial papel da ressonância magnética (MRI) no diagnóstico precoce do glaucoma e comparar com o *gold Standard* estrutural SD-OCT.

Para esta pesquisa foram selecionados 28 estudos. Os resultados mostraram que vários achados de OCT e MRI podem fornecer informações valiosas para um diagnóstico precoce de glaucoma na prática clínica. Demonstrou também que os achados estruturais da MRI parecem estar principalmente relacionados a RNFL e alterações no campo visual, enquanto os achados funcionais parecem estar mais relacionados às alterações da camada de células ganglionares (CGL). Estas alterações demonstraram uma forte relação não apenas com os achados clínicos do OCT, mas também com a gravidade da patologia. Por essa razão, esta revisão sistemática pode contribuir para uma melhor compreensão dos parâmetros da RM que podem desempenhar um papel importante no diagnóstico precoce do glaucoma juntamente com o OCT devido à sua relação com o estadio da patologia.

Desta forma podemos concluir que a ressonância magnética pode ser útil não apenas no diagnóstico, mas também no acompanhamento de alguns pacientes de glaucoma juntamente com o OCT e campos visuais.

Palavras-Chave: Glaucoma, Magnetic Resonance Imaging, Optical coherence Tomography, Systematic Review.

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ABBREVIATIONS LIST

AH - Aqueous Humor

B.Cgh - Bilateral Cingulum-Hippocampus

B.FX - Bilateral Fornix/Stria Terminalis

B.PTR - Bilateral Posterior Thalamic Radiation

B.SS - Bilateral Sagittal Stratum

BA - Brodmann Area

BOLD-fMRI - Blood Oxygenation Level-Dependent Functional Magnetic Resonance Imaging

C/D - Cup to Disc Ratio;

CASP - Critical Appraisal Skills Program

DIR - Double Inversion Recovery

dMRI - Diffusion Magnetic Resonance Imaging

DTI - Diffusion Tensor Imaging Resting State

FA - Fractional Anisotropy

FBA - Fixel-Based Analysis

FD - Fiber Density

FDC - Fiber Density And Cross-Section

fMRI - Functional Magnetic Resonance Imaging

FMRIB - Functional Magnetic Resonance Imaging of the Brain

GCL – Ganglion Cell Layer

GM - Gray Matter

GMV- Gray Matter Volume

GON - Glaucomatous Optic Neuropathy

HC - Healthy Controls

HTG- High Tension Glaucoma

ICAN - Intracanalicular

ICRAN - Intracranial

ILF - Inferior Longitudinal Fascicle

IO - Intraorbital

IOP- Intraocular pressure

LGN - Lateral Geniculate Nucleus

MD - Mean Diffusivity

MRI - Magnetic Resonance Imaging

MRS - Magnetic Resonance Spectroscopy

NAA - N-Acetyl Aspartate

NTG - Normal-Tension Glaucoma

OCT - Optical Coherence Tomography

ON - Optic Nerve

OND - Optic Nerve Diameter

ONH - Optic Nerve Head

OR – Optic Radiation

OT - Optic Tract

PACG - Primary Angle Closure Glaucoma

POAG- Primary Open Angle Glaucoma

PRISMA-P - Systematic Reviews and Meta-Analysis Protocols

pRNFL - Peripapillary Retinal Nerve Fiber Layer

PSD - Pattern SD

ReHo - Regional Homogeneity

RF - Radiofrequency

RGCL - Retinal Ganglion Cell Layer

RNFL - Retinal Nerve Fiber Layer

RNFLT - Retinal Nerve Fiber Layer Thickness

ROC - Receiver Operating Curve

rsfMRI-fALFF - Functional Magnetic Resonance Imaging Fractional Amplitude Of Low-Frequency Fluctuation

SA - Signal Alteration

SAP - Standard Automated Perimetry

SAR - Signal-Intensity Average Ratio

SD-OCT - Spectral Domain Optical Coherence Tomography

SF-MRI - Magnetic Resonance Imaging structural findings

SF-OCT – Optical Coherence Tomography Structural findings

VBM - Voxel-Based Morphometry

VC - Visual Cortex

VCDR - Vertical Cup To Disc Ratio

VF - Visual Field

VFMD - Visual Field Mean Deviation

WM - White Matter

WMV – White Matter Volume

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1. INTRODUCTION

1.1. MOTIVATION AND JUSTIFICATION OF THE THEME

Glaucoma, or glaucomatous optic neuropathy (GON), is the second most common leading cause of irreversible blindness in developed countries due to chronic and progressive damage to retinal ganglion cells and their axons, which form the retinal nerve fiber layer (RNFL). The characteristic sign and symptom of this pathology is the progressive and irreversible loss of the peripheral visual field, however, the structural lesions start long before the visual loss, being a silent pathology that is often diagnosed late. (Fukuda et al., 2018; Y. Q. Zhang et al., 2012)

The conventional diagnosis of glaucoma, as well as its monitoring, is carried out through three main approaches: measurement and control of the intraocular pressure (IOP), assessment of the visual field (VF), and structural evaluation by optical coherence tomography (OCT). However, continuous degradation of retinal layers cells occurs, and the traditional follow-up seems to be insufficient. OCT structural assessment has been crucial in primary open angle glaucoma (POAG) due to its similarities with clinical characteristics of normal tension glaucoma (NTG), which highlight the importance of finding and characterizing changes that can distinguish them. In these differences we can find a fundamental role for magnetic resonance imaging (MRI), increasing the possibility of differential diagnosis with possible gains in future therapeutic responses. (Silva et al., 2021; Nuzzi et al., 2020; Tavares & Mello, 2005; Umezurike et al., 2019)

As mentioned before, in the early stages of the pathology, conventional methods may not be enough, because long before it develops, changes in the optical pathway begin to appear. For example, Kosior-Jereca et al, 2020 described that the volume of the lateral geniculate body decreases significantly with the development of any type of glaucoma. There are still other alterations that have already been studied, such as hypersignal and tortuosity of the optic nerve, decreased chiasm width, and brain anomalies. (Chen et al., 2013; Jhon, Morrison, Irvin, 2003; Kosior-Jarecka, Pankowska, et al., 2020; X. Wang et al., 2018)

MRI can generate non-invasive images of the entire structure of the eyeball, orbit, and retrobulbar, without optical distortion (Smith G et al, 2009). The development of MRI components such as small surface radiofrequency (RF) coils makes it possible to visualize and study the entire eye *in vivo*. The application of this exam has been expanded to the level of ophthalmology, allowing the study of other eye conditions, such as myopia, glaucoma, and intraocular tumours (Glarin et al., 2021). For this reason, it is increasingly common in clinical practice to use MRI to obtain images of the eyeball and orbit. The only downside to MRI is that image quality can be degraded by image resolution, motion and/or susceptibility artefacts. Currently, MRI acquisition of the eyeball and orbit is done with a head coil at conventional field intensities (3T or 1.5T). The most commonly used imaging techniques are Diffusion Tensor Imaging Resting State (DTI), Functional Magnetic Resonance Imaging Fractional Amplitude Of Low-Frequency Fluctuation (rsfMRI-fALFF), Blood Oxygenation Level- Functional Magnetic Resonance Imaging (BOLD-fMRI), Magnetic Resonance Spectroscopy (MRS) and 3D MRI (Smith G et al, 2009; Chen et al., 2013; Glarin et al., 2021; Kosior-Jarecka, Pankowska, et al., 2020; X. Wang et al., 2018)Glarin et al., 2021; Kosior-Jarecka, Pankowska, et al., 2020; X. Wang et al., 2018)

For this reason, it would be interesting and enlightening to study the role of magnetic resonance imaging together with OCT, to seek a concordance between the features found at the intraocular level (through OCT) and the extraocular/intracranial level (through MRI). Therefore, the purpose of this systematic review is to bring together relevant studies on this topic that allow us to characterize the structural findings of OCT and MRI in GON, and to clarify the importance of the communion of these two complementary means of diagnosis. Since systematic reviews play an important role in research through the sharing of knowledge through the comparison and understanding of other studies on the subject, this work stands out for the lack of similarly published works, which makes the theme original and relevant.(Fukuda et al., 2018; Kosior-Jarecka, Wróbel-Dudzińska, et al., 2020; Lešták et al., 2020; Y. Q. Zhang et al., 2012)

This thesis was structured taking into account the guidelines of the authors Pereira A. and Poupa C. in "how to write a thesis, monograph or scientific book using word", 2018. It is divided into 5 chapters, the first of which contains a previous introduction to the topic, and the second presents the “state of the art” where the anatomy of the various structures involved in the development and progression of glaucoma is addressed

alongside its definition to the standard method of diagnosis and follow-up today, as well as an explanation of the usefulness of MRI in the pathology. In the third chapter, the entire methodology used in the elaboration of the research and respective objectives is described, as well as the protocol published in PROSPERO. The fourth chapter contains the systematic review in the form of an article that was submitted to the Optometry and Vision Science (Q2). The fifth chapter is focused on the conclusion of the thesis, the limitation of the study and suggestions for future studies. (Pereira & Poupa, 2018)

2. STATE OF THE ART

2.1. RETINA ANATOMY

The eye is an extremely complex organ despite its size and is composed of several structures that work together to provide us with a sharp and clear vision, some through the refraction of light rays, others through the conduction of electrical stimuli that will reach the visual cortex. For this study we will focus on the structures most affected by glaucoma, making an introduction to its anatomy.(Umezurike et al., 2019; Kolb H., 2012)

The retina is the most important membrane of the eye (figure 2.1), and it is responsible for transforming light into an electric pulse so that the information reaches the brain. It has 10 layers, and it is approximately 0.5 mm thick. The light starts by travelling through the retina until it strikes and activates rods and cones (figure 2.2), subsequently, the absorption of photons by the visual pigment of the photoreceptors is translated first into a biochemical message and then an electrical message that can stimulate all the succeeding neurons of the retina. The sensory retina has five different types of neurons: ganglion cells nerve cells whose axons form the optic nerve, bipolar cells, photoreceptors (cones and rods), horizontal cells, and amacrine cells. (Kolb H., 2012)

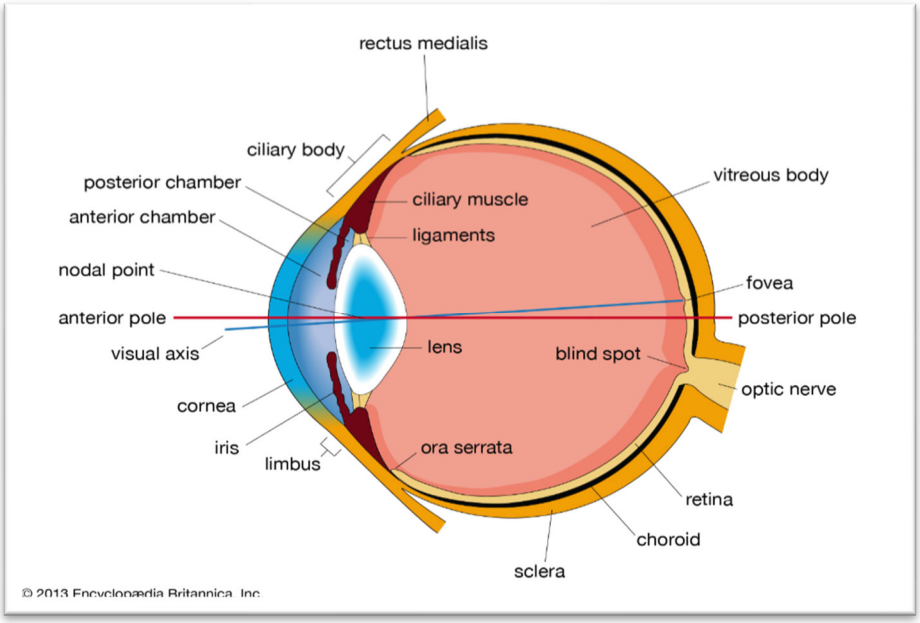


Figure 2.1.: Human eye Anatomy. (From: Encyclopaedia Britannica Inc., 2013 UK)

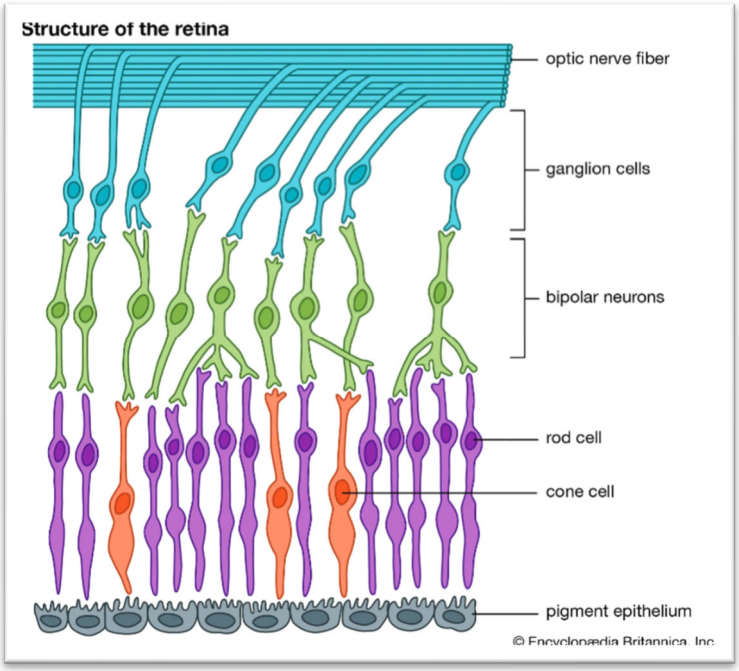


Figure 2.2.: Retina Layers illustration. (From: Encyclopaedia Britannica Inc., 2013 UK)

Retinal ganglion cell axons traverse the inner retina and converge at the optic nerve head, where they exit the eye and form the optic nerve (Fig. 2.3).

