Highlights

Epidemiology

- Each year, more than 1,800 people are diagnosed with MS in the Netherlands, making up a total of around 16,000 Dutch MS patients.
- Typically young females are affected, but males have a worse prognosis.
- MS has a huge impact on daily life and leads to high societal costs.

Clinical symptoms, diagnosis and treatment

- Whereas the inflammatory component is more prominent in RRMS, the neurodegenerative component is more prominent in progressive MS.
- MS is diagnosed based on clinical symptoms and signs of inflammation in the central nervous system that can be visualized using MRI.
- There are multiple treatment options available for patients with RRMS suppressing the inflammatory component of the disease, but no treatment options for progressive MS that limit the neurodegenerative component.

Role of MRI

- MRI has had a huge impact on the entire concept of MS.
- Traditionally, MS was seen as a focal inflammatory white matter disease.
- In the past years, neurodegeneration (especially gray matter loss) has been recognized as the key predictor of clinical disability.
Chapter 1

General introduction

Partly based on:

MRI in the diagnosis and monitoring of multiple sclerosis: an update
Mike P Wattjes, Martijn D Steenwijk, Martin Stangel
Multiple sclerosis: a general introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the brain and spinal cord (i.e., the central nervous system (CNS)). For years, the development of focal inflammatory demyelinating lesions in the white matter (WM) was considered as the most important pathological feature of MS (1). These lesions were thought to cause the wide range of neurological symptoms that patients with MS experience (2). Nowadays, it is known that the disease is much more widespread: amongst others, MS has a strong neurodegenerative component that severely affects the gray matter (GM) (1,3). In contrast to what was previously assumed, recent studies have shown that not the inflammatory white matter lesion load, but especially neurodegeneration is predictive of clinical impairment (4). The exact definition of neurodegeneration is the topic of an ongoing debate: in this thesis we defined neurodegeneration as loss of gray matter (atrophy) that is visible on magnetic resonance (MR) images of patients with MS. Although a curative treatment for MS does not exist, multiple treatment options that target the inflammatory component of the disease have become available in the past few years (5–11). Given the recent insights, development of new treatment strategies that specifically target the neurodegenerative component is necessary. This first requires a better knowledge of the mechanisms that drive gray matter atrophy in MS, which is one of the aims of this thesis.

Epidemiology

In the Netherlands, approximately 1,800 new patients are diagnosed with MS each year (12), while the total number of MS patients is estimated at around 16,000. A recent study longitudinally comparing incidence rates of MS in the Netherlands showed a significantly increased incidence rate in the past decade, indicating that MS is diagnosed more often than previously (13). Worldwide, a similar trend is seen: the estimated number of MS patients increased from 2.1 million in 2008 to 2.3 million in 2013 (14). Although MS can be found everywhere in the world, its prevalence shows great regional variation, being the highest in North America and Europe (140 and 108 per 100,000 respectively) and lowest in Sub-Saharan Africa and East Asia (2.1 and 2.2 per 100,000 respectively).

Usually diagnosed around the age of 30, MS is one of the most common neurological disorders in young adults (14). Although the disease affects women approximately twice as frequently as men, studies have reported that women do have a more favorable prognosis (15). In the Netherlands, it is estimated that the total amount of societal costs of an individual MS patient range between €9,000 and €79,000 per year depending on the level of disability (16). Given these very high annual costs, the typically young age of onset, and the (common) inability
of MS patients to participate in society (e.g., social isolation, inability to work), MS is a very expensive disease with a large impact on daily life and society. This illustrates the urgent need for more effective and efficient treatment options. Unfortunately, the exact cause of MS is still not known; however, it is thought that several genetic and environmental risk factors might play a role (2).

**Multiple sclerosis pathology**

For years, focal inflammatory demyelinating lesions (also known as “sclerotic plaques”) in the white matter of the brain were considered as the most important pathological hallmark of MS (2,17). These plaques represent the end stage of a process that involves an autoimmune response towards the myelin that surrounds the axons, which is histopathologically characterized by leakage of the blood-brain barrier, influx of immune cells, inflammation of the tissue, and – as a result – focal demyelination. The scars that remain in the tissue can be visualized using magnetic resonance imaging (MRI).

