Neuroanatomical changes in patients with loss of visual function
Prins, Doety

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CHAPTER 5

Neuroanatomical changes of the visual pathways in patients with a monocular visual field defect due to primary open angle glaucoma
Abstract

Introduction. Primary open-angle glaucoma (POAG) is associated with neuroanatomical changes in the brain. However, it is unclear whether this indicates that POAG is an eye disease that also causes neuroanatomical brain changes, due to functional deprivation or transsynaptic degeneration, or if this supports that POAG should be considered part of a more generalized neurodegenerative disease. Previous structural brain studies in POAG mainly focused on POAG patients with binocular visual field defects. However, a large fraction of the POAG patients has a monocular visual field defect. Here, we assess whether POAG with a monocular visual field defect is associated with neuroanatomical brain changes.

Methods. High-resolution T1-weighted magnetic resonance images in 19 POAG patients with a monocular visual field defect, 20 age-matched healthy controls, and 15 monocularly blind controls. Using voxel- and surface-based morphometry, we compared the volume of the grey and white matter, cortical thickness, mean curvature and surface area between the POAG patients and both control groups.

Results. We found extensive neuroanatomical changes in pregeniculate white matter volume and cortical thickness in the structures of the visual pathways in POAG patients with a monocular visual field defect, compared to both control groups.

Discussion. The neuroanatomical changes found in POAG patients are more widespread than the changes in monocularly blind patients. This is remarkable, given that all the POAG patients had monocular visual field loss only, that is, less extensive loss of visual input than the monocularly blind patients. Therefore, the widespread neuroanatomical changes throughout the visual pathways that we found in POAG patients cannot exclusively be explained by functional deprivation or transsynaptic degeneration. Hence, we conclude that POAG might be part of a more generalized neurodegenerative disorder that affects both the eye and the brain.
5.1 Introduction

Primary open angle glaucoma, an eye disease which is associated with visual field defects, is the second leading cause of blindness in the world. (Resnikoff et al. 2004) The visual field defects typically appear in the periphery of the visual field, and expand towards the center of the visual field if the disease progresses. An elevated intraocular pressure is an important risk factor. However, the pathophysiology of POAG is yet not fully understood. Previous research has shown that POAG is associated with neuroanatomical changes in the grey and white matter of the visual pathways. (Boucard et al. 2009, Chang et al. 2013, Chen et al. 2013, Chen et al. 2013, Dai et al. 2013, Doerfler et al. 2012, El-Rafei et al. 2013, Garaci et al. 2009, Hernowo et al. 2011, Li et al. 2012, Liu et al. 2012, Murai et al. 2013, Wang et al. 2013, Williams et al. 2013, Zhang et al. 2012)

However, it is still not known whether POAG is primarily an eye disease that also causes neuroanatomical changes in the brain – due to transsynaptic degeneration or due to functional deprivation as a result of a decreased input – or if POAG should be considered part of a more generalized neurodegenerative disease that affects both the eye and the brain. The latter idea has been supported by the possible link between POAG and Alzheimer’s disease. (Cumurcu et al. 2013, Ghiso et al. n.d., Inoue, Kawai and Tanihara 2013, Janssen et al. 2013, Kessing et al. 2007, Kirby, Bandelow and Hogervorst 2010, Ou et al. 2012, Sivak 2013, Tamura et al. 2006, Wostyn, Audenaert and De Deyn 2010)

Previous structural brain MRI-studies in POAG mainly focused on POAG patients with binocular visual field defects. However, a monocular visual field defect commonly occurs in POAG patients. If we determine whether neuroanatomical changes also occur in POAG patients with a monocular visual field defect, then we would gain more insight in the pathophysiology of POAG. In POAG patients with a monocular visual field defect the visual input from the contralateral visual field is still intact. Therefore, finding neuroanatomical changes in POAG patients with a monocular visual field defect would suggest that such changes are not a direct consequence of the decreased input of visual information – i.e. functional deprivation – but might either be caused by transsynaptic degeneration or indicate that POAG is part of a more generalized neurodegenerative disease affecting both the eye and brain. Similarly, if neuroanatomical changes in the visual pathways would be absent in this group, then the previously reported changes in POAG patients with binocular visual field defects might exclusively be caused by functional deprivation.

