

The role of optical coherence tomography and infrared oculography in assessing the visual pathway and central nervous system in Multiple Sclerosis

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Abstract

In this review a current overview is provided of how optical coherence tomography (OCT) and infrared oculography (IO) can aid in assessing the visual system and central nervous system (CNS) in patients suffering from multiple sclerosis (MS). Both afferent and efferent problems of the visual system are common in MS and visual impairment can have a tremendous impact on daily functioning. Both OCT and IO can detect and quantify visual disorders with high accuracy, but also serve as quantitative markers for inflammation, neurodegeneration and network changes in patients with MS. The assessment of the efferent and afferent visual pathways is relevant for monitoring and predicting the disease course, but is also potentially valuable as an outcome measure in therapeutic trials.

INTRODUCTION

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) affecting more than 2 million people worldwide and is one of the most common neurological disease in young people.(1) Patients experience a wide range of symptoms including muscle weakness, sensory disturbances, problems with coordination, fatigue and cognitive problems.(2) It is now understood that MS is characterized by inflammatory as well as degenerative components.(3)

Inflammation is the main contributing factor in the early stage of the disease. This relapsing remitting disease course (RRMS) is characterized by a first episode of focal neurological dysfunction, which is referred to as a clinically isolated syndrome (CIS), followed by recurrent episodes of neurological worsening with a various degree of recovery and residual damage(4). Eventually, most of these patients will enter the secondary progressive phase (SPMS) characterized by slowly progressive and permanent disability. A small proportion of patients have a primary progressive disease course (PPMS). This is characterized by a progressive course from onset without having acute relapses. In SPMS and PPMS, neurodegeneration is thought to play the main role.(5, 6) The course of the disease, even among patients with the same type, is highly variable and still difficult to predict.(1) Magnetic resonance imaging (MRI) is the cornerstone in the diagnosis of MS, providing evidence for dissemination in space and dissemination in time, but has limited ability to predict disease outcome.(7-9) Likewise, the often reported Expanded Disability Status Scale (EDSS) has its limitations. The EDSS score measures neurological disability in MS patients, but is heavily biased towards the pyramidal system. Other common problems such as cognitive decline, fatigue but also visual functioning are relatively undervalued. Thus, there is a need for a sensitive and accurate biomarker to monitor disease activity and progression for patients with MS.

One sophisticated system overcoming these issues is the visual pathway. The visual pathway is often affected in MS (2) and visual symptoms can either be due to problems in the afferent

visual system leading to loss of vision or due to problems with the efferent visual system leading to diplopia or focusing problems for example.

Being easily assessable, the visual system forms a convenient place to study the effects of MS, especially because nowadays non-invasive and accurate techniques for assessing both the afferent (optical coherence tomography (OCT)) and efferent system (infrared oculography (IO)), are available. Studying the visual system not only allows for assessment of damage caused by MS directly to the visual system but it also gives us insights in what is happening in the central nervous system (CNS) on a more global scale (see figure 1), especially for the neurodegenerative part of the disease. The aim of this review is to provide a current overview of how OCT and IO can aid in assessing the visual system and the CNS in MS.

VISUAL SYMPTOMS IN MS

Up to 80% of MS patients experience visual disturbances during the course of the disease, including both afferent and efferent disorders.(10-13) It is estimated that about one third of patients suffer from persistent visual complaints, unrelated to a recent relapse. Of the patients with persistent visual complaints, the majority presents with combined afferent and efferent visual pathway deficits. These deficits often lead to visual disabilities in daily life and reduced vision-related quality of life.(13, 14) MS patients value visual functioning as important as lower limb function when rating different dimensions of physical bodily functions, especially in late MS.(15) The impact of visual complaints on daily functioning and quality of life is in sharp contrast with the number of outcome measures assessing visual function in clinical care and trials. In the next section afferent and efferent visual pathway disorders in MS are discussed and the aid of modern techniques in understanding and monitoring these deficits.

