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Chapter 8

Summary and general discussion

The general aim of this thesis was to explore the possibility to detect changes related to amyloid deposition in vivo using ultra-high field MRI.

In chapter 2 we demonstrated that abnormalities can be observed in *post-mortem* human brain specimens with cerebral amyloidosis including patients with Alzheimer's disease (AD), Down Syndrome (DS), sporadic and hereditary cerebral amyloid angiopathy (CAA), and healthy controls on a human 7 Tesla (T) MRI system. These abnormalities comprise hypointense foci and less circumscript areas of decreased signal intensity that give rise to an inhomogeneous, grainy aspect of the cortex. These changes could be detected on T_2^*-weighted sequences, using clinically acceptable acquisition times, suggesting that these techniques are applicable in a clinical setting.

In chapter 3 we continued our work using this same technique in patients with AD and healthy controls in order to translate our ex vivo findings to the in vivo situation. In this study we could not replicate the ex-vivo finding of hypointense foci, that might represent amyloid plaques. Nevertheless, this study showed that using this novel ultra-high field imaging approach at 7T, patients with clinical symptoms of AD demonstrated an increased cortical phase shift on T_2*-weighted images. These phase shifts between AD patients and control subjects have a high specificity, independent of age and gender. Moreover, these phase shifts correlated with individual mini mental state examination (MMSE) scores. Of all cortical areas studied, the parietal cortex showed the highest specificity combined with the highest sensitivity for the diagnosis AD and the strongest correlation with MMSE.

In chapter 4 we refined the method we used in the previous chapter in order to be able to quantitatively assess cortical phase differences not only at the level of cerebral lobes, but with a higher anatomical resolution in sub-regions of the major lobes. We used this method to assess phase differences between two types of AD patients: those with an early (EOAD) and those with a late onset (LOAD) of the disease symptoms. Both groups were also compared to controls. EOAD and LOAD patients showed an increased phase difference in the cortex compared to controls. Using this new method we were also able to observe a cortical phase difference between LOAD and EOAD patients. Mean regional phase contrast was higher in EOAD patients as compared to LOAD patients in the superior medial frontal gyrus, middle frontal gyrus, anterior and middle

cingulate gyrus, postcentral gyrus, superior parietal gyrus, inferior parietal gyrus and precuneus independent of disease severity measured by MMSE. The finding of an increased phase shift in EOAD patients as compared to LOAD patients suggests that iron accumulation, possibly due to amyloid deposition, is more severe in the EOAD patients within specific regions of the brain.

The aim of the work presented in chapter 5 was to investigate whether phase changes reflect relatively early cerebral AD changes. Therefore we studied patients with subjective cognitive impairment (SCI), who as a group have an increased risk of developing AD dementia and presumably also include patients with a relatively early phase of AD. In addition, in this heterogeneous group of patients we assessed whether phase changes were associated with cognitive function. In this study, we found that in SCI subjects an increased cortical phase shift is associated with poorer memory performance, although as a group, SCI did not show an increased phase shift compared to controls.

In chapter 6 the prevalence of microinfarcts in AD patients and their association with cognitive function and CAA was investigated using 7T MRI. Recently, there has been accumulating evidence that so-called microinfarcts are a common neuropathological finding in the aging brain in cognitively normal elderly people [1], AD patients [2] and CAA patients [3-5]. Autopsy studies have shown an independent relation between the presence of cortical microinfarcts and cognitive dysfunction [6-8]. Using 1.5 and 3T MRI systems remote microinfarcts are hard to detect and are seen rarely [9]. Recently, it has been demonstrated that using 7T MRI the in vivo detection of remote microinfarcts can be improved [2,10,11]. At 7 Tesla we found an increased number of cortical microinfarcts in AD patients in comparison to controls, and these lesions were associated with cognitive dysfunction. The presence of these microinfarcts was mainly AD-related, although our results indicate that they might be CAA-related as well: however, the contribution of AD was more significant. The detection of these lesions *in vivo* opens up the possibility to obtain a better understanding of the contribution of microinfarcts to the pathophysiology of several diseases, such as AD and vascular dementia, using 7T MRI.