In this study, we compared the following neuroanatomical properties between POAG patients with a monocular visual field defect and two different control groups: grey and white matter volume, cortical thickness, surface area, and mean curvature. The first control group consisted of age-matched healthy subjects (HC), in which there was no functional deprivation, no transsynaptic degeneration, and no generalized neurodegenerative disease. The second control group consisted of age-matched
subjects who were long-standing monocularly blind (MBC) due to a trauma or after surgery for a tumor, but otherwise healthy. In the latter control group there occurred functional deprivation, but no transsynaptic degeneration, and they do not have generalized neurodegenerative disease. We addressed the following research questions. 1) Do the above-mentioned neuroanatomical properties differ between POAG patients with a monocular visual field defect and age-matched HC? 2) Do the above-mentioned neuroanatomical properties differ between POAG patients with a monocular visual field defect and age-matched MBC? The comparison of MBC to HC is addressed in a different paper. Using voxel-based morphometry (VBM) and surface-based (SBM) analyses, we specifically assessed the visual pathways, as this is where we expected the changes in the neuroanatomical properties to occur.

5.2 Methods

5.2.1 Ethics statement
The Medical Ethical committee of the University Medical Center Groningen approved this study. The study conformed to the tenets of the Declaration of Helsinki. All subjects gave written informed consent before participating in the study.

5.2.2 Subjects
The characteristics of the three subject groups are given in Table 5.1. Figure 5.1 shows the mean location of the visual field defect of the POAG patients. This visual field is only shown for the left eye. For the patients with a visual field defect in their right eye, we mirrored the right visual field along the vertical meridian to match the left visual field. We included 54 subjects: 19 POAG patients with a monocular visual field defect (12 with left visual field defect, mean MD-value -22 dB; 7 with right visual field defect, mean MD-value -16 dB), 15 age-matched MBC (8 with blind left eye; 7 with a blind right eye) and 20 age-matched HC. The inclusion criteria for the POAG patients were that they suffered from a monocular visual field defect due to POAG, pseudo-exfoliation, or pigment dispersion syndrome. The contralateral eye had to have an intact visual field (Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Jena, Germany) 30-2 SITA with glaucoma hemifield test “within normal limits”) and a good visual acuity (Snellen visual acuity at least 0.8 (0.1 logMAR or less). Moreover, they had to be free of any other ocular disease. MBC had to be light-perception negative in one eye for at least five years, due to a trauma (n = 11, in 11 subjects eye removed) or after surgery for a tumor (n = 4, in 3 subjects eye removed). The contralateral eye had to have an intact visual field and a good visual acuity. HC had to have an intact visual field and a good visual acuity in both eyes. All controls, MBC as well as HC, were free of any degenerative ocular disease. None of the subjects was previously diagnosed with neurological or psychiatric disorders.
Table 5.1. Subject characteristics

Number of subjects, median age, gender proportion, median BCVA and median NFI-number are given for all groups. BCVA and NFI-number were split up for the POAG group in median values for the better eye and median values for the worse eye. Mean visual field defect was only given for the POAG group, split up in median values for the better eye and median values for the worse eye.

<table>
<thead>
<tr>
<th></th>
<th>POAG patients</th>
<th>HC</th>
<th>MBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>19</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Age, median (interquartile range), years</td>
<td>59 (56 – 72)</td>
<td>64 (58 – 67)</td>
<td>62 (58 – 67)</td>
</tr>
<tr>
<td>Male, %</td>
<td>47%</td>
<td>61%</td>
<td>47%</td>
</tr>
<tr>
<td>BCVA, median (interquartile range), logMAR</td>
<td>0 (0 to -0.1)</td>
<td>0.2 (0.25 to 0)</td>
<td>0 (0 to -0.1)</td>
</tr>
<tr>
<td>NFI, median (interquartile range)</td>
<td>24 (19 – 31)</td>
<td>86 (63 – 98)</td>
<td>21 (15 – 26)</td>
</tr>
<tr>
<td>Visual field defect, median (interquartile range), MD, dB</td>
<td>-1.5 (-0.7 to -2.3)</td>
<td>-15.5 (-11.7 to -27.5)</td>
<td></td>
</tr>
</tbody>
</table>