2.2. OPTIC NERVE ANATOMY

The optic nerve is also located in the back of the eye and contains, additionally, incoming blood vessels that open into the retina to vascularize the retinal layers and neurons. (Tavares & Mello, 2005; Kolb H., 2012)

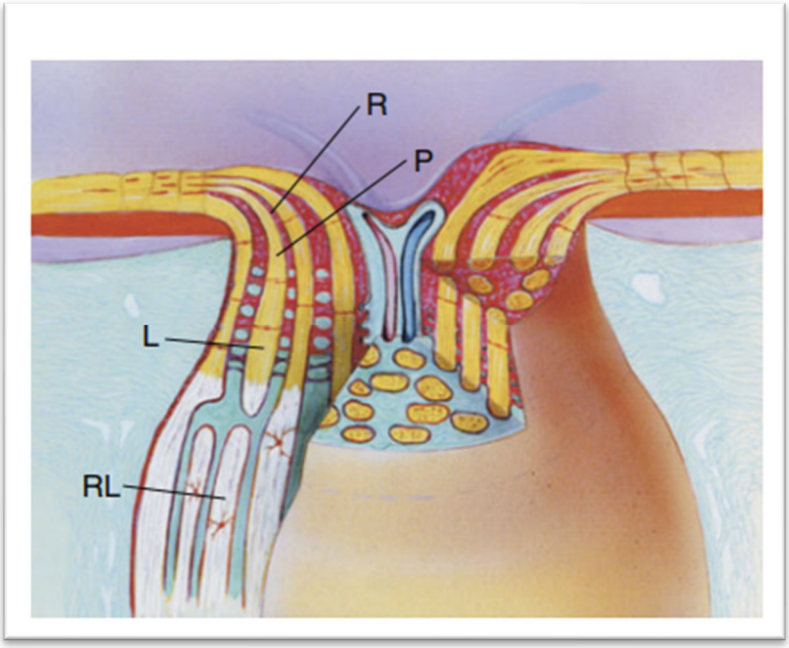


Figure 2.3.: Representation of the primate optic nerve head, illustrating its organization into four regions: R, retinal nerve fiber layer; P, prelamina; L, lamina cribrosa; RL, retrolamina. (From: Kline LB. Optic Nerve Disorders. San Francisco: Am Acad Ophthalmol; 1996:1–20)

The optic nerve head, visible clinically as the optic disc, is the site of major axonal damage in glaucoma. Optic discs that present a larger dimension, and an excavation characteristically with ill-defined edges and disproportion between the increased size of the excavation and the defect in the visual field are peculiarities of Glaucoma (Fig. 2.4). (Tavares & Mello, 2005; Kolb H., 2012)

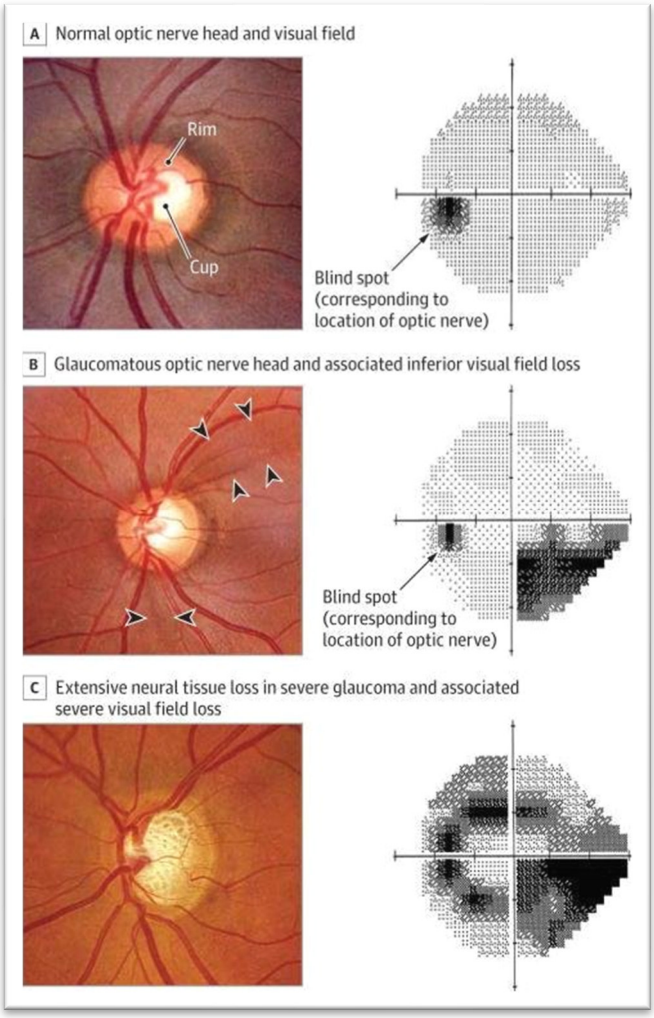


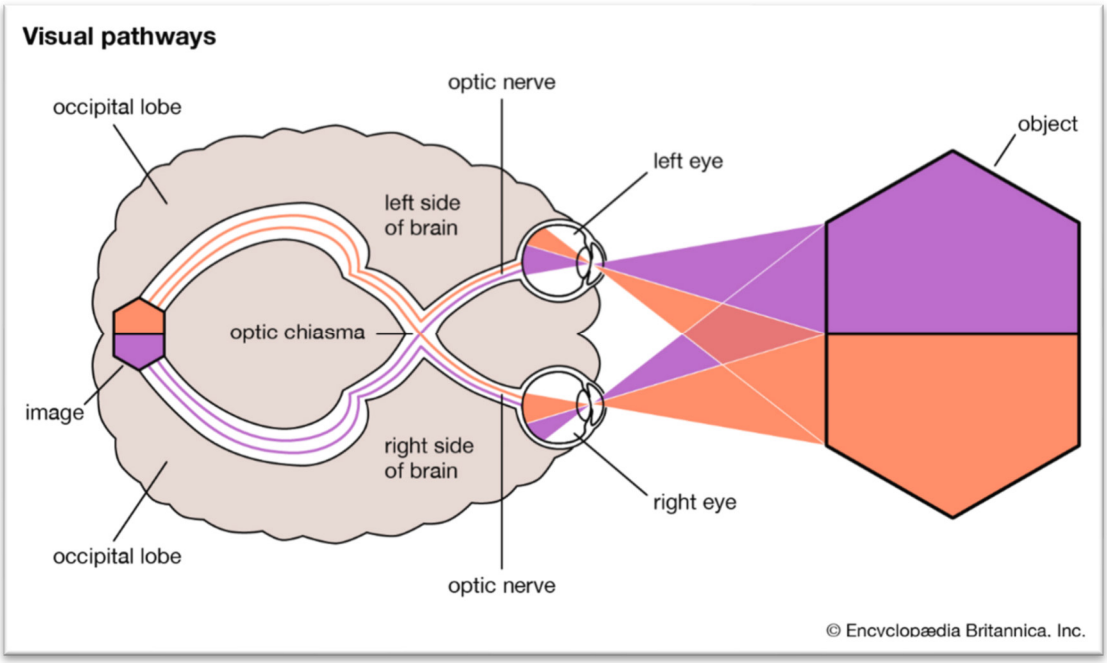
Figure 2.4.: Glaucoma changes in retinography and visual field. From: (Umezurike et al., 2019)

2.3. OPTIC PATHWAY ANATOMY

The optic pathway is composed of several structures in which the nerve impulse that will originate images travels, starting in the retina and ending in the occipital cortex (Figure 2.5.). (Gupta M, Bordoni B., 2020)

The nerve impulse mentioned above is generated in the retina, more precisely by the ganglion cells and their axons, after light passes through the photoreceptor layer where the phototransduction takes place. From there, the information travels through the optic nerve, later crossing into the chiasm. Beyond the chiasm, two distinct tracts form, each carrying the temporal fibers from the contralateral eye and the nasal fibers from the ipsilateral eye. (Gupta M, Bordoni B., 2020)

After the optic tracts, it reaches the lateral geniculate body (LGB) of the midbrain, which functions as an extension of the thalamus. Some of the information also passes into the superior colliculus and Edinger-Westphal nuclei, allowing pupil innervation.



Subsequently, most of the fibers eventually reach the primary visual cortex, more precisely the cuneus gyrus and lingual gyrus, Broadmann area number 17. (Gupta M, Bordoni B., 2020)

Figure 2.5.: Visual pathways in the human brain. (From: Encyclopaedia Britannica Inc., 2013 UK)

2.3. GLAUCOMA

2.3.1 DEFINITION

Glaucoma is a multifactorial optic neuropathy that causes structural, functional, and atrophic changes in the optic nerve. It can be symptomatic or asymptomatic depending on its type. In asymptomatic forms of glaucoma, usually, the diagnosis is late, and patients end up with severe peripheric VF defect, although if it progresses to a severe state, it can also deteriorate the central vision as well leading to blindness. (Pezzullo et al., 2018; Silva et al., 2021; Umezurike et al., 2019a)

2.2.2 EPIDEMIOLOGY

This pathology can occur in any population, but some ethnicities appear to be more susceptible to its appearance, with open-angle glaucoma being more common in the African population and closed-angle glaucoma in the Asian population.(Lusthaus & Goldberg, 2019)

It is currently the second leading cause of irreversible blindness in developed countries, affecting about 67 million people, of whom an estimated 85-90% have POAG. According to a 2014 study by Tham YC *et al*, it was also estimated that the number of people affected by glaucoma in developed countries would rise to 76 million in 2020 and will likely rise to 111.8 million in 2040, maintaining a high prevalence of POAG. As this is a pathology that leads to blindness, it also entails high costs for the state caused by the social and health impact generated by this condition, since it can cause, for example, loss of productivity for the patient and their caregivers, loss of quality of life, as well as lead to falls or other accidents that cause physical injuries and even depression. For example, in the UK, blind patients, regardless of pathology, represent an annual direct cost of £735 million and an indirect cost of £5.65 million. (Pezzullo et al., 2018; Silva et al., 2021; Umezurike et al., 2019a; Tham YC et al., 2014)

2.3.3 TYPES OF GLAUCOMA

Glaucoma is classified into two major types: POAG and Primary angle closure glaucoma (PACG). The main factor that distinguishes these two types is the cause of intraocular hypertension that happens when IOP goes above 21 mmHg. In POAG the IOP gets progressively high, but the drainage angle formed by the cornea and iris is preserved, and in PACG this angle is blocked, causing a more sudden increase of IOP accompanied by hyperemia and ocular pain (Fig.4.1). From these two main types, glaucoma divides into innumerous subtypes, but we will focus on the POAG since it is the hardest one to identify due to its long period of asymptomatic changes.(Umezurike et al., 2019)

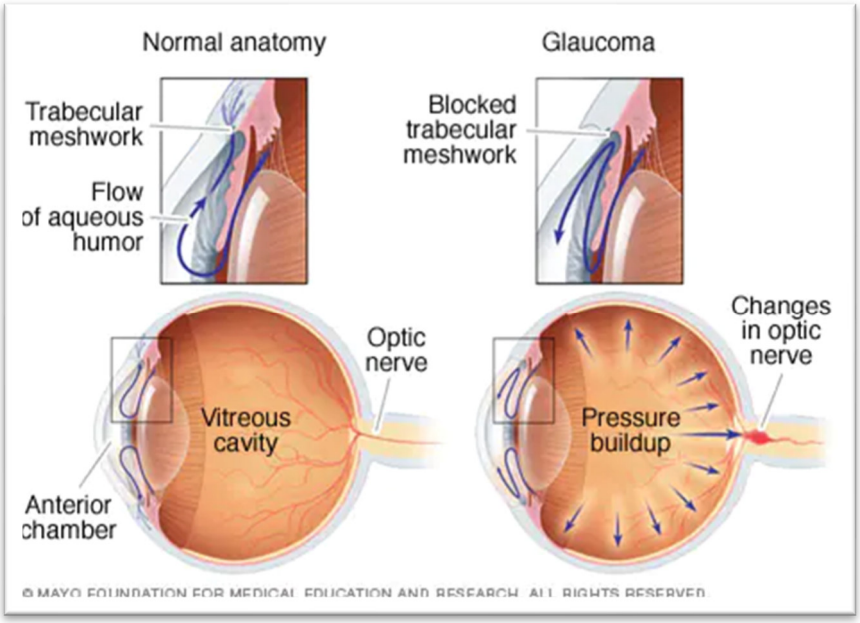


Figure 2.6:. Angle closure Glaucoma vs. Normal flow of AH. (From: Mayo foundation for medical education and research available at: https://www.mayoclinic.org/diseases-conditions/glaucoma/multimedia/open-angle-glaucoma/img-20007729)

Though the underlying cause is still unknown, POAG is highly attributed to an imbalance in the production and drainage of the aqueous humor (AH), which raises the IOP. The elevated IOP pushes harder against the optic nerve fibers, causing blockage of a proper blood supply, depriving it of oxygen and nutrients, with subsequent optic nerve damage and irreversible vision loss. The diagnosis of POAG is made through IOP measuring, OCT evaluation, Retinography and VF. (Jhon, M., Irvin, 2003; Umezurike et al., 2019b)

2.4 OCT IN GLAUCOMA DIAGNOSIS AND FOLLOW UP

As said before, the conventional diagnosis of glaucoma, as well as its monitoring, is made through the relationship between the functional loss and the structural alterations evaluated in the VF and OCT. OCT is a strong tool for the diagnosis of basically any eye disease, due to its ability to produce high-quality images of the inside part of the globe. Retina, vitreous humor and optic disc are the principal structures evaluated in OCT. In the OCT, we try to follow up/assess the progression of the RNFL loss of thickness and the increase in optic disc cupping. In the visual field, we tried to follow up/evaluate the progression of visual field loss, which in this pathology initially occurs in the form of a

"nasal step" and which evolves to the entire peripheral vision, preserving only the central vision until the terminal stages of the disease, in which even central vision is affected. In any case, the visual field is the most ineffective method for early diagnosis, because for a visual field defect to exist, about 70% of the fibers have already been damaged.(Jhon, Morrison, Irvin, 2003; Kuo et al., 2016; Sartoretti et al., 2019; Umezurike et al., 2019)

However, OCT may become insufficient in the diagnosis and follow-up of these patients, as it exclusively assesses intraocular structures/changes, leaving aside the various changes at the level of intracranial structures that also have their relevance in the development and progression of the pathology. (Sartoretti et al., 2019)

2.5. MAGNETIC RESONANCE IN GLAUCOMA

Visual cortex and visual pathway changes in glaucoma have already been described in experimental studies such as Li *et al*., 2020 and Rafael Lacerda Furlanetto *et al*. (2018), the main ones being the degeneration/contraction of volume and a decrease in the number of neurons in the visual cortex and the lateral geniculate body, due to trans-synaptic compromise and abnormalities in the flow and microstructure in the visual cortex. These often appear at an earlier stage of the disease than the changes seen on OCT and VF. There are also studies, such as Wang *et al*., 2019, in which it was shown that functional magnetic resonance imaging (fMRI) can assess functional brain changes in the development of glaucoma with increased and decreased regional homogeneity (ReHo) values in various regions of the brain. (Ciò et al., 2020; Esporcatte & Tavares, 2016; Kosior-Jarecka, Wróbel-Dudzińska, et al., 2020; Lešták et al., 2020; Li et al., 2020; Y. Wang et al., 2019; Y. Q. Zhang et al., 2012).

