Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: Findings from neuropathological and neuroimaging studies.

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ABSTRACT

Primary pathologies including amyloid-β (Aβ) plaques and neurofibrillary tangles (NFT) develop many years before the onset of dementia symptoms in Alzheimer's disease (AD). Age-related small vessel disease (SVD) is common in elderly subjects and may contribute to the clinical syndrome of AD. Each type of pathology shows a specific spatio-temporal sequence of spreading in the brain. Here we review neuropathological and neuroimaging findings (PET tracers of Aβ and NFT, MRI markers of SVD) to assess whether staging of these primary pathologies is useful to predict clinical symptoms in AD. On the basis of neuropathological data, early stages of Aβ plaque and NFT pathology distribution occur in preclinical AD, but advanced stages with spreading into further brain regions are associated with dementia symptoms. Amyloid PET presumably detects Aβ in advanced neuropathological Aβ stages, and increased global amyloid PET uptake is associated with clinical worsening in mild cognitive impairment (MCI) and possibly elderly cognitive normal subjects. Tau PET may provide additional predictive value by detecting NFT in the allocortex. There is weak evidence that SVD is related to amyloid or NFT pathology. Global volume of MRI-assessed white matter hyperintensities (WMH) contribute independently from biomarker levels of Aβ to cognitive decline. Regional differences of the effect of WMH on cognition have been demonstrated but are not yet established as a biomarker in AD. Accordingly, biomarkers for amyloid and τ-pathology allow a distinction between early and advanced stages of AD and potentially relevant vascular co-pathologies but a subgroup of pathologically identified preclinical AD cases is not identified by the current biomarkers

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INTRODUCTION

The biomarker aided diagnosis of Alzheimer's disease (AD) is the new diagnostic paradigm which is reflected in recent proposals to define the pre-dementia phase of AD[1]. According to National Institute on Aging and Alzheimer's Association (NIA-AA) criteria, preclinical AD is defined as the presence of abnormal biomarker levels of Aβ (i.e. reduced levels of cerebrospinal fluid (CSF) or increased amyloid PET binding) in the absence of cognitive impairment[1]. More advanced stages of the preclinical phase of AD include the presence of neurodegeneration as measured by biomarkers (e.g hippocampus atrophy, temporo-parietal FDG-PET hypometabolism or reduced CSF tau levels) and slight cognitive decline [1]. For the diagnosis of mild cognitive impairment (MCI) of the AD type (also called prodromal phase of AD), the presence of amnestic MCI plus abnormal biomarker levels is necessary[2]. Since it cannot be excluded that non-demented individuals diagnosed as preclinical AD according to current research diagnostic criteria [1] do not progress to the dementia stage, some authors prefer the term asymptomatic AD instead of preclinical AD. In the light of current recommendations we use the term preclinical AD to describe all non-demented cases with AD pathology regardless whether they will progress to the symptomatic stages or not. Apart from primary pathologies of AD including Aβ plaques and neurofibrillary tangles (NFTs), small vessel disease (SVD) is considered an additional pathology that may contribute to cognitive worsening in aging and AD. Although no quantitative consensus diagnostic criteria for SVD exist, the defining MRI-detectable features of SVD include small subcortical infarcts, lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces, and cerebral microbleeds[4]. Neuropathological studies showed that SVD is present in the majority of elderly subjects and the occurrence of high Aβ pathology coincides with vascular co-pathology in a substantial portion of elderly subjects [5]. Consistent with these post-mortem findings are results from neuroimaging studies, showing that white matter hyperintensities are present in up to 80% of subjects diagnosed with AD dementia[6]. Although it is not clear whether Aβ or tau are associated with the occurrence of SVD, age-related SVD may exacerbate neurodegeneration in AD and thus accelerate clinical

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progression [3].

A major question concerns the association between the severity of these pathologies and the manifestation of cognitive deficits and clinical impairment. In order to address this question, we will review first the neuropathological staging models of Aβ plaques, NFTs, and SVD within the preclinical and prodromal phase of AD. Secondly, we will review findings on the spreading of each type of pathology at the level of neuroimaging including PET and MRI findings with regard to 1) confirmation of the neuropathological spatio-temporal staging models for Aβ-plaque and NFT pathologies and 2) as a predictor of cognitive and clinical worsening in the pre-dementia phase of AD.