5.2.3 Data acquisition

MR-images of all subjects were obtained on a 3.0 Tesla MRI scanner (Philips Intera, Eindhoven The Netherlands) at the Neuroimaging Center of the University Medical Center Groningen. We acquired whole brain T1-weighted images with a voxel dimension of 1 mm x 1 mm x 1 mm using a sequence of T1W/3D/FFE, 30° flip angle, repetition time 25 ms, matrix size 256 x 256, field of view 256 x 160 x 204, yielding 160 slices.

The visual acuity was measured with a Snellen chart with optimal correction for the viewing distance (6 m). The Nerve Fiber Indicator (NFI) was measured by the Glaucoma Diagnostic instrument (GDx; Carl Zeiss Meditec, Jena, Germany). In the POAG patients,
the visual field was measured by using the HFA (see above). In the control groups, we used Frequency Doubling Technology (FDT; Carl Zeiss Meditec, Jena, Germany) in C20-1 screening mode to verify that they had an intact visual field. For a normal visual field, all test locations had to be intact (P≥1%).

5.2.4 Data analysis

Voxel-based morphometric (VBM) analysis
We compared the volumes of the grey and white matter between patients and controls using VBM. We used the FMRIB Software Library analysis tools (FSL, version 5.0.6, available at: http://www.fmrib.ox.ac.uk/fsl).(Jenkinson et al. 2012, Woolrich et al. 2009) First, we applied nonlinear noise reduction using Smallest Univalue Segment Assimilating Nucleus (SUSAN). Second, we segmented the brain from non-brain tissue, using the Brain Extraction Tool (BET).(Smith 2002) Subsequently, we performed bias field correction and segmented the brain into grey matter, white matter and cerebrospinal fluid with FMRIB’s Automated Segmentation Tool (FAST).(Zhang, Brady and Smith 2001) We registered all the images to the template of the Montreal Neurological Institute (MNI template) with FMRIB’s Linear Image Registration Tool (FLIRT) and FMRIB’s Non-linear Image Registration Tool (FNIRT), and applied the registration to the grey and white matter segments.(Jenkinson et al. 2002, Jenkinson and Smith 2001)

Surface-based morphometric (SBM) analysis
We compared the cortical thickness, mean curvature and surface area between patients and controls using the surface-based approach of Freesurfer (version 5.3.0, available at: http://surfer.nmr.mgh.harvard.edu/). We removed the non-brain tissue,(Ségonne et al. 2004) performed automated Talairach transformation and intensity normalization. (Sled, Zijdenbos and Evans 1998) Subsequently, tessellation of the grey/white and grey/cerebrospinal fluid boundaries and automatic correction of topologic inaccuracies was performed, which we customized by setting the value for the lower threshold of the white matter to an appropriate value for our dataset.(Fischl, Liu and Dale 2001, Ségonne, Pacheco and Fischl 2007) The process continued with surface deformation and inflation,(Dale, Fischl and Sereno 1999, Fischl, Sereno and Dale 1999) registration to a spherical atlas (Fischl et al. 1999) and automatic parcellation of the cortical surface based on gyral and sulcal organization.(Desikan et al. 2006, Fischl et al. 2004)

