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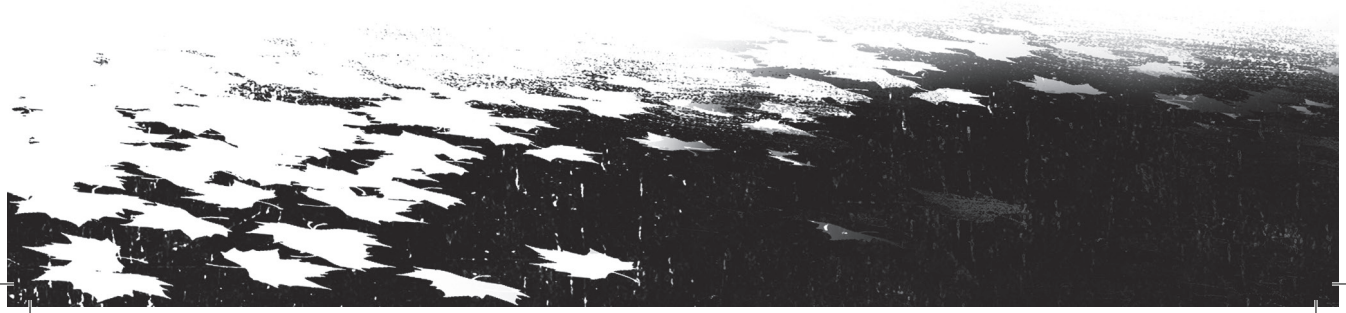
Summary and general discussion



The overall objective of this thesis was to investigate functional connectivity and cerebral perfusion in patients with (early) AD and other types of dementia caused by neurodegenerative diseases by means of several imaging and analysis techniques. With our overall objective, we aimed to obtain a better understanding of the studied diseases, and to attribute to the possible role of functional and perfusion MRI in the workup of dementia patients. The previous chapters described these studies in detail. The present chapter summarizes the main findings and provides a discussion of relevant issues related to the studies. The chapter closes with suggestions for future research.

SUMMARY

Chapter 2 consists of resting state BOLD fMRI studies, in which we investigated functional connectivity in patients with MCI and AD. In **chapter 2.1** we studied functional connectivity within RSNs by comparing subject-specific RSN functional coherence maps that were created with the dual-regression method.[1] Analyses were corrected for age, sex and additionally for gray matter volume. Compared to controls, AD patients showed lower default mode network functional connectivity in the precuneus and posterior cingulate cortex, independent of cortical atrophy. Mean functional connectivity values of MCI patients in this region were numerically in between those of controls and AD patients. Only the difference between AD patients and non-converting MCI patients was statistically significant. A relationship within AD patients between functional connectivity and performance on the Rey Figure Copy test illustrated the clinical relevance of functional connectivity changes within the default mode network.

Using the same analysis technique, in **chapter 2.2** we compared functional connectivity within RSNs of patients with early-onset AD (i.e., before the age of 65) and patients with late-onset AD. Compared to age-matched healthy controls, we found lower functional connectivity in early-onset AD patients within all eight RSNs, and lower functional connectivity in late-onset AD patients within the default mode network. When comparing early-onset and late-onset AD patients, early-onset AD patients showed lower functional connectivity in five of the eight RSNs compared to late-onset AD patients. However, these findings did not remain significant after correcting for multiple testing. Late-onset AD patients showed no regions of lower functional connectivity in any of the RSNs compared to early-onset AD patients. Regional functional connectivity differences were more extensive than gray matter volume differences. Across AD patients, lower functional connectivity within the default mode network was associated with worse performance on visuoconstruction, and lower functional connectivity in the right dorsal-visual system was associated with worse performance on attention tasks.

In **chapter 2.3** we used Eigenvector centrality to compare functional connectivity of AD patients and healthy controls. Centrality expresses the importance of nodes in a network. The benefit of a centrality analysis is that it can be used to investigate the global organization of the whole-brain network, as opposed to investigating functional connectivity within specific sub-networks (such as the above described RSNs). Because the output of a centrality analysis is a single map per subject, group analysis is possible without selecting sub-networks of interest. In this chapter we found that AD patients showed regions of lower Eigenvector centrality in the bilateral occipital cortex, and regions of higher Eigenvector centrality in the medial frontal cortex compared to healthy controls. Across diagnostic groups, Eigenvector centrality changes within these regions were related to cognitive performance and levels of CSF biomarkers amyloid-β and total-tau. Within controls, AD-like occipital Eigenvector centrality changes were related to worse cognitive performance.

