Is the eye an extension of the brain in CNS disease?

L. De Groef[1,2], M.F. Cordeiro[1,3,4]

[1]Glaucoma and Retinal Neurodegenerative Disease Research Group, Institute of Ophthalmology, University College London, 11-43 Bath Street, London EC1V 9EL, United Kingdom

[2]Neural Circuit Development and Regeneration Research Group, Department of Biology, University of Leuven, Naamsestraat 61 box 2464, 3000 Leuven, Belgium

[3]Western Eye Hospital, Imperial College Healthcare NHS Trust, 171 Marylebone Road, London NW1 5QH, United Kingdom

[4]ICORG, Department of Surgery and Cancer, Imperial College London, London SW7 2AZ, United Kingdom

Corresponding author:

Prof. dr. M.F. Cordeiro

Glaucoma and Retinal Neurodegenerative Disease Research Group

Institute of Ophthalmology

University College London

11-43 Bath Street

London EC1V 9EL

United Kingdom

Tel/Fax: 44(0)207 608 6938/9

E-mail: m.cordeiro@ucl.ac.uk

Word count: 1854 words

Neurodegenerative diseases – next-generation challenges

Since 1950, global average life expectancy has been steadily increasing at a rate of more than 3 years per decade (with the exception of the 1990's),[1] with accompanying growth in age-related neurodegenerative diseases, such as Alzheimer's (AD), Parkinson's (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and stroke. The limited capacity of self-repair of the adult mammalian central nervous system (CNS) and the general lack of preventive and restorative treatments for these conditions leads to progressive debilitation and eventually death. Not only does this result in a diminished quality of life for patients (and their families), it also impacts society by placing tremendous demands on social welfare and health systems. How to "ensure healthy lives and promote well-being for all at all ages" – one of the Sustainable Development Goals for 2030, adopted by the United Nations General Assembly – is thus a challenge to be tackled by the next generation of researchers, clinicians and policy makers.

Despite decades of intensive research, diagnosis and treatment remain challenging for neurodegenerative diseases. This treatment gap is believed to be the result of our still incomplete understanding of the complex interplay of pathological processes that underlie these conditions. In addition, many of them – most notoriously AD and PD – have a long prodromal phase, and by the time symptoms suggestive of a clinical diagnosis appear, neurodegeneration may have led to damage too extensive to repair. Early diagnosis during the asymptomatic stages of the disease could therefore open a therapeutic window during which therapies that act to delay or prevent neurodegeneration can be effective.

Although modern brain-imaging techniques (e.g., magnetic resonance imaging, positron emission tomography, single photon emission computed tomography) and blood/cerebrospinal fluid sampling have become most valuable tools in differentiating manifestations of healthy aging from pathological conditions, their high cost, necessity of using radioactive tracers, limited resolution and/or invasiveness prevent their use for population-wide screening of preclinical signs and for longitudinal follow-up of patients. Accumulating evidence now suggests that, rather than trying to access information about the disease state of the CNS in the brain, one could exploit the unique properties of the eye. *In vivo* assessments of retinal integrity and perfusion, electrophysiological function, and performance of vision-driven tasks, have revealed signs of deterioration in many neurodegenerative diseases, notably AD, PD, ALS and MS. Techniques such as optical

coherence tomography, confocal scanning laser ophthalmoscopy, electroretinograms and oximetry – which are all becoming increasing available at low cost –, could therefore represent a novel means for identifying patients at risk that need further neurological examinations, or for longitudinal follow-up of disease progression.

Common disease processes in the CNS - the eye as a research tool

The renewed interest in the occurrence of retinal symptoms in subjects with neurodegenerative diseases seems to have finally launched the eye as a 'window to the brain', enabling diagnosis and monitoring of disease. We believe, however, that the eye has even more to offer. As an integral part of the CNS, the retina is strikingly similar to the brain and spinal cord with respect to its anatomy, functionality, response to insult, and immunology, and cellular and molecular mechanisms underlying neurodegeneration appear to be conserved. Indeed, many ocular diseases share characteristics typical of neurodegenerative disorders. This leads us to advocate the use of the eye as a model organ to study common disease mechanisms, including: vascular abnormalities, inflammation, mitochondrial dysfunction, aggregation of misfolded proteins, blood-brain/retina barrier disruption, and changes in fluid (aqueous humour/cerebrospinal fluid) dynamics (Figure 1).[2]