The development of MRI components, such as small surface RF coils, makes it possible to visualize and study the entire eye *in vivo*. For this reason, it is increasingly common in clinical practice to use MRI to obtain images of the eyeball and orbit, and it is usually performed with a head coil in conventional field intensities (3T or 1.5T). (Kosior-Jarecka et al., 2020; Lešták et al.,2020; Zhan get al., 2012)

Some of the most used imaging techniques are:

- Diffusion Tensor Imaging Resting State (DTI) - Because it provides noninvasive measures of microstructural white matter (WM) integrity and is highly sensitive in detecting axonal injury; (Zikou et al., 2012)
- Functional Magnetic Resonance Imaging Fractional Amplitude Of Low-Frequency Fluctuation (rsfMRI-fALFF) - Because it can determine the state of spontaneous neuronal activity in the brain; (Rao et al., 2014)
- Blood Oxygenation Level-Dependent Functional Magnetic Resonance Imaging (BOLD-fMRI) - Because it is proven that blood perfusion tends to decrease in the brain's visual cortex in the development of glaucoma; (Dou & Yang, 2019)
- Magnetic Resonance Spectroscopy (MRS) - Because it provides noninvasive real-time examinations that may reveal crucial information about physiological and pathological changes; (S. Zhang et al., 2021)
- 3D MRI - Because it provides 3-dimensional images from the visual pathways and orbits. (Case et al., 2020)
- Voxel-based Morphometry (VBM) provides the measurement of any changes in local grey matter volume (GMV), white matter volume (WMV), and general brain volume. Currently, VBM has been used in the study of various ophthalmic diseases, including optic neuromyelitis, advanced monocular blindness, amblyopia, concomitant strabismus, glaucoma and acute eye pain due to the presence of altered brain tissue morphology in these conditions. This provides important information for clinical practice. (Zhao et al., 2021)
- Surface-based Morphometry (SBM) provides morphological measurements to assess the thickness of brain structure. In high tension glaucoma (HTG), visual cortex thinning was already described, as well as a correlation between the thickness of the visual cortex and the severity of HTG. (Wang et al., 2020)

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3. GENERAL OBJECTIVES AND METHODOLOGY

3.1. OBJECTIVES

The main objective of this study was to carry out a systematic review of the relationship between structural findings obtained by OCT with structural findings obtained by MRI in patients with POAG. The application/clinical impact of the association between OCT structural findings (SF-OCT) and MRI structural findings (SF-MRI) was studied and the following specific objectives were developed:

1. Identify and compare the OCT and MRI features in GON.

2. Compare which are the most frequent SF-MRI in the initial phases of GON.

3. Study which SF-MRI are most frequent in the advanced stages of GON.

3.2. METHODOLOGY

This Systematic review and its protocol follow the recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and aims to answer the following starting question "What is the relationship between structural findings in the early and advanced stages of GON obtained through OCT and MRI?".(Page et al., 2021)

Exclusion criteria previously established were Review articles, author letters, studies with pediatric patients, animal studies and studies with a publication date greater than 10 years. Screening the search results was performed separately by three reviewers. For the work research, we used multiple databases such as MEDLINE (NLM PubMed), Scopus, and Cochrane Library to find and choose the articles that best fit the review. The studies included in this review were mainly experimental, cross-sectional, cohort and case-control studies.

After the titles and abstracts were initially assessed to find potentially eligible studies selection of articles, they were imported and introduced in the online platform Systematic Reviews Web Application (Rayyan QCRI) where they were analyzed by all stakeholders.

In the second phase, the articles were carefully evaluated, and all discrepancies and cases of doubt were discussed by the three reviewers to reach the final decision on inclusion or exclusion.

To assess the quality and risk of bias of the different studies, the reviewers followed the Critical Appraisal Skills Program (CASP) for clinical trials, cohort and case control. Additionally, for cross-sectional studies, the Effective Public Health Practice Project tool criteria. The analysis of data found in the articles was gathered, analyzed and represented in the form of tables where they were compared with each other.

The population for this systematic review was determined based on the PICO strategy, in which the participant are patients diagnosed with POAG; the intervention was patients diagnosed with POAG who underwent OCT; the comparator was the patients diagnosed with POAG who underwent MRI and, finally, the outcomes were the decrease in RNFL, optic disc diameter, optic nerve degeneration/tortuosity and volume degeneration/contraction in the cortex visual and lateral geniculate body (SF-MRI).

3.3. SYSTEMATIC REVIEW PROTOCOL

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

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Review question

"What is the relationship between structural findings in the early and advanced stages of NOG

obtained through OCT and MRI?"

Searches

MEDLINE, a highly sensitive strategy provided by the PubMed platform, will be used to search articles matching the PICO strategy using the following keywords:

#1: "tomography, optical coherence"[MeSH Terms] OR ("tomography"[All Fields] AND "optical"[All Fields] AND "coherence"[All Fields]) OR "optical coherence tomography"[All Fields] OR ("optical"[All Fields] AND "coherence"[All Fields] AND "tomography"[All Fields]) OR ("tomography, optical coherence"[MeSH Terms] OR ("tomography"[All Fields] AND "optical"[All Fields] AND "coherence"[All Fields]) OR "optical coherence tomography"[All Fields] OR ("OCT"[All Fields] AND "tomography"[All Fields]) OR "oct tomography"[All Fields]) OR "OCT"[All Fields] OR (("spectral"[All Fields] OR "spectrally"[All Fields]) AND ("domain s"[All Fields] OR "domains"[All Fields] OR "protein domains"[MeSH Terms] OR ("protein"[All Fields] AND "domains"[All Fields]) OR "protein domains"[All Fields] OR "domain"[All Fields]) AND "OCT"[All Fields]) OR "Spectralis"[All Fields]

#2: ("magnet s"[All Fields] OR "magnetical"[All Fields] OR "magnetically"[All Fields] OR "magnetics"[MeSH Terms] OR "magnetics"[All Fields] OR "magnetic"[All Fields] OR "magnetisation"[All Fields] OR "magnetisations"[All Fields] OR "magnetised"[All Fields] OR "magnetism"[All Fields] OR "magnetisms"[All Fields] OR "magnetization"[All Fields] OR "magnetizations"[All Fields] OR "magnetize"[All Fields] OR "magnetized"[All Fields] OR "magnetizing"[All Fields] OR "magnets"[MeSH Terms] OR "magnets"[All Fields] OR "magnet"[All Fields]) AND "ressonance"[All Fields]) OR ("magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "mri"[All Fields])

#3: "glaucoma"[MeSH Terms] OR "glaucoma"[All Fields] OR "glaucomas"[All Fields] OR ("glaucoma, open angle"[MeSH Terms] OR ("glaucoma"[All Fields] AND "open angle"[All Fields]) OR "open-angle glaucoma"[All Fields] OR ("open"[All Fields] AND "angle"[All Fields] AND "glaucoma"[All Fields]) OR "open angle glaucoma"[All Fields]) OR "OAG"[All Fields] OR ("ocular hypertension"[MeSH Terms] OR ("ocular"[All Fields] AND "hypertension"[All Fields]) OR "ocular hypertension"[All Fields])

#4: #1 AND #2 AND #3

Types of study to be included

Articles from experimental studies, observational, cross-sectional, cohort and case-control studies will be included in this study.

Condition or domain being studied

Glaucoma, optical Coherence Tomography measurements, magnetic resonance imaging, retina and optic

nerve.

Participants/population
Human subjects

Intervention(s), exposure(s)
Patients diagnosed with primary open-angle glaucoma who underwent OCT.

Comparator(s)/control
Patients diagnosed with primary open-angle glaucoma who underwent MRI.

Main outcome(s)
Nerve fiber layer/ganglion cell layer thickness, optic disc diameter, optic nerve degeneration/tortuosity, and volume degeneration/contraction in the visual cortex and lateral geniculate body.

Additional outcome(s)
Not applicable

Data extraction (selection and coding)
Screening the search results is performed separately by tree reviewers. For all the research, MEDLINE will be used, a highly sensitive strategy provided by the PubMed platform, to find and choose the articles that best fit the review. Only articles published between 2011 and 2021 will be elected.

After the titles and abstracts are initially assessed to find potentially eligible studies selection of articles, they will be imported and introduced in the online platform Systematic Reviews Web Application (Rayyan QCRI) where they will be analyzed by all stakeholders. In a second phase, the articles will be carefully evaluated, and all discrepancies and cases of doubt will be discussed by the tree reviewers in order to reach the final decision (inclusion/exclusion).

Risk of bias (quality) assessment
In order to assess the quality and risk of bias of the different studies to be included, the reviewers will follow the Critical Appraisal Skills Program (CASP) for clinical trials, cohort and case-control. Additionally, for cross-sectional studies, the Effective Public Health Practice Project tool criteria.

Strategy for data synthesis
The analysis of the data found in the articles will be gathered, analyzed and represented in the form of tables where they will be compared with each other.

Analysis of subgroups or subsets
Subgroup analysis will be carried out if necessary data is available.

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08 October 2021

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

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4. RESULTS

Structural findings obtained through Optic Coherence Tomography and Magnetic Resonance in Glaucoma: Systematic Review

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(Waiting for review in Optometry and Vision Science (OVS))

ABSTRACT

Significance: Glaucomatous Optic Neuropathy (GON) is structurally characterized by chronic and progressive damage to retinal ganglion cells and the retinal nerve fibre layer. With the evidence that glaucoma can affect, silently, other components of the visual pathway and visual cortex, the link between MRI and OCT findings might be useful to clarify the development and progression of GON. Ophthalmology benefits greatly from the assessment of the optic pathway and other intracranial structures, as they are entirely interconnected and in the last 5 years, this is the first systematic review in this field, to include information on both structural and functional findings.

Purpose: To study the relationship between MRI and OCT and understand its value in the early identification of changes in the visual system, in GON staging and also in the ability to identify potential neurotherapeutic targets.

Methods: Using the PRISMA guidelines, a systematic review of the current literature was conducted by searching in PubMed, Scopus and the Cochrane Library for the Medical Subject Headings (MeSH) with keyword variation between optical coherence tomography, OCT, spectral domain, magnetic resonance imaging, MRI and glaucoma. The three reviewers identified 719 articles, of which 28 met all inclusion criteria after review.

Results: Structural MRI findings appear to be mostly related to RNFL and visual field changes, while metabolic findings appear to be more closely related to GCL changes. The most relevant structural findings the thinning of some areas in the visual cortex, and significantly smaller LGN height and volume in glaucoma patients. The most significant metabolic findings were functional network disruption indices and changes in cerebral blood flow.

Conclusions: These results suggest that MRI can be a strong ally to OCT in the assessment of GON changes, especially in the early stages where there are still no significant changes in OCT.

Keywords: Glaucoma, Magnetic Resonance, Optical coherence Tomography, Ophthalmology

INTRODUCTION

Glaucomatous optic neuropathy (GON), is the second most common leading cause of irreversible blindness in developed countries, affecting 57.5 million people worldwide. In Europe, about 7.8 million people are affected by primary open-angle glaucoma (POAG) (Allison et al., 2020) that would likely result in high economic, social and health impacts due to this condition. In the UK, blind patients (regardless of pathology) represent

an annual direct cost of £735 million and an indirect cost of £5.65 million.(Allison et al., 2020; Pezzullo et al., 2018; Silva et al., 2021)

GON is characterized by chronic and progressive damages to the retinal ganglion cell sand their axons, which form the retinal nerve fiber layer (RNFL). Despite this structural changes, a silent, progressive, and irreversible loss of visual field occurs (Fukuda et al., 2018; Zhang et al., 2012) making an earlier diagnosis challenging.(Mariottoni et al., 2021a).

Although late stages are easier to follow-up (Sarossy et al., 2021), some patients show a continuous VF/RNFL/RGCL degradation even with the right intraocular pressure (IOP) Thus, the classical approach, damage caused to the retinal ganglion cells (RGC) and their axons, through optical coherence tomography (OCT), may be insufficient to fully explain the disease progression. Focusing on intraocular structures/alterations, some intracranial structure changes may be lost, and they can be important in the early development and progression of the pathology (Aksoy et al., 2019). (Esporcatte & Tavares, 2016; Nuzzi et al., 2020; Sartoretti et al., 2019; Aksoy et al., 2019)

Visual cortex and visual pathway changes have already been described in experimental studies such as Li et al., 2020 and Rafael Lacerda Furlanetto et al. (2018). The key findings were the degeneration/contraction of volume and the decrease in the number of neurons in the visual cortex and the lateral geniculate body. There seems to be a trans-synaptic compromise and abnormalities in the axonal flow and microstructure in the visual cortex in glaucoma patients prior to traditional OCT and VF changes. Wang et al. 2019 work was shown that Functional magnetic resonance imaging (fMRI) can assess functional brain changes in the development of glaucoma showing regional homogeneity (ReHo) differences in various brain locations. (Ciò et al., 2020; Esporcatte & Tavares, 2016; Kosior-Jarecka et al., 2020; Lešták et al., 2020; T. Li et al., 2020; Y. Wang et al., 2019; Zhang et al., 2012). The development of Magnetic Resonance Imaging (MRI) components, such as small surface radio frequency (RF) coils, makes it possible to visualize and study the entire eye in vivo.(Li et al., 2020) For this reason, the use of MRI in clinical practice has been increasing to obtain images of the eyeball and orbit with a head coil in conventional field intensities (3T or 1.5T). (Kosior-Jarecka et al., 2020; Lešták et al.,2020; Zhang get al., 2012)

For these reasons, and adding the fact that the existing systematic reviews are old and do not gather the same information as this one, it would be interesting to study the role of MRI combined with OCT, to seek a concordance between the intraocular findings (OCT) and the extraocular/intracranial findings in the MRI. Therefore, the purpose of this systematic review is to gather relevant studies on this topic that allow the characterization of the structural findings obtained through OCT and MRI in POAG patients and clarify the application/clinical impact of the association between both methods to better understand the importance of the communion of these two complementary means of diagnosis.(Fukuda et al., 2018; Kosior-Jarecka et al., 2020; Lešták et al., 2020; Zhang et al., 2012)

A specific approach was performed to (1) Identify and compare OCT and MRI findings in POAG; (2) Compare the most frequent MRI findings in the early stages of POAG, and (3) Study which are the most frequent MRI findings in the advanced stages of POAG.

METHODS

This Systematic Review and its protocol follow the recommendations described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). The protocol is already registered on the PROSPERO platform with the following ID: CRD42021284152. The study in question aims to answer the following question "What is the relationship between structural findings in the early and advanced stages of GON obtained through OCT and MRI?"

