Ventral striatal atrophy in Alzheimer's disease : exploring a potential new imaging marker for early dementia

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CHAPTER 1

General introduction

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GENERAL INTRODUCTION

Brain & cognition: a spearhead on the Dutch research agenda

Cognitive problems are considered to have the biggest influence on the quality of life of older people compared to other chronic diseases that occur with ageing for example rheumatic, heart and vessels, diabetes and pulmonary complaints (Lavender 2008). In ageing populations, like in the Netherlands, the rise in incidence and prevalence of dementia is an important social and economic concern. Dementia will, most probably, become the number one cause of death in 2040 (The Dutch National Institute for Public Health and the Environment 2017). To prepare for the upcoming decades the Netherlands Organization for Scientific Research and the Royal Netherlands Academy of Arts and Sciences launched several initiatives between 2000-2017 that made brain and cognition the cornerstone of the Dutch research agenda (https://www.hersenenencognitie.nl/publications/64). Regarding dementia and cognitive decline, research was supported that could 1) improve our understanding of the pathophysiology of cognitive decline and dementia, 2) identify early markers of dementia, 3) identify modifiable risk factors that can counteract or delay the onset of cognitive decline, and 4) ultimately find a way of preventing or cure dementia. The research presented in this thesis was part of this larger movement and focused for one part on finding early markers of dementia on structural magnetic resonance imaging (MRI) and for another part on improving our knowledge on how to perform volumetric and morphometric studies of the human brain in face of neurodegenerative changes.

Theoretical concepts of Alzheimer's disease

In 1907, Alois Alzheimer presented a case of a woman of 51 years with progressive cognitive decline leading to the clinical description of a condition he named "pre-senile dementia" (Alzheimer 1907). Although asylum carers had been familiar with dementia in older people for centuries, the condition of Alzheimer's case had attracted his attention because of the rapid course of the disease and the relatively young age of the patient. He examined her brain after she died and found large quantities of neurofibrillary tangles and amyloid plaques. Nowadays, this form of dementia would perhaps be classified as a familial form of Alzheimer's disease (AD). This form of AD is relatively uncommon, constituting merely 3–5% of all AD cases (Fjell and Walhovd 2012). However, research throughout the 20th century showed that the most common form of dementia in older people is also characterized by accumulated amyloid-β (Aβ) plaques and neurofibrillary tangles (Ingelsson et al. 2004). This form of dementia is now known as

late onset sporadic AD. The current lifetime risk for a 65-year to develop this disease is estimated around 10.5% (Sperling et al. 2011). Definite diagnosis of AD is still made by postmortem analysis of the brain tissue. In clinical practice, however, people with suspected dementia are evaluated relative to the consensus NINCDS–ADRDA criteria (McKhann et al. 1984). The diagnosis of "probable AD" requires 1) progressive cognitive decline present in at least 2 areas of cognition in an individual between 40-90 years and 2) absence of other causes of the cognitive decline. These diagnostic criteria identify AD patients relatively late when the disease has already entered a full clinical stage. Researchers in the field, however, have an interest in selecting AD patients much earlier in their disease process. The update of the criteria in 2011 fulfilled this need to uniformly identify and stage patients in preclinical phases of AD by incorporating markers for Aβ accumulation and markers for neuronal degeneration (Jack, Albert, et al. 2011). Although making the diagnosis has reached global standardization, the cause of AD is still unknown and widely debated. Our current understanding of the pathological process leading up to the clinical presentation of AD is encapsulated in two different theoretical models.

Cholinergic hypothesis of Alzheimer's disease

The first model considers AD as the result of a reduction of the activity of the cholinergic system. This hypothesis was based on observations made in the late 60s and early 70s of the 20th century, of substantial neo-cortical deficits in choline acetyltransferase, an enzyme responsible for the synthesis of acetylcholine, reduced acetylcholine release, and loss of cholinergic cells in the nucleus basalis of Meynert in patients with AD. The cholinergic system is housed in the subcortical gray matter nuclei consisting of the striatum, basal nucleus of Meynert, other basal forebrain complex structures, and amygdala and has numerous downstream projections to cholinergic receptors on pyramidal neurons of allocortical and isocortical areas (Francis et al. 1999). There is no consensus on how cholinergic dysfunction influences the function of the cortex. It has been postulated that loss of cholinergic excitatory input to the pyramidal neurons may lead to hypoactivity with maintained inhibition by GABAergic neurons (Francis et al. 1999). However, others have postulated that low levels of acetylcholine may allow "runaway synaptic" modifications to form, leading to excitotoxicity of glutamatergic cortical neurons. This would be especially damaging for the medial temporal lobe, being one of the most constantly active structures in the brain due to its constant synapse formation supporting episodic memory (Hasselmo and Schnell 1994; Spitzer 1999). Regardless of the exact effect of acetylcholine on the cortex, this cholinergic model of AD considers the subcortical basal forebrain complex as the primary site of pathology leading to secondary neurodegen-

