The Spatial Evolution of Tau Pathology in Alzheimer's Disease: Influence of Functional Connectivity and Education

Inaugural Dissertation

zur

Erlangung des Doktorgrades

Dr. nat. med.

der Medizinischen Fakultät

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ABSTRACT

Alzheimer's disease is neuropathologically characterized by extracellular accumulation of amyloid β plaques and intracellular aggregation of misfolded tau proteins, which eventually lead to neurodegeneration and cognitive impairment. With the recent advances in neuroimaging, these two proteinopathies can now be studied *in vivo* using positron emission tomography (PET). Combining this imaging technique with functional magnetic resonance imaging has consistently revealed a spatial overlap between amyloid β accumulates and functional connectivity networks (Buckner *et al.*, 2009; Grothe *et al.*, 2016), indicating functional connectivity as mechanistic pathway in the distribution of neuropathologies. While the infiltration of these neuronal networks by amyloid β deposits seems uniform across individuals with Alzheimer's disease, there nevertheless exists inter-individual differences in the clinical expression of the disease despite similar pathological burden (Stern, 2012). This observation has fuelled the concept of existing resilience mechanisms, which are supported by lifetime and –style factors and, which magnitude varies between individuals, contributing to the clinical heterogeneity seen in Alzheimer's disease.

Even though the spreading and resilience mechanisms in the phase of amyloid β accumulation are now better understood, no information on tau pathology *in vivo* were available in this regard until recently. Given the recent introduction of tau PET compounds, this thesis therefore aimed to address two questions: 1) whether functional connectivity contributes to the distribution of tau pathology across brain networks, and 2) whether the consequence of tau pathology on cognitive and neuronal function is mitigated by a resilience proxy, namely education. Using [^{18}F]-AV-1451 PET imaging to quantify tau pathology in a group of Alzheimer's disease patients, we observed that tau pathology arises synchronously in independent components of the brain, which in turn moderately overlap with known functional connectivity networks. This suggest that functional connectivity may act as contributing factor in the stereotypical distribution of tau pathology. Moreover, the results of this thesis demonstrate that the consequence of regional tau pathology on cognition differs depending on the level of education. Despite equal clinical presentation, higher educated patients can tolerate more tau pathology, already in regions related to advanced disease stage, than lower educated patients. Furthermore, tau pathology is less paralleled by neuronal dysfunction at higher levels of education. Thus, higher educated individuals show a relative preservation of neuronal function despite the aggregation of misfolded tau proteins. This maintenance of neuronal function may in turn explain the relative preservation of cognitive function albeit progressive tau pathology aggregation.

Taken together, the results of this thesis provide novel insights into the spreading mechanisms and the role of resilience factors towards tau pathology aggregation, which may not only be relevant for Alzheimer's disease, but other neurodegenerative diseases, in particular,

tauopathies. Better understanding of the spreading mechanisms in these diseases will permit a more precise prediction of disease progression and will thus be valuable for disease monitoring. Concomitantly, the development of sensitive biomarkers for disease monitoring is crucial for the evaluation of anti-tau-based therapies. Regarding the development of pharmacological strategies, the current results also indicate that proxy measures of resilience, such as education, need to be considered when allocating patients to treatment groups. Biased allocation may otherwise lead to a misinterpretation of observed effects that are not due to the drug but the group characteristics. Aside from this, sensitive tools for the early identification of at-risk individuals with high resilience need to be established to allow for a timely intervention. Current hypothesis is that an early intervention has the highest chance of success in modifying the disease course. However, as demonstrated by this work, individuals with high resilience remain undiagnosed until late in the disease course. Further research into resilience mechanisms may thus support the development of sensitive diagnostic tools and additionally offer potential targets that can be harnessed for novel treatment strategies. Hopefully, one day supporting the development of effective disease-modifying treatments.

ZUSAMMENFASSUNG

Die Alzheimer-Erkrankung ist neuropathologisch gekennzeichnet durch die extrazelluläre Ansammlung von Amyloid β Plaques und die intrazelluläre Aggregation von fehlgefalteten Tau-Proteinen, die schließlich zu Neurodegeneration und charakteristischen kognitiven Beeinträchtigungen führen. Mit den neuesten Fortschritten in der Hirnbildgebung können diese Proteinopathien *in vivo* mittels der Positronen-Emissions-Tomographie (PET) untersucht werden. Die Kombination dieser Bildgebungstechnik mit der funktionellen Magnetresonanztomographie hat dabei konsistent eine räumliche Überlappung zwischen Amyloid β Akkumulationen und funktionellen Konnektivitätsnetzwerken bei Patienten/Innen mit einer Alzheimer-Erkrankung ergeben (Buckner *et al.*, 2009; Grothe *et al.*, 2016). Diese räumliche Überlappung weist darauf hin, dass die funktionelle Konnektivität zur Verteilung von Neuropathologien beiträgt. Während die Infiltration dieser neuronalen Netzwerke durch Amyloid β Plaques bei Individuen mit einer Alzheimer-Krankheit konsistent erscheint, gibt es dennoch interindividuelle Unterschiede zwischen der pathologischen Belastung und dem klinischen Ausdruck der Erkrankung (Stern, 2012). Diese Beobachtung deutet auf Resilienzmechanismen hin, die durch Lebensstilfaktoren unterstützt werden, und deren Ausmaß individuell variiert und dadurch zur klinischen Heterogenität der Alzheimer-Erkrankung beiträgt.

Auch wenn die Ausbreitungs- und Resilienzmechanismen der Amyloid β Pathologie inzwischen besser erforscht sind, lagen diesbezüglich bis vor Kurzem keine Informationen über die *in vivo* Tau-Pathologie vor. Angesichts der jüngsten Verfügbarkeit von Tau-PET-Substanzen in klinischen und Forschungseinrichtungen war daher das Ziel dieser Dissertation folgende Fragestellungen zu untersuchen: 1. ‚Trägt die funktionelle Konnektivität zur Verteilung der Tau-Pathologie entlang bestimmter Gehirnnetzwerke bei?‘; 2. ‚Wird die Konsequenz der Tau-Pathologie in Bezug auf die kognitive und neuronale Funktion durch ein Resilienzmaß, nämlich Bildungsniveau, gemildert?‘. Die Analyse von [^{18}F]-AV-1451 PET-Bildgebungsdaten zur Quantifizierung der Tau-Pathologie bei einer Gruppe von Alzheimer-Patienten/Innen ergab, dass die Tau-Pathologie synchron in unabhängigen Komponenten des Gehirns auftritt, die wiederum moderat räumlich mit bekannten funktionellen Konnektivitätsnetzwerken überlappen. Dies deutet darauf hin, dass die funktionelle Konnektivität als beitragender Faktor für die stereotype Verteilung der Tau-Pathologie fungiert. Darüber hinaus zeigen die Ergebnisse dieser Arbeit, dass die Konsequenzen der regionalen Tau-Pathologie für die Kognition abhängig vom Bildungsniveau sind. Trotz gleicher klinischer Schwere können hoch gebildete Patienten/Innen eine schwerwiegendere Tau-Pathologie tolerieren als niedrig gebildete Patienten/Innen. Zusätzlich scheint der neurotoxische Effekt der Tau-Pathologie bei einem höheren Bildungsniveau weniger stark ausgeprägt zu sein. So zeigen hochgebildete Patienten/Innen eine relative Erhaltung der neuronalen Funktion trotz der Aggregation der Tau-Pathologie. Diese Präservation der neuronalen Funktion ermöglicht

vermutlich wiederum die relative Erhaltung der kognitiven Funktion trotz erhöhter Tau-Pathologie-Last.

Insgesamt dienen die Ergebnisse dieser Arbeit einem besseren Verständnis des Ausbreitungsmechanismus der Tau Pathologie und dem Beitrag von Resilienzfaktoren zur Aggregation der Tau-Pathologie, die nicht nur für die Alzheimer-Erkrankung, sondern auch für andere neurodegenerative Erkrankungen, insbesondere Tauopathien, relevant sein können. Ein erweitertes Verständnis der Ausbreitungsmechanismen dieser Krankheiten wird eine genauere Vorhersage des Krankheitsverlaufs ermöglichen und somit für das Krankheitsmonitoring wertvoll sein. Gleichzeitig ist die Entwicklung sensitiver Biomarker für das Krankheitsmonitoring entscheidend für die Auswertung von anti-Tau-basierten Therapien. Im Hinblick auf die Entwicklung von pharmakologischen Strategien deuten die aktuellen Ergebnisse darauf hin, dass bei der Zuordnung von Patienten/Innen zu Behandlungsgruppen Annäherungsmaße der Resilienz, wie z.B. Bildung, berücksichtigt werden müssen. Eine einseitig vorgenommene Zuordnung kann ansonsten zu einer Fehlinterpretation der beobachteten Effekte führen, die nicht auf das Medikament, sondern auf die Gruppeneigenschaften zurückzuführen sind. Darüber hinaus müssen sensitive Instrumente für die frühzeitige Identifizierung von Risikopersonen mit hoher Resilienz entwickelt werden, um eine rechtzeitige Intervention zu ermöglichen. Die aktuelle Hypothese ist, dass eine frühzeitige Intervention die höchste Erfolgschance in der Modifikation des Krankheitsverlaufes besitzt. Wie diese Arbeit jedoch zeigt, werden Personen mit einer hohen Resilienz erst zu einem späten Zeitpunkt im Krankheitsverlauf diagnostiziert. Insgesamt kann die Erforschung von Resilienzmechanismen zur Entwicklung von sensitiven Diagnoseinstrumenten beitragen. Zusätzlich bieten identifizierte Resilienzmechanismen potenzielle Ansätze, die für neue Behandlungsstrategien genutzt werden können. Die Ergebnisse werden hoffentlich eines Tages auch die Entwicklung effektiver krankheits-modifzierender Behandlungsstrategien unterstützen.

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ABBREVIATIONS

AICD	amyloid precursor protein intracellular domain	**FDG**	fluorodeoxyglucose
ApoE 4	apolipoprotein E4	**(f)MRI**	(functional) magnetic resonance imaging
APP	amyloid precursor protein	**ICA**	independent component analysis
BDNF	brain derived neurotrophic factor	**MAO**	monoamine oxidase
BM	brain maintenance	**MAPT**	microtubule-associated tau protein
BR	brain reserve	**MCI**	mild cognitive impairment
CBD	corticobasal degeneration	**NFT**	neurofibrillary tangles
PiB	Pittsburgh Compound B	**NIA-AA**	National Institute on Aging and Alzheimer's Association
CR	cognitive reserve	**PCA**	posterior cortical atrophy
CSF	cerebrospinal fluid	**PET**	positron emission tomography
CTF	C-terminal fragment	**PSP**	progressive supranuclear palsy
DMN	default mode network	**TPN**	tau pathology network
DTI	diffusion tensor imaging	**TSPO**	translocator protein-18 kDa

LIST OF PUBLICATIONS

This dissertation is based on the following publications:

1) Hoenig MC, Bischof GN, Seemiller J, Hammes J, Kukolja J, Onur ÖA, Jessen F, Fliessbach K, Neumaier B, Fink GR, van Eimeren T, Drzezga A. *Networks of tau distribution in Alzheimer's disease.* Brain, 2018 Feb 1;141(2):568-581. doi: 10.1093/brain/awx353. PubMed PMID: 29315361.

2) Hoenig MC, Bischof GN, Hammes J, Faber J, Fliessbach K, van Eimeren T, Drzezga A. *Tau pathology and cognitive reserve in Alzheimer's disease.* Neurobiology of Aging, 2017 Sep;57:1-7. doi: 10.1016/j.neurobiolaging.2017.05.004. PubMed PMID: 28577411.

3) Hoenig MC, Bischof GN, Onur ÖA, Kukolja J, Jessen F, Fliessbach K, Neumaier B, Fink GR, Kalbe E, Drzezga A, van Eimeren T. *Level of education mitigates the impact of tau pathology on neuronal function*. European Journal of Nuclear Medicine and Molecular Imaging, 2019 Aug;46(9):1787-1795: 1787. doi: 10.1007/s00259-019-04342-3. PubMed PMID: 31183635.

In addition, this dissertation contains data in form of two abstracts:

a. Hoenig MC, Bischof GN, Onur ÖA, Jessen F, Fliessbach K, Neumaier B, van Eimeren T, Drzezga A. *Regional susceptibility of the default mode network is associated with clinical phenotypes of Alzheimer's disease*. Presented at: Deutsche Gesellschaft für Nuklearmedizin, 2019, Bremen, Germany.

b. Hoenig MC, Bischof GN, Lopes Alves I, Ahlswede M, Sakagiannis P, Jessen F, Schmidt S, Barkhof F, van Eimeren T, Drzezga A for the AMYPAD Consortium. *Hippocampal intrinsic connectivity supports cognitive reserve in amyloid-positive cognitively normal subjects and Alzheimer's disease patients.* Presented at: AAIC, 2019, L.A., USA.

Co-authorships:

Hammes J, Theis H, Giehl K, Hoenig MC, Greuel A, Tittgemeyer M, Fink GR, Drzezga A, van Eimeren T. *Dopamine metabolism of the nucleus accumbens and fronto-striatal connectivity modulate impulse control.* Brain, 2019 Mar 1;142(3):733-743. doi: 10.1093/brain/awz007. PubMed PMID:30753324.

Bischof GN, Ewers M, Franzmeier N, Grothe M, Hoenig MC, Kocagoncu E, Neitzel J, Rowe JB, Strafella A, Drzezga A, van Eimeren T on behalf of the MINC faculty. *Connectomics and molecular imaging in neurodegeneration.* European Journal of Nuclear Medicine and Molecular Imaging, 2019 Jul 11. Epub ahead of print. doi: 10.1007/s00259-019-04394-5. PubMed PMID: 31292699.

Seemiller J, Bischof GN, Hoenig MC, Tahmasian M, van Eimeren T, Drzezga A. *Indication of retrograde tau spreading along Braak stages and functional connectivity pathways.* Acta Neuropathologica, *submitted*

INTRODUCTION

"Where are you right now?"

„Here and everywhere. Here and now. You must not think badly of me."

Alois Alzheimer & Auguste D.

It has been more than a century since Alois Alzheimer first reported on the case of Auguste D., who showed a progressive loss of memory and speech as well as agitation. The brain autopsy of Auguste D. revealed an accumulation of senile plaques, neurofibrils, and general atrophy, which Alois Alzheimer concluded to cause the clinical symptoms. Several years later, Emil Kraepelin introduced the term "Alzheimer's disease", which was initially considered a rare disease, but has become the most common neurodegenerative disease world-wide, currently affecting around 50 million people above the age of 65 (Gaugler *et al.*, 2019). With the demographic change in Western societies, it is anticipated that the prevalence will triple by 2050, increasing the societal and economic burden tremendously. Despite all efforts, there is still no disease-modifying treatment available. Consensus is that only an early diagnosis and intervention has the highest chance of success in modifying this devastating disease.

The incremental growth in scientific knowledge about Alzheimer's disease over the past decades has revealed that the neuropathological hallmarks of Alzheimer's disease, namely amyloid β plaques and neurofibrillary tangles (composed of misfolded tau proteins), begin to accumulate more than 20 years before initial clinical symptoms occur. Importantly, these neuropathological characteristics can nowadays be visualized and studied *in vivo* using positron emission tomography (PET). Especially the recent introduction of tau PET compounds has opened new possibilities in research and clinical settings. By means of tau PET imaging, information on the molecular mechanisms and distribution patterns of tau pathology in Alzheimer's disease and its interaction with other pathophysiological processes can now be gathered *in vivo*. This is further important for the identification of underlying resilience mechanisms against the spatial evolution of tau pathology and its neurotoxic effects given the heterogeneity in clinical expressions seen in Alzheimer's disease. Some individuals can tolerate more neuropathology albeit similar clinical severity than others and some never even develop clinical symptoms despite showing the neuropathological hallmarks of Alzheimer's disease (Stern, 2012). Understanding the mechanisms driving this resilience against brain pathology is crucial for the development of sensitive diagnostic and prognostic biomarkers as well as novel treatment strategies.

This dissertation is intended to examine the role of functional connectivity as potential spreading mechanism of tau pathology employing tau PET imaging ([^{18}F]-AV-1451) in combination with resting-state functional magnetic resonance imaging (MRI). Moreover, this thesis work elucidates the contribution of a resilience surrogate, namely education, concerning the impact of tau pathology aggregation on cognition and neuronal function. This investigation

is important on the one hand regarding the understanding of the mechanistic pathways of the pathophysiological processes in Alzheimer's disease, and on the other hand concerning the interpretation of potential resilience mechanisms modifying the clinical expression of Alzheimer's disease.

In the introduction of this dissertation, a brief overview on the current knowledge about the neuropathological hallmarks of Alzheimer's disease, their temporo-spatial evolution and a description of potential mechanisms supporting resilience against these pathologies is provided, with an emphasis on PET imaging studies. The introduction is followed by three publications, which focus on the role of functional connectivity and education regarding the spread and neuronal consequences of tau pathology. Finally, the papers will be discussed in a larger context.

CLINICAL PRESENTATION AND DIAGNOSIS OF ALZHEIMER'S DISEASE

Sporadic late-onset Alzheimer's disease usually occurs in individuals older than 65 years and accounts for more than 95% of all cases with Alzheimer's disease (Gaugler *et al.*, 2019). The remaining cases relate to familial and early-onset forms of Alzheimer's disease with an age of onset ranging from 30 to 65 years. Within the realm of this dissertation, the term Alzheimer's disease will refer to sporadic late-onset Alzheimer's disease.

The cardinal symptom of Alzheimer's disease is a progressive loss of memory, with subsequent appearance of executive, visual-spatial, language and neuropsychiatric impairments. At advanced stages of the disease, motor symptoms such as difficulties with swallowing and walking may also occur. Despite the typical presentation of Alzheimer's disease, also atypical forms exist. These atypical forms present the same neuropathological characteristics, namely amyloid β plaques and misfolded tau proteins, but are characterized by different clinical phenotypes. These variants have been associated with an earlier disease onset (Snowden *et al.*, 2007; Koedam *et al.*, 2010) and encompass posterior cortical atrophy (PCA), the logopenic variant and the dysexecutive/ behavioural variant of Alzheimer's disease. PCA is characterized by predominant visual-spatial deficits, the logopenic variant by language difficulties and the behavioural variant by deficits in executive function. Independent of the typical or atypical phenotype of Alzheimer's disease, the clinical symptoms eventually interfere with activities of daily living, rendering the individual with Alzheimer's disease dependent on others. The average life-expectancy after the diagnosis of Alzheimer's disease is about 8-10 years, but significantly depends on how impaired the individual already is at the point of diagnosis (Larson *et al.*, 2004; Helzner *et al.*, 2008).

At present, the clinical diagnosis of Alzheimer's disease is based on the recommended diagnostic National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines from 2011 (Albert *et al.*, 2011; Jack Jr *et al.*, 2011; McKhann *et al.*, 2011; Sperling *et al.*, 2011) and the international working group criteria on Alzheimer's disease (Cummings *et al.*, 2013; Dubois *et al.*, 2014). According to the NIA-AA guidelines, Alzheimer's disease is a continuum, which can be categorized into three stages: preclinical, mild cognitive impairment (MCI), and Alzheimer's dementia. In the preclinical stage, molecular changes are detected including amyloid β build-up, but no significant cognitive deficits are yet observable (Sperling *et al.*, 2011). In the MCI stage, initial memory impairments occur that are greater than of an age-matched person, but which do not yet interfere with daily living (Albert *et al.*, 2011). In addition to the accumulation of amyloid β, a marker of neuronal injury including tau becomes abnormal, which can be assessed using PET or cerebrospinal fluid (CSF) markers (Albert *et al.*, 2011). In the final stage, Alzheimer's dementia, cognitive deficits interfere with the person's ability to function independently and both biomarkers are abnormal (McKhann *et al.*, 2011). Importantly,

the guidelines for the symptomatic stages were intended to support the clinical diagnosis, whereas the preclinical definition was meant to offer researchers a common definition for the identification of participants, who show abnormal Alzheimer's disease biomarkers in absence of clinical symptoms. Moreover, the integration of Alzheimer's disease biomarkers in form of PET imaging or CSF analysis is considered as aid for the clinical setting, but the recommended guidelines are primarily based on clinical criteria.

The current diagnostic guidelines have therefore shifted from a syndromal to a biological construct, which have recently been outlined in a new research framework (Jack Jr *et al.*, 2018a). In this framework, the presence or absence of abnormal Alzheimer's disease biomarker profiles are the building blocks used to describe the Alzheimer's disease spectrum, while considering cognitive impairment as the result of the disease rather than its definition. The workgroup suggested the so-called A-T-N classification scheme, which is based on brain imaging (i.e., PET or MRI) and CSF biomarkers. "A" refers to amyloid pathology, "T" to tau pathology, and "N" to neurodegeneration. In addition to the presence or absence of these three markers, a fourth factor namely the cognitive continuum can be included. Importantly, in contrast to the NIA-AA guidelines, a clear distinction is set between tau pathology and neurodegeneration/neuronal injury. The A-T-N classification states that abnormal amyloid and tau levels are a necessary condition for Alzheimer's disease, whereas neurodegeneration is not specific to Alzheimer's disease. As it is currently only a research framework, it still needs to be validated in clinical settings. However, so far, it appears to be a well-suited tool for the biological diagnosis of Alzheimer's disease by taking advantage of the currently available biomarkers for the quantification of the neuropathological hallmarks of Alzheimer's disease.

NEUROPATHOLOGICAL HALLMARKS OF ALZHEIMER'S DISEASE

Alzheimer's disease is a dual proteinopathy characterized by the extracellular deposition of amyloid β in senile plaques and the intracellular aggregation of neurofibrillary tangles (NFTs). According to the prominent amyloid cascade hypothesis (Hardy and Higgins, 1992), amyloid β deposition is the initial event, which triggers the formation of senile plaques and NFTs. This in turn leads to neuronal death and ultimately to dementia. Much support has been provided for this hypothesis. Nonetheless, there remain objections against it – one being that no phase 3 clinical trial targeting amyloid β plaques has yet been successful in modifying the disease course (Gilman *et al.*, 2005; Doody *et al.*, 2014; Salloway *et al.*, 2014; Siemers *et al.*, 2016; Honig *et al.*, 2018) and another one being that these two proteinopathies may actually act independently with tau pathology preceding amyloid β deposition, as recently suggested by autopsy data (Jack Jr *et al.*, 2013). Despite the uncertainties regarding the temporal trajectory of the pathogenesis of Alzheimer's disease, there is no doubt that the two neuropathological hallmarks take on a key role in the pathogenic cascade of Alzheimer's disease, as elucidated in the following.

Amyloid β

The extracellular accumulation of amyloid β peptides was first discovered as main constituents of senile plaques in Alzheimer's disease and Down's Syndrome (Glenner and Wong, 1984; Masters *et al.*, 1985a; Masters *et al.*, 1985b). A while later, genetic studies on familial Alzheimer's disease found that mutations in genes encoding the amyloid precursor protein (APP) (Goate *et al.*, 1991), preselin-1 and preselin-2 (Levy-Lahad *et al.*, 1995; Sherrington *et al.*, 1995) were associated with elevated levels of amyloid β. It is now known that preselin-1 and -2 are involved in the APP processing pathway. Although the functional role of APP itself remains unresolved, much knowledge has been gathered about the formation of amyloid β deposits:

The amyloid β peptide is derived from APP, a transmembrane protein which can undergo two proteolytic pathways, the α-pathway or β-pathway. The former represents the non-amyloidogenic and the latter the amyloidogenic pathway (*see* Figure 1). In the non-amyloidogenic process, APP is sequentially cleaved close to the membrane by α-secretase, liberating sAPPα and generating an alpha-C-terminal fragment (CTFα). Cleavage of CTFα by γ-secretase generates a small p3 fragment and a cytosolic element, the APP intracellular domain (AICD), which remains bound to the membrane and carries a role in signal transduction (Chen *et al.*, 2017). The catalytic subunit of γ-secretase is encoded by either presilin-1 or presilin-2. In the amyloidogenic pathway, APP is cleaved by β-secretase, which results in a large derivative, sAPPβ, and a beta-C-terminal fragment (CTFβ) that remains bound to the membrane (Selkoe, 1994; Olsson *et al.*, 2014). CTFβ is then cleaved by γ-secretase, which results in the soluble amyloid β peptide and the membrane-bound AICD.

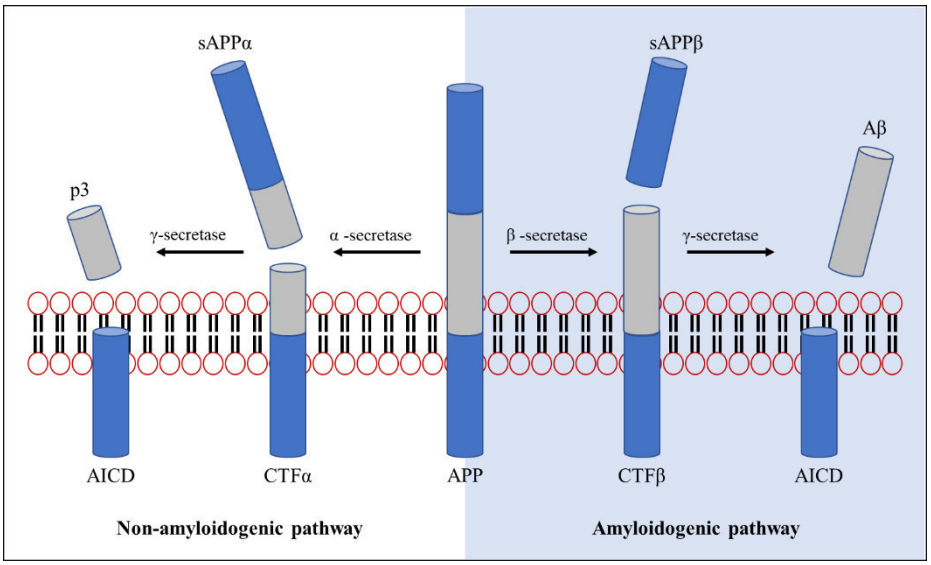


Figure 1– Proteolytic pathways of the transmembrane amyloid precursor protein (APP). In the non-amyloidogenic pathway, APP is cleaved by α-secretase generating sAPPα and CTFα followed by cleavage of γ-secretase, liberating p3 and producing AICD. In the amyloidogenic pathway, β -secretase cleavage results in sAPPβ and a larger CTFβ fragment followed by γ-secretase producing amyloid β and AICD. CTF = C-terminal fragment; AICD= APP intracellular domain. Adapted from Cheignon et al., 2018.

As the cleavage process in the amyloidogenic pathway is somewhat imprecise, numerous species of amyloid β exist (Takami *et al.*, 2009). The most common species are amyloid β40 and amyloid β42, which are more hydrophobic and fibrillogenic than shorter forms of amyloid β (Takami *et al.*, 2009). It is assumed that the deposition of amyloid β is likely a consequence of impaired clearance and degradation mechanisms, which promote the assembly of amyloid β monomers to oligomers, protofibrils and eventually to amyloid plaques in the brain parenchyma (Mawuenyega *et al.*, 2010). Importantly, it was recently reported that the soluble forms of amyloid β are more toxic to neuronal cells than senile plaques (Bao *et al.*, 2012; Esparza *et al.*, 2013). Given their solubility, these forms can spread throughout the brain (Chen *et al.*, 2017), disrupt synaptic function and trigger downstream toxic pathways (Mucke and Selkoe, 2012). Moreover, in accordance with the amyloid cascade hypothesis, transgenic experiments demonstrated that soluble amyloid β forms increase tau phosphorylation (Seino *et al.*, 2010) and induce tau aggregation and seeding (De Felice *et al.*, 2008; Seino *et al.*, 2010; Vergara *et al.*, 2019), which represents the second neuropathological hallmark of Alzheimer's disease.

Neurofibrillary tangles

Neurofibrillary tangles (NFTs) are intracellular aggregates, which are composed of the hyperphosphorylated tau protein. The tau protein in its native form is abundant in the axons of neurons and carries an important role in the stabilization of the microtubules and axonal transport (Morris *et al.*, 2011). It is encoded by the microtubule-associated tau protein (MAPT) gene (Weingarten *et al.*, 1975; Grundke-Iqbal *et al.*, 1986) and contains four areas: an N-terminal region, a proline-rich domain, a microtubule-binding domain, and a C-terminal projection region (Mandelkow *et al.*, 1996). In the adult human brain six isoforms of tau are present, which are produced by alternative splicing of exon 2, 3, and 10 (*see* Figure 2). These isoforms can further be separated based on the length of their repeat binding domain, namely three or four carboxy repeat domains (3R and 4R). In the adult human brain, the 3R and 4R forms of tau are equally expressed, but this ratio changes in neurodegenerative diseases (Gao *et al.*, 2018). Tau aggregation is not only a characteristic hallmark of Alzheimer's disease, but also other neurodegenerative diseases known as tauopathies (e.g., progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD)). These tauopathies can be classified based on the overexpression of the tau isoforms, namely: 3R-tauopathies (e.g., Pick's disease), 4R-tauopathies (e.g., PSP or CBD), and 3R/4R tauopathies, to which Alzheimer's disease belongs. Albeit the differences in tau isoform expression, the pathological tau lesions are highly phosphorylated across tauopathies, whereby in Alzheimer's disease both forms of tau (3R and 4R) undergo hyperphosphorylation (Buée *et al.*, 2000). The exact mechanism leading to this hyperphosphorylation remains elusive. But given that various kinases and phosphatases regulate tau phosphorylation in the normal state, it has been suggested that an imbalance between these enzymes causes hyperphosphorylation of tau (Noble *et al.*, 2013).

Importantly, the hyperphosphorylation of tau appears to precede the aggregation of misfolded tau proteins into paired helical filaments and then into insoluble NFTs (Alonso *et al.*, 2001;

Chohan *et al.*, 2005). The aggregation process, in turn, is facilitated through mechanisms such as impaired degradation, truncation, or missorting of tau (Guillozet-Bongaarts *et al.*, 2006; Dickey *et al.*, 2007). Regarding the truncation of tau, it was shown that it suppresses the formation of the so called paperclip structure, which usually hinders tau to aggregate (Jeganathan *et al.*, 2006). Notably, tau in its native form is unfolded and does not tend to aggregate (Mukrasch *et al.*, 2009). However, through the truncation process, tau loses the paperclip formation, which in turn promotes the aggregation of tau proteins. Moreover, recent studies showed that the hyperphosphorylation of tau can lead to missorting of tau from the axon to the somato-dendritic compartment (Thies and Mandelkow, 2007; Hoover *et al.*, 2010; Zempel *et al.*, 2010; Zempel *et al.*, 2017), which can cause synaptic dysfunction (Thies and Mandelkow, 2007; Hoover *et al.*, 2010).

Overall, a multitude of processes involved in the hyperphosphorylation and aggregation of misfolded tau proteins have been identified so far (for a detailed review see Morris *et al.*, 2011; Wang and Mandelkow, 2016). Nevertheless, the exact trigger of tau pathology in Alzheimer's disease remains unknown as the MAPT gene is not genetically linked to Alzheimer's disease. This lack of genetic association to Alzheimer's disease suggests that tau pathology is a downstream process of the amyloid β- induced neurodegenerative cascade – a cascade, which is further characterized by pathophysiological alterations including the loss of synapses, initial hippocampal and later general atrophy, neuroinflammation in form of reactive astrocytes and activated microglia, and depletion of distinct neurotransmitter systems (Luca *et al.*, 2018). Importantly, with the developments in PET imaging, several processes of this pathophysiological cascade can nowadays be visualized and studied *in vivo.* The principle of PET imaging and the main PET compounds used in Alzheimer's disease research and diagnosis will therefore be discussed in the next section.

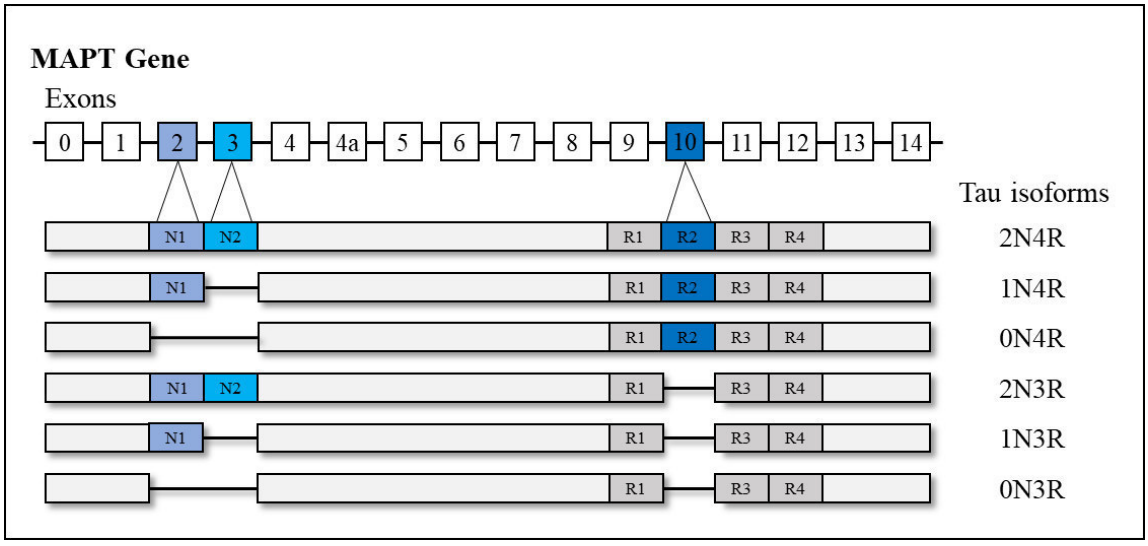


Figure 2 - The human microtubule-associated tau protein (MAPT) gene and its isoforms. Representation of the six isoforms of the tau protein produced by alternative splicing of exon 2 ,3, and 10 is illustrated. In Alzheimer's disease, 3R and 4R isoforms are equally hyperphosphorylated. N= N-terminal; R = microtubule-binding repeat domain. Adapted from Wang and Mandelkow, 2016.