Although MS was primarily considered to be located in the white matter of the brain, demyelination of the cerebral cortex was already observed in the last decade of the 19th century (18). Due to predominant attention on the white matter abnormalities and difficulties involving the visualization of cortical abnormalities with conventional histochemical staining procedures, this topic was disregarded for years (19). The role of gray matter abnormalities was reconsidered in the first decade of the 21th century, when histochemical staining procedures and MRI acquisition techniques improved (20). It was only then, that it became clear that the histopathological substrate of gray matter lesions differs considerably from its white matter counterpart (21), and that gray matter demyelination can be very extensive, affecting up to 70% of the cortex in severe cases (22).

Only in the last decade, tissue loss in the form of brain atrophy became apparent as an important pathological feature in MS (21,23). Despite being strongly related to physical impairment and cognitive decline, the substrate of brain atrophy in MS is largely unknown. Recently, a combined histopathology and MRI study has made a first attempt to unravel the pathological substrate of cortical gray matter atrophy and found that MRI-measured tissue loss can be particularly explained by reduced numbers neurons and axons (24). The question as to which mechanism drives the tissue loss, is topic of an ongoing debate (20).

**Clinical symptoms**

Clinically, MS is associated with a wide range of neurological symptoms. For instance, patients may experience numbness, tingling, weakness, vision loss, bladder dysfunction,
gait impairment, problems with coordination, imbalance, spasms, fatigue and cognitive impairment (2,25). The most common first symptom of MS is unilateral loss of vision, mostly due to optic neuritis. In the past years, much attention has been paid to the cognitive deficits that 40–70% of the patients with MS experience (26). Cognitive impairment is reported early in the disease, and affects various cognitive domains, including attention, information processing speed, executive functioning, and memory. Processing speed, visual learning and long-term memory seem to be most commonly affected.

Clinically, different MS disease courses can be discriminated. These were standardized by Lublin et al. in 1996 (28), and revised in 2014 (29). Up to 85% of the MS patients initially experience discrete episodes (relapses or ‘schubs’) of neurological dysfunction (14). This disease course is called ‘relapsing-remitting’ (RRMS) and is characterized by an (almost) complete clinical recovery after the symptoms have disappeared spontaneously or with treatment within days or weeks (see Figure 1). It is thought that in these patients especially the inflammatory disease component is important. In the initial phase of the disease, patients may present with discrete neurological episodes but not fulfill the complete MS diagnostic criteria (see section ‘Diagnosis’ below). This disease course is referred to as clinically isolated syndrome (CIS) and also includes those patients with clinical symptoms but without MRI-visible pathology. Although studies vary widely in the rate of CIS patients that develop MS, it is estimated that 60 to 80% of the CIS patients that present with brain lesions suggestive of MS will convert to MS. Vice-versa, patients may also present with brain lesions suggestive of MS, but without clinical symptoms: this is called radiologically isolated syndrome (RIS). In contrast to CIS, RIS is not considered to be part of the MS spectrum, as patients do not experience clinical symptoms. About 80% of the RRMS patients will, at some point in their disease, convert to the ‘secondary-progressive’ (SPMS) disease course. In this phase, the disease steadily progresses without the presence of clear distinct relapses. It is thought that in SPMS the inflammatory disease component becomes less important while the neurodegenerative component gains importance. Therefore, unfortunately, SPMS is often marked by a more rapid accumulation of

“Neurodegeneration is the loss of gray matter (atrophy) that is visible on magnetic resonance images of patients with MS.”
The last group of MS patients typically faces progressive disease course right from the onset of their disease. This disease course is referred to as ‘primary-progressive’ (PPMS). Compared to RRMS, the age of onset is approximately 10 years older in PPMS, and in addition, a gender predominance is absent (31).

**Diagnosis**

The diagnosis of MS is primarily based on the history and clinical symptoms of a patient as evaluated during a neurological examination. However, after incorporation of MRI criteria in the International Panel (McDonald) criteria in 2001, with refinements in 2005 and 2010, MRI has become increasingly important (32). Critical concepts in the diagnostic MRI criteria are dissemination in space (i.e., multiple parts of the CNS should be involved) and dissemination in time (i.e., multiple disease events should have occurred), which both should have occurred before MS can be diagnosed. Apart from neurological and MRI examinations, several other (para)clinical tests may be used for diagnosis, including analysis of the cerebrospinal fluid (CSF) to investigate the presence of oligoclonal bands, that are found in up to 90% of the MS patients (2). Differential diagnoses of MS include various disorders that affect the CNS and follow a relapsing-remitting or progressive course, for instance systemic vasculitis, tumors or structural lesions.
General introduction