Identification of afferent visual pathway disorders

The optic nerve is frequently involved in MS, most commonly in the form of optic neuritis.(2) Optic neuritis is characterized by inflammation of the optic nerve(16) and is when it is caused by MS, it is typically referred to as MS associated optic neuritis (MSON). MSON is the presenting symptom in about 20% of MS patients and approximately 50-80% of MS patients will experience one or more episodes of MSON during the course of their disease.(17) It is characterized by loss of vision, dyschromatopsia and pain on eye movements that gradually worsens over the course of a few days to weeks before it (partially) recovers.(2) The diagnosis is based on clinical observations but can be supported by ancillary tests like visual evoked potentials. Making an early diagnosis of MSON can be challenging, but is important for treatment options.(18) Retinal OCT will play an important role in the assessment of MSON as it has proven its use in not only the diagnosis, but also prognosis of MSON.(18)

Retinal OCT is a non-invasive imaging technique that uses near infrared light to generate high resolution cross-sectional or 3D images of the retina.(19, 20) Current spectral domain OCT devices have an axial resolution of 3-7 μm making it possible to distinguish each individual retinal layer.(21-23) Due to the high accuracy (1.14 – 2.39 μm) it is possible to detect small changes in thickness over time.(24) In MS, two layers are of particular interest: the peripapillary retinal nerve fiber layer (pRNFL) which contains of unmyelinated axons that will eventually form the optic nerve, and the combined macular ganglion cell - inner plexiform layer (mGCIPL) in which the retinal ganglion cells reside.(25) The pRNFL thickness is measured by performing a circular scan around the optic nerve head. The thickness of the mGCIPL is measured by performing a macular volume scan centered on the fovea. (Figure 2)

Gabilondo et al. have described the dynamics of retinal injury in acute optic neuritis. At the onset of an episode of acute MSON there is thickening of the pRNFL (caused by edema) but not the mGCIPL, followed by progressive atrophy of both layers. The rate of atrophy is highest in the first couple of months and decreases after approximately 3 months. This study also

showed that the amount of atrophy in the first month was indicative of the degree of recovery (at six months).(26)

Thinning of the pRNFL and mGCIPL is caused by retrograde degeneration of axons and neurons in the retina and seems to stop at the inner nuclear layer (INL).(27) The eventual amount of atrophy in eyes following an episode of MSON is on average 20.1 μm for the pRNFL and 16.4 μm for the mGCIPL, compared to healthy controls.(28) Nonetheless, this amount varies between patients and depends on several factors (like severity of the episode), which means there is no absolute value of inner retinal layer thickness which indicates a previously experienced episode of MSON. The inter-eye asymmetry overcomes this problem because the inner retinal layers in the two eyes of patients who have never experienced MSON are more or less equal in thickness. Finding a difference in pRNFL or mGCIPL thickness between the two eyes of an MS patient is thus suggestive of a previous episode of MS. A recent study showed that an inter-eye percentage difference (IEPD) as low as 5-6% had a high diagnostic accuracy for distinguishing healthy eyes from uni- and bilateral MSON eyes.(29) Likewise, Nolan et al. demonstrated that an inter-eye difference of 5-6 μm in pRNFL thickness would be a robust threshold for identifying unilateral MSON, which is comparable to the 5-6% IEPD by Coric et al.(30) In the recently proposed revisions of the diagnostic criteria for MS it is advocated to include the optic nerve as a fifth anatomical location (next to periventricular, juxta-cortical, infratentorial and spinal) to fulfil criteria for dissemination in space.(31) In this case the IEPD would be especially of use for the establishment of optic nerve involvement in patients experiencing their first clinical episode (CIS patients) that is not MSON and who do not yet meet criteria for dissemination in space, with the goal of establishing an earlier diagnosis of MS.

Identification of efferent visual pathway disorders

Disorders of the efferent visual pathway are also common in MS. Based on clinical examination, the prevalence is estimated at 36-84%.^(10, 14, 32) Many reviews described the extensive range of abnormalities that have been found in MS patients.⁽³³⁻³⁶⁾ Two common groups of eye movement disorders are ocular misalignments (including internuclear ophthalmoplegia) and fixational instability (nystagmus and saccadic intrusions). Eye movement disorders can result in complaints as diplopia, blurred vision, oscillopsia or difficulties with focusing.

