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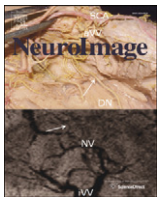

# Gray matter alterations in visual cortex of patients with loss of central vision due to hereditary retinal dystrophies

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ABSTRACT

In patients with central visual field scotomata a large part of visual cortex is not adequately stimulated. Over time this lack of input could lead to a reduction of gray matter in the affected cortical areas. We used Voxel Based Morphometry to investigate structural brain changes in patients with central scotomata due to hereditary retinal dystrophies and compared their results to those of normal sighted subjects. Additionally we correlated clinical and demographic characteristics like duration of disease, scotoma size, visual acuity, fixation stability and reading speed to the amount of gray matter in whole brain analyses within the patient group. We found a decrease in gray matter around the lesion projection zone in visual cortex of patients in comparison to controls. Gray matter loss along the posterior and middle portions of the calcarine sulcus is also correlated with scotoma size, indicating that indeed the lack of functional input provokes the gray matter alterations. In whole brain regression analyses within the patient group we found an additional cluster in the right superior and middle frontal gyri, slightly anterior to the frontal eye fields, where gray matter correlated positively with fixation stability. This could be regarded as a consequence of oculomotor learning.



## Introduction

The hereditary retinal dystrophies, Stargardt's disease and cone–rod dystrophy, usually start between the age of 10 and 30 years and lead to a progressive loss of photoreceptors in the retina. The cones are primarily affected resulting in a disturbed macular function. Therefore, the patients suffer from a reduced visual acuity and binocular central visual field scotomata (Glazer and Dryja, 2002; Scullica and Falsini, 2001). Due to the loss of central vision, a large part of visual cortex is not adequately stimulated (Van Essen and Anderson, 1995) and thus appears predestined for gray matter reductions.

There are numerous reports pointing to cortical and subcortical reorganization as well as structural changes due to sensory deprivation. This has, in addition to those for the visual system, also been shown for the somatosensory system (e.g. Draganski et al., 2006a; Flor et al., 1995; Jurkiewicz et al., 2006; Merzenich et al., 1984; Ramachandran and Hirstein, 1998; Kaas et al., 2008), the olfactory system (Bitter et al., 2010a, b) and the auditory system (Emmorey et al., 2003; Landgrebe et al., 2009; Mühlau et al., 2006; Penhune et al., 2003; Schneider et al., 2009; Shibata, 2007).

Several studies have indicated that the visual system is especially affected by sensory deprivation. Ptito et al. (2008) found significant atrophy along the visual pathways including primary and associative visual cortex in congenitally blind adults. Similar results are shown for early blind adults, who lost sight before the age of two (Noppeney et al., 2005) or before the age of six (Pan et al., 2007). Abnormalities in the structure of the visual cortex are also detected in children and adults with amblyopia (Mendola et al., 2005; Xiao et al., 2007), as well as in albinism (Hoffmann et al., 2003). Furthermore studies on albinos found differences in the visual pathways (Schmitz et al., 2003) and a reduction of gray matter in the foveal representation area of the visual cortex, assumed to occur as a consequence of a decreased number of ganglion cells in the fovea (Von dem Hagen et al., 2005).

When it comes to visual field defects acquired later in life, several studies have found neural degeneration in glaucoma patients. Gupta et al. (2006) reported evidence for neural degeneration along the optic nerve, the lateral geniculate nucleus (LGN) and the visual cortex in a

*Abbreviations:* AMD, age-related macular degeneration; ANCOVA, analysis of covariance; ANOVA, analysis of variance; BA, Brodmann area; FEF, frontal eye field; FOV, field of view; FWE, family wise error; FWHM, full width at half maximum; LGN, lateral geniculate nucleus; LPZ, lesion projection zone; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PALS, Population-Average, Landmark- and Surface-based; PRL, preferred retinal locus; SPM, Statistical Parametric Mapping; VBM, voxel-based morphometry; VOI, volume of interest.