Region-of-interest (ROI) analysis
In the ROI-based analyses, we used masks of the various grey and white matter structures of the visual pathways. Figure 5.2 depicts the ROIs: the pregeniculate structures, which contains the optic nerves (ON), the optic chiasm (OC) and optic tracts (OT); the lateral geniculate bodies (LGB); the optic radiations (OR); the supracalcarine cortex (SCC); the
intracalcarine cortex (ICC); the occipital pole (OP); the inferior lateral occipital cortices (iLOC) and the superior lateral occipital cortices (sLOC). The masks for the pregeniculate structures were created manually, and were adjusted to the individual subject if needed. The masks for the LGB and for the OR were obtained from the Jülich histological atlas (Bürgel et al. 2006, Bürgel et al. 1999). The masks for the SCC, the ICC, the OP, the iLOC and the sLOC were obtained from the Harvard-Oxford cortical structural atlas. (Desikan et al. 2006) In all these ROIs, we analyzed the volume of the grey or white matter using VBM. In the SCC, the ICC, the OP, the iLOC and the sLOC we also analyzed the cortical thickness, gyrification pattern and surface area using SBM.

Statistics
We examined differences between POAG patients and both the MBC and HC applying MANCOVA, using the IBM SPSS Statistics software package, version 20. The white matter volume, grey matter volume, cortical thickness, gyrification pattern, and surface area for each hemisphere and ROI were included as dependent variables, and the subject groups were entered as a fixed factor. We added age as a covariate in the analysis. We performed a Tukey post-hoc test to determine whether significant differences occurred between subject groups. The threshold for significance was set to a p-value <0.05.

Correction for visual field defect asymmetry
Not all POAG patients had their visual field defect in the same eye. Therefore, we performed the ROI analysis in two stages. In the first analysis, we compared the volumes of the optic nerves between POAG patients and both control groups. This analysis was divided in two parts: first, we compared POAG patients with their visual field defect in the right eye to the HC and to the MBC with a blind right eye; second, we compared POAG patients with their visual field defect in the left eye to the HC and to the MBC with a blind left eye. In the second analysis, we analyzed the visual pathway structures.
onwards from the optic chiasm to the posterior parts of the visual pathways in the entire group of POAG patients, compared to both control groups. Once they have passed the optic chiasm, the nerve fibers that carry the information from the homonymous hemifields of both eyes travel together to the visual cortex. For this reason, after this stage we expected no detectable volumetric differences between the POAG patients with their visual field defect in either the right or the left eye. This justified a combined analysis.

*Exploratory whole-brain analysis*

We performed additional exploratory whole-brain analyses using both VBM and SBM. With VBM, we assessed whole-brain grey matter and white matter volume, whereas with SBM we assessed the cortical thickness, area, and mean curvature across the entire brain. In both analyses, age was added as a covariate.

### 5.3 Results

In summary, in POAG patients with a monocular visual field defect – compared to both control groups – we found neuroanatomical changes in pregeniculate white matter volume and cortical thickness in the structures of the visual pathways. We will describe these results in more detail below.

#### Table 5.2a

<table>
<thead>
<tr>
<th>ROI</th>
<th>Hemi</th>
<th>Parameter</th>
<th>POAG</th>
<th>HC</th>
<th>MBC</th>
<th>POAG vs. HC</th>
<th>POAG vs. MBC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Volume</td>
<td>VFD OS</td>
<td>80 ± 12</td>
<td>142 ± 10</td>
<td>139 ± 11</td>
<td>13 ± 4</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>Volume</td>
<td>158 ± 11</td>
<td>139 ± 10</td>
<td>144 ± 11</td>
<td>144 ± 18</td>
<td>27 ± 5</td>
</tr>
</tbody>
</table>

**Table 5.2.** ROI morphometric values

- **VFD OS**: Volume of the left and right ON in the separate subgroups of POAG patients with a visual field defect in the left eye and POAG patients with a visual field defect in the right eye; each group was compared to the HC and to the MBC with a blind eye on the same side as the POAG patients had the visual field defect.
- **Blind OS**: Parameters in OC, OT, LGB, OR, OP, ICC, SCC, ILOC, and sLOC were compared between POAG patients and HC and between POAG patients and MBC.

