“The scientific man does not aim at an immediate result. He does not expect that his advanced ideas will be readily taken up. His work is like that of the planter - for the future. His duty is to lay the foundation for those who are to come, and point the way. He lives and labors and hopes.”

(Nikola Tesla)

Chapter 5

SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

Summary, general discussion and future perspectives

Citius, altius, fortius. Looking at the Olympic motto from a broader perspective: we are always searching for optimal performance and ways to improve. In the field of MRI systems, technical developments are on going: the first MRI was a 0.05 Tesla (T) system, at present, standard-field 1.5T and high-field 3T systems are used in the clinical setting. Going faster, higher and stronger, in this thesis we aimed to study the added value of moving to ultrahigh-field 7T MRI in MS. To address this aim we made use of 3T and 7T MRI systems in an in vivo and postmortem study setting, including histopathology. This final chapter summarizes and discusses the results of six studies investigating the technical possibilities of 7T MRI, and its possible clinical role. Subsequently, a view on future directions regarding this topic is proposed.

Benefits from a technical perspective

In this chapter we explored the benefits of ultrahigh-field 7T MR imaging compared with the clinically available high-field 3T MR system. In **CHAPTER 2.1** we aimed to compare MS lesion detection at 7 T versus 3 T using a clinical scan protocol.[1] Whereas initial 7T research - showing improved cortical lesion detection and classification - was based on phase and T2*w sequences,[2–8] we were especially interested in the performance of the 7T system with respect to T1w, T2w and fluid attenuated inversion recovery (FLAIR) sequences, which are recommended in the standard imaging protocol for MS diagnosis at 1.5 T.[9] Images of 38 MS patients were acquired on both 7T and 3T scanners. Increased cortical lesion detection was found at 7 T with all sequences; 7T FLAIR even detected up to 238% more cortical lesions than 3T FLAIR.

Considering this increased cortical lesion detection at 7T, we aimed to identify which particular sequence at 7 T performed best. At 1.5 T and 3 T, a grey matter (GM) specific double inversion recovery (DIR) sequence had been developed and proved to increase cortical lesion detection.[10–14] This DIR sequence is not implemented in the standard clinical scan protocol, merely because of long acquisition times, and a moderate agreement between raters when assigning cortical lesions.[15] In **CHAPTER 2.2** we compared sensitivity in cortical lesion detection of the clinically recommended sequences (T1w, T2w and FLAIR) with this GM specific DIR at 7 T.[16] Image analysis of 37 MS patients showed that highest lesion detection was found with FLAIR: 89% more lesions than DIR, 87% more than T2w, and 224% more than T1w sequences. This is in contrast to lower field strengths, at which the GM specific DIR always comes out best.[11,12,14] Our statement the that GM specific DIR sequence is less helpful at ultrahigh field is probably due to the fact that with increasing field strengths, T1 and T2 relaxation times of various tissue types converge. This makes it more difficult to suppress particular tissues with an inversion pulse. Furthermore at 7T, the DIR sequence showed higher noise levels and more artifacts, hampering the scoring process according to the protocol as developed by the MAGNIMS study group.[15] It might also be, that at 7 T the inversion pulses also suppress additional tissue types including parts of lesions, which impedes visibility.

At this point in the thesis, we knew that cortical lesion detection at ultrahigh-field 7 T is higher than at high-field 3 T. However, we still did not know how much of the cortical lesions we actually see and - more importantly - how many we still miss. That is why, in **CHAPTER 2.3**, we verified the higher cortical lesion detection at 7 T with histopathology.[17] Coronal hemispheric brain slices of 19 deceased MS patients and 4 controls were scanned on a 3T and 7T system using a multicontrast protocol. Lesion detection was verified by comparing MR images to

histopathology as reference. As was reported in our in vivo study, also in a postmortem study setting 7 T showed an increase in cortical lesion detection with all sequences. The largest improvement was seen with 7T FLAIR, which detected 225% more cortical lesions than 3 T (which is comparable to our in vivo study results reporting an increase of 238% in cortical lesion detection with FLAIR).