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**Table 1**
Characteristics of patients (P1–P26) and controls (C1–C26) according to gender, age, duration of disease in years, diagnosis, decimal visual acuity, scotoma size (diameter in degree visual angle), fixation stability (percentage of fixation in 2° and 4° visual angle around fixation target; patients fixated with their PRL, except P16, who fixated with his fovea, as did the controls) and reading speed (in words per minute); m = male; f = female; Stargardt = Stargardt's disease; CACD = central areolar choroidal dystrophy; MD = unclassified hereditary macular dystrophy; Cone D = cone dystrophy; Cone–rod D = cone–rod dystrophy; OS = oculus sinister; OD = oculus dexter; CF = counting fingers; characteristics of the better eye of each patient are reported in bold, that are correlated with MRI data. For the controls the respective eye was chosen.

| Subject # | Gender | Age | Duration of disease in years | Diagnosis | Decimal visual acuity | | Scotoma size (diameter in degree visual angle) | | Fixation stability | | | | Reading speed (words per minute) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | OD | | OS | | |
| | | | | | OD | OS | OD | OS | 2° | 4° | 2° | 4° | |
| P1 | m | 12 | 2 | Stargardt | .08 | **.08** | 25 | **10** | 10 | 46 | **62** | **97** | 95 |
| P2 | f | 19 | 9 | Stargardt | .05 | **.05** | n.a. | **15** | 7 | 14 | **0** | **2** | 110 |
| P3 | f | 24 | 11 | Stargardt | .08 | **.05** | 20 | **20** | 83 | 100 | **86** | **100** | 132 |
| P4 | f | 25 | 8 | Stargardt | **.08** | .05 | **20** | 25 | **20** | **57** | 47 | 64 | 77 |
| P5 | m | 25 | 8 | Stargardt | **.1** | .05 | **10** | 25 | **100** | **100** | 20 | 23 | 98 |
| P6 | m | 29 | 5 | Stargardt | **.1** | .1 | **10** | 10 | **95** | **100** | 69 | 99 | 76 |
| P7 | f | 35 | 6 | Stargardt | **.1** | .1 | **10** | 10 | **98** | **100** | 55 | 97 | 83 |
| P8 | m | 39 | 14 | Stargardt | .05 | **.067** | 30 | **30** | 18 | 67 | **68** | **93** | 78 |
| P9 | m | 43 | 24 | Stargardt | .1 | **.1** | 20 | **20** | 58 | 74 | **69** | **77** | 60 |
| P10 | f | 43 | 9 | Stargardt | **.1** | .08 | **15** | 15 | **80** | **95** | 83 | 99 | 78 |
| P11 | f | 43 | 28 | Stargardt | **.1** | .1 | **10** | 10 | **26** | **28** | 70 | 93 | 60 |
| P12 | m | 45 | 23 | Stargardt | .1 | **.2** | 10 | **10** | 99 | 100 | **96** | **100** | 96 |
| P13 | m | 55 | 16 | Stargardt | **.1** | .1 | **15** | 15 | **32** | **59** | 52 | 95 | 83 |
| P14 | m | 62 | 14 | Stargardt | **.02** | .03 | **60** | 65 | **5** | **9** | n.a. | n.a. | n.a. |
| P15 | m | 66 | 13 | Stargardt | **.05** | .02 | **30** | 20 | **44** | **72** | 2 | 5 | 22 |
| P16 | m | 42 | 12 | CACD | **.5** | .1 | **15** | 15 | **100** | **100** | 100 | 100 | 81 |
| P17 | f | 44 | 29 | CACD | **.05** | .067 | **10** | 25 | **15** | **37** | 14 | 50 | 57 |
| P18 | m | 53 | 23 | MD | **.08** | .05 | **10** | 15 | **46** | **59** | 59 | 60 | 137 |
| P19 | m | 50 | 18 | Cone D | **.1** | .2 | **10** | 10 | **41** | **69** | 42 | 73 | 56 |
| P20 | m | 33 | 8 | Cone–rod D | .08 | **.08** | 25 | **25** | 47 | 48 | **100** | **100** | 27 |
| P21 | f | 41 | 28 | Cone–rod D | .08 | **.1** | 30 | **25** | 75 | 96 | **83** | **100** | 19 |
| P22 | m | 42 | 22 | Cone–rod D | **.04** | CF | **60** | 60 | **48** | **92** | n.a. | n.a. | n.a. |
| P23 | m | 44 | 42 | Cone–rod D | **.001** | .001 | **40** | 30 | **1** | **4** | n.a. | n.a. | n.a. |
| P24 | m | 59 | 16 | Cone–rod D | **.1** | .1 | **10** | 10 | **20** | **21** | 10 | 18 | 80 |
| P25 | m | 65 | 6 | Cone–rod D | .03 | **.05** | 35 | **30** | 4 | 9 | **78** | **97** | 14 |
| P26 | m | 65 | 17 | Cone–rod D | .05 | **.1** | 30 | **30** | 33 | 81 | **43** | **48** | 31 |
