Neurodegenerative diseases pose several challenges in clinical practice. At presentation, these disorders have overlapping features, and a typical clinical syndrome may become clear only at later disease stages. Parkinson’s disease (PD) is a case in point. Other neurodegenerative parkinsonian disorders, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), also present with bradykinesia and rigidity, and are frequently misdiagnosed as PD. Clinicopathologic studies have shown that the clinical diagnosis of PD is inaccurate in approximately 26% of patients (Rizzo et al., 2016, Jellinger et al., 2016). The diagnostic accuracy is higher (84%) when patients are evaluated by experts in movement disorders, provided that follow-up is sufficiently long (~4 years). In a patient presenting with cognitive decline, the clinical diagnosis can be equally challenging. If a neurodegenerative cause is considered, differentiation between Alzheimer’s disease (AD), Dementia with Lewy Bodies (DLB) and Frontotemporal Dementia can be difficult (Hyman et al., 2012). These challenges hamper proper treatment and prognostic counselling in patients with parkinsonism or dementia.

Early, accurate diagnosis is also needed to select patients for clinical trials. Therapeutic interventions for AD and PD may have a better chance of success if initiated at the earliest disease stages. Individuals in the prodromal stages of a neurodegenerative disease may be ideal candidates. The strongest prodromal marker of PD is idiopathic rapid eye movement sleep behavior disorder (iRBD), a parasomnia that can be diagnosed with a polysomnography. Patients with iRBD fail to suppress muscle tone during the REM sleep stage, leading to dream enactment. Longitudinal studies have shown that >80% of patients initially diagnosed with iRBD developed PD, DLB, or incidentally MSA in the following decades (Postuma et al., 2009, Postuma et al., 2012, Iranzo et al., 2013b, Schenck, Boeve & Mahowald, 2013, Iranzo et al., 2014). Patients with iRBD, by definition, have not yet developed motor symptoms or dementia, and provide a unique opportunity to study the early (prodromal) stages of a patient subgroup with α-synucleinopathy (Berg et al., 2015). In addition, a construct referred to as mild cognitive impairment (MCI) precedes the dementia syndrome in AD, but is not disease specific (Petersen et al., 1999). Biomarkers that can detect the underlying neurodegenerative disease at its prodromal stages, and that can determine its rate of progression, are essential for future efforts to slow down or halt the neurodegenerative process before the onset of debilitating symptoms.
Although the common sporadic neurodegenerative forms of PD and AD are the ultimate targets of biomarker development, rare genetic neurodegenerative disorders can provide valuable models. For instance, inherited neurodegenerative diseases such as Huntington’s disease and spinocerebellar ataxia (SCA) are caused by cytosine-adenine-guanine (CAG) repeat expansions (Tang et al., 2013, Pedroso et al., 2013). Diagnosis in these cases is less reliant on experience of the clinician, because they can be confirmed with genetic testing. However, even in these clearly defined disorders certain aspects remain elusive, for instance why patients with the same repeat expansion can have various clinical phenotypes, and what determines the rate of disease progression.

Most neurodegenerative disorders share two core features: (1) They are associated with abnormal accumulation of misfolded proteins, and (2) they are characterized by distinctive patterns of progressive neuronal dysfunction across the brain (Warren, Rohrer & Hardy, 2012). In neurodegeneration, synaptic dysfunction exceeds neuronal loss, and depletion of synapses and synaptic proteins correlates better with clinical manifestations than does the abundance of local pathology (Palop, Chin & Mucke, 2006). In other words, neuronal activity is disrupted especially at the level of synapses. Synapses are the contact sites of neurons to pass signals via neurotransmission. The number of synapses and their transmission efficiencies determine information processing in neural networks (i.e. connectivity between neurons). Abnormal protein depositions seem to trigger synaptic deficits, altered neuronal activity, disintegration of neural networks, and, ultimately, failure of neurological functions.

Combined with advanced analytical methods, \(^{18}\)F-FDG PET imaging may provide insight to underlying synaptic dysfunction in neurodegeneration, and at the same time may provide a biomarker that can be implemented in clinical practice and clinical trials. The radiotracer \(^{18}\)F-FDG is analogous to glucose and provides an index for the first step of the cellular glycolytic pathway. Cerebral glucose metabolism measured with \(^{18}\)F-FDG is closely associated with synaptic activity and integrity (Attwell, Laughlin, 2001, Rocher et al., 2003, Sokoloff, 1977). Changes in synaptic activity are visible as relative in- or decreases in \(^{18}\)F-FDG uptake. Regions with correlated metabolic activity are considered to be functionally interconnected. Therefore, \(^{18}\)F-FDG PET can visualize the effect of local pathology on brain networks.

