
Review Article

Structural brain MRI studies in eye diseases: are they clinically relevant? A review of current findings

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ABSTRACT.

Many eye diseases reduce visual acuity or are associated with visual field defects. Because of the well-defined retinotopic organization of the connections of the visual pathways, this may affect specific parts of the visual pathways and cortex, as a result of either deprivation or transsynaptic degeneration. For this reason, over the past several years, numerous structural magnetic resonance imaging (MRI) studies have examined the association of eye diseases with pathway and brain changes. Here, we review structural MRI studies performed in human patients with the eye diseases albinism, amblyopia, hereditary retinal dystrophies, age-related macular degeneration (AMD) and glaucoma. We focus on two main questions. First, what have these studies revealed? Second, what is the potential clinical relevance of their findings? We find that all the aforementioned eye diseases are indeed associated with structural changes in the visual pathways and brain. As such changes have been described in very different eye diseases, in our view the most parsimonious explanation is that these are caused by the loss of visual input and the subsequent deprivation of the visual pathways and brain regions, rather than by transsynaptic degeneration. Moreover, and of clinical relevance, for some of the diseases – in particular glaucoma and AMD – present results are compatible with the view that the eye disease is part of a more general neurological or neurodegenerative disorder that also affects the brain. Finally, establishing structural changes of the visual pathways has been relevant in the context of new therapeutic strategies to restore retinal function: it implies that restoring retinal function may not suffice to also effectively restore vision. Future structural MRI studies can contribute to (i) further establish relationships between ocular and neurological neurodegenerative disorders, (ii) investigate whether brain degeneration in eye diseases is reversible, (iii) evaluate the use of neuroprotective medication in ocular disease, (iv) determine optimal timing for retinal implant insertion and (v) establish structural MRI examination as a diagnostic tool in ophthalmology.

Key words: eye diseases – magnetic resonance imaging – visual cortex – visual pathway

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Introduction

Recently, numerous magnetic resonance imaging (MRI) studies have shown that eye diseases are associated

with brain changes, in particular in the visual pathways (an overview of what we mean by the general term ‘brain changes’ is given in Box 1) (Xiao et al. 2007; Xie et al. 2007; Boucard et al.

2009; Barnes et al. 2010; Hernowo et al. 2011; Plank et al. 2011; Bridge et al. 2012; Hernowo et al. 2014). These brain changes have primarily been shown in eye diseases that reduce visual acuity or are associated with the occurrence of visual field defects, such as glaucoma, age-related macular degeneration (AMD) and hereditary retinal dystrophies.

The potential role of MRI studies in ophthalmology is increasing due to current advances in ophthalmic therapeutic strategies, such as the development of retinal implants and neuroprotective agents. The success of these therapies may require that the central visual system is still capable of transmitting and processing the retinal signals. Therefore, it is becoming increasingly important to establish the integrity of the visual pathways and brain and their ability to transmit and process potentially restored input. Furthermore, parallel developments in brain imaging and analysis techniques make it more and more feasible that brain imaging could perhaps be used as a diagnostic tool or to evaluate the response to neuroprotective agents.

We reviewed the current literature on structural brain changes in humans associated with the eye diseases albinism, amblyopia, hereditary retinal dystrophies, AMD and glaucoma. For each eye disease, we focused on two main questions. First, what have structural studies found thus far, and second, what is the potential clinical relevance of these findings? In our discussion, we will generalize our findings and give directions for future research.

Box 1: Concepts of neurodegeneration and plasticity

Neurodegeneration

In general, neurodegeneration can be explained as progressive loss of neuronal structure, function and cell death. Neurodegenerative diseases each have their own characteristic profile of regional neuronal cell death. Also referred to as neuronal degeneration or transsynaptic degeneration (Przedborski, Vila, & Jackson-Lewis, 2003).

Neuroplasticity

Neuroplasticity indicates changes in the organization of the brain as a result of development, learning, memory, experience or recovery from brain injury. It can occur on different levels, ranging from changes in synapses and neural pathways (*synaptic plasticity*) due to learning, to major changes in the cortical representation of the body in response to bodily injury (*cortical remapping*) (Liepert et al. 2000; Pascual-Leone et al. 2005).