Internuclear ophthalmoplegia (INO) is caused by a demyelinating lesion in the medial longitudinal fasciculus (MLF) and results in a delay in velocity of the adducting eye during horizontal saccades. It can be accompanied by limitation of adduction, overshoot of the abducting eye and abduction nystagmus shortly after the saccade. Prevalence is estimated between 24% and 55% (10, 37-39), but most studies encompass small sample sizes and/or are based on outdated oculography techniques or clinical examinations. It is known that clinically the diagnosis can be easily missed, especially in subtle cases.⁽⁴⁰⁾ It is also well known that in MS patients with INO, both horizontal and vertical vestibulo-ocular reflexes are impaired, due to disruption of the involved pathways through the MLF. This can result in gaze instability and oscillopsia during body or head movements.⁽⁴¹⁾ Patients may find it difficult to read a road sign whilst walking, but do well when standing still.

Pendular nystagmus is regarded as the most distressing oculomotor finding in MS, with continuous complaints of oscillopsia and blurred vision, interfering in daily activities. The prevalence in MS is unknown and the pathophysiology in MS not completely understood.⁽⁴²⁻⁴⁴⁾ Hypotheses regarding the pathophysiology include abnormal optic feedback due to demyelination of the optic nerve and instability of the neural integrator.⁽⁴⁵⁾ Treatment with gabapentin or memantine can reduce the amplitude and frequency of the oscillation and improve visual acuity.⁽⁴⁶⁾

Systematic examination of eye movements is essential in the evaluation of MS patients. Besides the possible impact of eye movements disorders on visual functioning in daily life, it can be useful in making the diagnosis of MS, monitoring the progression of disease and studying fatigue and medication effects.(11, 33, 47-49) Standard clinical evaluations of MS patients often lack systematic eye movement testing. With the development of the King-Devick Test, a brief bedside screening tool of efferent visual dysfunction is provided.(50) This rapid number-naming test depends on correct execution of saccades, but also involves visual acuity, reading, language and attention. For more detailed discrimination and quantification of (subtle) eye movement disturbances, more sophisticated methods are needed. With high-frequency IO, a non-invasive and accurate technique is available for measurement of eye movements. **It uses the center of the pupil and the corneal reflection (created by infrared light) to determine the gaze direction.** Different eye movement abnormalities can be visualized easily (see figure 3 and 4) and with automated algorithms different parameters can quantify these abnormalities. The reproducibility of parameters in standardized tasks is high. (Nij Bijvank, JA et al. A validated multicenter protocol for quantification of saccadic eye movements: DEMoNS. under review). With IO, prevalence of eye movement disorders as INO can be established more accurately and can be linked to visual complaints and visual functioning. By this it can aid in differentiating unexplained visual complaints in MS patients. Assessment of saccadic eye movements is also shown to be promising for objective testing of fatigue severity.(48, 51)

THE VISUAL PATHWAY AS A REFLECTION OF CNS PROCESSES

To understand the interplay between different disease mechanisms which contribute to (irreversible) disability in MS, focus has shifted from investigating MS as a white matter disease, to a broader perspective in which grey matter pathology and network dysfunction receiving more attention. Brain atrophy, and especially thalamic atrophy, is strongly related to physical disability and cognitive decline, even in early phases of disease.(52-55) Furthermore,

fMRI and MEG studies have shown that changes in functional connectivity of the brain, which are often interpreted as compensatory mechanisms for structural deficits (56, 57), are shown to play a crucial role in early deterioration in clinical and cognitive status.(58-60)

The increasing focus of this type of MS research on cognitive decline besides physical disability is essential. It is difficult to localize lesions or disease processes which cause cognitive dysfunction, due to the complex nature of cognitive functioning, which require communication between a broad range of brain regions.(61) Cognitive dysfunction is however increasingly recognized as an important aspect of MS, although it is not included in standard clinical evaluation. The prevalence is estimated at 40-70% and it can be apparent at early stages of disease.(60, 62-64) It has a great impact on daily functioning and quality of life of MS patients. (53, 65, 66)

The ultimate goal is to study the brain in total as a functional and structural network . However, the exact interplay between different pathogenic mechanisms, as atrophy and disruption of cortical networks, is unknown. There is need for non-invasive methods to investigate these interactions that contribute to (irreversible) disability, especially cognitive dysfunction. In the following section the (expected) value of measuring retinal layers by OCT and eye movements by IO in reflecting CNS processes in MS is discussed.