POSITRON EMISSION TOMOGRAPHY IN ALZHEIMER'S DISEASE

Positron emission tomography (PET) is an imaging technique permitting the visualization of molecular changes and protein aggregations *in vivo* by injection of radioactively labelled tracers into the blood, which bind to the biomolecules of interest. Briefly, PET imaging is based on the following technique: The radioactively labelled tracers contain short-lived positron-emitting radionuclides such as fluorine-18 or carbon-11. The beta decay of these radionuclides (e.g., ^{18}F) attached to the target biomolecule (e.g., glucose) results in the emission of a positron that annihilates with an electron after travelling less than 1mm in the tissue. The annihilation process results in two gamma-photons being emitted in opposite directions. These gamma-rays are then detected by scintillation detectors, which register the annihilation photons in coincidence and store the events. Finally, using computer analysis, the PET activity distributions are reconstructed as three-dimensional images based on the coincidence events. The final images are then used for diagnostic or research purposes.

Up to now, several PET tracers have been developed, which can cross the blood brain barrier and visualize Alzheimer's disease-related pathophysiological changes. The most commonly used tracers, which will be discussed in the following, can visualize amyloid pathology, tau pathology and changes in glucose metabolism (*see* Figure 3).

Amyloid PET

The most widely studied amyloid tracer is [^{11}C]-Pittsburgh Compound B ([^{11}C]-PiB), which was developed by Chet Mathis and William Klunk in 2002 (Mathis *et al.*, 2002). This tracer shows high affinity and selectivity to fibrillar amyloid in senile plaques (Mathis *et al.*, 2002; Cohen *et al.*, 2012). However, given the short half-life of [^{11}C]-PiB of only 20 minutes, its use is limited to centres that have a cyclotron and a department of radiochemistry on-site. Due to this limitation, F18-labelled tracers with similar affinity profiles, but a half-life of around 120 minutes, were developed, among them: [^{18}F]Florbetapir (Wong *et al.*, 2010), [^{18}F]Florbetaben (Rowe *et al.*, 2008), and [^{18}F]Flutemetamol (Rinne *et al.*, 2012). Ever since these amyloid tracers have been available, a large body of evidence has been gathered supporting the utility of these tracers as diagnostic tool for dementia due to Alzheimer's disease. In addition, these tracers have been useful for patient selection and the evaluation of drug efficacy in clinical trials (Fleisher *et al.*, 2011). However, the drawback of the currently available amyloid tracers is that they only bind to insoluble plaques and not to the more toxic and soluble forms of amyloid β (Haass and Selkoe, 2007). Moreover, albeit its major role in defining Alzheimer's disease, amyloid PET imaging appears not to be suitable for the short-term prediction of individuals converting from prodromal stages or MCI to Alzheimer's dementia (Iaccarino *et al.*, 2017). Furthermore, amyloid PET shows relatively low correlation with clinical and cognitive parameters (Brier *et al.*, 2016), indicating that this PET modality is less well-suited for staging

of the disease. Thus, for better information regarding the progression and staging of the disease, [^{18}F]-Fluorodeoxyglucose ([^{18}F]-FDG) PET and more recently tau PET compounds have been considered.

Tau PET

The complexity of the tau protein given its heterogenous isoforms and its intracellular location have been major challenges in the development of selective tau PET tracers. Overcoming these challenges, several radioactive substances have recently been developed. The most widely studied are: [^{18}F]-THK5117 (Harada *et al.*, 2015), [^{18}F]-THK5351 (Harada *et al.*, 2016), [^{18}F]-AV-1451 (Chien *et al.*, 2014), and [^{11}C]-PBB3 (Maruyama *et al.*, 2013). Before that time, solely CSF measures could provide information on abnormalities in tau phosphorylation in the central nervous system, but no information on the regional distribution of tau pathology could be obtained. The introduction of tau PET tracers has therefore led to new possibilities for diagnostic and research-oriented considerations (van Eimeren *et al.*, 2017). A progressively accumulating body of evidence suggests that tau PET is a suitable progression and staging marker, because it is more closely associated with neurodegeneration and cognitive decline than amyloid PET (Bischof *et al.*, 2016; Brier *et al.*, 2016; Ossenkoppele *et al.*, 2016; Schöll *et al.*, 2016; Schwarz *et al.*, 2016). Additionally, recent longitudinal tau PET studies have provided first insights into the pathogenic cascade of Alzheimer's disease (Chiotis *et al.*, 2018a; Jack Jr *et al.*, 2018b; Southekal *et al.*, 2018). Importantly, in contrast to amyloid PET, tau PET allows differentiation between typical and atypical phenotypes of Alzheimer's disease, and primary tauopathies from secondary tauopathies[1] (Kikuchi *et al.*, 2016; Ossenkoppele *et al.*, 2016; Dronse *et al.*, 2017; Hammes *et al.*, 2017; Passamonti *et al.*, 2017; Whitwell *et al.*, 2017; Whitwell *et al.*, 2018b). It is thus a meaningful biomarker for differential diagnosis. However, despite the advances of tau PET imaging, an unresolved issue of the first-generation tau PET tracers remains the off-target binding to subcortical structures (Marquié *et al.*, 2015; Lowe *et al.*, 2016; Ng *et al.*, 2017) and the lower affinity to different tau isoforms (Smith *et al.*, 2017). Therefore, second-generation tracers have been developed with improved binding properties and lower off-target signal, among them [^{18}F]-PI-2620 (Mueller *et al.*, 2017) and [^{18}F]-MK-6240 (Walji *et al.*, 2016). These tracers are currently under investigation for their clinical and research utility (Hostetler *et al.*, 2016; Villemagne *et al.*, 2018). Aside from this, tau PET imaging provides unique information on underlying disease mechanisms, which are not only relevant for Alzheimer's disease but also for other tauopathies.

FDG PET

The PET compound with the longest history in the investigation and diagnosis of neurodegenerative diseases is FDG PET, which is sensitive to changes in glucose metabolism.

[1] Primary tauopathies are considered diseases with misfolded tau proteins being the predominant pathological signature such as PSP or CBD. Secondary tauopathies account for diseases such as Alzheimer's disease, which are characterized by tau aggregation in combination with other toxic accumulates such as amyloid β plaques.

It has been postulated that FDG PET measures synaptic function rather than overall neuronal function (Harris *et al.*, 2012). Thus, a decrease in FDG PET signal (i.e., hypometabolism) reflects an index of synaptic failure (Iaccarino *et al.*, 2017). Over the past two decades, FDG PET has been demonstrated to provide high diagnostic accuracy. Like tau PET, FDG-PET can aid in the differential diagnosis given that it offers information on the underlying pattern of neuronal dysfunction (Foster *et al.*, 2007). Accordingly, distinct regional patterns of hypometabolism have been observed for the clinical phenotypes of Alzheimer's disease (Ossenkoppele *et al.*, 2016; Dronse *et al.*, 2017). Moreover, a close spatial relationship between the tau PET signal and the FDG PET signal has been reported by several studies, whereas this is not the case for amyloid PET (Bischof *et al.*, 2016; Brier *et al.*, 2016; Ossenkoppele *et al.*, 2016). However, in contrast to amyloid and tau PET, FDG imaging does not provide any information on the underlying neuropathology. Therefore, an additional marker such as liquor measurements or PET imaging is necessary to confirm the diagnosis of Alzheimer's disease or another neurodegenerative disease. Despite this, FDG PET may nevertheless be preferred to novel and more expensive PET compounds in the clinical setting given that it comes at relatively low costs in comparison to other PET tracers (van Eimeren *et al.*, 2017).

Collectively, the use of these three PET modalities provide unique information on the evolution of the molecular characteristics in Alzheimer's disease. The additional use of other PET compounds in research settings, for example for the visualization of neuroinflammation (e.g., [^{11}C]-PBR28) and changes in synaptic density (e.g., [^{11}C]-UCB-J), permits the investigation of the temporo-spatial relationship between these markers in the pathogenic cascade of Alzheimer's disease. In addition, combining these PET modalities with neuroimaging techniques such as diffusion tensor imaging (DTI) or functional MRI (fMRI) allows the investigation of spreading mechanisms across structural and functional pathways, which will support better understanding of this complex neurodegenerative disease (Bischof *et al.*, 2019).

Figure 3– Illustration of PET tracers and their binding sites. AV-1451 is used to visualize paired helical filaments and neurofibrillary tangles in the neuron. C-PiB binds to amyloid β plaques in the extracellular space and FDG is a marker of metabolic consumption mainly at the synapse. The pathological processes of Alzheimer's disease are accompanied by the accumulation of reactive astrocytes and activated microglia, which can also be visualized using different PET compounds. C-PiB = Pittsburgh compound B; FDG = fluorodeoxyglucose. Created with BioRender.com.

TEMPORAL EVOLUTION OF ALZHEIMER'S DISEASE BIOMARKERS

An ever-increasing body of evidence suggests that the two neuropathological hallmarks of Alzheimer's disease appear to evolve in temporal order with a long preclinical phase (Braak *et al.*, 2011). In 2010, Jack and colleagues introduced a hypothetical model of Alzheimer's disease biomarker evolution for the *in vivo* staging of Alzheimer's disease. This model was based on evidence from cross-sectional, longitudinal and autopsy studies (Jack Jr *et al.*, 2010). Three years later the model was revised to incorporate the observed variability in clinical expressions despite similar pathological burden and to specify the temporal ordering of certain biomarkers (Jack Jr *et al.*, 2013). According to this well-established model (*see* Figure 4), abnormalities in amyloid β42 in the CSF followed by abnormalities in amyloid PET imaging are detected up to two decades before clinical symptom onset. Following amyloid β accumulation, abnormalities in tau CSF become apparent closely followed by biomarker abnormalities of neuronal function, such as measured with FDG PET, or of atrophy, as quantified by structural MRI. The trajectories of tau pathology, neuronal dysfunction and atrophy patterns are thereby more closely associated in time with the onset of clinical symptoms. By the time cognitive symptoms occur, amyloid pathology begins to plateau, whereas tau pathology and neurodegeneration continue to disperse. The onset of clinical symptoms can differ between individuals as represented by two trajectories relating to cognitive decline over time for individuals at low and high risk of developing mild cognitive impairment and Alzheimer's dementia. Importantly, all trajectories are considered to be sigmoidal implying an initial phase of acceleration followed by a deceleration and plateau.

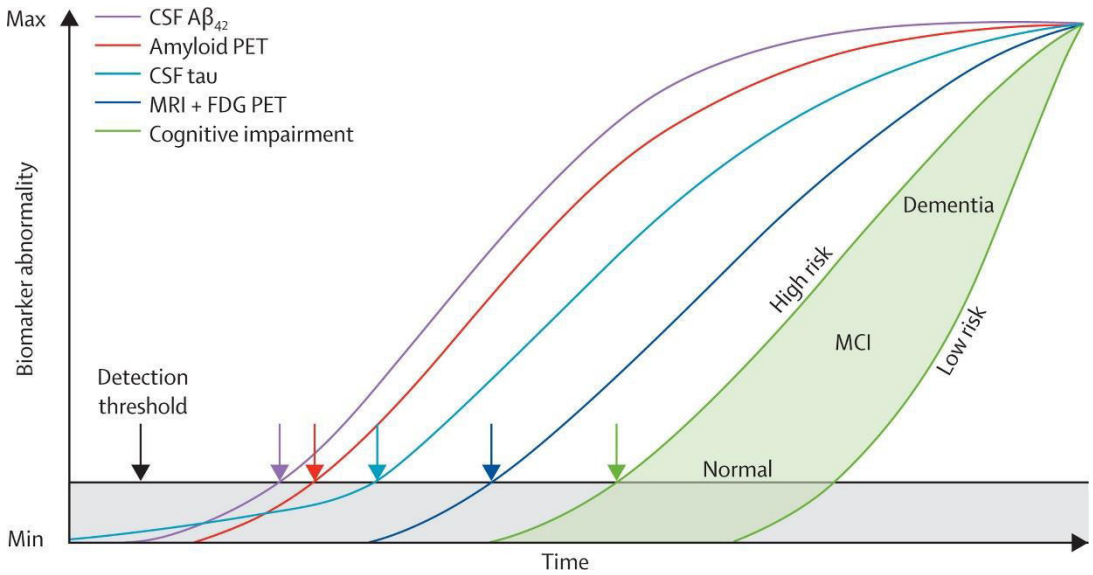


Figure 4 – Update on hypothetical model of Alzheimer's disease biomarkers (Jack Jr et al., 2013). Temporal evolution of currently available Alzheimer's disease biomarkers, which are colour- coded as depicted in the upper left corner. CSF = cerebrospinal fluid; Aβ = amyloid β; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography;MCI = mild cognitive impairment.

Notably, the model is based on currently available and detectable abnormalities in Alzheimer's disease biomarkers based on CSF, PET or structural MRI, which may not be sensitive enough to detect the earliest changes in the neurodegenerative cascade of Alzheimer's disease. This may explain the discrepancy to recent autopsy studies, which suggested that tau pathology already appears in young people below 30 years of age, whereas amyloid β plaques start accumulating in the fourth age-decade (Braak *et al.*, 2011). Based on this evidence, it was proposed that tau and amyloid β may represent independent pathophysiological processes sharing an upstream causative factor, as also proposed by the dual pathway hypothesis (Small and Duff, 2008). Further investigations are required to proof or refute this assumption. Yet, the current body of evidence is unambiguous regarding the fact that Alzheimer's disease has a long preclinical phase and that by the time initial clinical symptoms occur, amyloid pathology is already widely distributed across many brain regions, whereas tau pathology and neurodegeneration continue to spatially disperse in a stereotypical manner.

SPATIAL DISTRIBUTION OF ALZHEIMER'S DISEASE BIOMARKERS

One of the most puzzling features of the amyloid cascade hypothesis remains the spatial disconnection between amyloid β and tau pathology. Autopsy studies and recent PET imaging studies indicate that both proteinopathies follow distinct topographies, which initially occur in distal regions of each other. The stereotypical distribution patterns have been summarized for amyloid pathology by the Thal phases (Thal *et al.*, 2002) and for tau pathology by the Braak stages (Braak and Braak, 1991; Braak *et al.*, 2006), which are both based on autopsy data.

According to the Thal phases, amyloid β initially occurs in the neocortex, in particular in frontal areas (Phase 1), followed by accumulation in the hippocampus and entorhinal cortex (Phase 2), the basal ganglia (Phase 3), the brainstem (Phase 4), and finally the cerebellum (Phase 5). In contrast, tau pathology first gradually deposits in the transentorhinal cortex (Braak I) from where it spreads to the entorhinal region and hippocampal formation (Braak II), to temporal areas (Braak III), the precuneus (Braak IV), the parietal, occipital, and frontal regions (Braak V) and finally to the somatosensory cortex (Braak VI). Braak stages I-II represent the prodromal phase, Braak sages III-IV the early-moderate phase, and Braak V-VI the advanced and final stage of the disease. More recently, it was suggested that tau pathology may already start in the locus coeruleus and spread from there to subcortical and neocortical regions in a stereotypical manner (Braak *et al.*, 2011).

Both staging systems suggest a well-defined neuroanatomical propagation pattern of the two proteinopathies (*see* Figure 5). However, interestingly, studies comparing autopsy data and *in vivo* imaging revealed that the earliest Thal phases cannot be visualized using amyloid PET (Murray *et al.*, 2015; Thal *et al.*, 2015). In contrast, tau PET imaging studies consistently showed that tau pathology *in vivo* follows the neuropathologically defined Braak stages (Schöll

et al., 2016; Schwarz *et al.*, 2016; Hoenig *et al.*, 2017). Moreover, the spread of tau pathology is spatially more closely related with measures of neuronal dysfunction and neurodegeneration than the amyloid distribution patterns. This is the case for typical and atypical forms of Alzheimer's disease such as PCA, the logopenic and the dysexecutive variant as illustrated in Figure 6 (Bischof *et al.*, 2016; Ossenkoppele *et al.*, 2016; Dronse *et al.*, 2017; Whitwell *et al.*, 2018).

Up to date, several factors and hypotheses have been considered concerning the stereotypical spread of these neuropathologies, such as susceptibility of distinct neuron groups (Shen *et al.*, 2016), gene expression patterns (Grothe *et al.*, 2018; Sepulcre *et al.*, 2018), and cell-to-cell transmission processes (Clavaguera *et al.*, 2009; De Calignon *et al.*, 2012). Furthermore, multimodal imaging studies consistently reported that the topographies of neurodegenerative disease pathologies overlap with large-scale neuronal networks (Drzezga, 2018). This suggests that functional and structural connectivity between regions promotes the distribution of these pathologies across neuronal networks, an observation that is summarized by the network degeneration hypothesis (Palop *et al.*, 2006; Seeley *et al.*, 2009), which will be elaborated on in the following.

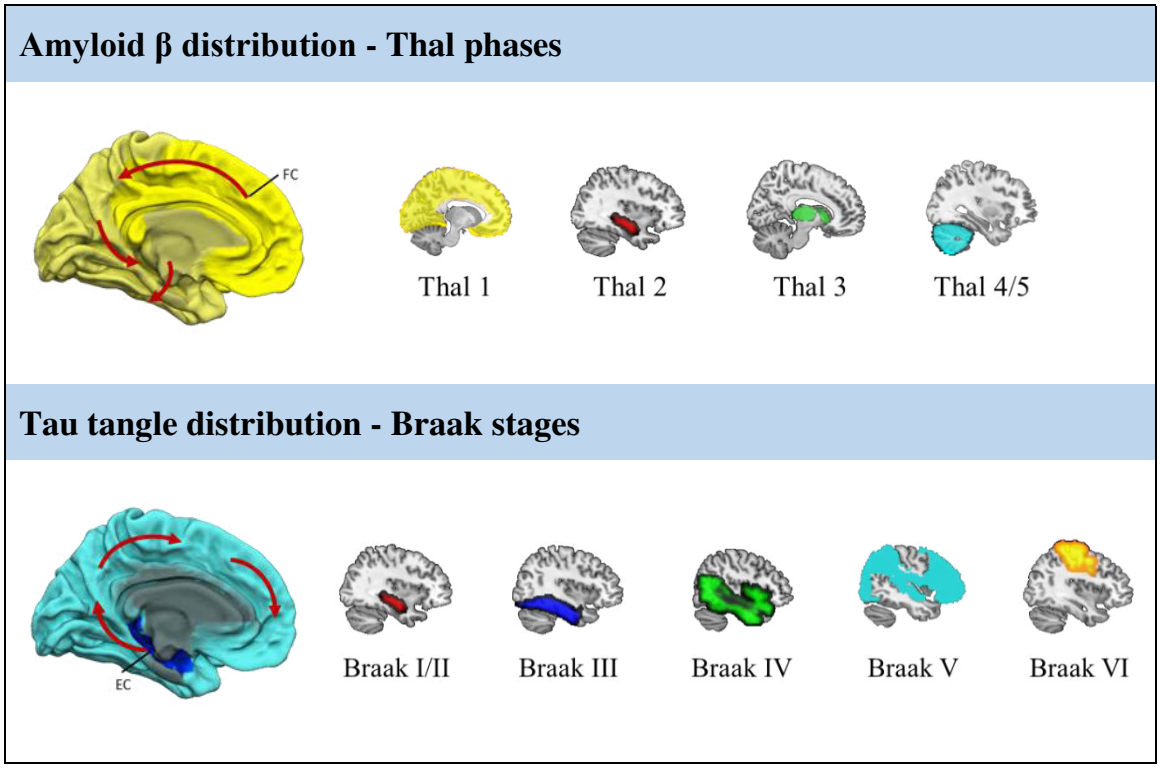


Figure 5 – The stereotypical distribution pattern of amyloid and tau pathology in Alzheimer's disease. Brain regions of initial amyloid accumulation contain the frontal cortex (dark yellow) from where it spreads throughout the neocortex to subcortical regions and cerebellar regions. Tau pathology initially occurs in the entorhinal cortex (dark blue) from where it spreads to limbic and neocortical regions. The spatial distribution of amyloid plaques is defined by the Thal phases (top row) and the tau pathology distribution pattern is defined by the Braak stages (bottom row). The highlighted regions represent the newly affected region. FC= frontal cortex; EC=entorhinal cortex.

THE NETWORK DEGENERATION HYPOTHESIS

An accumulating body of evidence indicates that neurodegenerative diseases do not randomly spread across the brain, but coincide with specific functional brain networks (Tahmasian *et al.*, 2016). Based on these observations, the network degeneration hypothesis has been formulated, which postulates that neurodegenerative disease pathologies expand along functional networks eventually leading to failure of them (Palop *et al.*, 2006; Seeley *et al.*, 2009). Network failure ultimately results in clinical symptomatology, which corresponds to the functional network being affected. This hypothesis suggests that functional connectivity between cortical nodes of neuronal networks acts as driver in the spread of pathology.

Over the past decade, several functional connectivity networks have been identified such as the executive control, language, visual-spatial, and the default mode network (DMN) (Yeo *et al.*, 2011), each carrying the name of the supporting cognitive domain. Compelling evidence has been gathered by studies combining fMRI and structural MRI or FDG PET, which reported a susceptibility of the aforementioned networks to neurodegeneration (Desgranges *et al.*, 2002; Seeley *et al.*, 2009; Drzezga *et al.*, 2011). In particular, the DMN has consistently been found to be disrupted in Alzheimer's disease (Greicius *et al.*, 2004; Buckner *et al.*, 2005; Buckner *et al.*, 2009; Jones *et al.*, 2015). The DMN is a highly active network during rest and is deactivated during externally oriented tasks. Interestingly, amyloid PET imaging studies demonstrated predominant amyloid accumulation in hubs of the DMN (Buckner *et al.*, 2005), which eventually leads to disconnection of this network (Jones *et al.*, 2015). Importantly, although some studies have pointed at a susceptibility of amyloid β in hub regions of functional networks, network degeneration appears to rather depend on global levels of amyloid β than local levels (Drzezga *et al.*, 2011; Iaccarino *et al.*, 2018). This may be due to the location of amyloid β, which distributes diffusely in the extracellular space throughout the brain. Therefore, it was recently suggested that tau pathology due to its intracellular location, its trans-synaptic spreading potential, and its close relationship to neurodegeneration, better relates to network dysfunction and degeneration in Alzheimer's disease. With the recent development of tau PET compounds in combination with fMRI, investigation of functional network infiltration by tau pathology is now feasible. Indeed, first *in vivo* studies have documented a close relationship between functional networks and tau pathology distribution patterns in typical Alzheimer's disease (Hansson *et al.*, 2017; Jones *et al.*, 2017; Hoenig *et al.*, 2018), as will be elaborated on in publication I and the discussion. Whether similar mechanisms also account for atypical forms of Alzheimer's disease still needs to be investigated. However, these atypical forms represent characteristic topographic patterns of hypometabolism and tau pathology, which resemble known functional connectivity networks (*see* Figure 6). A PET imaging study combing amyloid and FDG PET revealed that these variants are indeed associated with degeneration of phenotype-specific networks (Lehmann *et al.*, 2013). In contrast, amyloid deposition only accounted for a small proportion in the topographic heterogeneity of the phenotypes (Lehmann

et al., 2013). This points towards a role of tau pathology in specific network degeneration in atypical Alzheimer's disease, as will be discussed later.

Generally, it is not yet clear why brain pathologies affect distinct brain networks. It could be explained by a combination of cell-to-cell transmission processes, inherent genetical, developmental susceptibility or by the type of underlying pathological aggregation (Drzezga, 2018). Notably, the consequences of the observed network degeneration differ between individuals. For example, it was recently shown that modulation in efficacy of affected networks supports maintenance of cognitive performance in the phase of Alzheimer's disease-related brain pathology (Weiler *et al.*, 2018). Some individuals are thus capable of coping with network dysfunction or degeneration, thereby contributing to the clinical heterogeneity seen in Alzheimer's disease.

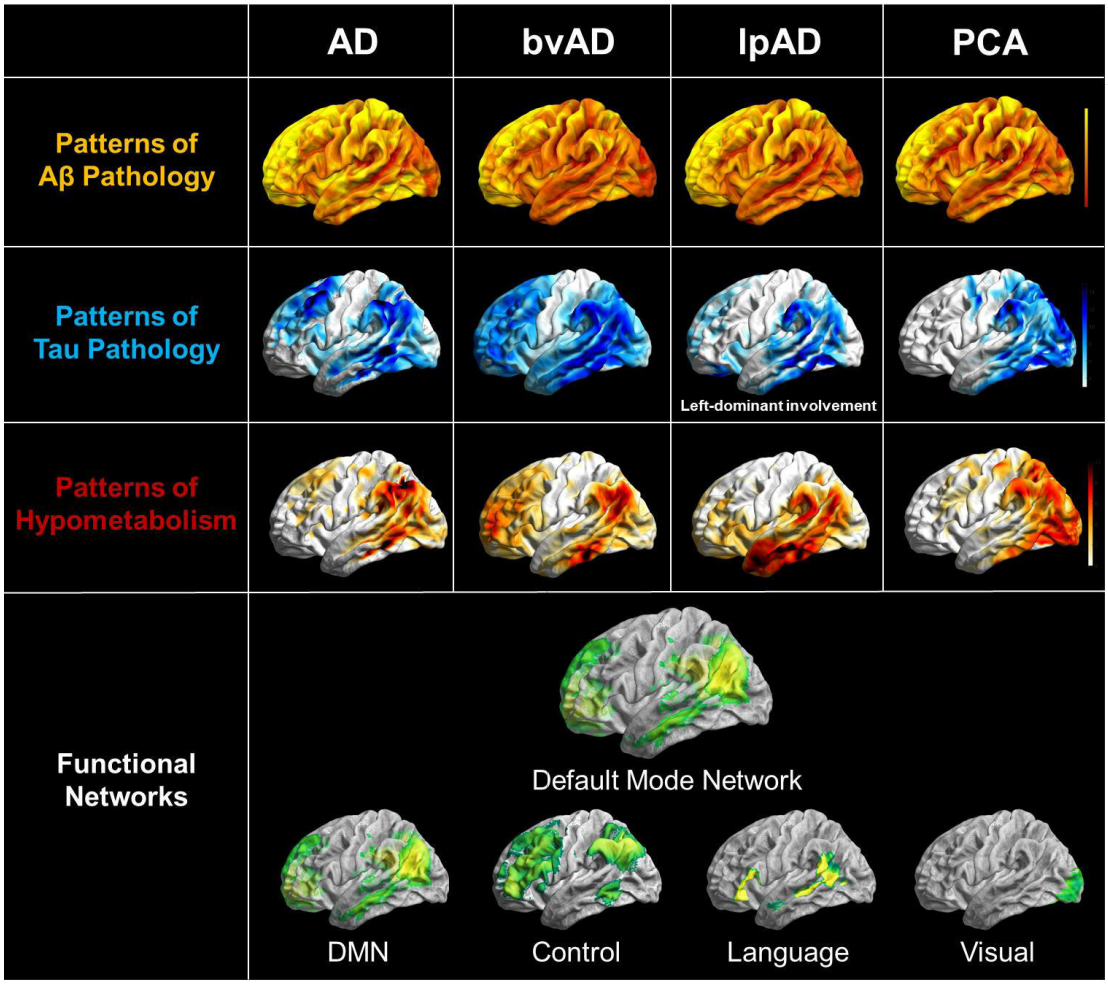


Figure 6 – Pathophysiological topographies and their overlap with functional connectivity networks in the clinical phenotypes of Alzheimer's disease. Illustrated are the distribution patterns of amyloid pathology (yellow), tau pathology (blue), neuronal dysfunction (red), and resembling functional connectivity networks (green) for typical and atypical phenotypes of Alzheimer's disease. Tau pathology and neuronal dysfunction patterns appear closely associated with distinct functional networks, but with predominant susceptibility of the posterior DMN across phenotypes. AD = Alzheimer's disease; bvAD = behavioural variant of Alzheimer's disease; lpAD = logopenic variant of Alzheimer's disease; PCA = posterior cortical atrophy; DMN = default mode network. This figure was adapted from the originally published figure (courtesy of Merle Hönig) in the Journal of Nuclear Medicine. Drzezga A. The Network Degeneration Hypothesis: Spread of Neurodegenerative Patterns Along Neuronal Brain Networks. J Nucl Med. 2018; 59(11): 1645-8. © SNMMI.

THE HETEROGENEITY IN CLINICAL EXPRESSIONS OF ALZHEIMER'S DISEASE - THE ROLE OF RESILIENCE

Already in the late 80s, Katzman and colleagues reported a disparity between the extent of brain pathology and the individual clinical expression in patients with dementia (Katzman *et al.*, 1988). Over the past decades, it turned out that the rate of cognitive decline given a certain level of pathological burden is highly variable between individuals. This notion has been acknowledged, among other things, by the revision of the Jack model integrating two trajectories for low and high risk of cognitive decline (Jack Jr *et al.,* 2013). These trajectories are based on coping mechanisms, which are associated with factors such as greater educational attainment, higher IQ and grey matter volume. As several terms have been used across studies to define the disparity between brain pathology and clinical symptoms, a framework was recently published to harmonize terminologies (Arenaza-Urquijo and Vemuri, 2018). According to this framework, resistance is defined as a mechanism to avoid brain pathology, thus preventing Alzheimer's disease-related pathology aggregation. In contrast, resilience is referred to coping with Alzheimer's disease-related pathology. This framework further incorporates the concepts of cognitive reserve, brain reserve and brain maintenance, while simultaneously distinguishing between the presence and relative absence of brain pathology (Arenaza-Urquijo and Vemuri, 2018). An overview of the framework on resistance and resilience is provided in Figure 7. Importantly, within the realm of this dissertation, the focus will be laid on resilience mechanisms as the studies conducted as part of this dissertation are based on data of individuals, which already present Alzheimer's disease pathology.

In the following, the potential coping mechanisms in form of cognitive reserve, brain reserve and maintenance will be elucidated in more detail:

Cognitive reserve

Cognitive reserve (CR) refers to the adaption of cognitive processes in the presence of brain pathology (Stern, 2002, 2009; Stern *et al.*, 2018a). Most commonly used surrogate measures of CR are education, occupation, lifetime experience, verbal and general IQ (Yoo *et al.*, 2015). It is believed that CR acts through the more efficient use and modulation of distinct brain networks or recruitment of additional brain areas in the phase of pathology aggregation. Recent imaging studies support this assumption (Morbelli *et al.*, 2013; Yoo *et al.*, 2015; Franzmeier *et al.*, 2017a; Franzmeier *et al.*, 2017b; Stern *et al.*, 2018b; Weiler *et al.*, 2018). In particular, these studies showed that network adaptations and compensation are associated with higher levels of educational attainment (Morbelli *et al.*, 2013; Yoo *et al.*, 2015; Franzmeier *et al.*, 2017a; Franzmeier *et al.*, 2017b; Stern *et al.*, 2018b; Weiler *et al.*, 2018). The adaptation of network efficacy and recruitment of additional brain areas may in turn provide a coping mechanism for increased pathological burden as reported by recent PET studies. These studies demonstrated that individuals with higher levels of education can maintain higher cognitive function at similar

levels of amyloid burden than lower educated individuals (Roe *et al.*, 2008). Likewise, individuals with higher CR can tolerate more amyloid pathology (Kemppainen *et al.*, 2008), hippocampal atrophy (Vuoksimaa *et al.*, 2013) and hypometabolism in temporo-parietal areas than lower educated individuals with similar clinical impairment (Kemppainen *et al.*, 2008; Ewers *et al.*, 2013; Morbelli *et al.*, 2013). Information regarding tau pathology load *in vivo* and CR is still relatively limited due to the only recent availability of tau PET compounds (Hoenig *et al.*, 2017; Rentz *et al.*, 2017; Shimada *et al.*, 2017). Publication II of this dissertation is one study investigating the association between level of education, as proxy measure of CR, and tau pathology in Alzheimer's disease.

Brain reserve

Although the observations relating to CR may be explained by network adaptations, it needs to be noted that these adaptations would not be possible without a biological foundation such as neuroplasticity, which in turn relates to the concept of brain reserve (BR). BR thereby refers to the neurobiological capital, hence brain integrity, of an individual (Stern *et al.*, 2018a). The concept of BR is based on a threshold model, which states that an individual with high BR can tolerate greater amounts of brain damage or brain pathology than individuals with low BR before showing clinical symptoms (Stern, 2002). This is because an individual with high BR obtains enough neuronal substrate to compensate the brain damage or pathology. Most commonly, grey matter volume, intracranial volume, but also head circumference have been used as surrogate measures of BR. Several structural MRI studies have provided support for the concept of BR using these proxies and further implicated higher education with better brain integrity (Schofield *et al.*, 1997; Perneczky *et al.*, 2010; Chang *et al.*, 2016; Groot *et al.*, 2018). Thus, highly educated individuals presenting greater pathology burden may not only possess higher CR, but also better brain integrity to cope with the harmful effects of neuropathology. In publication III, this assumption is elaborated on by assessing the effects of tau pathology on neuronal function at different levels of education (Hoenig *et al.*, 2019).