For the work research, we used multiple databases such as MEDLINE (NLM PubMed), Scopus, and Cochrane Library. We began with the MeSH builder in MEDLINE and Cochrane Library, to find and choose the articles that best fit the research with the following keywords:

#1: "tomography, optical coherence"[MeSH Terms] OR ("tomography"[All Fields] AND "optical"[All Fields] AND "coherence"[All Fields]) OR "optical coherence tomography"[All Fields] OR ("optical"[All Fields] AND "coherence"[All Fields] AND "tomography"[All Fields]) OR ("tomography, optical coherence"[MeSH Terms] OR ("tomography"[All Fields] AND "optical"[All Fields] AND "coherence"[All Fields]) OR "optical coherence tomography"[All Fields] OR ("OCT"[All Fields] AND "tomography"[All Fields]) OR "oct tomography"[All Fields]) OR "OCT"[All Fields] OR (("spectral"[All Fields] OR "spectrally"[All Fields]) AND ("domain s"[All Fields] OR "domains"[All Fields] OR "protein domains"[MeSH Terms] OR ("protein"[All Fields] AND "domains"[All Fields]) OR "protein domains"[All Fields] OR "domain"[All Fields]) AND "OCT"[All Fields]) OR "Spectralis"[All Fields]

#2: ("magnet s"[All Fields] OR "magnetical"[All Fields] OR "magnetically"[All Fields] OR "magnetics"[MeSH Terms] OR "magnetics"[All Fields] OR "magnetic"[All Fields] OR "magnetisation"[All Fields] OR "magnetisations"[All Fields] OR "magnetised"[All Fields] OR "magnetism"[All Fields] OR "magnetisms"[All Fields] OR "magnetization"[All Fields] OR "magnetizations"[All Fields] OR "magnetize"[All Fields] OR "magnetized"[All Fields] OR "magnetizing"[All Fields] OR "magnets"[MeSH Terms] OR "magnets"[All Fields] OR "magnet"[All Fields]) AND "ressonance"[All Fields]) OR ("magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "mri"[All Fields])

#3: "glaucoma"[MeSH Terms] OR "glaucoma"[All Fields] OR "glaucomas"[All Fields] OR ("glaucoma, open angle"[MeSH Terms] OR ("glaucoma"[All Fields] AND "open angle"[All Fields]) OR "open-angle glaucoma"[All Fields] OR

("open"[All Fields] AND "angle"[All Fields] AND "glaucoma"[All Fields]) OR "open angle glaucoma"[All Fields]) OR "OAG"[All Fields] OR ("ocular hypertension"[MeSH Terms] OR ("ocular"[All Fields] AND "hypertension"[All Fields]) OR "ocular hypertension"[All Fields])

Through the Scopus preview we were also able to gain access to more articles using the following keywords:

"open AND angle AND glaucoma AND oct AND tomography AND mri AND PUBYEAR > 2005 AND PUBYEAR < 2023 AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACTKEYWORD , "Humans") OR LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Optical Coherence Tomography") OR LIMIT-TO (EXACTKEYWORD , "Controlled Study") OR LIMIT-TO (EXACTKEYWORD , "Tomography, Optical Coherence") OR LIMIT-TO (EXACTKEYWORD , "Glaucoma") OR LIMIT-TO (EXACTKEYWORD , "Pathology") OR LIMIT-TO (EXACTKEYWORD , "Retinal Nerve Fiber Layer Thickness") OR LIMIT-TO (EXACTKEYWORD , "Nuclear Magnetic Resonance Imaging") OR LIMIT-TO (EXACTKEYWORD , "Diagnostic Imaging") OR LIMIT-TO (EXACTKEYWORD , "Optic Nerve") OR LIMIT-TO (EXACTKEYWORD , "Optic Disk") OR LIMIT-TO (EXACTKEYWORD , "Retinal Ganglion Cells") OR LIMIT-TO (EXACTKEYWORD , "Retina Ganglion Cell") OR LIMIT-TO (EXACTKEYWORD , "Retina") OR LIMIT-TO (EXACTKEYWORD , "Pathophysiology") OR LIMIT-TO (EXACTKEYWORD , "Open Angle Glaucoma") OR LIMIT-TO (EXACTKEYWORD , "Visual Field") OR LIMIT-TO (EXACTKEYWORD , "Nerve Fibers") OR LIMIT-TO (EXACTKEYWORD , "Visual Acuity") OR LIMIT-TO (EXACTKEYWORD , "Nerve Fiber") OR LIMIT-TO (EXACTKEYWORD , "Magnetic Resonance Imaging") OR LIMIT-TO (EXACTKEYWORD , "Glaucoma, Open-Angle") OR LIMIT-TO (EXACTKEYWORD , "Prospective Study") OR LIMIT-TO (EXACTKEYWORD , "Visual System Parameters") OR LIMIT-TO (EXACTKEYWORD , "Visual Fields") OR LIMIT-TO (EXACTKEYWORD , "Diffusion Tensor Imaging") OR LIMIT-TO (EXACTKEYWORD , "Spectral Domain Optical Coherence Tomography") OR LIMIT-TO (EXACTKEYWORD , "Perimetry") OR LIMIT-TO (EXACTKEYWORD , "Visual System") OR LIMIT-TO (EXACTKEYWORD , "Prospective Studies") OR LIMIT-TO (EXACTKEYWORD , "Young Adult") OR LIMIT-TO (EXACTKEYWORD , "Optical Coherence Tomography Angiography") OR LIMIT-TO (EXACTKEYWORD , "Optic Nerve Diseases") OR LIMIT-TO (EXACTKEYWORD , "Aged, 80 And Over") OR LIMIT-TO (EXACTKEYWORD , "Optic Nerve Disease") OR LIMIT-TO (EXACTKEYWORD , "Retina Blood Vessel") OR LIMIT-TO (EXACTKEYWORD , "Retinal Nerve Fiber Layer") OR LIMIT-TO (EXACTKEYWORD , "Disease Severity") OR LIMIT-TO (EXACTKEYWORD , "Comparative Study") OR LIMIT-TO (EXACTKEYWORD , "Retinal

Thickness") OR LIMIT-TO (EXACTKEYWORD , "Retinal Vessels") OR LIMIT-TO (EXACTKEYWORD , "Optic Chiasm") OR LIMIT-TO (EXACTKEYWORD , "Follow Up") OR LIMIT-TO (EXACTKEYWORD , "Visual Field Defect") OR LIMIT-TO (EXACTKEYWORD , "Neuroimaging") OR LIMIT-TO (EXACTKEYWORD , "Functional Magnetic Resonance Imaging") OR LIMIT-TO (EXACTKEYWORD , "Optic Tract") OR LIMIT-TO (EXACTKEYWORD , "Optic Nerve Head") OR LIMIT-TO (EXACTKEYWORD , "Macular Thickness") OR LIMIT-TO (EXACTKEYWORD , "Retina Nerve Cell") OR LIMIT-TO (EXACTKEYWORD , "Retina Macula Lutea") OR LIMIT-TO (EXACTKEYWORD , "Optical Tomography") OR LIMIT-TO (EXACTKEYWORD , "Ocular Hypertension") OR LIMIT-TO (EXACTKEYWORD , "Intraocular Hypertension") OR LIMIT-TO (EXACTKEYWORD , "Diffusion Weighted Imaging") OR LIMIT-TO (EXACTKEYWORD , "Diffusion Magnetic Resonance Imaging") OR LIMIT-TO (EXACTKEYWORD , "Blood Vessel Density") OR LIMIT-TO (EXACTKEYWORD , "Tomography") OR LIMIT-TO (EXACTKEYWORD , "MRI") OR LIMIT-TO (EXACTKEYWORD , "Brain")) AND (LIMIT-TO (LANGUAGE , "English"))"

Only works published between 2009 and 2021 were elected. After the selection of articles, they were imported and introduced in the online platform Systematic Reviews Web Application (Rayyan QCRI) where they were analyzed by all intervening parties. Only English and Portuguese language articles were eligible.

In the first screening, the titles and abstract of each article were evaluated and, in the second phase, only the potentially eligible articles' full text were carefully evaluated in detail. In both phases, which took place in a hidden way, all discrepancies and cases of doubt were discussed as a team to reach the final decision to include or exclude published papers.

INCLUSION AND EXCLUSION CRITERIA

The inclusion or exclusion of an article was decided according to the stipulated inclusion and exclusion criteria. The exclusion criteria included: 1. study outcomes rather than GON; 2. studies investigating retinal structure or function among non-glaucomatous participants; 3. studies reporting results from diagnostic tests other than MRI; 4. letters, comments, editorials, reviews and meta-analyses; 5. Articles with publishing date older than 2009.

Studies were eligible for inclusion if they reported results from different techniques of MRI preformed in GON patients. The type of studies included were experimental, observational, cross-sectional, cohort and case-control studies.

QUALITY ASSESSMENT

To assess the quality and risk of bias of the different studies, the reviewers followed the Critical Appraisal Skills Program (CASP) for clinical trials, cohort and case control. Additionally, for cross-sectional studies, the Effective Public Health Practice Project tool criteria. The analysis of data found in the articles was gathered, analyzed and represented in the form of tables where they were compared with each other.

PICO STRATEGY

The population for this systematic review will be determined based on the PICO strategy where (P) refers to population or patient, (I) refers to intervention or exposure, (C) refers to comparison, and (O) refers an outcome. The population are patients diagnosed with POAG; the intervention will be patients diagnosed with POAG who underwent OCT; the comparator will be patients diagnosed with POAG who underwent MRI and, finally, the outcomes will be RNFL/RGCL, optic disc diameter OCT degeneration/tortuosity of the optic nerve and volume of the visual cortex and in the lateral geniculate body (MRI).

The neuroimaging techniques included in this search were:

- Diffusion tensor MRI (DT MRI/ DTI)

- Voxel-based Morphometry (VBM)

- Surface-based Morphometry (SBM)

- Functional Magnetic Resonance Imaging (fMRI)

- Resting-state fMRI (rs-fMRI)

- Magnetic resonance spectroscopy (MRS)

RESULTS

Study Selection and Characteristics:

A total of 719 studies were screened using the described search strategy. At the end of the selection process, 28 were included in this systematic review. The 2020 Prisma flow diagram, presented in Figure 1, gives all the details on the screening processes.

Twenty out of 28 studies (≈ 71%) were focused on Structural abnormalities/parameters and 8 studies (≈ 29%) were focused on functional abnormalities/parameters showing brain changes following glaucomatous degeneration. A total of 1,321 participants were considered in this review, of which 781 were glaucoma patients and 540 were healthy controls.

Twelve studies included exclusively POAG patients and two included exclusively NTG patients being the less studied type, the other 14 studies included both POAG and NTG. More detailed information is presented in Tables 1 and 2.

The severity or progression of glaucoma varies from early to severe stages, but the severity classification used was not consistent in all studies, and most authors included different stages of glaucoma in the same case.

Outcomes of Structural Analysis:

As mentioned before, 24 out of 28 studies focused on structural analyses of glaucoma patients versus controls with the DTI approach being the most used. All findings and corresponding articles are discriminated in table 3.

The main brain abnormalities founded using MRI and/or Blood Oxygenation Level-Dependent Functional Magnetic Resonance Imaging (BOLD-fMRI) were in the visual cortex. Atrophy and thinning findings in different areas of the visual cortex, particularly in the left hemisphere of the brain, were correlated with the RNFL thickness profile. These results were obtained in studies 3,10,14,17,20, 21 and 27.

Related to the optic nerve, in studies 2,7,11,24 and 28 were found correlations between RNFL thickness, ON volume/diameter and cup-to-disc ratio showing a pathologic involvement of the optic nerve in both normotension and high-tension glaucoma.

Studies 12,13,25 and 26 focused on Lateral Geniculate Nucleus and mostly found that LGN height and volume were significantly smaller in glaucoma patients. Specifically in study 13, it was described that Nasal RNFL thickness correlated with the volume of the contralateral LGN ($r = 0.471$, $p = 0.05$). Temporal RNFL thickness correlated with the volume of the ipsilateral LGN ($r = 0.603$,$p = 0.015$).Even though most of these studies didn't find any direct correlation between RNFL thickness and LGN parameters. In study 13 is described that RNFL thickness seemed to be correlated with the volume of the contralateral LGN.

Optic radiations and optic tracts were studied in three articles (6,20, 23) and the vertical cup-to-disc ratio (VCDR), were more strongly associated with homolateral optic radiations diffusion parameters than with contralateral parameters. The optic tracts (OTs) assessment of glaucoma patients showed a significant correlation with the average pRNFL thickness.

Other visual pathway changes, such as significantly increased IOP and significantly decreased RNFL thickness values present in patients with glaucomatous optic neuropathy and pathologic optic nerve DIR hyper signal, were found and described in studies 4,5,15 and 18.

Outcomes of Functional and Metabolic Analysis:

Some studies focused on the changes in the activity of the brain in glaucomatous patients, using mostly rsfMRI-fALFF. Resting-state fMRI is used to study the human

brain's functional connectivity in a resting state, without any visual stimulation (Biswal et al., 2010).

Studies 1,8,14,16,17,19 and 22 showed that there were significant positive associations between functional network disruption indices and VFI, Macula GCL and RNFL. Damage to the RNFL appeared as atrophy in the Brodmann area.

On the other hand, study 9 focused on the cerebral blood flow, and positive correlations were found between GCC thickness and zCBF in area V2 and area VP of the right hemisphere. Also, correlations between RNFL thickness and zCBF in area V2 and area VP of the right hemisphere.

DISCUSSION

This study shows several OCT and MRI findings that can be related to favoring an earlier diagnosis of glaucoma in clinical practice. Making it the first recent systematic review to gather and relate results from various MRI techniques to OCT findings. It also showed that structural MRI findings appear to be mostly related to RNFL changes and visual field changes, while metabolic findings appear to be more closely related to GCL changes.

Most Relevant Functional and Structural results:

The most relevant findings for this study were obtained by analyzing table 3, where we found that most structural abnormalities observed in the visual pathway (studies 2,4,5,6,7,11,12,13,15,18,20,23,24,25,26,28) and visual cortex (studies 3,10,14,17,20,21,27) using different MRI techniques were significantly correlated with RNFL thickness, although some are also strongly related with the visual field. This goes according to the knowledge we have about the relationship between RNFL and brain abnormalities, because as we know, average RNFL thickness is under investigation as a biomarker for neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease, under the premise that anatomic abnormalities in the anterior visual pathway correlate with greater central nervous system disease burden (Nagla et al., 2016). So, we believe that this principle might be the same reason why we found this correlation.

As previously mentioned, for this research the most relevant findings would be those associated with earlier stages of the disease and cases of normal IOP, since they are more difficult to diagnose. However, this association was difficult due to the heterogeneity of classification of glaucoma stages and the lack of distinction between glaucoma patients with high and normal IOP in several studies. The most relevant findings for NTG patients were showed in studies 10,13 and 24. In study 10, the NTG subgroup demonstrated decreased FA and increased MD in B.PTR and B.SS. B.PTR, B.SS, B.CgH, and B.FX/ST which were positively correlated with the MDVF ($P < 0.05$) and RNFL thickness ($P < 0.05$). Which means that Atlas-based DTI analysis indicated WM damage in the four regions associated with visual and visual-related functions in NTG patients, having a

strong possibility to be useful in early diagnosis and investigating disease progression and pathologic changes.

In study 13, NTG group showed significantly reduced LGN volume. But even more interesting, was the correlation found between nasal RNFL thickness and the volume of the contralateral LGN ($r = 0.471$, $p = 0.05$). Also, Temporal RNFL thickness was correlated with the volume of the ipsilateral LGN ($r = 0.603$, $p = 0.015$). This study shows, once again, the possibility of DTI being a strong technic to access changes before vision loss occurs.

Different from the other two studies, study 24 showed us that even though optic nerve volume was significantly lower in both the left and right eyes of the severe glaucoma group (168.70±46.28 mm3; 167.40±45.36 mm3) than in the mild glaucoma group (264.03±78.53 mm3; 264.76±78.88 mm3) and the control group (297.80±71.45 mm3; 296.56±71.02 mm3), this results are better indicators for follow up rather than early diagnosis.

On the other hand, functional brain alterations (studies 1,8,9,14,16,17,19,22) such as activity variations and blood flow seem to be correlated not only with RNFL but also with GCL thickness. This goes according to the fact that in some studies in mice, it was found structural changes that include a reduction in the dendritic arbour area, the length of dendrites and the number of dendrites, which are correlated with the severity of the disease (Sarossy M., et al, 2021). However, functional alterations do not have a great relevance for this specific study, since usually they are found in advanced stages of glaucoma, and what this study seeks to compare are relevant findings for the differential diagnosis in early stages and normotension glaucoma.