**Treatment**

Although a curative treatment for MS does not exist, multiple treatment options that target the inflammatory component of the disease have become available for RRMS patients in the past few years. First line injectable therapies, such as interferon beta and glatiramer acetate, aim to slow down the immune response and are moderately effective. They are reasonably tolerated and reported to reduce the number of relapses by approximately 30% (5–9). More recently, teriflunomide and dimethyl fumarate entered the market with similar efficacy (33,34). Second line therapies aim to block the immune response completely by preventing the passage of immune cells through the blood-brain barrier (natalizumab) (10) or preventing the departure of immune cells from the lymph nodes (fingolimod) (11). While these second line therapies are much more effective in suppressing the immune response resulting in a relapse rate reduction up to 60–70%, the side effects can also be much more severe: for instance, progressive multifocal leukoencephalopathy (PML) is a relatively common side effect of natalizumab that may also occur during treatment with fingolimod and dimethyl fumarate. The occurrence of such severe side effects has led to the general understanding that safety monitoring is extremely important when using this new class of treatments (35). In the case of natalizumab-associated PML, the importance of regular screening is further emphasized by the fact that detection of PML lesions in an asymptomatic stage is associated with a positive effect on survival and functional outcome in the case of early and professional therapeutic intervention (36).

It should be noted again that all treatment options discussed above are exclusively indicated for use in RRMS patients: at the moment, no treatment options are registered for use in patients with progressive MS. Moreover, the long-term effect of the newer second line therapies on the neurodegenerative component is rather unclear.

**Role of MRI in multiple sclerosis**

The first MRI-scans of MS patients were published by Young et al. in 1981 (37), visualizing abnormalities on a scale that was not seen before, even during autopsy. After that time, the use of MRI dramatically changed the entire concept of MS: it became apparent that radiological events could occur without clinical symptoms and that patients may display contradictory radiological and clinical profiles (also called the ‘clinico-radiological paradox’; see Figure 2). Years later, it became also clear that the brain of patients may experience considerable tissue loss (also called ‘brain atrophy’) which is considered as a surrogate marker of neurodegeneration.
Nowadays, it is not possible to talk about MS without mentioning MRI, having a role extending from diagnosis and monitoring to research applications and use of imaging measures as study outcomes in clinical trials (32,38). This is because the rapid development of MRI-techniques has resulted in new approaches that allow for visualization of a much wider spectrum of alterations in MS than the characteristic MS lesions only, including ‘active’ lesions, cortical pathology, atrophy, metabolic changes, damage to normal-appearing tissue and functional changes. Box 1 (see end of this Chapter) provides a comprehensive overview of the MRI-techniques that will be used in this thesis.

**Whole-brain atrophy in multiple sclerosis**

Brain atrophy in MS occurs early in the disease, accelerates during the course of the disease, and explains clinical impairment to a greater extent than white matter lesions (4,39). Atrophy can be measured using automated techniques that allow for quantification at the whole-brain level, but also separately in gray and white matter, or in more specific compartments such as the cortical and deep gray matter. Whole-brain atrophy is reported to proceed at rates of 0.4–0.8% per year in MS patients, compared to approximately 0.1% per year in healthy control subjects (39–41). Furthermore, it is thought that whole-brain atrophy progresses faster in patients with a progressive clinical course (39). However, a large multi-center study could not
Nevertheless, due to its strong association with clinical impairment, whole-brain atrophy measures gained such importance that they have already been used as secondary outcome measures in clinical trials (11,38). Unfortunately, it seems that brain atrophy is mostly unaffected by the therapeutic options that are currently available.

**Gray matter atrophy in multiple sclerosis**

Of special interest is gray matter atrophy, which shows even stronger associations with clinical (especially cognitive) impairment in MS (39,43). Gray matter atrophy is present early in the disease, across all clinical subtypes, is associated with a longer disease duration, and tends to accelerate in the progressive phase of the disease (39,43–53). Gray matter atrophy occurs both in the cortical (see Figure 3) and deep gray matter (see Figure 4) regions. Whereas studies on the predilection sites of gray matter atrophy in MS are often inconsistent (44,47,51), the thalamus is repeatedly reported as a site of deep gray matter atrophy in MS – even in the earliest phases of the disease (43,48). The notion of the importance of gray matter atrophy in MS dramatically changed the general perception of the disease: whereas MS was traditionally considered a purely neuroinflammatory white matter disease, neurodegeneration is now thought to be a crucial factor (1,54).