The third chapter of this thesis describes our findings when using pseudo-continuous ASL to study cerebral perfusion in different neurodegenerative diseases. In **chapter 3.1** we examined total and regional CBF of AD patients, MCI patients and controls (consisting of patients with subjective complaints), and the relation between CBF and cognitive performance. Both uncorrected and partial-volume-corrected CBF was studied, and analyses were performed in a region-of-interest and a voxel-wise fashion. We found AD patients to show lower CBF values compared to controls in all brain regions except the cerebellum. Quantitative CBF values of MCI patients were intermediate between those of AD patients and controls, and significantly lower compared to controls in the parietal and occipital lobes. Voxel-wise comparisons showed largest CBF decreases in AD and MCI patients in the posterior cingulate, precuneus and more extended bilateral parietal areas. Correlation analyses showed a strong relation between CBF and cognitive function within the group of AD patients.

Purpose of **chapter 3.2** was to compare perfusion patterns of patients with AD, DLB and the behavioural variant of FTD. Regional CBF values were compared using analyses-of-variance for repeated measures, which resulted in the finding that regional CBF patterns differed between the diagnostic groups. Lowest regional CBF values were seen in DLB, with a preservation of temporal CBF. In AD, CBF was most prominently decreased in the posterior brain regions. Supratentorial partial-volume-corrected gray matter CBF values were lowest in the frontal lobes in FTD patients, and in the temporal lobes in AD patients. Voxel-wise comparisons confirmed the region-of-interest based results, and provided spatial maps visualizing the between-group CBF differences.

In **chapter 3.3** we studied CBF in predementia AD. Predementia AD stages were based on the National Institute on Aging – Alzheimer's Association (NIA-AA) scientific criteria.[2,

[3] For scientific purposes, these criteria offer the possibility to subdivide predementia patients into different AD stages, using amyloid-β and neuronal injury biomarkers. We used CSF biomarkers amyloid-β and total-tau to subdivide patients with subjective complaints (SC) and mild cognitive impairment (MCI) into four different stages: a) stage 0 (control group), consisting of SC patients with normal CSF amyloid-β and total-tau, b) stage 1 predementia AD, consisting of SC and MCI patients with abnormal CSF amyloid-β and normal total-tau, c) stage 2 predementia AD, consisting of SC and MCI patients with abnormal CSF amyloid-β and total-tau, and d) stage 3 AD dementia, consisting of patients with probable AD and abnormal CSF amyloid-β and total-tau. Results showed that lower CBF was related to more advanced stages of AD, which was demonstrated by the dose-response relationships found between CBF and (predementia) AD stages. There were no significant regional CBF differences between predementia patients and controls. Furthermore, CBF was related to cognitive performance across AD stages and within the group of clinically demented AD patients.

Besides cortical atrophy, expressions of small vessel disease are a common finding on structural MRI in patients with AD. In **chapter 3.4** we aimed to improve our understanding on how both neurodegeneration and small vessel disease are related to CBF in AD. We found that smaller brain volumes and larger WMH volumes were both, independently, associated with lower CBF in AD. In controls, larger WMH volume tended to be associated with lower CBF, and brain volume was not associated with CBF. These findings indicate that low CBF in AD patients is not only related to neurodegeneration, but to cerebral small vessel disease as well.

