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

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CHAPTER 8

Summary and general discussion

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Importance of structural imaging markers of AD

Alzheimer's disease (AD) is a growing socio-economic concern for ageing populations and the search for a treatment or prevention of AD is pressing. Today, it is believed that the therapeutic window of AD may be during its preclinical phase (Sperling et al. 2011). Finding early imaging markers of AD is of interest because they may facilitate the selection of people at risk for developing AD in a noninvasive manner. Most prior imaging studies of AD have focused on cortical degeneration and in particular on allocortical degeneration. However, pathological studies have shown the involvement of deep gray matter structures in AD as well. The striatum plays a central role in the limbic system and the cholinergic system, which are both affected in AD. Therefore the striatum can be considered a key candidate structure to be affected early in the disease. Part one of this thesis bundled the results of several volumetric and morphometric structural MRI studies of the striatum in older people and especially in patients with AD. Identifying pathological (focal) brain atrophy is, however, complex and a simple estimation of brain structure volumes of an individual patient does not lead to a diagnosis but needs to be assessed relative to group volumes and premorbid brain size. Therefore, in part two of this thesis two large population studies were included that focused on improving our understanding of the physiologic variability of brain structure and degeneration.

Part 1 Ventral striatal atrophy in AD

Volume loss of the ventral striatum in AD

Like other brain structures, the striatum loses volume with ageing. However, as described in chapter 2 striatal volume loss is higher in patients diagnosed with probable AD compared with their peers with normal cognitive test scores. A study of 139 brain MRI from a memory clinic population showed that this striatal volume loss was not homogeneous, but more pronounced in the nucleus accumbens and the putamen. Since, there are no sharp anatomical borders between striatal substructures, the study of only striatal volumes with artificially drawn borders is limited. A study of the shape of the striatum provided more information on which parts are affected in AD. Especially the ventral surface of the putamen and medio-ventral head of the caudate nucleus in patients with AD showed an inward change compared to study participants with normal cognitive test scores. This indicates that striatal volume loss in AD can, for a large part, be attributed to atrophy in the ventral striatum. Theoretically, the finding of pronounced ventral striatal volume loss in AD fits well with already established knowledge on atrophy patterns of the brain in AD. The ventral striatum is an important part of the limbic sys-

tem (Olmos and Heimer 1999). Like in the rest of the brain where AD affects first and mostly the allocortical and limbic areas (Callen et al. 2001), the striatum also displays most severe losses of volume in the limbic part. The studies of striatal atrophy in AD presented in this thesis were among the first imaging studies that focused specifically on striatal atrophy in AD. Recent studies have confirmed the presence of striatal atrophy in AD with disproportionate loss of the ventral part (Pievani et al. 2013; Roh et al. 2011; Yi et al. 2016).

Ventral striatal volume loss predicts cognitive decline

In order to assess the implication for cognitive functioning of striatal atrophy in AD, the relation between striatal atrophy and change in cognitive function was examined in a large population based sample of older individuals including those with diagnosis of vascular dementia or AD. Furthermore, the relation of striatal atrophy and the trajectory in cognitive function was compared to the relation of hippocampal volume loss and change in cognitive function. Cognitive function was repeatedly assessed in 4 sessions spanning a decade. Brain, striatal, and hippocampal volume measurements were based on brain MRI performed at the second session. Thus, cognitive data were available for study participants diagnosed with dementia prior, at time of, and after volume measurements of the striatum and hippocampus. The volumes of the total striatum, nucleus accumbens, putamen, and hippocampus were all smaller in participants diagnosed with dementia. But, interestingly, the volume of the nucleus accumbens was also significantly smaller in those who were going to be diagnosed with dementia years after the brain scan. Nucleus accumbens volume predicted cognitive decline in people with dementia diagnosed 3 years prior to, at the time of, and up to 6 years after brain scanning. Moreover, nucleus accumbens volume also predicted cognitive decline in participants that did not receive the diagnosis of dementia throughout the entire follow-up duration. This predictive value of the nucleus accumbens volume for cognitive function was independent of the effect of the predictive value of hippocampal volume and was stronger than the predictive value of hippocampal volume for participants that never received the diagnosis of dementia during follow-up.