Despite the recognition of MS being (partly) a neurodegenerative disease, the underlying mechanisms largely remain to be elucidated (3). A first attempt to unravel the pathological substrate of gray matter atrophy was made by a recent post-mortem study, demonstrating that
Chapter 1

Figure 4. Figure illustrating typical deep (as well as evident cortical) grey matter atrophy in multiple sclerosis (MS): a 39-year-old female healthy control (HC) and a 48-year-old female patient with relapsing-remitting MS, disease duration of 21 years and Expanded Disability Status Scale score of 3.5. Figure modified from (42).

MRI-measured gray matter atrophy in MS in particular consists of neuronal and axonal loss (55). Whether this reduction of neurons and axons is driven by primary gray matter damage, or is secondary to white matter pathology, is the topic of an ongoing debate.

**Understanding the shrinking brain in multiple sclerosis: grand challenges**

Although gray matter atrophy is now recognized as an important predictor for clinical and dysfunction and cognitive impairment in MS; the exact role of neurodegeneration in MS is unknown. In this thesis, a number of issues will be addressed that primarily aim to achieve a better understanding of the role of neurodegeneration in MS. Given the complex interrelationship of gray matter atrophy with other MS pathology (in terms of methodological interference as well as on the pathophysiological level), we will not solely focus on gray matter atrophy but also investigate other types of MS pathology. The issues addressed in this thesis range from quantification to understanding its relationship with other types of pathology and clinical disability. The following sections will briefly introduce the different aspects.

**Quantification of pathology from magnetic resonance images in multiple sclerosis**

Since gray matter atrophy in MS can be rather subtle on MRI but has major clinical implications, an important contribution to a better understanding of neurodegeneration in
MS can be made by more accurate quantification (56). Improved accuracy and sensitivity of MS pathology measures will reduce the number of patients required in clinical MS research, will reduce the number of patients required for measuring treatment effects in clinical trials, and may ultimately allow for individualized measurements that can be used for personalized treatment. The desire to use improved measurement methods is not limited to gray matter atrophy measures alone, but also includes the measurement of focal lesions and quantification of normal-appearing tissue damage.

Vrenken et al. recently identified three aspects of MS pathology quantification which should be improved to obtain more accurate and sensitive MS pathology measures (56). Firstly, image acquisition should be performed in 3D to increase spatial resolution and reduce interpolation artefacts. Secondly, automated image analysis should be improved such that the interference of focal pathology with atrophy measurements is minimized. And lastly, standardized test data sets should be set up to facilitate development, calibration and objective evaluation of image analysis methods in MS.

In this thesis, we will adhere to these recommendations as much as possible in order to obtain a better understanding of neurodegeneration in MS. On the image acquisition level, we will make use of state-of-the-art near-isotropic high spatial resolution images to minimize interpolation artefacts. Moreover, we will investigate how white matter lesions can be reliably segmented from these high-resolution images and how the integrity of normal-appearing tissue can be quantified more accurately.
Chapter 1

The relationship between neurodegeneration and other pathology in multiple sclerosis

Several MRI studies investigated the presumed relationship between gray matter atrophy and white matter pathology, most of them reporting moderate to weak associations between the gray matter loss and lesion load (46,47,50,51,53,57–59). In addition, a number of studies explored whether there is a spatial relationship between white matter pathology and gray matter atrophy. Using voxelwise statistics, they found that co-localized white matter pathology partly explained gray matter atrophy in some regions (60–62). A few studies used tractography (i.e., diffusion tensor imaging) to assess the association between white matter pathology and gray matter loss in connected areas. Those studies focused mostly on specific gray matter regions or white matter tracts in patients with a short disease duration, and found stronger relationships between white matter pathology and gray matter atrophy in anatomically connected regions than in unconnected regions (63,64). Still the measures of white matter pathology only explained about half of the variance observed in gray matter atrophy. Several studies also investigated the relationship between white matter lesion load and ongoing gray matter loss in a longitudinal manner: these studies showed that only a limited part of accumulating gray matter loss can be explained by increasing white matter pathology (65,66).