DISCUSSION

Clinical implications

In this thesis we used BOLD fMRI and ASL MRI to study functional connectivity and CBF in patients with (early) AD, driven by the assumption that functional neuroimaging techniques provide early markers for AD.[4-6] In line with the pertinent literature, AD patients displayed decreased functional connectivity and cerebral perfusion, (most prominently) located in the posterior brain regions.[7-10] Our studies showed that these functional changes were related to cognitive performance, which was most outspokenly the case for ASL-measured CBF within the group of clinical AD patients. In accordance with that finding, prodromal AD patients consistently showed functional connectivity and CBF values that were in between those of controls and AD patients. Furthermore, cerebral perfusion was shown to decrease with increasing (NIA-AA based) predementia AD stages. These findings endorse that BOLD fMRI and ASL measures decrease in a

predementia stage,[8, 11-15] and continue to change along the course of AD without reaching a floor effect in an early stage of the disease,[16] which is also suggested by the current hypothetical biomarker models.[4-6] This characteristic makes both measures suitable as tools to estimate disease severity and to monitor disease progression, e.g. in the setting of clinical trials.

Besides monitoring disease progression, ASL-MRI also has the potential of playing a future role in the diagnostic workup of dementia patients. Currently, FDG-PET is the standard clinical imaging tool to assess functional changes in terms of hypometabolism in (prodromal) AD. Since glucose metabolism and perfusion are closely related, ASL is considered a potential alternative for the visualization of cerebral (and neuronal) function in the workup of dementia patients.[17-19] When added to the standard scanning protocol, ASL may prevent the necessity of acquiring an FDG-PET scan in (some of) the cases that currently undergo FDG-PET. This could result in decreasing costs, radiation exposure and patient burden. However, further studies are needed to address the reliability of ASL at the single-subject level.

Neuronal function and perfusion

Although voxel-wise comparisons show regional associations between FDG-PET and ASL, the exact relationship between metabolism and perfusion in AD is not fully understood. In a broader sense, the question that remains unanswered is how neuronal dysfunction and CBF alterations are related, and which one precedes the other in AD. In chapter 3.3 we showed that ASL does not decrease until at least CSF amyloid-β and total-tau are both abnormal. In an FDG-PET study by a different group, glucose metabolism was shown to decrease in healthy controls with abnormal CSF amyloid-β alone.[20] This would suggest that metabolism decreases at an earlier AD stage than perfusion, suggesting that perfusion decreases are a response to decreased neuronal function in AD. A direct comparison of perfusion and metabolism in predementia AD is essential to confirm this idea. Furthermore, those regions that are found to be functionally most connected, have also been shown to be particularly vulnerable to amyloid deposition, hypometabolism and cortical atrophy. This poses the idea that high neuronal activity leads to amyloid deposition, resulting in neuronal dysfunction and neurodegeneration, which eventually leads to decreased cerebral perfusion because of a lower demand as opposed to vascular damage.[21-23]

By contrast, other studies suggest that vascular damage may as well be a driving factor in the cascade of functional changes in AD.[24-28] A group that compared vascular dementia to AD showed cortical ASL-CBF to be generally lower in patients with subcortical ischemic

vascular dementia than in patients with AD, and subcortical white matter lesion burden to be inversely correlated with cortical CBF.[27] In chapter 3.4 of this thesis, we found that lower CBF in AD was not only related to smaller brain volumes (neurodegeneration), but, independently, to larger WMH volumes (small vessel disease) as well. Similarly, a study that investigated vasoreactivity to hypercapnia in MCI patients and controls found that ASL-measured CBF changes in the hippocampus were inversely correlated with the Framingham cardiovascular risk profile (FCRP). This relationship was strongest in the MCI patients, who also more generally exhibited decreased vasoreactivity compared to controls regardless of FCRP, suggesting that there may be independent effects of early neurodegeneration and vascular risk on vessel function.[25, 29] A model presented by Cordonnier and Van der Flier, in their search for the role of brain microbleeds in the pathogenesis of AD, illustrates how vascular damage, either caused by the amyloid-cascade or vascular risk factor pathway, may lead to hypo-perfusion and ischemia that precedes neuronal dysfunction,[24] advocating a precipitating influence of perfusion in AD brain dysfunction. ASL offers great potential as a tool to better understand the vascular changes that appear to occur in conjunction with AD-related pathology, which may be closely related to the pathophysiology and progression of AD.[29, 30]