Optical coherence tomography

In MS patients who experienced MSON, OCT shows substantial atrophy of the inner retinal layers.(28) However, MS patients who have not experienced an episode of MSON (MSNON) also show atrophy of the mGCIPL and pRNFL, albeit to a lesser degree. The amount of atrophy varies but is on average 7.4 μm for the pRNFL and 6.3 μm for the mGCIPL, compared to healthy controls.(28) It is believed that in MSNON patients, the atrophy is a reflection of the neuro-axonal damage in the CNS. Several hypotheses have been put forward as possible

explanations for the retinal atrophy seen in MS/NON patients. Retrograde, trans-synaptic degeneration is the most widely accepted and has been shown to occur within the visual system.(67-69) The association between atrophy of the pRNFL and mGCIPL and global measures of neurodegeneration would suggest that this mechanism extends beyond the visual system. Another explanation is the presence of a global process of neurodegeneration affecting the whole CNS including the optic nerve and retina.(67) A third possible explanation is that of local microinflammatory processes occurring within the optic nerve.(70)

Independent of the causal process, it has been shown that atrophy of the two inner retinal layers is associated with brain volume. Both cross-sectional as well as longitudinal studies have found associations between thinning of the pRNFL and mGCIPL with gray and white matter atrophy.(67, 71-73)

As stated earlier, the amount of atrophy is dependent on several factors. For example, both the pRNFL as well as mGCIPL thickness decline with age, even in healthy people. However, MS patients show an accelerated rate of atrophy compared to healthy controls.(74-76) Interestingly, although patients show more retinal thinning with longer disease duration, multiple studies have shown that the *rate* of retinal thinning (i.e. the amount of μm per year) is highest early in the MS disease course.(70, 74)

The amount of retinal atrophy differs between different types of MS. Patients with SPMS show more atrophy than RRMS, which is expected since SPMS is characterized by a large amount of neuroaxonal degeneration. On the other hand, PPMS patients show the least amount of atrophy of the retina which is probably explained by the fact that the anterior visual pathway is less often affected in PPMS. In addition, PPMS patients tend to have more spinal cord atrophy/lesions and presumably, spinal cord damage is reflected less in the retinal layers. (77, 78) Cross-sectional studies have linked atrophy of the inner retinal layers to increased physical disability, as measured by the EDSS score.(79, 80) Likewise, there is an association between atrophy of the pRNFL and mGCIPL and cognitive impairment across multiple cognitive

domains.(81, 82) Essentially, the more atrophy there is, the higher the risk of disability or cognitive impairment.

A major challenge when applying OCT as a surrogate marker for neurodegeneration is the confounding effect of MSON. The extensive amount of atrophy caused by MSON masks most cross-sectional associations with clinical or MRI metrics which would mean OCT would be of no use in patients who have experienced this in the past. Fortunately, since MSON eyes seem to show the same amount of atrophy over time as MSNON eyes this problem can be bypassed by looking at changes over time.(76, 83)

A recent study by Pisa et al. showed that pRNFL thinning was correlated with disability progression. They also found that patient with no evidence of disease activity (NEDA, defined as a combination of absence of clinical relapses, MRI activity and disability progression) had less pRNFL atrophy over time. Disability progression was the main contributing factor to pRNFL loss. The study also showed that greater pRNFL loss over time was associated with a higher likelihood of not being NEDA.(84) An earlier study by Ratchford et al. showed that these characteristics of disease activity, including disability progression, are also associated with faster atrophy rates of mGCIPL atrophy.(70)

The first study to investigate the predictive value of OCT is the multicentre study by Martinez-Lapiscina et al. and this study showed that patients with a baseline pRNFL thickness of 88 μm or below (lowest tertile in the study cohort) had almost twice (hazard ratio of 1.98) the risk of disability worsening in the five years of follow-up.(85)