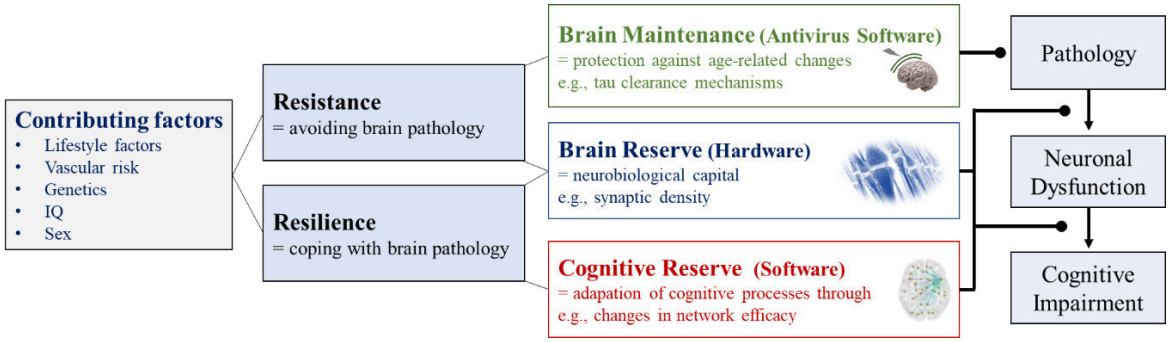


Figure 7 – The framework of resistance and resilience in Alzheimer's disease. Contributing factors that support resilience and resistance mechanisms are for example lifestyle factors or distinct genes. Resistance is associated with brain maintenance, whereas resilience is closely associated with brain reserve and cognitive reserve. These three concepts in turn modulate the relationship between pathology build-up, neuronal dysfunction and cognition. Adapted from Arenaza-Urquijo and Vemuri, 2018.

Brain maintenance

Importantly, the current definition of BR also encompasses processes that support maintenance of the neuronal substrate, thus interconnecting the concept of brain maintenance (BM). Accordingly, BM relates to neuroprotective mechanisms (Stern *et al.*, 2018a), and thus to resistance based on the framework of Arenaza-Urquijo and Vemuri. Possible BM mechanisms may encompass clearance mechanisms of tau and amyloid that prevent the accumulation of these proteinopathies. Several epidemiology studies have shown that higher education and better lifestyles are associated with a lower risk of developing dementia (Mortimer *et al.*, 2003; Verghese *et al.*, 2003; Brayne *et al.*, 2010) – a finding which could relate to BM mechanisms. Like BR, BM appears to be modifiable by lifetime experience. However, while BR is associated with brain integrity at a specific point in time, BM relates to mechanisms that reduce age-related changes over time (Stern *et al.*, 2018a). Hence, BR can be measured in cross-sectional studies, whereas BM can only be investigated in longitudinal designs. Nonetheless, BM and BR are interconnected concepts since higher BR is likely sustained by better BM (Stern *et al.*, 2018a).

Summing up these three concepts in a more metaphorical way (*see* Figure 7), CR can be considered as the software of the brain, which can be adapted or 'updated' in the phase of brain pathology. In contrast, BR represents the hardware of the brain as it is based on the neurobiological capital of an individual. Both concepts are interconnected via the wetware since CR could not exist without a biological foundation. Likely, BM mechanisms foster the build-up of CR and BR. These BM mechanisms can be regarded as the antivirus software of the brain. All three concepts are associated with lifetime factors including education, risk factors (genetic risk i.e., apolipoprotein E4 (ApoE 4), or vascular risk), and sex. These factors contribute to resilience, thus coping mechanisms against brain pathology (BR & CR) but can also support resistance against the aggregation of brain pathology (BM & BR). These mechanisms overall modulate the relationship between pathology build-up, subsequent neuronal dysfunction and cognitive impairment. Thus, the clinical expression of Alzheimer's disease patients depends on the individual magnitude of the underlying resilience, but also resistance capacity. Independent of the terminologies used to describe these mechanisms, the existence of protective factors influencing the manifestation and the course of Alzheimer's disease represents an important field of research, as will further be elaborated in the discussion of this dissertation.

RATIONALES AND AIMS OF THE DISSERTATION

The overall aim of this dissertation is to elucidate the role of functional connectivity and the influence of a resilience surrogate measure, namely education, concerning the spread of tau pathology and its effects on neuronal function using PET imaging. To address these aims, three manuscripts have been published as part of this thesis project. A brief overview on the specific rationales, research questions and main methods for each publication are mentioned below. Please note that the publications are not listed in chronological order, but in order of content.

Rationale & Aim I

The stereotypical propagation pattern of tau pathology in Alzheimer's disease is indicative of misfolded tau proteins disseminating across interconnected regions. Indeed, recent evidence from cellular and rodent studies suggest that misfolded tau proteins can spread trans-synaptically from neuron-to-neuron in a stereotypical fashion (Clavaguera *et al.*, 2009; Guo and Lee, 2014; Guo *et al.*, 2016). Importantly, these experiments further demonstrated that misfolded tau proteins are released in an activity-dependent manner (Pooler *et al.*, 2013; Wu *et al.*, 2016). These findings point towards a contribution of functional connectivity in the spreading of tau pathology across connected brain regions of neuronal networks. This infiltration likely results in the degeneration of the affected network, as postulated by the network degeneration hypothesis. Given that no information on the relationship between tau pathology distribution and the functional connectome was available *in vivo*, the first aim of this dissertation was to assess the spatial overlap of tau pathology distribution patterns and functional connectivity networks, using [^{18}F]-AV-1451 PET in a group of Alzheimer's disease patients and resting-state fMRI in a group of young healthy controls, respectively.

Publication I

Title: Networks of tau distribution in Alzheimer's disease

Research question: Does tau pathology arise in independent networks, which overlap with functional connectivity networks?

Methods: Independent component analysis (Gift toolbox), seed-based functional connectivity analysis (DPARSF toolbox), dice similarity coefficient (MATLAB)

Rationale & Aim II

Even though the spatiotemporal disease mechanisms in Alzheimer's disease are now better understood, a striking feature remains the observed disparity between brain pathology burden and clinical expression in individuals with Alzheimer's disease, which might be driven by resilience factors such as CR or BR. In case of amyloid β pathology and neurodegeneration it has already been reported that individuals with higher education can tolerate more pathology burden and neurodegeneration than lower educated with similar cognitive impairment (Kemppainen *et al.*, 2008; Ewers *et al.*, 2013; Morbelli *et al.*, 2013; Vuoksimaa *et al.*, 2013). Information regarding the relationship between the level of education, a proxy of resilience, and *in vivo* tau pathology were lacking until recently. The investigation of possible associations between resilience and tau pathology load, however, is important, as the extent of tau pathology in the brain, in contrast to amyloid β, correlates strongly with the degree of cognitive impairment and neurodegeneration (Nelson *et al.*, 2012). Thus, the second aim of this dissertation was to examine the association between a surrogate measure of resilience, namely education, and tau burden in individuals with Alzheimer's disease.

Publication II

Title: Tau pathology and cognitive reserve in Alzheimer's disease

Research question: Do higher educated Alzheimer's disease patients show more tau pathology than lower educated Alzheimer's disease patients with similar cognitive impairment?

Methods: Region-of-interest analysis based on the neuropathologically defined Braak stages (MATLAB), whole-brain voxel-wise analysis (SPM8)

Rationale & Aim III

According to current concepts of CR, BR and BM, two potential assumptions can be formulated explaining why higher educated individuals can tolerate more neuropathology than lower educated Alzheimer's disease patients with similar clinical expression. Concerning the concept of CR, it can be assumed, based on previous research (for review Stern, 2012), that higher educated people can better compensate for the harming effects of pathology for example through the more efficient use of neuronal resources. On the other hand, one may speculate that the effects of brain pathology on neuronal function are less harmful in patients, who have been physically and cognitively active throughout their lives, either due to BR-associated mechanisms such as higher neuron count or synaptic density and/or due to BM-associated neuroprotective mechanisms. These mechanisms may in turn support neuronal resilience to brain pathology. Importantly, both assumptions are not exclusive of each other. However, the second assumption can be assessed by means of FDG PET imaging, which represents an index of synaptic function. Combining FDG PET with tau PET imaging, the third aim of this dissertation was to investigate whether glucose metabolism remains relatively preserved at higher levels of education despite tau pathology aggregation. Thus, we assessed whether the consistently reported relationship between tau pathology and neuronal dysfunction is mitigated by a resilience proxy.

Publication III

Title: Level of education mitigates the impact of tau pathology on neuronal function

Research question: Can higher educated Alzheimer's disease patients tolerate more tau pathology, because the effects of tau pathology on neuronal function are less pronounced at higher levels of education?

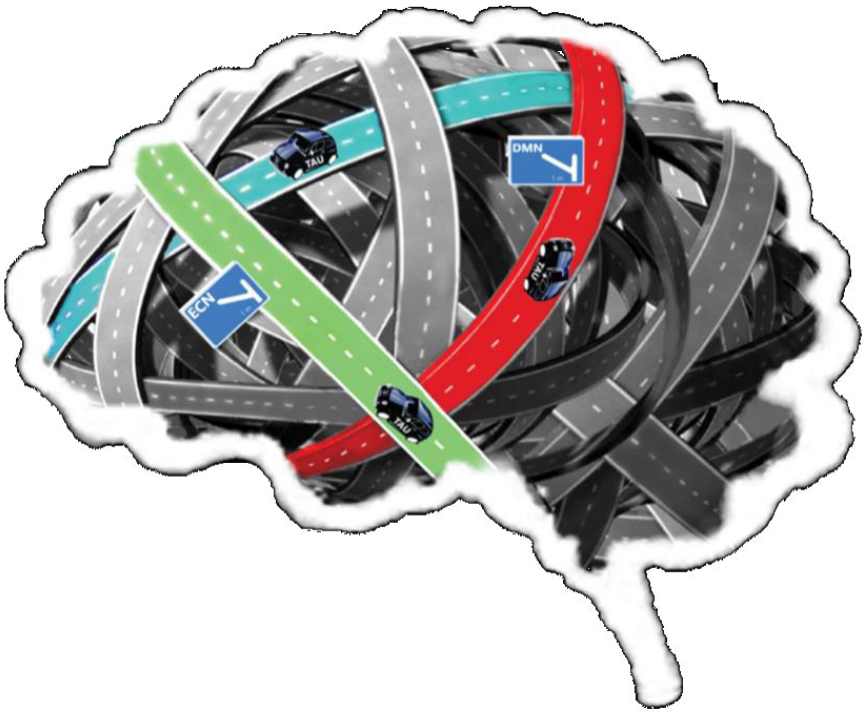
Methods: Volume-based approach (MATLAB, SPM12)

PUBLICATION I

Networks of tau distribution in Alzheimer's disease

Hoenig MC, Bischof GN, Seemiller J, Hammes J, Kukolja J, Onur ÖA, Jessen F, Fliessbach K, Neumaier B, Fink GR, van Eimeren T, Drzezga A.

Brain 2018



Summary: To determine whether tau pathology arises in independent networks of the brain, and coincides with functional connectivity networks, we performed an independent component analysis on [^{18}F]-AV-1451 PET data of Alzheimer's disease patients. Based on the resulting components, the seeds of maximal tau pathology were extracted and used in a subsequent functional seed-based connectivity analysis based on data of young healthy controls. Finally, the spatial overlap between the tau pathology networks, the seed-based networks and already known resting-state functional connectivity networks was quantified using the dice similarity coefficient. We observed a fair-to-moderate overlap between the tau pathology networks and the seed-based networks, which in turn coincided with known functional networks such as the DMN and the executive control network. Tau burden in these independent components correlated with disease progression and global cognitive decline. Overall, the results of this study suggest that tau pathology arises synchronously in independent pathways, which overlap with known functional connectivity networks and are associated with disease progression. These findings are in line with the network degeneration hypothesis and provide a possible mechanistic pathway in the spread of tau pathology.

Contribution to this work

This work was a team-effort of the Multimodal Neuroimaging Group, Department of Nuclear Medicine, University Hospital Cologne in collaboration with Joseph Seemiller from the Geisinger Commonwealth School of Medicine, Scranton PA, USA and the Departments of Neurology, Psychiatry and Radiochemistry of the University Hospital Cologne and the Department of Neurodegenerative Diseases and Geriatric Psychiatry of the University Hospital Bonn. Merle Hönig, Dr. Gérard Bischof, Joseph Seemiller, Prof. Dr. Thilo van Eimeren, and Prof. Dr. Alexander Drzezga were involved in the conception and design of the study and drafting the manuscript. Merle Hönig had full access to the data in the study and performed the analyses. Dr. Jochen Hammes supported the implementation of MATLAB scripts required for the data analysis. The remaining co-authors were involved in the acquisition of the data and drafting of the manuscript. Publication of the results approximately took one year starting with the initial analyses in fall 2016 and receiving the acceptance letter from Brain (impact factor: 11.81) for publication end of November 2017. Given the invitation to draft a cover image, Merle Hönig designed the "independent highways of tau pathology", which was accepted as cover art for the February issue of Brain in 2018 (Brain, Volume 141, Issue 2, February 2018, https://academic.oup.com/brain/issue/141/2, depicted on previous page).

Additional information

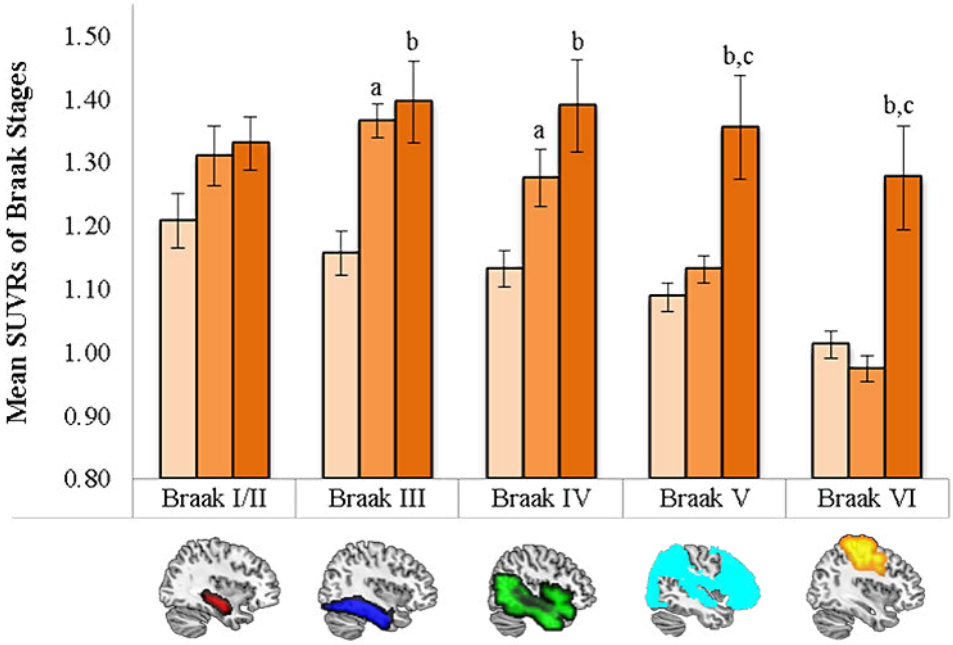
Dr. Jennifer Whitwell wrote a scientific commentary on this article, which is listed in the reference list under "Whitwell, 2018a".

The publication can be found in the attachments under Appendix – B1.

PUBLICATION II

Tau pathology and cognitive reserve in Alzheimer's disease

Hoenig MC, Bischof GN, Hammes J, Faber J, Fliessbach K, van Eimeren T, Drzezga A.
Neurobiology of Aging 2017



Summary: To investigate whether higher educated Alzheimer's disease (HEAD) patients can tolerate more tau pathology than lower educated Alzheimer's disease (LEAD) patients with similar clinical severity, we performed, based on [^{18}F]-AV-1451 data, a voxel-wise whole brain analysis and a region-of-interest (ROI) analysis using the neuropathologically defined Braak stages as ROIs. We compared tau pathology load across the brain and in the ROIs between three groups, the HEAD, LEAD and an age-matched healthy control (HC) group. The results yielded higher and more wide-spread tau pathology in the HEAD (dark orange in graph above) than the LEAD (orange in graph above) and HC (light orange in graph above) groups. The HEAD group already presented tau pathology in advanced Braak stages, whereas tau pathology in the LEAD group was still confined to temporal areas when compared to HC, respectively. Overall, the results are in line with the concept of CR given that HEAD patients can tolerate more tau pathology than LEAD patients with similar cognitive impairment.

Contribution to this work

The study was conducted in collaboration of the Multimodal Neuroimaging Group, Department of Nuclear Medicine, University Hospital Cologne and the Department of Neurodegenerative Diseases and Geriatrics, University Hospital Bonn. Merle Hönig, Dr. Gérard Bischof, Prof. Dr. Thilo van Eimeren and Prof. Dr. Alexander Drzezga were involved in the conception and design of the study and drafting the manuscript. Dr. Jochen Hammes helped with the implementation of MATLAB scripts required for the data analysis. Merle Hönig was responsible for the information collection on the educational attainment of the patients, had full access to the data in the study and performed the analyses. The remaining co-authors were involved in the acquisition of the imaging data and drafting of the manuscript. The initial analyses were conducted in May 2016. The paper was submitted end of December 2016 to Neurobiology of Aging (impact factor: 5.15) and published in May 2017.

Additional information

This work has been awarded with two poster prizes, one at the Alzheimer's Association International Conference (AAIC), 2017 in London, UK, and one at the 1st International Conference for Cognitive Reserve in Dementias (ResDem), 2017 in Munich, Germany.

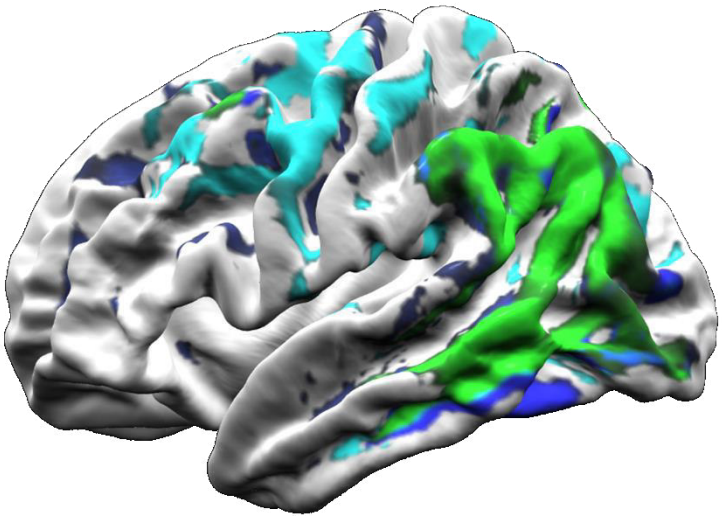
The publication can be found in the attachments under Appendix-B2.

PUBLICATION III

Level of education mitigates the impact of tau pathology on neuronal function

Hoenig MC, Bischof GN, Onur ÖA, Kukolja J, Jessen F, Fliessbach K, Neumaier B, Fink GR, Kalbe E, Drzezga A, van Eimeren T.

European Journal of Nuclear Medicine and Molecular Imaging 2019



Summary: To examine whether the harmful effects of tau pathology ([^{18}F]-AV-1451 PET) on neuronal function ([^{18}F]FDG PET) are mitigated by the level of education, we used a novel volume-based approach on PET data from patients with typical and atypical Alzheimer's disease. The volume-based approach comprised the following technique: all PET scans were z-score standardized and thresholded at a z-score >= 3.0 using an FDG and tau PET template based on data of an age-matched healthy control sample. Three volumes were extracted based on the z-maps: 1) the tau-specific volume (i.e., regions with only tau), 2) the overlap volume (i.e., regions with both tau and changes in neuronal function), 3) the FDG-specific volume (i.e., regions with only changes in neuronal function). Regression analyses were performed including the respective volumes and the z-scores within these volumes as dependent variables and education as predictor. We found that higher education is associated with a greater tau-specific volume (depicted in blue in picture above) and greater tau burden in the overlap volume (depicted in green in picture above). The results indicate that tau pathology is less paralleled by neuronal dysfunction at higher education, which may explain why higher educated patients can tolerate more tau pathology than lower educated patients albeit similar cognitive impairment levels. These findings further support the concepts of BR and BM mechanisms.

Contribution to this work

This study was performed in collaboration of the Multimodal Neuroimaging Group, Department of Nuclear Medicine, University Hospital Cologne with the Departments of Neurology, Psychiatry, Radiochemistry and Medical Psychology, University Hospital Cologne and the Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn. Merle Hönig, Dr. Gérard Bischof, Prof. Dr. Alexander Drzezga and Prof. Dr. Thilo van Eimeren were involved in the conception and design of the study and drafting the manuscript. Merle Hönig had full access to the data in the study and performed the analyses. The co-authors contributed to the content of the manuscript and gave valuable feedback to the current work. The paper was submitted end of February 2019 to the European Journal of Nuclear Medicine and Molecular Imaging (impact factor: 7.23) and accepted for publication in April 2019.

Additional information

This work has been ranked under the 15 best papers of young researchers at the European Association of Nuclear Medicine (EANM) conference, 2018 in Dusseldorf, Germany, and has been awarded with the junior faculty award at the Alzheimer's and Parkinson's disease congress (ADPD), 2019 in Lisbon, Portugal.

The publication can be found in the attachments under Appendix-B3.

DISCUSSION

By means of multimodal imaging, a potential mechanism in the spread of misfolded tau proteins and the role of a resilience proxy, namely education, were examined as part of this thesis, resulting in the following findings:

1) Tau pathology arises synchronously in independent components of the brain, which coincide with functional connectivity networks, and which are associated with disease progression and global cognitive dysfunction (Hoenig *et al.*, 2018).

2) Higher educated Alzheimer's disease patients present more extended tau pathology, already in advanced Braak stages, than lower educated Alzheimer's disease patients despite similar cognitive impairment (Hoenig *et al.*, 2017).

3) At higher levels of education, the extent of tau pathology is less paralleled by a reduction in glucose metabolism (i.e., neuronal dysfunction) and more tau pathology appears necessary to induce neuronal dysfunction (Hoenig *et al.*, 2019).

Collectively, the results of this doctoral thesis suggest that the spread of misfolded tau proteins is facilitated by functional connectivity between brain regions belonging to distinct neuronal networks. The more affected these networks are by tau pathology, the further the disease has already progressed, and global cognitive function declined. The early lifetime factor education, in turn, appears to alter the deleterious consequence of tau pathology on the disease manifestation. The current findings indicate that higher educated individuals with Alzheimer's disease can tolerate more tau pathology while maintaining their cognitive function up to a certain extent. A possible explanation for this observation relates to the final finding of this thesis, namely that the effects of tau pathology appear less harmful to neuronal function at higher levels of education.

In the following, these results will be discussed in the context of a) factors contributing to the spreading of tau pathology, b) distinct network susceptibility, and c) resilience factors that potentially modify the pathophysiological consequences of tau pathology. Lastly, d) the role of education as resilience proxy will be considered in more detail.

Spreading mechanisms of tau pathology

Given the spatial and temporal lag of the neuropathological hallmarks of Alzheimer's disease, and the previous lack of methods to assess cerebral tau deposition *in vivo*, it remained unknown not until just recently, whether tau pathology also follows distinct connectivity networks. In the first publication of this dissertation we therefore addressed the role of functional connectivity in the spread of tau pathology in patients with Alzheimer's disease employing the data-driven approach of independent component analysis (ICA). We observed tau pathology networks

(TPNs) comprising regions not anatomically adjacent to each other and which coincided with functional connectivity networks, which have previously been reported to be impaired in Alzheimer's disease (Hoenig *et al.*, 2018). This signifies that tau pathology arises synchronously, but not homogenously in independent compartments of the brain, which in turn relate to distinct functional networks. The observation of synchronous aggregation of tau pathology in distal brain regions points towards a common mechanism, which contributes to the coherent aggregation of tau pathology. According to the assumptions of ICA, regions within an independent component can be inferred to be spatially correlated, either by structural or functional connections (Cohen *et al.*, 2008). Hence, the topographic characteristics of the identified TPNs potentially reflect the underlying neural architecture of existing structurally or functionally linked networks. In this study, we showed the contribution of functional connectivity to tau spread, whereas the role of structural connectivity still needs to be investigated, as detailed below.

Prion-like spreading mechanisms of tau pathology

Over the years, persuasive evidence in support of prion-like spreading of tau has been gathered indicating that pathogenic forms of tau are capable to seed into tau aggregates, which can induce further aggregation of non-aggregated tau and be transmitted trans-synaptically (for review see Soto, 2012; Mudher *et al.*, 2017). Repetition of this seeding process potentially results in the infestation of synaptically linked networks (Mudher *et al.*, 2017). Supporting the prion-like seeding behaviour, several studies have demonstrated that injection of pathogenic tau forms from different tauopathies or brain homogenates of Alzheimer's disease patients into the brain of transgenic and wild-type mice led to the expression of the corresponding tauopathy's inclusion (De Calignon *et al.*, 2012; Liu *et al.*, 2012; Clavaguera *et al.*, 2013; Guo *et al.*, 2016; He *et al.*, 2018). Importantly, it was not only reported that injection of brain homogenates of tau led to tau seeding, but also to a time-dependent spread of tau pathology across structurally connected regions (De Calignon *et al.*, 2012; Liu *et al.*, 2012; Clavaguera *et al.*, 2013; Guo *et al.*, 2016; He *et al.*, 2018). Moreover, the distribution of tau pathology is associated with synaptic connectivity, thus structural connections, rather than spatial proximity (Ahmed *et al.*, 2014). The suggested prion-like spreading of tau pathology across structural connections likely contributed to the observation of distinct TPNs in publication I, which involved remote brain areas. In addition, the time-dependent seeding process of tau may further explain why the TPNs were characterized by varying loads of tau pathology and associated with disease progression. Hence, TPNs with low levels of tau burden may represent regions that are affected later in the disease than TPNs with higher tau burden. The more severe these networks are affected, the further has the disease progressed. However, as we only had cross-sectional data available, these assumptions remain speculative and require longitudinal assessment. Up to date, longitudinal evidence regarding the structural distribution of tau pathology in patients with Alzheimer's disease is still sparse. Recently, Jacobs and colleagues, employing DTI and tau PET imaging, reported that tau tangles distribute from the hippocampus to the parietal cortex via axonal pathways in amyloid positive individuals (Jacobs *et al.*, 2018). In line with this,

Strain and colleagues found that tau pathology was closely associated with a decline in white matter integrity in anterior temporal regions (Strain *et al.*, 2018). These studies overall offer first insights into the mechanistic pathways of structural connectivity in the distribution of tau pathology. Furthermore, these findings may provide an explanation of the spatial pattern and load of tau pathology of the identified TPNs in publication I. Notably, further investigation on the actual underlying structural connectivity patterns of the TPNs are required using for example tract -based analysis based on DTI data. Additionally, investigation of tract alterations such as changes in fractional anisotropy (i.e., a measure of white matter integrity) and their association with tau pathology aggregation in regions connected downstream to the region of maximal tau pathology within a respective TPN will provide further insights into the spreading mechanisms across these networks.

The role of functional connectivity in the spread of tau pathology

Importantly, in contrast to structural connectivity analyses, which reflect the presence of anatomical linkage, functional connectivity analyses provide insights on the functional interaction of specific brain regions. Here, we observed a spatial link between the TPNs and tau-dependent seed-based functional connectivity networks indicating that functional connectivity between regions supports the distribution of tau pathology across these connections. The investigation of functional connectivity as a driver of tau pathology spread has recently been expanded upon. Results from our group in collaboration with the Faculty of Mathematics and Natural Sciences of the University Cologne suggest that the spread of tau pathology and tau burden of the affected regions depends on the overall functional in-/output (functional weights) rather than the metabolic rate of that region (Weller *et al.*, 2019). This is in line with a recently published study demonstrating that strongly connected regions accumulate more tau pathology in Alzheimer's disease independent of the metabolic demands (Cope *et al.*, 2018). Also, in animal models, exacerbated pathological tau aggregation *in vivo* was found upon increased neuronal activity (Wu *et al.*, 2016) and normal tau was released in an activity-dependent manner (Pooler *et al.*, 2013). Together these findings suggest that synchronous neuronal activity, thus the temporal coherence between functionally connected regions, may act as an amplifier enhancing tau pathology to accumulate in functionally connected brain sites. The tau maxima of the TPNs identified in the current study, which corresponded to highly functionally connected brain regions such as the precuneus or the posterior cingulum, may thereby act as "susceptibility seeds" and relays for tau aggregates to further propagate along connected regions of neuronal networks. Arguably, the prion-like spreading mechanisms are rather in support of structural connectivity in the distribution of tau. However, functional connectivity is associated with higher synaptic activity and thereby with greater axonal transport, which may ultimately lead to increased release of tau aggregates into the synaptic cleft (Soto, 2012). Functional connectivity between structurally connected regions may thus stimulate the synchronous propagation of tau along these connections. Indeed, it was just recently shown that higher functional connectivity between regions was related to similar tau levels in these regions in MCI and Alzheimer's disease patients (Franzmeier *et al.*, 2019).

This may also explain the synchronous aggregation of tau pathology in the identified independent components of publication I.

Overall, the results of publication I and other recent studies on functional connectivity and tau pathology (Hansson *et al.*, 2017; Jones *et al.*, 2017; Cope *et al.*, 2018; Franzmeier *et al.*, 2019) offer one potential mechanistic perspective for the spreading of tau pathology in Alzheimer's disease by means of which synchronous oscillatory activity between connected brain regions contributes to the propagation of tau pathology within distinct neural networks. However, despite the investigation of structural and functional connectivity patterns, also the role of neuroinflammation and genetic vulnerability factors need to be considered in the spread of tau pathology, which shall briefly be mentioned below.

Factors beyond structural and functional connectivity

Recently, it was suggested that neuroinflammatory processes may actually precede tau seeding and overt tau pathology (Wang and Mandelkow, 2016). Concordantly, also PET imaging studies proposed that neuroinflammatory processes may peak early in the temporal evolution of Alzheimer's disease-related pathophysiological processes (Rodriguez-Vieitez *et al.*, 2016). Furthermore, a close relationship between microglia activation and tau aggregation patterns has been observed (Dani *et al.*, 2018; Terada *et al.*, 2019). Thus, patterns of neuroinflammation may represent an early marker of subsequent network infiltration by tau pathology. However, these findings need to be cautiously interpreted, as it remains still unknown whether the observed patterns are a cause or a consequence of tau pathology aggregation. To address the questions of the temporal sequence of biomarkers and network susceptibility to neuroinflammation, it will be crucial to develop sensitive PET ligands for the visualization of neuroinflammatory processes in cognitively normal individuals at risk of developing Alzheimer's disease (e.g., ApoE 4 carriers). After two decades of research, a challenge remains the development of sensitive ligands for neuroinflammation since it is a complex, dynamic and multicellular process. Currently available tracers such as the translocator protein-18 kDa (TSPO) compounds, which are used to quantify microglia activation, lack cellular specificity and present difficulties in quantification (Narayanaswami *et al.*, 2018). Thus, radiotracer development for neuroinflammation beyond the TSPO ligands represents an important field of research since neuroinflammatory constitutes potentially provide viable targets for the treatment of Alzheimer's disease and insights into its cascade (Narayanaswami *et al.*, 2018).

Aside from the neuroinflammatory signatures potentially preceding overt tau pathology, it has recently been shown that connected brain regions belonging to certain brain networks, present similar gene-expression patterns (Richiardi *et al.*, 2015). Depending on the gene-expression patterns in these regions, the susceptibility of Alzheimer's disease pathology may in turn increase (Grothe *et al.*, 2018; Sepulcre *et al.*, 2018). Indeed, according to these studies, regional expression levels of the APP gene were associated with amyloid deposition as measured with [^{18}F]AV45 PET, but not neurodegeneration as quantified by structural MRI (Grothe *et al.*, 2018). Furthermore, regional MAPT gene expression patterns predicted the spreading of tau

pathology, measured with longitudinal [^{18}F]-AV-1451 PET in cognitively normal older individuals (Sepulcre *et al.*, 2018). These studies suggest that regional vulnerability in addition to functional and structural correlates relate to the expression and stereotypical distribution of Alzheimer's disease-related pathology. Arguably, these studies are based on post-mortem gene expression patterns of six adult individuals from the Allen brain atlas, which were related to *in vivo* brain pathology of different individuals. Hence, a direct assessment of *in vivo* brain pathology and subsequent post-mortem investigation of gene expression patterns is still pending.

Nonetheless, collectively, the results of publication I and the above-mentioned *in vivo* studies suggest that the distribution of tau pathology is partly driven by mechanistic pathways in terms of structural and functional connectivity, but also by predetermined regional susceptibility to Alzheimer's disease pathology. Future longitudinal multimodal studies using DTI, fMRI and PET tracers are necessary to elucidate the structural and functional underpinnings contributing to the propagation of misfolded tau proteins within neuronal networks and its interaction with amyloid β accumulation, neuroinflammation, and genetic vulnerability. This will shed light into the pathogenic cascade of Alzheimer's disease, which is crucial for the development and timing of target-specific interventions (Bischof *et al.*, 2019). Additionally, better understanding of the spreading mechanisms of tau pathology in Alzheimer's disease may also be relevant for other tauopathies and the monitoring and diagnosis of these diseases.

Susceptibility of the default mode network to tau pathology

Regarding the evolution of pathogenic events, evidence from molecular studies suggests that tau seeding does not affect a certain cell population, but rather commences in a vulnerable location from where its spreads via neuronal connections (Guo and Lee, 2014; Goedert, 2015). This is in line with several studies on network degeneration suggesting that pathologies distribute along functional networks from a central starting point (Drzezga, 2018). In the first study of this thesis, we observed TPNs that coincided with known resting-state networks such as the DMN, salience or higher-visual network (Hoenig *et al.*, 2018). This indicates that tau pathology does not only affect one distinct network but accrues in different neuronal networks depending on the most vulnerable locations. In accordance with this, recent imaging studies examining tau-dependent functional network infiltration observed that tau pathology arises in various functional networks, but also reported a particular vulnerability of the DMN (Hansson *et al.*, 2017; Jones *et al.*, 2017). This accords with the results of publication I as several of seed-based derived networks overlapped with the DMN.