In chapter 7, the diagnostic value of two recently discovered MRI manifestations of sCAA, microbleeds (MBs) and superficial siderosis (SS), was assessed in patients with hereditary cerebral hemorrhage with amyloidosis- Dutch type

(HCHWA-D). In contrast with the previous chapters in which ultra-high field imaging was used, in this chapter 1.5T MRI was used. We aimed to analyze and refine the imaging components of the Boston criteria for CAA based on T_2^*-weighted 1.5T MRI in a group of symptomatic and asymptomatic HCHWA-D patients. This analysis exploits the ability of noninvasive genetic testing to diagnose HCHWA-D, allowing the results to be extended to patients without available neuropathologic specimens. Our data show that using T_2^*-weighted 1.5T MRI in patients with proven CAA, the Boston criteria have a high sensitivity for the interpretation of a hemorrhagic lesion as a manifestation of CAA. The sensitivity of the criteria is increased by inclusion of corticosubcortical MBs and is not reduced by excluding hemorrhagic lesions in the deep white matter, basal ganglia, thalamus, or brainstem. SS is relatively common in our population but did not influence the sensitivity of the Boston criteria in the studied subjects.

The central finding of the work presented in this thesis is the cortical phase change on T_2^*-weighted sequences that we observed in AD patients. It has been demonstrated that such phase measurements are a reliable indicator of iron content in the brain [12-15]. It is known that amyloid depositions co-localize with iron accumulations. However, in autopsy material of AD patients, in addition to amyloid deposition, neurofibrillary tangles as well as tau deficiency were also found to co-localize with neuronal iron accumulation [16-18]. In addition to iron, myelin and deoxy-hemoglobin also contribute to phase changes [19]. Although the exact origin of the observed phase changes in AD is not completely clear, these changes could have value for diagnostic purposes and as a biomarker.

Several issues need to be investigated further. From a practical perspective, the 7T MRI contra-indications are very strict. As we experienced in our research which started in 2009, many participants had to be excluded, because they had for example stents, gall blather removal clips or implanted metallic materials in their mouth. In the older population of the memory clinic these kind of metallic implants in the body are very common and therefore form a restriction to scan larger populations from the memory clinic. In the meantime, a lot of work has been done to solve this issue as multiple metallic implants have been tested and have been shown to be safe in the 7T scanner. More metallic implants are still being tested for safety. So concerning the 7T MRI contra-indications aspect, 7T MRI will be applicable for many more memory clinic patients in the near future.

From a clinical perspective, it will be very important to investigate whether our 7T methods are able to differentiate between different forms of dementias, such as frontal temporal dementia, Lewy body dementia and vascular dementia. AD and these other forms of dementia are in some cases hard to distinguish based on the tools we use now in the clinic. So far, we have only investigated (early stages of) AD versus controls: however, for 7T MRI to become useful in a memory clinic population, we have to investigate whether the changes we found in AD are specific for AD or are also observed in other types of dementia.

With respect to detecting amyloid deposition in an early stage, we have performed many exploratory studies. We did not find abnormalities in SCI subjects as a group. However, because this is a very heterogeneous group in which probably only 20% will develop AD, and multiple factors can contribute to the presence of cognitive complaints, it is very difficult to interpret the results and several explanations of our findings are possible. A longitudinal study in SCI subjects, but also in amnestic mild cognitive impairment subjects, should be performed to investigate the ability to detect AD pathology in an early stage of the disease. Such a longitudinal study would also allow studying the progression of the presumed pathology over time.