Infrared oculography

Eye movements, especially saccades, show exceptional high velocities, short latencies and ballistic behavior, compared to other movements. Therefore, eye movements rely on very precise integration of signals which initiate and control the movement. An extensive cortical network is involved in control of eye movements and even small disruptions in this network are

expected to result in changes of eye movement parameters(49), which can be precisely measured with IO. In various neurological and psychiatric disorders, such as Alzheimer's disease and other kinds of dementia, Parkinson's disease and autism, changes in eye movements related to functioning of the brain have been found.(86-89)

In MS, a few studies have shown an association between eye movement parameters and cognitive functioning. In two studies the latency and proportion of errors in an anti-saccade task and a memory-guided tasks were increased in MS patients compared to controls, and correlations with cognitive tests as the paced auditory serial addition test (PASAT) and the symbol digit modalities test (SDMT). Latency and number of errors of all tasks were linearly related to disease duration and clinical disability and alteration were already apparent in CIS patients.(90, 91) Another study showed a relation between peak-velocity, latency and amplitude of pro-saccades and (general) cognitive impairment in MS patients. (92) To date, there are no studies investigating the relationship between eye movements and brain networks in MS patient, in order to better understand these correlations.

With the current insights in the mechanisms of eye movement control, investigation of precise eye movement measures represents a novel but promising strategy to investigate the integrity of cognitive processing networks in MS. Further exploration and confirmation of the robustness of these measures is needed, by investigating the discriminatory value for individual patients and relating these measures to functional and structural imaging of the brain.

DISCUSSION

OCT and IO have developed into reliable and accurate non-invasive methods for assessing the visual system. Visual disorders such as MSON and INO can readily and precisely be captured using these techniques. OCT and IO are very valuable in the assessment of patients suspected of, or suffering from these conditions.(18, 39, 93). Furthermore, both techniques are promising

tools for assessing the structure-function relationship in disease processes. The exact place of these techniques in clinical care for monitoring the disease and providing prognostic and diagnostic information, has yet to be established. With OCT we are able to monitor disease progression. However, the ultimate goal, *predicting* disease progression using OCT in an early stage when patients experience no or little disability, is still challenging. For this purpose, new research should focus on the longitudinal assessment of structural and functional outcome measures of the visual pathway and direct relationships with clinical parameters of disability and patient-reported outcome measures such as quality of life.

As newer therapies become increasingly available, even for progressive MS types, it is important to have biomarkers with prognostic value regarding the disease course. This is because more effective therapies tend to have more (severe) side-effects and personalized therapy is of the essence in maximizing the therapeutic effect with acceptable side-effects. (94) Conventional MRI techniques are not sufficiently capable of predicting disease outcome. Although OCT and IO will never replace MRI, they could complement it in assessing a patients 'neurodegenerative' status which may help to select the most suitable treatment on an individual level.

A recent trial has confirmed the use of IO in testing medication effects.(95) In this double-blind study, the positive effect of fampridine on horizontal saccades in INO patients was demonstrated. This suggest that IO is useful and valid for testing the effect of potential remyelinating therapies in future treatment trials. As OCT enables an accurate assessment of retinal layer thickness, it is a valuable outcome marker for clinical trials evaluating new therapies in patients with acute MSON. In addition, it has been suggested as a secondary outcome measure in several clinical trials investigating the efficacy of neuroprotective drugs in progressive MS patients.

A new and exciting application of OCT is the investigation of the inner nuclear layer (INL) as a potential marker for inflammatory activity in MS. In a recent study Knier et al., showed that

a reduction in INL was associated with the absence of inflammatory disease activity.(96) Currently, a large multicenter study is taking place investigating the relationship between INL volume changes and inflammatory disease activity.