erative effects in the cortex exhibiting a localized vulnerability. In accordance with this model, the only validated treatment available today for AD patients in early phases of the clinical process is pharmacological inhibition of acetylcholinesterase. Acetylcholinesterase inhibitors have been shown to give moderate symptoms relieve in the early stages of the disease (JT O'Brien et al. 2017).

Amyloid cascade model

The second model considers AD as the result of accumulation of Aβ plaques and the pathological events that follow from that. This model has focused on the finding of the abundance of neurofibrillary tangles and amyloid plaques in the cortex in post mortem brain specimens of patients with AD compared to those who were not suspected to have AD. Both are considered primary markers for establishing the definite diagnosis of AD, although neither is exclusively present in AD. Neurofibrillary tangles are also found in other taupathies diseases i.e., Parkinson's disease, Lewy body dementia (Iqbal and Grundke-Iqbal 2004) and amyloid plaques are also found in patients without signs of dementia before their death (Snowdon 2003; Latimer et al. 2017). Neurofibrillary tangles and amyloid plaques are not distributed in the same temporospatial way throughout the brain. An influential study published in 1991 described the spread of neurofibrillary tangles in a highly predictable temporospatial manner (H Braak and E Braak 1991). This temporospatial spreading pattern, known as the Braak and Braak stages, predicts the appearance of neurofibrillary tangles first in the transentorhinal and entorhinal cortices (stage I and II) after which they appear in the hippocampus (stages III and IV) and finally there is extensive neocortical involvement (stages V and VI). Neurofibrillary tangles are composed of aggregates of hyperphosphorylated tau protein and thought to represent remains of pyramidal neurons that have undergone a degenerative process. The stages of neurofibrillary tangle accumulation have shown to parallel the stages of brain atrophy in AD, which is encountered first in the medial temporal lobe, then in other limbic areas, and eventually affecting the whole brain (Dallaire-Théroux et al. 2017). The accumulation of amyloid plaques occurs in a different manner. These are found throughout the cortex in early stages (Thal et al. 2002). The main constituent of amyloid plaques is Aβ_{42}, which is proteolytically derived from amyloid precursor protein (APP). The accumulation of Aβ plaques has been attributed to inability of clearance of the insoluble Aβ form. It has not been clarified why Aβ plaques starts appearing in the brain, but it is suspected that genetic predisposition plays an important role, given that genetic mutations associated with familial AD are encoded on the APP gene (Fjell and Walhovd 2012). The formation of Aβ plaques is thought to hamper the neuronal synaptic function and ultimately leads to neuronal death (Takahashi et al. 2002; Oakley et al. 2006). However, toxicity of

Aβ plaques is debated because about one third of elderly without cognitive or clinical symptoms is found to have plaques. This may suggest that the presence of Aβ plaques in the brain is not sufficient to cause AD. Contrary to the cholinergic hypothesis, the amyloid cascade model of AD considers AD a primarily cortical disease.

Regardless of the underlying model, AD is suspected to have a very long asymptomatic prodromal period of 1 or 2 decades before clinical symptoms appear (Amieva et al. 2008). Indeed accumulation of Aβ can be detected in 4% of adults in their 40s without symptoms (H Braak, Thal, et al. 2011). After failure of many attempts to find a therapy for AD in the clinical phase of the disease, research is starting to aim at preventive interventions in preclinical stages of the disease. Identifying early markers of the disease in this prodromal period is essential for this kind of research.