\(^{18}\)F-FDG PET is widely accessible in routine clinical practice. Visual assessment of \(^{18}\)F-FDG PET is performed in most neurology and nuclear medicine departments. International workgroups and consortia advocate \(^{18}\)F-FDG PET imaging in the diagnostic work-up of parkinsonism (Meyer et al., 2017, Walker et al., 2018) and dementia (Morbelli et al., 2015, Garibotto et al., 2017, Perani et al., 2014) in routine clinical practice. Visual assessment of \(^{18}\)F-FDG PET in the context of neurodegenerative diseases requires training, and may be difficult in patients with
early-stage disease, when only subtle changes are present. Quantification or semi-quantification of \textsuperscript{18}F-FDG PET images could be helpful, but sufficiently validated quantitative approaches are currently lacking (Meyer et al., 2017, Nobili et al., 2018).

A straightforward approach to the analysis of \textsuperscript{18}F-FDG PET images is the application of univariate models in the software package statistical parametric mapping (SPM). Voxels are compared between controls and patients with multiple \(t\) tests, and regions with significantly altered relative \textsuperscript{18}F-FDG are identified. A key characteristic of univariate approaches is that every region or voxel is treated separately. Information concerning the relationship between voxels is discarded. However, it is increasingly recognized that neurodegenerative diseases are characterized by stereotyped connectivity changes, and that studying networks, rather than separate regions, provides more insight in pathophysiological mechanisms.

So-called spatial covariance analyses identify relevant patterns in \textsuperscript{18}F-FDG PET data by taking into account the relationship (covariance) between voxels across subjects, and are therefore considered appropriate to explore network activity. Such an approach is the Scaled Subprofile Model and Principal Component Analysis (SSM PCA). With this method, disease-related patterns (also referred to as metabolic connectivity networks) have been identified in several neurodegenerative diseases. An important advantage of SSM PCA is that once a pattern is identified, the degree of its expression can be quantified in any \textsuperscript{18}F-FDG PET scan. The degree of pattern expression is reflected by the subject score (a single numeric value). By quantifying disease-related pattern expression on a scan-by-scan basis, this technique allows objective assessment of disease activity in individual subjects. Because of this property, there is increasing interest in using SSM PCA as a biomarker in specific neurodegenerative diseases (Schindlbeck, Eidelberg, 2018).

The aim of this thesis is to further investigate the potential of SSM PCA analysis of \textsuperscript{18}F-FDG PET data as a biomarker in neurodegenerative diseases. Our efforts are especially focused towards the early disease stages, such as iRBD in \(\alpha\)-synucleinopathies, and the MCI stage in AD.

Basic concepts in \textsuperscript{18}F-FDG PET imaging and SSM PCA are explained in \textbf{Chapter 2}. The results of relevant \textsuperscript{18}F-FDG PET studies in PD are reviewed in \textbf{Chapter 3}. Especially the PD-related pattern (PDRP) has shown promise as a biomarker. In \textbf{Chapter 4}, we validate the PDRP in several populations of PD patients, including de novo, treatment naïve PD patients, and patients in a more advanced disease stage. The universal PDRP topography is characterized by relatively increased metabolism of subcortical regions such as the thalamus, putamen, brainstem and cerebellum, and by widespread cortical hypometabolism.
Although there appears to be one typical PD-related pattern, it is well-known that many clinical PD subtypes exist. Pathology in PD is widespread, involving neurotransmitter systems other than dopamine, and distributed brain regions participating in neural networks. In addition to parkinsonism, PD patients may experience multiple non-motor symptoms including cognitive, mood, sleep, olfactory and autonomic disorders. Cognitive dysfunction especially, is an important determinant of quality of life. In Chapter 5, we investigate whether a separate metabolic pattern exists that can be used to track cognitive dysfunction in PD patients.

In Chapter 6, the results of neuro-imaging studies in iRBD are reviewed. In Chapter 7, we show that the PDRP is significantly expressed in patients with iRBD compared with healthy controls. This underscores the value of the PDRP as a potential disease biomarker in idiopathic RBD, and perhaps in early PD in general. To understand why patients with iRBD express the PDRP, we also investigate the metabolic topography of iRBD itself. The results are discussed in Chapter 8.

In Chapter 9, we study expression of the AD-related pattern (ADRP) in a large cohort of MCI patients with long-term clinical follow-up. We found that ADRP expression was significantly higher in MCI patients who progressed to AD dementia compared with both healthy elderly and non-converting MCI patients. This indicates that spatial covariance analysis may have a role in tracking disease progression in AD as well.

Spinocerebellar ataxia type 3 (SCA3) is caused by an abnormal trinucleotide (CAG) repeat expansion in exon 10 of the ATXN3 gene on chromosome 14. In addition to ataxia, patients with SCA3 may also have variable other disease manifestations, including parkinsonism. In Chapter 10, we study the spatial covariance pattern in SCA3.

Finally, Chapter 11 provides an overview, discussion and future perspectives of the disease-related brain patterns presented in this thesis.