Regenerative brain plasticity

This term is used to describe that neuroplasticity occurred despite of previously observed neurodegeneration.

Cortical structural changes

This paper uses the term cortical structural changes when grey or white matter changes (e.g. increase or decrease) are observed using neuroimaging without making an assumption of the cause. Also described in this paper as brain changes.

Retinotopic-specific neuronal degeneration

Neurodegeneration caused by decreased visual input. In the occurrence of a visual field defect, the corresponding part of the retinotopic organized visual cortex no longer receives input. The absence of stimulation can result in cell death. This phenomenon is an example of anterograde transsynaptic degeneration (Boucard et al. 2009).

Anterograde transsynaptic degeneration

Neurodegeneration caused by a loss of input or after injury. Breakdown of presynaptic neurons at the primary injury site spreads towards connected postsynaptic neurons (e.g. distal axon terminal), causing the death of these cells. Also described in the literature as anterograde degeneration (Cowan, 1970).

Retrograde transsynaptic degeneration

Retrograde transsynaptic degeneration is the degeneration in the opposite direction of anterograde degeneration. Breakdown of an axon from the point of damage spreads back towards the proximal cell body (e.g. presynaptic neurons). This occurs when target tissues no longer receive trophic support (Cowan, 1970).

Although numerous animal and functional MRI (fMRI) studies have also been performed, we limited the scope of our review to the results obtained in humans with structural imaging and analysis techniques such as voxel- and surface-based morphometry (VBM/SBM) and diffusion tensor imaging (DTI) (see Box 2). (For reviews focusing on fMRI, we refer to Wandell & Smirnakis (2009) and Haak et al. (2013).)

Methods

Search protocol

The database search was updated last on December 2014. The searched databases are EMBASE, PubMed and Web of Science.

Search terms

For each eye disease, a specific search string was used. The part of the search string that corresponds to structural neuroimaging was equal

for all eye diseases. An example of the search string for glaucoma is given below. Search strings for each eye disease can be found in Supplement 1.

Example of search string for glaucoma

glaucoma[Title] AND (diffusion tensor imaging [Title] OR magnetic resonance imaging [Title] OR grey matter [Title] OR gray matter [Title] OR white matter [Title] OR Morphometric analyses [Title]) AND humans[Filter] NOT ('review'[Publication Type] OR 'review literature as topic'[MeSH Terms] OR 'review'[All Fields]).

Inclusion criteria studies

All articles were screened and selected for inclusion according to several criteria. Inclusion was based on the following criteria:

Methodology: use of structural neuroimaging (e.g. DTI, VBM or conventional MRI examination) and use of human population

Research question: investigation of brain changes

Type of eye disease: albinism, amblyopia, hereditary retinal dystrophies, AMD and glaucoma

Results

Albinism

Pathology

Albinism refers to a heterogeneous group of genetically determined disorders that are characterized by hypopigmentation in the skin, hair and eyes. Ocular features in albinism are reduced visual acuity and nystagmus, which are related to the degree of ocular pigmentation, hypoplasia of the fovea, hypopigmentation of the fundus, translucency of the iris, strabismus, high refractive errors and red deviation in colour vision (Kinnear et al. 1988).

What has been found?

A conventional MRI study revealed structural abnormalities in albino

Box 2: Structural brain imaging techniques

The first approaches to identify brain changes in ocular diseases have been carried out using conventional magnetic resonance (MR) imaging. Brain regions are delineated and measured based on reliable anatomical landmarks.

Voxel-based morphometry (VBM) comprises a location-by-location statistical comparison of the local tissue concentration of grey matter volume, white matter volume or cerebrospinal fluid between different groups of subjects. Therefore, VBM can quantify the magnitude of structural differences between patients and healthy controls (Ashburner & Friston 2000; Good et al. 2001; Bookstein 2001, Ashburner & Friston 2001).