Relevance of neuroimaging studies in the assessment of AD

Today brain MRI is an established part in the assessment of patients with cognitive decline and suspected dementia (Sperling et al. 2011). The current role of structural brain MRI in clinical practice is twofold. First, MRI is used to exclude other (potentially treatable) causes of cognitive decline such as tumors or ischemic disease. And second, MRI is used to differentiate between different types of dementias. One way in which this done is by determining whether a typical pattern of cortical atrophy is present. For example, predominant atrophy of frontal and anterior temporal pole is suggestive of frontotemporal dementia, whereas predominant atrophy of the medial temporal lobe is suggestive of AD (Bocti et al. 2006). Also, other additional findings are supportive for certain diagnoses like cortical diffusion restriction is specific for Creutzfeldt–Jakob disease in the appropriate clinical context. However, clinical assessment of the patient is still the most important for establishing the eventual diagnosis. Abnormal cognitive test scores mark the beginning of the clinical disease, but the onset of this is influenced by the pre-morbid cognitive level of functioning and/or cognitive reserve (Stern 2012). Therefore, studies are conducted to explore extending the use of neuroimaging as a screening tool for AD especially for preclinical stages. Structural MRI as a screening method is most elegant, because of its widespread availability and noninvasive character. Global or focal loss of brain volume on structural MRI is thought to reflect loss of pyramidal neurons. Loss of medial temporal volume is considered the hallmark imaging marker for AD. In predicting change in cognitive functioning, neuroimaging markers have proven to be superior to CSF Aβ measurement (Walhovd et al. 2010; Da et al. 2014). Other imaging methods to evaluate those in preclinical stages of AD are amyloid and FDG PET scanning. Use of these methods is however limited, because they are expensive and invasive, and without perspective on adequate treatment they are not yet suitable

as a screening tool.

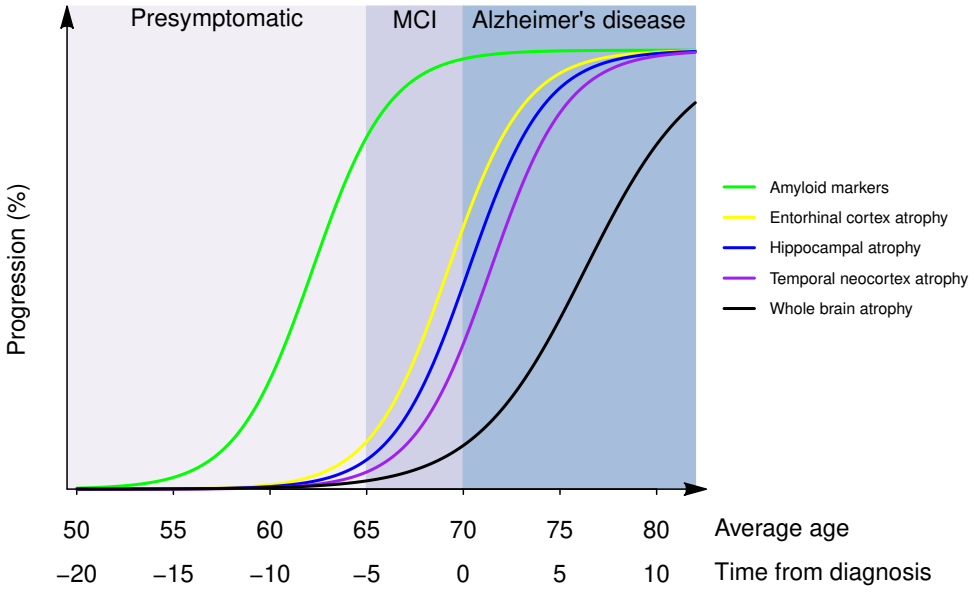
Hippocampal atrophy as imaging marker in AD

