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Neuroanatomical changes in patients with loss of visual function

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CHAPTER 1

General introduction of the topic
and a review of the literature

Based on: Doety Prins, Sandra Hanekamp & Frans W. Cornelissen. Structural brain MRI studies in eye diseases: are they clinically relevant? A review of current findings.

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1.1 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 I mean by the general term “brain changes” is given in Box 1.1). (Barnes et al. 2010, Boucard et al. 2009, Bridge et al. 2012, Hernowo et al. 2011, Hernowo et al. 2014, Plank et al. 2011, Xiao et al. 2007, Xie et al. 2007) These brain changes have primarily been shown in eye diseases that reduce visual acuity or are associated with the occurrence of retinal defects, such as glaucoma, age-related macular degeneration (AMD) and hereditary retinal dystrophies.

Box 1.1: 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 et al. 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 literature as anterograde degeneration. (Nauta and Ebesson 1970)

Retrograde transsynaptic degeneration

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

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.

I 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, I 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 the discussion of this thesis I will generalize these findings and give directions for future research.

Although numerous animal and functional MRI (fMRI) studies have also been performed, I limited the scope of this literature 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 1.2). (For reviews focusing on fMRI, I refer to *Wandell and Smirnakis (2009)* and *Haak et al. (2014)*).

Box 1.2: Structural brain imaging techniques

The first approaches to identify brain changes in ocular diseases have been carried out by 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 and Friston 2000, Ashburner and Friston 2001, Bookstein 2001, Good et al. 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) 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 et al. 1999a, Jones et al. 1999b)

1.2 Methods

Search protocol

The data base 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

1.3 Results

1.3.1 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 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.* 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 (von dem Hagen et al. 2005). 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 if the reported brain abnormalities in albinism are congenital, or if 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 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 in the disorder itself.

1.3.2 Amblyopia

Pathology

Amblyopia is a reduction of best-corrected central visual acuity by misuse of 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.

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 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. 2013a). In summary, this indicates that amblyopia is linked to changes in the pregeniculate 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.

1.3.3 Hereditary retinal dystrophies

Pathology

Hereditary retinal dystrophies are a collective name for Medelian genetic eye diseases such as Juvenile macular degeneration (e.g. Stargardt's disease and 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).

What has been found?

When analysed with VBM, patients with a binocular central visual field defect due to hereditary retinal dystrophies showed a reduction of 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.

In an earlier DTI study in (only) 6 patients with acquired blindness, of which 5 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) Hernowo et al (2014) observed white matter changes in JMD patients in the optic radiations and visual cortex. Taken together, these results show that in hereditary retinal dystrophies post-geniculate 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 post-geniculate 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

1.3.4 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.(Arden 2006, Gehrs et al. 2006, Holz et al. 2004, Zarbin 2004) AMD is the most prevalent cause of visual impairment in the European adult population. (Augood et al. 2006)

What has been found?

By 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 post-geniculate changes, frontal changes are observed as well.

What is the potential clinical relevance of the findings?

Degeneration in the post-geniculate 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 (MCI) or AD.(Hernowo et al. 2014, Ikram et al. 2012, Klaver et al. 1999, Woo et al. 2012)

Several studies have revealed that AMD and AD 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. Contrarily, it seems that these two diseases have a different genetic background (Proitsi et al. 2012). Further, in a recent AMD cohort of 65,984 people concluded that the chance of developing AD 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 and 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.

1.3.5 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 (Chang and Goldberg 2012, Fechtner and Weinreb 1994, Nickells 1996). 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 lateral geniculate nucleus (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 as well as decreases of grey matter in various areas of the brain.(Chen et al. 2013, Li et al. 2012, 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 diffusion MR imaging, also referred to as 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.(Chang et al. 2013, Chen et al. 2013, Dai et al. 2012, Doerfler et al. 2012, El-Rafei et al. 2013, Garaci et al. 2009, Liu et al. 2012, Murai et al. 2013, Wang et al. 2013, Zhang et al. 2012) *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-analyse 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 I 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, since 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 (Chen et al. 2013, Dai et al. 2012, Garaci et al. 2009, Michelson et al. 2013, Wang et al. 2013), 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 (AD) and glaucoma. Glaucoma and AD share several characteristics: they are both neurodegenerative, chronic, progressive, age-related and cause irreversible neuronal cell loss. This may indicate that glaucoma and AD 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 AD (Bayer et al. 2002, Tamura et al. 2006), while other studies do not.(Kessing et al. 2007, Ou et al. 2012) In support of the hypothesis that glaucoma may be part of a neurodegenerative disease, some studies examined trans-lamina cribrosa pressure difference (TLCPD), which is calculated as the intraocular pressure (IOP) minus the cerebrospinal fluid pressure (CSFP). These studies suggest that TLCPD has a better association with glaucoma presence than IOP (Jonas et al. 2014, Wang et al. 2013, Wostyn et al. 2013, Zhang et al. 2014). This could be an indication that glaucoma should be seen as part of a neurological disorder.