So far, it remains unknown why the DMN is particularly affected in this disease. Several explanations and hypotheses have been put forward, such as the role of developmental, evolutionary, and metabolic aspects (Buckner and Krienen, 2013). The DMN is an association network, which is phylogenetically relatively young, potentially rendering these regions more vulnerable to disease-related changes. Moreover, the "wear and tear" hypothesis suggests that

excessive use of neuronal resources leads to their dysfunction and destruction (Swaab, 1991). As the DMN is a highly active network during rest, its continuous activation throughout life may render it vulnerable according to this hypothesis. Differences in network activation throughout life may also explain resilience to disease-related changes late in life. Although speculative, individuals with low cognitive engagement (e.g., low resilience) may be prone to the development of Alzheimer's disease, because of high DMN activation throughout life leading to pathology accumulation and concomitant failure of this network. In contrast, individuals with high resilience may more efficiently switch between networks allowing for a more balanced energy consumption across networks reducing the risk of "network tearing" or disconnection and slowing brain pathology accumulation. Despite the "wear and tear" hypothesis, another explanation for the susceptibility of the DMN may signify the initial starting point of pathophysiological changes, which determines the distribution of tau pathology in a posterior-anterior fashion across this network as seen in Alzheimer's disease (Jones *et al.*, 2015). Notably, the mentioned explanations are not exclusive of each other and may collectively lead to an increased susceptibility of the DMN to tau pathology, as observed in publication I.

Interestingly, the posterior part of the DMN is not only affected in typical, but also in atypical Alzheimer's disease (*see* Figure 8). Following the idea of a central starting point in the spread of tau pathology and concomitant network degeneration, we performed a preliminary analysis to elucidate whether differential susceptibility of the posterior DMN can explain the clinical phenotypes of Alzheimer's disease (Appendix – Abstract A1, page 64). The results suggest that the peak of tau pathology in the posterior DMN regionally differs between the clinical phenotypes. In turn, these peaks of tau pathology are functionally associated with connectivity networks outside the posterior DMN that correspond to the respective clinical phenotype e.g., visuo-spatial network in PCA. This suggests that the tau-peak in the posterior DMN may determine the spread of tau pathology across distinct functional networks (Hönig *et al.*, 2019). According to the network degeneration hypothesis, the spread of tau along these networks eventually results in network dysfunction and cognitive decline relating to the clinical phenotype.

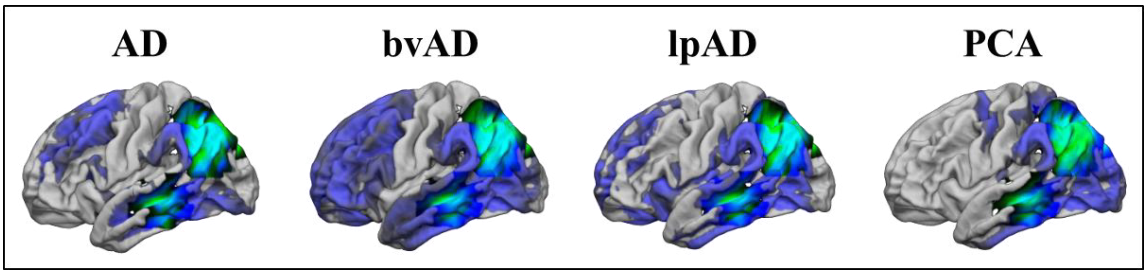


Figure 8 – Regional susceptibility of the posterior default mode network in phenotypes of Alzheimer's disease. The tau pathology distribution pattern for each phenotype is depicted in blue. In addition, the topography of the posterior default mode network (in green) is superimposed on the respective tau distribution patterns. AD=Alzheimer's disease; bvAD=behavioural variant of Alzheimer's disease; lpAD = logopenic variant of Alzheimer's disease; PCA = posterior cortical atrophy.

There remain several unanswered questions and somehow contrasting evidence regarding the network degeneration seen in Alzheimer's disease and other neurodegenerative diseases. For example, it needs to be elucidated why in similar neurodegenerative diseases such as primary tauopathies different network pathways are affected (Drzezga, 2018). Moreover, it remains unknown how the spreading theory of tau pathology along functional connectivity networks is compatible with the stage-wise progression according to the neuropathological Braak stages, which have been replicated *in vivo* by tau PET imaging studies (Schöll *et al.*, 2016; Schwarz *et al.*, 2016). Work from our group, which is currently under revision, indicates that tau spreading from lower to higher Braak stages is mediated by intrinsic functional connectivity, partly supporting the network degeneration hypothesis (Seemiller *et al.*, 2019).

Albeit these uncertainties, multimodal imaging studies including our study have consistently shown a relation between distribution patterns of neurodegenerative diseases, functional networks, and network dysfunction supporting the current hypothesis of network degeneration (for a more detailed discussion see Drzezga, 2018). Importantly, recent fMRI studies indicate that network signatures derived from ICA may provide a non-invasive biomarker of neurodegenerative diseases (Zhou *et al.*, 2010). This suggest that multimodal imaging of network degeneration carries potential in the classification of neurodegenerative diseases and likely also for the monitoring of disease progression. In line with this, TPNs identified in publication I were associated with disease progression and varying loads of tau pathology indicating that tau burden within these TPNs provide information on the progression of the disease. The data-driven approach of ICA hereby offers a suitable tool to define characteristic network patterns as it is not based on predefined significance thresholds, but a blind source separation technique. Furthermore, independent components derived from tau or amyloid PET imaging may yield a marker with the potential to detect disease-related network changes before the degenerative process emerges, which will be important for the early diagnosis and intervention. In addition, this hypothesis-free approach can be used to elucidate distinct network signatures depending on the level of resilience that an individual possesses. Thus, comparison of network signatures derived from structural/functional MRI or PET may provide information on differences in network flexibility and vulnerability depending on the level of resilience. Overall, reliable discrimination patterns for neurodegenerative diseases, including the influence of resilience mechanisms, will be important for diagnostic and prognostic purposes.

Resilience against the evolution of tau pathology

Over the past decade, resilience mechanisms have received increased interest as they may account for the clinical heterogeneity and are hence important for the diagnosis and prognosis of the Alzheimer's disease. In studies on resilience, parameters of individuals' lifetime experiences including education, occupation as well as leisure activities have been discussed as surrogate measures of resilience. However, no information had yet been available regarding the relation between these measures and tau pathology in Alzheimer's disease. In publication II, we showed that higher education is associated with the relative preservation of cognitive performance in the phase of tau pathology aggregation (Hoenig *et al.*, 2017). Moreover, as shown in publication III, there appears to be a longer temporal delay between tau pathology aggregation and concomitant neuronal dysfunction at higher levels of education, potentially explaining the prior finding (Hoenig *et al.*, 2019). In the following, these findings will be discussed in the light of mechanisms associated with the concepts of CR and BR, animal models for the investigation of resilience and the significant contribution of early lifetime factors, such as education, to protective or compensatory mechanisms late in life.

An interpretation based on cognitive reserve and brain reserve

Our finding of higher educated patients being able to tolerate more advanced tau burden than lower educated patients with similar cognitive impairment may be due to an adaptation of cognitive processes, as defined by the concept of CR (Hoenig *et al.*, 2017). This adaptation of cognitive processes likely occurs through the modulation of brain networks and additional recruitment of brain areas. Importantly, Neitzel and colleagues recently demonstrated that left frontal connectivity mitigated the deleterious effects of tau pathology on cognitive function in non-demented elderly and MCI patients (Neitzel *et al.*, 2019). This region has also been demonstrated to provide compensation in the phase of emerging neuronal dysfunction (Franzmeier *et al.*, 2017b). Presumably, similar mechanisms may have acted in the patient cohort assessed in publication II. But it remains to be assessed whether the reported effects by Neitzel et al. are transferrable to patients who have already advanced to Alzheimer's disease. It will thus be of interest to investigate how this potential CR mechanism changes in the course of the disease from MCI to Alzheimer's dementia, thus whether it is up- or downregulated as the disease progresses and at which point of the disease course the compensatory effect fails to work. As recently suggested, CR mechanisms support cognitive maintenance in prodromal phases of Alzheimer's disease, but from the onset of diagnosis cognitive function declines more rapidly in individuals with higher reserve, likely because a certain threshold is reached at which compensatory CR effects fail (van Loenhoud *et al.*, 2019).

Importantly, while CR mechanisms can be quantified with fMRI or DTI, current imaging techniques of BR allow for a crude estimation of BR based on grey matter or intracranial volume analyses in humans (Chang *et al.*, 2016; Groot *et al.*, 2018). However, also FDG PET measures may provide a surrogate measure of BR. Using this technique, we demonstrated in publication III that education mitigates the spatial relationship between tau pathology

aggregation and neuronal dysfunction (Hoenig *et al.*, 2019). In addition, we observed that more tau burden is required to induce neuronal dysfunction at higher levels of education. These observations may be driven by individual differences in brain integrity (i.e., BR), such as synaptic density, which permits compensation for the effects of tau pathology on neuronal function and, in turn, influences the FDG signal. However, no direct conclusion regarding the underlying neuronal composition, hence number of synapses, can be drawn by means of FDG PET and is thus still pending. Intriguingly, the newly introduced PET imaging technique for the visualization of synaptic density, such as the SV2A PET tracer (Chen *et al.*, 2018; Finnema *et al.*, 2018), has opened a new avenue to study the compensatory effects of BR. Using this technique, quantification of the underlying synaptic density is now feasible and the effects of tau pathology on neuronal and cognitive function in groups with high and low synaptic density can directly be assessed. Quantifying BR based on the underlying synaptic density may thereby provide novel insights into the effects of lifetime and environmental factors on disease-related changes late in life.

Animal models for the investigation of resilience and maintenance mechanisms

Aside from the novel developments in PET imaging, rodent models exposed to enriched environments may yield another possibility to study the effects of lifelong cognitive and physical engagement on the molecular and cellular level, which may then be transferrable to humans. Using these paradigms, researchers reported increased synaptogenesis, neurogenesis, gliogenesis and angiogenesis after exposing the animals to enriched environments (for detailed review see Gelfo *et al.*, 2018). Moreover, in terms of BM mechanisms, these studies demonstrated a reduction of amyloid β burden (Berardi *et al.*, 2007) and mitigation of the neurotoxic effects of tau pathology (Belarbi *et al.*, 2011). Additionally, an up-regulation of neurotrophic factors such as the brain-derived neurotrophic factor (BDNF) was consistently observed (Wolf *et al.*, 2006; Hu *et al.*, 2013). Also, epigenetic modifications (i.e., gene-environment interactions) in form of non-coding RNAs, histone modifications or DNA methylation patterns have been found after exposure to environmental enrichment paradigms, and which were associated with beneficial effects on cognition (for review see Fischer, 2014). Whether these findings can be translated to humans, and thus to the findings of publication II-III, still needs to be assessed. However, recent imaging studies reported a relationship between lifestyle factors, BDNF, vascular and insulin growth factor levels, better cognition, and greater brain volume in humans (Coelho *et al.*, 2014; Westwood *et al.*, 2014; Hohman *et al.*, 2015). In particular, lifelong physical exercise appears to be associated with an upregulation of BDNF in brain tissue and peripheral blood samples (Szuhany *et al.*, 2015; Håkansson *et al.*, 2017). Interestingly, the BDNF Val66Met polymorphism appears to moderate the relationship between resilience and executive function (Ward *et al.*, 2015). Thus, for future assessments on BR, serum levels of BDNF as well as polymorphisms of the gene encoding BNDF may be used as proxy measures. Aside from this, Pereira and colleagues derived an imaging correlate of exercise-induced neurogenesis for humans based on observations in mice (Pereira *et al.*, 2007). The group found that dentate gyrus cerebral blood volume as measured with MRI correlated

with post-mortem measurements of neurogenesis in mice and cardiopulmonary and cognitive function in exercising humans.

Taken together, there are a multitude of molecular and cellular factors that appear to be modulated by lifestyle and environmental factors and which may have contributed to the findings of this thesis work. The abovementioned studies indicate that by means of translational research novel mechanisms of brain resilience can be derived, which can be employed as better measures of BR in humans. Importantly, across these studies it was reported that the quantity of cognitive and physical activity appears to be essential regarding the upregulation of these factors. Nonetheless, also the timing may play a pivotal role (Nithianantharajah and Hannan, 2009), which will briefly discussed in the following.

The role of early lifetime intervention

Findings from rodent and clinical studies suggest that resilience can be built up over a long period of time and may prevent aging- or disease-related processes late in life (Nithianantharajah and Hannan, 2009). In particular, early lifetime exposure to enriched environments appear to have long-lasting impact on the function of the brain in rodents (Wagner *et al.*, 2000; Bloss *et al.*, 2011). In our studies, we used education as proxy variable of resilience, which is an early lifetime factor occurring when the brain is still developing and most plastic (Hoenig *et al.*, 2017). It is closely related with beneficial mid- and late-life factors (Jefferson *et al.*, 2011). In line with this, a recent imaging study reported that early lifetime factors are positively associated with age-related structural brain trajectories and cognitive function late in life (Walhovd *et al.*, 2016). This indicates that these factors contribute to the build-up of resilience mechanisms crucial for late life cognition and complies with the findings from the aforementioned animal studies (Wagner *et al.*, 2000; Bloss *et al.*, 2011). However, these early lifetime factors such as education have also consistently been associated with higher IQ, healthier lifestyles, less chronic stress and higher socioeconomic status (Fritsch *et al.*, 2007) and may also relate to genetic predispositions (Rowe *et al.*, 1998). Thus, early lifetime factors are interrelated with several societal, familial, genetic and environmental factors throughout life rendering it difficult to decipher the actual contribution of early lifetime exposure to late- life brain health. Nonetheless, these factors may lay the foundation for the build-up of resilience and resistance mechanisms that become crucial as we age and are therefore valuable proxies for late life functional and structural differences, as also indicated by the publications of this dissertation.

Implications of resilience for the diagnosis, prognosis and drug evaluation

The abovementioned studies including ours document that early lifetime factors, as education, contribute to the shaping of the brain in a way to protect it against or to cope with disease-related changes. Importantly, not only can these factors alter brain structure and function in the phase of pathology through mechanisms associated with CR and BR, these factors also support maintenance of the neuronal substrate over life, thereby on the one hand decreasing the risk of developing dementia (Stern *et al.*, 1994; Dekhtyar *et al.*, 2016; Wang *et al.*, 2017) and on the

other hand slowing the accumulation of brain pathology (Landau *et al.*, 2012; Brown *et al.*, 2013; Wirth *et al.*, 2014).

Important implications can be drawn from this regarding the clinical diagnosis and prognosis, the evaluation and development of drug therapies, and the general conception of the disease:

1) Concerning the clinical diagnosis and prognosis, consistent evidence (including publication II) signifies that individuals with high education remain under the diagnostic radar for a longer time as indicated by the more advanced pathology burden at the point of diagnosis. Hence, it will be important to develop sensitive diagnostic tools for the identification of individuals with high levels of resilience, who are still in the prodromal phase of the disease. This is particularly crucial given that a person with high resilience tends to decline quicker from the point of diagnosis, likely because of the high pathological burden (Stern *et al.*, 1999; Scarmeas *et al.*, 2006; van Loenhoud *et al.*, 2019). Detecting individuals with high resilience at the earliest stages of the disease, which requires neuropsychological tests with high ceiling effects, is also crucial for the early intervention with pharmacological treatments.

2) Regarding the development of pharmacological strategies, proxy measures of resilience such as education need to be considered when allocating patients to treatment groups of drug-based therapies. Results may otherwise lead to a biased interpretation of the results or an observation of effects that is not due to the drug, but resilience capacity interfering with pathophysiological processes. Aside from that, novel drugs could be developed that directly tackle maintenance and resilience mechanisms thereby yielding a treatment to either prevent or prolong the neurodegenerative disease process. Also, lifestyle, cognitive and physical intervention strategies in mid-life and late-life may offer potential to prolong the onset of the disease.

3) Moreover, resilience factors need to be considered in the general conception of the disease. The results of publication III suggest that the consistently reported relationship between tau pathology aggregation and neuronal dysfunction differs depending on the level of education. This is in line with other findings suggesting a slowing in pathophysiological processes at higher levels of resilience (Landau *et al.*, 2012; Brown *et al.*, 2013; Wirth *et al.*, 2014). Therefore, the currently discussed trajectories for the temporal and spatial evolution of Alzheimer's disease biomarkers should not be considered uniform across patients (as shortly discussed in the next chapter).

Overall, further investigation is necessary to determine direct neuronal mechanisms of resilience and resistance. Multimodal approaches including neuroimaging in combination with genetic and epigenetic screenings and lifestyle assessments will provide novel insights in this regard. In particular, the investigation of individuals who show exceptional cognitive performance and lower than expected brain pathology will be essential as these individuals

must obtain mechanisms allowing them to become so-called *super-agers*. Indeed, lower DNA damage, high genomic stability, telomere maintenance has been observed in these individuals (Wagner *et al.*, 2018). Interestingly, also lower frequencies of tau tangles were found in super agers when compared to typical agers in a histopathological study (Gefen *et al.*, 2015). Hence, super-agers represent a model of successful aging as they have avoided or postponed age-related diseases. In contrast, patients with Alzheimer's disease represent the model for unsuccessful and unhealthy aging. Comparison of both extremes (i.e., super-aging and Alzheimer's disease) with a multimodal approach may thus provide information on underlying mechanisms preventing or fostering the accumulation of aging-related damage in healthy aging and disease. Overall, identified factors such as for example epigenetic modifications may thereby be harnessed in therapeutic interventions that may not only be relevant for Alzheimer's disease, but other aging-related diseases such as vascular diseases or other forms of dementia.

Resilience mechanisms prompt refinement of current model of Alzheimer's disease biomarkers

In terms of explaining the results of publication II and III, the focus was put on the current framework of resistance vs. resilience introduced by Arenaza-Urquijo & Vemuri in 2018 as it comprehensively summarizes the common terms used in this field of research (Arenaza-Urquijo and Vemuri, 2018). In the past months, recent discussions have come up arguing for and against a revision of terminologies in the field of resilience such as the introduction of the term 'neurocognitive reserve' instead of 'cognitive and brain reserve' (Cabeza *et al.*, 2018, 2019; Stern *et al.*, 2019). While a consistent and well-defined nomenclature is important for study designs and interpretation of results and mechanisms, it is even more important to address the implications of the studies' findings concerning the conception of the disease, namely identifying factors that prevent from or modulate the course of Alzheimer's disease. As elucidated above, more and more progress has been made in this regard. Consideration of these factors has among other things led to revision of the well-established model of Alzheimer's disease biomarkers (Jack Jr *et al.*, 2013). However, the accumulating body of evidence on resilience prompts for further refinement of this current model. Dichotomizing individuals into low- and high-risk groups based on the extent of pathophysiological changes may not be sufficient given that the temporal and spatial evolution of Alzheimer's disease biomarkers and the disease trajectories may differ depending on the resilience capacity an individual possesses.

In Figure 9, a hypothetical model of the temporal evolution of Alzheimer's disease and the disease course for individuals with low and high resilience is depicted. According to this model, there exists a temporal delay in individuals with high resilience concerning the initial accumulation of amyloid and tau pathology, and subsequent neuronal dysfunction. Moreover, the temporal association between tau pathology and neuronal dysfunction is closer at lower levels of resilience. Importantly, at the point of initial symptom occurrence, individuals with high resilience show more brain pathology than individuals with lower levels of resilience. Consequently, the prodromal phase is longer at high levels of resilience. But from the point of

diagnosis individuals with high resilience tend to decline more rapidly. This accelerated deterioration is likely due to greater pathological burden at the point of diagnosis.

Notably, this hypothetical model is based on the current body of evidence concerning resilience mechanisms mostly evaluated in cross-sectional designs and based on educational attainment levels. Moreover, the term "resilience" is used to encompass various mechanisms contributing to the slowing of pathology build-up (i.e., resistance), its effects on neuronal function and cognition. Longitudinal approaches are certainly necessary to underpin the assumptions of this model. Nonetheless, it may provoke discussions concerning the currently tested model of Alzheimer's disease biomarkers. These discussions may overall refine the current conception of the disease, lead to the development of diagnostic tests for the early diagnosis of individuals with high resilience and potentially foster novel research ideas and approaches. Furthermore, it may lead to the establishment of more precise measures of resilience in contrast to the currently used surrogate measures such as education.

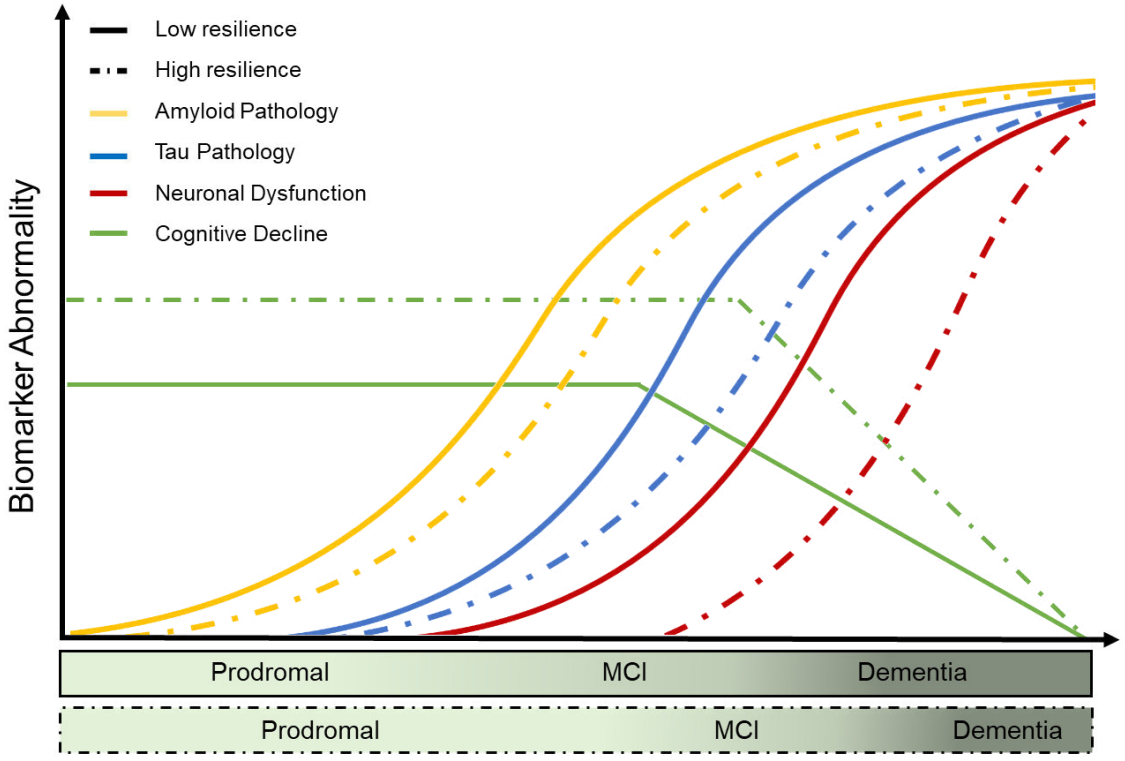


Figure 9 – Hypothetical model on the evolution of Alzheimer's disease biomarkers based on the level of resilience. At high levels of resilience, the onset of pathophysiological processes of Alzheimer's disease is temporally delayed and slowed down including a longer prodromal phase in comparison to individuals with low resilience. Moreover, the temporal relationship between tau pathology and neuronal dysfunction is less close at higher levels of resilience. At the point of initial symptom occurrence, individuals with high resilience show greater levels of amyloid β and tau pathology, a faster disease progression and cognitive decline. MCI = mild cognitive impairment.

From education towards a more direct measure of resilience

In the discussed studies of publication II and III, we employed education as surrogate marker of resilience like numerous other studies on resilience. However, education only represents an indirect measure of resilience, which is influenced by several other lifetime factors. In addition, considering that in the younger generations more and more individuals tend to graduate at higher levels of education as compared to the older generations, education may become a less meaningful surrogate measure in the future. Aside from this, it was recently reported that general cognitive ability measured early in life was a better predictor of late-life cognition than education (Kremen *et al.*, 2019). Nonetheless, early lifetime factors such as education or general IQ are static and are based on one single value measured at a single point in time. They may thus not capture the entire picture and are less dynamic. Therefore, a residual approach has recently been introduced. This approach considers the variance in cognition that is not explained by demographic and brain predictors such as grey matter volume or pathology burden as measure of CR (*see* Figure 10A) (Stern *et al.*, 2018a). To measure BR, the variance in grey matter volume that is not explained by demographic and brain pathology needs to be derived when using the residual method (*see* Figure 10B). Studies employing this approach so far showed a close association between derived CR residuals and changes in network integrity (Lee *et al.*, 2019) and the level of education (van Loenhoud *et al.*, 2017; Lee *et al.*, 2019). Moreover, the residual approach has been suggested to be more dynamic in terms of change over time as it allows the continuous quantification of resilience at different disease stages (Arenaza-Urquijo and Vemuri, 2018). In line with this, recent studies demonstrated that the residuals derived from different time points were better predictors for cognitive deterioration and disease progression over time than education (Reed *et al.*, 2010; Zahodne *et al.*, 2015; van Loenhoud *et al.*, 2017).

In a subproject of this thesis, we employed this approach to investigate whether residuals derived from amyloid PET and cognitive variables are associated with years of education and changes in intrinsic connectivity based on resting-state fMRI (Appendix – Abstract A2, page 65). By means of this approach we aimed to identify a neuronal correlate of CR. The results yielded a relationship between the CR residuals and education. More importantly, we found an association between the CR residuals and regional upregulation in intrinsic connectivity of the right hippocampus in preclinical and clinical phases of Alzheimer's disease. The positive correlation between the residuals and intrinsic connectivity of the right hippocampus was stronger in the early Alzheimer's disease group than the amyloid-positive cognitively normal group, indicating that the early Alzheimer's disease patients have a higher need for CR. The results suggest that cognition may be maintained by upregulations of this area, representing a potential CR support mechanism.

Taken together, the accumulating body of evidence signifies that the residual approach could be used to study resilience mechanisms more directly and dynamically than when using education as proxy (Stern *et al.*, 2018a). However, it contains a major drawback, namely that it

is primarily based on the error that is not explained by the model (Arenaza-Urquijo and Vemuri, 2018). To increase the predictive power of the residuals, numerous variables need to be included and there is no proof that these variables can sufficiently explain the relationship of interest. Poorly defined models may therefore result in noisy residuals that are not associated with resilience, but other factors that had not been considered. Moreover, caution needs to be taken when modelling certain relationships and deriving the residuals from them since these associations may not be purely linear, but of exponential or cubic nature. In our preliminary study, we therefore performed a model fit to address at least this issue of the residual approach and used the best fit to derive the residuals.

Despite these disadvantages, the current evidence suggests that the residual approach can be used to measure resilience-related mechanisms. Importantly, with the advances in neuroimaging, even better measures of resilience can be established. For example, with the recent development of PET tracers for the visualization of changes in synaptic density (Chen *et al.*, 2018; Finnema *et al.*, 2018), an opportunity is provided to directly investigate BR mechanisms. Moreover, recent fMRI studies have determined a task-invariant covariance network (Stern *et al.*, 2018b). The activation or deactivation of this network during a task may represent a direct measure of CR according to the authors (Stern *et al.*, 2018b). Overall, employment of brain imaging methods will facilitate better knowledge on potential mechanisms contributing to resilience to Alzheimer's disease and provide better means of quantifying resilience in comparison to the currently available surrogate measures.

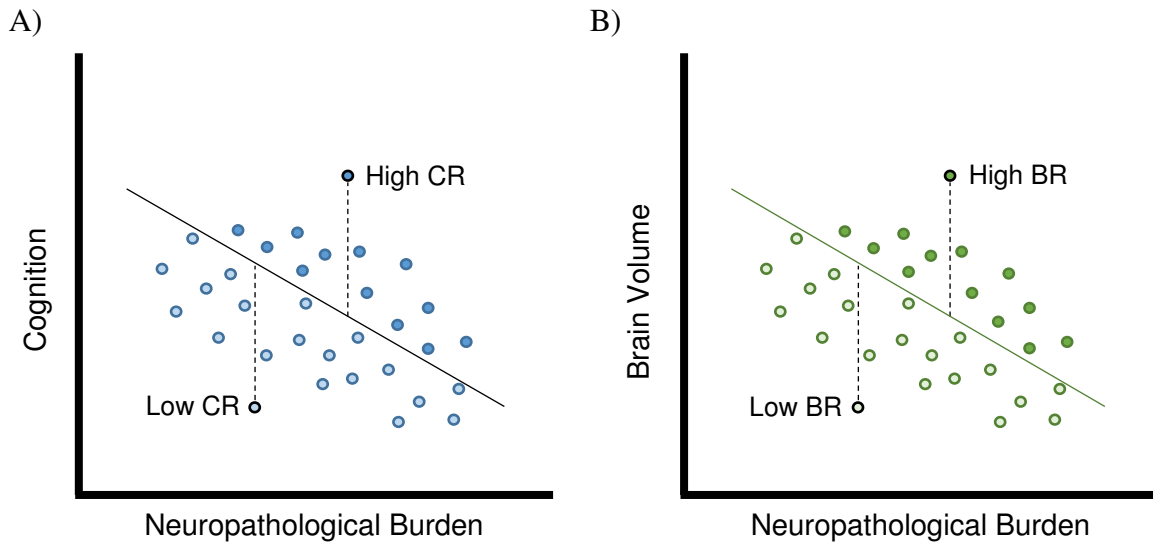


Figure 10 – Illustration of the residual approach for the quantification of cognitive and brain reserve. A) Residuals represent the variance in cognition that is not explained by the neuropathological burden. Residuals above the slope relate to better than predicted cognitive performance (i.e., high cognitive reserve, dark blue) and residuals below the slope indicate lower than expected cognitive performance (i.e., low cognitive reserve, light blue). B) Residuals represent the variance in brain volume that is not explained by the neuropathological burden. Residuals above the slope indicate relative maintenance of brain volume at a given level of neuropathological burden (i.e., high brain reserve, dark green), while residuals below the slope indicate greater volume loss than predicted (i.e., low brain reserve, light green). CR = cognitive reserve; BR = brain reserve.

LIMITATIONS

A few general methodological limitations and caveats should be considered regarding the discussion of the results of publication I-III.

First generation tau PET tracers

First, all three publications included the data analysis of the first-generation tau PET tracer [^{18}F]-AV-1451. Although this tracer was reported to show high affinity for Alzheimer's disease tauopathy in form of 3R/4R tau (Marquié *et al.*, 2015), off-target binding to subcortical structures, especially in the basal ganglia has consistently been observed in healthy controls and Alzheimer's disease patients. This off-target potential is not only observed in case of [^{18}F]-AV-1451, but all current first-generation tau PET tracers (Chiotis *et al.*, 2018b). A potential binding site may represent monoamine oxidase (MAO) A and B activity (Lemoine *et al.*, 2017; Saint-Aubert *et al.*, 2017), but results have so far been inconsistent (Xia *et al.*, 2013; Hansen *et al.*, 2018). Despite off-target binding to these subcortical regions, also vascular structures such as the choroid plexus and the dural venous sinuses are affected (Marquié *et al.*, 2015; Lowe *et al.*, 2016). Given the close proximity of the choroid plexus to the hippocampus, spill-over effects might bias the quantification of tracer retention in the hippocampus (Lemoine *et al.*, 2018). Therefore, partial volume corrections are recommended when considering this region in analyses. In our studies, we carefully inspected each image to rule out significant off-target signal in this area and signal retention in the hippocampus was considered with caution. In addition to this caveat, off-target binding in the dural venous sinuses may lead to an underestimation of the tracer retention in cortical regions given its close location to the cerebellum, which is commonly used as reference region (Lemoine *et al.*, 2018). Despite the limitations of this tracer, *in vitro* and *in vivo* evidence exists demonstrating binding of [^{18}F]-AV-1451 to paired helical filaments containing tau (Smith *et al.*, 2016). Moreover, currently available studies on tau PET suggest that these tracers coincide with the regional distribution of tau pathology in Alzheimer's disease as determined by histopathological studies (Schöll *et al.*, 2016; Schwarz *et al.*, 2016). Also, in publication II of this study, we observed tracer binding that resembled the neuropathological Braak stages. It remains to be elucidated, which factors cause the off-target binding of the first-generation tau PET tracers. The recent introduction of second-generation tau PET tracers, which show lower off-target binding to subcortical structures, may provide better means to quantify tau pathology in Alzheimer's disease and other tauopathies. Nonetheless, further comparisons are necessary to determine whether these novel tracers are superior to the first-generation tracers.

Current lack of longitudinal tau PET studies

Given the novelty of tau PET imaging, most studies including ours are restricted to the analysis of cross-sectional data. Thus, no interferences can be drawn regarding the spread of tau pathology along functional networks as well as how this spread is modulated by resilience

mechanisms over time. So far, first longitudinal studies demonstrated that tau pathology arises uniformly in certain regions of the brain outside the medial temporal lobe (Jack Jr *et al.*, 2018b). Moreover, a time lag was observed between tau pathology aggregation and changes in neuronal function confirming the current model of Alzheimer's disease biomarkers (Chiotis *et al.*, 2018a). But these longitudinal studies are currently limited to follow-up assessments of 1 to 1.5 years. Therefore, the effect of change over time may be relatively small. Despite this, longitudinal tau PET may potentially be used in the evaluation of drug efficacy, although currently available tracers may not be sufficient for the determination of the earliest accumulation of tau pathology such as abnormal phosphorylation of tau (Hansson and Mormino, 2018). Moreover, the methodology of tau PET needs to be further assessed, in particular regarding the processing of longitudinal data including the determination of appropriate reference regions and methods for partial volume effects (Southekal *et al.*, 2018). Given the availability of tau PET compounds for more than five years now, it is expected that more longitudinal studies with longer follow-up periods will soon be conducted allowing for a better understanding of the intracerebral progression of tau pathology and the methodological caveats associated with longitudinal tau PET. Moreover, future tau PET imaging studies with longitudinal designs will allow to investigate whether tau pathology is triggered, accelerated or independent of amyloid β accumulation (Villemagne *et al.*, 2017) and how resilience influences the progression of tau pathology over time.