Besides our studies on AD, we also investigated HCHWA-D with the purpose of developing better diagnostic criteria for the sporadic variant, sCAA. We demonstrated that by including cerebral microbleeds in the Boston criteria for CAA the diagnostic performance of these criteria improved. However, the ability to detect vascular amyloid deposits in these patients would be very helpful to understand the disease process, might give more insight in the prognosis of the disease and could aid in therapeutic trials. This would be beneficial for both sCAA patients as well as HCHWA-D patients as there is still much unknown about these diseases. As imaging methods using 7T improved over time and we developed new methods to analyze 7T images based on AD, it would be relatively easy to apply these same methods in HCHWA-D patients as well. Moreover, with the higher resolution and sensitivity for iron, we might also be able to detect smaller hemorrhagic lesions and in much more detail which will give us a better insight into the pathological mechanisms of the disease. At this moment, work on HCHWA-D using 7T MRI is in progress and results are expected soon.

References

1. Sonnen JA, Santa CK, Hemmy LS et al. Ecology of the aging human brain. Arch Neurol. 2011;68:1049-1056.
2. Brundel M, de BJ, van Dillen JJ et al. Cerebral microinfarcts: a systematic review of neuropathological studies. J Cereb Blood Flow Metab. 2012;32:425-436.
3. Charidimou A, Gang Q, Werring DJ. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. J Neurol Neurosurg Psychiatry. 2012;83:124-137.
4. Okamoto Y, Yamamoto T, Kalaria RN et al. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. Acta Neuropathol. 2012;123:381-394.
5. Soontornniyomkij V, Lynch MD, Mermash S et al. Cerebral microinfarcts associated with severe cerebral beta-amyloid angiopathy. Brain Pathol. 2010;20:459-467.
6. Gold G, Kovari E, Hof PR et al. Sorting out the clinical consequences of ischemic lesions in brain aging: a clinicopathological approach. J Neurol Sci. 2007;257:17-22.
7. Kovari E, Gold G, Herrmann FR et al. Cortical microinfarcts and demyelination affect cognition in cases at high risk for dementia. Neurology. 2007;68:927-931.
8. Kovari E, Gold G, Herrmann FR et al. Cortical microinfarcts and demyelination significantly affect cognition in brain aging. Stroke. 2004;35:410-414.
9. Ii Y, Maeda M, Kida H et al. In vivo Detection of Cortical Microinfarcts on Ultrahigh-Field MRI. J Neuroimaging. 2012.
10. Jouvent E, Poupon C, Gray F et al. Intracortical infarcts in small vessel disease: a combined 7-T postmortem MRI and neuropathological case study in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Stroke. 2011;42:e27-e30.
11. van Veluw SJ, Zwanenburg JJ, Engelen-Lee J et al. In vivo detection of cerebral cortical microinfarcts with high-resolution 7T MRI. J Cereb Blood Flow Metab. 2012.
12. Ogg RJ, Langston JW, Haacke EM et al. The correlation between phase shifts in gradient-echo MR images and regional brain iron concentration. Magn Reson Imaging. 1999;17:1141-1148.
13. Haacke EM, Cheng NY, House MJ et al. Imaging iron stores in the brain using magnetic resonance imaging. Magn Reson Imaging. 2005;23:1-25.
14. Haacke EM, Ayaz M, Khan A et al. Establishing a baseline phase behavior in magnetic resonance imaging to determine normal vs. abnormal iron content in the brain. J Magn Reson Imaging. 2007;26:256-264.
15. Yao B, Li TQ, van Gelderen P et al. Susceptibility contrast in high field MRI of human brain as a function of tissue iron content. Neuroimage. 2009;44:1259-1266.

16. Duce JA, Tsatsanis A, Cater MA et al. Iron-Export Ferroxidase Activity of beta-Amyloid Precursor Protein Is Inhibited by Zinc in Alzheimer's Disease. Cell. 2010;142:857-867.
17. Lei P, Ayton S, Finkelstein DI et al. Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export. Nat Med. 2012;18:291-295.
18. Smith MA, Harris PL, Sayre LM et al. Iron accumulation in Alzheimer disease is a source of redox-generated free radicals. Proc Natl Acad Sci U S A. 1997;94:9866-9868.
19. Duyn JH. Study of brain anatomy with high-field MRI: recent progress. Magn Reson Imaging. 2010;28:1210-1215.