Diffusion tensor imaging (DTI) visualizes the axonal architecture of white matter fibres based on the diffusion of water molecules in each voxel along axons. The diffusion of water molecules is described by anisotropy and related to axonal integrity. Several parameters can be derived which describe the anisotropy in each voxel. Fractional anisotropy quantifies the underlying fibre tract orientation (measure of shape) and is assumed to be sensitive in a broad spectrum of pathological conditions. Other parameters are mean diffusivity, which quantifies the diffusion freedom that water molecules have in a voxel (a volume element analogous to a pixel), radial diffusivity (a measure of diffusion orthogonal to axon) that is thought to be modulated by myelin in the white matter and axial diffusivity (a measure of diffusion parallel to axon), which is more specific to axonal degeneration (Alexander et al. 2007; Basser et al. 2000, Jones, Horsfield & Simmons 1999, Jones et al. 1999).

patients: the diameters of the optic nerves and optic tracts and the width of the chiasm were smaller, and the shape of the chiasm was different (Schmitz et al. 2003).

In more recent VBM studies, more subtle changes in the brain have been shown. Von dem Hagen et al. (2005)

found a regionally specific decrease in grey matter volume at the occipital poles in albinism. The location of the decrease in grey matter corresponds to the cortical representation of the central visual field. This reduction was possibly a direct result of decreased ganglion cell numbers in the central retina in albinism. Moreover, the calcarine fissure was shorter and the mean surface area of the calcarine fissure was smaller in albinism than in healthy controls (Neveu et al. 2008). More recently, Bridge et al. (2012) reported increased grey matter volume in the calcarine sulcus in albinism, which was related to increased cortical thickness. They also found decreased grey matter volume in the posterior ventral occipital cortex. These results suggest that albinism is associated with pregeniculate and postgeniculate changes.

What is the potential clinical relevance of the findings?

It is unclear whether the reported brain abnormalities in albinism are congenital or whether they are secondary to the ocular symptoms in albinism. The hypoplasia of the fovea, the subsequently reduced visual acuity and the nystagmus can all cause abnormal input. This abnormal input could be a plausible explanation for the observed alterations in the brain.

No curative therapy for albinism is currently available. Therapy is aimed at treatment of the symptoms of albinism, such as the prevention of possible development of amblyopia, appropriate refraction and protection against sun. Therefore, at present, the findings of brain abnormalities do not have implications for the treatment of albinism, but they do provide us more insight into the disorder itself.

Amblyopia*Pathology*

Amblyopia is a reduction in best corrected central visual acuity by misuse or disuse during the critical period of visual development. It has no exact identifiable organic cause, although it is thought to originate in the central nervous system. Disuse or misuse mostly occurs because of deprivation, unequal refractive errors, or strabismus and is classified accordingly. The decrease in vision develops in the first

decade of life and does not decline thereafter. It occurs most often unilaterally, but it can also appear bilaterally (Day 1997).

What has been found?

Using VBM, decreased grey matter density in the visual cortex has been found in children with amblyopia, compared to children with normal sight (Xiao et al. 2007; Xie et al. 2007). In a study of children and adults with anisometropic or strabismic amblyopia, decreased grey matter volume was found in the visual cortex in both age groups, although this volumetric reduction was more widespread in children than in adults (Mendola et al. 2005). Moreover, Barnes et al. (2010) found decreased grey matter concentration in the lateral geniculate nucleus (LGN) in adult patients with strabismic amblyopia. Lv et al. (2008) found no difference in mean global cortical thickness and the mean regional thickness of the primary and secondary visual cortex (V1 and V2) in amblyopic subjects, compared to healthy controls. However, in the unilateral amblyopic subjects, a difference between the two hemispheres was shown. More recently, grey and white matter changes were observed in a group of unilaterally amblyopic children. These changes contained both increases and decreases in the visual cortex and around the calcarine areas. The volumetric loss occurred in cortices related to spatial vision (Li et al. 2013). In summary, this indicates that amblyopia is linked to changes in the postgeniculate and geniculate part of the visual pathways.

What is the potential clinical relevance of the findings?

From these studies, we may conclude that both the grey and white matter of the visual pathways are involved in amblyopia. This has mostly been shown in the visual cortex. The reduced visual acuity probably causes a lack of information transported through the visual pathways to the visual cortex. It is unknown whether regeneration of the visual cortex is possible. However, the fact that occlusion therapy in amblyopia is often successful in children indicates that the visual pathways are still capable of receiving input from the affected side in childhood, but not necessarily in adults.