**ROI** - region of interest; **Hemi** - hemisphere; **Parameter**: Surface area in mm², average cortical thickness in mm, mean curvature in mm⁻¹ and volume in mm³; **VFD** – visual field defect; **OS** – oculus sinister; **OD** – oculus dexter; values indicate mean ± standard error of the mean. **F-values**, **degrees of freedom (df)** and **p-values** are given.

* indicates a significant difference between the patients group and both age-matched control groups (p ≤ 0.05 after Tukey post-hoc).
Table 5.2 lists the results of the ROI analyses in the ONs, the OC, the OT, the LGB, the OR, the SCC, the ICC, the OP, the iLOC, and the sLOC. We found a lower volume of the left ON in the POAG with a visual field defect in the left eye compared to the HC. We found a higher volume of the ON on the affected side in the POAG compared to the MBC. A MANCOVA analysis including all ROIs showed the presence of differences between groups (p<0.001). After performing Tukey’s post-hoc test, we found a significantly lower volume of the OC in the POAG patients compared to the HC and MBC. Additionally, we
found a thinner cortex in the POAG in the OP and sLOC compared to both HC and MBC. We also found a thinner cortex in the SCC and iLOC in the POAG patients compared to the MBC.

Using whole-brain analyses, we found no further unexpected neuroanatomical differences beyond the previously examined visual pathways ROIs.

5.4 Discussion

Neuroanatomical changes in POAG patients with a monocular visual field defect occur in the ON, the OC and in various areas of the visual cortex. We did not find any changes at the level of the OT, the LGB, and OR.

As in these patients the visual input from the contralateral visual field is still intact, we expected no or only very limited influence of functional deprivation. Not finding changes in the OT, LGB, and OR indicates that the changes in the visual cortex are not due to transsynaptic degeneration. Therefore, this implies that the neuroanatomical changes in the visual cortex in the POAG patients are a consequence of POAG being part of a neurodegenerative disease that also directly affects the brain. This is also supported by the finding that monocular POAG affects the brain more than monocular blindness. Below, we will discuss the results and these conclusions in more detail.

5.4.1 ROI analysis

Grey and white matter volume

We found volumetric differences between POAG patients and both control groups in the pregeniculate structures. We found lower volumes compared to the HC, and higher volumes compared to the MBC. Compared to the HC, we found a lower volume of the left ON in POAG that had their visual field defect in the left eye, and we found a lower volume of the OC. We expected to find degeneration in the ON on the side of the affected eye, as a consequence of direct degeneration of the ON in POAG. However, we did not find a lower volume of the right ON in the POAG with the visual field defect in the right eye. This might be due to the fact that the POAG with the visual field defect in the right eye had a smaller visual field defect (MD value -16 dB) than the POAG with the visual field defect in the left eye (MD value -22 dB). Although this difference seems modest, with disease progress the central part of the visual field becomes more involved, and a central visual field defect causes more loss of nerve fibers than a peripheral visual field defect.

We found higher volumes of the ONs in the affected eye compared to the MBC. This was expected, as substantial volumetric decrease of these structures occurred in the MBC due to direct degeneration.
We found no differences in the volume of the OT, LGB, OR, or any of the structures of the visual cortex. The absence of volumetric differences in the OT, LGB, and OR suggests that transsynaptic degeneration might not play a role in the neuroanatomical changes in POAG.

Cortical thickness

Compared to HC and MBC, we found a thinner cortex in the OP and the sLOC in the POAG patients. We also found a thinner cortex in the SCC and the iLOC in the POAG compared to the MBC. Cortical thinning in the visual cortex could be explained by functional deprivation due to the visual field defect. However, in our previous study in which we compare the MBC to the HC, we found volumetric decrease in the sLOC, but no differences in cortical thickness. Since the MBC have complete loss of their visual field in one eye, while the POAG only have a visual field defect in one eye, one would expect to find less neuroanatomical changes in the POAG than in the MBC, if these changes were a consequence of functional deprivation. Therefore, we think that a more feasible hypothesis is that the cortical thinning is the result of a more generalized neurodegenerative process.