NEUROPATHOLOGY OF SYMPTOMATIC AND PRECLINICAL AD

Neuropathological hallmarks of AD

Alzheimer's disease is neuropathologically characterized by the presence of amyloid plaques and NFT [7]. Both pathological features are also frequently seen in non-demented individuals [8]. The presence of Aβ plaques is considered to represent AD pathology as recommended by the NIA-AA regardless of the presence of clinical signs of dementia [3]. Accordingly, all non-demented cases with Aβ plaque pathology should be considered as pathologically diagnosed preclinical AD cases (p-preAD) [10]. Whether Aβ plaques in other disorders such as Lewy body disease or traumatic brain injury respresent AD-related copathology or are part of the primary disease is not yet clear and requires further clarification.

Amyloid plaques consist of Aβ aggregates [12]. Modified forms of Aβ, such as pyroglutamate modified AβN3pE and phosphorylated Aβ (pAβ), were detected in a hierarchical sequence throughout the development of AD. [12]The presence of pAβ in Aβ aggregates was, thereby, associated with clinical symptoms of dementia whereas most non-demented cases with Aβ plaques did not show detectable amounts of pAβ [10] (Tab. 1). Neuritic plaques are a subset of Aβ plaques that exhibit dystrophic neurites. Although a development from diffuse, non-neuritic plaques to

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neuritic plaques has been suggested and may be true for some plaques [15, 18] there are diffuse plaques that never transform into neuritic plaques, e.g. lake-like amyloid in the subicular region [18, 19].Aβ plaques expand from its initial site of occurrence, the neocortex, into further brain regions in a hierarchical sequence that is described by five phases (Tab. 2a). In different regions of the brain morphologically different types of plaques occur that all contribute to this five-phase sequence of Aβ plaque regional expansion throughout the brain [16, 20].

NFTs are intracellular aggregates of abnormal phosphorylated τ-protein that form cytoplasmic fibrils [21, 22]. The first sign of τ-pathology in a neuron is the presence of abnormal phosphorylated τ-protein in the axon, soma and the dendrites. The neurons at this stage still look morphologically normal [21]. The next step is the detection of fibrillar τ-containing material in the cytoplasm that grows and step by step occupies more and more parts of the cell soma until the nucleus is displaced and the cell dies. After neuron death the NFT remains as extracellular "ghost-tangle" [21, 24] (Tab. 1). In addition to NFTs τ-aggregates also occur as neuropil threads within dendrites [25] and as dystrophic neurites in neuritic plaques [26].

NFT pathology consisting of silver-stainable fibrillar τ-aggregates starts in pyramidal neurons of the transentorhinal region (Brodmann area 35) [27]. Interestingly, subcortical nuclei such as the locus coeruleus and the raphe nuclei develop somatic abnormal phosphorylated τ-protein long before the first fibrillar tangles occur in the transentorhinal region [28]. After occurrence of NFTs in the pyramidal neurons of the transentorhinal region in Braak-NFT-stage I NFTs expand into further brain regions in a hierarchical sequence (table 2b) [27]. The distribution of abnormal phosphorylated τ-protein precedes that of fibrillar NFTs [21, 24] and shows a similar distribution pattern as described by the original Braak NFT-stages considering only neurofibrillary tangles detectable by silver methods[29, 30] [40, 41][42-44]

Amyloid pathology and NFT in preclinical and symptomatic AD

The earliest sign of τ or Aβ pathology is the accumulation of abnormal phosphorylated τ in neurons

of the locus coeruleus found as early as 6 years of age [31, 32]. Brain stem τ-pathology is seen in most individuals of 40 years of age and older [32]. At this point in time Aβ and fibrillar NFTs start to develop as represented by early stages and phases of NFT and amyloid plaque pathology (Suppl. Fig. 1). With increasing age the prevalence of early as well as of late stages and phases increase until nearly every individual has at least initial NFT pathology at 80 years of age [32]. However, Aβ plaques were seen only in 80 % of the individuals in this age group as demonstrated in our case collective (Suppl. Fig. 1) and published by other authors [32].