Hereditary retinal dystrophies

Pathology

Hereditary retinal dystrophies are a collective name for genetic eye diseases such as Stargardt's disease, Best's vitelliform retinal dystrophy (Best's disease), cone-rod dystrophy, central areolar choroidal dystrophy and retinitis pigmentosa. They start early in life and lead to dysfunction and cell death of various retinal cell types. Non-progressive forms of this disease often result in reduced visual acuity and visual field defects. Forms in which cell death predominates mostly lead to permanent vision loss. In many of these diseases, there is progressive appearance of pigmentary deposits in the retina as a result of changes in the retinal pigment epithelium, often accompanied by the death of the retinal photoreceptors (PRs) (Hamel, 2014).

What has been found?

When analysed with VBM, patients with a binocular central visual field defect due to hereditary retinal dystrophies showed a reduction in grey matter volume around the calcarine sulcus in both hemispheres, particularly on the posterior part of the calcarine sulcus (Plank et al. 2011). This suggests that neuronal degeneration is retinotopically related to the location of the visual field defect. Moreover, Hernowo et al. (2014) observed white matter changes in the optic radiations and visual cortex.

In an earlier DTI study in (only) six patients with acquired blindness, of which five patients were blind due to retinitis pigmentosa, no significant difference in the fractional anisotropy of the visual fibre tracts was found in blind patients compared to the healthy control subjects (Schoth et al. 2006). Taken together, these results show that in hereditary retinal dystrophies, postgeniculate changes are observed.

What is the potential clinical relevance of the findings?

The various eye conditions that are described in hereditary retinal dystrophies are usually considered to be exclusively eye diseases. The finding of degeneration in the postgeniculate part of the visual pathways in these patients can have extensive consequences for the treatment with artificial retinal implants or stem-cell-derived retinal implants. Such implants have been

used experimentally in humans with retinitis pigmentosa, thus far with rather variable results (Stingl et al. 2010). Brain involvement in hereditary retinal dystrophies could be an explanation for these results, because the central visual system in these patients should still be capable of transmitting and processing visual signals for these therapies to be successful. Degeneration of the pathways and cortex could interfere with this. Hence, a retinal implant might be more effective when implanting it at an earlier stage of the disease, ideally at the time when degeneration of the visual pathways has not yet occurred.

Age-related macular degeneration

Pathology

In AMD, the retinal metabolism is obstructed by the accumulation of drusen in the macular area. This in turn induces degeneration of the macula, which causes a central visual field defect (Holz et al. 2004; Zarbin 2004; Arden 2006; Gehrs et al. 2006); AMD is the most prevalent cause of visual impairment in the European adult population (Augood et al. 2006).

What has been found?

Using VBM, Boucard et al. (2009) found an association between visual field defects caused by long-standing glaucoma and AMD, and reductions in grey matter density in the occipital cortex. In AMD patients, the main reduction was found near the occipital pole (primarily in the left hemisphere), particularly around the posterior part of the calcarine sulcus. Hernowo et al. (2014) confirmed such grey matter changes in the visual cortex and additionally found white matter reductions in the optic radiations and visual cortex. Interestingly, a white matter decrease in the frontal lobe was found. Collectively, this means that besides postgeniculate changes, frontal changes are observed as well.

What is the potential clinical relevance of the findings?

Degeneration in the postgeniculate part of the visual pathways of patients with AMD could be explained by decreased input from the visual field towards the visual cortex. However, Hernowo et al. (2014) found white matter volumetric reduction in the frontal lobe of AMD