Proxies of resilience

Finally, regarding the investigation of resilience mechanisms, we employed the indirect measure of educational attainment as proxy for resilience, which is correlated with other lifestyle factors rendering the investigation of the sole contribution of education to late-life effects difficult. To gain further insights into lifestyle factors associated with resilience, more elaborate information on lifetime experience such as physical activity or nutrition needs to be gathered. By means of this, specific lifestyle components could be extracted and set in relation to a distinct resilience mechanism. Potentially, physical activity is more closely associated with better vascular systems or neurogenesis factors, whereas education or lifetime cognitive stimulation is more closely associated with adaptations of network structures and functions. Moreover, most studies have, so far, mainly focused on the maintenance of cognitive function and less studies have focused on the actual underlying brain mechanisms such as changes in neuronal plasticity. The use of the residual approach in a different way as it has previously been used, may yield novel insights into resilience based on brain measurements. Hence, instead of taking cognitive function as the dependent variable, one may instead examine a distinct brain measurement such as synaptic density and test which factors are associated with maintenance of this measurement. Overall, with the advancements in the research field of resilience and resistance, the focus will eventually shift from observational studies towards the development of intervention therapies and prevention strategies (Arenaza-Urquijo and Vemuri, 2018).

CONCLUSION & OUTLOOK

It is certainly of utmost importance to understand the pathophysiological mechanisms and risk factors of a given disease in order to find an effective treatment. In the past decades, researchers have continuously accumulated knowledge regarding the underlying mechanisms of Alzheimer's disease. Despite the ever-increasing knowledge of the disease mechanisms, a cure has not been found yet. Striving to find the trigger of the disease may be one option in the development of effective treatment strategies. Another approach, however, lies in the identification of mechanisms that protect against or prolong the detrimental effects of neuropathology. The development and use of innovative neuroimaging techniques and the advancement of PET tracer development offer new avenues to study the *in vivo* characteristics of Alzheimer's disease and factors that protect against the progression of the disease, as signified by this thesis work. Combination of these neuroimaging techniques with blood-based markers, epi-/genetic screenings and neuropsychological testing will provide a better understanding of the disease mechanisms and the contribution of resilience factors in the conception of the disease. To extend on the current knowledge on Alzheimer's disease, we are therefore collecting data on several lifestyle factors including physical activity, occupation, social environment, stress resilience and nutrition and assessing their relation to epigenetic changes. In combination with PET imaging, this study may further provide insights into the underlying disease mechanisms of Alzheimer's disease and determine protective molecular mechanisms.

Importantly, the results of thesis and the ongoing study may not only bear crucial implications for the treatment of Alzheimer's disease, but other age-related neurodegenerative diseases, in particular, tauopathies. Better understanding of the spreading mechanisms in these diseases will permit a more precise prediction of disease progression and will thus be valuable for disease monitoring. Moreover, identified resilience mechanisms may potentially be transferable to other neurological conditions. Several studies have shown that early lifetime factors such as education are associated with protection of performance in the face of brain pathology such as in small-vessel disease (Zieren *et al.*, 2013; Pinter *et al.*, 2015), stroke (Nunnari *et al.*, 2014), multiple sclerosis (Sumowski *et al.*, 2009; Benedict *et al.*, 2010), fronto-temporal dementia (Premi *et al.*, 2013) and Parkinson's disease (Guzzetti *et al.*, 2016; Hindle *et al.*, 2016). Thus, mechanisms associated with resilience may be harnessed for their therapeutic treatment across neurological conditions. This will hopefully one day contribute to the development of effective disease-modifying treatments.

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APPENDIX

A. Conference abstracts

1) Regional susceptibility of the default mode network is associated with clinical phenotypes of Alzheimer's disease

2) Hippocampal intrinsic connectivity supports cognitive reserve in amyloid-positive cognitively normal subjects and Alzheimer's disease patients

B. Publications

1) Networks of tau distribution in Alzheimer's disease

2) Tau pathology and cognitive reserve in Alzheimer's disease

3) Level of education mitigates the impact of tau pathology on neuronal function

A1.) Abstract I

Title: Regional susceptibility of the default mode network is associated with clinical phenotypes of Alzheimer's disease

Authors: Hoenig MC, Bischof GN, Onur ÖA, Jessen F, Fließbach K, Neumaier B, van Eimeren T, Drzezga A

Presented at: Deutsche Gesellschaft für Nuklearmedizin, 2019, Bremen, Germany (talk)

Background: Alzheimer's disease (AD) is characterized by heterogeneous clinical phenotypes, which present distinct tau-pathology patterns. The posterior default mode network (pDMN) seems, however, to be similarly affected by tau-pathology across clinical phenotypes. In this study, we investigated whether the tau-peaks in the pDMN of AD variants are associated with different functional connectivity networks.

Methods: We included three age-matched groups: a typical AD group (n=14), a group with the logopenic variant (n=6), and a group with posterior cortical atrophy (n=6). For all patients, an [^{18}F]AV-1451 scan was available, which was normalized, intensity-standardized to the cerebellum, and z-transformed employing a [^{18}F]AV-1451 template of a healthy control sample. Following the z-standardization, one-sample t-tests were performed ($p < .0001$) for each group, respectively, in SPM12. The coordinate of maximum t-value coinciding in the pDMN was extracted for each group and used in a seed-based analysis conducted on functional imaging data of a healthy control group (FWE corrected). Finally, using the dice similarity coefficient, the spatial overlap was computed between the seed-based networks (SBNs), known functional connectivity networks, and the thresholded t-maps of the three groups.

Results: The three seeds were located in middle-superior temporal and parietal regions. The AD-derived SBN fairly overlapped with the executive control network (Dice=35%), the PCA-derived SBN overlapped well with the visuospatial network (Dice=51%), and the SBN of the logopenic group coincided with the language network (Dice=24%). The respective SBNs poorly-to-fairly overlapped with the group-specific tau-pathology patterns (Dice=9-27%).

Conclusion: The tau-peak in the pDMN may determine the spread of tau-pathology across distinct functional networks, which are associated with clinical phenotypes of AD.

A2.) Abstract II

Title: Hippocampal intrinsic connectivity supports cognitive reserve in amyloid-positive cognitively normal subjects and Alzheimer's disease patients

Authors: Hoenig MC, Bischof GN, Lopes Alves I, Ahlswede M, Sakagiannis P, Jessen F, Schmidt M, Barkhof F, van Eimeren T, Drzezga A for the AMYPAD Consortium

Presented at: AAIC, 2019, L.A., USA (poster presentation)

Background: Cognitive reserve (CR) accounts for maintaining functionality despite brain pathology. Recently, a residual approach was introduced as a more specific measure of CR. This approach considers the variance in cognition not being explained by demographic and neuroimaging predictors as CR measure. Here, we aimed to determine a functional neuronal correlate of CR from resting-state functional MRI (rs-fMRI).

Methods: 103 cognitively normal subjects (*mean age* 72.01 ± 5.98) and 36 early amyloid-positive Alzheimer's disease (AD) patients (74.08 ± 7.33) were included, for whom neuropsychological data, an amyloid PET, and a rs-fMRI scan were available at the Open Access Series of Imaging Studies (OASIS; https://www.oasis-brains.org/). Information on global amyloid load was assessed based on the Freesurfer-ROIs available in OASIS. Cognition residuals were computed regressing global amyloid, ApoE status, age and sex onto cognitive test performance using an exponential model fit. Positive residuals indicate higher cognitive performance than predicted. Intrinsic connectivity (IC) maps were extracted based on the pre-processed rs-fMRI data using the CONN toolbox. Using general linear modeling in SPM12 ($p < .0001$, *uncor.*), we first examined the voxel-based association between the individual IC maps and the cognition residuals in the early AD group, assuming this group requires a high need for reserve. To determine if the identified neuronal CR correlate extends to the preclinical phase of AD, we extracted the beta values of IC of the identified neuronal CR correlate in the amyloid-positive cognitively normal group (SUVR > 1.1., n=57) and examined the relationship between cognition residuals and IC.

Results: Only increased IC in the right hippocampus was associated with higher residuals in the early AD group. In the amyloid-positive cognitively normal group, the IC in this area was also correlated with greater residuals ($r=.34$, $p<.05$). The effect of the neuronal correlate and the residuals was stronger in the AD group when comparing both groups in terms of their correlation strengths.

Conclusion: The findings indicate that intrinsic hippocampal connectivity might contribute to CR seen in both preclinical and clinical phases of AD. Moreover, the residual approach proves to be sensitive to compensatory effects of IC in the face of AD-pathology.

Networks of tau distribution in Alzheimer's disease

Reference:
This is a pre-copyedited, author-produced version of an article accepted for publication in Brain following peer review. The version of record Hoenig et al. Networks of tau distribution in Alzheimer's disease. Brain, 2018 Feb 1;141(2):568-581 is available online at:
https://academic.oup.com/brain/article/141/2/568/4791255; doi: 10.1093/brain/awx353.

Title Page

Title

Networks of tau distribution in Alzheimer's disease

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Running title:

Tau pathology networks in Alzheimer's disease

Abstract

A stereotypical anatomical propagation of tau pathology has been described in Alzheimer's disease. According to recent concepts (network degeneration hypothesis), this propagation is thought to be indicative of misfolded tau proteins possibly spreading along functional networks. If true, tau pathology accumulation should correlate in functionally connected brain regions. Therefore, we examined whether independent components could be identified in the distribution pattern of *in vivo* tau pathology and whether these components correspond with specific functional connectivity networks. 22 [^{18}F]AV-1451 PET scans of patients with amnestic Alzheimer's disease (*M(Age)*= 66.00 ± 7.22 years, 14M/8F) were spatially normalized, intensity standardized to the cerebellum, and z-transformed using the mean and deviation image of a healthy control sample to assess Alzheimer's disease-related tau pathology. First, to detect distinct tau pathology networks, the deviation maps were subjected to an independent component analysis. Second, to investigate if regions of high tau burden are associated with functional connectivity networks, we extracted the region with the maximum z-value in each of the generated tau pathology networks and used them as seeds in a subsequent resting-state functional MRI analysis, conducted in a group of healthy adults (n=26) who were part of the 1000 Functional Connectomes Project. Third, to examine if tau pathology co-localizes with functional connectivity networks, we quantified the spatial overlap between the seed-based networks and the corresponding tau pathology network by calculating the dice similarity coefficient. Additionally, we assessed if the tau-dependent seed-based networks correspond with known functional resting-state networks. Finally, we examined the relevance of the identified components in regard to the neuropathological Braak stages. We identified 10 independently coherent tau pathology networks with the majority showing a symmetrical bi-hemispheric expansion and coinciding with highly functionally connected brain regions such as the precuneus and cingulate cortex. A fair to moderate overlap was observed between the tau pathology networks and corresponding seed-based networks (Dice range: 0.13-0.57), which in turn resembled known resting-state networks, particularly the default mode network (Dice range: 0.42-0.56). Moreover, greater tau burden in the tau pathology networks was associated with more advanced Braak stages. Using the data-driven approach of an independent component analysis, we observed a set of independently coherent tau pathology networks in Alzheimer's disease which were associated with disease progression and coincided with functional networks previously reported to be impaired in Alzheimer's disease. Together, our results provide novel information regarding the impact of tau pathology networks on the mechanistic pathway of Alzheimer's disease.

Keywords: Tau pathology networks, PET, independent component analysis, resting-state networks.

Abbreviations

Aβ - amyloid beta

CSF - cerebrospinal fluid

DMN – default mode network

DSC – dice similarity coefficient

ICA – independent component analysis

ROI – region of interest

rs-fMRI – resting-state functional MRI

TPN – tau pathology network

Introduction

Alzheimer's disease is characterized by two neuropathological hallmarks, i.e., the accumulation of extracellular β-amyloid (Aβ) plaques and the intracellular aggregation of misfolded tau proteins in form of neurofibrillary tangles. Aβ pathology initially spreads across neo- and allocortical brain regions and only propagates downstream to the brainstem in late stages of the disease (Thal *et al.*, 2002), whereas tau pathology first occurs in the locus coeruleus and the entorhinal cortex from where it expands upstream to limbic and isocortical regions (Braak and Braak, 1991; Braak and Braak, 1995). Several hypotheses have been suggested to explain the spreading and distribution of these pathologies across the brain. One prominent proposal is the *network degeneration hypothesis*, which postulates that neurodegenerative disease pathologies expand along functional networks, consequently leading to failure of these networks (Palop *et al.*, 2006; Seeley *et al.*, 2009). Network dysfunction then in turn likely provokes clinical symptomatology. In the past decade, multimodal imaging studies have provided compelling evidence in support of the network degeneration hypothesis: A spatial overlap between the deposition of Aβ plaques and neuronal networks, in particular the default mode network (DMN), has been reported (Buckner *et al.*, 2005; Buckner *et al.*, 2009; Grothe and Teipel, 2016; Jones *et al.*, 2016). Similar results were obtained when investigating the convergence between Alzheimer's disease-related grey matter volume reduction and large-scale networks (Seeley *et al.*, 2009). Furthermore, it was suggested that elevated Aβ deposition in regions of the DMN in asymptomatic cognitively normal individuals could serve as an indicator of incipient Alzheimer's disease (Sperling *et al.*, 2009). So far, it remains unknown whether tau pathology similarly expands along functional networks as the visualization of tau pathology *in vivo* has only recently become available. However, the stereotypical anatomical distribution pattern of tau pathology is indicative of misfolded tau proteins spreading throughout interconnected regions (Clavaguera *et al.*, 2009). This assumption is supported by recent findings from studies in rodent models of early Alzheimer's disease proposing that neurofibrillary tangles may exhibit prion-like properties (Clavaguera *et al.*, 2009; de Calignon *et al.*, 2012; Liu *et al.*, 2012). These properties may foster the spreading of tau pathology through axons and across synapses to other neurons, potentially consecutively affecting connected brain regions and eventually leading to severe neurodegeneration that causes cognitive impairment.

With the development of PET ligands for the visualization of tau depositions, disease-specific distribution patterns of tau pathology can now be detected and studied in humans *in vivo*. The radioactive tracer [^{18}F]AV-1451 appears especially useful for the visualization of

separate patterns of tau pathology distribution within the Alzheimer's disease spectrum (Ossenkoppele *et al.*, 2016; Dronse *et al.*, 2017), and across different tauopathies (Passamonti *et al.*, 2017). In order to assess distinct pathways of Alzheimer's disease-related tau pathology based on [^{18}F]AV-1451 PET imaging data, the multivariate approach of an independent component analysis (ICA) may represent a particularly well-suited tool. ICA is a blind source separation technique used to establish common features within a given dataset by decomposing the data into independent patterns (McKeown *et al.*, 2003). ICA is based on a whole-brain data-driven approach that is not limited to a set of pre-defined regions of interest (Fan *et al.*, 2008). Even though ICA has often been used to study properties of brain networks based on functional MRI (fMRI) data (Calhoun and Adali, 2012), several studies also confirmed the utility of ICA for the analysis of PET data (Illán *et al.*, 2011; Di *et al.*, 2012; Toussaint *et al.*, 2012; Shaffer *et al.*, 2013; Yakushev *et al.*, 2013; Savio *et al.*, 2017). For example, ICA identified distinct metabolic networks in [^{18}F]Fluorodeoxyglucose- PET scans, which resembled known resting-state functional connectivity networks (Di *et al.*, 2012; Yakushev *et al.*, 2013; Savio *et al.*, 2017).

Using ICA within the realm of structural or functional brain imaging analyses, regions within an independent component can be inferred to be spatially correlated either through structural or functional connections (Cohen *et al.*, 2008; Di *et al.*, 2012). However, the detection of independent components in PET imaging data does not necessarily allow drawing conclusions about the functional or structural connections of the associated brain regions within a given independent components. Consequently, systematic comparison of such components with information on existing functional or structural networks is required.

Here, in order to gain insights into the mechanistic pathways of tau pathology and to identify independent tau pathology networks (TPNs), we employed an ICA approach on [^{18}F]AV-1451 tau-PET imaging data of 22 patients with mild to moderate amnestic Alzheimer's disease. Subsequently, we systematically assessed the relationships between the identified TPNs and the functional network architecture of the brain. For this purpose, we first extracted the region of maximum tau deposition from each of the generated TPNs. Next, we employed these regions as seeds for a seed-based resting-state fMRI (rs-fMRI) analysis in a group of healthy control subjects (derived from the 1000 Functional Connectomes Project). The seed-based networks were established to identify regions of strongest connections to the seed of tau pathology of a given TPN. We assessed the spatial conformity of these (tau-dependent) functional connectivity networks with the detected TPNs as well as with established functional resting-state networks (Shirer *et al.*, 2012). Finally, we assessed whether higher tau burden in

the identified TPNs was associated with a more advanced Braak stage as well as global cognitive dysfunction as assessed by the Mini Mental State Examination (MMSE). We hypothesized that the ICA would yield TPNs that coincide with functionally connected networks resembling known resting-state networks, such as the DMN. Moreover, we assumed that increased tau burden within distinct TPNs would be associated with a more advanced Braak stage and negatively correlate with global cognitive function.

Materials & Methods

Participants

We included 22 patients with typical amnestic Alzheimer's disease (Table 1) who were diagnosed with probable Alzheimer's disease dementia according to the recommended NIA-AA guidelines (McKhann *et al.*, 2011) and based on the results of diagnostic PET imaging and cerebrospinal fluid (CSF) measurements. Out of the 22 patients, 16 patients were amyloid positive (based upon their amyloid PET scan). In addition, three patients were amyloid positive based upon the assessment of their CSF. In the remaining three patients, diagnosis of Alzheimer's disease was established without assessment of amyloid status, based on the NIA-AA guidelines. All patients underwent an [^{18}F]AV-1451 PET scan as part of their clinical evaluation in the Department of Nuclear Medicine at the University Hospital Cologne, Germany, and gave informed consent for the scientific evaluation and publication of their data. Key inclusion criteria for the patient sample were: 1) diagnosis of probable typical Alzheimer's disease according to the NIA-AA criteria, 2) age range: >55 ≤ 80, and 3) evaluable [^{18}F]AV-1451 scan. The study was performed according to the Declaration of Helsinki and was in compliance with the requirements of the ethics board of the Faculty of Medicine at the University of Cologne and of the responsible local regulatory authorities.

Characteristic	**Mean ± SD**	**Min**	**Max**
Age	66.00 ± 7.22	55	75
Education	13.80 ± 3.11	8	18
MMSE	24.45 ± 4.38	15	30
Sex	M=14; F=8		
Race	Caucasian		

Table 1 – Demographic characteristics. The range and average age in years, years of education, level of cognitive dysfunction as assessed by the MMSE, sex distribution, and race are listed in this table. SD = Standard deviation; M = Male; F=Female; MMSE = Mini Mental State Examination.

PET data

The PET scans were collected from a PET-CT Siemens Biograph mCT Flow 128 Edge (Siemens, Knoxville, TN). A low dose transmission scan was performed with CT for attenuation correction prior to the beginning of the PET scanning. PET scans were acquired in list mode (15 minutes) 90 minutes after an intravenous injection of a mean dose of 230 MBq of [^{18}F]AV-1451. The scans were iteratively reconstructed using a 3D OSEM algorithm of four iterations and 12 subsets, and were smoothed with a Gaussian filter of 5 mm FWHM on a 128x128 matrix.

Rs-fMRI data

To identify functional networks in a group of healthy adults, we employed the publically available rs-fMRI dataset by Berlin-Margulies (Rohr *et al.*, 2013), which is part of the 1000 Functional Connectomes Project (http://www.nitrc.org/frs/?group_id=296). The dataset included 26 healthy controls (13M/13F) aged between 23 and 44 years (*M(Age)*=29.77 ± 5.21 years). The rs-fMRIs were acquired on a 3T Trio Tim Siemens Magnetom (Siemens, Erlangen, Germany). The scanning protocol was as follows: repeat time (TR) = 2300 ms, echo time (TE) = 30 ms, time points =195, slice number= 34, flip angle = 90°, voxel size = 3x3x4 mm^3, field of view (FOV) = 192 x 192.

PET image preprocessing

The [^{18}F]AV-1451 PET scans were preprocessed using Statistical Parametric Mapping (SPM) version 8 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London). The images were spatially normalized to a tau template of a healthy control group. This template was previously established by our group based on a dataset of [^{18}F]AV-1451 PET scans from 19 healthy controls (*M(Age)*=56.63 ± 16.65 years) provided by Avid Radiopharmaceuticals, Inc, Philadelphia (Bischof *et al.*, 2016; Hammes *et al.*, 2017). The normalized PET scans were smoothed using a Gaussian filter of 12 mm FWHM. Using the whole cerebellum as reference region, standard uptake value ratios (SUVRs) images were computed utilizing in house scripts in MATLAB R2016a (The MathWorks, Inc., Natick, MA, USA). To assess specific Alzheimer's disease-related tau pathology patterns, images were z-transformed using the mean and deviation image from a healthy control sample. A detailed description of the sample and z-transformation can be found elsewhere (Bischof et al. 2016). The generated z-transformed images were then subjected to an ICA.

Rs- fMRI image preprocessing

The rs-fMRI dataset was pre-processed using the pipeline of the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox, version 4.3 (Yan and Zang, 2010). The pipeline consists of the following steps:

Initially, the first 10 time points of each subject were removed and the remaining slices were processed with slice timing. Second, nuisance variables were regressed including white matter, CSF, and global mean signal. To control for head motion, the Friston 24 parameter model was applied (Friston *et al.*, 1996). Third, the realigned images were normalized to the default EPI template provided by the DPARSF toolbox. In a final step, the images were smoothed with a Gaussian filter of 8 mm. All pre-processed images were visually checked to assure that the normalization process had not resulted in distorted images. The pre-processed images were then used for the seed-based functional connectivity analysis.

Statistical Analysis

Independent component analysis

To identify independently coherent TPNs, we performed an ICA on the z-standardized tau-PET images using the group ICA function of the fMRI Toolbox (GIFT toolbox, version 4.0a, 2015; MIALAB, The Mind Research Network, University of New Mexico, Albuquerque, NM, USA). To avoid overfitting of the data based on the given number of input images and to create meaningful orthogonal components, the default setting of 20 components was reduced to 10 components (Särelä and Vigário, 2003). We then applied the *Infomax* algorithm implemented in the GIFT toolbox to extract common tau pathology features from the PET dataset.

To support our ICA approach and in order to evaluate the possible influence of confounding factors that might bias the results, we performed a series of additional analyses: We ran the ICA with different numbers of allowed components (5 and 20 components), with a different Gaussian kernel (8mm instead of 12mm), and, in addition, an ICA including only scans from patients who were amyloid positive on their amyloid PET scan (n=16). Moreover, we conducted a conventional SPM t-test to identify peaks of tau pathology. For this, we compared the Alzheimer's disease group against a group of healthy controls (n=19) using a voxel-based independent t-test. The identified peaks of tau pathology were employed as seeds in a following seed-based fMRI analysis.

Seed-based functional connectivity analysis

To assess if regions of high tau burden are involved in functional connectivity networks, we conducted a seed-based analysis using the pre-processed rs-fMRI dataset by Berlin-Margulies (Rohr *et al.*, 2013). As seeds for the functional connectivity analysis, we extracted the coordinate of the maximal peak z-score from each generated TPN. The seeds of maximum tau burden were each defined as a sphere centered at the respective peak coordinate with a radius of 5 mm. Given that we allowed 10 components to be generated by the ICA, we obtained 10 tau-dependent seeds, which were submitted to the functional connectivity analysis using the DPARSF toolbox.

Following the pipeline of the DPARSF toolbox for the functional connectivity analysis, the motion parameters, white matter, CSF, and global mean signal were regressed out. Next, the images were band pass filtered at 0.01-0.1 Hz. In order to reduce the number of comparisons for the connectivity analysis conducted in SPM 12, we included a grey matter mask. Then, the correlation of the rs-fMRI time series between the respective seed and coherently active regions were computed for each subject yielding individual functional connectivity maps for each seed. In a last step, we conducted one-sample t-tests in SPM 12 (FWE, $p < .05$) comprising the individual functional connectivity maps for each seed. Age and gender were included as covariates. The SPM analyses yielded the respective functional connectivity maps for each seed.

Evaluation of spatial overlap: Dice Similarity Coefficient

To examine the overlap between the TPNs and the corresponding tau-dependent seed-based networks, we next calculated the Dice Similarity Coefficient (DSC). The DSC is a measure that quantifies the spatial overlap between two binarized maps and is calculated as follows:

$$\mathrm{DSC} = \frac{2n_t}{(n_x + n_y)}$$

where n_t denotes the volume intersection between the image volume n_x and n_y, which is divided by the sum of the respective image volumes n_x and n_y. The DSC thereby yields the percentagewise overlap between two maps/networks. It is interpreted as follows: <0.2 reflects poor, 0.2-0.4 fair, 0.4-0.6 moderate, 0.6-0.8 good, and > 0.8 near complete overlap (Savio *et al.*, 2017).

In order to calculate the DSC, we first binarized the generated t-maps of the seed-based networks. Next, the generated TPNs were binarized at a z-score of $z > 2.0$. We then compared

the spatial overlap between the TPNs and the corresponding seed-based networks. Furthermore, to characterize the topography of the seed-based networks, we compared these networks with previously established functional connectivity networks obtained by a rs-fMRI study in 27 healthy subjects at the FIND lab of Stanford University (Shirer *et al.*, 2012). The Stanford networks consist of 14 networks, including the DMN, salience network and language network, and have consistently been used by other studies to characterize resting-state functional connectivity networks (Lehmann *et al.*, 2013; Leonardi *et al.*, 2014; Lim *et al.*, 2014). We quantitatively compared the spatial overlap of each binarized seed-based network against all binarized resting-state networks. The resting-state network with the highest dice coefficient was chosen as best match for the seed-based network.

Relation between Braak stages and tau pathology networks (TPNs)

To examine the association between tau pathology in the respective TPNs and the individual Braak stage of each patient, we extracted mean SUVRs for Braak stages I/II-VI for each patient based on the region of interest (ROI)-based Braak staging approach previously used (Schöll *et al.*, 2016; Hoenig *et al.*, 2017). Moreover, we computed the median SUVR for each Braak stage across the patient sample. Patients, who had a mean SUVR greater than the median, were determined to be positive for the respective Braak stage, whereas patients who had a lower SUVR than the median were classified as negative. The highest positive Braak stage was used for final classification. Patients could obtain a score ranging from 2-6 (corresponding to Braak stage I/II-VI) and were grouped into either an early Braak (score 2-3) or advanced Braak group (stage 4-6). Finally, we compared the mean SUVRs of each TPN between the early (n=10) and the advanced (n=12) Braak group. We extracted the mean SUVRs for the respective components based on the intensity standardized images using the binarized component maps. As the assumptions for normality and homoscedasticity were not given, the Mann-Whitney-U test was used for comparison. Results were corrected for multiple comparison using Bonferroni correction ($p^* = .005$).

Relation between cognitive function and tau burden in tau pathology networks (TPNs)

We further examined whether tau burden within distinct TPNs was associated with global cognitive dysfunction. We used the MMSE as a measure of global cognitive function (Folstein *et al.*, 1975). Both, tau burden within each component and global cortical tau was quantified based on the individual SUVR images employing the binarized component maps and a whole-brain cortical grey matter ROI, respectively. The extracted SUVRs for each component

and for global cortical tau burden of each patient were correlated with the individual MMSE scores including age and gender as covariates. The analyses were corrected for multiple comparisons using Bonferroni correction ($p^* = .0045$).

Results

Tau pathology networks (TPNs)

The ICA resulted in the detection of independent TPNs, which spatially resembled established language, frontal control, default mode, visuospatial, and hippocampal networks (Fig. 1). Some of the TPNs showed a symmetrical bi-hemispheric expansion (Component 2-4,6,8, & 10), whereas the remaining components were lateralized (Component 1,5,7, & 9). Moreover, the TPNs were characterized by varying loads of tau pathology (Table 2). The generated TPNs coincided with highly functionally connected regions predominantly involving parietal and temporal areas. The total percent variance explained by all ten components was 95.7%. The topographical distributions of the TPNs are depicted in blue in Fig. 3.

TPN	Mean SUVR (SE)
1	1.70 (0.09)
2	1.66 (0.11)
3	1.57 (0.12)
4	1.68 (0.90)
5	1.52 (0.08)
6	1.71 (0.10)
7	1.38 (0.07)
8	1.42 (0.07)
9	1.59 (0.09)
10	1.51 (0.04)

Table 2 – Tau load of independent tau pathology networks. Mean SUVR and standard error for each tau pathology network are provided. TPN = tau pathology network; SUVR = standard uptake value ratio; SE = standard error.

The different ICA settings revealed similar components confirming the statistical stability of the generated TPNs. Importantly, the ICA including only amyloid positive patients resulted in similar components as the initial ICA (Supplementary Fig. 4). Moreover, the conventional SPM approach using a t-test yielded four peaks of tau pathology, which resembled the tau maxima detected by the ICA (Supplementary Table 1). Further details of the additional analyses can be found in the supplementary data.

Tau-dependent seed-based functional networks

The tau maxima of the respective TPNs used for the seed-based approach corresponded to the following regions; temporal middle gyrus, precentral gyrus, precuneus, superior occipital region, fusiform gyrus, posterior cingulate cortex, cuneus, frontal medial orbital region, superior temporal gyrus and parahippocampal gyrus (Table 3). The seed-based functional

connectivity analysis resulted in specific functional connectivity networks for each tau maxima. For several seed-based analyses, the functional networks included remote brain regions which were not anatomically adjacent to the corresponding seed region (seed-based networks: 1,2,6,8,9, & 10). Furthermore, the tau-dependent seed-based networks were characterized by a symmetrical bi-hemispheric functional connectivity pattern. The respective projections of the seed-based networks are depicted in red in Fig. 3.

TPN	Max Z-Score	Coordinates			AAL Region
		X	Y	Z	
1	5.54	-60	-46	0	L Temporal Middle Gyrus (85)
2	6.53	-48	0	46	L Precentral Gyrus (1)
3	5.95	8	-52	52	R Precuneus (68)
4	7.11	28	-68	26	R Superior Occipital Region (50)
5	8.06	-40	-66	-12	L Fusiform Gyrus (55)
6	5.10	0	-46	28	L Posterior Cingulate Cortex (35)
7	5.32	10	-72	24	R Cuneus (46)
8	3.96	6	50	-6	R Frontal Medial Orbital Region (26)
9	6.32	58	-48	16	R Superior Temporal Gyrus (82)
10	3.93	-24	-5	-22	L Parahippocampal Gyrus (39)

Table 3- Coordinates and z-scores of the tau pathology networks. The maximum z-score and the peak coordinates of each tau pathology network with the corresponding brain region based on the automated anatomical labeling atlas are listed (Tzourio-Mazoyer et al., 2002). TPN= tau pathology network; Max = Maximum; AAL = Automated anatomical labeling atlas; R = Right; L= Left.

Spatial overlap between distribution of tau pathology and functional networks

The comparison between the identified TPNs and the tau-dependent seed-based functional connectivity networks yielded moderate spatial overlap (DSC: 0.4-0.6) for components 3, 5, and 10 with their corresponding tau-dependent seed-based functional networks. In addition, TPN components 1, 4, 7, 8, and 9 were fairly (DSC: 0.2-0.4) associated with the corresponding tau-maximum seeded functional network. Only poor overlap (DSC < 0.2) was found between the seed-based networks and the remaining components (2 & 6). The respective DSCs are reported in Table 4A.

The comparison between the tau-dependent seed-based networks with known resting-state functional connectivity networks yielded moderate overlap (DSC: 0.4-0.6) for seed-based networks 3,4,6,8, & 9, predominantly with regions associated with the ventral and dorsal DMN. Moreover, fair overlap (DSC: 0.2-0.4) was observed between the seed-based networks 1,2,5, and 7 and the language, the salience, higher visual, and primary visual network. The seed-based

network 10 strongly resembled the hippocampal network. As the hippocampal network is not part of the predefined Stanford networks, we could not quantitatively assess the actual spatial overlap. The respective DSCs are reported in Table 4B.

Fig. 2 provides an exemplary illustration of the best overlapping TPN, the corresponding seed-based network, and the best matching Stanford resting-state network on a rendered brain surface. Fig. 3 illustrates the spatial resemblance between the respective components (highlighted in blue) and the corresponding seed-based network (highlighted in red) and the best-matching Stanford resting-state network (highlighted in green), respectively. This figure further includes the DSCs for the quantification of the spatial overlap between the respective TPNs and the seed-based networks (first DSC) and between each seed-based network and the corresponding Stanford resting-state network (second DSC).