Previous postmortem studies have shown that prospective MRI detection of cortical MS lesions (without revealing the histopathological location of lesions to the MRI reader) is very low: at 1.5 T up to 95% of the intracortical lesions go undetected using T2w sequences, even a move to 4.7 T left 90% of cortical lesions undetected with T2.[18,19] The development of the GM specific DIR sequence meant an increase in sensitivity to 18% prospectively, but this was still only the "tip of the iceberg".[20] At 7 T, we found a radically higher sensitivity, up to 35% and 31% with respectively T2w and FLAIR sequences. In this study, the detection of subpial lesions was particularly high, with a prospective sensitivity of 68% for type IV (7T T2) and 32% for type III subpial lesions (7T T2*). Subpial lesions have always been challenging to detect, especially type III lesions, because of their location in the upper sparsely myelinated cortical layers, which in turn produce little MRI contrast when demyelinated. However, a lot of interest goes out to these subpial lesions in MS, since they can be extensive,[21] are related to more progressive forms of the disease,[22] as well as to higher physical disability and worse cognitive performance.[6,23]

Although our results harbor greater promise, we realize that (subpial) cortical pathology in MS is more extensive than what ultrahigh-field 7T images can reveal. As even retrospectively - when the histopathological location of the lesion was revealed to the image reader - approximately 40% of all cortical lesions were still missed. Why not all cortical MS lesions are visible on MRI remains unclear, but MRI visibility is most probably related to lesion size and varying degrees of inflammatory activity within lesions.[4,20]

Considering white matter (WM), no significant increase in lesion counts was seen with 7T MRI when compared to 3 T, neither in our in vivo nor in our postmortem studies. This in contrast to earlier comparative studies between 1.5 T and 7 T, which did show improved WM lesion detection.[5,24] This shows that the largest gain for WM lesion detection lies in moving from 1.5 T to 3 T, whereas the additional step to 7 T does not add to higher sensitivity.

In this chapter we have shown that ultrahigh-field 7T MRI is of added value in MS from a technical perspective: in terms of increased (subpial) cortical lesion detection, performance is better than high-field 3T MRI.

Opportunities for clinical application

Besides the improvement in cortical lesion detection, 7T MRI made it possible to study morphology of MS lesions in a more precise way. Higher magnetic field strength is accompanied by increased susceptibility effects, which can be used to our advantage in T2*w sequences. Initial 7T T2* studies have shown improved visibility of small parenchymal veins, without the necessity to use intravenous contrast.[25,26] This made it possible to study the typical perivascular orientation of MS lesions,[2,25,27–29] as has been originally described by Dawson.[30] Furthermore, 7T phase imaging has shown characteristics of MS lesions such as hypointense lesions and hypointense rims around lesions.[4–6,28] The pathological substrate of these morphological features has been extensively studied, but remains a matter of debate.[31] Initially, the rims were believed

to reflect active iron laden macrophages, and hence chronic active MS lesions;[4,28] however, serial in vivo 7T imaging showed that the rims did not disappear in a period of 2.5 years and therefore do not reflect transient active MS lesions.[32] Postmortem studies suggested that hypointensities on 7T phase imaging were due to abnormal iron deposition in the MS brain.[33,34] However, more recent studies claim that hypointense phase MS lesions cannot always be interpreted as lesions that contain iron.[35,36] In this thesis we did not intend on taking part in this debate by investigating the underlying pathological substrate of the new morphological aspects of MS lesions. Instead, we wanted to look at the new morphological features from a more clinical perspective: Why do they occur only in a subgroup of MS patients? Are they related to the clinical profile of MS patients (or to one of the MS disease subtypes)? Can they distinguish MS lesions from other WM lesions?

To investigate the morphology of MS lesions, we implemented a new image technique at 7 T, which was described earlier at 3 T, the so-called FLAIR*.[37] Sati and colleagues developed FLAIR* as a combination of two sequences into one single image: FLAIR images for the detection of MS lesions and attenuation of CSF, and T2*w images for the detection of parenchymal veins. Benefits of implementing the FLAIR* technique at 7 T were that no intravenous contrast was necessary to visualize veins, and that the high resolution resulted in higher lesion detection and visibility of small parenchymal veins.[16,25]

