SUMMARY

In **module 1** Alzheimer's disease (AD), the most prevalent type of neurodegenerative dementia, is introduced as a rapidly increasing problem in our aging population. A thorough understanding of the disease mechanism is lacking, and no effective cure exists. An essential aspect of cognitive processing is particularly poorly understood: the role of brain *dynamics*. Greater knowledge of how cognitive processes are coordinated in the brain might clarify the complex relation between observed structural brain damage and clinical symptoms in AD.

The first step is to capture and describe large-scale brain dynamics in a reliable way. To provide a short background, basic neurophysiologic principles are outlined, ranging from single neuron action potentials to synchronization between large groups of neurons. The concept of functional connectivity is introduced as a method to describe interaction between brain regions, and EEG & MEG are discussed as neurophysiological data acquisition techniques. A short, focused overview of the existing neurophysiological literature in AD is provided. When describing large-scale brain dynamics, we find out that the brain is a complex dynamical system. Complex network theory is introduced as a method to interpret complex systems, and to explain how changes in network structure relate to changes in network function. It is argued that the application of concepts from network theory to neuroscientific patient data could help to better relate both structural and dynamical brain changes to cognitive symptoms.

To conclude this section, the aims and outline of this thesis are listed.

In **module 2**, we report that resting-state brain activity as measured by MEG relative power is altered in a wide range of frequencies and different cortical regions in AD. The overall observed diffuse slowing of brain activity is in agreement with existing EEG literature, and adds more detail by demonstrating the regional heterogeneity in dynamical changes. However, since this approach does not take into account interaction between different regions, increases and decreases are hard to interpret. A large-scale network perspective is desired.

Module 3 starts with a description of functional network structure in resting-state EEG data, and shows that different types of dementia lead to different types of network disturbance: both AD and FTD patients demonstrate a loss of balance between local and global network connectivity ('small-worldness'), but in opposite directions. This difference might reflect different underlying pathology, which could lead to useful diagnostic tests in the future. Next, an MEG study in AD patients is reported to show network disruption in more detail: again, a loss of small-world structure and a shift towards a more random network organization is observed. AD-related network damaged is also compared to two theoretical damage models: one of random damage, and one where highly connected hub regions are preferentially damaged. The last model resembles the damage in AD most, which suggests that hubs are especially vulnerable in AD. After

these demonstrations of local and global functional network damage, the third study in this section deals with an intermediate terrain where sub-networks or modules are investigated. In AD, a loss of modularity, a vulnerability of the parietal hub region, and a particular vulnerability of *inter*modular connections is found, which correlates with cognitive impairment. These studies illustrate a relevant relation between brain connectivity and impaired cognition.

Module 4 takes a different, more algebraic approach to describe network properties. Graph spectral analysis has proven its usefulness in other research areas, and has several methodological advantages compared to topological graph theory. With graph spectral techniques, we again detect large-scale network connectivity changes in AD, as well as differences in robustness and network synchronizability. Hub status of regions is examined again using eigenvector centrality, and the earlier reported hub status of the parietal region is confirmed.

The observed hub vulnerability in AD is an intriguing finding, and since a link between hub regions and amyloid deposition was reported, as well as a direct influence of excessive neuronal activity on amyloid deposition, we hypothesized that the high connectivity level of hubs requires a high level of activity, and that this chronic, high activity of hubs makes them susceptible to degeneration. In short, we speculated that dynamics might have a *causal* role in AD pathogenesis.

To test this hypothesis, a computational neural mass model that is based on realistic human brain topography and dynamics was employed. We demonstrate in **Module 5** that brain hubs are indeed the most active regions, and that when regions are damaged based on their level of activity, model-generated data shows many neurophysiological hallmarks of AD, such as oscillatory slowing and a loss of functional connectivity and functional network disruption. These findings suggest that excessive neuronal activity indeed plays a significant role in AD pathogenesis.

In this module a review of relevant recent literature discusses the important role of brain connectivity for our understanding of neurodegenerative dementias. Subsequently, the main outcomes of the studies in this thesis are summarized, and interpreted with regard to the original aims of this thesis and existing literature. This is followed by a discussion of the most relevant methodological considerations. In the final paragraphs, recommendations for future research are provided, and the section ends with a more personal view on the potential usefulness of the approach followed in this thesis.