A first example to illustrate this concept comes from the striking similarities between AD, glaucoma and age-related macular degeneration (AMD). All three are neurodegenerative diseases with age as the primary risk factor, though AD and glaucoma also have in common vascular dysregulation[3-6] and decreased cerebrospinal fluid/aqueous humour turnover[7, 8] – the latter leading to ocular hypertension, the sole modifiable risk factor and current therapeutic target for glaucoma – as potential elicitors of disease. Accumulating deposition of aggregated amyloid β and hyperphosphorylated Tau protein (pTau) have been observed by histopathologic study in all three diseases,[9] and especially for AD and AMD there are striking similarities in the protein composition of senile plaques and drusen, respectively.[10, 11] Furthermore, the deficits in axonal transport that have been proposed to result from Tau hyperphosphorylation are a common theme in the aetiology of both AD and glaucoma.[12, 13] Also the chronic neuroinflammatory response – characterized by activated microglia, complement activation, secretion of cytokines and creation of oxidative and nitrosative stress, and elicited by amyloid β – is a recurrent theme in all three diseases.[9, 14-16] Strikingly, AD and AMD even share a genetic connection, with APOE alleles being associated with both.[17,

18

As a second example, we present Leber's hereditary optic neuropathy, the first human disease to be associated with mitochondrial DNA defects,[19, 20] which may provide a window on mitochondrial neurodegenerative diseases. The eye appears to be particularly vulnerable to mitochondrial disease, as optic nerve atrophy appears to be a common hallmark of multi-systemic mitochondrial diseases.[21, 22] Retinal ganglion cells and their axons can therefore be used as model system to gain insight into mitochondrial network dynamics, fusion and fission, and mitophagy. Intriguingly, mitochondrial neurodegenerative diseases are associated with a characteristic pattern of retinal nerve fibre loss that predominantly affects the papillomacular bundle.[22-24] Corroborating abnormal mitochondrial dynamics/distribution as a key feature of PD, this typical pattern of axonal loss is also seen in PD patients[20, 21, 24] – but not in AD patients, in which the pattern of neurodegeneration more closely resembles that in glaucoma.[23] Indeed, Leber's hereditary optic neuropathy and PD are both associated with a complex I defect, leading to increased production of reactive oxygen species and subsequently neuronal apoptosis.[24-26]

These examples suggest that besides studying retinal changes in 'classical' animal models of neurodegenerative disease (*i.e.*, models with an original focus on the brain), one could also make use of the vast array of well-characterized and validated models of ocular diseases to gain novel insights into the processes driving CNS disease. In the end, key pathophysiological processes such as angiogenesis, inflammation or protein aggregation, are driven by conserved mechanisms and molecules. Revisiting the examples described above, animal models for AMD can be used to explore disease mechanisms such as protein aggregation, immune system dysregulation and oxidative stress, and thereby advance our understanding of both AMD and AD;[27] while extensive phenotyping of the retina/optic nerve in animal models of Leber's hereditary optic neuropathy could, for instance, unveil biomarkers of diseases that are also applicable to other diseases associated with mitochondrial dysfunction (e.g., PD).[28] In addition, repurposing existing drugs or following common approaches for related retina/brain diseases seems a valuable strategy for developing new neuroprotective therapies, and a breakthrough in the retina may promote advances in the development of therapies for the brain and *vice versa*. In the case of AD/glaucoma/AMD, early successes with neuroprotective treatments for AD in the brain, e.g., delivery of ciliary neurotrophic factor via a cell encapsulation approach, have added to the application of this therapy in the eye of AMD

patients;[9, 29] and amyloid targeting therapies originally tested/developed in the AD brain, have shown promising neuroprotective effects in animal models of ocular hypertension and drusen formation.[30, 31] Conversely, given the implication of complement activation in AD, the results from ongoing clinical trials with therapeutic approaches targeting the complement cascade in AMD could advance their use in AD as well.[32-34] Other examples of common therapeutic strategies for both eye and CNS diseases – either under development or in clinical trials – include neurotrophin supplementation (e.g., for AD, ALS, Huntington's disease, retinitis pigmentosa, geographic atrophy),[35-37] memantine (approved for AD, disappointingly failed for glaucoma),[38] and anti-TNF therapeutics (e.g., for AD, PD, stroke, glaucoma, uveitis).[39-42]