In **CHAPTER 3.1** we explored the feasibility of FLAIR* at 7 T, plus the morphological characteristics of MS lesions and their relation to patient characteristics, in 33 MS patients and 7 healthy controls.[38] Three morphological features of MS lesions were visualized. Firstly, the perivascular orientation of MS lesions, as is seen by a central vessel (CV) running through the lesion. A CV was present in 78% of all MS lesions. Where previous 7T T2* studies focused only on perivascular orientation of MS lesions in the (deep) WM, we also investigated perivascular orientation of other (cortical) lesiontypes. We found that the proportion of lesions with a CV was highest in the periventricular region (94%) and decreased towards the cortex (deep white matter 84%, juxtacortical 66%, leukocortical 52%); intracortical lesions hardly showed a CV (25%). Hypothetically, this might be due to the fact that cortical lesions evolve in a different way. As a second morphological feature we detected hypointense rims around MS lesions. The third morphological feature was that FLAIR* lesions were found that were hypointense (compared to surrounding WM) at T2, whereas they appear isointense most commonly. The presence of hypointense (rims around) lesions was not related to clinical characteristics and could not be related to any of the MS disease subtypes. Similar results were found recently in a study that compared lesion morphology characteristics at 7 T between a group of RRMS and PPMS subjects, and found no differences.[39] We suggest that the presence of rimlike and hypointense lesions appears to be an MS-broad phenomenon. Hypothetically, the hypointense rims and lesions resemble a different subtype of lesions or just a different phase in lesion development, which could not be discerned at lower field.

In **CHAPTER 3.2** we compared these three morphological features of lesions at 7T FLAIR* between 16 MS patients from our own cohort, and 16 patients with vascular pathology from the Secondary Manifestations of ARTerial disease (SMART) cohort.[40,41] Lesions in the MS group were significantly more often perivascularly oriented. Furthermore, in the MS group, some lesions were surrounded by a hypointense rim or were hypointense on T2*. Though not very common, these phenomena proved to be fairly specific for MS, since they were not visible in the vascular group. Subsequently, we determined optimal cut off points for the diagnosis of MS,

and calculated the specificity of differentiating deep WM lesions in MS from vascular lesions on 7T FLAIR*. Specificity increased when the presence of a CV was taken into account (from 69% to 94%). This study also pointed out the importance of periventricular and juxtacortical lesions for MS diagnosis, since their appearance was more common in the MS group. This is well-known, and a reason why lesion location (dissemination in space) was included in the MRI diagnostic criteria.[42] Additionally, in our study, the presence of cortical GM lesions showed very high specificity for MS diagnosis. Several other studies have used 7T T2*w sequences to investigate the differentiatio n of MS lesions from other lesions, and showed that 7T T2* can improve differentiation of MS from Susac syndrome, neuromyelitis optica and asymptomatic WM lesions.[43–45]

In this chapter we have shown characteristic lesion morphology features of MS lesions at 7 T that appear to be MS broad phenomena. Nevertheless, they are highly specific for MS pathology and have proved to be of aid in differentiating MS from other diseases, indicating an opportunity for clinically application of 7T MRI in MS.

Beyond lesions: quantification of the 'unseen'

In the last part of this thesis, we explored the possible applications of 7 T to look beyond MS lesions.

While analyzing the 7T images for the other studies in this thesis, we noticed the prominence of Virchow Robin Spaces in patients with MS. These enlarged perivascular spaces are also seen at lower field strength, but in less detail, since they are very small. VRS have been associated with vascular and neurodegenerative diseases,[46–49] but strangely in MS the presence of VRS was associated with neuroinflammation.[50] In **CHAPTER 4.1**, we analyzed the frequency and size of VRS in 34 MS patients and 11 healthy controls, and found that VRS are more common in MS patients.[51] However, they are not larger. The presence of VRS in MS patients was associated with supratentorial brain atrophy (as a marker of neurodegeneration) and not with lesion count (as a marker of neuro-inflammation), which suggests that VRS might rather serve as a neurodegenerative than a neuro-inflammatory marker in MS.

