10.

Summary and general discussion

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 cogntive 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 intervation, such as selecting (sub)networks of interst. Futhermore, 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}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}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}C]PIB, performed best in distinguishing AD patients from controls (94%) and was used as gauge modality. In line with other studies, [^{18}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}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%).

General discussion

Amyloid and its effect on brain function

The discovery of Biswal and colleagues [1] that correlated co-activation of brain regions during rest was related to functional organization, prompted the shift from task-based fMRI to resting-state functional connectivity analyses [2]. Since then it has become apparent that functional connectivity is affected in AD patients, and AD may thus be characterized as disconnection syndrome [3]. The DMN seems most vulnerable in AD [4-6], indicated by the striking co-localization of amyloid-β plaques within this network [7]. Based on these observations, it was then shown that lowered functional connectivity is already observed in amyloid-positive, cognitively healthy elderly subjects [8-10]. Therefore, functional connectivity is considered to change relatively early in the disease course. In line with the proposed cascade of events in AD [11], it was hypothesized that functional connectivity changes as a consequence of amyloid-plaque formation. However, functional connectivity already changes before amyloid-β accumulates [12]. Investigating the link between amyloid and functional connectivity will help understanding pathological mechanisms in AD. In chapter 3 we investigated whether amyloid-plaques within the DMN did not only co-localize but were also directly associated with functional connectivity of this network. In line with other studies, amyloid-plaque formation in the DMN was increased in AD and MCI patients [13]. Lower functional connectivity of the DMN was observed in subjects with increased amyloid vs. subjects with low amyloid. However, no direct association was observed within diagnostic groups between the amount of plaques with functional connectivity. As was described in chapter 2, no significant association was found between amyloid depositions and cortical volume loss over time in AD. It was hypothesized that this was due to the plateau-effect of amyloid-plaque formation in AD patients; several studies have described amyloid built-up stagnates in the clinical stage of AD [14-16]. This may also explain why amyloid plaque formation was not associated with changes in functional connectivity in patients. In contrast, others did identify associations of amyloid levels and alterations of functional connectivity in brain regions with many functional connections [17-18], although different measures for functional connectivity were used in these studies; this is discussed later in more detail. Even though the exact course of events is not yet clear, the remarkable vulnerability of the DMN for amyloid-β plaque formation is evident [7]. Perhaps other 'downstream' factors, such as hypometabolism or neurofibrillary tangle formation, mediate between amyloid-β and functional connectivity [19-20]. In order to understand the course of events, the preclinical phase of AD should be investigated, where continuous build-up of amyloid-plaques still occurs [21-22]. This may answer the question whether amyloid-plaque formation results in loss of functional connectivity, or that, as evidence from cellular studies has suggested [23], high baseline activity of the DMN might trigger amyloid production. This latter hypothesis is in line with Filipini

et al. [12]: DMN functional connectivity was increased in healthy young subjects at risk for AD. It should be noted that although increased co-activation does not directly signify increased activity, the energy consumption of the DMN is very high [17,24]. The link between amyloid and functional connectivity may also explain why a relative large part (~25%) of elderly subjects are amyloid-positive, but do not experience cognitive problems [25]. These subjects may cope better with pathological changes related to AD [26], indicating that either mediating factors work different in these subjects, or compensatory mechanisms, such as cognitive reserve, come into play. For example, it has been found that education modulates functional connectivity of the posterior cingulate cortex (PCC). This shows the potential of the brain in coping with pathological changes [26].