Medial temporal lobe volume loss is the most studied neurodegenerative marker of AD. It has been found to correlate with diagnosis of AD, to predict progression from mild cognitive impairment to AD, and to relate to disease severity (Jack, Petersen, PC O'Brien, et al. 1992; Fox et al. 1996; Jack, Petersen, Xu, et al. 2000; Schuff et al. 2009; Devanand et al. 2007). Medial temporal lobe atrophy is easily detected when visually inspecting the thickness of the hippocampus on MRI. Clinicians successfully integrated medial temporal lobe atrophy in daily clinical practice due to its high reproducibility, both when assessed semiquantitatively by visual scoring (Scheltens score) as when estimated quantitatively by manual or automated segmentation (Zandifar et al. 2017). Also, cognitive testing together with assessment of medial temporal lobe atrophy was shown to improve the accuracy of diagnosis as compared to cognitive testing alone (Da et al. 2014). Although medial temporal lobe volume loss was shown to correspond well with the accumulation of neurofibrillary tangles as predicted by the Braak and Braak stages and clinical progress of the disease, it is thought to occur relatively late in the disease process. The current dominating view within research on the relation of biomarkers and AD is captured in the dynamic biomarker model (figure 1). This model presumes that biomarkers reflecting levels of amyloid-β accumulation in the brain become abnormal long before hippocampal or whole brain atrophy and clinical symptoms occur (Jack, Knopman, et al. 2010). Based on the temporal relation of biomarkers and AD proposed by this model, use of medial temporal lobe atrophy is suited as a marker in secondary prevention trials in patients presenting with the earliest clinical stage of the disease or as an outcome measure (Cavedo et al. 2014). In the asymptomatic preclinical stages, however, medial temporal lobe atrophy may not be an adequate marker but amyloid markers may show more-substantial abnormalities (Frisoni et al. 2010). Thus, despite 3 decades of intensive neuroimaging research in AD, no accurate *preclinical* structural MRI marker for AD has been identified. Besides the study of atrophy of different structures of the medial temporal lobe, the allocortical cingulate gyrus and whole brain atrophy, there are some structures in the brain that have been given surprisingly little attention on structural MRI in AD. These are the subcortical structures that host the cholinergic system.

Why focus on the striatum when studying AD?

The first part of this thesis focused on volumetric and morphometric changes in the striatum in AD. There were three main arguments for studying the striatum in relation

Figure 1: Theoretical model of the progression of biological markers of AD



Adapted from Giovanni B. Frisoni, Nick C. Fox, Clifford R. Jack, Jr, Philip Scheltens, and Paul M. Thompson, The clinical use of structural MRI in Alzheimer's disease Nature, Rev neurol (2010).

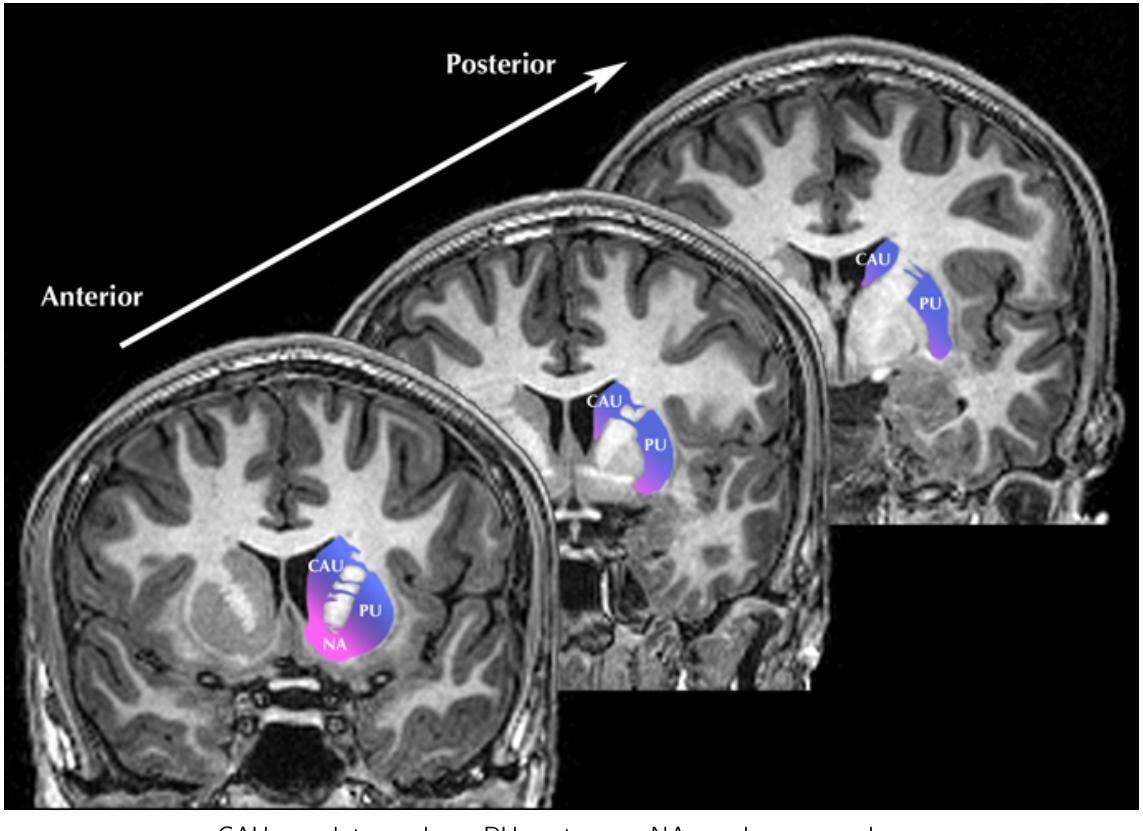
to AD and in particular as a candidate structure for being affected early in the disease process. First, the ventral striatum is an integrated part of the limbic system. The structure and function of all other limbic structures, i.e., entorhinal cortex, amygdala, hippocampus, basal forebrain, fornix, cingulate gyrus and medial prefrontal lobe, have been shown to be affected earlier in AD than neocortical structures (Mielke et al. 2012). The striatum forms the largest deep gray matter nucleus in the brain and consists of the caudate nucleus and putamen. The caudate nucleus and putamen are phylogenetically the same structure, which in the human brain, as opposed to for example rodent brains, is dispersed by the traversing internal capsule (Steiner and Tseng 2010). The function of the striatum is not fully understood. Historically, the striatum is thought to play a role in motor function, based on its association with neurodegenerative disorders affecting the control of movement, such as Parkinson's and Huntington's disease. However, the