From the rather limited amount of gray matter variance that could be explained in those previous studies, it is clear that the amount of gray matter loss that occurs in MS patients cannot be explained by white matter lesions alone. Moreover, the increasing atrophy rate during the course of the disease suggests the presence of an independent primary neurodegenerative process. However, in the patients with short disease durations that were investigated in most studies, this independent neurodegenerative effect may not have had enough time to yield measurable effects, especially if it acts more globally.

Therefore, in this thesis, we will investigate the relationship between gray matter atrophy and other types of MS pathology more comprehensively in a large cohort of patients with long-standing disease. Measures of pathological and physical decline will be more pronounced in these patients, which might allow for a more reliable recognition of possible differences between clinical subtypes and mechanisms.

The impact of neurodegeneration on clinical disability in multiple sclerosis

Although brain atrophy has been reported to explain clinical (especially cognitive) impairment to a greater extent than white matter lesions (4), it is not exactly known whether this is primarily the result of ‘diffuse’ atrophy, tissue loss in specific regions or a combination of pathologies. Results of previous studies are inconsistent and it has also been suggested that clinical disability may be the result of different types of MS pathology. A meta-analysis
combining the findings of 19 voxel based gray matter atrophy studies identified only one single area (left motor cortex) as a significant statistical predictor of physical impairment (67). Simultaneously, thalamic atrophy and reduced white matter integrity have been thought to play a role in cognitive decline (43,68,69). Different explanations may account for the inconsistencies in the literature, including differences in patient sample selection and issues related to imaging methods. Moreover, most studies investigated MS patients with a short disease duration whereas neurodegenerative aspects of the disease may be more suitably addressed in cohorts of patients with long-standing disease (22).

Therefore, in this thesis, we will reassess the clinical impact of gray matter atrophy compared to other types of pathology in MS while addressing the limitations of those previous studies. We will investigate the clinical relevance of a wide spectrum of imaging measures in patients with long-standing disease, while using advanced image acquisition and analysis methods to minimize the methodological issues discussed before.

**Aim of this thesis**

The general aim of the studies presented in this thesis was to better understand the role of neurodegeneration in MS, highlighting its relationship with other types of MS pathology and clinical impairment. We used novel and advanced high-resolution multi-modal MR imaging techniques to address this question in a large cohort of patients with long-standing MS. More specifically, our aims were as follows:

1. To improve the quantification of MS pathology on high-spatial resolution MR images to facilitate more accurate quantification of gray matter atrophy and allow for more reliable detection of relationships with other imaging and clinical measures.

2. To investigate the relationship between neurodegeneration and other pathology in MS.

3. To assess the impact of neurodegeneration and other types of pathology on clinical dysfunction in MS.

**Thesis outline**

**Chapter 2** focuses on improving the quantification of MS pathology using high spatial resolution MR images. In **Chapter 2.1** an accurate method for automated white matter lesion segmentation was developed and evaluated, which was used as a basis for the majority
of the other work in this thesis. In **Chapter 2.2** the integrity of the normal-appearing gray matter in MS patients was investigated using high spatial resolution T1 relaxometry.

The relationship between gray matter atrophy and other pathology in long-standing MS will be extensively studied in **Chapter 3**. In **Chapter 3.1** this relationship was first assessed at the whole-brain level. **Chapter 3.2** took this a step further and investigated whether regional gray matter atrophy can be explained by white matter pathology in anatomically connected tracts. In **Chapter 3.3** the focus shifted to the spatiotemporal characteristics of gray matter atrophy itself and investigated whether gray matter atrophy in MS develops according to specific patterns.

**Chapter 4** addresses the clinical relevance of gray matter atrophy and other types of pathology in MS. **Chapter 4.1** investigated the variables that are most useful when discriminating cognitively impaired patients from cognitively preserved patients by looking at white matter integrity, lesion location and regional gray matter volume. In **Chapter 4.2** we took this approach one step further by investigating the role of individual thalamic nuclei and their associated tracts in relation to cognitive impairment and personality changes. In **Chapter 4.3** we investigated how damage in different compartments of the motor system contributes to motor impairment in long-standing MS. In **Chapter 4.4** a similar multi-parametric analysis was performed to identify the strongest neuroimaging predictors of cognitive impairment in long-standing MS.