Clinical symptoms of AD are found in patients showing advanced stages and phases of NFT-pathology and Aβ plaque pathology (Fig. 1A) [20]. Non-demented elderly individuals often showed initial stages and phases of NFT and Aβ plaque pathology (Fig. 1A) [9, 20]. This group of p-preAD cases includes those preAD cases that also exhibit AD biomarkers as recommended for the clinical diagnosis of preAD but may also include cases that do not exhibit a pathological biomarker profile. Therefore, we use the term p-preAD cases to clarify that p-preAD cases may not be fully identical with clinically diagnosed preAD cases.

VASCULAR PATHOLOGY

Atherosclerosis

Atherosclerosis (AS) is frequent in the elderly and affects large to medium-sized arteries of the entire cardiovascular system (large-vessel disease). AS is characterized by intima proliferation with subsequent accumulation of blood derived lipids and proteins (e.g., cholesterol) in the vessel wall. This may lead to the development of atherosclerotic plaques, which may calcify, and to fibrosis of the vessel wall. In the brain it mainly affects arteries of the circle of Willis and the carotid arteries, in particular at the level of the carotic bifurcation. AS may cause narrowing of the arteries' lumina, thereby reducing the blood blow for the supported region, while rupture of atherosclerotic plaques often leads to thrombosis that results in either occlusion of the vessel or thromboemboli (for review see: [35]). AS in the circle of Willis has been linked to AD [37] while others, however, saw no

direct association between AS and AD pathology [39]. Zheng and colleagues recently found AS to be associated with microinfarcts and cystic infarcts while no association with AD pathology was seen [40]. However AS of the intracranial vessels is an independent and important risk factor for dementia due to stroke and other potentially reversible pathologies unrelated to AD [41].

Small vessel disease

SVD refers to pathological changes in the walls of small arteries and arterioles that cause thickening of the vessel wall. These changes include arteriosclerosis/atherosclerosis, lipo- or fibrohyalinosis and arteriolosclerosis. While small vessel arteriosclerosis/atherosclerosis is similar to AS of larger arteries, lipohyalinosis is characterized by asymmetric areas of fibrosis and hyalinosis associated with foam cells. Arteriolosclerosis describes the concentric hyaline thickening of the vessel wall (for review see: [35]). SVD is commonly seen in basal ganglia, in particular in the putamen and globus pallidus as well as in the white matter. Small brain stem arteries develop arteriosclerosis only in end stages of SVD and cortical vessels usually do not show signs of SVD [42]. SVD is a frequent cause of white matter lesions (WMLs, leukoaraiosis) and may lead to infarcts, microinfarcts and microbleeds in the basal ganglia. On neuropathological examination WMLs are associated with demyelination, axon loss, lacunar infarcts or enlarged perivascular spaces, most frequently in the frontal, parietal, and occipital white matter [43]. Of note, in addition to SVD neurofibrillary (neurodegenerative) pathology in the overlying cortex has been shown to be associated with WMLs, suggesting axonal loss caused by Wallerian like degeneration as a possible mechanisms for white matter lesions [44]. Routine histological assessment may underrate mild to moderate WML, but MRI imaging of fixed *post-mortem* brains is useful to detect and grade WML [45].

Recent findings from the Oxford Project to Investigate Memory and Ageing (OPTIMA) suggest that SVD does not promote AD pathology [47]. In our own cohort of cases the stage of SVD distribution [42] did not differ between p-preAD and AD patients (Fig. 1B). Taken together the findings suggest that severe SVD may indeed cause clinical dementia, but may not represent a causal factor for the

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development of AD.

Cerebral amyloid angiopathy

CAA is an AD-related vessel disorder affecting leptomeningeal, cortical and subcortical vessels by the deposition of Aβ within the vessel wall [35, 42]. The distribution of CAA throughout the brain is similar to that of Aβ plaques [42] (for further details see supplementary material).

