Neuroanatomical changes in patients with loss of visual function

Prins, Doety

CHAPTER 6

General discussion of the topic

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In chapter 1 of this thesis, I described the current state of knowledge of structural MRI studies in various eye diseases. Within it, I 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. I summarized the current findings, the relevance of these findings for understanding the aetiology of eye diseases and its current and future clinical relevance. Below, I answer our main questions and give directions for future research.

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

Regarding the current research findings, in all eye diseases described in the introduction – glaucoma, hereditary retinal dystrophies, AMD, albinism, and amblyopia – MRI studies have shown the presence of structural changes in the visual pathways. Changes in the post-geniculate 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.

Furthermore, the studies described in chapter 4 and 5 of this thesis show that pregeniculate as well as cortical changes also occur in monocularly blind patients and glaucoma patients with a monocular visual field defect.

6.2 What is the potential clinical relevance of the findings?

Clinical focus

The brain changes in the eye diseases that I reviewed here have several implications for clinical practice. Presently, 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 in patients who are blind to restore their visual function (da Cruz et al. 2013, Zrenner 2002). The results

of these implanted devices are encouraging, but rather variable. Since 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 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 aptosis (Shahsuvaryan 2012). The target neurons should be in the visual pathways, in particular the RCGs for glaucoma and photoreceptors and retinal pigment epithelial cells for retinitis pigmentosa (Cottet & Schorderet 2009, Doonan & Cotter 2004). 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 (Chang & Goldberg 2012, Gupta & Yücel 2007, Nucci, Strouthidis & Khaw 2013, Osborne 2009, Pascale, Drago & Govoni 2012). 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 that 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. Additional studies on the role of reversibility results from two functional MRI studies. In a functional MRI study, an AMD patient who underwent treatment with intravitreal antiangiogenic 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). A study by Lou et al. (2013) examined changes in grey matter volume after cataract surgery in patients with unilateral cataract. Compared to two days after surgery, six weeks after surgery grey matter volume was increased in the V2 area contralateral to the operated eye. 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. Since these eye diseases are of diverse origin, I 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 mechanisms 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 and Alzheimer's disease, and after stroke (Balk et al. 2014, Gabilondo et al. 2014, Jindahra et al. 2010, Kirbas et al. 2013, Klistorner et al. 2014, Tanito & Ohira 2013).

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. In chapter 5 of this thesis I described neuroanatomical changes in glaucoma patients with a monocular visual field, which could not be explained by functional deprivation or transsynaptic degeneration. Furthermore, recent studies found possible links between Alzheimer's disease and the two eye diseases described here that occur later in life: glaucoma (Cumurcu et al. 2013, Inoue, Kawaji & Tanihara 2013, Tamura et al. 2006) and AMD (Ikram et al. 2012, Klaver et al. 1999, Woo et al. 2012). Moreover, an association between fluctuations in intracranial pressure and glaucoma has been found (Wostyn et al. 2013, Zhang et al. 2013, Zhang et al. 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 of frontal white matter in AMD patients also supports this theory (Hernowo et al. 2013).

6.3 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 if 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 if 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 that 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 if the retinal implant influences the brain, and if 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.

6.4 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).