last decades have shown the function of the striatum to be more complex mediating the full range of goal-directed behaviors, from motivation, reward and reinforcement based learning, decision making, to shaping final motor outcome (Haber 2016). The striatum receives input from nearly all areas of the cortex, the thalamus, and the dopaminergic cells of the brainstem in a roughly topographic organization (Haber 2016). The striatum projects GABAergic neurons to the internal segment of the globus pallidus and substantia nigra pars reticulata, termed the direct pathway, and to the external segment of the globus pallidus and subthalamic nucleus, termed the indirect pathway. From there projections arise via the thalamus back to mainly the frontal cortex (Shipp 2017). A distinction is made between the dorsal striatum and the ventral striatum. The ventral striatum occupies over 20% of the striatum (Haber 2011) and includes the nucleus accumbens, the medial and ventral portions of the caudate and putamen. There are no clear cytoarchitectonic borders between the ventral and the dorsal striatum but there is a gradual transition between areas with some differences in cellular composition (figure 2). The ventral striatum receives projections from the allocortical areas whereas the dorsal striatum receives projections from the neocortical areas (Gray 1999). The ventral striatum is considered part of the limbic system, projecting via the ventral pallidum and substantia nigra, subsequently the medial nucleus of the thalamus back to the ventral medial pre frontal cortex, the orbitofrontal cortex, dorsal anterior cingulate cortex and medial temporal lobe (Haber and McFarland 1999). Figure 3 schematically displays the main connections of the dorsal and ventral striatum with the rest of the brain. Given the central role of the ventral striatum in the limbic circuitry both receiving and projecting to other limbic structures, one of the focuses of the research presented in this thesis was to investigate whether the ventral striatum also showed stigmata of degeneration and in what stage of AD.

The second argument for investigating the striatum in AD was related to the known loss of cholinergic cells in AD. The largest concentrations of cholinergic cells in the brain are found in the basal forebrain complex and in the striatum (Havekes, Abel, and Van der Zee 2011). In AD a marked loss of the magnocellular cholinergic neurons is found in the basal nucleus of Meynert especially those areas that project to the medial temporal lobe, temporal pole and superior temporal lobe (Liu et al. 2015). Atrophy of the basal forebrain complex has been found to correlate with Aβ burden (Kerbler et al. 2015). However, the striatum, rich of magnocellular cholinergic neurons, has not been studied extensively on brain MRI in relation to AD.