Cognition reflected by functional connectivity

Besides being a potential early marker, functional connectivity is of interest in AD for its links to cognitive functioning [27-29] and compensatory mechanisms [26]. Not surprisingly, cognition is often described as the integrated use of multiple brain regions. DMN integrity has been associated with memory [30], emotional processing [4] and self-referential thought [31-32]. For this reason, functional connectivity analyses often include other RSNs [35]. Functional connectivity may provide insight into the extensive cognitive problems early-onset AD patients present with [33,34]. Compared to late-onset AD patients, widespread disruption of functional connectivity was observed in early-onset AD within the DMN, auditory, sensory-motor and bilateral dorsal-visual system. Functional connectivity of the DMN was associated with visuo-construction and functional connectivity of the right dorsal-visual system with attention. These associations are not likely to reflect a one-to-one relationship but are probably best explained by the specific function of the brain region affected within that RSN. For example, within the DMN the PCC was most affected, which has been linked to visuo-spatial processing in a [^{18}F]FDG-PET study [36]. Overall, the widespread disruption in functional connectivity seems to explain extensive cognitive problems of early-onset AD patients. That leaves the question *why* functional connectivity is so strongly affected in early-onset AD. Evidence from structural MRI and PET fails to explain these functional connectivity changes and cognitive problems. Higher amyloid-β plaque load [37] and extensive atrophy have been reported in parietal regions in early-onset AD patients [38-39]. Lower metabolism is also seen in parietal cortex [37,40], frontal brain regions [41] and subcortical structures [42] in early-onset vs. late-onset AD patients. These results together show that local disruptions have widespread effects on functional connectivity. RSNs work together to integrate information, and communication is disrupted when part of this total brain network deteriorates due to AD pathology. For example, the DMN serves as major pathway in information processing by linking other networks [4,43]. Assessing functional connectivity at different levels, may improve our understanding of brain function. In late-onset AD patients no association of functional connectivity with memory function was found, since the standard RSNs did not include medial temporal areas. Therefore, seed-based analysis including hippocampal regions will provide more insight into memory problems.

Resting-state network vs. whole brain functional connectivity

In this thesis, two fMRI analyses were used for assessing functional connectivity, dual-regression (DR) [44] and eigenvector centrality (EC) [45]. The DR method, tested multiple RSNs. Chapter 3 and 8 focused on a single RSN, the DMN, based on the aforementioned vulnerability in AD. Investigating integrity of other RSNs not directly vulnerable to AD pathology provided additional information in AD (see chapter 4). Different measures of functional connectivity provide information on different levels of functional organization. For example, 'zooming in' with seed-based analysis is useful for examining connectivity based on a well-defined hypothesis of a single brain region. Zooming out looks at the brain as one complex network. To illustrate, disruption of functional connectivity within the DMN is most pronounced within the PCC [4-6]. When examining total brain connectivity, it becomes evident that the PCC plays a remarkable role in the brain; it is a region with a disproportionate number of structural and functional connections with other brain regions. This region is therefore also referred to as 'hub' region [46-47]. Information is continuously processed and transported between functionally linked brain regions and hub regions play an important role [27]. With graph analysis, different properties of the network can be described: network efficiency and robustness, or importance of specific nodes in the network. Importance of a node (i.e. brain region or voxel) can be expressed by a measure called centrality [48]. Centrality measures have only recently become part of functional neuroimaging [45,49-51]. Centrality can be expressed in several ways, where EC has been shown robust to physiological effects [50] and related to cognitive performance using MEG [52]. EC takes into account the centralities of the node's direct neighbors. In chapter 5, we were the first to analyze EC using fMRI in AD patients. In line with previous research [50], parietal and occipital cortices showed highest centrality values in healthy controls and are therefore 'important' within the functional brain network. Lowered centrality in parietal regions was expected in AD patients [7,17,24]. Surprisingly, decreased centrality in AD patients was observed in bilateral occipital cortex and increased in the anterior cingulate cortex. Since EC takes into account different layers of functional hierarchy, this could reflect pathological changes associated with AD in the parietal cortex. EC is a relative measure; decreases within one part of the network are always accompanied by increases elsewhere. However, localized increased centrality in anterior cingulate cortex seems to point towards a true change in network organization. Increased connectivity is often regarded as a compensatory mechanism. Long-range posterior-anterior connections seem to decrease in AD, whereas local frontal connections increase [53]. A seed-based approach of regions with changed centralities may provide insight in what changes in centrality represent. This will translate network analysis results to local connectivity measures.