But why would one want to use the eye as a model organ? First, the availability of state-of-the-art technologies for ocular imaging, retinal electrophysiology, and behavioural testing of visual function, generates an objective and quantifiable comprehensive dataset about a specific disease. Although at present this wealth of information cannot be gathered in any other part of the CNS, findings are likely to be translatable to the entire CNS. As these non-invasive techniques allow longitudinal and simultaneous follow-up of multiple processes *in vivo*, they substantially lower the number of animals used – which is cost saving, but also ethically important – and revolutionize the quantity and quality of the experimental data. Second, the fact that identical read-outs/equipment can be used for patients and laboratory animals confers high clinical relevance to these end-point measures, and unique possibilities in terms of translatability to the clinic. Finally, adding to its strength as a preclinical research tool, the eye is easily accessible and manipulable, in contrast to the brain and spinal cord that are both protected by bony structures. The anterior chamber and vitreous cavity can furthermore be considered local drug reservoirs, allowing administration of substances in small doses and with less systemic side effects. The latter is illustrated by the success of, for example, ciliary neurotrophic factor delivery via intraocular encapsulated cell technology implants in patients with retinitis pigmentosa and geographic atrophy,[43] intravitreal injections of steroids and anti-VEGF therapeutics for a variety of indications (e.g., AMD, diabetic retinopathy),[44, 45] gene therapy for Leber's hereditary optic neuropathy, Leber's congenital amaurosis, and Usher syndrome,[46-48] and the ongoing development of cell transplantations to provide trophic support, repair and replacement of retinal neurons.[49]

Outlook

Although the idea of using the retina as a model organ to study the CNS as a whole, or employing the eye as a means of assessing the pathophysiological state of the brain, has increasingly gained momentum, it has only had a limited impact on neurodegenerative disease research. Implementation of the concept of 'the eye as a window to the brain' may, however, lead to multiple applications providing unique opportunities for researchers, clinicians and patients. First, there is increasing research into brain and eye diseases, highlighting the use of *in vivo* retinal imaging as a tool for early diagnosis and follow-up of treatment/disease progression. Therefore, low-cost, non-invasive imaging of the retina could revolutionise clinical practice and open up a new time window for treatment. Furthermore, applying the same *in vivo* measures of disease progression (e.g., OCT, cSLO, and ERG) in preclinical and clinical disease, validates the use of clinically relevant end points, making the eye particularly attractive for preclinical development as well as fundamental research. In addition, evidence for common disease mechanisms in the retina and the brain continues to emerge, with animal models of ocular disease providing valuable research tools to gather new insights that can be translated to the CNS.[50-52] Altogether, studies of retinal degenerative diseases have opened up new insights into the pathophysiology of, and potential therapies for, neurodegenerative diseases of the brain and spinal cord. Nevertheless, at the same time, many diseases are still waiting to be approached in this way. Motor neuron diseases, progressive supranuclear palsy, Leigh disease, systemic lupus erythematosus – just to name a few – have been intensively studied with respect to the pathological manifestations in the brain, yet are nevertheless still poorly understood and untreatable. Studies of the eye, retina and vision in these disorders would be 'eye-opening' and may lead to breakthroughs in the management of these diseases.

Disclosures

No competing financial interests exist.

Acknowledgements

Lies De Groef is a FWO (Fonds Wetenschappelijk Onderzoek, Research Foundation Flanders) postdoctoral fellow.

References

The aim of this manuscript is to comment on recent developments and future applications, rather than giving a complete overview of the literature. We apologize to authors that have not been referenced due to space limitations.