Vascular risk factors are not related to striatal volume loss

Although the striatum, particularly the ventral striatum, seems to be affected in an early stage of the dementia process, it is not clear what the histopathological basis for the volume loss of the striatum observed in AD as shown in chapters 2–4 is. One of the hypotheses was that striatal volume loss might be due to other disease processes that

often co-occur with AD, like large and/or small vessel disease. The striatum is known to be particularly prone to arteriolosclerosis with the frequent occurrence of lacunar infarcts and microbleeds in the striatum under hypertensive conditions (Shi and Wardlaw 2016). Perhaps the accumulation of small focal vascular damage eventually leads to atrophy of the overall volume of the striatum and thalamus. However, as described in chapter 5 the presence of cardiovascular risk factors, APOE $\varepsilon 4$ status, body mass index, cholesterol, smoking history, drinking history, diabetes, and hypertension were not related to a higher rate of striatal atrophy measured over 2.5 years. In contrast, the hippocampus atrophied faster in the presence of hypertension and APOE $\varepsilon 4$ status. Albeit this being a selective study on only cardiovascular risk factors, so far no alternative explanation was found for striatal volume loss in AD than the disease process itself.

Embedding ventral striatal atrophy in existing models of AD

How does ventral striatal atrophy fit into the existent knowledge on pathological brain changes in AD and what may be the responsible pathological mechanism for volume loss in this area? The best hypothetical explanation available today is based on older histopathological studies of the striatum in AD. First, some studies have shown that cell bodies of the cholinergic interneurons are almost entirely filled with neurofibrillary tangles and that there is a disproportionate loss of cholinergic interneurons in the ventral striatum (Lehéricy et al. 1989; Selden, MM Mesulam, and Geula 1994; H Braak and E Braak 1990; Oyanagi et al. 1987). Although, cholinergic interneurons constitute 1–2% of all striatal cells, their soma is large (up to 40 μm), and their highest concentrations are found in the ventral striatum (Steiner and Tseng 2010). Thus, the volume loss of the ventral striatum in AD may be based on loss of cholinergic interneurons. The striatal cholinergic cells show the same pathological changes as magnocellular cholinergic forebrain complex. Loss of the cholinergic interneurons is a widespread phenomenon in the basal forebrain in AD, in particular the posterior part of the nucleus basalis of Meynert, and some studies found it to occur early in the process of AD (M Mesulam et al. 2004; Grothe, Heinsen, and Teipel 2013; Teipel et al. 2014). It is not known why cholinergic cells are lost in AD. The cholinergic cells are highly dependent for their existence on nerve growth factor. Some studies have shown the loss of nerve growth factor to precede cholinergic cell loss in the basal forebrain and striatum (Strada et al. 1992; Latina et al. 2017). And nerve growth factor signaling at cholinergic terminals on its turn has been shown to be sensitive to the toxic effect of Aβ (Triaca and Calissano 2016). But these relations need further confirmation. Another possible explanation for cholinergic cell loss in AD may be the more direct toxicity of Aβ in the striatum. The striatum of AD patients is heavily infiltrated by amyloid deposits (H Braak and E Braak

1990). In familial variants of AD cases and in Down syndrome, amyloid deposits have been shown to accumulate first in the striatum (Klunk et al. 2007; Annus et al. 2016; Villemagne et al. 2009). And in late onset AD the presence of striatal amyloid deposits together with cortical amyloid deposits on PiB/PET predicts Braak neurofibrillary stage and clinicopathologic stage of AD *in vivo* (Beach et al. 2012). However, it is not clear whether striatal Aβ depositions occur early in the disease process of late onset AD. Recently, a thorough florbetapir (^{18}F) PET study to preclinical stages of AD, as defined by presence of number of biomarkers/ cognitive markers and NIA-AA criteria, found subcortical amyloid deposition to occur early in the disease process especially in the nucleus accumbens and putamen. The same study reported that the buildup of amyloid may be more complete in subcortical areas relative to cortical areas, even in the earliest phases of preclinical AD. These findings contrast the more dominant theoretical model that predicts a downward progression of Aβ from neocortex to subcortical regions (e.g., thalamus and striatum) (H Braak and Del Tredici 2015; Thal et al. 2002). In summary, the cause of ventral striatal atrophy in AD loss is unknown, but previous studies have shown important loss of cholinergic cells and dense amyloid deposition in the striatum in preclinical stages of the disease.

Can ventral striatal atrophy serve as a marker for early AD?

