

## Summary

Examining functional connectivity changes in Alzheimer's disease (AD) is important since neuronal dysfunction is observed early in the disease course. However, changes in functional connectivity in AD are still not completely understood. The aim of this thesis was to explore functional connectivity changes in AD and reflect this against other AD biomarkers. For this purpose, both (f)MRI and PET data were examined. Functional connectivity fMRI was explored using various analysis techniques, in order to understand changes in brain organization at different hierarchical levels. This chapter summarizes the results from the studies described in this thesis and then discusses them in an integrated manner.

In chapter 2 the effect of amyloid-plaque formation and glucose metabolism on cortical volume loss over time was examined. Understanding how AD biomarkers behave over time and how they are related to each other is crucial in understanding underlying mechanisms of the disease. Amyloid-plaque formation was not associated with ongoing cortical volume loss and might therefore not be sensitive for disease progression. This is in line with the ceiling effect of amyloid-plaque formation in the clinical phase of AD. In contrast, glucose metabolism, at baseline was associated with volume loss over time in AD patients.

In chapter 3 it was investigated whether amyloid-plaque formation within the default mode network (DMN) was directly related to decreases in functional connectivity within this same network. A striking spatial overlap of amyloid depositions and regions belonging to the DMN has been observed, but not completely understood. The DMN was shown to have lower functional connectivity in AD patients, and to a lesser extent in mild cognitive impairment (MCI) patients, compared to healthy elderly controls. In line with other studies, amyloid-plaque formation co-localized with areas belonging to the DMN and functional connectivity of the DMN was lower in amyloid-positive subjects when compared to amyloid-negative subjects. However, no associations of the amount of amyloid-plaques with functional connectivity of the DMN within diagnostic groups were found which may have been due to the ceiling effect in amyloid-plaque formation in patients.

In chapter 4 the link between functional connectivity and cognition in early-onset and late-onset AD patients was examined. Age at onset of AD has an important clinical influence on cognitive performance, but is not explained by pathology. It was reasoned that cognitive performance may be reflected by functional connectivity. Early-onset AD patients showed more widespread disruptions in functional connectivity compared to late-onset AD patients, in 5 of the 8 resting-state networks (RSNs). Changes in functional connectivity explained disruptions in cognitive function to a certain extent, although these relationships remain to be further explored.

In chapter 5, a new method for functional connectivity changes was examined with fMRI: eigenvector centrality (EC). Graph analytical measures such as EC allow for investigating functionality of the brain as a whole. This allows for group analysis without

expert intervention, such as selecting (sub)networks of interest. Furthermore, it provides insight into the hierarchical functional structure of the brain. In healthy subjects, high centrality values were observed in parietal and occipital cortex. Results from the group analysis showed a shift in centrality (or node prominence) of parietal to more frontal regions in AD patients compared to controls. Furthermore, centrality across subjects was associated with pathological concentrations in cerebral spinal fluid (CSF), and with global cognitive performance in controls only.

Chapter 6 described the similarities and clinical applicability of glucose metabolism and functional connectivity (both measures of neuronal dysfunction) in AD. Both techniques are believed to measure similar mechanisms in AD, but only few studies examined this in patients. The results indicated that although parietal and occipital cortices were identified with both techniques, no direct associations exist. The coupling between glucose consumption and functional connectivity may be disturbed in AD. Furthermore, glucose metabolism was most robust with highest diagnostic power when distinguishing AD patients from controls.

In chapter 7 it was investigated whether cerebral blood flow (CBF), measured with arterial spin labeling (ASL) MRI, was showing similar diagnostic results as to glucose metabolism, measured with [ $^{18}\text{F}$ ]FDG PET. Similar patterns of reduced CBF and hypometabolism were observed in regions typically associated with AD, suggesting that ASL provides comparable information as [ $^{18}\text{F}$ ]FDG. This study illustrates the promising added value of ASL in a memory clinic setting.

In chapter 8, imaging modalities were integrated in order to enhance diagnostic accuracy of AD with a pattern recognition approach. As expected, [ $^{11}\text{C}$ ]PIB, performed best in distinguishing AD patients from controls (94%) and was used as gauge modality. In line with other studies, [ $^{18}\text{F}$ ]FDG and structural MRI reached high accuracy as well (86% and 88%). Combining kernels in a regional multi-kernel approach outperformed voxel-wise analysis. The combination of DMN functional connectivity, EC maps and gray matter integrity resulted in a good accuracy of 81%. This shows the possibilities of using only MR for automatic image-based classification of AD patients.

In chapter 9 the effect of MR-based attenuation correction (MR-AC) on a relatively new amyloid tracer, [ $^{18}\text{F}$ ]Flutemetamol (FMM), was examined. Integrated PET/MR systems have recently been introduced, allowing for both PET and MRI scanning in a single session, which is very patient friendly. However, attenuation correction on PET/MR could introduce bias since it ignores bone. It was shown that PET/MR was useful for visual rating of FMM and can be used in a clinical setting. For quantitative analysis, higher FMM SUVr values on PET/MR compared to standard imaging on PET/CT were found (6%).