A. DSC for overlap between TPN and SBN		B. DSC for overlap between SBN and RSN	
TPN 1 & SBN 1	0.39	SBN1 & Language Network	0.37
TPN 2 & SBN 2	0.17	SBN 2 & Salience Network	0.28
TPN 3 & SBN 3	0.57	SBN 3 & Ventral DMN	0.56
TPN 4 & SBN 4	0.34	SBN 4 & Ventral DMN	0.42
TPN 5 & SBN 5	0.41	SBN 5 & Higher Visual Network	0.33
TPN 6 & SBN 6	0.13	SBN 6 & Dorsal DMN	0.51
TPN 7 & SBN 7	0.36	SBN 7 & Primary Visual Network	0.23
TPN 8 & SBN 8	0.25	SBN 8 & Dorsal DMN	0.55
TPN 9 & SBN 9	0.38	SBN 9 & Language Network	0.52
TPN 10 & SBN 10	0.46	SBN 10 & Hippocampal Network	na

Table 4 – Dice similarity coefficient for the overlap between networks. The table summarizes the quantification of the overlap between the tau pathology network and the corresponding seed-based network (A) and the seed-based network and best-matching Stanford resting-state network (B). DSC = Dice similarity coefficient; TPN = Tau pathology network; SBN = Seed-based network; RSN = Resting-state network; DMN = Default mode network; na = Not available.

Relationship between Braak stages and tau pathology networks (TPNs)

The advanced Braak group showed significantly higher SUVRs in eight components when compared to the early Braak group (Fig. 4). Mean SUVRs in component 3 and 7 did not significantly differ between groups after correcting for multiple comparison ($p^* = .005$), although a trend was observed. A summary of the *U*-statistics can be found in the supplementary data (Supplementary Table 2).

Cognitive function and tau burden in distinct tau pathology networks (TPNs)

Global cognitive function was negatively correlated with tau burden in components 4 ($r(18)$= -.496, p= .026), 5 ($r(18)$= -.554, p= .011), and 7 ($r(18)$= -.641, p= .002). A trend significant effect was observed for global cognitive function and component 3 ($r(18)$= -.440, p= .052). Global cortical tau burden, assessed based on a cortical gray matter ROI, was not negatively correlated with global cognitive function ($r(18)$= -.305, p= .190). Exclusively, the negative association between global cognitive function and tau burden in component 7 survived correction for multiple comparison (p^* = .0045). The tau maximum of component 7 coincided with cuneal regions, whereas the tau maximum of component 3 was located in precuneal areas, of component 4 in superior occipital, and of component 5 in fusiform gyral areas.

Discussion

In the current study, we identified a set of independently coherent networks of tau pathology in a sample of patients with mild to moderate Alzheimer's disease. This finding supports the idea that the aggregation of tau pathology in the brain follows several independent pathways and partly develops coherently in different compartments of the brain. The peaks of tau within these detected TPNs included, among others, the precuneus, parahippocampus, and posterior cingulate cortex, regions known to be involved in various functional networks. In accordance with this, the TPNs overlapped distinctly with seed-based functional connectivity networks, some of which have previously been reported to be impaired in Alzheimer's disease, including the DMN (Greicius *et al.*, 2004; Zhang *et al.*, 2010; Zhou *et al.*, 2010) and the frontal control network (Lehmann et al., 2013; Agosta et al., 2012; Balthazar et al., 2014). Moreover, tau burden within the TPNs was associated with the advancement along Braak stages and global cognitive dysfunction, indicating that the identified networks may bear clinical relevance. In the following, we discuss our findings in the context of (a) distribution of tau pathology along independent pathways, (b) the relevance of TPNs in regard to disease progression and cognitive profiles, and (c) the relationship of these TPNs with functional connectivity networks.

Properties of independent tau pathology networks

Here, we determined a set of distinct TPNs by means of ICA. Some of the TPNs involved regions that were not anatomically adjacent. This is per se of interest as it indicates that tau pathology does not distribute homogenously across the brain, but importantly

propagates across independent pathways and possibly arises synchronously in different brain compartments at certain stages of the disease.

Interestingly, several TPNs were characterized by a symmetrical distribution pattern across hemispheres, whereas some were asymmetric. This characteristic difference in the symmetry of the TPNs may be partly attributed to early disease stage, where tau pathology may not have advanced to a symmetric pattern across hemispheres within a given network, but has centered on the most susceptible regions of tau accumulation. Indeed, according to recent models of tau propagation misfolded tau proteins predominantly spread along the most interconnected regions of the seed of tau pathology (Fox *et al.*, 2011; Liu *et al.*, 2012; Menkes-Caspi *et al.*, 2015). Thus, depending on the stage of the disease and the anatomical location of the seed of pathology, which may be represented by the tau maxima of each independent component, tau distribution patterns may differ in their symmetry. Moreover, the current finding of asymmetric components accords with the known fact that neurodegenerative disorders may start in one hemisphere and initially spread dominantly across this hemisphere before eventually affecting the other hemisphere in later stages of disease (Shi *et al.*, 2009; Claassen *et al.*, 2016). In this regard, the implications of employing ICA as an analysis method also need to be considered. ICA is a data-driven approach that is based on the underlying tau pathology distribution of the patient sample, which in this study consists of patients with mild to moderate Alzheimer's disease. Consequently, component patterns of coherent tau pathology can be identified that may be characterized either by an asymmetric distribution pattern, likely reflecting earlier stages of the disease, or by symmetric and bi-hemispheric patterns, potentially reflecting a more advanced disease stage. ICA hence defines independent regional patterns of coherent tau pathology, which do not necessarily have to be symmetric supporting the current finding of asymmetric and symmetric component patterns.

As discussed above, ICA can determine unique disease-specific and coherent patterns of tau pathology without any a priori knowledge or topographic assumptions (Pagani *et al.*, 2016). This blind source separation technique contrasts conventional voxel-based statistical parametric mapping approaches that are often based on a priori hypotheses regarding the cortical disease localization and require categorical distinction into significant and non-significant voxels depending on the intensity values of the voxels. ICA, on opposite, provides a more graduated consideration, where significance is not based on severity but regional coherence of pathology and thus regional interrelations. Importantly, ICA does thereby not exclusively provide components of highest tau pathology, but can also determine regional distribution patterns of lower pathology load, which are nevertheless characterized by

synchronous tau pathology aggregation. In compliance with this, in the current study the conventional SPM approach only yielded four peaks of tau pathology, whereas by means of ICA several additional TPNs were established. Importantly, the TPNs identified by ICA were characterized by varying loads of tau pathology pointing towards different susceptibility of these TPNs potentially depending on the stage of the disease. Intriguingly, the components involving orbito-frontal and cuneal areas showed lowest tau burden. These regions are known to be affected relatively late in Alzheimer's disease according to the neuropathological Braak stages (Braak and Braak, 1991; Braak and Braak, 1995). Interestingly, when directly assessing the relationship between the neuropathological Braak stages and the identified TPNs, we observed that individuals in an advanced Braak stage demonstrated higher tau pathology burden in the established TPNs as compared to individuals at an earlier Braak stage. This result indicates that the accumulation of tau pathology within the identified TPNs may contribute to the advancement along Braak stages. Moreover, in the early Braak stage group highest tau burden was observed in the TPN associated with the parahippocampus, whereas the advanced Braak stage group presented highest tau pathology in the TPN associated with the posterior cingulate cortex. This may suggest that distinct TPNs exist as a determinant of each Braak stage. Larger data samples of early and advanced Braak stage groups will be required to investigate this assumption further. Overall, the current findings suggest that the differential load of tau pathology in the independent TPNs may track the expansion of tau pathology at various disease stages.

In addition to the implications of the TPNs with respect to the neuropathological Braak staging, tau pathology within the TPN including cuneal and primary visual areas was also associated with decreased global cognitive function. This finding points towards a specific deleterious effect as soon as tau pathology strikes visual cortical brain regions (Braak and Braak, 1991; Braak and Braak, 1995) underscoring the regional specificity of a tau-cognition relationship. Moreover, these findings are consistent with recent findings reporting a relationship between cognitive function and regional tau pathology (Brier *et al.*, 2016; Ossenkoppele *et al.*, 2016; Shimada *et al.*, 2016). To achieve a more fine-grained characterization of distinct cognitive profiles in Alzheimer's disease, future studies may employ an elaborate neuropsychological assessment and examine its correspondence with the TPNs identified here. Alternatively, as atypical cases of Alzheimer's disease such as posterior cortical atrophy or the logopenic variant of Alzheimer's disease express distinct cognitive profiles, which are dissociable from amnestic cases, further investigations are warranted that explore whether these clinical variants are also characterized by variant-specific TPNs.

Overall, our results provide first evidence of independently coherent tau pathology networks, which not only appear to track disease progression but are also, at least in part, relate to global cognitive dysfunction. Importantly, these networks of interrelated tau deposition point towards brain regions potentially being synchronously affected by tau pathology in the course of the disease, providing new insights into the mechanistic pathway of the disease. Given that the identified TPNs differed in their topographical distribution and in the degree of tau pathology, it will be of great interest to investigate the influence of additional factors on the generation of these networks. In particular, a putative synergistic effect of Aβ and tau pathology may be of interest with regard to the propagation of tau pathology along the identified networks. Moreover, investigating how the cellular, functional, and structural composition underlying specific networks influences the propagation of tau pathology and thereby the generation of these distinct TPNs will provide further information on the pathophysiological processes underlying Alzheimer's disease.

Relation between independent tau pathology patterns and functional connectivity networks

Some of the identified TPNs involved anatomically distant regions, indicating that these regions may share a joint mechanism, which could be of structural or functional nature and which may contribute to the coherent accumulation of tau pathology in these compartments. In the current study we focused on the role of seeded functional connectivity in regard to *in vivo* tau distribution patterns for two reasons: First, seed-based connectivity networks include regions which show highest connectivity to the seed and thus comply with recent models of tau propagation. Second, functional connectivity hubs have been suggested to be most susceptible to the development of neuropathology (Buckner *et al.*, 2009; Drzezga *et al.*, 2011; de Haan *et al.*, 2012). From these hubs pathology may then spread to connected brain regions (Buckner *et al.*, 2009; Drzezga *et al.*, 2011; de Haan *et al.*, 2012). Indeed, a number of studies consistently demonstrated striking similarity and overlap of Aβ plaque pathology with functional connectivity networks (Buckner *et al.*, 2005; Buckner *et al.*, 2009; Lehmann *et al.*, 2013; Grothe and Teipel, 2016). In accordance with this, we observed tau-dependent seed-based functional networks, characterized by a symmetrical bi-hemispheric activation, which in part spatially corresponded to the established TPNs.

Some of the seed-based networks resembled the salience, the primary visual, the higher visual, the language, and the hippocampal network indicating that tau pathology does not exclusively distribute along one particular network. This finding is in accordance with recently provided evidence demonstrating that the Alzheimer's disease- associated tau pathology pattern

corresponds to several cognition-relevant networks (Hansson *et al.*, 2017). Interestingly, the majority of tau-dependent seed-based networks established in the current study predominantly overlapped with regions of the ventral and dorsal DMN. This suggests that the DMN may be particularly susceptible to not only Aβ pathology, as previously shown (Buckner *et al.*, 2005; Buckner *et al.*, 2009; Grothe and Teipel, 2016), but also to tau pathology. Note, however, that all identified seed-based networks overlapping with the DMN had different origins, suggesting that the networks identified in our study may represent subnetworks of a more superordinate network. The existence of such subnetworks within a superordinate network has been recently proposed (Doucet *et al.*, 2011). These subnetworks may differently be affected depending on the stage of the disease and therefore, by using ICA, several components, each with a different pathological load, can actually belong to a more superordinate network. Thus, directly comparing the spatial overlap between ICA-derived patterns of tau load and an entire resting-state network such as the DMN may not be an appropriate comparison, as the ICA patterns may only reflect subnetworks of the resting-state networks. Therefore, generating seed-based functional connectivity networks from the ICA-derived patterns likely allows to more accurately compare the functional networks related to tau pathology distribution patterns.

Although we observed an overlap between the TPNs, the tau-dependent seed-based networks, and known resting-state networks, the overlap was moderate. Several aspects may contribute to this moderate spatial correspondence:

As the seed-based functional connectivity networks in the current study were defined based on a group of healthy young adults, they likely differed from the functional networks present in Alzheimer's disease patients (Jones *et al.*, 2016; Teipel *et al.*, 2016). Following the concept of tau propagation, tau pathology may no longer be able to expand along these networks due to disease-related disconnection between regions within a given network, changes in the location of network hubs, or functional breakdown of the entire network. Thus, the overlap between the tau-dependent seed-based networks and the TPNs may have been moderate due to disease-related and/or age-related changes in network architecture. Based on the proposed prion-like mechanisms of tau, tau pathology may propagate along reorganized networks that may differ from the ones identified in the young.

Furthermore, although a close link between structural and resting-state functional connectivity has been reported (Greicius *et al.*, 2009), functional connectivity maps only capture the superficial structure of regions and collapse several sub-regions into one. Given that tau pathology appears to follow synaptic connectivity (Clavaguera *et al.*, 2009; de Calignon *et al.*, 2012; Liu *et al.*, 2012), the spreading pattern may depend on structural connectivity rather

than functional connectivity. It is thus possible that the overlap between structural networks and the established TPNs is more coherent. Future multimodal studies using diffusion tensor imaging and fMRI are warranted to understand the structural and functional underpinnings contributing to the propagation of misfolded tau proteins within neuronal networks.

Finally, we only included patients with mild to moderate Alzheimer's disease in our current analyses. Thus, tau pathology in the current patient cohort may just have started to spread from the initial seed, thereby rendering the overlap with the corresponding seed-based network rather moderate. Longitudinal studies are necessary to assess whether at advanced stages of Alzheimer's disease, the overlap between the TPNs and the corresponding seed-based networks becomes more concordant.

Despite these arguments, it appears that the functional connections between regions, which are characterized by synchronous oscillatory activity, may provide a pathway contributing to the propagation of tau pathology within distinct neural networks. Longitudinal tau-PET and functional imaging data from the same Alzheimer's disease cohort will be necessary to establish whether the functional coherence between regions acts as an amplifying mechanism for tau pathology to spread.

Limitations

A few limitations need to be considered when interpreting our results. First, our analysis was restricted to a relatively small PET dataset. Studies that include larger patient cohorts are needed to confirm that the established TPNs are characteristic for Alzheimer's disease patients. Secondly, it has to be noted that we employed a rs-fMRI dataset of young healthy controls, which was used to establish seed-based functional networks associated with the healthy state. Using a rs-fMRI data set of age-matched healthy older controls would have allowed us to investigate the possible age-related pattern of tau distribution along neural networks. However, including an age-matched control sample would have required additional PET or CSF measurements to exclude any existing ageing-related pathology, which may have already affected (subclinically) network structures. Moreover, we cannot exclude spill-over effects from the choroid plexus influencing the signal in hippocampal regions. However, given that only one component was associated with hippocampal regions, we believe that the potential influence was marginal at most. Finally, we used a cross-sectional approach to assess the existence of TPNs and their relation to functional networks. Longitudinal designs may be better suited to explore the temporal spread of tau pathology along functionally connected brain regions.

Conclusion

The results of this study indicate that in Alzheimer's disease, the spatial distribution of tau pathology is not homogeneous but seems to progress within independent, coherent networks. Moreover, tau pathology load in these identified networks is associated with the advancement along Braak stages. In addition, the independent, coherent networks were characterized by differential distribution patterns, which in turn partially corresponded with functional connectivity networks. The relationship between functional connectivity network and TPNs may offer new insights into the possible mechanism of tau propagation across brain regions. Longitudinal approaches are warranted to further elucidate the temporal spreading pattern of tau pathology across large-scale networks, which will provide important information on the mechanisms underlying Alzheimer's disease and may further inform investigation of anti-tau based treatment efficacy.

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Figures

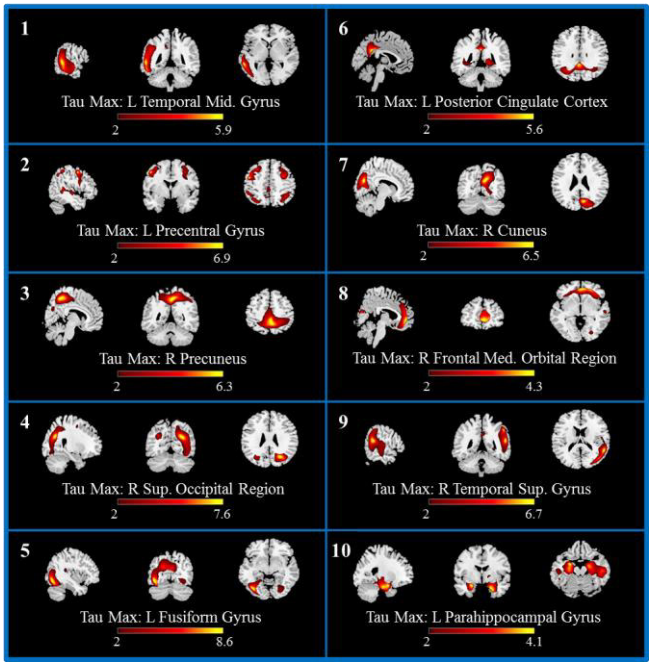


Fig. 1 – Illustration of independently coherent tau pathology networks. The respective region corresponding to the peak coordinates of each component and the z-score range are depicted below each component. The components are projected on the Colin brain in MNI space. Max = Maximum.

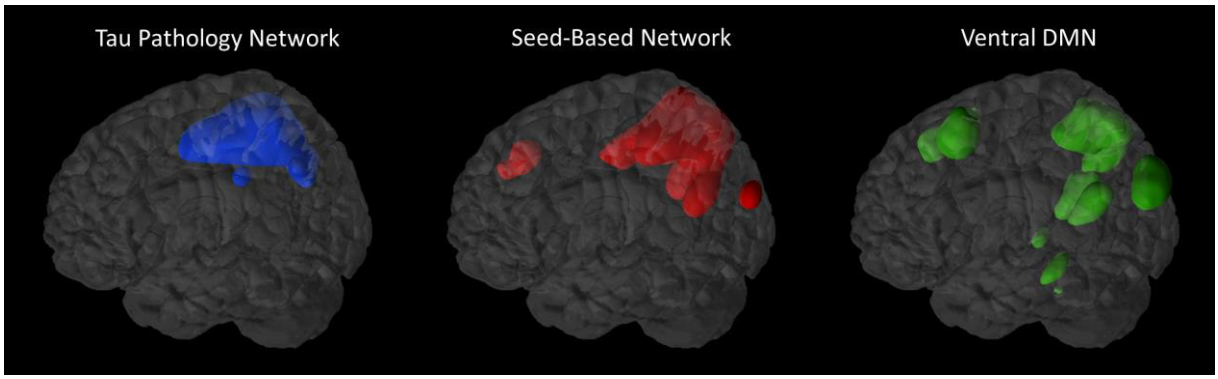


Fig. 2 – Exemplary illustration of the distribution pattern of respective networks. The networks are rendered on the inflated Colin brain in MNI space. Blue = Tau pathology network, Red = Seed-based network, Green = Ventral default mode network. DMN = Default mode network.

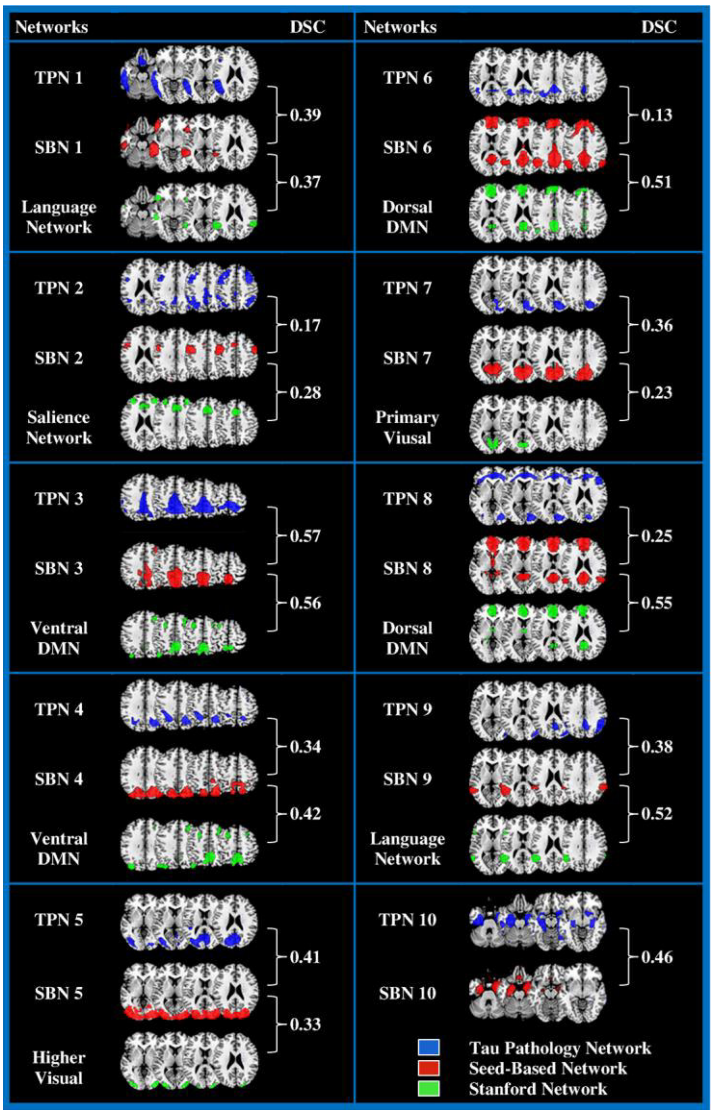


Fig. 3 – Illustration of networks and corresponding dice similarity coefficient. The respective tau pathology networks are illustrated in blue, the corresponding seed-based networks in red, and the best-matching resting-state Stanford network in green. The first dice similarity coefficient per cell represents the spatial overlap between the tau pathology network and the seed-based network, the second coefficient relates to the overlap between the seed-based and the resting- state Stanford network. All networks are projected on the Colin brain in MNI space. DSC = Dice similarity coefficient; TPN = Tau pathology network, SBN = Seed-based network; DMN = Default mode network.

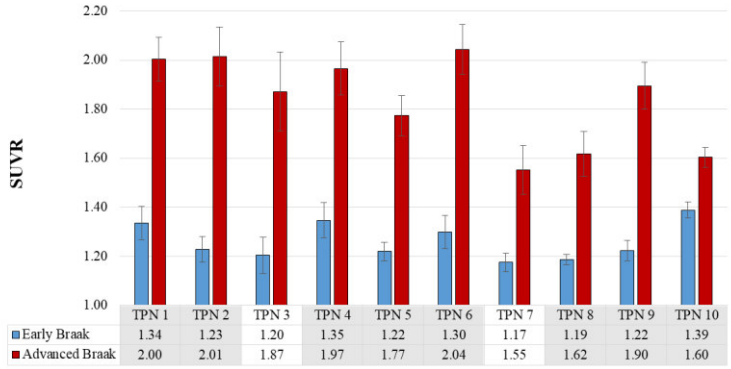


Fig. 4 – Illustration of tau burden in each independent component for the early and advanced Braak group. Mean SUVRs and standard error for each component are depicted for the early Braak (blue) and advanced Braak (red) group. Significant differences after multiple comparison correction are marked with an asterisk. SUVR = Standard uptake value ratio, TPN = Tau pathology network.

Supplementary Data

Results of confirmatory ICA analyses

The ICA with the default setting of 20 components revealed 20 components, out of which a few resembled the major components obtained in our initial analysis. Some of the remaining components were lateralized and occurred separately for the respective hemisphere, while other components involved the same region in both hemispheres (Supplementary Fig. 1).

Reducing the default setting from 20 components to 5 components yielded similar components as the initial analysis thereby confirming the statistical stability of the established TPNs. The total variance explained by the components was 84.70%, thus lower than the variance of the ICA including 10 components (Supplementary Fig. 2).

Decreasing the smoothing kernel from 12mm FWHM to 8mm FWHM provided similarly looking TPNs explaining 95.16% of the variance, additionally supporting the setting of our ICA approach (Supplementary Fig. 3).

Running an ICA with 8 allowed output components only including patients, from who we had obtained a positive amyloid PET scan (n=16), yielded similarly looking TPNs (Supplementary Fig. 4).

Results of conventional SPM analysis

We complemented our analyses with a conventional SPM-based approach to identify tau maxima as seeds for a seed-based functional connectivity analysis. To extract the tau maxima, we employed a voxel-based t-test comparing tau pathology load between the Alzheimer's disease patients and a group of healthy controls (n=19). Thereby, we were able to identify four peaks of tau pathology. Interestingly, these maxima (parahippocampus, fusiform gyrus, cuneus, frontal middle gyrus) resembled the tau maxima from the independent components detected by the ICA. When submitting these four maxima as seeds to a seed-based functional connectivity analysis of resting state fMRI data, we obtained similar networks and dice coefficients as produced by the initial seed-based analysis based on the independent components (Supplementary Table 1).

Seeds	Dice for overlap between SBN & RSN	
L Parahippocampus	SBN 1 & dDMN	0.40
R Fusiform Gyrus	SBN2 & dMN	0.07
R Cuneus	SBN3 & vDMN	0.61
R Frontal Middle Gyrus	SBN4 & ECN	0.27

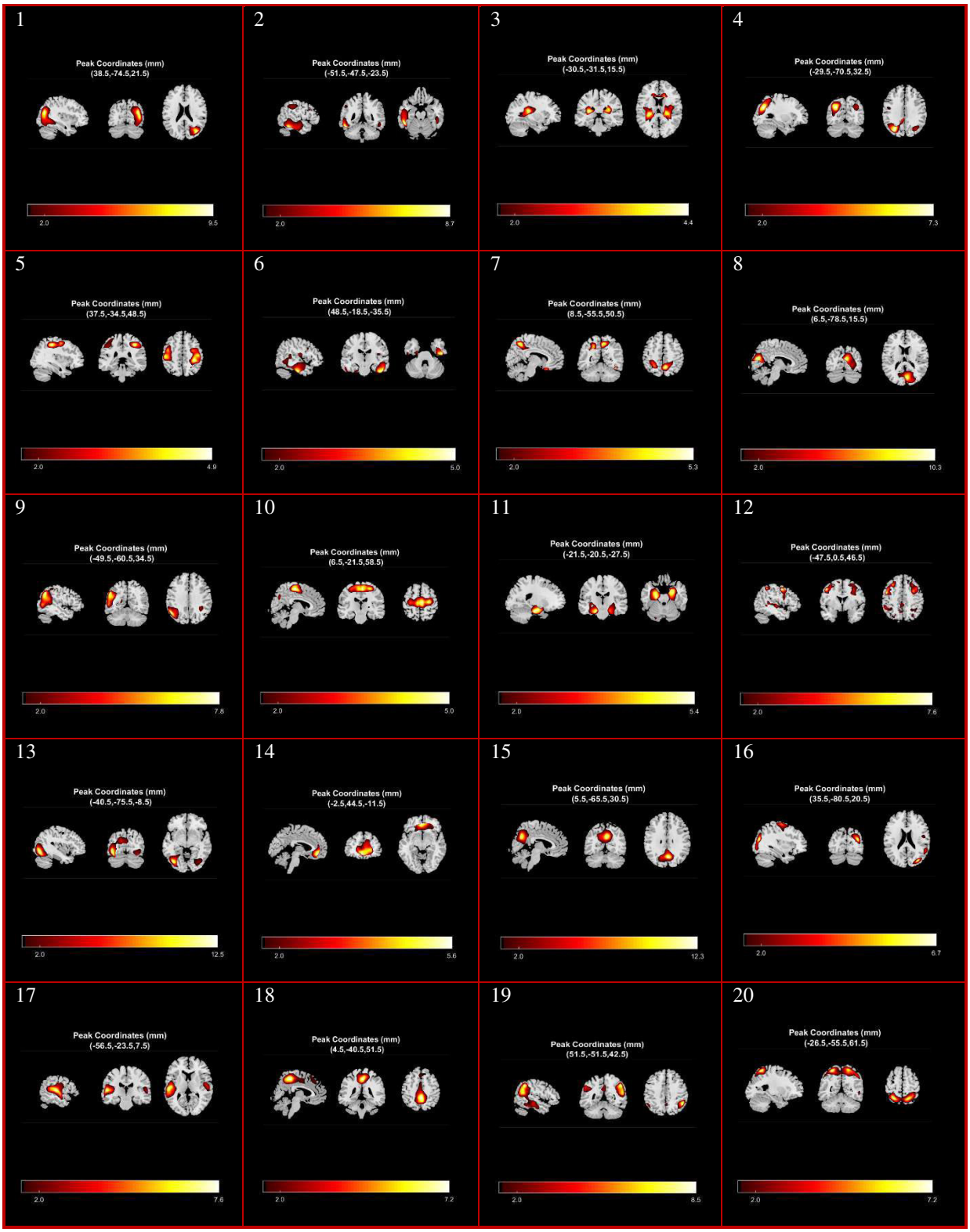
Supplementary Table 1 – Seed regions and overlapping seed-based and resting-state networks derived from a conventional SPM-approach. SBN = Seed-based network, RSN = Resting-state network, DMN = Default mode network, ECN = Executive control network, na = Not available

Results of comparison tau load per component between early and advanced Braak group

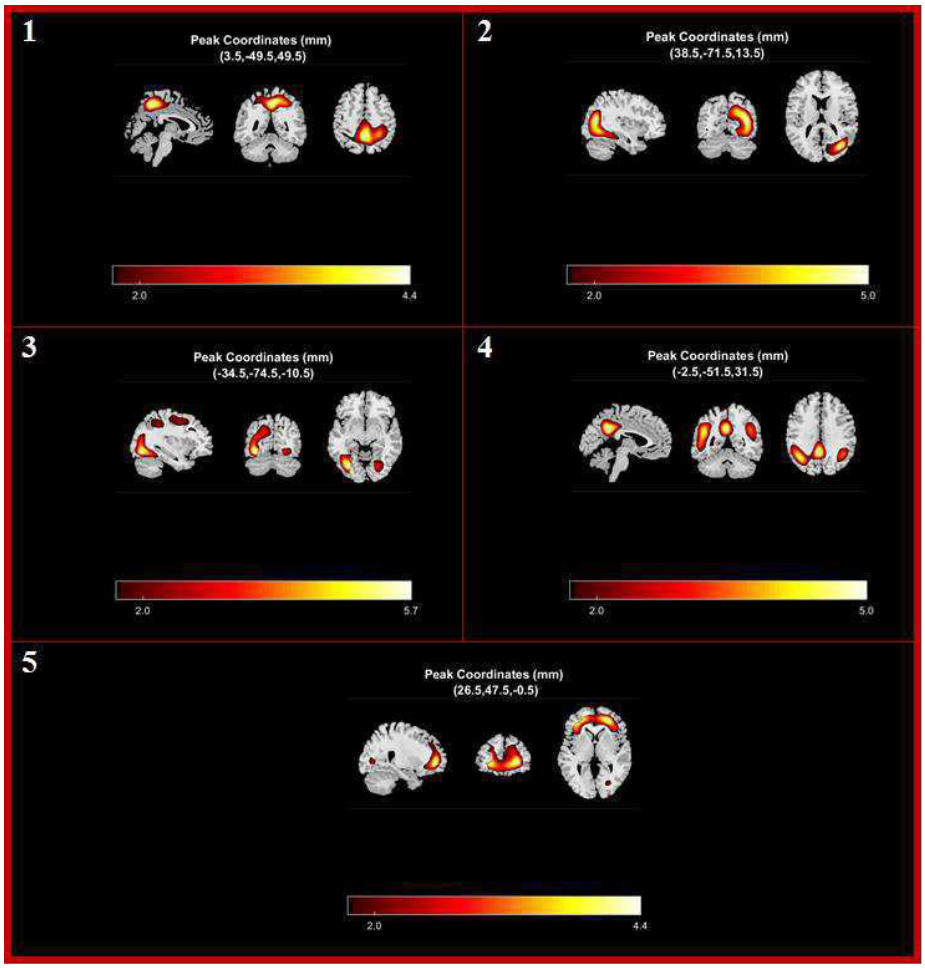
A significant difference between the two groups was observed for 8 components after correcting for multiple comparisons ($p^* = .005$). The table below provides the U-statistics of the comparisons. Significant differences are marked with an asterisk.