Correlation of functional and structural results with Glaucoma Severity:

In both methods analyzed, the most interesting and relevant findings in the early stages of GON were shown in studies 5, 11, 13 and 24. In study 5, it was described that NAA values obtained from CGL in glaucoma suspect cases were lower than the healthy control group (both $p= 0.025$, $p= 0.011$), this might be useful for early diagnosis of glaucoma when there are still no structural abnormalities found in OCT.

Study 11 described that eyes with a mild signal alteration (SA) had a significantly narrower neural rim area, larger cup volume, and larger average and vertical cup-to-disk ratios compared with those without an SA ($P = 0.011$, 0.003, 0.004, and 0.004, respectively), if more studies can confirm this, those metrics might be helpful detecting early stages of glaucoma in suspects.

DTI proved to be a strong ally in the early diagnosis of glaucoma since many of the findings precede the onset of visual loss. In study 13, it was described that Temporal RNFL thickness correlated with the volume of the ipsilateral LGN ($r =0.603$, $p = 0.015$), this might be an interesting finding to detect early damage of RNFL when there is still no repercussion in the visual field, but it needs more studies to support the accuracy of these finding in all glaucoma cases.

Studies 6, 20 and 23 found a positive correlation between diffusivity parameters and glaucoma severity, revealing that the visual pathway damage correlates with clinical severity in glaucoma. This means that DTI can detect axonal and microstructural injury in the visual pathway at an early stage, even before the visual field defect can be detected in perimetry.

LIMITATIONS

We faced 4 main limitations in this study, the first two being differences in classification and parameters used to divide patients and the fact that most studies did not distinguish the severity of different glaucoma patients and normal tension glaucoma patients. Another limitation consisted in the heterogeneity of age and duration of disease in patients between the studies selected. The last limitation we faced was the variety of techniques used, in which different parts of the cortex and the visual pathway were evaluated, which makes it difficult to directly relate some of the findings.

CONCLUSIONS

In this systematic review, the various alterations along the optic pathway and the visual cortex in glaucomatous patients are addressed through MRI. These changes demonstrated a strong relationship not only with the clinical findings of the OCT but also with the severity of the pathology. MRI proved to be a strong ally to access GON changes not only in the early stages but also in later stages with more severe changes such as LGN height and volume and optic radiation diffusion parameters, for example. So, we can conclude that MRI may be useful not only in the diagnosis, but it is also as the best way to follow up patients alongside with OCT and the visual field.

The main MRI techniques that can help us understand GON changes better are especially DTI, rsfMRI-fALFF, BOLD-fMRI and MRS to access both brain and visual pathway changes.

We had the opportunity to compile information from two different techniques for the first time, and despite the difficulties, there seems to be potential to take advantage of different information at different times of the disease.

For that reason, we believe this review contributes to a better understanding of which MRI parameters may play an important role in the early diagnosis of glaucoma due to their relationship with the stage of the pathology.

AUTHORS CONTRIBUTIONS STATEMENT

The authors Joana Rita Creado and Pedro Camacho were responsible for study conception and design. The author Joana Rita Creado was responsible for data collection. Joana Rita Creado, Pedro Camacho and Marco Caetano made the analysis and interpretation of results. Joana Rita Creado wrote the manuscript with input of all authors.

All authors reviewed the results and approved the final version of the manuscript.

FIVE-YEAR VIEW

We believe that in the future, more patients will be diagnosed in the early stages of glaucoma, using the complementarity that exists between the traditional ophthalmological diagnosis and MRI. Briefly, there are 3 main potential gains from this study: 1- This approach will allow a better understanding/characterization of the disease; 2- It may be useful for early detection of patients who may have a more severe evolution of the disease; 3- Contribute to relate OCT with non-invasive structural biomarkers.

With patients diagnosed earlier, there will be fewer cases of severe glaucoma and consequent blindness as the therapeutic intervention will be much more successful. When we reach this level, both parties will benefit from it, because patients will have a better quality of life and the costs and other disadvantages associated with MRI will be offset by the decrease in cases of blindness, which, in turn, also entails high and long-term costs.

CONFLICT OF INTEREST STATEMENT

None.

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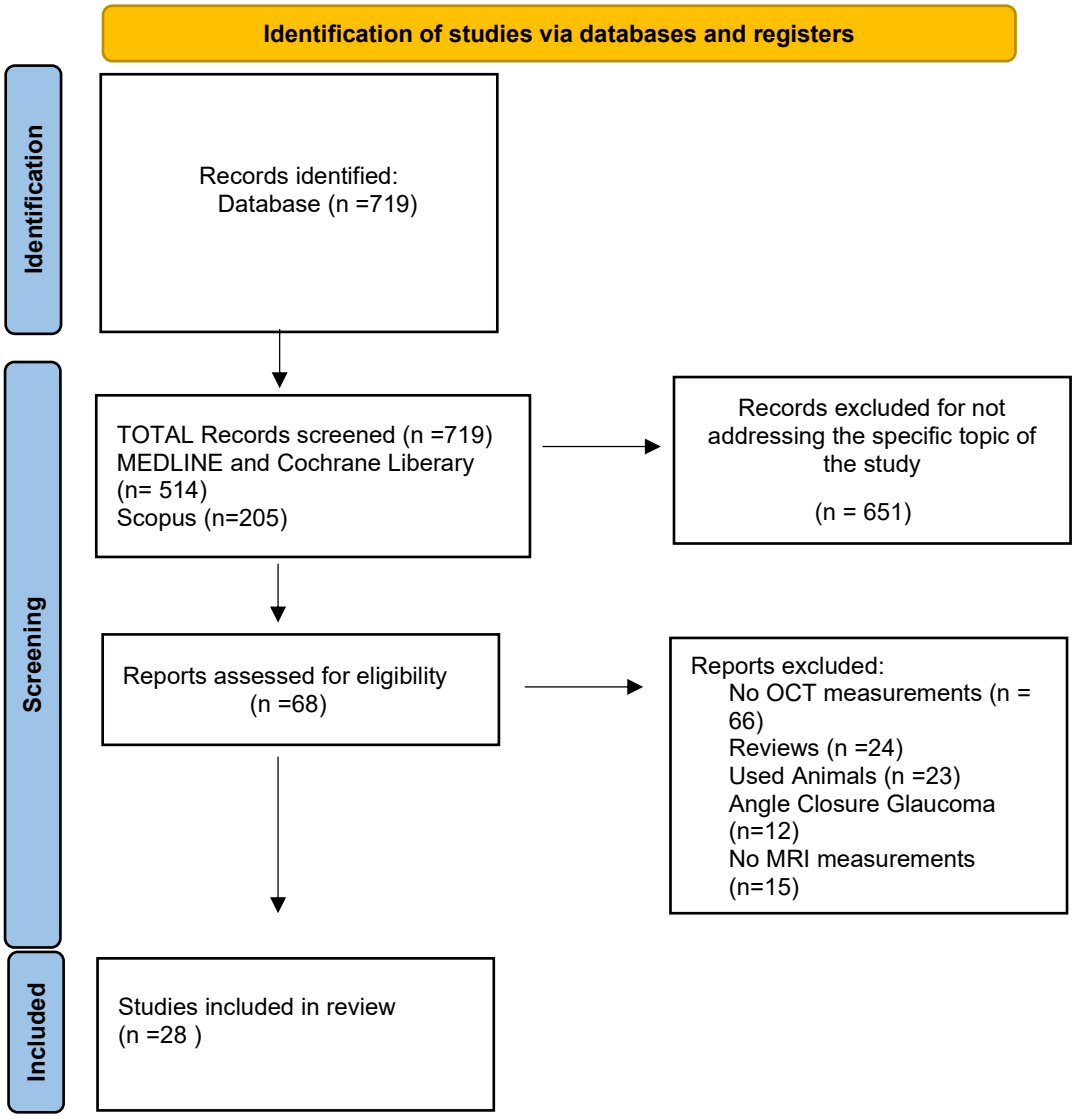
Figure 4.1 – PRISMA 2020 Flow Diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Twenty out of 28 studies (≈ 71%) were focused on Structural abnormalities/parameters and 8 studies (≈ 29%) were focused on functional abnormalities/parameters showing brain changes following glaucomatous degeneration. A total of 1,321 participants were considered in this review, of which 781 were glaucoma patients and 540 were healthy controls.

Twelve studies included exclusively POAG patients and two included exclusively NTG patients being the less studied type, the other 14 studies included both POAG and NTG. More detailed information is presented in Tables 1 and 2.

The severity or progression of glaucoma varies from early to severe stages, but the severity classification used was not consistent in all studies, and most authors included different stages of glaucoma in the same case.

Table 5.1: Selected articles

Article	*Authors (year)*	*Title*	*Study Design*	*Population/Sample*
1	Han-Lin Li et al. (2020)	**Use of rsfMRI-fALFF for the detection of changes in brain activity in patients with normal-tension glaucoma**	Prospective, cross-sectional study.	20 patients with Glaucoma and 20 healthy controls.
2	Shereif Haykal, Nomdo M. Jansonius b, Frans W. Cornelissen (2020)	**Investigating changes in axonal density and morphology of glaucomatous optic nerves using fixel-based analysis.**	Prospective, cross-sectional study.	15 patients with Glaucoma and 15 healthy controls.
3	Carolina P.B. Gracitelli et al. (2020)	**Structural Analysis of Glaucoma Brain and its Association With Ocular Parameters**	Prospective, cross-sectional study.	30 patients with glaucoma and 18 healthy controls.
4	Thomas Sartoretti et al. (2019)	**Long segment 3D double inversion recovery (DIR) hypersignal on MRI in glaucomatous optic neuropathy**	Retrospective, cross-sectional study.	21 patients with glaucoma.
5	Direnç Özlem Aksoy et al. (2019)	**Magnetic Resonance Spectroscopy Features of the Visual Pathways in Patients with Glaucoma**	Prospective, cross-sectional study.	86 patients with glaucoma or glaucoma suspect and 30 healthy controls.
6	Shereif Haykal et al. (2019)	**Fixel-Based Analysis of Visual Pathway White Matter in Primary Open-Angle Glaucoma**	Prospective, cross-sectional study.	12 patients with glaucoma and 16 healthy controls.
7	Nathaniel Miller et al. (2019)	**Linking neural and clinical measures of glaucoma with diffusion magnetic resonance imaging (dMRI)**	Prospective, cross-sectional study.	6 patients with glaucoma and 6 healthy controls.
8	Silvia Minosse et al. (2019)	**Primary Open Angle Glaucoma Is Associated With Functional Brain Network Reorganization**	Prospective, cross-sectional study.	19 patients with glaucoma and 16 healthy controls.
9	Qian Wang et al. (2018)	**Reduced Cerebral Blood Flow in the Visual Cortex and Its Correlation With Glaucomatous Structural Damage to the Retina in Patients With Mild to Moderate Primary Open-angle Glaucoma**	Prospective, cross-sectional study.	15 patients with glaucoma and 20 healthy controls.
10	Rong Wang et al. (2018)	**White Matter Abnormalities and Correlation With Severity in Normal Tension Glaucoma: A**	Prospective, cross-sectional study.	35 patients with glaucoma and 25 healthy controls.

		Whole Brain Atlas-Based Diffusion Tensor Study		
11	Jong Yeon Lee et al (2018)	**Signal Alteration in the Optic Nerve Head on 3D T2-weighted MRI: a Potential Neuroimaging Sign of Glaucomatous Optic Neuropathy**	Prospective, cross-sectional study.	35 patients with glaucoma and 31 healthy controls.
12	Rafael Lacerda Furlanetto et al. (2018)	**Structural and functional analyses of the optic nerve and lateral geniculate nucleus in glaucoma**	Prospective, cross-sectional study.	41 patients with glaucoma and 12 healthy controls.
13	Manuel A. Schmidt et al. (2018)	**Investigation of lateral geniculate nucleus volume and diffusion tensor imaging in patients with normal tension glaucoma using 7 tesla magnetic resonance imaging**	Prospective, cross-sectional study.	20 patients with glaucoma and 16 healthy controls.
14	Mana Fukuda et al. (2018)	**Quantitative MRI evaluation of glaucomatous changes in the visual pathway**	Prospective, cross-sectional study.	31 patients with glaucoma and 20 healthy controls.
15	Mehmet Giray Ersoz et al. (2018)	**MR Imaging of the Anterior Visual Pathway in Primary Open-Angle Glaucoma: Correlation with Octopus 101 Perimetry and Spectralis Optical Coherence Tomography Findings**	Prospective, cross-sectional study.	28 patients with glaucoma and 26 healthy controls.
16	Wei Zhou et al. (2017)	**Retinotopic fMRI Reveals Visual Dysfunction and Functional Reorganization in the Visual Cortex of Mild to Moderate Glaucoma Patients**	Prospective, cross-sectional study.	9 patients with glaucoma and 9 healthy controls.
17	Ming-Ming Jiang et al. (2017)	**Structural and functional brain changes in early- and mid-stage primary open-angle glaucoma using voxel-based morphometry and functional magnetic resonance imaging**	Prospective, cross-sectional study.	13 patients with glaucoma and 13 healthy controls.
18	Wei Zhou et al. (2017)	**MRI study of the posterior visual pathways in primary open Angle glaucoma**	Prospective, cross-sectional study.	11 patients with glaucoma and 11 healthy controls.
19	Paolo Frezzotti et al. (2016)	**Early Changes of Brain Connectivity in Primary Open Angle Glaucoma**	Prospective, cross-sectional study.	57 patients with glaucoma and 29 healthy controls.

20	Laury Tellouck et al. (2016)	**Optic Radiations Microstructural Changes in Glaucoma and Association With Severity: A Study Using 3TeslaMagnetic Resonance Diffusion Tensor Imaging**	Prospective, cross-sectional study.	50 patients with glaucoma and 50 healthy controls.
21	Longhua Yu et al. (2015)	**Progressive Thinning of Visual Cortex in Primary Open-Angle Glaucoma of Varying Severity**	Prospective, cross-sectional study.	37 patients with glaucoma and 20 healthy controls.
22	Vanessa M. Gerente et al. (2015)	**Evaluation of Glaucomatous Damage via Functional Magnetic Resonance Imaging, and Correlations Thereof with Anatomical and Psychophysical Ocular Findings**	Prospective, cross-sectional study.	17 patients with glaucoma and 8 healthy controls.
23	Megha Kaushik et al. (2015)	**A Topographical Relationship Between Visual Field Defects and Optic Radiation Changes in Glaucoma**	Prospective, cross-sectional study.	9 patients with glaucoma and 9 healthy controls.
24	Norlina M. Ramli et al. (2014)	**Novel use of 3T MRI in assessment of optic nerve volume in glaucoma**	Prospective, cross-sectional study.	60 patients with glaucoma and 30 healthy controls.
25	Jong Yeon Lee et al. (2014)	**An Investigation of Lateral Geniculate Nucleus Volume in Patients With Primary Open-Angle Glaucoma Using 7 Tesla Magnetic Resonance Imaging**	Prospective, cross-sectional study.	18 patients with glaucoma and 18 healthy controls.
26	Zhiqi Chen et al. (2014)	**Correlation between lateral geniculate nucleus atrophy and damage to the optic disc in glaucoma**	Prospective, cross-sectional study.	23 patients with glaucoma and 23 healthy controls.
27	Longhua Yu et al. (2013)	**Reduced Cortical Thickness in Primary Open-Angle Glaucoma and Its Relationship to the Retinal Nerve Fiber Layer Thickness**	Prospective, cross-sectional study.	36 patients with glaucoma and 40 healthy controls.
28	Wolf A. Lagre`ze et al. (2009)	**Retrobulbar Optic Nerve Diameter Measured by HighSpeed Magnetic Resonance Imaging as a Biomarker for Axonal Loss in Glaucomatous Optic Atrophy**	Prospective, cross-sectional study.	27 patients with glaucoma and 9 healthy controls.

