Summary and Conclusions

SUMMARY

The aim of this thesis was to develop methods to enable the use of 7 Tesla MRI in clinical practice. Since the installation of the first whole body 7 Tesla magnet, less than 15 years ago, research in this field has seen a rapid increase, with over 40 human in vivo studies published in 2011 (PubMed). However to date, the number of clinical studies has been rather limited. One of the reasons is that translating existing techniques from lower field strengths to 7 Tesla is far from trivial in many cases. Intrinsic properties related to the high field, such as increased sensitivity to magnetic field inhomogeneities and reduced homogeneity of transmit and receive fields require specific sequence and hardware modifications. A simple translation of protocols from lower field strength to higher field is likely to deliver sub optimal results, or even worse results than obtained at lower field strengths. In this thesis a number of technical developments have been performed to facilitate clinical studies and to achieve the full potential that high field has to offer in terms of increased signal-to-noise, contrast and spatial resolution.

The first part describes techniques to improve MR applications in the heart and calf muscle.

Chapter 2 describes the development of a local transmit-receive coil to facilitate cardiac imaging. Different coil configurations have been tested to achieve a B_1 transmit field without tissue induced signal voids, caused by destructive B_1 interference due to the small RF wavelength. Empirically different coils were optimized, using a single loop configuration and a quadrature dual loop configuration. It was shown that using a relatively simple quadrature local transmit-receive coil sufficient coverage to image a large part of the heart could be obtained without introducing any signal voids in this region. RF safety validations were performed to ensure imaging experiments stayed within specific absorption rate (SAR) limit. Several applications of this coil were shown to be feasible, including functional cine moving heart imaging and morphological imaging of the right coronary artery (RCA)

The coil and techniques described in the previous chapter are used in **chapter 3** to image the RCA and to compare the results with a similar protocol at 3 Tesla. Ten healthy volunteers were included and images of the RCA were obtained at 3 Tesla and at 7 Tesla, while keeping the protocols as comparable as possible. The following measurements were performed at both field strengths to quantify the visualization of the coronary artery. Contrast-to-noise ratio between blood and epicardial fat, signal-to-noise ratio of the blood pool, RCA vessel sharpness, diameter, and length; and navigator efficiency. Incre-

ased vessel sharpness and signal-to-noise ratio were found at 7 Tesla. Overall in young healthy volunteers the image quality at 7 Tesla was equal or better than obtained at 3 Tesla.

In **chapter 4** a new calibration method is introduced that measures the B_1 transmit field in a small region of interest. To achieve a certain flip angle the RF amplifier needs to be calibrated depending on location, coil positioning and subject size. Conventionally this is done over a large region, because at lower field strengths the flip angle can be considered constant to a high degree. At 7 Tesla this assumption does not hold, because of the smaller wavelength of the RF field and the frequent use of local intrinsically inhomogeneous transmit coils therefore a new calibration method was developed. Because this method needs to be performed before each scan, it should be very fast without user interaction. The method that was developed used the ratio of two stimulated echoes to derive the actual flip angle. The power setting of the RF amplifier was subsequently iterated to reach the desired flip angle. Using this method an increased signal-to-noise ratio was obtained for localized spectroscopy scans acquired from the calf muscle compared to the conventional calibration method. The exact increase was dependent on the location with respect to the partial volume transmit-receive coil. Generally increases were larger for regions where the local B_1 field was more inhomogeneous.

The second part is concerned with technical developments for high resolution brain imaging.

In **chapter 5** high resolution T_2^*-weighted imaging is performed in Alzheimer's disease (AD) patients. One of the hallmarks of this disease is the aggregation of a protein (amyloid β) that is co-localized with iron. High resolution T_2^*-weighted imaging is a promising technique to image these deposits especially at high magnetic field strengths. However the image quality was found to be severely reduced in AD patients compared to previously acquired images in healthy volunteers. It was hypothesized that the images were degraded due to dynamic fluctuations of the static magnetic field (B_0 fluctuations). This was subsequently confirmed in healthy volunteers where comparable artifacts were observed when similar magnetic field fluctuations were synthetically added to the acquisition. These B_0 fluctuations are introduced by respiration and coughing, but also likely due to body movements not related to head motion. In addition, it was shown that the effect of typical translational and rotational head motion had a much smaller effect on the resulting image-quality. The T_2^*-weighted sequence was modified to include a navigator echo to dynamically estimate magnetic field changes during image acqui-

sition. Retrospectively this information was used in image reconstruction to substantially improve image quality in all cases enabling high quality imaging in AD patients.

