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**Title:** Monitoring Alzheimer's disease in transgenic mice with ultra high field magnetic resonance imaging  
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Summary

Dementia due to AD has had tremendous impact on the affected individuals, caregivers and medical healthcare system. Both developed and developing countries will face the challenge of coping with a high frequency of AD, which is a characteristic of aging societies. However, there is still no effective treatment for AD and the underlying mechanisms of the disease remain largely unknown.

While aging remains one of the most significant risk factors for development of AD, increasing evidence strongly points to the potential roles of cerebrovascular and white matter abnormalities in AD development. A better understanding of the manner in which these abnormalities contribute to disease progression can be achieved by in vivo characterization of AD related pathologies. To this end, MR based techniques such as magnetic resonance angiography and relaxometry serve as effective non-invasive tools to longitudinally monitor changes in AD brain. The resolution and sensitivity of these MR based techniques used in clinical studies, however, are hampered by low magnetic fields (≤3T). To overcome this limitation, MRI systems having high field strength (≥7T) have been developed. Ultra high magnetic field MRI provides high sensitivity, increased resolution and better spectral dispersion of brain metabolites. These systems may cause a paradigm shift in AD research through the in vivo observation of subtle structural, metabolic and functional changes in the AD brain.

An advanced understanding of AD pathology can be achieved by validating in vivo changes with histology. To this end, transgenic mouse models of AD, which develop amyloid pathology, serve as valuable preclinical models to study the disease. In vivo imaging of these mouse models at ultra high magnetic field strengths can permit a better understanding of the underlying cellular mechanism of AD. This knowledge can be used to develop potential biomarkers and promising treatment strategies to impede and/or prevent AD progression.
In this thesis, a variety of MR based techniques were optimized and employed to longitudinally monitor the AD progression in transgenic mouse models of the disease at 9.4 T and 17.6 T. The relevance of this work is summarized in Chapter 1.

In Chapter 2, age-dependent blood flow alterations were examined in a Tg2576 mouse model of Alzheimer's disease using MR angiography at 17.6 T. AD is linked to abnormalities in the vascular system. Here ultra-high field MRA was employed to monitor age-dependent cerebrovascular alterations in the Tg2576 model. The blood flow alterations observed in the middle cerebral artery and anterior communicating artery increased in the Tg2576 mice compared to the wild-type mice over time. Histological data revealed that these alterations such as signal voids might be correlated with severity of Aβ type of CAA. These results show that ultra-high field MRA is a valuable tool to monitor blood flow alterations longitudinally in living mice.

In Chapter 3, in vivo T2 changes were longitudinally monitored in the corpus callosum, the largest white matter structure in the brain, of the Tg2576 mice. Being sensitive marker for tissue pathology, in vivo T2 changes depicted severe pathology in the corpus callosum as well as in the gray matter regions of Tg2576 mice. In particular, a marked increase in T2 values was observed in the 10 months of age Tg2576 mice suggesting early microstructural changes in the white matter. These pathologies were correlated with gliosis, demyelination, and Aβ deposition.

In Chapter 4, age-dependent regional brain T1 and T2 changes in C57BL/6J mice were established at 17.6T. Being the main component of contrast in MRI, the estimates of in vivo T1 and T2 will be useful in future studies to optimize pulse sequences for optimal image contrast at 17.6T and will serve as baseline values against which disease related relaxation changes could be assessed in mice. Chapter 5 presents general discussion and future outlook of the thesis.