Techniques and software are evolving quickly and more attention is given to standardization of measurement and analysis, and quality control of the data. Longitudinal data is already available and more large scale studies are expected in the near future. Therefore, standardized protocols, quality control criteria and reporting guidelines are important to ensure consistency and quality of the data.(97, 98) (Nij Bijvank, JA et al. A validated multicenter protocol for quantification of saccadic eye movements: DEMoNS. Unpublished)

In conclusion, OCT and IO are two convenient, non-invasive methods which allow for assessment of the visual pathway in MS and thereby provide information not only on the state of the afferent and efferent visual pathways but also allows for insight in the neurodegenerative status on a global CNS scale. Currently, the clinical applicability of both methods is evolving quickly and further understanding of changes in the afferent and efferent visual pathway will be valuable in monitoring disease activity and progression and thereby selecting the right therapy.

Figures

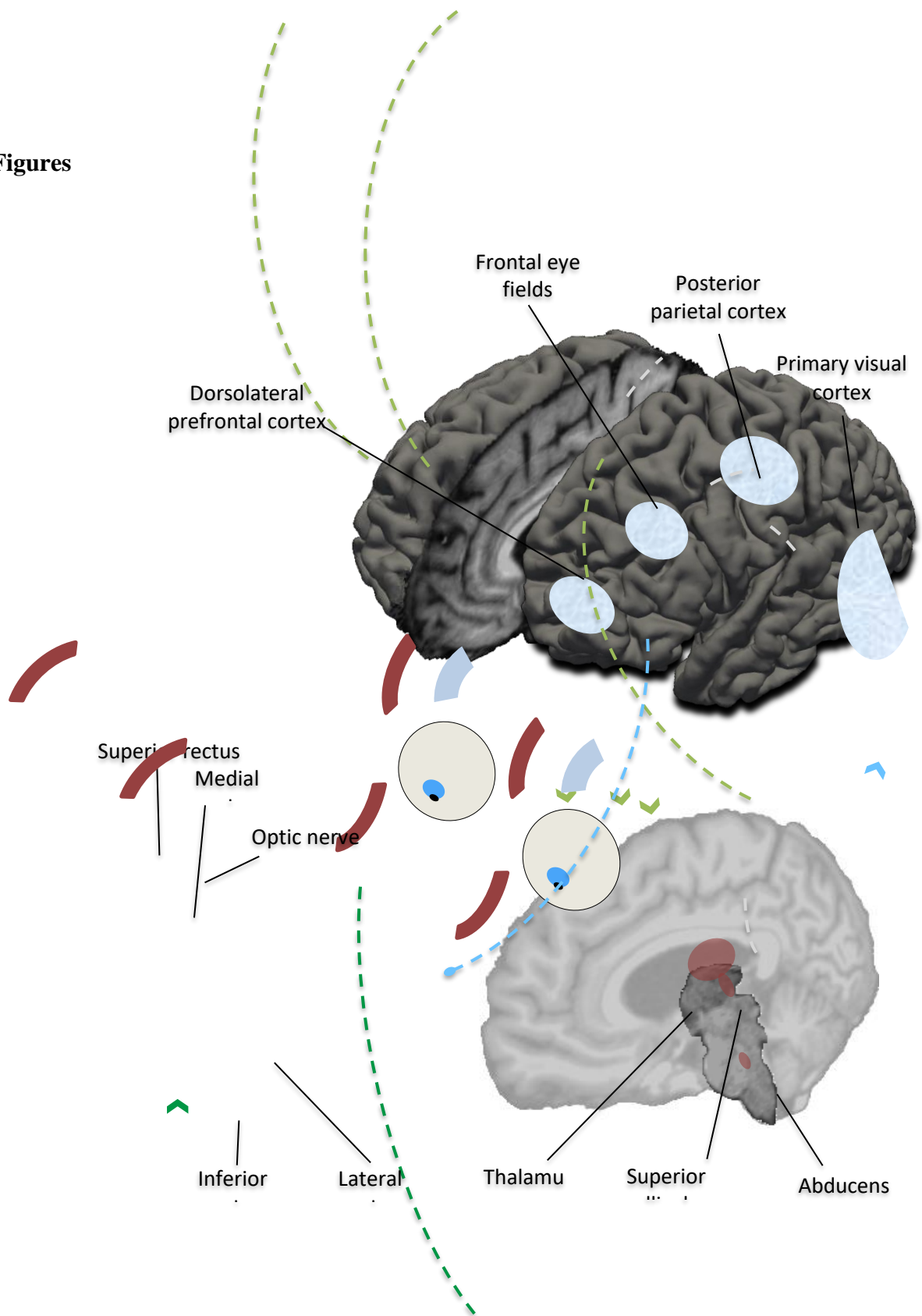


Figure 1. Schematic overview of important structures and pathways in the visual system. The afferent visual pathways (blue lines) originates in the retina, where bipolar cells connect with the retinal ganglion cells (RGCs), which project to the lateral geniculate nucleus (LGN) in the thalamus (dark blue lines). From the LGN the signal continues through the optic radiations (light blue lines) towards the primary visual cortex. The efferent visual pathway (green lines) originates in a broad network of cerebral regions, extending from parietal and (pre)frontal areas, which connect through the thalamus to the superior colliculus (light green lines). Through connections with the three oculomotor nuclei (oculomotor, trochlear (both not shown) and abducens nucleus), signal are sent to cranial nerves (III, IV and VI) innervating the extraocular muscles (dark green line). The cerebellum (not shown) is also a key component in the efferent visual pathway, with connections to areas in both the brainstem and the prefrontal cortex, and is involved in fine motor and cognitive control of eye

Figure 2: optic nerve head scan

Horizontal eye position (degrees)