SPATIO-TEMPORAL DYNAMICS OF IMAGING MARKER FOR Aβ, TAU AND SMALL VESSEL DISEASE

Spatial patterns of Amyloid PET uptake in AD

Global amyloid PET uptake is abnormally increased in an age-dependent manner in elderly cognitively healthy (HC) subjects, ranging from 18% in HC subjects 60-69 years old to over 65% in subjects > 80 years[49]. In amnestic MCI, the majority of subjects show abnormally increased global amyloid PET uptake[50]. Regional differences in the cerebral distribution of abnormally increased amyloid PET signals have been reported in presymptomatic subjects with autosomal-dominantly inherited AD [51]. Amyloid PET revealed lower signals in the hippocampus compared to neocortical brain areas including the prefrontal cortex and the posterior cingulate/precuneus [99], suggesting that the spreading of Aβ is more prominent in neocortical (SUVR > 1.4) than allocortical brain regions (e.g. hippocampus: SUVR 1.2-1.4) as predicted by post-mortem pathological findings[52],[53]. Staging of amyloid PET uptake within subcortical structures may be complicated by the fact that amyloid PET images are usually intensity normalized to the pons or cerebellum, i.e. brain regions predicted to be affected in the last phase of Aβ deposition[52]. In addition, amyloid PET tracers may bind to fibrillar rather than to early stage diffuse Aβ plaques. [101]The PET tracers PIB and flutemetamol are highly associated with ß-sheet (fibrillar) Aβ (PIB tracer) but not with diffuse plaques (PIB and flutemetamol tracers)[53]. The initial pathological stages of Aβ are presumably dominated by the deposition of diffuse plaques [15, 52], rendering it thus likely that

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amyloid PET selectively detects only later stages of amyloid PET. These observations are a possible explanation for the bimodal frequency distribution of global amyloid PET uptake [50, 54] across different clinical stages of AD. Whether CAA has impact on amyloid PET is still not clear. Most frequently we would expect no separate effect of CAA because of a similar distribution pattern as the usually coexisting Aβ plaque pathology [42]. However, a single CAA case with a positive PIB-PET but negligible plaques pathology has been described [Ducharme et al. 2013; JamaNeurology 70: 912-14]. Thus, further research is required to clarify the role of CAA in amyloid PET.

Amyloid PET as a predictor of clinical progression to AD dementia

Increased global AV45-PET uptake is associated with faster rates of cognitive decline in non-demented subjects [56]. In a pooled analysis of 5 studies, the conversion rate from MCI to AD dementia over 1 – 3 years of clinical follow up was 53% in subjects with increased global PIB-PET bindings compared to 7% in MCI subjects with normal PIB-PET uptake[50]. [1]Among elderly HC subjects, 16% of subjects with abnormally high PIB-PET developed MCI or AD dementia after 20 months and 25% after 3 years of follow up, but only 1 out of 73 subjects (1.4%) with low global PIB uptake developed MCI[57]. Similarly, abnormal levels of Aβ (as measured in CSF) were associated with significantly increased risk to progress from HC status to the symptomatic stage (clinical dementia rating (CDR) = 0.5) [58]. [111]Together these results suggest that abnormal global amyloid PET tracer retention is associated with faster rates of clinical worsening in both the preclinical and prodromal stage of AD.

*Spatial patterns of PET tracer uptake of NFT*Several PET markers highly specific to NFT are currently tested in humans such as the ^{18}F-labeled tracers THK-5105[11], THK-5223[61], T807[62], T808[63], and the ^{11}C labeled tracer PBB3 [64]. For detecting NFT in AD, *in vitro* studies in AD brain homogenates showed that such tracers (THK5105 or T808) have a high affinity for tau fibrils, which is 25 - 27 times higher than that for Aβ fibrils[65][11]. Okumara et al. reported that in a group

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of 8 AD dementia patients the [^{18}F] THK-5105 PET tracer showed increased uptake within the orbitofrontal and venterolateral prefrontal cortex, temporal lobe and posterior parietal lobe [66]. The effect sizes of the group differences were highest within the inferior and superior temporal lobes. Co-assessed PIB-PET showed a different pattern of cortical PET uptake, with a more pronounced uptake being observed within the prefrontal cortex, cingulate gyrus and parietal cortex [66]. These first results – though based on small sample sizes per study - confirmed neuropathological distribution patterns for tau and Aβ pathology exhibiting different distribution patterns in AD.