5.4.2 Comparison with previous structural brain MRI-studies

In contrast to the current study in POAG patients with a monocular visual field defect, previous research on neuroanatomical changes in POAG focused mainly on POAG patients with binocular visual field defects. In POAG patients with binocular visual field defects, Boucard et al. found a lower grey matter density in POAG patients in the anterior region of the calcarine sulcus. (Boucard et al. 2009) Hernowo et al. found volumetric decreases in both grey and white matter throughout the entire visual pathway in POAG. (Hernowo et al. 2011) Others studies found decreases as well as increases of grey matter volume in POAG patients in various areas of the brain, also outside of the visual pathways. (Chen et al. 2013, Li et al. 2012, Williams et al. 2013) The abovementioned studies analyzed neuroanatomical changes in POAG patients with binocular visual field defects, whereas in the present study we included only POAG patients with a monocular visual field defect. This indicates that the extent of the visual field defect does not play an important role in the development of neuroanatomical changes in POAG.

5.4.3 Underlying mechanism of the association between POAG and neuroanatomical changes

Overall, we conclude that the extensive neuroanatomical changes in the visual cortex that we found here in POAG patients with a monocular visual field defect are unlikely to be explained exclusively based on functional deprivation or transsynaptic degeneration. Therefore, we hypothesize that these changes might reflect the presence of more generalized neurodegenerative processes. Hence, POAG might be part of
a more generalized neurodegenerative disorder, which affects the brain and the eye simultaneously. This latter theory has been supported by a suggested link between POAG and Alzheimer’s disease, although the reports on this topic show conflicting results. (Cumurcu et al. 2013, Ghiso et al. 2013 Inoue, Kawaji and Tanihara 2013, Janssen et al. 2013, Kessing et al. 2007, Kirby, Bandelow and Hogervorst 2010, Ou et al. 2012, Sivak 2013, Tamura et al. 2006, Wostyn, Audenaert and De Deyn 2010)

5.4.4 Limitations
In this study, we included POAG patients with a monocular visual field defect. Since not all patients had their visual field defect on the same side, we decided to perform the ROI analysis in two stages. We analyzed the ONs separately for the POAG patients that had their visual field defect in the left eye, which we compared to the MBC with a blind left eye and to the HC. For the POAG patients that had their visual field defect in the right eye, we performed the same procedure. In the OC, the nerve fibers from the nasal parts of the retinas of both eyes decussate. Therefore, we reasoned that the structures from the OC to the visual cortex could be analyzed in all POAG patients together.

We used both VBM and SBM to assess various neuroanatomical properties. These methods pre-process the data in different ways and assess different aspects of brain anatomy. As a consequence, their results may not always be congruent, as we also observed. For example, we found no volumetric changes in areas where the cortex was thinner.

5.4.5 Future research
By determining that neuroanatomical changes occur in POAG patients with a monocular visual field defect, we contributed to the knowledge on the etiology of neuroanatomical changes in POAG patients. However, it is still not fully clear in which stage of the disease such neuroanatomical changes occur and if the changes are reversible when applying for example neuroprotective agents. Therefore, future research should focus on longitudinal data from POAG patients; such research should reveal how the exact development of neuroanatomical changes takes place. Furthermore, in an intervention study with neuroprotective agents, it would be possible to determine whether neuroanatomical changes are stoppable or even reversible.
5.4.6 Conclusion
Extensive neuroanatomical changes in pregeniculate white matter volume and cortical thickness occur in the visual pathways in both hemispheres in POAG patients with a monocular visual field defect. Remarkably, these changes are more widespread than neuroanatomical changes that were found in the brains of monocularly blind patients. Therefore, we conclude that the possible effect of the loss of visual input – through functional deprivation or transsynaptic degeneration – on the neuroanatomical properties in POAG patients can not explain all of the changes in the brain that we found here. Hence, our findings support the notion that POAG might be part of a more generalized neurodegenerative disorder that affects both the eye and the brain.