Legend: rsfMRI-fALFF = Resting State Functional Magnetic Resonance Imaging Fractional Amplitude Of Low-Frequency Fluctuation; **MR=** Magnetic Ressonsnce; **MRI=**Magnetic Ressonance Imaging; **3T**= 3 Tesla

Table 5.2: Information on each study

Article	*Objectives*	*Methods*	*Results*
1	Investigate the altered spontaneous brain activity in patients with NTG through the resting state functional magnetic resonance imaging fractional amplitude of low-frequency fluctuation (rsfMRI-fALFF) technique, and to explore the relationship with optical coherence tomography (OCT) and visual field.	Spontaneous cerebral activity variations were investigated using the rsfMRI-fALFF technique in all individuals. The average fALFF values of patients with NTG and HCs were compared. Structural (OCT) and functional (Visual Fields) assessment were performed.	The values showed statistically significant negative correlation with those of the retinal nerve fiber layer (right angular gyrus: r ¼ 0.607, *P*-value ¼ .010; right precuneus: r ¼ 0.504, *P*-value ¼ .020). In the NTG group, there was no significant correlation between the fALFF value of the right cerebral angular gyrus and right anterior cuneiform lobe and the MD value of the visual field. - GP: Mean RNFL thickness in both eyes (µm)- 61.3 ± 6.1. - - HC: Mean RNFL thickness in both eyes (µm)- 127.5 ± 12.1.
2	Characterize neurodegeneration of glaucomatous optic nerves (changes in axonal density and morphology) using fixel-based analysis (FBA). Explore the potential of FBA measures as biomarkers of glaucomatous ON degeneration.	ONs were tracked and segmented into their three anatomical segments: intraorbital (IO), intracanalicular (ICAN) and intracranial (ICRAN). Peripapillary retinal nerve fiber layer (pRNFL) thickness and visual field mean deviation (VFMD) were assessed.	All glaucomatous ON segments showed a significant loss of FD and FDC compared to the controls (*P*-value <.01), while a loss of FC was found in the IO and ICRAN segments only. Average FBA and DTI measures of the anatomical segments of glaucomatous ONs showed varying degrees of correlation with the average pRNFL thickness and the VFMD. The strongest correlation was found between the FDC of the IO segment and VFMD (ρ2 = 0.83, *P*-value < .001), while the FC of all segments showed no correlation with either of the ophthalmic tests. - GP: pRNFL (µm)- 65.1 ± 7.4. - HC: pRNFL (µm)- 99.5 ± 7.8.

3	Evaluate structural brain abnormalities in glaucoma patients using 3-Tesla magnetic resonance imaging and assess their correlation with associated structural and functional ocular findings.	All participants underwent standard automated perimetry, spectral domain optical coherence tomography, and 3.0-Tesla magnetic resonance imaging.	There was a significant difference between the surface area of the occipital pole in the left hemisphere (p=0.043) of glaucoma patients (1253.9 ± 149.3 mm2) and that of control subjects (1341.9 ± 129.8 mm2). The surface area of the occipital pole in the left hemisphere was significantly correlated with perimetry mean deviation values (*P*-value =.001), visual acuity (*P*-value <.001), age (*P*-value =.010), and retinal nerve fiber layer thickness (*P*-value =.006). - GP: RNFL OCT (µm) 76.72 ± 2.13. - HC: RNFL OCT (µm) 97.36 ± 1.58.
4	Study the relationship between intraocular pressure (IOP), retinal nerve fiber layer (RNFL) thickness and pathologic hypersignal in optic nerve segments on 3D double inversion recovery (DIR) MR sequence in 21 patients with proven glaucoma of different origin was evaluated.	All patients were examined on a 3 T MR Philips® scanner. Pathologic optic nerve DIR hypersignal was determined in four different nerve segments. RNFL thickness was measured with optical coherence tomography (OCT Heidelberg Engineering Spectralis®).	In patients with glaucomatous optic neuropathy (GON) and pathologic optic nerve DIR hypersignal, significantly increased IOP and significantly decreased RNFL thickness values are present. 3D DIR hypersignal was associated with increased IOP (*P*-value = .008) and decreased RNFL thickness (*P*-value < .001). - GP: RNFL OCT (µm)- 76.72 ± 2.13. - HC: RNFL OCT (µm)- 97.36 ± 1.58.
5	Investigate any metabolic changes on magnetic resonance spectroscopy (MRS) throughout the visual pathway of the brain in patients with glaucoma and a control group and correlate the results with clinical findings.	A single voxel MRS on TE 30ms was performed by placing the volume of interest (VOI) on the corpus geniculatum laterale (CGL) and primary visual cortex (VC). Peak values of metabolites, such as N-acetyl aspartate (NAA), were investigated on MRS. The MRS results were correlated with age, intraocular pressure (IOP), retinal nerve fiber length (RNFL), mean deviation (MD) and cup disk ratio (CD).	RNFL Glaucoma suspect: 90.19 ± 10.25; Healthy Controls: 102.94 ± 9.43; Glaucoma 65.80 ± 12.57. The NAA values obtained from CGL in glaucoma suspect cases were lower than the healthy control group (both *P*-value = .025, *P*-value = .011). There was a negative correlation between age and RNFL in both glaucoma (*P*-value = .048, r = –0.399) and glaucoma suspect (*P*-value = .004, r = –0.676).

6	Study glaucomatous degeneration of the pre geniculate optic tracts (OTs) and post geniculate optic radiation (ORs) in POAG.	Multi-shell diffusion-weighted images were acquired. The RNFL thickness was measured by OCT using a Canon OCT-HS100 scanner.	Compared with the controls, the OTs of the patients exhibited a significant decrease in FD and FC, whereas their ORs exhibited a significant decrease in FD but not in FC. FD of the OTs of glaucoma patients showed a significant correlation with the average pRNFL thickness and VFMD (*P*-value < .01 and, *P*-value < .05, respectively), whereas FD of the ORs showed a significant correlation with pRNFL thickness only (*P*-value < .05). pRNFL thickness (μm): - Right Eye GP: 71.3 (10.1); - Right Eye HC 97.3 (7.9) <0.001 - Left Eye GP: 70.8 (12.7); - Left Eye HC 97.8 (8.5) <0.001
7	To link optic nerve (ON) structural properties to clinical markers of glaucoma using advanced, semi-automated diffusion magnetic resonance imaging (dMRI) tractography in human glaucoma patients.	All participants underwent probabilistic dMRI tractography and their results were compared with OCT measurements.	Comparing the ratios of ON FA in glaucoma patients to those of healthy controls, was determined that this difference was beyond that expected from normal anatomical variation (*P*-value < . 005). Finally, the dMRI measures of ON FA to standard clinical glaucoma measures. ON vertical cup-to-disc ratio (vCD) predicted ON FA (*P*-value < .01), retinal nerve fiber layer thickness (RNFL) predicted ON FA (*P*-value < .01).
8	Explore a putative reorganization of functional brain networks in glaucomatous patients and evaluated the potential of functional network disruption indices as biomarkers of disease severity in terms of their relationship to clinical variables as well as select retinal layer thicknesses.	All subjects underwent Optical Coherence Tomography (OCT), visual field index (VFI) quantification and rs-fMRI examination at 3T.	There were significant positive associations between disruption indices and VFI, MaculaGCL and RNFL. Significant positive associations with RFNL were found in several regions, including the right parahippocampal gyrus (*P*-value =.023) and right transverse temporal gyrus (*P*-value =.048).

9	To investigate the correlations between reduced cerebral blood flow (CBF) in early and higher-tier visual cortical areas and glaucomatous changes in the retinas of patients with mild to moderate POAG.	3D pseudo continuous arterial spin labelling magnetic resonance imaging at 3 T was performed. Regions of interest were selected based on the Population-Average, Landmark- and Surface-based (PALS) atlas of the human cerebral cortex.	Positive correlations were found between GCC thickness and zCBF in area V2 (r=0.583, *P*-value = .029) and area VP (r=0.663, *P*-value =.008) of the right hemisphere, between RNFL thickness and zCBF in area V2 (r=0.528, *P*-value =.052) and area VP (r= 0.586, *P*-value =.028) of the right hemisphere.
10	Detect injury of whole brain white matter (WM) in normal tension glaucoma (NTG) patients by using diffusion tensor imaging (DTI) and to analyze the correlations between DTI parameters and glaucoma indices.	Atlas-based diffusion tensor analysis was performed.The subjects underwent ophthalmologic examinations, including optic intraocular pressure, slit-lamp microscopy, standard automated perimetry and RNFL thickness using the SD-OCT. NTG patients were further divided into three subgroups (mild, moderate, and severe NTG).	Compared with the NC group, the mi-NTG subgroup demonstrated decreased FA and increased MD in B.PTR and B.SS. B.PTR, B.SS, B.CgH, and B.FX/ST were positively correlated with the MDVF (*P*-value < .05) and RNFL thickness (*P*-value < .05). The MD and RD values in these four regions were negatively correlated with MDVF (*P*-value < .05) and RNFL thickness (*P*-value < .01). RNFL thickness, µm: - Mild Subgroup: 82.69 ± 12.37; - Moderate Subgroup: 68.54 ± 10.38; - Severe Soubgroup: 54.11 ± 10.08; - HC: 104.64 ± 8.86;
11	To investigate whether a signal alteration (SA) in the optic nerve head (ONH) on 3D T2- weighted magnetic resonance imaging (MRI) is associated with glaucomatous optic neuropathy.	All subjects underwent 3D high-resolution T2-weighted MRI and detailed ophthalmologic examinations including spectral-domain optical coherence tomography (OCT). The prevalence of SAs was compared between the two groups with the chi-square test. The OCT measurements were compared among the eyes with a mild or prominent SA and those without an SA using the Kruskal–Wallis test	The eyes with a prominent SA had a significantly different average retinal nerve fiber layer thickness (*P*-value = .002) and the ONH parameters except for the disk area (all *P*-value < .001) than those without an SA. The eyes with a mild SA had a significantly narrower neural rim area, larger cup volume, and larger average and vertical cup-to-disk ratios compared with those without an SA (*P*-value = .011, .003, .004, and .004, respectively). RNFL thickness, µm: - GP: 73.20 ± 15.59; - HC: 95.77 ± 8.24.

12	To analyze the correlation between structural characteristics of intraorbital optic nerve (ION) and lateral geniculate nucleus (LGN) measured by 3-Tesla magnetic resonance imaging (3T MRI), and the severity of glaucomatous damage.	All subjects underwent standard automated perimetry (SAP) and frequency doubling technology (FDT) as functional evaluation; optic disc stereophotograph, spectral-domain optical coherence tomography (OCT) and confocal scanning laser tomography as ocular structural evaluation and 3T MRI. Structure-structure and structure-function correlation were performed using bootstrap resampling method for clustered data.	There were significant correlations between CSA and cpRNFLT (r = 0.82, *P*-value < .001) and HFA MD (r = 0.79, *P*-value < .001). The high correlation found between optic nerve CSA and cpRNFLT suggests that optic nerve CSA is a good indicator of glaucomatous structural damage, and that it is consistent with cpRNFLT. Although LGN height was significantly smaller in glaucoma group (*P*-value = .005), LGN parameters were not associated with any ocular structural or functional parameter. RNFL thickness, µm: - GP: 64.7 ± 10.6 - HC: 95.4 ± 6.9
13	Study potential benefits of volumetry of the lateral geniculate nucleus (LGN) and diffusion tensor imaging (DTI) using a new 7T scanner.	LGN volume and fractional anisotropy (FA) of the optic tract (OT) and the optic radiation (OR) and their correlation with RNFL (retinal nerve fiber layer) thickness were analyzed.	LGN volume was significantly reduced in NTG (60.9 vs 88.3; *P*-value < .05). FA of the OT (right: 0.35 vs 0.66, left: 0.36 vs 0.67; *P*-value < .05) and of the OR (right: 0.41 vs 0.70, left: 0.41 vs 0.69; *P*-value < .05) was also significantly reduced. Nasal RNFL thickness correlated with the volume of the contralateral LGN (r = 0.471, *P*-value = .05). Temporal RNFL thickness correlated with the volume of the ipsilateral LGN (r = 0.603, *P*-value = .015).
14	Investigate glaucomatous morphological changes quantitatively in the visual cortex with voxel-based morphometry (VBM), and to clarify the relationship between glaucomatous damage and regional changes in the visual cortex of patients with open-angle glaucoma (OAG).	The cross-sectional area (CSA) of the optic nerve was manually measured with T2-weighed MRI. Measurements of ocular parameters were made by 3D OCT-2000 software.	There were significant correlations between CSA and cpRNFLT (r = 0.82, *P*-value < .001) and HFA MD (r = 0.79, *P*-value < .001).

15	Investigate structural changes in the visual pathway measured by magnetic resonance imaging (MRI) and its relationship with the clinical severity of glaucoma in primary open-angle glaucoma (POAG) patients.	All the subjects underwent spectral domain optical coherence tomography (OCT) of the peripapillary retina nerve fiber layer (RNFL). The optic nerve diameter (OND), chiasma height (Ch), and lateral geniculate nucleus height (LGNh) were measured bilaterally using a 1.5-Tesla MRI system.	The mean values of the OND and LGNh were significantly lower in the POAG group (OND: right P-value = .043 and left P-value = .048; LGNh: right P-value = .008 and left P-value = .025). The OND was correlated with the ipsilateral RNFL thickness. The Ch was correlated with the ipsilateral clinical stage (right r = −0.536, P-value = .004; left r = −0.537, P-value = .004) and average RNFL thickness (RNFL) (right r = 0.655, P-value < .001; left r = 0.626, P-value < .001).
16	Investigate retinotopic functional representation in the visual cortex of mild to moderate primary open-angle glaucoma (POAG) participants and age-matched normal volunteers using high-resolution retinotopic blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI).	A wide-view visual presentation (± 55 degrees) was used to evaluate central and peripheral vision. Cortical magnification factors and BOLD% changes as a function of eccentricity. Correlation analysis between BOLD% changes and visual field scores, and between BOLD% changes and retinal nerve fiber layer thicknesses was performed by OCT.	BOLD fMRI data were correlated with visual field function and RNFL thickness of the corresponding visual field quadrants. BOLD changes by quadrants were significantly correlated with the mean RNFL thickness of the corresponding quadrants (r = 0.447, P-value < .01).
17	To investigate structural and functional brain changes in patients with primary open-angle glaucoma (POAG) by using voxel-based morphometry based on diffeomorphic anatomical registration through exponentiated Lie algebra (VBM-DARTEL) and blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI), respectively.	High-resolution structural brain imaging and blood flow imaging were acquired on a 3.0-Tesla magnetic resonance imaging (MRI) scanner. Structural and functional changes between the POAG and control groups were analyzed. An analysis was carried out to identify correlations between structural and functional changes acquired in the previous analysis and the retinal nerve fiber layer (RNFL).	Patients in the POAG group showed a significant (P-value <.001) volume increase in the midbrain, left brainstem, frontal gyrus, cerebellar vermis, left inferior parietal lobule, caudate nucleus, thalamus, precuneus, and Brodmann areas 17, 18, and 46. Damage to the RNFL appeared as atrophy in Brodmann area 19 (P-value =.87), increased volume in Brodmann area 18 (P-value =-.92), and large BOLD signal changes in Brodmann area 17.
18	To evaluate neurodegeneration along brain visual pathways in primary open angle glaucoma (POAG) using improved analysis methods of volumetric and diffusion-tensor MRI data.	Surface-based segmentation was applied to structural MRI to obtain visual cortical area and volume. Fiber tracking was applied to diffusion-tensor data to obtain diffusion parameters along the optic tract and optic radiation. MRI parameters were compared with the corresponding left and right visual fields and retinal nerve fiber layer thicknesses, instead of with the left and right eye.	None of the MRI parameters were significantly correlated with RNFL thickness (P-value > .05). Visual field scores were also not significantly correlated with RNFL thickness (P-value > .05).