patients, which was proposed to be the neural correlate of a previously described association between AMD and mild cognitive impairment or Alzheimer's disease (Klaver et al. 1999; Ikram et al. 2012; Woo et al. 2012; Hernowo et al. 2014). Several studies have revealed that AMD and Alzheimer's disease share multiple clinical and pathological features. This supports the notion that AMD could be the manifestation of a more general neurodegenerative disease, of which the visual pathway degeneration may be the primary manifestation (Kaarniranta et al. 2011). Contrarily, it seems that these two diseases have a different genetic background (Proitsi et al. 2012). Further, a recent AMD cohort of 65 984 people concluded that the chance of developing Alzheimer's disease after AMD is no different from that expected by chance (Keenan et al. 2014). For the treatment of AMD, the distinction between eye disease and neurodegenerative disease is highly relevant. Studies on treatments that aim to restore visual function in AMD patients have been performed, such as macular translocation (Eckardt & Eckardt 2002) and retinal pigment epithelium transplantation (Van Zeeburg et al. 2012). These studies showed varying results in improvement of visual function. However, if AMD turns out to be a neurodegenerative disease, then the neurodegenerative component might be responsible for the sometimes poor effects of such treatments. So far, studies on treatment of AMD have mainly been focused on ocular treatment only.

Glaucoma

Pathology

Primary open angle glaucoma (POAG) is a common neurodegenerative disease of retinal ganglion cells (RGCs) characterized by axon degeneration of the optic nerve, causing progressive loss of peripheral visual fields and ultimately blindness. The exact pathophysiology of POAG is not yet fully understood (Fechtner & Weinreb 1994; Nickells 1996; Chang & Goldberg 2012). Although RGC and optic nerve damage is often associated with the presence of elevated intraocular pressure (IOP), glaucoma with normal levels of IOP – normal tension glaucoma – is commonly diagnosed as well.

What has been found?

There have been a number of structural MRI studies investigating brain changes in glaucoma. By conventional examination of MR images, earlier studies found that patients with glaucoma had a lower optic chiasm height (Iwata et al. 1997; Kashiwagi et al. 2004) and smaller optic nerve diameter (Kashiwagi et al. 2004). More recently, MRI studies have confirmed degeneration of the LGN (Gupta et al. 2009; Zhang et al. 2012; Zikou et al. 2012).

Using VBM, Boucard et al. (2009) found reduced grey matter density in glaucoma patients in the region of the calcarine sulcus. In agreement with the more peripheral location of visual field defects in glaucoma, this reduction was more pronounced in the anterior than in the posterior region. Together with their results in AMD, this suggests that long-term cortical deprivation – due to retinal lesions acquired later in life – is associated with retinotopic-specific neuronal degeneration of the visual cortex. A follow-up study by Hernowo et al. (2011) indicated decreased volume along the full length of the visual pathway in glaucoma in both grey and white matter. More recently, studies examining grey matter volume in glaucoma patients have reported both increases and decreases of grey matter in various areas of the brain (Li et al. 2012; Chen et al. 2013a; Williams et al. 2013). Inconsistent findings with respect to grey matter volume changes may be explained by differences in glaucoma stages of the patients included in these various studies.

Brain involvement in glaucoma has also been observed using DTI. Previous studies using DTI have reported white matter abnormalities in different parts of the visual pathway, such as the optic nerve, optic tract, chiasm, optic radiation and occipital lobe (Garaci et al. 2009; Dai et al. 2013; Doerfler et al. 2012; Liu et al. 2012; Zhang et al. 2012; Chang et al. 2013; Chen et al. 2013b; El-Rafei et al. 2013; Murai et al. 2013; Wang et al. 2013a). Zikou et al. (2012) demonstrated white matter changes in brain structures that play a role in visuospatial processing. In support of this, the robustness of white matter changes in glaucoma is recently confirmed by a meta-analysis of existing DTI studies by revealing changes in the optic nerve, optic radiation and optic tract changes compared to controls.

Together with age, glaucoma severity was found to be an important factor correlated with the extend of the damage (Li et al. 2014).

In summary, although the specific results still vary, the common finding in all these VBM and DTI studies is that the pregeniculate, geniculate and post-geniculate structures are affected in glaucoma, at least in later stages of the disease. In addition, some studies reveal changes in other parts of the brain as well.

What is the potential clinical relevance of the findings?