In **CHAPTER 4.2** we took part in a multicenter MAGNetic resonance In MS (MAGNIMS) study, investigating iron deposition in MS patients with R2* mapping at 3T MRI. Seven European MS centers included 97 MS patients of different disease subtypes, and 81 healthy controls. We found that, compared to healthy controls, MS patients showed significantly increased R2* values in all deep GM regions, with the exception of the globus pallidus and the substantia nigra. R2* increase was most pronounced in the progressive stage of the disease as primary progressive (PP) and secondary progressive (SP) MS patients had significantly higher R2* values in all regions compared to relapsing remitting (RR) patients. Furthermore, R2* increase was independently predicted by disease duration and disability, reflecting advanced disease. In lesions, R2* was inversely correlated with disease duration and higher total lesion load.

In this last chapter we have shown that (ultra)high-field MRI in MS is able to visualize tissue damage in MS brain tissue beyond lesions, which is important for future research into pathogenic mechanisms of the disease and its different subtypes.

Future perspectives: from technical development to clinical implementation

"Will patients ever actually benefit from higher magnetic field strengths in clinical MRI and MRS, or will this field stay an academic playground?"

Moser[52]

The red line through this thesis is a transition from technological studies to more clinically oriented studies. The use of ultrahigh-field 7T MRI in MS research worldwide has focused a lot on the technical performance of the scanner and questions regarding the pathological mechanisms of the disease. Results are promising, and provide an optimistic view on its clinical potential. Therefore I will answer the question "Is there a future for 7T MRI in multiple sclerosis?" with an unreserved "YES". There is a future for 7T MRI in MS, in the clinical as well as in the research setting.

7T MRI in multiple sclerosis: clinical needs

At this moment, clinical application of 7T MRI is limited. Ultrahigh-field MR systems are still considered investigational devices. In 2003, the American Food and Drug Administration published guidelines stating that high-field (until 4T) MR systems can be used in the clinical setting, and that the risk concerning ultrahigh-field (until 8T) MR systems is considered as non-significant in the research setting.[53] Not only in the field of MS, but in general, we are still rather early in the development of clinical ultrahigh-field imaging.[54,55]

In the process of clinical implementation of a new diagnostic device, in general, three steps have to be considered:[56]

1. Regulation: safety and performance of the device. In this category, proof of principle and proof of concept research has to be done: Can we make the technology work (in the MS field)?

2. Assessment: clinical effectiveness, ethics, social and organizational issues. To evaluate this, studies on clinical efficacy and cost-effectiveness have to be done: Does use of the new device improve healthcare outcome compared to standard care? Are the outcomes clinically meaningful? Are the costs acceptable?

3. Management: procurement, selection, training, use. After implementation, "real life" follow up studies have to be done: Are expected benefits realized?

Research with 7T systems in the field of MS, particularly the research in this thesis, has focused merely on step 1. Early feasibility studies have shown 7T imaging to be safe and well tolerated, and have developed robust image sequences like 3D FLAIR and 3D DIR that could be used in MS studies.[57,58] The research described in this thesis has focused on performance of the 7T scanner, which has led to improved detection of cortical GM lesions and improved differentiation of MS from vascular lesions. Further research regarding clinical implementation of 7T MRI in MS, should move on to step 2 and investigate clinical efficacy, building on results presented in this thesis. After this, studies on cost-effectiveness can be planned.

Considering what the MS clinician wants, putting myself in the chair of a radiologist, there are two main goals that future research into clinical efficacy has to address:

1. Diagnosis: with a more sensitive (earlier) and a more specific diagnosis, morbidity can be reduced since more effective initiation of treatment will be possible. At the same time, there will be less uncertainty for the patient.

2. Monitoring: development of new imaging biomarkers, which will improve monitoring of disease progression and treatment.

This thesis sets a basis for future research investigating these two goals. To start with determining a more sensitive diagnosis. Our in vivo as well as our postmortem sensitivity studies showed no improved detection of WM lesions in MS at 7 T. We believe that with increasing field strength, WM lesion detection improves, but it reaches its plateau at high resolution 3T imaging.[1,17] Since the current diagnostic criteria are based solely on the presence of WM lesions in different anatomical regions of the brain, we are reserved regarding the impact of 7T MRI in terms of establishing a more sensitive - or earlier - diagnosis. However, when we anticipate on a revision of the MRI diagnostic criteria, in which the presence of cortical lesions will probably be incorporated, then a substantial clinical influence of 7T imaging on the diagnosis of MS can be expected, since our proof-of-principle studies showed increased cortical lesion detection with 7 T. Future studies investigating sensitivity of MS diagnosis at 7T MRI in patients with clinically isolated syndrome (CIS) can investigate this further. Nevertheless, one has to keep in mind that with a higher resolution, also the risk of incidental findings/ false positives might increase. Although not part of this thesis, we started a similar multicenter study with the European MAGNIMS group, investigating the sensitivity of the MRI diagnostic criteria for MS, comparing high-field 3T versus standard care 1.5T systems. An earlier study has shown no impact of 3T scanning on the diagnosis of MS, however a small sample was used in this single center, single vendor study.[59,60]