1. WHO. World health statistics 2016: monitoring health for the SDGs, sustainable development goals.: World Health Organization; 2016.
2. Cordeiro MF. Eyeing the brain. *Acta Neuropathologica*. 2016; 132:765-766.
3. Einarsdottir AB, Hardarson SH, Kristjansdottir JV, Bragason DT, Snaedal J, Stefansson E. Retinal oximetry imaging in Alzheimer's disease. *J Alzheimers Dis*. 2015; 49:79-83.
4. Feke GT, Hyman BT, Stern RA, Pasquale LR. Retinal blood flow in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement (Amst)*. 2015; 1:144-151.
5. Williams MA, McGowan AJ, Cardwell CR, Cheung CY, Craig D, Passmore P, Silvestri G, Maxwell AP, McKay GJ. Retinal microvascular network attenuation in Alzheimer's disease. *Alzheimers Dement (Amst)*. 2015; 1:229-235.
6. Moore D, Harris A, Wudunn D, Kheradiya N, Siesky B. Dysfunctional regulation of ocular blood flow: A risk factor for glaucoma? *Clin Ophthalmol*. 2008; 2:849-861.
7. Silverberg GD, Mayo M, Saul T, Rubenstein E, McGuire D. Alzheimer's disease, normal-pressure hydrocephalus, and senescent changes in CSF circulatory physiology: a hypothesis. *The Lancet Neurology*. 2003; 2:506-511.
8. Gabelt BAT, Kaufman PL. Changes in aqueous humor dynamics with age and glaucoma. *Progress in Retinal and Eye Research*. 2005; 24:612-637.
9. Sivak JM. The aging eye: common degenerative mechanisms between the Alzheimer's brain and retinal disease. *Invest Ophthalmol Vis Sci*. 2013; 54:871-880.
10. Ohno-Matsui K. Parallel findings in age-related macular degeneration and Alzheimer's disease. *Prog Retin Eye Res*. 2011; 30:217-238.
11. Johnson LV, Leitner WP, Rivest AJ, Staples MK, Radeke MJ, Anderson DH. The Alzheimer's A beta -peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2002; 99:11830-11835.
12. Reddy PH. Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease. *Brain Res*. 2011; 1415:136-148.
13. Almasieh M, Wilson AM, Morquette B, Cueva Vargas JL, Di Polo A. The molecular basis of retinal ganglion cell death in glaucoma. *Prog Retin Eye Res*. 2012; 31:152-181.
14. Soto I, Howell GR. The complex role of neuroinflammation in glaucoma. *Cold Spring Harb Perspect Med*. 2014; 4.
15. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhratsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT, Kummer MP. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015; 14:388-405.
16. Buschini E, Piras A, Nuzzi R, Vercelli A. Age related macular degeneration and drusen:

neuroinflammation in the retina. *Prog Neurobiol*. 2011; 95:14-25.
17. Thakkinstian A, Bowe S, McEvoy M, Smith W, Attia J. Association between apolipoprotein E polymorphisms and age-related macular degeneration: A HuGE review and meta-analysis. *Am J Epidemiol*. 2006; 164:813-822.
18. Liu C-C, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol*. 2013; 9:106-118.
19. Wallace DC, Singh G, Lott MT, Hodge JA, Schurr TG, Lezza AM, Elsas LJ, 2nd, Nikoskelainen EK. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science*. 1988; 242:1427-1430.
20. Carelli V, La Morgia C, Valentino ML, Barboni P, Ross-Cisneros FN, Sadun AA. Retinal ganglion cell neurodegeneration in mitochondrial inherited disorders. *Biochim Biophys Acta*. 2009; 1787:518-528.
21. Maresca A, la Morgia C, Caporali L, Valentino ML, Carelli V. The optic nerve: a "mito-window" on mitochondrial neurodegeneration. *Mol Cell Neurosci*. 2013; 55:62-76.
22. Yu-Wai-Man P, Griffiths PG, Gorman GS, Lourenco CM, Wright AF, Auer-Grumbach M, Toscano A, Musumeci O, Valentino ML, Caporali L, Lamperti C, Tallaksen CM, Duffey P, Miller J, Whittaker RG, Baker MR, Jackson MJ, Clarke MP, Dhillon B, Czermin B, Stewart JD, Hudson G, Reynier P, Bonneau D, Marques W, Jr., Lenaers G, McFarland R, Taylor RW, Turnbull DM, Votruba M, Zeviani M, Carelli V, Bindoff LA, Horvath R, Amati-Bonneau P, Chinnery PF. Multi-system neurological disease is common in patients with OPA1 mutations. *Brain*. 2010; 133:771-786.
23. Maresca A, la Morgia C, Caporali L, Valentino ML, Carelli V. The optic nerve: A “mito-window” on mitochondrial neurodegeneration. *Molecular and Cellular Neuroscience*. 2013; 55:62-76.
24. Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. *Prog Retin Eye Res*. 2004; 23:53-89.
25. Smigrodzki R, Parks J, Parker WD. High frequency of mitochondrial complex I mutations in Parkinson’s disease and aging. *Neurobiology of Aging*. 2004; 25:1273-1281.
26. Greenamyre JT, Sherer TB, Betarbet R, Panov AV. Complex I and Parkinson's disease. *IUBMB Life*. 2001; 52:135-141.
27. Fletcher EL, Jobling AI, Greferath U, Mills SA, Waugh M, Ho T, de Iongh RU, Phipps JA, Vessey KA. Studying Age-Related Macular Degeneration Using Animal Models. *Optometry and Vision Science*. 2014; 91:878-886.
28. Lin CS, Sharpley MS, Fan W, Waymire KG, Sadun AA, Carelli V, Ross-Cisneros FN, Baciu P, Sung E, McManus MJ, Pan BX, Gil DW, Macgregor GR, Wallace DC. Mouse mtDNA mutant model of Leber hereditary optic neuropathy. *Proc Natl Acad Sci U S A*. 2012; 109:20065-20070.
29. Zhang K, Hopkins JJ, Heier JS, Birch DG, Halperin LS, Albini TA, Brown DM, Jaffe GJ, Tao W, Williams GA. Ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for treatment of geographic atrophy in age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2011; 108:6241-6245.
30. Guo L, Salt TE, Luong V, Wood N, Cheung W, Maass A, Ferrari G, Russo-Marie F, Sillito AM, Cheetham ME, Moss SE, Fitzke FW, Cordeiro MF. Targeting amyloid-beta in glaucoma treatment. *Proc Natl Acad Sci U S A*. 2007; 104:13444-13449.
31. Ding JD, Johnson LV, Herrmann R, Farsiu S, Smith SG, Groelle M, Mace BE, Sullivan P, Jamison JA, Kelly U, Harrabi O, Bollini SS, Dilley J, Kobayashi D, Kuang B, Li W, Pons J,