Many morphological and pathological processes occur in brains of AD patients, but not all of them are related to or crucial to the development of the eventual characteristic clinical presentation. For instance, the accumulation of amyloid in the cortex of older people is a well-known process in AD. Although the presence of amyloid plaques is a hallmark of AD, the presence of these plaques has a small effect on episodic memory but not on other cognitive domains (Hedden et al. 2013) and also does not exclusively occur in patients with AD but also in a considerable percentage of people that have died without cognitive decline (Wolf et al. 1999; Latimer et al. 2017). The challenge for studies on AD is therefore to unravel the temporal order of pathological events and to try to identify those key events in the pathological cascade that eventually lead to cognitive impairment. The findings of this thesis together with recently published data are promising indications that the ventral striatum may be one of the structures relatively early affected in the pathological cascade of AD and can predict cognitive decline. Especially supportive to this hypothesis are the observations described in chapter 4 that smaller ventral striatal volume is detectable in people before clinical diagnosis of dementia and predictive for cognitive decline up to 6 years before dementia diagnosis. Also, volume of the nucleus accumbens was independent from hippocampal volume in predicting cognitive decline. However, there are some limitations of the ventral striatal atrophy/volume

to function as a predictive structural imaging marker for AD. For instance, hippocampal atrophy can be easily approximated by visual assessment. A major advantage to this visual assessment is the anatomical proximity of the temporal horn of the lateral ventricle. Contrarily, the ventral striatum is surrounded by and part of the complex anatomical region encompassing the ventrostriatopallidal system and extended amygdala for which precise anatomy is still subject to debate (Olmos and Heimer 1999). Also, current MRI protocols in daily clinical practice use volumetric T1-weighted imaging with whole brain coverage and perhaps coronal T2 weighted imaging, but these are not optimized to show anatomical detail in the region of the striatum and basal forebrain. Therefore, ventral striatal atrophy at this stage cannot be used as a marker for AD in an individual patient.