A more specific diagnosis of MS by using 7T MRI can be further investigated, building on our proof-of-principle study that showed improved differentiation between WM lesions in MS patients versus vascular patients with 7T FLAIR*. The real specificity of 7 T has to be determined by investigating these morphological features of MS lesions in a clinical sample, preferably in a multicenter study set up with patients with unsure diagnosis. Such a single center study investigating whether the presence of a central vessel on 7T T2* could influence diagnosis of MS, has showed encouraging results already.[61]

For the second goal, concerning better monitoring of disease progression and treatment effects, the clinical influence of 7 T has to be investigated in future research. In the coming years many trials with new drugs will be performed. 7T MRI can detect subtle changes in cortical pathology, which were recently shown to be correlated to neurological and cognitive status of the MS patient,[23] and might become a new biomarker for accurate monitoring of the treatment effects. Furthermore, with high-resolution 7T MRI it is possible to zoom in on small - but clinically highly relevant - brain structures, such as the hippocampus (cognitive function) and hypothalamus (endocrine function). From pathological studies, it is known that these areas are affected in MS patients, but it is complex to visualize the small substructures of these areas on standard-field MRI. At 7 T, perhaps additional demyelinating pathology can be visualised. It is interesting to see whether demyelinating lesions in the hippocampus and hypothalamus are related to lesions in the WM and GM, and if they will strengthen the relation with clinical symptoms as cognitive impairment (e.g. memory loss) and endocrine dysfunction (e.g. increased stress-hormone levels). 7 T might also lead to an improved measurement of

neurodegeneration, with better visibility of VRS and more accurate determination of GM and WM volumes. Results of such studies might serve as outcome parameters for future monitoring of disability and treatment effect in the clinical setting or in clinical trials.

Not only in MS research, but also in several other fields investigating 7T imaging, the same point has been reached: there is a need to investigate the possible clinical role of 7T MR systems. 7T research remains reserved to several niches, for instance the use of 7 T in musculoskeletal studies is rapidly developing.[62] But it is still mainly used in the field of neuroradiology, since brain coils were available first, there are less field strength dependent artefacts in the brain (compared to the abdomen for instance), and the advantages of higher resolution are of high impact for visibility of microanatomy in the brain. The most promising results with 7 T are booked in multiple sclerosis, cerebrovascular diseases (micobleeds, aneurysms), brain tumours and neurodegenerative diseases (Parkinson's, Alzheimer's disease). For instance, 7T MRI offers a detailed view of the substantia nigra in Parkinson's disease and of the hippocampus in Alzheimer's disease, possibly leading to earlier diagnosis in the future.[63–66] 7T susceptibility weighted imaging may better characterize intratumoral microvasculature and microstructure of brain gliomas, and therewith offers a potential marker of tumor grade and a better planning of biopsies and surgical treatment in the future.[67] Another possible clinical role for 7 T lies in the depiction of aneurysms with 7T time of flight MR angiography, and the imaging of cerebral microbleeds with 7T T2*.[68–71]

7T MRI in multiple sclerosis: research promises

Besides its potential clinical role, there is an unquestionable future for 7T MRI in the MS research setting. In the first place, future studies can continue to optimize 7T pulse sequences. For instance, a GM specific sequence such as phase sensitive inversion recovery (PSIR), has shown potential in detecting cortical lesions at lower field strengths.[72] Possibly, when PSIR is implemented at 7 T, this may further improve. Further improvement in the detection of cortical pathology remains an ongoing search and is important to be able to better monitor disability of patients, and to be of aid in the development of future therapeutic options. What is furthermore important is to investigate the pattern of pathology throughout the cortex of MS patients. Regarding this, very recently it was suggested that the outer cortical layers are most severely affected and that cortical pathological processes are driven from the pial surface.[73,74] Mainero et al. used 7T T2* maps to investigate quantitative differences throughout the cortex, and they detected -in vivo- a gradient in the expression of cortical pathology in MS, across disease stages, which was related to clinical disability. In future 7T studies, we must also focus on the 'unseen' cortical damage, and its patterns of distribution, which might provide more information about the underlying pathogenic mechanisms and the course/ progression of the disease.