It should be cautioned that PET shows inherent limitations such as relatively low spatial resolution that renders it difficult to adequately detect NFT within subcortical structures, where according to the neuropathological staging models tau pathology likely occurs first.

A difference between the tau tracers is the sensitivity for labeling different types of tau lesions across the spectrum of tauopathies. Tau deposits consist of up to 6 isoforms of tau including 3 repeat (3R tau), 4 repeat (4R tau) and mixed 3 and 4 repeat (3/4 R tau) isoforms and show disease specific morphologies[67]. The ^{18}F-tracers THK-5223 labels exclusively NFT (mixed 3/4 repeat isoforms) present in AD but not tau lesions occurring in Pick's disease (3R tau), corticobasal degeneration (CBD, 4R tau) and progressive supranuclear palsy (PSP, 4R tau). The ^{11}C labeled tracer PBB3 detects however all of these tau lesions [64]. Thus, these tracers possess different clinical applicability, either as a general marker of tauopathies across AD and fronto-temporal lobe degeneration (PBB3) or for the differential diagnosis to distinguish between tauopathies (THK523).

MICROVASCULAR MRI CHANGES

SVD-related changes including arteriosclerosis and lipohyalinosis are thought to underlie MRI detectable leucoaraiosis (synonymous with WMH) and lacunar lesions in the white matter as discussed above. Neuropathological studies suggest that SVD spreads in a spatio-temporally specific way [68]. A staging model of SVD proposes that microvascular pathologies emerge first in the basal ganglia and the deep white matter (stage I), subsequently the thalamus and cortical brain

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areas (stage II), and finally the brain stem (stage III)[42].

In MRI based studies in subjects with genetically caused small vessel disease (CADASIL), the first brain areas affected by vascular changes include the periventricular brain areas (WMH) and basal ganglia (lacunes)[69]. Results from a population based study in elderly subjects corroborate that WMH show a similar region-specific distribution depending on the severity of SVD[70] . Thus, these MRI findings are in general agreement with the post-mortem established staging model of SVD.

For the association between WMH and cognitive decline and clinical progression, a meta-analysis showed that in population based studies, WMH were associated with a higher risk of incident amnestic MCI and AD dementia, as well as faster rates of cognitive decline in executive function and memory [75] despite varying reports in the literature [71,73]. Global WMH volume predicted cognitive decline independently from amyloid pathology, suggesting that SVD contributes to the cognitive decline in AD [76].

Even though the majority of the studies on WMH, used a lump measure of WMH within the whole brain, results from several studies suggest that the locality of WMH is critical for the clinical picture, with periventricular WMH being stronger associated with executive function compared to WMH in the deep white matter[75]. WMH may exert an effect onto cognitive dysfunction by disrupting fiber tracts and thus exerting locally specific effects onto neural network function [77]. In subjects with MCI, reduced episodic memory and executive function were each associated with a different topology of WMH distribution in patients with MCI [78]. A ROI-analysis of WMH within *a priori* hypothesized neural networks showed that WMH selectively within fronto-parietal and basal ganglia/cerebellar brain regions were associated with faster decline in executive function in subjects with MCI[79].

Together these results suggest that 1) WMH contribute to cognitive decline and clinical worsening independently from amyloid pathology and 2) WMH location matters for the prediction of decline in specific cognitive domains in subjects at increased risk of AD. Future studies will need to explore

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whether neural-network specific measures of WMH are predictive of the clinical progression in the course of AD.