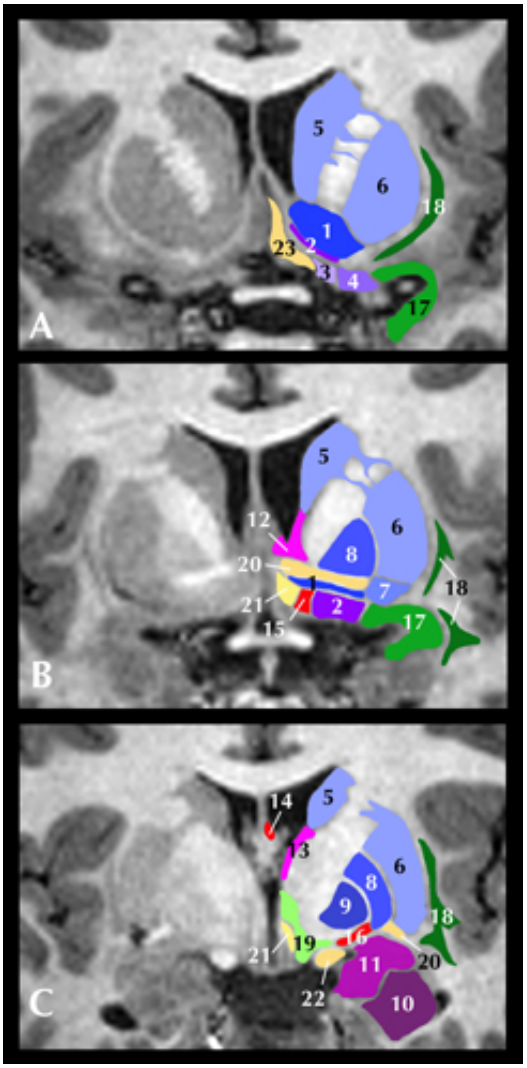
Limitations and future directions

There are two general limitations of the research presented in this thesis. The first limitation is related to the anatomical precision of the automated segmentation techniques used especially for segmenting the ventral striatum and nucleus accumbens. The nucleus accumbens is histologically well defined, being it the only structure in the striatum that is composed of a core and a shell. The ventral striatum includes besides the nucleus accumbens, also the ventral putaminal and caudate areas, olfactory tubercle, and anterior perforated substance (Heimer, Alheid, and Zahm 1993). The basal forebrain area surrounding the nucleus accumbens is packed with multiple white matter tracts and gray matter nuclei of the ventral striatopallidal system and extended amygdala, which are closely adjacent and in some areas continuous with each other. The extended amygdala is a concept that describes the phylogenetic continuity of the centromedial nuclei of the amygdala and the bed nucleus of the stria terminalis. The cortical-laterobasal part of the amygdala, provides important input to both the extended amygdala and to the ventral striatopallidal system (Olmos and Heimer 1999). Several studies have shown atrophy in the region of the basal forebrain in early AD, but the anatomical nomenclature used is not consistent. One study showed that atrophy in the basal nucleus of Meynert precedes atrophy of the entorhinal cortex (Schmitz et al. 2016). Others have pointed to disproportionately high degeneration of the gray matter in the basal forebrain in cholinergic magnocellular regions Ch1-4, corresponding to the medial septal nucleus (Ch1), vertical and horizontal limb of the diagonal band of Broca (Ch2-Ch3) and the basal nucleus of Meynert (Ch4) (MM Mesulam et al. 1983). This basal forebrain atrophy in the predementia stage of AD first appeared in the posterior part, also known as the basal nucleus of Meynert (Grothe, Heinsen, and Teipel 2013). These studies used a probabilistic atlas based on superposition of several cytoarchitectonic maps on an MNI brain (Zaborszky et al. 2008) to segment the cholinergic basal forebrain nuclei. Another study manually

traced the substantia innominata by comparing the MR image to a Nissl-stained coronal section of the basal forebrain region and found the region to be atrophied in mild AD (George et al. 2011). Although the term substantia innominata has become obsolete, judging from the description in the latter study, the substantia innominata probably corresponded to area basal nucleus of Meynert. These studies highlight the importance of the basal nucleus of Meynert in early AD. However, they tend not to be critical towards segmenting different nuclei with sometimes a millimeter thickness (Mai, Majtanik, and Paxinos 2015) on MRI with insufficient resolution and contrast to discriminate these cholinergic cell clusters from the ventrostriatopallidal system or extended amygdala. A schematic representation of the anatomical structures of the basal forebrain area and striatum is given in figure 1. The automated segmentation methods used in the studies presented in previous chapters, may suffer as well from difficulties in discriminating atrophy of the ventral striatum from atrophy in the cholinergic cell clusters of the basal forebrain notably the basal nucleus of Meynert. However, the nucleus accumbens was segmented as the region anterior to the anterior commissure, both in the segmentation tool of FSL (chapters 2, 3, and 4) as in the segmentation pipeline of the AGES-Reykjavik study (chapter 5) (Patenaude et al. 2007). Thus, the volumetric estimations of the nucleus accumbens may be underestimated but at least do not include the basal nucleus of Meynert, which is located underneath/ventral to the ventral globus pallidus. Likewise the estimations regarding the putamen, in particular the morphological contraction in the ventral putamen in AD, should not be affected by the atrophy in the basal nucleus of Meynert. Future studies should be directed towards a finer grained segmentation of this intricate anatomical forebrain region requiring higher resolution MRI with a focused field-of-view.

The second limitation is related to the role of the ventral striatum in cognition and consequences of its volumetric decline for functioning of the patient. It has been postulated that the nucleus accumbens plays a pivotal role in memory and learning processes and selecting responses (Goldenberg et al. 1999; Gonzalez-Burgos and Feria-Velasco 2008; Graybiel 2008). In the studies described in this thesis the cognitive function of the study participants was tested by several cognitive tests but none of them was specifically directed to the function of the ventral striatum. Furthermore, since the function of the cholinergic cells in the striatum in particular is still not completely clarified (Apicella 2007), no test for function of these cells has yet been developed. The precise impact of ventral striatal atrophy on the clinical presentation of AD is therefore not known and perhaps underestimated. Interestingly, since the olfactory tubercle is an integrated part of the ventral striatum, perhaps olfaction tests form a good marker for ventral striatal degeneration. Indeed, olfaction is the only sense that is affected early in the disease process of AD (Naudin, Mondon, and Atanasova 2013).