Lin JC, Bowes Rickman C. Anti-amyloid therapy protects against retinal pigmented epithelium damage and vision loss in a model of age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2011; 108:E279-287.
32. Flight MH. Neurodegenerative disease: Avoiding bad complement in Alzheimer's disease. *Nat Rev Neurosci*. 2009; 10:623-623.
33. Ricklin D, Lambris JD. Complement-targeted therapeutics. *Nat Biotech*. 2007; 25:1265-1275.
34. Taskintuna I, Elsayed ME, Schatz P. Update on Clinical Trials in Dry Age-related Macular Degeneration. *Middle East African journal of ophthalmology*. 2016; 23:13-26.
35. Emerich DF, Orive G, Thanos C, Tornoe J, Wahlberg LU. Encapsulated cell therapy for neurodegenerative diseases: From promise to product. *Advanced Drug Delivery Reviews*. 2014; 67–68:131-141.
36. Josephy-Hernandez S, Jmaeff S, Pirvulescu I, Aboulkassim T, Saragovi HU. Neurotrophin receptor agonists and antagonists as therapeutic agents: An evolving paradigm. *Neurobiology of Disease*. 2017; 97, Part B:139-155.
37. Kolomeyer AM, Zarbin MA. Trophic factors in the pathogenesis and therapy for retinal degenerative diseases. *Survey of Ophthalmology*. 2014; 59:134-165.
38. Osborne NN. Recent clinical findings with memantine should not mean that the idea of neuroprotection in glaucoma is abandoned. *Acta Ophthalmologica*. 2009; 87:450-454.
39. Tweedie D, Sambamurti K, Greig NH. TNF-alpha inhibition as a treatment strategy for neurodegenerative disorders: new drug candidates and targets. *Curr Alzheimer Res*. 2007; 4:378-385.
40. McCoy MK, Tansey MG. TNF signaling inhibition in the CNS: implications for normal brain function and neurodegenerative disease. *J Neuroinflammation*. 2008; 5:45.
41. Cueva Vargas JL, Di Polo A. Neuroinflammation in glaucoma: soluble tumor necrosis factor alpha and the connection with excitotoxic damage. *Neural Regeneration Research*. 2016; 11:424-426.
42. Khalili H, Lee RW, Khaw PT, Brocchini S, Dick AD, Copland DA. An anti-TNF-α antibody mimetic to treat ocular inflammation. *Scientific reports*. 2016; 6:36905.
43. Kauper K, McGovern C, Sherman S, Heatherton P, Rapoza R, Stabila P, Dean B, Lee A, Borges S, Bouchard B, Tao W. Two-year intraocular delivery of ciliary neurotrophic factor by encapsulated cell technology implants in patients with chronic retinal degenerative diseases. *Invest Ophthalmol Vis Sci*. 2012; 53:7484-7491.
44. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011; 56:95-113.
45. Sarao V, Veritti D, Boscia F, Lanzetta P. Intravitreal Steroids for the Treatment of Retinal Diseases. *The Scientific World Journal*. 2014; 2014:14.
46. Feuer WJ, Schiffman JC, Davis JL, Porciatti V, Gonzalez P, Koilkonda RD, Yuan H, Lalwani A, Lam BL, Guy J. Gene Therapy for Leber Hereditary Optic Neuropathy: Initial Results. *Ophthalmology*. 2016; 123:558-570.
47. Lopes VS, Williams DS. Gene Therapy for the Retinal Degeneration of Usher Syndrome Caused by Mutations in MYO7A. *Cold Spring Harb Perspect Med*. 2015; 5.
48. Bainbridge JWB, Mehat MS, Sundaram V, Robbie SJ, Barker SE, Ripamonti C, Georgiadis A, Mowat FM, Beattie SG, Gardner PJ, Feathers KL, Luong VA, Yzer S, Balaggan K, Viswanathan A, de Ravel TJL, Casteels I, Holder GE, Tyler N, Fitzke FW, Weleber RG, Nardini M, Moore AT, Thompson DA, Petersen-Jones SM, Michaelides M,

van den Born LI, Stockman A, Smith AJ, Rubin G, Ali RR. Long-Term Effect of Gene Therapy on Leber's Congenital Amaurosis. *New England Journal of Medicine*. 2015; 372:1887-1897.

49. Mead B, Berry M, Logan A, Scott RAH, Leadbeater W, Scheven BA. Stem cell treatment of degenerative eye disease. *Stem Cell Research*. 2015; 14:243-257.
50. Yu-Wai-Man P, Votruba M, Burté F, La Morgia C, Barboni P, Carelli V. A neurodegenerative perspective on mitochondrial optic neuropathies. *Acta Neuropathologica*. 2016; 132:789-806.
51. Hart NJ, Koronyo Y, Black KL, Koronyo-Hamaoui M. Ocular indicators of Alzheimer's: exploring disease in the retina. *Acta Neuropathologica*. 2016; 132:767-787.
52. Normando EM, Davis BM, De Groef L, Nizari S, Turner LA, Ravindran N, Pahlitzsch M, Brenton J, Malaguarnera G, Guo L, Somavarapu S, Cordeiro MF. The retina as an early biomarker of neurodegeneration in a rotenone-induced model of Parkinson's disease: evidence for a neuroprotective effect of rosiglitazone in the eye and brain. *Acta Neuropathologica Communications*. 2016; 4:1-15.