19	Assess in primary open angle glaucoma (POAG), , whether diffuse brain changes in advanced stage can be detected since the early stage.	Multimodal magnetic resonance imaging (MRI) was used and Voxelwise statistics was performed with nonparametric permutation testing. Optical coherence tomography Peripapillary RNFL thickness was measured using the Optic Disc Cube 200 × 200 scanning protocol of the Cirrus OCT (Carl Zeiss Meditec, Dublin, CA).	Lower RNFL values showed voxelwise correlations with abnormalities in the visual system: lower FA in the OR (ILF) (r = 0.40, *P*-value = .003) and lower GM volume (r = 0.32, *P*-value = .02).
20	Compare microstructural changes along the optical radiations and brain structure volumes between glaucoma and control subjects using in vivo magnetic resonance imaging and to analyze their association with severity of the disease.	Underwent detailed ophthalmologic examinations including visual field and spectral-domain optical coherence tomography) as well as diffusion tensor imaging (DTI) using 3.0-Tesla magnetic resonance imaging. Fractional anisotropy (FA), mean diffusivity, radial diffusivity (RD), and axial diffusivity (AD) were quantified semiautomatically along the optical radiations. DTI parameters and volumes of specific brain structures were compared between cases and controls using conditional logistic regression.	For the homolateral side, significant associations were found between optic radiations FA and mean deviation of the VF (b ¼ 0.22; *P*-value ¼ .03), VCDR (b ¼ 0.42; *P*-value ¼ .0003), and RNFL (b ¼ 0.22; *P*-value ¼ .03). The direction of the association is opposite for RNFL, because RNFL decreases with higher severity of glaucoma.
21	Investigate possible changes of cortical thickness in the visual cortex in primary open-angle glaucoma (POAG).	The associations of cortical thickness (V1, V2, ventral V3, V4 and V5/MT+) with retinal nerve fiber layer (RNFL) thickness and mean deviation (MD) of visual field were analyzed. The participants were organized in 3 groups: severe patints, Mild patients and Healthy Controls.	Mean RNFL thickness in the POAG patients was positively correlated with cortical thickness in the V2 (ρ = 0.38, p = 0.02) and V5/MT+ (ρ = 0.44, p = 0.006) regions. Decreased cortical thickness was detected in the bilateral V5/MT+ areas in the MP group. RNFL thickness, μm: - SP: 54.6 ± 12.1 - MP: 82.9 ± 11.8 - HC: 110.5 ± 6.7
22	Evaluate the functional magnetic resonance imaging (fMRI) response to binocular visual stimulation and the association thereof with structural ocular findings and psychophysical test results in patients with glaucoma, and controls.	Participants underwent a complete ophthalmic examination, including Humphrey 24-2 visual field (VF) testing and optical coherence tomography. fMRI (3 T) was performed using a bilaterally presented polar angle stimulus, and the accompanying changes in blood oxygen level-dependent (BOLD), the patients were assigned to three subgroups: (1) initial glaucoma, (2) asymmetrical glaucoma and (3) severe glaucoma	Significant associations between quadrant binocular VF sensitivities and fMRI responses were found in the occipital pole ROIs (*P*-value = .033) and the calcarine ROIs (*P*-value = .045). In glaucoma severity subgroup analysis, retinal nerve fiber layer (RNFL) thickness was associated with the BOLD response of the calcarine (*P*-value =.002) and occipital pole ROIs (*P*-value = .026).

23	Investigate the topographic relationship between glaucomatous retinal ganglion cell loss and changes in the optic radiation (OR) using diffusion tensor imaging (DTI).	A comparative DTI analysis was conducted between OR fibers connected to the affected and unaffected visual hemifield in the glaucoma group and corresponding OR in the control group.	In both eyes, the average RNFL thickness was significantly lower in the region corresponding to the affected visual hemifield in comparison with the relatively spared region of RNFL (*P*-value < .001.)
24	Measure optic nerve (ON) volume using 3 T magnetic resonance imaging (MRI), to correlate ON volume with retinal nerve fiber layer (RNFL) thickness	All subjects underwent standard automated perimetry, RNFL analysis and 3 T MRI examinations. All participants were organized in 3 groups: Severe patients, mild patients and Healthy controls.	Optic nerve volume was significantly lower in both the left and right eyes of the severe glaucoma group (168.70±46.28 mm3; 167.40±45.36 mm3) than in the mild glaucoma group (264.03±78.53 mm3; 264.76±78.88 mm3) and the control group (297.80±71.45 mm3; 296.56±71.02 mm3). Moderate correlation was observed between: RNFL thickness and ON volume (r=0.51, *P*-value <.001), and in MD and optic nerve volume (r=0.60, *P*-value <.001). RNFL thickness, µm: - SP: Right Eye (58.50±6.97) Left Eye (58.60±9.05) - MP: Right Eye (76.37±11.35) Left Eye (76.87±12.01) - HC: Right Eye (84.47±10.44) Left Eye (83.60±10.36)
25	Investigate lateral geniculate nucleus (LGN) volume of primary open-angle glaucoma (POAG) patients compared with age- and sex-matched controls using ultra-high field 7.0T magnetic resonance imaging (MRI).	All subjects underwent imaging on a high-resolution 7.0-T MRI system. Bilateral LGNs were identified and manually delineated, and LGN volumes were compared. Peripapillary retinal nerve fiber layer (pRNFL) thickness, optic nerve head parameters and combined thickness of the ganglion cell layer and inner plexus layer (GC-IPL) were measured by SD-OCT.	POAG group: LGN volume (right 83.97mm3; left 65.12); GC-IPL (right 42micras; left 32 micras); IOP (mmHg) Control group: LGN volume (right 83.97mm3; left 65.12); GC-IPL (right 42micras; left 32 micras); IOP (mmHg) Significantly differences were found in LGN volume (*P*-value <.05), GC-IPL (*P*-value =.01) and between GC-IPL with LGN volume.

26	Investigate the relationship between morphological changes in the lateral geniculate nucleus (LGN), as measured by magnetic resonance imaging (MRI), and damage to the optic disc in primary open-angle glaucoma (POAG) patients.	Cup-to-disc ratio (CDR) and retinal nerve fiber layer thickness (RNFLT) were measured, and 3.0-Tesla MRI examinations performed. Bilateral LGNs were identified and manually extracted, and their maximum heights and volumes compared with the clinical damage to the optic disc.	In POAG patients, morphological changes in LGNs and RNFLT were consistently varied (P-value < .05), while a negative correlation between LGN measurements and CDR was observed (P-value < .05). LGN height was more significantly correlated with damage to the optic disc than was LGN volume. in the glaucoma group, the heights of both right and left LGNs were statistically significantly correlated with both CDR (r = —0.43 to —0.613, P-value < .05) and RNFLT (r = 0.487 to 0.658, P-value < .05). On the other hand, LGN volume correlated with damage to the optic disc except for CDR and RNFLT values for right eyes.
27	Examine possible changes in cortical thickness and their relationship to retinal nerve fiber layer (RNFL) thickness in patients with primary open-angle glaucoma (POAG).	All subjects underwent a comprehensive ophthalmologic examination and a high resolution structural magnetic resonance scan. Cortical thickness analysis was used to assess the changes between patients and controls. Correlations between the thickness of the visual cortex and RNFL thickness were also analyzed.	POAG patients showed significant bilateral cortical thinning in the anterior half of the visual cortex around the calcarine sulci (left BA 17 and BA 18, right BA17) and in some smaller regions located in the left middle temporal gyrus (BA37) and fusiform gyrus (BA19). The thickness of the visual cortex correlated positively with RNFL thickness (left, r = 0.44, P-value = .01; right, r = 0.38, P-value = .03). Significant differences between mild and severe groups were observed with regard to both RNFL thickness and the thickness of bilateral visual cortex (P-value < .05).

28	Assess a novel magnetic resonance imaging (MRI) protocol for quantifying the optic nerve diameter (OND) as a measure of axonal loss in the optic nerve.	Each subject underwent automated perimetry, scanning laser polarimetry, optic coherence tomography, scanning laser tomography, and ultrafast high-resolution MRI at 3 T. OND was determined 5, 10, and 15 mm behind the eye with a half Fourier-acquired single-shot turbo spin-echo (HASTE)-sequence requiring 1.5 seconds of data acquisition time per slice and providing a spatial resolution of 0.11 mm. A multiple linear regression model was applied to determine correlations (r) among the different techniques.	The correlation (r) was <0.37 for OND measurements taken 5 mm behind the eye. At 10 mm behind the eye, *r* increased to 0.57 and was statistically significant in four out six instances. In the orbital apex 15 mm behind the eye, *r* reached a maximum of 0.80 and was statistically significant in all instances. OND correlated best with the retinal nerve fiber layer thickness measured by optic coherence tomography

Legend: BA= Brodmann area; **C/D=** cup to disc ratio; **FA=** fractional anisotropy; **FMRIB=** Functional MR Imaging of the Brain; **GM=** gray matter; **LGN=** lateral geniculate nucleus; **MD=** mean diffusivity; **OCT=** optical coherence tomography; **ON=** optic nerve; **POAG=** primary open-angle glaucoma; **PSD=** pattern SD; **RNFLT=** retinal nerve fiber layer thickness; **SAR=** signal-intensity average ratio; **VBM** =voxel-based morphometry; **WM=** white matter; **DTI=** Diffusion Tensor Imaging; **SD-OCT=** Spectral Domain optical coherence tomography; **MRI=** Magnetic Ressonance Imaging; **dMRI** = Diffusion Magnetic Ressonance Imaging; **rsfMRI-fALFF** = Resting State Functional Magnetic Resonance Imaging Fractional Amplitude Of Low-Frequency Fluctuation; **BOLD-fMRI** = Blood Oxygenation Level Dependent Functional Magnetic Resonance Imaging; **DIR=** Double Inversion Recovery; **MRS** =Magnetic Resonance Spectroscopy; **FDC=** Fiber Density And Cross-Section; **FD=**Fiber Density; **HC=** Healthy Controls; **FBA=** Fixel-Based Analysis; **IO=** Intraorbital; **ICAN=** Intracanalicular; **ICRAN=** Intracranial; **Prfnl** = Peripapillary Retinal Nerve Fiber Layer; **VFMD** = Visual Field Mean Deviation; **DIR=** Double Inversion Recovery; **VC=** Visual Cortex; **CD=** Cup/Disk Ratio; **NAA=** N-Acetyl Aspartate; **B.PTR=** Bilateral Posterior Thalamic Radiation; **B.SS** = Bilateral Sagittal Stratum; **B.Cgh=** Bilateral Cingulum-Hippocampus; **B.FX=** Bilateral Fornix/Stria Terminalis; **SA=** Signal Alteration; **ONH=** Optic Nerve Head; **SAP=** Standard Automated Perimetry; **ILF** = Inferior Longitudinal Fascicle; **OR** = Optic Radiation; **ROC=** Receiver Operating Curve; **OND=** Optic Nerve Diameter; **ON=** Optic Nerve; **OT=** Optic Tract.

Table 5.3: Resume of the main findings through the visual pathway.

Studies	***Approach***	***Findings***
2,7,11,24 and 28	a) SD-OCT; MRI and/or dMRI b) Density/Morphology of Optic Nerves	Moderate negative correlation was observed between: RNFL thickness and ON volume and ON diameter and larger average and vertical cup-to-disk ratios.

6	a) SD-OCT; DTI b) Optic Tracts	OTs of glaucoma patients showed a significant correlation with the average pRNFL thickness and VFMD and whereas FD of the ORs showed a significant correlation with pRNFL thickness only.
12,13,25 and 26	a) SD-OCT; MRI and/or DTI b) Density/Morphology of Lateral Geniculate Nucleus (LGN)	LGN height and volume were significantly smaller in glaucoma patients. Temporal RNFL thickness correlated with the volume of the contralateral LGN and LGN height was more significantly correlated with damage to the optic disc.
6,20 and 23	a) SD-OCT; DTI b) Optic Radiation	Glaucoma severity parameters (especially VCDR) were more strongly associated with homolateral optic radiations diffusion parameters than with contralateral parameters. Association of diffusivity parameters (mainly FA and RD), with the severity of glaucoma, suggesting that microstructural changes to the optic radiations is one of the components of the severity that could participate in the clinical status of the patients and the alteration of the VF.
3,10,14,17,20, 21 and 27	a) SD-OCT; MRI and/or BOLD-fMRI b) Structural Brain Abnormalities	The surface area of the occipital pole in the left hemisphere was significantly correlated with perimetry mean deviation values, visual acuity, age, and retinal nerve fiber layer thicknes. The DTI parameters of these WM regions correlated with the mean deviation of visual field (MDVF) and retinal nerve fiber layer (RNFL) thickness. There were significant correlations between CSA and cpRNFLT. Damage to the RNFL appeared as atrophy in Brodmann area 19, increased volume in Brodmann area 18, and large BOLD signal changes in Brodmann area 17. POAG patients showed significant bilateral cortical thinning in the anterior half of the visual cortex
1,8,14,16,17,19 and 22	a) SD-OCT; DTI and/or rsfMRI-fALFF b) Cerebral Activity Variations	There were significant positive associations between disruption indices and VFI, Macula GCL and RNFL. Damage to the RNFL appeared as atrophy in Brodmann area.

9	a) SD-OCT; 3D MRI b) Density/Morphology of Cerebral Blood Flow	Positive correlations were found between GCC thickness and zCBF in area V2 and area VP of the right hemisphere, between RNFL thickness and zCBF in area and area VP of the right hemisphere.
4,5,15 and 18	a) SD-OCT; MRI and/or DIR; MRS b) Density/Morphology of Other Visual Pathway Changes	In patients with glaucomatous optic neuropathy (GON) and pathologic optic nerve DIR hypersignal, significantly increased IOP and significantly decreased RNFL thickness values are present. The OND was correlated with the ipsilateral RNFL thickness.