An extension of this technique is described in **chapter 6**. Even after correction using the navigator echo technique, the images remained typically of lower quality than images obtained in healthy volunteers. It was hypothesized that the magnetic field fluctuations observed in AD patients had a spatial distribution within an acquired slice, whereas the previously proposed navigator technique was capable of only measuring a global B_0 offset in a slice for each RF excitation. In this chapter a sensitivity encoded (SENSE) navigator was introduced that samples the magnetic field using the 32 receive channels that were available. Because each element sampled signal from a small location of the head only, a spatial estimation of the underlying magnetic field could be obtained by combining the navigator with separately acquired coil sensitivity profiles. This approach was extended to include a frequency readout gradient to improve the magnetic field estimation further. High resolution T_2^*-weighted images were acquired in volunteers while they were intentionally touching their nose or taking deep breaths, to mimic the worst case magnetic field fluctuations seen in AD patients. It was found that the SENSE navigator technique could accurately estimate the induced B_0-fluctuations. In the second part of this chapter a reconstruction framework is introduced that uses the spatially and dynamically fluctuating magnetic fields to retrospectively correct the images. The complexity of the reconstruction scales to the fourth power of the acquisition matrix, therefore an iterative solver was used based on conjugate gradient minimization to limit memory requirements and reconstruction times. Results show a much improved image quality. The approach using the SENSE navigator including frequency encoding yielded optimal results. Future patient studies are needed to validate this technique in clinical practice.

The long scan duration of most high resolution T_2^*-weighted sequences limits whole brain coverage, in **chapter 7** a new fast volumetric 3D echo planar imaging (EPI) protocol is introduced. By employing the high efficiency of EPI, typically used for fast low resolution functional brain imaging an improved SNR efficiency was obtained. The proposed sequence was compared to a conventional 3D T_2^*-weighted protocol, with the same resolution, amount of T_2^* weighting and scan duration. The spatial coverage of the EPI based protocol was a factor of 4.5 larger, while also the SNR was a factor of 2 increased. This effectively enabled whole brain acquisition of 0.5 mm isotropic resolution in less than 6 minutes of scanning time. The longer readout train in the

EPI protocol inevitably results in more spatial distortion and possibly areas of signal voids. However with the chosen parameters there were no apparent regions of signal voids and the distortion was less than 3 mm for the lowest slices. Due to magnetic field inhomogeneities these slices are most prone to distortion; the amount of distortion for the slices higher in the brain was therefore much less. The new sequence provides the necessary steps, such as resolution and coverage to utilize the high T_2^* contrast of high field MRI.

The third part of the thesis is focused on the current clinical applications of 7 Tesla MRI.

In **chapter 8** T_2^*-weighted imaging has been performed in AD patients to image changes occurring in the cortex related to the deposition of Amyloid-β and iron. The phase of the complex MRI signal of a T_2^*-weighted sequence is very sensitive to changes in iron deposition. Therefore T_2^*-weighted images were acquired in 15 mild to moderate AD patients and 16 control subjects. Phase measurements were performed in the cortex of different regions of the brain and in the hippocampus. It was found that the phase shift between gray and white matter in the cortex was increased in AD patients and that these differences were strongly associated to the Mini Mental State Examination, which tests basic cognitive functions. No differences were found in the hippocampus phase values. Therefore the increased cortical phase values on T_2^*-weighted images might provide a new biomarker that measures early changes related to amyloid pathology.

Chapter 9 reviews the current status of studies performed in patients with neurodegenerative diseases performed at 7 Tesla. Some of the technical challenges and solutions are discussed. Despite the limited number of purely clinical studies to date promising additional features in contrast can be obtained that may assist in better diagnosis of these disorders. High field MRI allowed to visualize the lenticulostriate arteries with great detail in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). In patients with AD and hippocampal sclerosis anatomical changes were observed using high resolution imaging. The increased contrast and resolution allowed visualizing the perivenous location of multiple sclerosis lesions and the frequent cortical involvement. Given the rapid progress over the last years it is expected that the contribution of 7 Tesla MRI especially in the field of neurodegenerative diseases will increase over time. Many of the initial problems related to magnetic and RF field inhomogeneities and the lack of optimized sequences have been solved or improved.