The results of these chapters will be summarized and discussed in **Chapter 5**. In addition, recommendations for future research are provided.

### Box A. Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a noninvasive medical imaging technique that is widely used to study the anatomy and physiology in healthy and diseased subjects. MRI scanners use a strong uniform magnetic field and radio frequency waves to excite protons which are for instance present in water molecules. The signal that is emitted, is subsequently used to reconstruct an image of the imaged area. MRI is most often used in vivo, but can also be applied ex vivo. The purpose of *conventional MRI techniques* is to produce images with a contrast that visualizes anatomical structures and pathologies. Different anatomical structures or pathologies can be emphasized by using different acquisition techniques or weighting schemes. Conventional MR images are particularly used for reading by a radiologist, volumetry of anatomical structures or quantification.
General introduction

Note that in conventional MR images the information is provided by the contrast in the image, not by the actual signal intensities that are stored in the image. In contrast, the purpose of quantitative MRI techniques is to quantitatively measure a physical or functional property of a specific region, or of processes taking place in the underlying tissue. As with conventional imaging, quantitative imaging allows to measure different properties by using different acquisition techniques. Although quantitative imaging is also frequently used in clinical practice, acquisition is generally much more challenging and requires proper calibration of the MR scanner used. In most cases, conventional and quantitative MR images can be acquired using both 2D sequences (i.e., typically ~3–5 mm thick slices) or 3D sequences (i.e., typically near isotropic 1 mm voxels, the whole volume is acquired simultaneously). In research applications, selection of the acquisition type may have major implications on the post-processing that can be applied (especially with regard to partial volume effects).

Conventional and quantitative MRI techniques that are employed in this thesis are introduced in the sections below.

**Figure A1.** 2D Proton-density (PD), T2- and T1-weighted image of a 34-year-old female patient with secondary-progressive multiple sclerosis (MS). Images are shown according to the radiological convention, showing the right hemisphere on the left, and vice-versa. The arrows highlight lesions on each image type. MS lesions appear as hyperintense regions on the PD and T2-weighted images. One lesion (in the left hemisphere) appears as a hypointense black hole on the T1-weighted image implicating severe tissue damage.
Chapter 1

Conventional MRI in multiple sclerosis

2D T1-, T2- and proton-density (PD) weighted images (see Figure A1) are most frequently used for MS diagnosis. T1-weighted images are used to visualize normal anatomy. In MS, T1-weighted images can also be used to visualize areas with severe persistent tissue damage appearing as hypointense lesions ('black holes') and to detect acute inflammatory (active) lesions after intravenous administration of MR contrast agent. PD/T2-weighted images are used to visualize pathological areas independent of the underlying neuropathological process: all (both acute and persistent) MS lesions appear hyperintense (bright) on these images. PD/T2-weighted images are most sensitive to lesions in the white matter. The total number or volume of PD/T2 visible lesions is often regarded as a measure of accumulated inflammation or burden of disease. Lesion counts and volumes are also used as study outcomes in clinical trials.

3D T1-weighted images (see Figure A2, first panel) also display normal anatomy, but are more suitable for volumetry than their 2D counterpart as a result of the near isotropic voxel size. Tissue loss as measured by volumetry on MRI is considered as 'atrophy'. In the brain, volumetrics may include whole brain volume, gray matter volume or white matter volume (see Figure A2, fourth panel). In addition, more regional (i.e., deep or regional cortical gray matter) or voxel-wise measurements may be performed to quantify regional or local atrophy. In the spinal cord, (average) spinal cord area can be quantified to determine atrophy of the cord. Just as on 2D T1-weighted images, it is important to note that MS...
(and vascular) lesions can appear hypointense on 3D T1-weighted images. Various studies have shown that these hypointense lesions cause misclassification in tissue segmentation algorithms and therefore can have a major impact on volume measurements (71,72). This measurement error can be reduced by 'filling' hypointense white matter lesions with white matter like intensities prior to performing volume measurements (see Figure A2, third panel) (71). A generally accepted solution for ‘filling’ hypointense intracortical and mixed gray and white matter lesions does not exist yet.