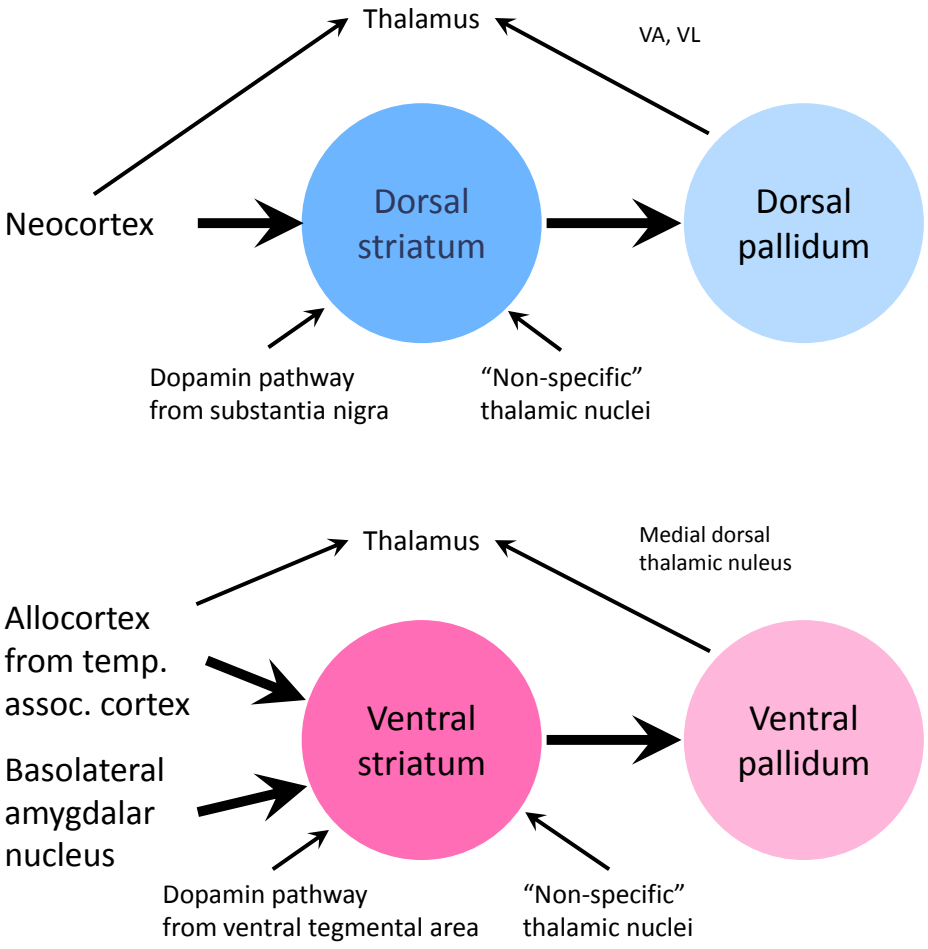
The last argument to study the striatum in relation to AD was related to recent findings of PiB PET amyloid imaging studies. In presenilin carriers associated with a familial form of AD, Aβ deposition was shown to start in the striatum around the age of 45, when there was yet no proof of Aβ deposition in the cortex or hippocampus

Figure 2: Striatum on coronal MRI



CAU, caudate nucleus; PU, putamen; NA, nucleus accumbens.
The color gradient represents the gradual transition from the ventral to dorsal striatum.

Figure 3: Schematic representation of the main connections of the ventral and dorsal striatum with the rest of the brain



Adapted from L Heimer and G van Hoesen (1979). Ventral Striatum. In: The Neostriatum. Ed. by I Divac and RGE Öberg. Oxford, UK: Pergamon, 147–158.

(Villemagne, Ataka, et al. 2009; Klunk et al. 2007). In mice studies, overexpression of Aβ protein was associated with a reduction in striatal neurons (Richner, Bach, and West 2009). Although studies to late onset sporadic AD have not confirmed the presence of early striatal Aβ depositions so far (Villemagne, Burnham, et al. 2013), the studies on familial AD suggest that the striatum is vulnerable to the presence of Aβ even in small quantities.

