1. Introduction
1.1 Magnetic Resonance Imaging in Multiple Sclerosis

The title of this thesis uses the term ‘High Field MRI’. Few terms are more subjective than ‘high field’ in this context. Where in the 1950s imaging by nuclear magnetic resonance started at a field strength far below 0.1 Tesla (T), in the early 1980s a 0.15 T system was state of the art (1). Nowadays 1.5 T has become standard field strength, classifying 3T as high field. And where magnetic resonance imaging (MRI) of the brain at 7T is only just becoming clinically feasible for a wider spectrum of sequences, some don’t even use the term ultra-high field here as MR equipment with even higher field strengths is already developed.

The popularity of higher magnetic fields is due to higher signal intensities. These can be used to increase contrast, to reduce image acquisition time or to increase spatial resolution. Especially in Multiple Sclerosis (MS) diagnosis a large increase in sensitivity and specificity was achieved through the use of MRI (2,3). Before, diagnostics were mostly based on clinical symptoms only, which left room for differential diagnoses that could only be ruled out over time. Later, criteria based on combinations of lesion quantities in specific areas of the central nerve system (CNS) were able to predict conversion to clinically definite MS with high fidelity (4,5).

Next to lesion detection in general, the location of lesions has become of interest. Where the current diagnostic criteria for MS (6) are still based on white matter (WM) lesions, researchers find more and stronger correlations between radiological observation and clinical impact when gray matter (GM) lesions are included (7). With this, emphasis is also put on cognitive decline next to physical disabilities. However, detection of GM lesions is more difficult than WM lesions because in majority they show no inflammation. Due to lack of pronounced oedema and a blood-brain-barrier (BBB) disruption they do not enhance after administration of gadolinium based contrast agents. By use of dedicated MR sequences like double inversion recovery (DIR), that suppresses the signal of both white and gray matter, detection rates of GM lesions increase (8). These results were already found on 1.5T MR images, and increased rates were found on 3T (9).

In post-mortem studies at ultra-high field MRI even higher detection rates for GM were found (10,11). However, due to extreme acquisition times, those protocols could not be used in clinical studies.

The development of whole body 7T magnets opened doors for ultra-high field MRI in a clinical setting. Unfortunately, MR sequences that performed well at 3T could not just be copied to 7T. Increased longitudinal relaxation times, standing wave issues and SAR limitations hamper researchers that want to implement MS protocols. Step by step now sophisticated solutions are found perform ultra-high field MR imaging that show both conventional and new contrasts.
1.2 General aim and outline

**High field Applications in MS**

This thesis focuses on the use of high field MRI in MS to examine whether the step to a field strength of 7T is a factor that again helps to unravel more and more of the unknown aspects of the disease. The inflammatory effect of MS on the CNS has been studied by MRI in many studies and Chapter 2 gives an overview of methods and results from high field MR applications. It also looks into possibilities and challenges for the future of high field MR imaging in MS. The challenge in (ultra-)high field MRI may not only be for increased sensitivity in lesion detection, additional value is also expected for its ability to show heterogeneity in pathology.

Application of lower field protocols on high field results in many cases in non-optimal contrast and/or loss of clinical feasibility because of largely extended acquisition times. Adaptation of sequences is therefore necessary. Chapter 3 describes the use of new MR sequences, developed for 7T, to obtain the well-known fluid-attenuated T2-weighted (FLAIR) and double inversion recovery (DIR) contrast on 7 Tesla. A sophisticated magnetization preparation prior to the standard fluid attenuation helps to decrease T1-weighting effects that result from short repetition times that are used to reduce acquisition times. The appearance of MR images with a high spatial resolution from 3D magnetization prepared (MP) FLAIR and 3D-MP-DIR sequences were analyzed for quality and lesion conspicuity. Results from this study raised the question if the application of these sequences in a clinical 7T MR imaging protocol would increase lesion detection compared to 3T. Therefore in Chapter 4 a study is described that compared 3T and 7T MRI. The brain of MS patients was imaged on both 3T and 7T MR equipment using protocols based on FLAIR, T1- and T2-weighted contrast. All images were analyzed and counted for lesion numbers in several typical brain locations. Besides total lesion numbers per area, also subject-wise analyses were used.

The development of the double inversion recovery sequence increased sensitivity for gray matter lesion detection on 1.5T and 3T compared to e.g. FLAIR. As this was not known for 7T the new magnetization prepared sequences were applied for a comparison of 7T DIR to FLAIR, T1- and T2-weighted contrasts. Results from this study are described in Chapter 5. In this study as in chapter 4, detected lesion numbers were compared in group-wise and subject-wise analyses.

**Quantitative Imaging**

Next to qualitative approaches described in the previous chapters also quantitative analysis of MR parameters have shown pathology dependent characteristics in the past (12). In many cases white matter of MS patients does not differ from healthy controls using qualitative image contrast. At lower field however, differences were observed in T1 relaxation time values of ‘normal appearing’ white and gray matter of MS patients compared to healthy controls. T1 relaxation time values increase with field strength and at 7T this might result in increased sensitivity for changes in WM. Chapter 5 describes a T1 relaxation time mapping study using several analysis methods to compare WM of MS patients and healthy controls.

**Iron**

Already in 1958, Hallgren and Sourander (13) showed that iron is accumulated in certain brain areas over time. This is a normal process that serves as a buffer for iron deficiency or overload. The highest levels are found in the basal ganglia. However, in many neurodegenerative and
inflammatory diseases the rate of iron accumulation is increased. These effects could be observed by histopathology, but after the development of iron sensitive sequences this could also be observed qualitatively and quantitatively by MRI. Also in MS these increased iron levels were observed and MRI therefore might serve as a tool to measure disease progression. The use of ultra-high field showed to be beneficial for iron sensitive sequences. Chapter 6 provides an overview of the development of MRI based iron mapping and restrictions of methods. It also looks into possible new approaches to relate iron accumulation to the clinical condition of MS patients.

As it has been shown that MRI has a high sensitivity for the presence of iron, administration of exogenous iron may function as a contrast agent, revealing new disease aspects. Chapter 7 shows results of a study on the application of a new contrast agent based on ultra small particles of iron-oxide (USPIO) in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. By means of active uptake by macrophages the agent may be transported to affected sites in the CNS. It could then show disease activity different from gadolinium based contrast agents that passively leak over an impaired BBB.