The acceptance of 7 Tesla MRI examinations by subjects is discussed in **chapter 10.** In order to fulfill the promise of increased spatial resolution and increased sensitivity for the identification of pathologies in the clinical setting, it is important to assess how well examinations are tolerated by subject and to identify potential adverse side effects. A total of 101 healthy subjects filled out a post scan survey with questions related to potential sensations of discomfort, such as nausea, vertigo and scanner noise. The most frequent (34% of subjects) mentioned negative finding was dizziness while moving in the scanner, followed by scanner noise (33%) and dizziness moving out (30%), also a metallic taste was reported in about 1 in 10 cases. Although the sensations of discomfort are mentioned more frequently than at lower field strength, overall the examinations were tolerated very well. Only 3% of the subjects rated the examination as unpleasant. These results provide further evidence that 7 Tesla MRI would be accepted by patients as with lower field strength examinations.

CONCLUSIONS

This thesis has shown that in order to fully benefit from the expected increase in signal-to-noise ratio and improved contrast of 7 Tesla specific sequence and hardware adaptations are necessary. Many standard techniques from lower field strength require to be redesigned taking into account the specific constraints of 7 Tesla MRI, such as inhomogeneous RF fields (**chapters 2, 3 and 4**) and increased sensitivity to B_0 artifacts (**chapters 5 and 6**). With proper adjustments it is possible to perform studies in almost all anatomies including difficult regions, such as the heart. The promises of 7 Tesla: higher SNR, resolution and faster scanning can be (partly) fulfilled. This has resulted in improved visualization of the right coronary artery, compared to 3 Tesla. With specific calibration sequences that take into account the inhomogeneous RF distribution the SNR of spectra obtained in the calf muscle could be improved. The high magnetic field strength results in very high contrast of T_2^*-weighted images; however the sensitivity to B_0 fluctuations can deteriorate the image quality substantially when applied in patients, who are typically more restless than healthy subjects. A correction technique was developed to reduce these artifacts, which allowed imaging of Alzheimer's disease patients with high image quality (**chapters 5, 6 and 8**). Improvements in the efficiency of T_2^*-weighted sequences resulted in whole brain acquisitions within acceptable scanning times (**chapter 7**), which is of great importance for the clinical introduction. Over the years the number of studies has steadily increased, however there is still only a limited number of pure clinical patient studies performed. The diagnostic added value of 7 Tesla MRI is

beginning to be demonstrated in patients with neurodegenerative diseases, which is also a large part of the patient studies performed so far (**chapter 9**). The largest advances are mainly seen in increased resolution resulting in more accurate visualization of Multiple sclerosis lesions, or visualization of small vessels that were previously not visible at lower field strengths. Visualization of microbleeds and changes in iron deposition, common to many neurodegenerative diseases, such as Alzheimer's disease is improved due to both the increased resolution and the increased sensitivity to iron deposition (**chapters 8 and 9**). The larger spectral separation of metabolites due to an increased chemical shift results in more accurate quantification of metabolites in for example Huntington's disease patients. Patient acceptance is of importance when 7 Tesla MRI is to be used in regular clinical practice, in healthy subjects the 7 Tesla examinations were tolerated very well (**chapter 10**).

These initial findings combined with the fact that 7 Tesla examinations are well tolerated by subjects will likely result in more clinical examinations performed at 7 Tesla. Due to some intrinsic issues (mainly B_1 and B_0) and the high cost, 7 Tesla MRI is not likely to replace all studies currently performed at lower field strength. Therefore it should probably not be considered to be a "one-stop-shop" technique; some applications are better served at lower field strength. High resolution brain imaging; especially combined with the increased sensitivity to the distribution of iron, or the ability to visualize very small arteries has already shown added value and could lead to new insight in early disease processes of neurodegenerative diseases. Future clinical research should focus on these areas, which could improve patient outcome. For most other anatomies more technical developments are needed before the full benefit of 7 Tesla MRI can be obtained.