Figure 1: Striatum and basal forebrain complex on coronal MRI



1 Nucleus accumbens; 2 Olfactory tubercle; 3 Anterior olfactory nucleus; 4 Olfactory area; 5 Caudate nucleus; 6 Putamen; 7 Fundus region of putamen; 8 External globus pallidus; 9 Internal globus pallidus; 10 Basolateral amygdaloid nucleus; 11 Basomedial amygdaloid nucleus; 12 Bed nucleus of the stria terminalis; 13 Stria terminalis; 14 Medial septal nucleus (Ch1); 15 Diagonal band of Broca (Ch2 and Ch3); 16 Basal nucleus of Meynert (Ch4); 17 Piriform cortex; 18 Claustrum; 19 Hypothalamic area; 20 Anterior commissure; 21 Medial forebrain bundle; 22 Optic tract; 23 Subcallosal area.

Part 2 Allometric scaling of brain structures

Allometric scaling of brain structures

The second part of the research presented in this thesis examined physiological variability in brain structure and degeneration depending on the size of the premorbid brain. To be able to differentiate pathological from normal atrophy pattern in the brain, it is essential to have a good understanding of the geometry of the brain. The human brain varies considerably in size. How can brains of different size be compared? The answer to this question is complex. Some adjustment methods rely on the preservation of isometry of substructures of the brain and use a ratio of region of interest to intracranial volume (ICV) or total brain volume (TBV) to adjust for overall brain size. However, as was shown in chapter 6, brain structures do not scale isometrically with ICV variation. A comprehensive study of three large datasets with together more than 4500 brain MRI proofed that people with larger ICV on average contained proportionally smaller volumes of cortical and deep gray matter and a proportionally larger volume of white matter. Although, allometric scaling was shown in previous studies for gray and white cortical matter volume and even for cortical thickness, the study described in chapter 6 is the largest such study ever to be conducted and was the first to thoroughly investigate the deep gray matter structures. Furthermore, allometric scaling of brain structures was found in three large different study samples and after extensive testing could not be attributed to age-associated atrophy, gender, ethnicity, or a systematic bias from study-specific segmentation algorithm. Larger brains have a smaller developmental outgrowth of deep gray matter structures compared to the cortex and a smaller outgrowth of gray matter compared to white matter. Structures that show the least variance are the striatum and the thalamus. These results show why methods of head size adjustment that rely on isometry of brain substructures lead to over- or underestimation of results, spark erroneous interpretations and should be avoided. Also, methods that rely solely on linear affine transformation of the brain should be handled with care.

Larger brains degenerate faster in later life

If the brain develops with allometric scaling of its substructures, do brains of different sizes involute differently with ageing? Previous literature suggests that in various clinical groups, those with larger ICV cope better facing the (relative) same amount of neurodegenerative changes when compared to those with smaller ICV. ICV is, therefore, by some regarded as a proxy for brain reserve. Why a larger ICV is beneficial in maintaining performance with ageing is, however, not understood. Hypothetically, a larger ICV could

be associated with a higher resistance to neurodegenerative changes and thus harbor less stigmata of neurodegeneration. Or, a larger ICV could be associated with an increased resilience (i.e., better than expected performance in face of neurodegenerative burden) to neurodegenerative changes. Whether or not larger ICV has a positive effect on the amount of neurodegenerative changes or whether or not ICV attenuates the effect of neurodegenerative changes on cognition are falsifiable scientific questions that have not been studied sufficiently. In chapter 7, the relation of ICV to three MRI markers of neurodegeneration, i.e., brain atrophy, ventricular dilatation, and white matter lesion load, was studied. Furthermore, the relation of ICV with change in cognitive speed was also examined. The study was conducted in a large sample of older people spanning the spectrum from normal cognition to dementia. Larger ICV was cross-sectionally associated with a proportionally smaller brain volume and larger ventricular and white matter lesion volumes. These relations were similar in different age groups, slightly more pronounced in MCI and dementia, and independent from other sample characteristics associated with larger ICV (among others sex and educational level). Furthermore, after a five year follow-up, larger ICV was significantly associated with a larger yearly increase in ventricular volume and white matter lesion load. In those with healthy cognition or MCI, larger ICV was also associated with a larger decrease in cognitive speed, which was partially mediated through the larger increase in ventricular dilatation and white matter lesions in larger ICV. Thus, contrarily to what is often proposed in literature, no evidence was found for the notion that ICV is associated with a higher resistance or resilience to neurodegenerative changes. Rather, a larger ICV was associated with relatively more brain atrophy, a higher WML load, and a faster decline in cognitive speed.

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