To consider the clinical relevance of these findings, it is important to know whether glaucoma should be considered as solely an eye disease, or as a neurodegenerative brain disease. Although we cannot yet conclude whether brain changes occurred before, simultaneously or after the development of the eye disease, the most plausible explanation seems to be that glaucomatous changes in the eye cause the brain changes, as thus far, no differences in grey matter volume have been found in early-stage POAG (Li et al. 2012). However, this may be a consequence of a lack of power in studies performed thus far. Moreover, several studies have found correlations between changes in visual pathway structures and glaucoma severity (Garaci et al. 2009; Dai et al. 2013; Chen et al. 2013b; Michelson et al. 2013; Wang et al. 2013a), which supports the notion that brain changes are caused by the eye disease itself. On the contrary, some researchers suggest an association between Alzheimer's disease and glaucoma. Glaucoma and Alzheimer's disease share several characteristics: they are both neurodegenerative, chronic, progressive, age-related and associated with irreversible neuronal cell loss. This may indicate that glaucoma and Alzheimer's disease are connected through the same underlying pathologic mechanism (Ghiso et al. 2013; Inoue et al. 2013; Janssen et al. 2013; Sivak 2013). However, this notion is still being questioned after the publication of conflicting epidemiologic reports. Some epidemiologic studies find an increased prevalence of glaucoma in Alzheimer's disease (Chandra et al. 1986; Bayer et al. 2002; Tamura et al. 2006; Helmer et al. 2013), while other

studies do not (Kessing et al. 2007; Bach-Holm et al. 2012; Ou et al. 2012). In support of the hypothesis that glaucoma may be part of a neurodegenerative disease, some studies examined translamina cribrosa pressure difference (TLCPD), which is calculated as the IOP minus the cerebrospinal fluid pressure. These studies suggest that TLCPD has a better association with glaucoma presence than IOP (Wang et al. 2013b; Wostyn et al. 2015; Zhang et al. 2013, 2014; Jonas et al. 2015). This could be an indication that glaucoma should be seen as part of a neurological disorder.

Discussion

This review commenced to describe the current state of knowledge of structural MRI studies in various eye diseases. Within it, we did not aim to resolve all outstanding issues nor to cover in depth the physiological mechanisms that can explain how eye diseases might cause brain damage, such as retinal remodelling or transsynaptic degeneration. We summarized the current findings, the relevance of these findings for understanding the aetiology of eye diseases and its current and future clinical relevance. Below, we answer our main questions and give directions for future research.

What have studies on structural brain changes in ocular diseases revealed thus far?

Regarding the current research findings, in all eye diseases described in this review – glaucoma, hereditary retinal dystrophies, AMD, albinism and amblyopia – MRI studies have shown the presence of structural changes in the visual pathways. Changes in the postgeniculate pathways are observed in glaucoma, hereditary retinal dystrophies, macular degeneration, albinism and amblyopia, whereas geniculate changes were seen in glaucoma and amblyopia, and pregeniculate changes were shown in glaucoma and albinism.

What is the potential clinical relevance of the findings?*Clinical focus*

The brain changes in the eye diseases that we reviewed here have several implications for clinical practice. Pre-

sently, the clinical focus is on the ocular treatment of these diseases. The primary goal of the current treatment is to maintain existing visual function and to prevent a further decline. However, our finding of brain involvement in all eye diseases suggests that the current clinical focus on treating the eye might have to be expanded to treating the brain as well. Involvement of the brain could also explain why some treatment strategies, such as restoring of visual function in AMD, have poor outcome results.

Treatments focused on restoring visual function

In retinitis pigmentosa, retinal implants are being used experimentally to restore visual function in patients who are blind (Zrenner 2002; Da Cruz et al. 2013). The results of these implanted devices are encouraging, but rather variable. As the central visual system needs to process the signals from these implants, it is questionable whether patients can benefit optimally from such a retinal implant if the eye disease has caused changes to the brain. Therefore, the timing of the insertion of a retinal implant in the disease process might have a substantial impact on the result of the retinal implant. A retinal implant might be more effective on the long term when implanting it at a stage in the disease in which degeneration of the visual pathways has not yet occurred. If in the future retinal implants become a broadly used therapy for retinitis pigmentosa, MRI-based group studies might help to determine the appropriate timing for the implanting of a retinal device and thus for the improvement of such treatment.