Component 1	$U = 5$, $p < .001$*
Component 2	$U = 3$, $p < .001$*
Component 3	$U = 21$, $p = .010$
Component 4	$U = 8$, $p = .001$*
Component 5	$U = 2$, $p < .001$*
Component 6	$U = 3$, $p < .001$*
Component 7	$U = 17$, $p = .005$
Component 8	$U = 5$, $p < .001$*
Component 9	$U = 2$, $p < .001$*
Component 10	$U = 13$, $p = .002$*

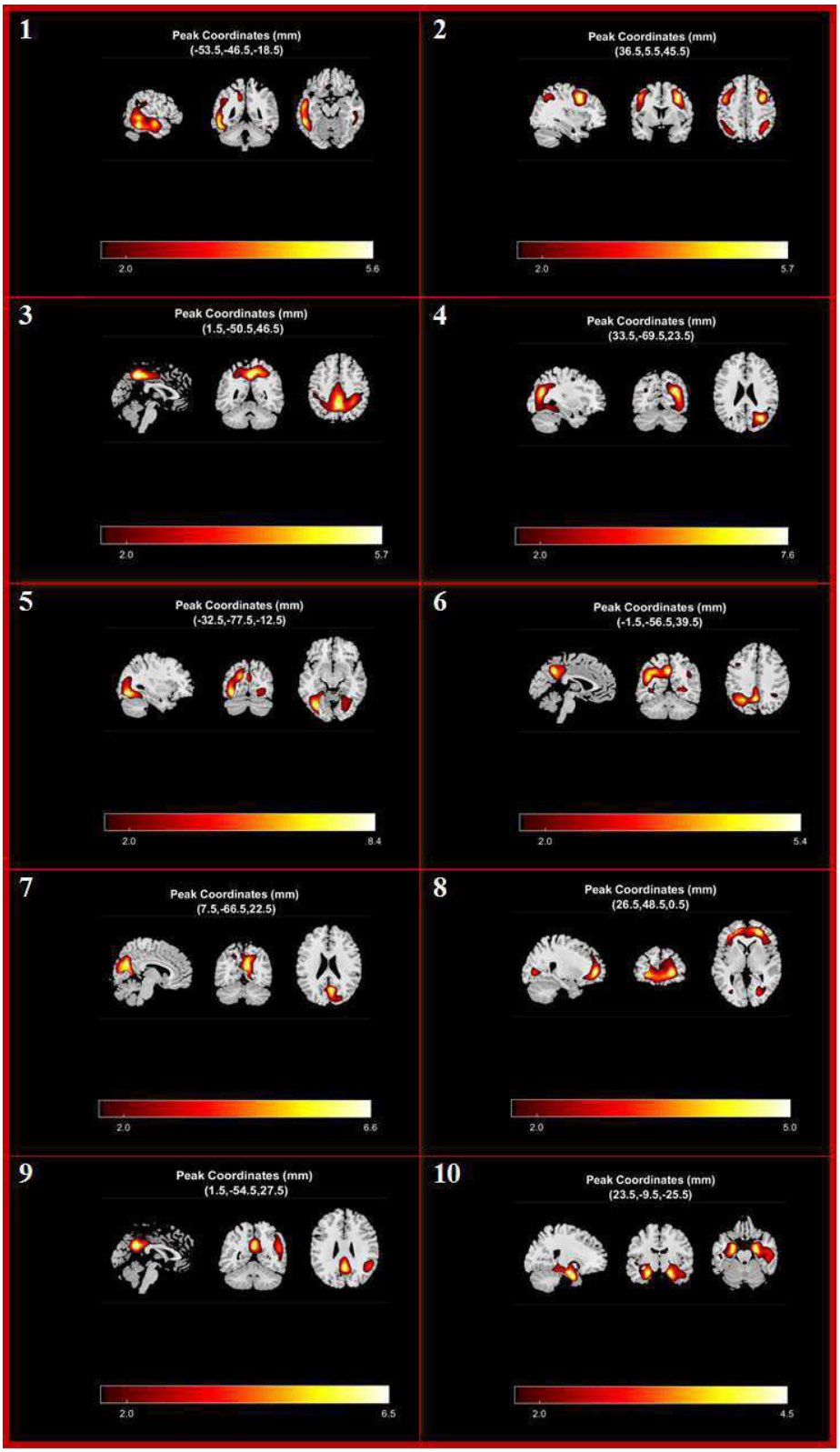
Supplementary Table 2 – Summary of the U-statistics based on the comparison between the early and advanced Braak group. Significant differences that survived multiple comparison correction are highlighted with an asterisk.



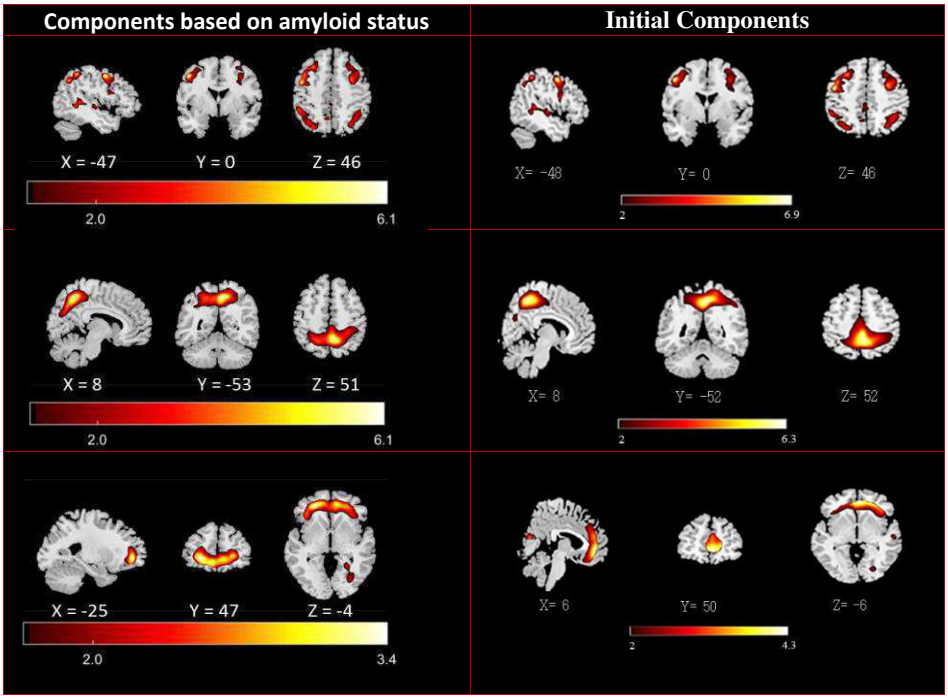
Supplementary Fig. 1 – Independent component analysis with the default setting of 20 allowed components. The peak coordinates, the brain projection, and the z-score range are depicted for each component.



Supplementary Fig. 2 – Independent component analysis with 5 allowed components. The peak coordinates, the brain projection, and the z-score range are depicted for each component.



Supplementary Fig. 3 – Independent component analysis using z-images smoothed with a FWHM kernel of 8mm instead of 12mm. The peak coordinates, the brain projection, and the z-score range are depicted for each component.



Supplementary Fig. 4 – Three exemplary independent components from the independent component analysis using z-images of patients with a positive amyloid PET scan. The peak coordinates, the brain projection, and the z-score range are depicted for each component.

Tau pathology and cognitive reserve in Alzheimer's disease

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Tau pathology and cognitive reserve in Alzheimer's disease

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Education

ABSTRACT

Cognitive reserve (CR) is defined as the ability to maintain functionality despite accumulating pathology. Education has been used as a proxy for CR. For example, by using positron emission tomography imaging, higher educated Alzheimer's disease (AD) patients presented increased amyloid β pathology than lower educated patients despite equal symptomatology. Whether similar associations exist for in vivo tau pathology remains elusive. We utilized [18F]AV-1451 positron emission tomography imaging to examine whether high-educated AD patients (n = 12) present more severe tau pathology compared with low-educated patients (n = 12) despite equal clinical severity in regions of interest corresponding to the pathologic disease stages defined by Braak & Braak. We report tau pathology in advanced Braak stages associated with parietal and frontal regions in high-educated AD patients, whereas in low-educated AD patients tau accumulation is still confined to lower Braak stages associated with temporal and cingulate regions. Highly educated AD patients seem to be able to tolerate more tau tangle pathology than lower educated patients with comparable cognitive impairment supporting the cognitive reserve hypothesis.

1. Introduction

Sporadic Alzheimer's disease (AD) is the most common cause of dementia with a world-wide prevalence of approximately 24 million people (Reitz and Mayeux, 2014). The neuropathologic hallmarks of AD are extracellular amyloid β (Aβ) plaque deposition and intracellular aggregation of misfolded tau proteins (neurofibrillary tangles). Based on the observed disparities between the extent of brain pathology and the individual clinical expression in patients with AD (Katzman et al., 1988), the theoretical construct of cognitive reserve (CR) has been introduced to explain this existing variance.

CR is defined as the ability to preserve functionality despite brain damage and/or accumulating pathology (Stern, 2002, 2006). So far, the precise neural implementations of CR-related mechanisms are still not completely understood. It has been suggested that CR may act through the recruitment of additional brain areas and/or through the more efficient use of pre-existing resources (Stern, 2002, 2016). Recently, it has further been argued that task-invariant neural networks may contribute to the CR-mediated maintenance of functioning despite increasing pathology and dysfunction of task-related networks (Stern, 2016). Several factors have been identified to be associated with greater CR such as parameters of individual's lifetime experiences including education, occupation as well as leisure activities (Stern, 2012). These factors possibly explain some heterogeneity in the clinical expression among patients with AD (Stern, 2012).

The degree of CR posits important implications for the time of diagnosis of AD as clinical symptoms may remain undetected for a longer period of time in AD patients with higher CR. Moreover, individuals with high levels of CR show a more rapid deterioration in cognitive function from the point of diagnosis compared with patients with lower CR (Andel et al., 2006; Stern et al., 1995). This accelerated decline is likely due to greater accumulation of pathologic burden already present by the time of diagnosis. Thus, these patients may have already progressed to more advanced Braak neuropathologic stages leading to severe neurodegeneration, which can no longer be counteracted via compensatory strategies by the time of diagnosis. Indeed, it was shown in a histopathologic study that higher levels of education were related to better cognitive function when AD neuropathology was still absent or mild, whereas the positive effect of education on cognition was

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attenuated when a person presented advanced neuropathology (Koepsell et al., 2008). Interestingly, recent positron emission tomography (PET) studies using the [^{18}F]AV-1451 tracer for the visualization of tau pathology indicated that the spreading pattern of tau pathology measured in vivo corresponded with the established neuropathologic stages of tangle deposition as described by Braak and Braak (1995) potentially allowing staging of the disease using this tracer (Cho et al., 2016; Schöll et al., 2016; Schwarz et al., 2016).

In the past decade, PET has provided valuable insights into the association between CR, cognitive function, and the extent of AD pathology. Higher educated AD patients demonstrated better cognitive function in the presence of similar levels of Aβ pathology in comparison to lower educated patients (Roe et al., 2008). Furthermore, focusing on prodromal (Morbelli et al., 2013) or probable AD stages (Kemppainen et al., 2008), patients with high CR showed greater Aβ burden and significantly more pronounced hypometabolism when compared with lower educated patients with similar clinical symptoms. These observations gave rise to the hypothesis that higher educated people might be able to use reserve mechanisms to compensate for the functional impairment resulting from the structural damage due to the AD-related brain pathology.

In addition to Aβ deposition, AD is characterized by the aggregation of pathologically misfolded tau proteins. Recent studies demonstrated that the degree of cognitive impairment or neural dysfunction was more closely correlated with the extent of tau pathology than the distribution of Aβ plaque deposition (Bischof et al., 2016; Brier et al., 2016; Nelson et al., 2012; Ossenkoppele et al., 2016). Whether this association is modulated by CR remains elusive. Just recently, first indications have been collected, suggesting that the negative association between tau pathology and cognitive function measured in vivo may be stronger in individuals with lower CR than in individuals with higher CR (Rentz et al., 2016). Based on these results, the authors proposed that AD patients with high CR might be able to preserve better cognitive function even when tau pathology has started to spread to neocortical areas. This assumption may require further substantiation, given that the examined study cohort included 133 clinically normal patients, 17 patients with mild cognitive impairment, and only 6 AD patients. Moreover, tau pathology was solely assessed in the inferior temporal region limiting the interpretation of these results regarding the effects of CR on the association between the global cortical spread of tau pathology and co-occurring cognitive decline.

Given the current body of evidence indicating that AD patients with high CR are able to cope better with increased brain pathology, we aimed to assess whether higher educated AD patients showed greater tau pathology burden and whether they had already progressed to more advanced Braak stages in comparison to lower educated AD patients with similar clinical expression. For that purpose, we analyzed tau pathology in different regions of interest (ROIs) representing a respective Braak stage in a sample of AD patients from whom we obtained [^{18}F]AV-1451 PET scans. Referring to the CR hypothesis, we anticipated that at comparable levels of cognitive impairment, patients with higher levels of educational attainment would demonstrate more severe tau burden as well as a more advanced distribution of tau pathology than patients with lower educational attainment.

2. Methods and materials

2.1. Participants

We included data from 14 healthy older adults and 24 patients with typical AD, who were diagnosed with probable AD dementia using the recommended NIA-AA guidelines (McKhann et al., 2011) and based on the results of the diagnostic PET imaging or CSF liquor measurements. All participants underwent a [^{18}F]AV-1451 PET scan for the in vivo assessment of tau pathology. The [^{18}F]AV-1451 PET scans of 17 AD patients were acquired in the Nuclear Medicine Department of the University Hospital Cologne. The remaining 21 scans of the 14 healthy controls and the 7 AD patients were collected on 3 sites as part of the multicenter trial investigating the clinical application of [^{18}F]AV-1451 conducted by AVID Radiopharmaceuticals, Inc, Philadelphia (NCT 02016560). Key inclusion criteria for the patient sample were: (1) diagnosis of probable typical AD according to the NIA-AA criteria; (2) age range: $>55 \leq 80$; (3) Mini Mental State Examination (MMSE) score ≥ 20; (4) evaluable [^{18}F]AV-1451 scan; and (5) self-report on educational attainment. The study was approved by the local ethic committees at the respective sites. All participants signed informed consent regarding the scientific evaluation and publication of their data.

2.2. Educational attainment and cognitive function

Educational attainment was defined as the sum of schooling and the following professional education in years (e.g., years of vocational or university training). The AD patients were grouped according to their level of educational attainment into a high-educated AD (HEAD) group and a low-educated AD (LEAD) group using a median split ($Mdn = 15.50$ years). The group of healthy controls consisted of 7 high-educated and 7 low-educated participants again based on a median split ($Mdn = 15$ years). Global cognitive function was assessed by the MMSE, which had been recorded during the clinical visit within 3 months before the scanning procedure (Folstein et al., 1975).

2.3. Positron emission tomography

The PET scans were acquired on a PET/CT Siemens Biograph mCT Flow 128 Edge (Siemens, Knoxville, TN, USA), a Siemens Biograph 64 PET/CT (Siemens, Erlangen, Germany), a Siemens HR+ (Siemens, Erlangen, Germany), and a GE Discovery PET/CT 600 (GE Healthcare, Milwaukee, WI, USA). PET scans collected on the Siemens Biograph mCT Flow 128 Edge ($n = 17$) were acquired in list mode for 15 minutes after an intravenous injection with a mean dose of 225 MBq of [^{18}F]AV-1451 and a rest period of 90 minutes. PET scans collected on the Siemens Biograph 64 ($n = 16$), the HR+ ($n = 3$), and the GE Discovery PET/CT 600 ($n = 2$) were acquired as 4×5 minute frames for 20 minutes after 90 minutes after injection of a mean dose of 384 MBq [^{18}F]AV-1451.

2.4. Data processing

All [^{18}F]AV-1451 PET scans were preprocessed using statistical parametric mapping (SPM), version 8 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology at University College London, London, UK). The images were spatially normalized to a tau template in Montréal Neurological Institute (MNI) space and smoothed with a Gaussian filter of 5 mm FWHM. The tau template was previously established by our group based on a dataset of [^{18}F]AV-1451 PET scans from 19 healthy controls ($M(age) = 56.63 \pm 16.66$ years) provided by AVID Radiopharmaceuticals (Hammes et al., 2016). Normalization of the individual [^{18F}]AV-1451 scans to this template resulted in successful preprocessing of the scans. Standard uptake value ratios (SUVRs) were calculated employing in-house scripts in MATLAB R2016a (The MathWorks, Inc, Natick, MA, USA) using the cerebellum as reference region. The cerebellum is a preferable reference region for tau-PET given that previous studies have shown that cerebellar regions are relatively spared of tau pathology

in AD (Braak and Braak, 1991; Marquie et al., 2015). The individual SUVR images were then submitted to further analyses.

2.5. Statistical analysis

2.5.1. Region of interest analysis for in vivo Braak staging

To assess whether HEAD patients had already advanced to higher Braak neuropathologic stages compared with LEAD patients with a comparable level of cognitive function, we conducted an ROI analysis by extracting mean SUVRs for ROIs representing different Braak stages. The set of ROIs (Table 1) was adapted from Schoell et al. (2016). Data from these ROIs were extracted using the automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002). Mean SUVRs for each ROI belonging to one respective Braak stage were averaged and submitted to the analysis. Proof of tau pathology within the ROIs belonging to one Braak stage was considered to represent the progression to the respective Braak stadium. A multivariate analysis of variance including age as a covariate was conducted looking at the main effect of group on tau pathology load at different Braak stages. Next, post hoc pairwise comparisons of the mean SUVR of the respective Braak stages between the 3 groups were carried out using SPSS, version 21 for Windows (SPSS Inc, Chicago, IL, USA). For the post hoc comparison between the AD groups with the healthy control group, respectively, we included age as a covariate, whereas for the post hoc comparison between the 2 AD groups we included age and MMSE as covariates. Multiple comparisons were corrected using the Sidak method (Šidák, 1967).

2.5.2. Voxel-wise whole brain analysis

To examine regions that were distinctly different between the AD groups and to assure that regional differences in tau pathology load were not masked out by the ROI analysis, we further conducted voxel-wise *t*-test comparisons between the 2 AD groups using SPM8 including age and MMSE score as covariates. Moreover, to investigate the spatial pattern of tau pathology in both AD groups, we compared the LEAD and the HEAD groups against the healthy control group, respectively, including age as a covariate. The voxel-based contrasts were set to investigate in which regions HEAD showed greater tau pathology than LEAD as well as in which regions AD groups presented greater tau burden compared with healthy controls, respectively. Reverse contrasts were performed to control for possible inverse relationships. For all comparisons, a binary grey matter mask was used as an explicit mask to reduce the number of voxel-wise comparisons to grey matter areas. The significance levels for the conducted comparisons were set to $p \leq 0.001$ (uncorrected). To rule out that the observed effects might have been influenced by different scanner types, we conducted a confirmatory analysis, comparing the scans of the HEAD (6 patients) and LEAD (11 patients) groups which had exclusively been scanned on the PET-CT Siemens Biograph mCT Flow 128 Edge against the healthy control group, respectively.

Table 1
Braak regions of interest

Braak stage	AAL ROIs
I/II	Hippocampus
III	Parahippocampal gyrus; fusiform gyrus; lingual gyrus; amygdala
IV	Inferior temporal cortex; middle temporal cortex; temporal pole; thalamus; posterior cingulate; insula
V	Frontal cortex; parietal cortex; occipital cortex; superior temporal cortex; precuneus; caudate nucleus; putamen
VI	Precentral gyrus; postcentral gyrus; paracentral gyrus; cuneus

The ROIs of each Braak stage used for the ROI analysis are summarized. Regions were adapted from Schoell et al. (2016) and extracted from the automated anatomical labeling atlas.
Key: AAL, automated anatomical labeling atlas; ROI, region of interest.

3. Results

3.1. Demographics of the groups

In total, scans of 24 AD patients and 14 scans of healthy controls were used for analysis. The demographics of the 3 groups are summarized in Table 2. No significant difference in the degree of global cognitive function as assessed with the MMSE was observed between the 2 AD groups. The 3 groups did not significantly differ in age, although the healthy control group was on average slightly younger.

3.2. Regional differences in tau load between high- and low-educated AD patients

The ROI analysis revealed that HEAD patients already presented tau pathology in regions, which were associated with Braak stages V and VI, whereas LEAD showed increased tau pathology still confined to regions associated with stages III and IV when compared with healthy controls. No significant differences were observed between groups for Braak stages I/II. The ANOVA corrected for age yielded a significant main effect of group on tau pathology load in Braak stages III ($F[2,34] = 7.229$, $p = 0.002$), IV ($F[2,34] = 7.665$, $p = 0.002$), V ($F[2,34] = 9.362$, $p = 0.001$), and VI ($F[2,34] = 12.352$, $p < 0.001$). No significant main effect of group on tau pathology load was observed for Braak stages I/II ($p = 0.411$). The post hoc comparison between the HEAD and LEAD group corrected for age and MMSE resulted in significantly higher tau pathology load in the HEAD group for stage V ($F[1,20] = 13.285$, $p = 0.002$) and VI ($F[1,20] = 19.302$, $p < 0.001$). The remaining regions did not significantly differ between groups. The post hoc tests between the LEAD and healthy control group corrected for age revealed significant differences for Braak stages III ($F[1,23] = 19.062$, $p < 0.001$) and IV ($F[1,23] = 6.800$, $p = 0.016$), whereas the remaining Braak stages I/II, V, and VI did not significantly differ between the 2 groups. Comparing the HEAD group against the healthy controls correcting for age yielded significant differences for Braak stages III ($F[1,23] = 8.443$, $p = 0.008$), IV ($F[1,23] = 11.170$, $p = 0.003$), V ($F[1,23] = 10.972$, $p = 0.003$), and VI ($F[1,23] = 12.221$, $p = 0.002$), but not for Braak stages I/II. A summary of the *F*-statistics can be found in the Supplementary Data (Table S1). The mean SUVRs of the respective Braak stages for each group are depicted in Fig. 1.

3.3. Effect of education on tau pathology burden in high- and low-educated AD patients

The voxel-wise comparison between HEAD and LEAD patients yielded significantly increased tau pathology burden in parietal and frontal regions in HEAD patients when compared with the LEAD cohort (Fig. 2) confirming the results of the ROI analysis. Furthermore, the voxel-wise comparisons of the 2 AD groups against the healthy control group, respectively, revealed different spatial patterns of tau pathology for the high- and low-educated groups (Fig. 3). The HEAD group showed increased tau burden in temporal, parietal, and frontal regions, whereas tau pathology in the LEAD group was confined to temporal and partly to inferior parietal regions when compared to the healthy control sample. The reverse contrasts comparing the healthy group against the AD groups and the LEAD against the HEAD group did not reveal significant differences. The peak activations and MNI coordinates of the voxel-wise comparisons are summarized in the Supplementary Data (Table S2).

Table 2
Group characteristics

Characteristic	HC group (n = 14)	LEAD group (n = 12)	HEAD group (n = 12)	Group differences (*p* values)		
				HC versus LEAD	HC versus HEAD	LEAD versus HEAD
Age	62.86 ± 11.57	68.08 ± 6.91	69.33 ± 6.08	*n.s*	*n.s*	*n.s*
Sex (M/F)	6/8	7/5	9/3	*n.s*	*n.s*	*n.s*
Education	14.71 ± 2.43	12.00 ± 1.76	17.33 ± 0.99	$p < 0.001$	$p < 0.001$	$p < 0.001$
MMSE	29.50 ± 0.52	25.50 ± 3.43	25.42 ± 3.15	$p < 0.001$	$p < 0.001$	*n.s.*

The demographic characteristics of the studied groups are depicted including the average age in years, sex distribution, years of education, and cognitive function as assessed by the MMSE. Statistical differences between groups are highlighted in the last column.
Key: F, female; HC, healthy control; HEAD, high-educated AD; LEAD, low-educated AD; M, male; MMSE, Mini Mental State Examination; n.s., not significant.

In the confirmatory analysis in the sample exclusively scanned on one identical scanner, we obtained very similar results (Supplementary Data, Fig. S3).

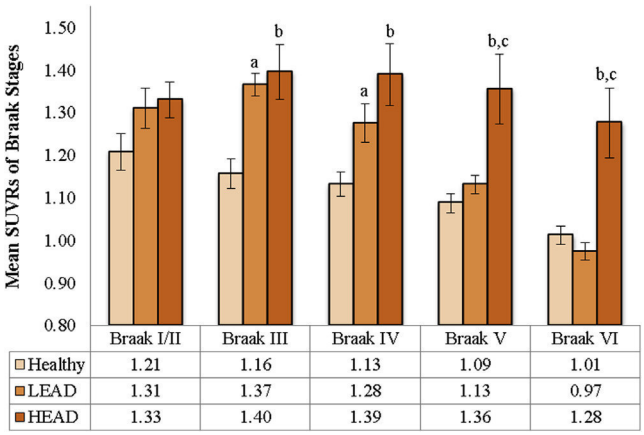
4. Discussion

This study demonstrated that tau pathology is more advanced in HEAD than in LEAD patients with comparable level of cognitive impairment. The ROI analysis revealed that HEAD patients presented tau pathology in regions, which are associated with Braak stages V and VI, whereas the LEAD group demonstrated increased tau pathology in regions still confined to stages III and IV when compared to healthy controls. Interestingly, no significant difference in tau pathology load in mediotemporal regions, associated with Braak stages I/II, were observed between the 3 groups. All of these results were further confirmed by a voxel-based whole brain analysis, which revealed that HEAD patients show a different spatial tau pattern compared with LEAD patients. In particular, HEAD patients demonstrated increased tau pathology load in parietal and frontal areas when compared with LEAD patients. Importantly HEAD and LEAD patients did not significantly differ in age and their global cognitive function.

4.1. Role of education on reserve capacity

Our results from the ROI and voxel-based analyses showed that the accumulation of tau pathology measured in vivo differs given the level of educational attainment as HEAD patients show more advanced tau pathology burden compared with LEAD patients with equal cognitive impairment. Thus, the relation between tau burden and symptomatic appearance in AD patients seems to be mitigated by CR-mechanisms acquired through factors such as education. These results are in line with the observation that the effects of other biomarkers of AD on cognitive function, such as the amount of Aβ burden or hypometabolism, are influenced by the level of education (Ewers et al., 2013; Kemppainen et al., 2008; Morbelli et al., 2013). Histopathologic studies revealed that higher levels of education were associated with better cognitive functioning, independent of the level of AD-related brain pathology (Bennett et al., 2003, 2005). In vivo PET studies investigating CR-related changes reported that higher levels of education were related to greater Aβ plaque deposition in frontal areas (Kemppainen et al., 2008), and a significant lower glucose metabolism rate (Ewers et al., 2013; Kemppainen et al., 2008; Morbelli et al., 2013) and greater depletion of blood flow in temporoparietal areas (Stern et al., 1992) compared with lower levels of education.

Given the provided body of evidence, it appears that education does not decelerate the accumulation of pathology, but may serve to alter the clinical expression of the underlying pathology by slowing down the progressive cognitive decline caused by the neurotoxic effects of pathology such as tau pathology. Education is a factor occurring early in life, when the brain is still developing and considered most plastic. It is widely accepted that early lifetime factors can have profound impact on a person's health status later in life. Indeed, evidence provided recently showed that early life factors such as general cognitive ability and parental education positively influenced age-related structural brain trajectories and cognition late in life (Walhovd et al., 2016). Aside from these early factors, higher education has consistently been associated with healthier lifestyles, less chronic stress, better socioeconomic status, lifelong mental stimulation and lower exposure to toxic factors. These variables may all subserve reserve capacities throughout life, which likely protect against the harming effects of age-related pathology (Adler et al., 2013; Fritsch et al., 2007; Kiecolt-Glaser et al., 2011; Springer et al., 2005).



	Braak I/II	Braak III	Braak IV	Braak V	Braak VI
Healthy	1.21	1.16	1.13	1.09	1.01
LEAD	1.31	1.37	1.28	1.13	0.97
HEAD	1.33	1.40	1.39	1.36	1.28

Fig. 1. Tau pathology load in different Braak stages. The mean SUVRs and the standard error across the respective ROIs for each Braak stage are depicted for the healthy control, the low-educated AD group, and the high-educated AD group. Significant differences ($p < 0.05$) between the groups, which survived the multiple comparison correction, are highlighted. Abbreviations: a, significant difference healthy controls versus low-educated AD group; b, significant difference healthy control versus high-educated AD group; c, significant difference between low-educated versus high-educated AD group; HEAD, high-educated AD patients; LEAD, low-educated AD patients; ROI, region of interest; SUVR, standard uptake value ratio.

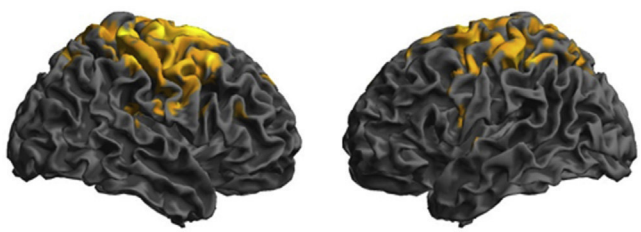


Fig. 2. HEAD versus LEAD. Voxel-wise comparison of tau pathology load between high-educated and low-educated AD patients corrected for age and MMSE score using statistical parametric mapping. Significance level was set to $p < 0.001$ (uncorrected). Abbreviations: HEAD, high-educated AD patients; LEAD, low-educated AD patients.

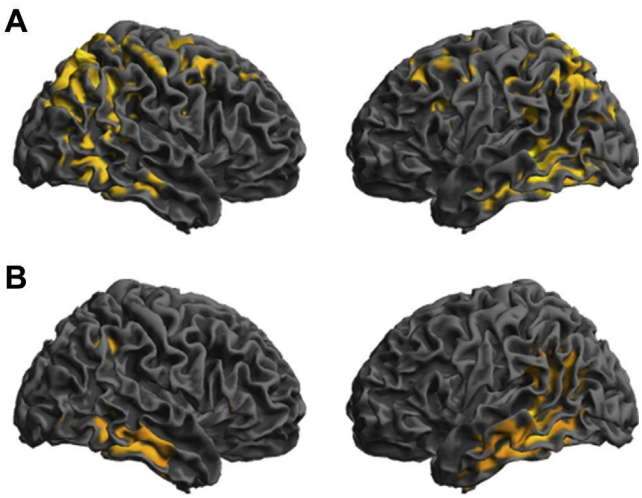


Fig. 3. Spatial patterns of tau pathology in HEAD and LEAD. Voxel-wise comparison of tau pathology load between (A) high-educated AD patients versus healthy controls and (B) low-educated AD patients versus healthy controls corrected for age using statistical parametric mapping. Significance level was set to $p < 0.001$ (uncorrected). Abbreviations: HEAD, high-educated AD patients; LEAD, low-educated AD patients.

Based on the current knowledge, it appears that early lifetime variables such as education contribute to late-life brain function. Education being associated with other lifetime factors may act on CR-related compensatory mechanisms, which render some individuals more resilient to the consequences of accumulating pathology than others, and in the current study more resistant toward the effects of accumulating tau pathology in the brain. Given that education is a relative term constantly shifting upward, it will be particularly important to develop tests with higher ceilings allowing detection of individuals with high levels of CR in clinical routine (Stern, 2012). Moreover, it will be crucial to determine whether other CR proxies such as lifelong cognitive and social engagement are more sensitive than the level of education in regard to CR-related changes.

4.2. Level of education and tau pathology load in Braak stages

Although both patient groups of this study were characterized by similar global cognitive function, the HEAD group showed a wider distributed tau pathology burden, which corresponded to advanced Braak stages (V and VI), reflecting the expansion of tau pathology to parietal and frontal regions. In contrast, the tau pathology load of the LEAD group only complied with moderately advanced Braak stages (III and IV), still largely restricted to temporal areas and the posterior cingulate cortex. These findings comply with the assumption by Rentz et al. (2016), mentioned earlier, presuming that CR exerts mitigating effects on cognition even when tau pathology has advanced to isocortical regions.

Several explanations for CR-related mechanisms have been put forward such as CR might act via increases in functional connectivity, via the recruitment of additional brain areas or via improved physiological properties such as increased dendrite density or enhanced vascular coupling (Soldan et al., 2015). Magnetic resonance imaging studies have reported increased functional connectivity, in particular, in the default mode network (Bozzali et al., 2015; Sole-Padulles et al., 2009) and CR-related changes in structural connectivity (Wook Yoo et al., 2015) in highly educated AD patients. Regarding CR-related mechanisms on physiological properties, higher CR levels were associated with enhanced acetylcholine esterase activity in hippocampal and cingulate areas (Garibotto et al., 2013) and elevated glucose metabolism rate in frontal areas (Morbelli et al., 2013). Overall, these changes on the functional, structural, and molecular levels are presumed to allow compensation for the aggregating pathologic burden, such as, for example, for accumulating tau pathology in temporal, parietal, and frontal areas as observed in this study.

Interestingly, when comparing the 3 groups regarding tau pathology load in regions, which were associated with Braak stages I/II, we did not observe any significant differences. Also in the voxel-wise comparison hippocampal areas remained spared of any group-related differences. These observations may be explained by the initial occurrence of tau pathology in medial temporal lobe regions in AD and the notion of primary age-related tauopathy (PART). PART is based on the findings from several postmortem studies demonstrating aggregation of tau pathology in medial temporal lobe regions in the absence of Aβ pathology in people, who were cognitively normal or only slightly cognitively impaired before death (Crary et al., 2014; Iseki et al., 2002). This process was recognized as part of the normal aging process given that PART was generally detectable at autopsy in elderly individuals. Also in this study, we observed slightly elevated levels of tracer retention in hippocampal regions in the healthy control group as compared with the retention rates of this group in other brain regions associated with more advanced Braak stages. Interestingly, the retention rates of the AD groups in this area did not significantly differ from the healthy group, but nonetheless were marginally higher. These findings suggest that tau pathology in hippocampal regions may be less disease specific and may occur as part of the aging process, whereas tau pathology in regions associated with Braak stages III–VI is related with AD (Crary et al., 2014). However, we cannot exclude that some of the healthy controls already presented an early form of AD possibly driving the observed increase of tau pathology in hippocampal regions. Recently, it has been suggested that the accumulation of tau in the absence of Aβ might present an early phase of AD (Duyckaerts et al., 2015). Moreover, it was argued that the current body of evidence is not sufficient to conclude that PART and AD are driven by different processes prompting for further investigation (Duyckaerts et al., 2015).

Assessing tau pathology at different Braak stages showed that HEAD patients can maintain their cognitive functioning despite a more extensively distributed pathologic burden compared with LEAD patients. These CR-related differences in disease manifestation have crucial implications for early detection of AD, prognosis of the disease progression, and the assessment of drug treatments. For example, the individual degree of CR might particularly be considered when assessing the efficacy of anti-tau–based pharmacotherapies. First of all, the response to these drugs could differ by the extent of underlying pathology. Second, groups which are not matched according to their level of CR may show different rates of cognitive decline that are actually not caused by the drug but by the level of CR as individuals with high CR tend to decline more rapidly after the initial diagnosis. Future longitudinal studies are, therefore, warranted to further investigate the mitigating effects of CR on the functional and structural levels in regard to accumulating AD-related pathology.