Also, the development of quantitative sequences at 7 T can be investigated, such as spectroscopy or functional MRI (BOLD) that will probably also benefit from the increased SNR and resolution. In a pilot study using diffusion tensor spectroscopy at 7 T, diffusion was measured across the corpus callosum, and showed that in MS, NAA diffusivity parallel to the axonal fibres was lower than in HC, and was inversely correlated with water diffusivity and clinical severity.[75] It has been suggested that damage to the optic radiation pathway as visualized at 7 T, is correlated to visual disability in MS patients.[76] To build on this and to further explore visual disability in MS, sequences could be designed to image the optic nerve with 7 T, so that (subclinical) damage to

the visual pathway can be investigated, perhaps in combination with OCT. High-resolution 7T imaging of the spinal cord in MS patients is also an interesting matter for future research, but will remain challenging, because of artefacts due to CSF and vessel pulsation.

Additionally, ultrahigh-field 7T MRI can play a role in studies providing more insight in the pathophysiology of MS. Future studies in a longitudinal setting could focus on lesion development and morphological detail of different types of MS lesions. A recent 7T T2* study showed differences in hypointense rims around active versus chronic MS lesions.[77] It would be helpful to be able to distinguish the complete evolution of MS lesions, in vivo. Can we visualize pre-lesional changes, for instance? Or, by building on our own observations in the histopathological verification study:[17] is it possible to differentiate between heterogeneous pathological substrates of MS, and distinguish demyelination from remyelination with 7T MRI? And can 7T MRI be used to distinguish axonal disruption in MS from other processes such as inflammation, edema, demyelination and gliosis? Also interesting, are vascular damage in MS and its role in lesion development. A 7T T2* study by Sinnecker et al., showed decreased vein density in MS and CIS patients.[78] Likewise in a minority of the MS lesions, there is shrinkage of intraluminal venous diameter, as is shown by 7T SWI-FLAIR imaging.[79] Possibly this is caused by hypoperfusion and hypometabolism of the MS brain, or by direct venular damage. Recently, at 7 T, group specific vein-atlases were created, which allow group comparison between MS and healthy controls, and perhaps in the future comparison with individual patients to monitor damage caused by MS.[80] In a marmoset 7T EAE study, prelesional changes in vascular permeability were shown to precede lesion development.[81] In stroke patients, 7 T enabled visualizing the intracranial vessel wall. When we apply this in MS patients, this might clarify the aforementioned 7T findings and enable us to show vascular damage in disease aetiology and progression.[82]

Conclusions

With 7T MRI we are able to visualize damage in the brains of living MS patients with a resolution similar to pathological assessment of brain tissue, hence the metaphoric term "macroscope" was introduced in this thesis. At present, creating a microscopic resolution with in vivo MRI remains an illusion and is not yet possible, merely because of acquisition time and SAR restrictions.

The overarching aim of this thesis was to study the added value of moving to ultrahigh-field 7T MRI in MS. It can be concluded that 7T MRI has added value from a technical perspective: performance is better than 3 T in terms of increased (subpial) cortical lesion detection. Furthermore, 7 T has the potential to be of added value clinically, as has been shown by describing characteristic lesion morphology features of MS lesions at 7 T, which are highly specific for MS and have proved to be of aid in differentiating MS from other diseases. Lastly, 7T MRI can be of added value in the quantification of 'unseen' damage beyond focal lesions, for instance in the search for possible (neurodegenerative) biomarkers in MS, by creating improved visibility of small anatomical structures such as perivascular spaces.

The next grand challenge in 7T research is putting our ideas and study results as described in this thesis - combined with 7T research from other leading centres in the world - in another perspective: we need to think beyond technical performance and we should start exploring the possible clinical application, relevance and efficacy of 7T imaging in MS.

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