CONCLUSIONS

Amyloid PET likely detects advanced stages of Aβ deposition possibly due to low uptake to diffuse plaques and increased uptake to more mature plaques, the latter of which are more frequent in later stages of Aβ deposition[15, 53]. It can be speculated that these plaque-type specific differences of amyloid PET tracer uptake contribute to the observation that subjects with an abnormal amyloid PET scan show globally increased amyloid PET uptake in the brain. This may limit the spatial information included in amyloid PET with regard to distinguish early vs late stage of Aβ deposition. The best established evidence for a predictive value is the classification of normal vs abnormal levels of amyloid PET uptake using a binary cut-off point of global amyloid PET uptake for the prediction of clinical progression in AD [50]. The proportion of "false positives" by biomarker-based classification of preclinical and prodromal AD is not sufficiently established and overdiagnosis of preclinical AD is a potential problem. The use of multiple markers focusing on co-pathologies such as NFT and SVD may partially alleviate this problem. Current biomarker based concepts of the progression of AD within the preclinical and MCI stage take neither SVD nor spatially specific patterns of the spread of Aβ plaques and NFTs into account. In addition, the occurence of amyloid PET-negative cases [53] fulfilling neuropathological criteria for AD pathology, indicates that current biomarkers do not sensitively detect all early stages of AD pathology. Based on post-mortem neuropathological criteria as the gold standard, at least two groups of p-preAD cases exist: 1. Amyloid PET-positive preAD cases and 2. Amyloid-PET negative, clinically silent p-preAD cases. Thus, two major questions remain to be addressed in future neuroimaging studies: 1) increasing the sensitivity of neuroimaging markers and summary statistics to detect those healthy control cases which show AD-like neuropathology but remain yet normal with regard to global amyloid PET and/or tau PET binding, and 2) assessing the clinically

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predictive value of neuroimaging markers of primary pathology in cognitive normal subjects in order to address the problem of over-diagnosing.

Legends:

Fig. 1 A: Boxplot diagram showing the distribution of Aβ phases and NFT-stages in non-AD control cases, p-preAD and symptomatic AD cases (N = 812). Symptomatic AD cases show end-stages of a process that is reflected by initial stages in p-preAD cases. In cases that are not considered as AD according to the NIA-AA criteria early stages of NFT-pathology are seen. **B**: The boxplot diagram of the stages of CAA and SVD distribution in 230 subjects [42] indicate higher CAA-stages in symptomatic AD cases than in p-preAD cases whereas p-preAD cases showed more advanced CAA than non-AD cases. The distribution of SVD stages also increased from non-AD to symptomatic AD cases whereas no obvious differences occurred between p-preAD and symptomatic AD cases. The 230 cases on whom data are shown in B were a subgroup of the total sample of 812 cases (panel A.) The selection criterion for this analysis was the availability of CAA-stages and SVD-stages determined in the context of previous studies [42, 80]. Statistical analysis by ANOVA corrected for multiple testing with Games-Howell post-hoc test.

Fig. 2 Differential uptake patterns of [^{18}F] THK-5105 PET tracer of NFT and [^{11}C] PIB-PET of Aβ in AD dementia. Adopted from[66].

Table 1. Maturation of Aβ aggregates and NFTs: Comparison between p-preAD and symptomatic AD

	Aβ-aggregation	NFT-generation	Cognitive status
p-preAD	Non-modified Aβ	abnormal τ-protein accumulation (soma & dendrites)	normal
		Aggregation of τ and NFT generation	
	AβN3pE	Neuron death and Ghost Tangle formation	
AD	pAβ	Expansion into further brain regions	MCI / demented

Table 2.
Spreading of Aβ plaque (**a**) and NFT pathology (**b**) in the human brain and its relation to Aβ phases and Braak-NFT-stages

a: Aβ plaques

Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Neocortex	Allocortex (hippocampus, amygdala, entorhinal region, cingulate gyrus)	Basal ganglia, Diencephalon	Midbrain, Medulla oblongata	Pons, Cerebellum

b: NFTs

Stage I	Stage II	Stage III	Stage IV	Stage V	Stage VI
transentorhinal region	Entorhinal region	hippocampus, basal temporal neocortex	superior temporal neocortex	neocortex except primary cortical fields	entire neocortex including primary cortical fields (e.g. primary visual cortex)