An interesting point in this context is the finding and meaning of functional increases in (early) AD. In chapter 2.3 of this thesis, AD patients showed increased functional connectivity in the anterior cingulate cortex, in addition to decreased functional connectivity in the posterior brain regions. Several other studies have detected functional connectivity increases within frontal regions,[31, 32] or between the frontal cortex and the posterior cingulate cortex [12, 33] or hippocampus [34] Similarly, regional hyper-perfusion has also been reported in at-risk controls and (early stage) AD patients, located in the frontal regions and the medial temporal lobes.[8, 35-37] Attempts at plastic remodeling, compensatory or pathological elevation of neural activity, inflammation, or elevated production of vasodilators are mentioned as possible explanations for these increases.[35, 37] Remarkable is the fact that these increases in functional connectivity and perfusion do not generally correspond with FDG-PET measured increases in glucose metabolism. While decoupling of glucose metabolism and perfusion in regions of hypoperfusion could be explained by vascular compromise, the explanation for decoupling in regions of hyperperfusion is unclear. Direct comparisons of neuronal function and perfusion measures in predementia AD may contribute to a better understanding of the (causal) relationship between neuronal function and perfusion.

So far, we have only preliminary data from our own center on the relationship between cerebral perfusion and neuronal function, and the influence of AD on this relation. We have analyzed ASL-MRI and resting state BOLD fMRI scans of 17 controls (age

57±9, 47% female, MMSE 28±2) and 24 AD patients (age 66±7, 38% female, MMSE 21±4). Preprocessing was performed as described previously.[38, 39] For each subject, we calculated voxel-wise Spearman correlations between a) CBF and mean of the BOLD signal and b) CBF and standard deviation of the BOLD signal. Correlation analyses were performed within subject-specific masks of the brain extracted fMRI scan, and also within a subject-specific mask of voxels that consisted for more than 90% of gray matter. Differences in mean voxel-wise Spearman correlations between diagnostic groups were analyzed using ANOVA with post-hoc Bonferroni tests, adjusting for age, sex and number of voxels included in the mask. Preliminary results showed that CBF and mean BOLD signal were strongly related in controls (min-max rho = 0.51-0.76, $p < 1x10^{-16}$) and that this association was significantly weaker (p=0.001) in AD patients (min-max rho = 0.30-0.71, $p < 1x10^{-16}$). CBF and standard deviation of the BOLD signal also showed a strong relationship in controls (min-max rho = 0.30-0.70, $p < 1x10^{-16}$) and AD patients (min-max rho = 0.33-0.65, $p < 1x10^{-16}$), and this association was similar for both groups. Results were similar when subject-specific gray matter masks were used, and so differences in cortical volume cannot explain the found group differences.

Mean CBF values were lower in AD patients than in controls ($p<0.05$), but there were no differences in mean BOLD signal values between both groups. The BOLD signal is the result of local changes in the ratio of oxygenated to deoxygenated hemoglobin in the blood. One could speculate that, in order for mean BOLD signal values to remain unchanged when CBF decreases, neuronal activity needs to be decreased in AD patients as well. This would then result in less deoxygenated blood and therefore similar oxygenated-to-deoxygenated hemoglobin ratios. However, further research is required to better understand current preliminary results. It would for example be informative to visualize and explore regional relations between CBF and mean BOLD signal values, in order to understand which regions drive the current preliminary results. Furthermore, neuronal activity and functional connectivity are two related but different measures. An additional exploration of regional relations between CBF and functional connectivity (as opposed to neuronal activity) would contribute to a more complete understanding of the relation between these different measures and their role in (patho)physiological functioning of the brain.

Methodological considerations

As previously mentioned, ASL is considered a potential measure for the visualization of cerebral function in the workup of dementia patients.[17, 19, 40] It is important to point out that all studies in this thesis were performed on a group level. Studies performed on the

individual level, in larger groups, and with more diagnostic variation, are necessary to confirm the additional value of ASL in the clinical setting.

In chapters 3 and 4 of this thesis, controls consisted of patients that visited our memory clinic with subjective complaints. Extensive clinical workup and neuropsychological testing showed no cognitive impairment or any other abnormalities in these patients. Although this may be considered a limitation, including patients with subjective complaints as controls actually provides a good reflection of the clinical reality. Moreover, the influence of such a control group will more likely result in an underestimation of between-group differences than in an overestimation.