Treatments focused on protecting the brain

Neurodegeneration can be considered as therapeutic target in eye diseases. Neuroprotective agents may be beneficial in treating eye diseases due to its ability to protect neurons from degeneration or apoptosis (Shahsuvaryan 2012). The target neurons should be in the visual pathways, in particular the RGCs for glaucoma and PRs and retinal pigment epithelial cells for retinitis pigmentosa (Doonan & Cotter 2004; Cottet & Schorderet 2009). In glaucoma for example, neuroprotective medication could be prescribed to prevent degeneration of visual pathway structures, in addition to the standard

treatment that is aimed at reducing intra-ocular pressure (Gupta & Yücel 2007; Osborne 2009; Chang & Goldberg 2012; Pascale et al. 2012; Nucci et al. 2013). With such combination therapies, it could even be possible to prevent brain damage.

MRI as a diagnostic tool

Some studies suggest that DTI examination can be helpful in the early diagnosis of glaucoma in individual patients (Li et al. 2014). However, statistical evidence for this is lacking. Current MRI findings are obtained in group studies and as of yet, no study has demonstrated that individual patient diagnosis can become more accurate when adding MRI information to the ophthalmological examination. In addition, the use of MRI examination in individuals requires a sufficient specificity and selectivity and cost-effectiveness. On the assumption that MRI could be used as a diagnostic tool in the future, it could contribute to the monitoring of the effect of neuroprotective medication. MRI research can reveal whether the visual pathways have been prevented from further degeneration or perhaps reversed degeneration during the use of neuroprotective medication in a group of glaucoma patients.

Reversibility

Given these findings, an important question on the topic remains: To what extent is structural brain damage in eye diseases reversible? To our knowledge, only one structural neuroimaging study has been performed so far to address the issue of reversibility of brain changes. A study of Rosengarth et al. (2013) showed an increase in grey and white matter in the posterior cerebellum in AMD patients after 6 months of oculomotor training, compared to AMD patients who were given sham training. Although this is the most relevant study performed so far on the role of reversibility of structural changes, it does not directly indicate that reversibility is possible. The increased grey and white matter in the cerebellum might reflect a general effect of learning to control eye movements rather than reversibility of degeneration of the visual pathways. Furthermore, a study by Lou et al. (2013) examined changes in grey matter volume after cataract surgery in patients with unilateral cataract. Compared to 2 days after

surgery, 6 weeks after surgery grey matter volume was increased in the V2 area contralateral to the operated eye. Additionally, in a functional MRI study, an AMD patient who underwent treatment with intravitreal anti-angiogenic injections with ranibizumab, and whose visual acuity improved after the treatment, showed an increased activation area in the visual cortex after the first treatment (Baseler et al. 2011). These studies provide some limited support for the notion that improving visual function – and therefore increasing the activity in the visual pathways – may induce neural regeneration in the visual cortex. However, this may not necessarily be true for all eye diseases for which changes in the brain have been reported.

Aetiology

With specific relevance to understanding aetiology, the presence of cortical structural changes raises the causality question. Did the manifestation of the eye disease subsequently cause changes in the visual pathways and visual cortex, or did the disease start with brain changes and subsequently – or simultaneously – affect the eye?

In all eye diseases described in this review, a decrease in visual acuity or a visual field defect occurs. Both of these symptoms cause sensory deprivation in the visual pathways. As these eye diseases are of diverse origin, we believe that the most parsimonious explanation is that eye diseases cause changes in the brain; this explanation requires the fewest disease-specific assumptions. Two mechanisms could support this hypothesis. First, visual deprivation can induce brain changes due to decreased activity along the visual pathways. This sensory deprivation can eventually lead to retinotopic-specific neuronal degeneration. Second, brain changes in eye diseases may be caused by anterograde transsynaptic degeneration, in which a breakdown of axons at the primary injury site spreads to connected neurons, resulting in axonal damage along the visual pathways towards the visual cortex. In support, this process has also been observed to occur in the opposite direction. In retrograde transsynaptic degeneration, breakdown of an axon from the point of damage spreads back towards the cell body. In other words, damage that occurs at the visual cortex will spread towards the eye resulting in

retinal atrophy. It has been suggested that this mechanism contributes to axon damage in a number of neurodegenerative disorders in which atrophy of the retinal layers was observed after a long-standing disease, such as multiple sclerosis, Parkinson's disease, Alzheimer's disease and after stroke (Jindahra et al. 2010; Kirbas et al. 2013; Tanito & Ohira 2013; Balk et al. 2014; Gabilondo et al. 2014; Klistorner et al. 2014).