Figure 1

Figure 2
http://brain.oxfordjournals.org/content/brain/137/6/1762/F5.large.jpg
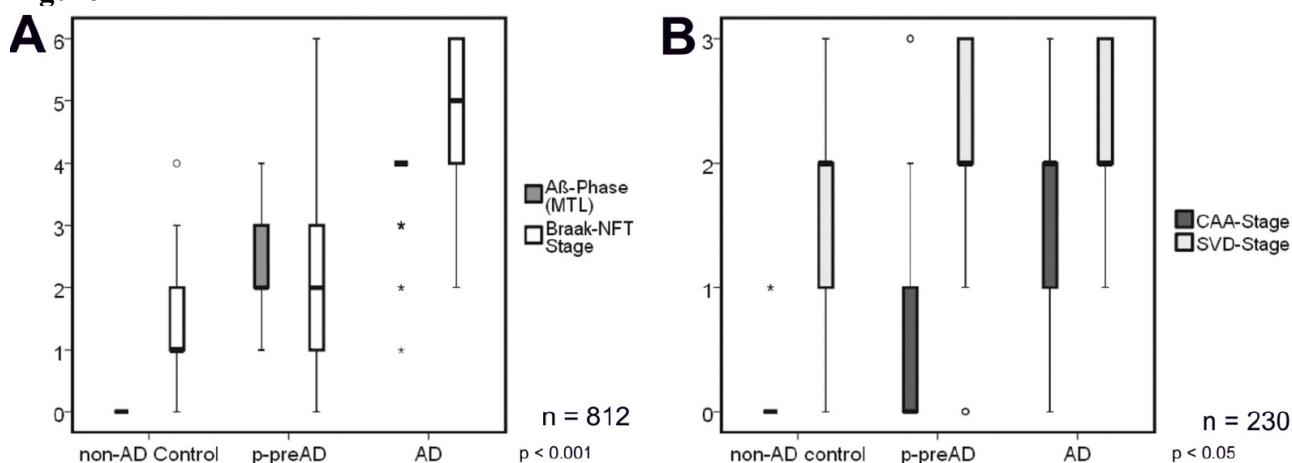
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Supplementary Material

Cerebral amyloid angiopathy

CAA is caused by focal to widespread deposition of Aβ within leptomeningeal and intracortical arteries, arterioles, capillaries, and rarely veins. The predominating Aβ species in CAA is Aβ-40 and the Aβ-40/Aβ-42 ratio is higher than in Aβ plaques [1-3]. CAA may cause fibrinoid necrosis, intimal thickening and microaneurysms. Of note, two types of CAA can be distinguished; *i)* CAA type 1 refers to Aβ deposits in the capillary wall and Aβ depositions in arteries and veins may be present in addition, while *ii)* no capillary Aβ is seen in CAA type 2 where Aβ deposits are only seen in arterial vessels [4]. Pericapillary Aβ on the other hand refers to Aβ deposits in the glia limitans and adjacent neuropil [5].

Sporadic, non-familial CAA is present in 82-98% of AD patients, but is also frequently observed in brains of elderly non-demented individuals with a prevalence of almost 100% in the oldest old [6, 7]. The stage of CAA distribution throughout the brain [8] was increased in AD cases compared to p-preAD cases (Fig. 1B). In AD, CAA is often associated with ApoE2 and ApoE4 alleles [9]. The occipital lobe has been reported to be the site most frequently and severely affected by CAA, followed by either frontal, temporal or parietal lobes (see [7, 10]).