Legend: a) methods assessment; b) anatomical assessment; **DTI=** Diffusion Tensor Imaging; **SD-OCT=** Spectral Domain optical coherence tomography; **MRI=** Magnetic Ressonance Imaging; **dMRI =** Diffusion Magnetic Ressonance Imaging; **rsfMRI-fALFF =** Resting State Functional Magnetic Resonance Imaging Fractional Amplitude Of Low-Frequency Fluctuation; **BOLD-fMRI =** Blood Oxygenation Level Dependent Functional Magnetic Resonance Imaging; **DIR=** Double Inversion Recovery; **MRS =**Magnetic Resonance Spectroscopy; **ON=** Optic Nerve; **OT=** Optic Tract; **pRNFL =** Papillary retinal fibre layer; **RNFL=** Retinal Nerve Fiber Layer; **VFMD=** Visual Field Mean Deviation; **OR=** Optic Radiation; **LGN=** Lateral Geniculate Nucleus; **VF=** Visual Field; **VCDR=** vertical cup to disc ratio.

Outcomes of Structural Analysis:

As mentioned before, 24 out of 28 studies focused on structural analyses of glaucoma patients versus controls being DTI methodology, the most used to investigate this. All findings and corresponding articles are discriminated in table 3.

The main brain structure abnormalities found using MRI and/or Blood Oxygenation Level-Dependent Functional Magnetic Resonance Imaging (BOLD-fMRI) were in the visual cortex. Mostly it was found atrophy and thinning in different areas of the visual cortex, and it was also described the correlation of those findings with the RNFL thickness. These results were obtained in studies 3,10,14,17,20, 21 and 27.

In the optic nerve, the main correlations found were between RNFL thinning, and increased ON volume/diameter and cup-to-disc ratio showing a pathologic involvement of the optic nerve in studies 2,7,11,24 and 28.

Studies 12,13,25 and 26 focused on Lateral Geniculate Nucleus and mostly found that LGN height and volume were significantly smaller in glaucoma patients. Even though most of these studies didn't find any direct correlation between RNFL thickness and LGN parameters. In study 13 is described that RNFL thickness seemed to be correlated with the volume of the contralateral LGN.

Optic radiations and optic tracts were studied in 6,20 and 23 articles. These have shown that Glaucoma severity parameters, especially vertical cup-to-disc ratio (VCDR), were more strongly associated with homolateral optic radiations diffusion parameters than with

contralateral parameters and optic tracts (OTs) of glaucoma patients showed a significant correlation with the average pRNFL thickness.

Other visual pathway changes, such as significantly increased IOP and significantly decreased RNFL thickness values present in patients with glaucomatous optic neuropathy and pathologic optic nerve DIR hyper signal, were found and described in studies 4,5,15 and 18.

Outcomes of Functional and Metabolic Analysis:

Some studies focused on the changes in the activity of the brain in glaucomatous patients, using mostly rsfMRI-fALFF. Resting-state fMRI is used to study the human brain's functional connectivity in a resting state, without any visual stimulation *(Biswal et al., 2010).*

Studies 1,8,14,16,17,19 and 22 showed that there were significant positive associations between disruption indices and VFI, Macula GCL and RNFL. Damage to the RNFL appeared as atrophy in the Brodmann area.

On the other hand, in study 9 focused on the cerebral blood flow, positive correlations were found between GCL thickness and zCBF in area V2 and area VP of the right hemisphere, between RNFL thickness and zCBF in area and area VP of the right hemisphere using MRI.

DISCUSSION

This study shows several OCT and MRI findings that can be related to favouring an earlier diagnosis of glaucoma in clinical practice. It also showed that structural MRI findings appear to be mostly related to RNFL changes and visual field changes, while metabolic findings appear to be more closely related to GCL changes.

Most Relevant Functional and Structural results:

The most relevant findings for this study were obtained by analyzing table 3, where we found that most structural abnormalities observed in the visual pathway (studies 2,4,5,6,7,11,12,13,15,18,20,23,24,25,26,28) and visual cortex (studies 3,10,14,17,20,21,27) using different MRI techniques were significantly correlated with RNFL thickness, although some are also strongly related with the visual field. This goes according to the knowledge we have about the relationship between RNFL and brain abnormalities, because as we know, average RNFL thickness is under investigation as a biomarker for neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease, under the premise that anatomic abnormalities in the anterior visual pathway correlate with greater central nervous system disease burden (Nagla et al., 2016). So, we believe that this principle might be the same reason why we found this correlation.

On the other hand, functional brain alterations (studies 1,8,9,14,16,17,19,22) such as activity variations and blood flow seem to be correlated not only with RNFL but also with GCL thickness. This goes according to the fact that in some studies in mice, it was found structural changes that include a reduction in the dendritic arbour area, the length of dendrites and the number of dendrites, which are correlated with the severity of the disease (Sarossy M., et al, 2021).

Correlation of functional and structural results with Glaucoma Severity:

In both methods analyzed, the most interesting findings in the early stages of GON were shown in studies 5, 11 and 13. In study 5, it was described that NAA values obtained from CGL in glaucoma suspect cases were lower than the healthy control group (both p= 0.025, p= 0.011), this might be useful for early diagnosis of glaucoma when there are still no structural abnormalities found in OCT.

Study 11 described that eyes with a mild signal alteration (SA) had a significantly narrower neural rim area, larger cup volume, and larger average and vertical cup-to-disk ratios compared with those without an SA (P = 0.011, 0.003, 0.004, and 0.004, respectively), if more studies can confirm this, those metrics might be helpful detecting early stages of glaucoma in suspects. Finally, in study 13, it was described that Temporal RNFL thickness correlated with the volume of the ipsilateral LGN (r =0.603, p = 0.015), this might be an interesting finding to detect early damage of RNFL when there is still no repercussion in the visual field, but it needs more studies to support the accuracy of these finding in all glaucoma cases.

Studies 6, 20 and 23 found a positive correlation between diffusivity parameters and glaucoma severity, revealing that the visual pathway damage correlates with clinical severity in glaucoma. This means that DTI can detect axonal and microstructural injury in the visual pathway at an early stage, even before the visual field defect can be detected in perimetry.

LIMITATIONS

We faced 4 main limitations in this study, the first two being differences in classification and parameters used to divide patients and the fact that most studies did not distinguish the severity of different glaucoma patients. Another limitation consisted in the heterogeneity of age, severity and duration of disease in patients between the studies selected. The last limitation we faced was the variety of techniques used, in which different parts of the cortex and the visual pathway were evaluated, which makes it difficult to directly relate some of the findings.

CONCLUSIONS

In this systematic review, the various alterations along the optic pathway and the visual cortex in glaucomatous patients are addressed through MRI. These changes demonstrated a strong relationship not only with the clinical findings of the OCT but also with the severity of the pathology. MRI proved to be a strong ally to access GON changes not only in the early stages but also in later stages with more severe changes such as LGN height

and volume and optic radiation diffusion parameters, for example. So, we can conclude that MRI may be useful not only in the diagnosis, but it is also the best way to follow up patients alongside with OCT and the visual field.

The main MRI techniques that can help us understand GON changes better are especially DTI, rsfMRI-fALFF, BOLD-fMRI and MRS to access both brain and visual pathway changes.

We had the opportunity to compile information from two different techniques for the first time, and despite the difficulties, there seems to be potential to take advantage of different information at different times of the disease.

For that reason, we believe this review contributes to a better understanding of which MRI parameters may play an important role in the early diagnosis of glaucoma due to their relationship with the stage of the pathology.

EXPERT OPINION

Glaucoma is an ocular pathology in which there is a need to increasingly improve early diagnosis. This is because advanced stages of glaucoma, in which vision has already been lost, are usually irreversible. When we diagnose glaucoma earlier, the probability of a positive response to therapy increases and, consequently, there is a significant improvement in the patient's quality of life. This early diagnosis becomes more or less difficult depending on the type and subtype of glaucoma, the most complicated being primary normotension open-angle glaucoma. This is due to the absence not only of symptoms but also of the main signs, such as an increase in IOP. *(Lowndes & Carvalho, 2011).*

Although irreversible, glaucomatous damage can be slowed with early detection and appropriate treatment. Early treatment for glaucoma has been shown to reduce the mean time to blindness in at least 1 eye from 23 to 35 years. The goal for screening in this pathology is to identify the disease at a stage where intervention may alter its course and preserve the vision that would otherwise be lost. *(Glarin et al., 2021)(Devience et al., 2018).*

Emphasizing that MRI would be useful in specific phenotypes of glaucoma, namely POAG, and in its early stages that must be known and characterized to direct intervention and/or monitoring. Although this is not a gold-standard strategy, it can be applied judiciously in defined groups and high-risk populations, such as the elderly, African descendants, and those with a family history of glaucoma or treatment-resistant patients. *(Devience et al., 2018).*

Since the retina and optic nerve are considered part of the CNS, glaucoma shares epidemiological and mechanistic similarities with other CNS neurodegenerations, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS), and Huntington's disease. Functional deficits in Axonal transport occur early in the progression of glaucoma, which is the main reason why MRI would be an interesting test to perform in patients at risk, for example. *(Crish & Calkins, 2011)*

This research demonstrates the impact that MRI can have in the diagnosis of glaucoma, due to changes found in the optic pathway in earlier stages of the disease when there are still no symptoms or structural changes at the intraocular level, such as atrophy and thinning in different areas of the eye, visual cortex, NAA values and changes in LGN height and volume.

In addition, MRI can also be an interesting way of patient follow-up due to its ability to assess structures that are not accessible by traditional complementary diagnostic methods in ophthalmology, such as OCT. Some of our results support this idea, namely some Glaucoma severity parameters, especially vertical cup-to-disc ratio (VCDR), were strongly associated with homolateral optical radiation diffusion parameters, which proves that DTI can detect axonal and microstructural injury in the visual pathway. Assessing more posterior structures of the optic pathway is what makes MRI stand out in early diagnosis, which can contribute to the detection and monitor new neuroprotective therapies. Some of these structures and respective changes, addressed in this study, are Damage to the RNFL that appeared as atrophy in the Brodmann area of the brain. Also, brain blood flow seems to be correlated not only with RNFL but also with GCL thickness.

The factor that can most constrain the adoption of MRI is its cost, as it entails more financial costs for the state and/or the institution. However, it would be something to consider for certain specific cases, for example in cases of suspected glaucoma in which there are still no changes in the ocular structures. This allows for an early diagnosis that significantly improves the prognosis of the disease and which, in turn, will lead to fewer expenses associated with this patient due to blindness in the future. In addition, in OCT there is no need for contrast administration, being a faster and less invasive exam for patients, leading to better collaboration. (Sotirchos & Saidha, 2018)

For future studies, we consider it pertinent to carry out prospective studies to help clarify these aspects and in which a more consistent number of patients with glaucoma and normal controls should be included. We also suggest that in these studies, all the patients involved are also properly characterized as to the stage of the pathology according to the guidelines available, and the results should be properly grouped according to this classification. Bearing in mind the great evolution of the areas of diagnosis and therapy under development, the usefulness and relevance of deepening and improving the relationship between these means of diagnosis are fundamental. Two findings that would be very interesting to study in the future would be the changes in LGN height and volume and brain blood flow changes. These are two findings that are directly related to anterior structures of the optic pathway (RNFL and GCL), and that reinforces the usefulness of MRI in these cases, structuring completely inaccessible by OCT, visual field, or any other ophthalmological examination.

These approaches will be critical for clarifying disease development, potential therapeutic targets, etc. and due to the number of studies being carried out, the next 5 to 10 years could mark some differences in the approach to GON.

FIVE-YEAR VIEW

We believe that in the future, more patients will be diagnosed in the early stages of glaucoma, using the complementarity that exists between the traditional ophthalmological diagnosis and MRI. With patients diagnosed earlier, there will be fewer cases of severe glaucoma and consequent blindness as the therapeutic intervention will be much more successful. When we reach this level, both parties will benefit from it, because patients will have a better quality of life and the costs and other disadvantages associated with MRI will be offset by the decrease in cases of blindness, which, in turn, also entails high and long-term costs.

CONFLICT OF INTEREST STATEMENT

None.

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5. CONCLUSIONS

5.1. GENERAL CONSIDERATIONS

In this research work, we studied the usefulness of MRI in the early diagnosis of POAG. Since this type of glaucoma is a pathology that is difficult to diagnose, due to the absence of obvious signs and symptoms, there is a need to resort to the evaluation of other structures of the optic pathways.

In summary, the results of this research point to a very positive influence of various MRI techniques in the diagnosis and follow-up of POAG. The main finding of the study was that structural MRI findings appear to be mostly related to RNFL and visual field changes, while metabolic findings appear to be more closely related to GCL changes. In the case of RNFL, this happens due to its strong connection with the brain and strong presence of nerve cells, considering even hypothetically that this layer of the retina is, in fact, almost an extension of it. The reflection of metabolic findings in GCL may be associated with the fact that changes that include reduction in the dendritic arbor area have already been described in studies carried out in rats. However, more focused and dedicated research on this subject is needed.

Something also important for the conclusions was the attempt to look for a correlation between the findings and the stage of the disease, since, as previously described, the main use of MRI would be in the initial forms of the pathology. As can be seen in the discussion and conclusion of the article in the previous chapter, there were several articles with different results on this topic, however, most of them lack further research. For this reason, it was considered that in both methods analyzed the most interesting findings in the early stages of GON were shown in studies 5, 11 and 13. In study 5, it was described that NAA values obtained from CGL in glaucoma suspect cases were lower than the healthy control group (both $p= 0.025$, $p= 0.011$), this might be useful for early diagnosis of glaucoma when there are still no structural abnormalities found in OCT.

This systematic review protocol allowed us to develop a study on this subject in a more comprehensive way, including the various MRI techniques applied within the scope of glaucoma. However, because we were faced with so many different findings, for future

studies we think that the selection of one to three types of MRI to include in the study would be ideal for more objective and limited research.

To conclude, we can say that this research work answers the starting question "What is the relationship between the structural findings in the initial phases? and advanced data from GON obtained through OCT and MRI?", because a good relationship was found between the findings of these two means of diagnosis in early stages of POAG. As a result, this systematic review may reveal some insights to understand how MRI, especially DTI, rsfMRI-fALFF, BOLD-fMRI and MRS parameters play an important role in the early diagnosis of glaucoma due to their relationship with the stage of the pathology.

5.2. LIMITATIONS AND FUTURE PROSPECTS

We faced 4 main limitations in this study:

- → Heterogeneity in the classification and parameters used to divide patients;
- → The fact that a lot of the studies did not distinguish the severity of different glaucoma patients;
- → Heterogeneity of age, the severity of damage and duration of disease in patients between the studies selected;
- → A variety of techniques was used, in which different parts of the cortex and the visual pathway were evaluated, which makes it difficult to directly relate some of the findings.

For future studies, we consider it pertinent to carry out prospective studies dedicated to helping separately clarify each of the MRI techniques included in this study, which should contain a consistent number of patients with glaucoma and normal controls. We also suggest that in these studies, all the patients involved are properly characterized as to the stage of the pathology and the results are also properly grouped according to this classification.

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