Functional connectivity and glucose metabolism

Hub regions are both energy demanding and at risk for hypometabolism and loss of functional connectivity, suggesting a similar mechanism in AD [11,17]. The brain requires energy, in the form of glucose, to support synaptic transmission, which is associated with the hemodynamic response [54-55] measured with fMRI [56].

Besides synaptic transmission, glucose is also necessary to sustain the resting potentials in neurons and glia [57-58]. Understanding the relationship between glucose consumption and functional connectivity is important for understanding AD [56] since increased cellular activity seems to enhance amyloid production [23] in hub regions. Although several studies have examined this link [17,59], it is not completely clear whether both measures investigate the same process in AD. Ongoing neural synchronization might provide more information about functional integrity of the brain, especially in early stages of AD when subtle changes occur, and local energy consumption might still seem intact [59]. Chapter 6 shows that although both lowered metabolism and EC values were seen in the parietal and occipital cortex, no associations were found between local metabolism and centrality. Higher degree of connectivity has been associated with nonlinear increases in metabolism in healthy controls [56]. It has been hypothesized that the coupling between glucose consumption and functional connectivity is disturbed in AD; since hub regions seem vulnerable in aging and AD [24] and altered energy demands might play a role in this process [23-60].

Integrated analysis of imaging biomarkers in AD

Functional connectivity helps us understand the underlying mechanisms of AD. On a single-subject level, functional connectivity is not yet suitable for diagnostic purposes. The use of fMRI in early diagnosis requires smarter use of functional connectivity measures. In chapter 8 we show the possibilities of integrated imaging modality information on automatic classification. Interestingly, for combinations of modalities, a regional multi-kernel learning approach yields the best results, even though information is reduced from the single-voxel level to brain region averages. Combining functional connectivity measures with structural MRI resulted in good diagnostic accuracy: almost equal to diagnostic accuracy of [^{11}C]PIB and [^{18}F]FDG [61], which are already in use for diagnostic purposes. Including only (f)MRI data for diagnostic purposes is beneficial because it is cheaper than PET and not invasive. In addition, functional connectivity provides important information early in the disease course. Early diagnosis is important, especially when anti-amyloid or other disease modifying therapies become available. Other than improving early diagnosis, integrated multimodal imaging provides exciting new opportunities in neurosciences. An important technical development in this field is the integrated PET/MR scanner. At present, PET/MR is not ideal for clinical imaging, because no perfect solution for attenuation correction (AC) on PET/MR exists [62,63]. MR-based AC does not include information on bone and might introduce bias. The effect of MR-based AC in a clinical setting was described in chapter 9, where it was found that amyloid imaging on PET/MR resulted in slightly higher regional values, but was useful for clinical imaging. This is also beneficial for patients, since both PET and MR can be acquired in a single scanning session.

Future

Many questions raised in this thesis remain unanswered and provide opportunities for future studies. As mentioned, the causal mechanism underlying the co-localization of amyloid and 'hub' regions is poorly understood. Longitudinal studies examining subjects at risk for developing AD, where continuous build-up of amyloid-β plaques still occurs, are the key to understanding the causality of events. Examining cognitive reserve in amyloid-positive healthy elderly with functional connectivity measures will provide insight in the coping mechanisms of the brain. Secondly, the accumulation of neurofibrillary tangles has been directly linked to cognitive decline [64-65] where amyloid is less informative. Recent studies show that increased cellular activity not only triggers production of amyloid-β, but also of tau [60]. Several promising new tau-tracers have become available: [^{18}F]T807, [^{18}F]T808 [66-67], [^{11}C]PPB3 [68] and [^{18}F]THK series [69], allowing the direct investigation of the link between of neuronal dysfunction and tau. Functional connectivity will also provide insight into why tau spreads trans-synaptically throughout the brain following structural connections [60]. Finally, the introduction of integrated PET/MR systems, will allow for simultaneous imaging of fMRI and PET. This can help elucidate more basic questions such as the link between ongoing neuronal synchronization and local energy demands.

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