| C1 | m | 13 | – | – | 1.0 | **1.0** | – | **–** | 81 | 86 | **99** | **100** | 127 |
| C2 | f | 23 | – | – | 1.0 | **1.0** | – | **–** | n.a. | n.a. | **100** | **100** | 112 |
| C3 | m | 23 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | n.a. | n.a. | 156 |
| C4 | f | 23 | – | – | 1.0 | **1.0** | – | **–** | 97 | 100 | **98** | **100** | 160 |
| C5 | m | 26 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | n.a. | n.a. | n.a. |
| C6 | m | 28 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | 100 | 100 | 127 |
| C7 | f | 34 | – | – | **1.0** | 1.0 | – | **–** | **n.a.** | **n.a.** | n.a. | n.a. | 173 |
| C8 | f | 34 | – | – | 1.0 | **1.0** | – | **–** | n.a. | n.a. | **100** | **100** | n.a. |
| C9 | f | 37 | – | – | 1.0 | **1.0** | – | **–** | 100 | 100 | **96** | **96** | n.a. |
| C10 | m | 37 | – | – | 1.0 | **1.0** | – | **–** | 89 | 89 | **100** | **100** | 169 |
| C11 | f | 37 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | 100 | 100 | 126 |
| C12 | m | 38 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | n.a. | n.a. | 139 |
| C13 | m | 40 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | n.a. | n.a. | 139 |
| C14 | m | 43 | – | – | 1.0 | **1.0** | – | **–** | 100 | 100 | **100** | **100** | 199 |
| C15 | f | 44 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | 61 | 61 | 164 |
| C16 | m | 45 | – | – | **1.0** | 1.0 | – | **–** | **96** | **96** | 77 | 77 | 153 |
| C17 | f | 51 | – | – | **1.0** | 1.0 | – | **–** | **97** | **100** | n.a. | n.a. | 123 |
| C18 | f | 54 | – | – | 1.0 | **1.0** | – | **–** | 89 | 89 | **100** | **100** | 156 |
| C19 | f | 55 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | 100 | 100 | 143 |
| C20 | m | 59 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | 100 | 100 | 107 |
| C21 | m | 60 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | 100 | 100 | 151 |
| C22 | f | 62 | – | – | 1.0 | **1.0** | – | **–** | n.a. | n.a. | **70** | **72** | 151 |
| C23 | f | 62 | – | – | 1.0 | **1.0** | – | **–** | n.a. | n.a. | **100** | **100** | 138 |
| C24 | m | 63 | – | – | **1.0** | 1.0 | – | **–** | **100** | **100** | 91 | 100 | 180 |
| C25 | f | 68 | – | – | **1.0** | 1.0 | – | **–** | **98** | **99** | 95 | 100 | 126 |
| C26 | m | 70 | – | – | 1.0 | **1.0** | – | **–** | 76 | 77 | **97** | **100** | 125 |

post-mortem case study, and Gupta et al. (2009) also found atrophy in the LGN in 10 glaucoma patients compared to controls using structural magnetic resonance imaging (MRI). In the case of glaucoma, this neural degeneration could be a consequence of trans-synaptic degeneration due to elevated intraocular pressure and injury to retinal ganglion cells (Gupta and Yücel, 2007) and thus might not be a direct consequence of visual defects in the peripheral field. Kitajima et al. (1997) used MRI to measure the width of the left and right calcarine sulcus in patients with different retinal degenerative diseases and found significant calcarine atrophy in comparison to controls. But it is unclear what kind of visual field defects those patients had.

In a recent study, Boucard et al. (2009) used voxel-based morphometry (VBM) to compare gray matter density in the visual cortex of glaucoma patients and patients with age-related macular degeneration (AMD). They assessed cortical gray matter in eight primary open-angle glaucoma patients with peripheral vision loss and nine AMD patients with central vision loss persisting in all patients for at least 3 years, as well as in an age-matched control group. For both patient groups they found a reduction of gray matter density in the respective lesion projection zones (LPZ) in the calcarine sulcus, suggesting that visual field scotomata can lead to retinotopic-specific structural changes in the visual cortex.