Allometric scaling in brain development and atrophy

The second part of this thesis focused on how premorbid brain size influences brain structure and degeneration. Brain atrophy is widely studied, because it is assumed that loss of (regional) brain volume is a predictor for disease and goes hand in hand with functional decline of the brain (area). Manual segmentation of brain MRI is, however, time-consuming and limits the size of a study population. In the last two decades several software packages became freely available enabling automated estimation of intracranial volume (ICV) and total brain volume, and automated segmentation of different tissue classes of gray matter, white matter, and cerebrospinal fluid (FreeSurfer software (Freesurfer Software website; cortical Reconstruction and volumetric segmentation (Accessed July 1, 2018; http://surfer.nmr.mgh.harvard.edu)), SPM software (Accessed July 1, 2018; http:// www.fil.ion.ucl.ac.uk/spm/)). This was followed in more recent years by the development of semiautomated brain segmentation tools dedicated to segmentation of the deep gray matter structures (FIRST website, (Accessed July 1, 2017; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST)). These automated segmentation techniques of brain MRI have led to a boom in comparative volumetric brain studies in clinical and epidemiological settings. Brain volumetric and morphometric studies are, however, met with criticism. On a group level, MRI-based measures of brain (substructure) volumes have proven their value by providing insight into the onset and spatial-temporal dynamics of cortical atrophy in normal ageing and neurodegenerative diseases such as AD. Nonetheless, results of brain comparative studies are not always useful for the individual patient because the predictive value of brain (structure) volumes for disease on individual patient level remains poor. The main reason for the poor predictability of brain volume for disease on individual level is the substantial variation in brain size in the general population. Brain volume or volume of its substructures cannot be studied directly, but are usually investigated relative to their maximal premorbid size. Head size or ICV are considered proxies for premorbid brain size and correction for either one of these in comparative brain studies is common practice (Barnes et al. 2010). One aspect in brain comparative studies that has not received enough attention is that some widely used methods of ICV adjustment are based on the assumption that brain substructures

scale linearly to ICV. For example, affine registration methods to align MR images of different individuals or the use of ratios of brain (substructure) volume to ICV, both assume that brains of different sizes are more or less linearly upscaled versions of each other. Although, this assumption is considerably influencing outcome measurements, it has not been tested sufficiently. As part of the efforts to improve accuracy and predictive value of brain volume for disease on a individual level, the second part of this thesis was dedicated to the study of scaling of sub-structures of the brain relative to ICV. Whether substructures of the brain scale isometrically to ICV was put to the test in a large population-based cohort. Furthermore, not only in brain development, but also current conceptions of degeneration of the brain and its influence on cognition are often based on assumptions of linearity. Therefore, in the last chapter the process of neurodegeneration, as reflected by several MRI markers of neurodegeneration, was studied relative to ICV in a population of older people spanning the spectrum from healthy cognitive ageing to dementia.

Aim of this thesis and brief outline

The aim of this thesis was first to investigate whether and to what extent the striatum undergoes degenerative changes in AD and whether striatal atrophy is related to cognitive decline in older people. The second aim of this thesis was to improve our knowledge on the physiological variability in brain structure and degeneration, which may result in a better understanding and identification of pathological atrophy patterns. Therefore this thesis is comprised of two complementary parts.

Part 1 investigated volumetric and morphometric changes of the striatum and its substructures in AD and its relation to cognitive decline. The central research question in **chapter 2** was whether the volumes of the striatum and its substructures were decreased in patients with AD compared to those who had healthy cognitive test scores. For this study brain MR images of a memory clinic population were investigated. In **chapter 3**, MR images of the same study population were further examined on the shape of the striatum. The question at stake was whether the striatum was losing volume in AD in a global manner or whether certain parts of the striatum were more affected than others. In particular it was investigated whether there was a difference between the ventral (limbic) and dorsal striatum. In **chapter 4**, the relation of the volume of the striatum and cognitive performance was studied with follow-up measurements of cognitive function spanning a decade. The relation of the volumes of the striatum (and its substructures) and global cognitive performance was compared with the relation of hippocampal volume and cognitive performance. Finally, since AD often co-occurs with large and/or small vessel disease, in **chapter 5**, it was examined whether change in striatal and hippocampal

volumes were influenced by the presence of cardiovascular risk factors.

Part two of the thesis investigated scaling of brain substructure volumes to ICV in a population based cohort of older adults. In **chapter 6** allometric scaling of substructures of the brain relative to ICV were investigated and the importance of scaling properties for adjustment methodologies in comparative brain volumetric studies discussed. In **chapter 7** the neurodegenerative process was studied relative to ICV in both cross-sectional and follow-up samples of older people spanning the spectrum from healthy cognition to dementia. More precisely, the influence of ICV on the amount of brain atrophy and white matter lesion load were studied, as well as the effect of ICV on the relation of these neurodegenerative markers and cognition.

Final **chapter 8** summarizes and provides a general interpretation of the results of the work presented in this thesis.

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