Neurodegenerative diseases such as AD are characterized by cortical atrophy. Decreases in gray matter volume directly affect functional MRI measures through increased partial volume effects. When investigating differences in functional connectivity or CBF between AD patients and controls, the effect of partial volume on tissue-specific functional MRI measures is therefore an important issue that needs to be addressed, especially when these functional measures are used for scientific purposes. Although there is no real consensus on which methods are best to correct for partial volume effects or cortical atrophy, we attempted to address this matter as good as possible in each of our studies. In chapters 2.1 and 2.2, normalized gray matter volumes and voxel-wise gray matter probability maps were added as covariates in the voxel-wise between-group analysis, whereas in chapter 2.3 voxel-based morphometry was used to examine and present differences in gray matter density between AD patients and controls. In chapter 3, tissue-specific CBF maps were calculated by using a regression algorithm assuming perfusion in cerebrospinal fluid to equal zero and tissue-specific perfusion to be locally homogeneous.[41] To respect the fact that ASL is considered both a potential diagnostic imaging tool in the dementia workup and a research tool that may contribute to a better understanding of the disease process in AD, we chose to report both uncorrected CBF values and partial volume corrected CBF values in our studies in chapter 3.

ASL scans used in this thesis were not acquired with several delay times to account for between-group differences in travel time. To alleviate the effect of delayed blood arrival in the brain of our study groups (e.g. age, cerebrovascular co-morbidity, delayed transit time due to underlying pathology), we used a post-label delay time of 2.0s instead of the commonly used 1.5s.[42] Furthermore, many factors may cause global between-subject perfusion variability. In the studies described in this thesis we did not apply a correction for possible confounders such as history of diabetes, depression, stage of digestion, smoking habits and recent caffeine intake. Future studies are needed to clarify the effect of these factors on CBF, and their contribution to between-subject variability.

Various studies have used reference regions (such as visual cortex and whole brain CBF) to normalize regional perfusion data. However, there is no consensus on which region to use best as reference region for CBF normalization. The absolute quantification of ASL-measured CBF in units of mL/100g/min makes it possible to compare CBF across sites and scanning sessions, and to present cut-off values for clinical practice.[29, 43] Despite of the disadvantage of intersubject-variability, we therefore chose to compare and present the absolute CBF values instead of normalized CBF in our studies.

SUGGESTIONS FOR FUTURE RESEARCH

Suggestions for future research are twofold. First, functional (i.e., BOLD and ASL) MRI may contribute to elucidating whether neuronal dysfunction leads to perfusion changes (as a result of the demand for glucose and oxygen), or whether perfusion changes (e.g., due to vascular damage) lead to neuronal dysfunction. Directly comparing different functional imaging measures in a longitudinal setting may help resolve this question and improve our understanding of the underlying disease process in AD. An extension of the previously described preliminary cross-sectional voxel-wise comparison between BOLD and ASL MRI will be a logical next step to further explore the relation between these processes under the influence of AD pathology. Including measures such as FDG-PET, MEG and gray matter connectivity, possibly even in combination with molecular and other structural imaging techniques, may further contribute to unravel the mystery of the order of functional pathological changes in AD from an imaging perspective.

Second, we showed that BOLD and ASL both detect functional MRI changes in AD and its prodromal stage, and that their measures continue to change along the course of the disease. These characteristics make these functional MRI techniques promising tools for disease monitoring of cases otherwise diagnosed with AD (for instance with amyloid PET), or for making prognostic estimates. Since all studies in this thesis were performed at a group level, further investigations are necessary to confirm whether both BOLD and ASL MRI are useful tools for disease monitoring at the individual level. As for ASL, it would be interesting to investigate its additional value when added to the standard (structural) MRI protocol, i.e., the additional value of ASL in the differential diagnosis of (early) dementia on top of structural MRI. Furthermore, since ASL could be an alternative for FDG-PET imaging, the comparability of FDG-PET and ASL at the individual level and in a qualitative setting needs to be examined. Support vector machine techniques may be of use for developing quantitative pattern recognition tools, inspired by the Herholz automated analysis tool for FDG-PET,[44] to increase clinical applicability and accuracy of ASL as a clinical diagnostic instrument.

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