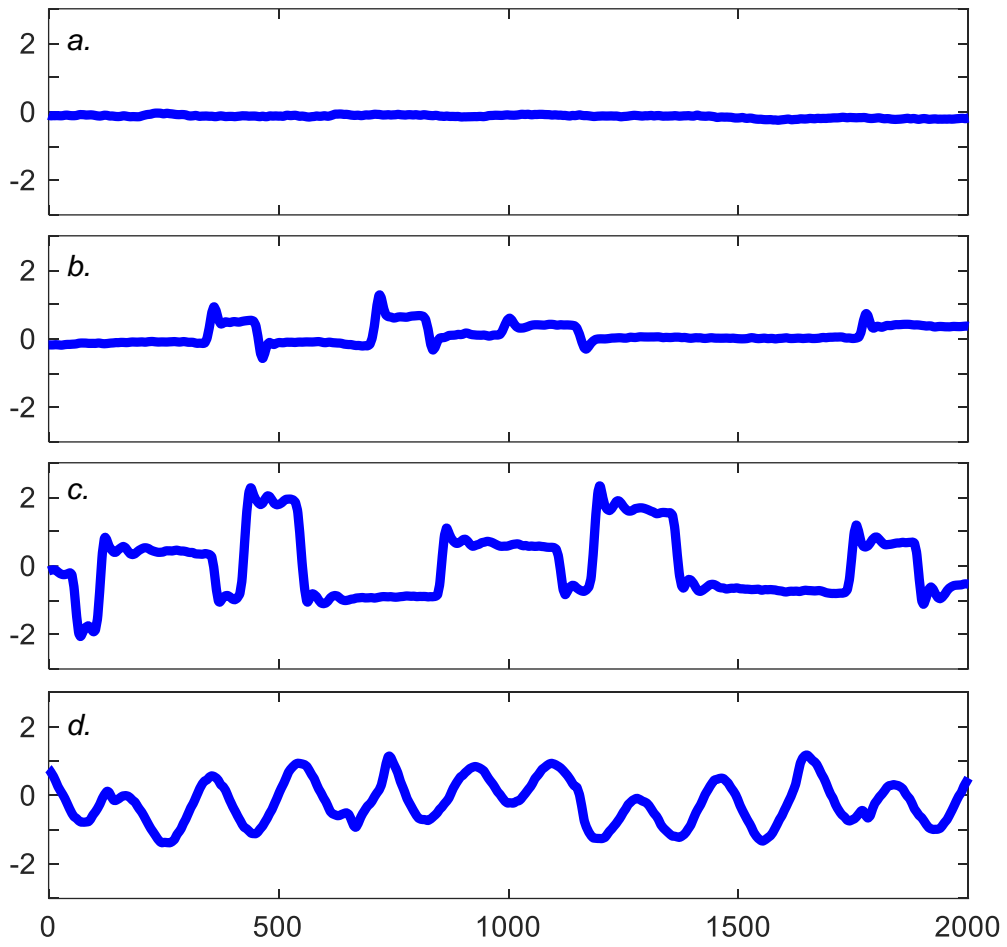


Figure 3. Recordings with infrared oculography of the horizontal eye position of the right eye during a fixation task. a. Stable fixation of a healthy control. b. MS patient with small square wave jerks. c. MS patient with macro square wave jerks. d. MS patient with pendular nystagmus

Horizontal eye position (degrees)

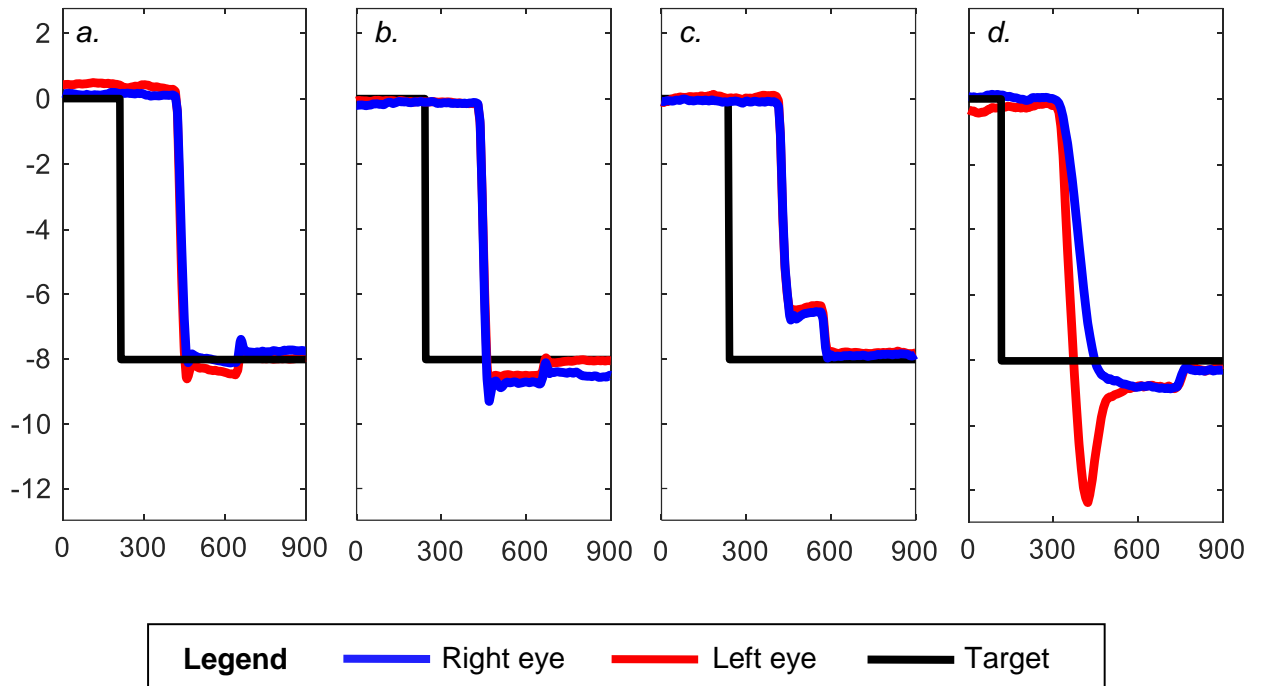


Figure 4. Recordings with infrared oculography of horizontal eye position of the left and right eye during a pro-saccadic task. a. Leftward saccade of a healthy control. b. Slightly hypermetric leftward saccade (overshooting the target) of a MS patient. c. Hypometric leftward saccade (undershooting the target) of a MS patient. d. Internuclear ophthalmoplegia during a leftward saccade of a MS patient. The velocity of the right eye is reduced and the left eye shows a dynamic overshoot of the target.

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