CAA may cause lobar intracerebral hemorrhages (ICH) and microbleeds [11] and is considered a risk factor for non-traumatic ICHs in the elderly where it is present in up to 20% of all cases with ICH [12]. However, in a large autopsy cohort the majority of cases with CAA related ICH had hypertension during life and the prevalence of ICH was similar in cases with and without CAA (around 5%) [13, 14] suggesting that additional factors might play a role and hypertension has been indeed suggested to be an important additional causal factor in patients with CAA-related ICH [15, 16]. On the other hand, CAA associated hemorrhages affect lobar regions, while hypertension alone is typically associated with hemorrhages in the deep gray matter and in surgically resected lobar hematomas CAA is frequently present [17]. While moderate to severe CAA is considered to be an

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independent risk factor for cognitive impairment [18] its influence on cognitive function is not clear. Studies that have shown a significantly increased prevalence of CAA in demented subjects often did not control for additional pathologies such as neuritic AD pathology [19, 20]. However, an association between severe CAA and dementia is well documented but may be partly attributed to the high co-occurence of CAA and other pathologies such as neuritic plaques [21, 22]. In familial forms of CAA with very severe CAA associations between CAA and dementia independent of concomitant pathology have been reported [23].

Vascular lesions that are caused by CAA include hemorrhage/microhemorrhage as well as cerebral ischemia and inflammatory changes which could directly contribute to dementia. In demented patients severe CAA has indeed been associated with old microinfarcts [24]. In addition, associations between CAA, white matter changes and cognitive impairment suggest that advanced CAA may cause clinically important vascular dysfunction [25]. CAA may also contribute to cognitive decline by impairing the perivascular drainage pathway [26] leading to increased soluble Aβ in the brain parenchyma, which correlates with cognitive decline [27].

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Suppl. Fig. 1 Frequencies of Aβ phases (A) and NFT-stages (B) in 812 cases between 0 and 100 years. The prevalence of a given phase is provided in % of all cases in given age group. This analysis of 812 cases (previously not included in our analysis of the prevalence of Aβ phases and Braak-NFT stages on 2332 cases [28] confirmed the earlier results.

A Frequencies of Aβ-Phases in cases from 0 - 100 years of age
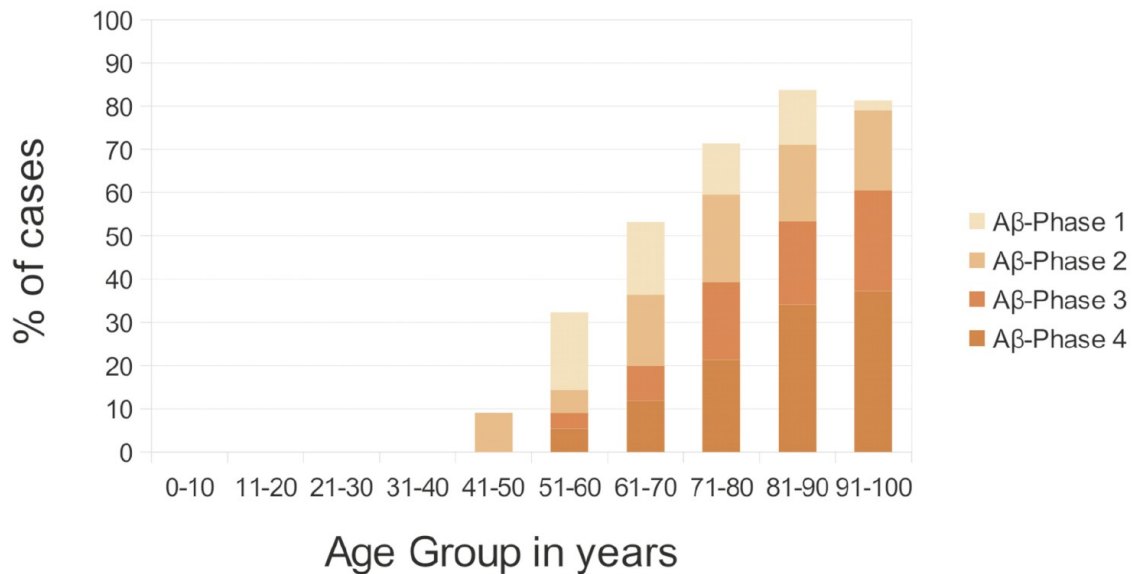
B Frequencies of Braak-NFT Stages in cases from 0 - 100 years of age