Besides that neurodegeneration can be caused by a decreased visual input, for glaucoma and AMD there is additional evidence for a primary neuronal degeneration process that could also explain the brain changes in these eye diseases. Recent studies found possible links between Alzheimer's disease and the two eye diseases described here that occur later in life: glaucoma (Tamura et al. 2006; Cumurcu et al. 2013; Inoue et al. 2013) and AMD (Klaver et al. 1999; Ikram et al. 2012; Woo et al. 2012). Moreover, an association between fluctuations in intracranial pressure and glaucoma has been found (Wostyn et al. 2015; Zhang et al. 2013, 2014). These findings contribute to the notion that in glaucoma and AMD, the changes to the visual pathways and the brain might – at least partially – be interpreted also as the primary manifestation of a neurological or neurodegenerative disease. The finding of volumetric reduction in frontal white matter in AMD patients supports this theory (Hernowo et al. 2014).

Recommendations for future research

Future studies on treatment of the aforementioned eye diseases should consider shifting their focus to research on therapies that can combine eye treatment with treatment of the neurodegeneration. Furthermore, the association between eye diseases and brain changes should be studied, particularly on the issue whether the eye disease causes the brain changes or whether the specific eye disease should be considered as part of a neurodegenerative disease. A longitudinal study could be performed in which patients with one of the aforementioned eye diseases undergo periodic structural brain scans. Ideally, patients would be included even before the disease is diagnosed, thus in a cohort study. In such a study, the development of

structural brain changes can be monitored. This could help answer the question of whether brain alterations occur due to the specific eye disease or whether the supposed eye disease is only a symptom of a more general neurodegenerative disease.

Furthermore, future research is needed on the issue of regeneration of brain changes in eye diseases. More specifically, it could address the question to what extend structural damage can be reversed following restoration of input by a retinal implant. It would be interesting to perform a study in which patients with retinitis pigmentosa who received a retinal implant would undergo a structural brain scan before treatment and several times after. In such a study, it would be possible to determine whether the retinal implant influences the brain and whether implanting such a device can reverse anatomical brain changes. Together with measurements of visual function in these patients, this would provide valuable information about the influence of the retinal implant on the brain and would help to determine whether a retinal implant is more effective if implanted early in the disease process.

Moreover, future MRI studies are needed to determine whether MRI examination on an individual basis can be helpful in the diagnosis and monitoring of treatment in eye diseases. For instance, in retinitis pigmentosa MRI would be helpful to determine the optimal timing of implanting a retinal device. For glaucoma, MRI can be a useful tool for monitoring the use of neuroprotective medication.

Main messages

In summary, structural brain MRI studies in eye disease have shown us the following:

- Glaucoma, hereditary retinal dystrophies, AMD, albinism and amblyopia are associated with structural changes in the visual pathways;
- The most parsimonious explanation for the association between eye diseases and structural changes in the visual pathways is that eye diseases cause changes in the brain;
- In addition, for glaucoma and AMD, there are indications that these eye diseases might be part of a more general neurological or neurodegenerative disorder;

- Treatment should perhaps be expanded to treatment of both the eye and the brain;
- Future structural brain MRI studies are needed to:

- Establish whether specific eye diseases (such as AMD and glaucoma) should be considered part of a more general neurodegenerative disease;
- Investigate the degree to which degeneration of the brain in eye diseases is reversible, relevant for effectively restoring vision following retinal restoration;
- Evaluate and monitor the effect of neuroprotective medication in ocular disease (e.g. in glaucoma);
- Determine the optimal timing for the insertion of a retinal implant, if in the future such treatment would become more common (e.g. in retinitis pigmentosa or MD);
- Assess whether MRI examination can be a useful diagnostic tool in certain eye diseases (i.e. has sufficient specificity and selectivity and cost-effectiveness for such a purpose).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Search strings specified for glaucoma, hereditary retinal dystrophies, AMD, amblyopia and albinism.