Fluid Attenuated Inversion Recovery (FLAIR) images (see Figure A2, second panel) can be seen as T2-weighted images in which the signal of the corticospinal fluid (CSF) is suppressed, particularly allowing for easier discrimination of periventricular MS lesions. Compared to PD/T2, FLAIR has improved sensitivity to detection of white matter lesions in periventricular and juxtacortical regions, but is less sensitive in the posterior fossa (73).

Double Inversion Recovery (DIR) images (see Figure A3) can be seen as T2-weighted images in which the signal of both white matter and CSF are suppressed, leaving only the signal of the gray matter. In MS, DIR images proved to be particularly useful for the visualization of cortical gray matter lesions. Compared to other sequences, DIR images demonstrated increased detection of intracortical lesions, as well as improved distinction between juxtacortical and mixed gray and white matter lesions (75). Moreover, it has been reported that DIR images allow for better detection of MS lesions in the infratentorial
Figure A4. Diffusion tensor imaging in a 54-year-old female with secondary-progressive multiple sclerosis (MS), Expanded Disability Status Scale of 3.5 and 29-year disease duration). The upper panels display the fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). RGB displays a color-coded FA map, where red indicates left-right oriented fibers, blue indicates superior-inferior oriented fibers, and green indicates anterior-posterior oriented fibers. In addition, NODIF displays the non-weighted diffusion image, T1 displays the corresponding structural 3D T1-weighted image, and FLAIR displays the corresponding 3D fluid-attenuated inversion recovery image. As can be seen, MS lesions display reduced FA values and increased diffusivity values.

Figure A5. Diffusion tensor imaging based tractography, visualizing the tracts (in green) between the frontal lobe and the anterior thalamic nuclei (in white).
Several years ago, consensus scoring guidelines were published to facilitate homogeneous DIR scoring (77).

Quantitative MRI in multiple sclerosis

Diffusion tensor imaging (DTI) (see Figure A4) measures the diffusivity of water and is used to 1) quantify microstructural integrity of brain tissue, and can also be used to 2) visualize structural connections in the brain (i.e., nerve bundles or tracts). From the DTI images, a voxelwise diffusion tensor can be computed which describes the predominant direction of water diffusion. From the diffusion tensor, several properties can be computed that are used to quantify microstructural tissue integrity. Common properties are: 1) fractional anisotropy (FA), which is a value between zero and one that describes the degree of anisotropy of a diffusion process (0 = isotropic, 1 = anisotropic); 2) mean diffusivity (MD), which is a value describing average diffusion in all directions; 3) axial diffusivity (AD, L1 or λ1), which is a value describing the diffusion in the main direction of the diffusion tensor; and 4) radial diffusivity (RD, L23 or λ23), which describes the average diffusion in the direction perpendicular to the main direction of the diffusion tensor. Typically, in MS, reduced tissue integrity is associated with lower FA, higher MD, higher AD and higher RD.
In addition, DTI is used together with tractography to identify structural connections in the brain (see Figure A5). By tracing the main diffusion direction, tractography allows to identify anatomically connected regions in the brain. In MS, however, this method seems to be of limited use since the low FA in MS lesions disturbs tractography algorithms.

Relaxation time (RT) mapping is a quantitative MRI technique that measures longitudinal (T1) or transverse (T2) relaxation times. T1-RT and T2-RT are the physical properties of the underlying tissue that, together with the magnetization vector, are responsible for the signal decay that is visible on an MR image. The exact substrate of relaxation time changes in the brain is largely unknown; however, T1-RT and T2-RT are typically expected to be longer when tissue damage increases. Figure A6 displays typical examples of T1-RT maps, and extensive additional information on T1-RT in MS is provided in Chapter 2.2.

The quantitative techniques applied in this thesis and discussed above are only a fraction of a much larger array of quantitative MRI techniques that is used in MS. For instance, magnetic transfer imaging (MTI) has been applied to quantify tissue integrity (79), magnetic resonance spectroscopy (MRS) has been applied to quantify metabolite differences, susceptibility weighted imaging has been applied to study iron changes (80), extensive investigations are carried out to determine the added value of imaging at ultra-high field strengths in MS (81), and functional MRI techniques have been widely applied to study changes in task-related and resting-state brain activation in MS (82). The latter technique has for instance led to the hypothesis that cognitive impairment in MS might be related to the inability of the brain to compensate (i.e., network collapse) for the structural damage that occurs (83).
References


Chapter 1


General introduction


Chapter 1


General introduction