Figure 1

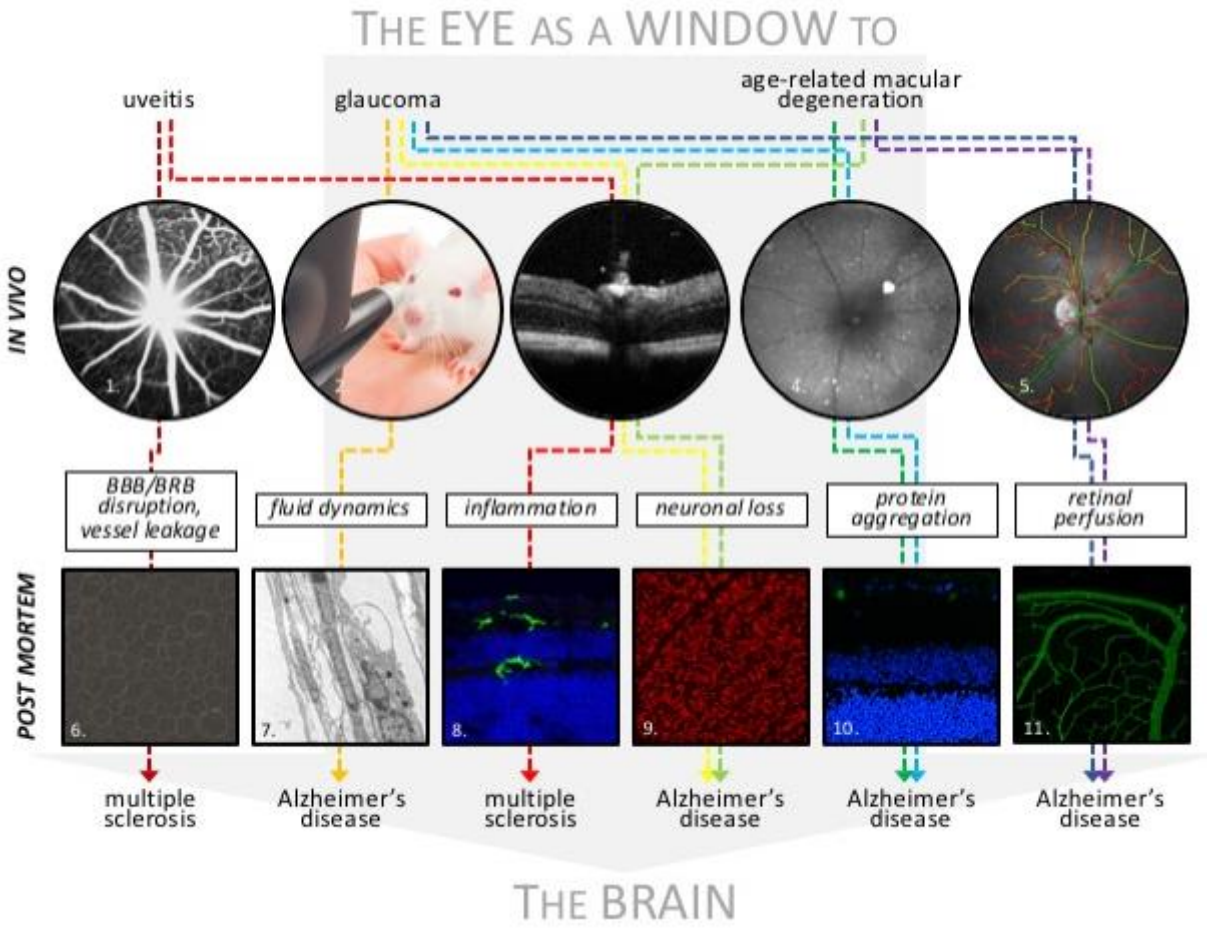

Figure 1. Compilation of examples to illustrate the concept 'the eye as a window to the brain'. Typical ocular diseases, such as uveitis, glaucoma and AMD, have in common several pathological mechanisms with CNS diseases, e.g. multiple sclerosis and AD. Both *in vivo* and *post mortem* examinations of the eye can therefore be used to study the disease mechanisms underlying these pathologies in the eye ànd brain. 1: fluorescein angiography; 2: intraocular pressure measurement; 3: OCT scan; 4: cSLO imaging of curcumin-labeled protein aggregates; 5: retinal oximetry; 6: ZO-1 tight junction immunostaining on wholemounted retina; 7: transmission electron microscopy image of trabecular meshwork; 8: Iba-1 microglia immunostaining on retinal section; 9: Brn3a retinal ganglion cell immunostaining on wholemounted retina; 10: β-amyloid immunostaining on retinal section; 11. Concanavalin A vessel labelling on wholemounted retina.