4.3. Limitations

Certain limitations need to be considered when interpreting the presented results of our study. In this study, the PET scans were acquired on different scanners. Although this inconsistency has likely introduced some noise to the data, all scans were successfully preprocessed and spatially normalized to a common template. Furthermore, the observed results did hold up, when re-assessed in a confirmatory analysis in a sample of subjects exclusively scanned

on one specific scanner. Moreover, the relative small sample size of the groups limits the interpretation of the findings in regard to the general population. In addition, although not significant, the healthy control group was slightly younger than the AD groups. Furthermore, with regard to the clinical level of impairment we only had access to MMSE data of all patients. Although MMSE is one of the most widely used assessments, a broad neuropsychological test battery would have allowed us a more detailed and accurate description of cognitive function. For future studies, it will be of interest to examine to what extent education and other proxies of CR moderate the deleterious effect of tau pathology on cognition.

5. Conclusion

In sum, AD patients with higher levels of educational attainment demonstrate more extensive tau burden than lower educated patients with equal cognitive function as measured with the MMSE. This corresponds well to previous studies investigating the concept of CR with regard to AD-related pathology. These findings may have important implications for the clinical diagnosis which may be delayed in individuals with high CR as compared with individuals with lower CR. Better understanding of CR-related mechanisms on the clinical expression of AD may improve the clinical diagnosis and prognosis regarding the disease and additionally promote the investigation of protective treatment strategies. Given the findings of this study, further investigations need to elucidate the role of CR and tau pathology in regard to cognitive function. Multimodal imaging approaches may thereby shed light into underlying mechanisms that render some individuals more resilient to disease-related changes than others.

Disclosure statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2017.05.004.

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Supplementary Data

Table S1 – *F*-Statistics for comparison of tau pathology in Braak Stages

Braak stages	HEAD vs LEAD	LEAD vs Healthy	HEAD vs Healthy
I/II	F(1,20)=.063, p=.805	F(1,23)=.918, p=.348	F(1,23)=1.633, p=.214
III	F(1,20)=.388, p=.540	F(1,23)=19.062, **p<.001**	F(1,23)=8.443, **p=.008**
IV	F(1,20)=4.310, p=.051	F(1,23)=6.800, **p=.016**	F(1,23)=11.170, **p=.003**
V	F(1,20)=13.285, **p=.002**	F(1,23)=1.177, p=.289	F(1,23)=10.972, **p=.003**
VI	F(1,20)=19.302, **p<.001**	F(1,23)=1.632, p=.214	F(1,23)=12.221, **p=.002**

Table S1 depicts the F-statistics for the comparison of the mean SUVRs in the six Braak stages between the high educated and low educated AD group corrected for age and MMSE score, and the comparison of the low educated and high educated AD groups with the healthy control group corrected for age, respectively ($p < .05$). HEAD = High Educated AD Patients, LEAD=Low Educated AD Patients; SUVR = Standard Uptake Value Ratio.

Table S2 – Peak activation of voxel-wise comparisons

HEAD > LEAD				
Region	t-value	x-coordinate	y-coordinate	z-coordinate
Left and Right Postcentral Gyrus/Right Supplementary Motor Area	5.29	32	-36	64
	5.83	-52	-2	50
	5.73	10	10	68
Right Superior Frontal Gyrus	4.98	12	46	44
Right Inferior Frontal Gyrus	4.56	48	30	18
Left Postcentral Gyrus	4.31	-52	-4	16
Left Supplementary Motor Area	4.22	-10	18	62
Right Angular Gyrus	4.07	36	-66	50
Left Inferior Parietal	3.87	-30	-72	46
	3.77	-36	-66	50
LEAD > Healthy				
Left Fusiform Gyrus & Left Parahippocampal Gyrus	6.27	-34	-20	-26
	6.16	-30	-4	-34
	6.11	-28	-24	22
Right Fusiform Gyrus & Right Inferior Temporal	5.75	30	-2	-36
	4.85	46	-40	-18
	4.72	38	-14	-32
Right inferior parietal, Right Middle Occipital & Right Supramarginal Gyrus	5.24	36	-48	40
	3.97	30	-60	38
	3.66	50	-40	34
Middle Cingulate	4.66	-2	-30	36
Right Cuneus	4.33	20	-72	22
	4.25	24	-62	24
Left Middle Frontal	4.11	-26	22	44
Left Precuneus	3.96	-10	-58	38
HEAD > Healthy				
Right Middle Occipital, Left Middle Cingulate & Left Cuneus	5.11	30	-64	34
	5.00	-6	-22	-38
	4.93	-18	-58	20
Right Precentral Gyrus & Right Supplementary Motor Area	4.41	26	-14	58
	4.39	10	-4	56
	4.27	26	-8	48
Left Middle Frontal Gyrus	4.31	-28	10	50
	4.31	-26	20	44
	4.01	-34	32	44
Left Inferior Frontal Gyrus	4.16	-36	12	26
Left Middle Frontal Gyrus/ Left Supplementary Motor Area	4.12	-12	-4	66
	4.00	-26	-10	48
	3.95	-10	-4	58
Left Inferior Parietal	4.04	-58	-30	46
Left Precentral	4.01	-48	0	52

Table S2 summarizes the t-statistics and MNI coordinates for voxel clusters with an extent threshold k=50 for the contrasts investigating in which regions high educated AD patients show more tau pathology than low educated AD patients and in which regions low educated AD and high educated AD patients present more tau pathology than healthy controls, respectively. HEAD = High Educated AD Patients, LEAD=Low Educated AD Patients.

Figure S3 – Exclusion of systematic error due to scanner differences

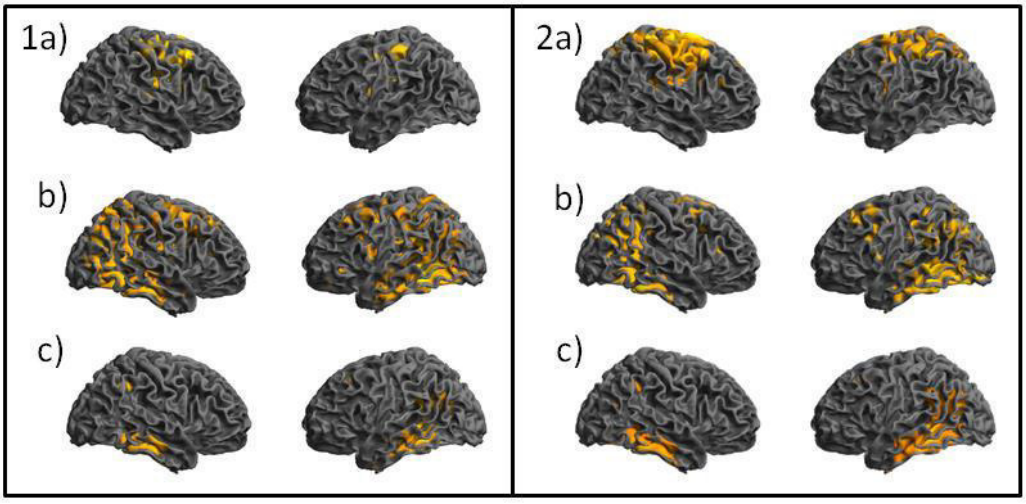

Figure S3 illustrates the results of the voxel-wise comparisons of tau pathology load between (1a-c) the AD groups only scanned on the Siemens Biograph mCT Flow 128 Edge (HEAD=6 patients; LEAD= 11 patients) against the healthy control group and (2a-c) the comparison of the AD groups including scans from the nuclear medicine department of the University Hospital Cologne and AVID Radiopharmaceuticals against healthy controls. a) HEAD vs LEAD, b) HEAD vs healthy control group, c) LEAD vs healthy control group. The p-value was set to p<.001 (uncorrected). Age and MMSE score were included as covariates for comparison a) and age was included as covariate for comparison b&c). HEAD = High Educated AD Patients, LEAD=Low Educated AD Patients.

Level of education mitigates the impact of tau pathology on neuronal function

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ORIGINAL ARTICLE

Level of education mitigates the impact of tau pathology on neuronal function

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Abstract

Purpose Using PET imaging in a group of patients with Alzheimer's disease (AD), we investigated whether level of education, a proxy for resilience, mitigates the harmful impact of tau pathology on neuronal function.

Methods We included 38 patients with mild-to-moderate AD (mean age 67 ± 7 years, mean MMSE score 24 ± 4, mean years of education 14 ± 4; 20 men, 18 women) in whom a [^{18}F]AV-1451 scan (a measure of tau pathology) and an [^{18}F]FDG scan (a measure of neuronal function) were available. The preprocessed PET scans were *z*-transformed using templates for [^{18}F]AV-1451 and [^{18}F]FDG from healthy controls, and subsequently thresholded at a *z*-score of ≥3.0, representing an one-tailed *p* value of 0.001. Next, three volumes were computed in each patient: the tau-specific volume (tau pathology without neuronal dysfunction), the FDG-specific volume (neuronal dysfunction without tau pathology), and the overlap volume (tau pathology and neuronal dysfunction). Mean *z*-scores and volumes were extracted and used as dependent variables in regression analysis with years of education as predictor, and age and MMSE score as covariates.

Results Years of education were positively associated with tau-specific volume ($\beta = 0.362$, $p = 0.022$), suggesting a lower impact of tau pathology on neuronal function in patients with higher levels of education. Concomitantly, level of education was positively related to tau burden in the overlap volume ($\beta = 0.303$, $p = 0.036$) implying that with higher levels of education more tau pathology is necessary to induce neuronal dysfunction.

Conclusion In patients with higher levels of education, tau pathology is less paralleled by regional and remote neuronal dysfunction. The data suggest that early life-time factors such as level of education support resilience mechanisms, which ameliorate AD-related effects later in life.

Keywords Glucose metabolism · Brain reserve · Brain maintenance · Resilience · [^{18}F]AV-1451 · [^{18}F]FDG

Introduction

The neuropathological hallmarks of Alzheimer's disease (AD), beta-amyloid (Aβ) plaques and neurofibrillary tangles, appear to evolve in temporal order with Aβ becoming abnormal first, followed by tau pathology and subsequently neuronal injury [1]. During these pathophysiological processes, tau pathology, in contrast to Aβ pathology, is more closely associated with neuronal dysfunction [2, 3] and symptom severity [4, 5] in individuals with typical AD and variants of AD such as posterior cortical atrophy, the logopenic variant and the behavioural variant [2, 6, 7].

While the direct relationship between tau pathology and neuronal injury in space and time is now better understood, substantial heterogeneity in clinical severity in individuals with comparable degrees of pathology remains a puzzling feature. To accommodate this heterogeneity, resilience-related concepts such as cognitive reserve, brain reserve (BR) and brain maintenance (BM) have been introduced,

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and have been suggested to weaken the relationship between AD-related pathophysiology and symptom severity. Cognitive reserve refers to the adaptability of cognitive processes to maintain functionality and BR accounts for differences in brain integrity [8, 9]. In turn, the concept of BM is associated with neuroprotective mechanisms supporting the preservation of brain integrity [10, 11].

Consistent with these concepts, we recently showed that patients with typical AD with higher levels of education are able to tolerate more severe and spatially extended tau pathology than AD patients with lower levels of education but similar cognitive impairment [12]. One possible explanation for this finding is that the impact of tau pathology on neuronal function is less harmful in patients with higher levels of education due to mechanisms associated with BR and BM. These mechanisms potentially support resilience to brain pathology [13] by, for example, boosting neuronal plasticity through the upregulation of neuronal growth factors.

To investigate these possibilities, we used a novel volume-based PET imaging approach to assess whether a resilience-related proxy, namely education, affects the association between tau pathology (i.e. [^{18}F]AV-1451 PET) and neuronal dysfunction (i.e. [^{18}F]FDG PET) in patients with typical AD and variants of AD. In each patient, we extracted three distinct volumes: (1) the tau-specific volume (all regions showing only significant tau pathology in the absence of neuronal dysfunction); (2) the FDG-specific volume (all regions showing significant neuronal dysfunction in the absence of tau pathology); and (3) the overlap volume (all regions showing significant tau pathology load and neuronal dysfunction). Assuming that level of education mitigates the effects of tau pathology on glucose metabolism, we hypothesized the following: (1) the tau-specific volume is larger despite relative preservation of regional glucose metabolism in individuals with higher levels of education; (2) the mean tau pathology load in the overlap volume is positively correlated with years of education; and (3) irrespective of level of education, the volume of reduced glucose metabolism is smaller than the tau volume given the presumed temporal evolution of AD biomarkers [14].

Materials and methods

Participants

The study group comprised 38 patients with mild-to-moderate AD recruited from the interdisciplinary memory centres of the University Hospital Cologne and the University Hospital Bonn. The patients were diagnosed with probable AD dementia using the recommended NIA-AA criteria [15] including diagnostic amyloid PET imaging or CSF measurements. All participants underwent a PET scan with [^{18}F]AV-1451 for the in-vivo assessment of tau pathology and a PET scan with [^{18}F]FDG for the evaluation of neuronal dysfunction at the Department of Nuclear Medicine of the University Hospital Cologne. All participants provided signed informed consent regarding the scientific evaluation and publication of their data.

PET acquisition

PET scans were performed on a Siemens Biograph mCT Flow 128 Edge scanner (Siemens, Knoxville, TN) and were iteratively reconstructed using a 3-D OSEM algorithm (four iterations, 12 subsets, gaussian filter, 5 mm full-width at half-maximum, matrix 128 × 128, slice thickness 3 mm). The two PET scans were acquired no more than 3 months and on average less than 1 month apart. Administration parameters are summarized in Table 1.

PET image processing

In each individual, the [^{18}F]AV-1451 scan was coregistered to the [^{18}F]FDG scan using SPM12 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, UK). The coregistered [^{18}F]AV-1451 scan and the native [^{18}F]FDG scan were then normalized to a [^{18}F]FDG PET template in MNI space [16]. Using in-house scripts in MATLAB R2016a (The MathWorks, Inc., Natick, MA, USA), the normalized scans were intensity-standardized to the whole cerebellum, which was used as the reference region. The preprocessed images were then z-transformed

Table 1 Descriptive characteristics

Characteristic	Value
Number of patients	38
Men	20
Women	18
Age (years), mean (SD)	67.11 (6.97)
MMSE score, mean (SD)	23.87 (4.45)
Years of education, mean (SD)	13.85 (3.92)
[^{18}F]AV-1451, mean (SD)	
Dose (MBq)	236.26 (48.11)
Administration time after injection (min)	94.81 (26.87)
[^{18}F]FDG, mean (SD)	
Dose (MBq)	216.92 (49.22)
Administration time after injection (min)	36.24 (10.55)

SD standard deviation, *MMSE* Mini Mental State Examination

using an [^{18}F]AV-1451 PET template and an [^{18}F]FDG PET template from a healthy control sample ($n = 15$, mean age at FDG scan 67.47 years, mean MMSE score at FDG scan 28.87, mean years of education 16.67) acquired at two different time points and provided by the Alzheimer's Disease Neuroimaging Initiative database (http://adni.loni.usc.edu/). The control sample was age-matched to our AD sample. Numerically, the mean years of education in the healthy control sample was slightly higher than in the patient sample, most likely reflecting differences in the German and North American educational systems ($U = 148$, $p = 0.007$). For further information on the processing of the healthy control templates see the Supplementary material.

The z-transformed images were thresholded at a z-score of ≥3.0 approximately corresponding to an one-tailed p value of 0.001. In a next step, using a batch script employing the imcalc function implemented in SPM12, three volumes were extracted: (1) the tau-specific volume comprising regions characterized by significant tau pathology but no significant change in glucose metabolism; (2) the FDG-specific volume comprising regions with significant changes in glucose metabolism in the absence of tau pathology; and (3) the overlap volume comprising regions in which both the [^{18}F]AV-1451 and the [^{18}F]FDG scan showed a z-score of ≥3.0. The difference between the tau-specific volume and the FDG-specific volume was also extracted. A positive difference value indicated a larger tau-specific volume than FDG-specific volume, whereas a negative value indicated the reverse. All computed volumes, the volume difference and z-scores of the volumes were then used for further statistical analysis.

To ensure that the results were not predominantly driven by the predefined z-score threshold of ≥3.0, the same analysis was performed with the PET scans thresholded at a more liberal z-score of ≥2.0, representing an one-tailed p value of 0.02. A subanalysis ($z \geq 3.0$) was also performed limiting the dataset to data from patients with typical AD to ensure that the results were not solely driven by the data from patients with variants of AD.

Statistical analysis

Multivariable regression analysis was performed with SPSS version 21 (IBM Corp., Armonk, NY USA). Years of education (that is, schooling and subsequent professional education including vocational or university training) was employed as the predictor with the volumes, mean z-scores within these volumes and the difference in volume as dependent variables, controlling for age and MMSE score. The models were further tested for a potential gender effect. As the gender effect was not significant, it was excluded from the final analysis. Moreover, one-tailed bivariate correlation analysis was performed to evaluate the association between the mean z-scores of the respective volumes. The significance threshold for all analyses was set at $p < 0.05$.

The graphs of the results were computed using R (R: A language and environment for statistical computing, 2018; R Core Team, R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). The brain surface illustrations were created using the CAT12 toolbox implemented in SPM and the Surf Ice toolbox (https://www.nitrc.org/projects/surfice/).

Results

Descriptive data

Of the 38 patients, 26 were diagnosed with typical AD, six with the logopenic variant, three with posterior cortical atrophy, two with the behavioural variant, and one with atypical AD without further specification. The patients with lower levels of education had on average 11 years of education, whereas the patients with higher levels of education level had on average ≥18 years of education (see Supplementary material for information on the German education system). Descriptive data of the group are presented in Table 1. One extreme outlier was removed from the analysis to fulfil the underlying assumptions for regression analysis.

Associations with level of education

A significant positive association was observed between years of education and tau-specific volume ($\beta = 0.362$, $t = 2.414$, $p = 0.022$). In other words, higher levels of education were associated with more brain areas showing preserved metabolism despite the presence of tau pathology. Furthermore, in regions with tau pathology and hypometabolism overlap, years of education was positively correlated with tau pathology load ($\beta = 0.303$, $t = 2.183$, $p = 0.036$), but not with the degree of hypometabolism ($\beta = -0.057$, $t = -0.385$, $p = 0.703$). Moreover, no significant effect was observed in the regression analysis between level of education and FDG-specific volume ($\beta = -0.242$, $t = -1.423$, $p = 0.164$). Furthermore, a significant positive relationship was observed between years of education and the difference between the tau-specific volume and the FDG-specific volume ($\beta = 0.342$, $t = 2.190$, $p = 0.036$). The difference values were not exclusively positive, meaning that in patients with the lowest levels of education the FDG-specific volume was even larger than the tau-specific volume.

Table 2 Results of regression analysis

	t	*β*	*P*	95% CI	*F*	df	*p*	Adjusted R^2
Tau-specific volume					5.306	3,33	0.004	0.264
Level of education	2.414	0.362	0.022	0.002, 0.025				
MMSE score	−1.903	−0.293	0.066	−0.021, 0.001				
Age	−2.558	−0.376	0.015	−0.014, −0.002				
Mean tau burden in overlap volume (tau-specific/FDG-specific overlap)					8.109	3,33	<0.001	0.372
Level of education	2.183	0.303	0.036	0.016, 0.465				
MMSE score	−2.835	−0.403	0.008	−0.511, −0.084				
Age	−3.150	−0.428	0.003	−0.317, −0.068				
FDG-specific volume					1.704	3,33	0.185	0.055
Level of education	−1.423	−0.242	0.164	−0.016, 0.003				
MMSE score	1.827	0.319	0.077	−0.001, 0.017				
Age	0.595	0.099	0.556	−0.004,0.007				
Volume difference (tau-specific – FDG-specific)					4.061	3,33	0.015	0.203
Level of education	2.190	0.342	0.036	0.001, 0.039				
MMSE score	−2.086	−0.334	0.045	−0.037, 0.000				
Age	−1.855	−0.284	0.072	−0.020, 0.001				

The table includes the statistical model summaries of all regression analyses

CI confidence interval, *df* degrees of freedom, *MMSE* Mini Mental State Examination

The results of the regression analysis are summarized in Table 2 and respective plots are shown in Fig. 1 and Supplementary Fig. 1a. Figure 2 illustrates a brain projection showing the increase in tau-specific volume with increasing years of education.

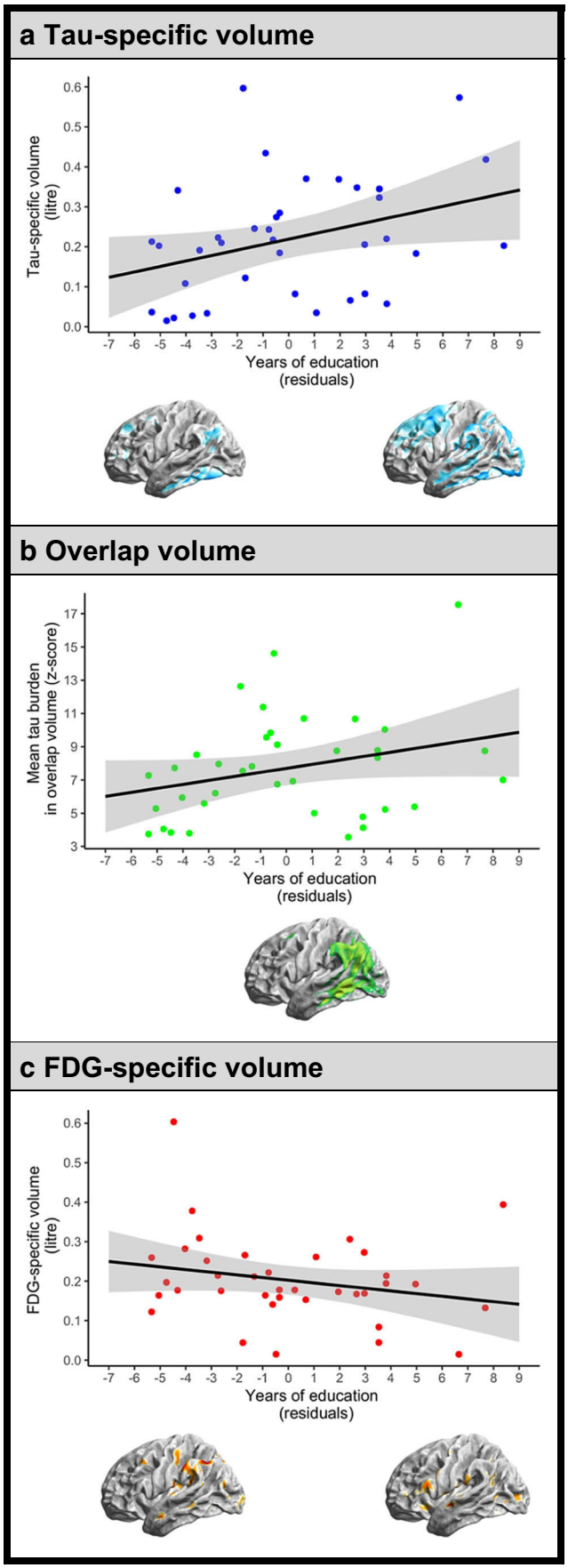
Aside from this, a positive trend for an association was found between the respective average *z*-scores for hypometabolism and tau pathology within the overlap volume ($r = 0.264$, $p = 0.057$; Supplementary Fig. 1b). In contrast, the average *z*-scores of the FDG-specific volume were not correlated with the average *z*-scores of the tau-specific volume ($r = -0.109$, $p = 0.260$; Supplementary Fig. 1c). Moreover, the subanalysis including only patients with typical AD showed a trend for significance of the main variables of interest (Supplementary Table 1). In addition, the confirmatory analysis using a threshold *z*-score of ≥2.0 yielded similar results, supporting our approach (Supplementary Table 2).

Discussion

Several studies using PET imaging have shown that the spatial extent of tau pathology is closely related to changes in glucose metabolism, a measure of neuronal dysfunction. Here, we report evidence that level of education mitigates the local impact of tau pathology on neuronal function. We observed that the volume of brain regions with relatively preserved metabolism despite the presence of significant tau pathology (i.e. the tau-specific volume) is greater in patients with higher levels of education. Furthermore, our data suggest that in regions characterized by coexisting tau pathology and neuronal dysfunction (i.e. the overlap volume), a greater tau burden is required to cause comparable metabolic dysfunction in individuals with higher levels of education. Taken together, our findings point towards the existence of protective mechanisms against tau pathology, which may be associated with the early life-time factor of education. We discuss below the current findings based on the concept of BR continued by an argumentation relating to resilience factors supporting BM.

An explanation based on the concept of brain reserve

Numerous studies have shown that life-time factors, such as education, play an important role in prolonging and slowing cognitive decline following the advent of brain pathology [12, 17–22]. Education, an early life-time factor, has consistently been associated with higher socioeconomic status, better health, less chronic stress and life-long mental stimulation, factors that probably contribute to better brain health later in life [23–26]. With an accumulating body of evidence across neurological conditions, it is believed that education can protect and provide resilience against the harmful effects of pathology [27]. In line with this, we found that higher levels of education are associated with less pronounced effects of tau pathology on neuronal function. Moreover, more tau pathology appears necessary to induce changes in glucose metabolism in individuals with higher levels of education.



◀ **Fig. 1** Regression analysis including years of education (residuals) corrected for MMSE and age as predictor and mean tau burden (*z*-score) and volumes (litre) as dependent variables (**a** *blue* tau-specific volume, **b** *green* mean tau burden in overlap volume, **c** *red* FDG-specific volume; *grey areas* 95% confidence intervals). Brain projections of the respective volumes are illustrated below each scatterplot. **a** and **c** show the volume extents in a patient with a low level of education (*left*) and a patient with a high level of education (*right*), and **b** depicts the average overlap volume in patients with typical AD. The respective volumes were rendered on a brain surface in MNI space using the CAT toolbox implemented in SPM12

These findings may first be explained based on the concept of BR, which accounts for the individual neurobiological capital such as neuron count and synaptic density [9]. Accordingly, individuals with a high BR will show less severe symptoms than individuals with a low BR despite similar brain pathology, because they possess more BR to counteract the brain damage. Hence, although the same numbers of neurons or synapses are rendered dysfunctional by misfolded tau aggregates in individuals with low and high levels of education, an individual with a higher level of education will be able to counteract the brain damage given that he/she possesses enough resources in the form of yet-unaffected neurons or synapses. Due to the activation of these (thus far) spared resources, the metabolic rate (i.e. FDG uptake on PET) in individuals with higher levels of education may in turn not significantly deviate from that detected in healthy controls despite tau aggregation. Furthermore, according to the BR-concept, a greater pathological burden is necessary to eventually affect the compensatory resources in individuals with higher levels of education, which may account for our finding of greater tau burden in the overlap volume in patients with higher levels of education.

Importantly, it has been postulated that glucose metabolism reflects synaptic function rather than overall neuronal function [28]. The possible BR-related compensatory process may thus be a matter rather of synaptic density and plasticity than of total neuron count. Indeed, several studies using rodent models have demonstrated that enriched environments, which are used to study the benefits of life-long cognitive stimulation, promote neuronal plasticity in the form of increased synaptic density [29–31] and dendritic branching [32, 33]. Similar effects are believed to occur in humans. With the recent development of PET tracers to visualize changes in synaptic density [34], future studies will be able to directly elucidate the protective effect of education on AD-related pathology.

Concerning our reasoning based on the BR concept, it must be emphasized that the neurotoxic effects of tau pathology on neuronal function are considered similar at different levels of education. Yet, the detectable and measurable outcome (i.e. the FDG PET signal) of regional tau pathology on neuronal function differs according to the individual extent of underlying compensatory resources. One may, however, also argue

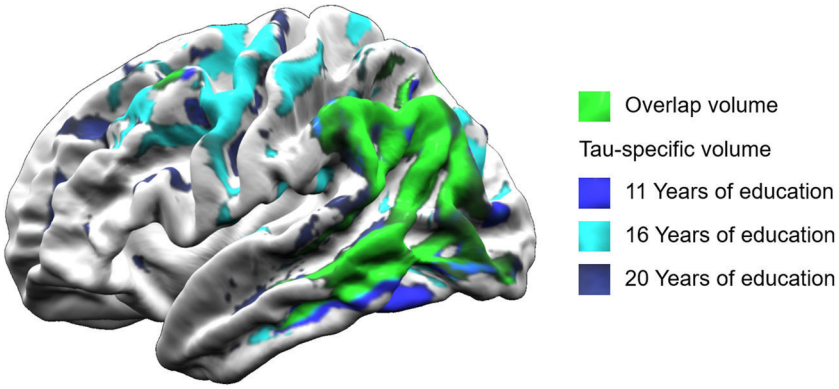


Fig. 2 Brain projection showing the tau-specific volume in relation to level of education: *green* average overlap volume (i.e. significant tau pathology and neuronal dysfunction) in patients with typical AD, *blue* average tau-specific volumes in three groups with different levels of education (average 11, 16 and 20 years) surrounding the overlap volume. Importantly, the volumes shown were derived solely from patients with typical AD, because those with atypical AD showed different topographical patterns. Moreover, the tau-specific volume in the patients with an average of 16 years of education is in addition to the volume of those with an average of 11 years of education. Likewise, the volume in the patients with an average of 20 years of education is in addition to the two volumes of the groups with less education. The respective volumes were rendered on a brain surface in MNI space using the Surf-Ice toolbox

that in individuals with higher levels of education the impact of tau pathology on neuronal function is ameliorated by resilience factors supporting BM, as discussed below.

An explanation based on resilience factors supporting brain maintenance

Again, rodent studies have provided valuable information on resilience factors that are associated with life-long engagement and facilitate clearance or decreases in tau pathology and neuroinflammation, thereby supporting maintenance of brain integrity. These factors are potentially associated with level of education in humans and thus contribute to the current findings. Given the complexity of these resilience factors, we mention, within the scope of this discussion, only a few examples that may have contributed to the current findings.

Over the past decade, several cellular growth factors have been reported to be neuroprotective, such as the brain-derived neurotrophic factor (BDNF). BDNF has been demonstrated in vitro to alter the phosphorylation of tau [35] and has consistently been found to positively affect memory processes even in subjects with dementia (for review see [36]). More recently, elevated CSF levels of vascular endothelial growth factor [37] and increased serum levels of insulin growth factor [38] have also been associated with healthier brain ageing and brain volume late in life. Aside from the upregulation of these growth factors, distinct proteomic signatures [39] and genes [40, 41] have been related to neuronal resilience. For example, increased expression of genes involved in the control of lysosomes has been found after long-term physical exercise. This upregulation appears to ameliorate the neurotoxic effects of hippocampal tau pathology in rodents [41]. Interestingly, the lysosomal pathway has been suggested to mediate the degradation of tau isoforms [42, 43].

So far, it remains unknown whether these molecular underpinnings are directly associated with early life-time factors, such as education, or whether they are more closely related to life-long cognitive and physical engagement. Longitudinal studies, including elaborate questionnaires of life-time cognitive and physical activities, are necessary to gain further insights into the relationship between early life-style factors and protective molecular signatures later in life.

Downstream effects of regional tau pathology

Despite the observation that tau pathology appears to be less harmful to neuronal function in individuals with higher levels of education, we conversely observed that changes in neuronal function in the absence of local tau pathology appear to be potentiated in individuals with lower levels of education. These changes may represent effects of neuropathology aggregation in remote but functionally connected brain regions in the sense of functional deafferentation or diaschisis.

Interestingly, molecular studies have shown that tau pathology preferentially affects long-range projection neurons rather than locally projecting neurons [44, 45]. Thus, signal changes detected on [^{18}F]FDG PET probably represent downstream projection sites from the neuron affected by tau pathology. This may cause a topographic discordance between the [^{18}F]AV-1451 and [^{18}F]FDG signals. Indeed, recently, it has been suggested that the topographic overlap between tau pathology and neuronal dysfunction becomes less coherent as the disease progresses [46]. Given these findings, it may be that the disease in individuals with lower levels of education in

our sample had already progressed to more advanced stages. Furthermore, the downstream effects of tau pathology could be more severe in patients with lower levels of education, because they do not possess sufficient compensatory or maintenance mechanisms to counteract the local upstream effects of misfolded tau aggregates. This would explain why in patients with lower levels of education the FDG-specific volumes were greater than the tau-specific volumes.

Limitations

We used a volume-based approach with a predefined threshold, which may have led to underestimation or overestimation of the overall tau pathology and hypometabolism pattern. Yet the analysis based on a more liberal threshold yielded similar results, supporting the current findings. Moreover, with the approach used, we were able to perform a group analysis including individuals with different variants of pathology distribution. However, as the patient groups with atypical AD were relatively small, we could not run subsequent analyses for each group. Moreover, the potential contribution of Aβ pathology could not be considered in the analyses as amyloid PET scans were not available in all patients. Nonetheless, all patients were amyloid-positive based on either CSF or PET imaging measures. Moreover, we cannot rule out the possibility that our findings, although less likely, were driven by a faster spatial spread of tau pathology in patients with higher levels of education. Lastly, we used an indirect proxy of neuronal resilience, namely educational attainment, as there is no direct measure available yet. It is possible that more elaborate measures of resilience such as life-long cognitive engagement, physical activity or even nutrition may be more closely associated with the observed effects. Overall, future studies in larger cohorts using elaborate questionnaires on life-time experience are required to establish direct measures of neuronal resilience.

Conclusion

The results of this study indicate that level of education is associated with resilience capacity, which ameliorates the neurotoxic effects of misfolded tau aggregates on neuronal function in AD. This finding potentially explains why AD patients with higher levels of education can tolerate more tau pathology than those with lower levels of education and similar cognitive impairment. It would be of interest to examine whether the current findings are transferrable to other tauopathies such as progressive supranuclear palsy, corticobasal syndrome and frontotemporal dementia. These tauopathies are characterized by morphological differences in tau aggregates, but the disease mechanisms appear similar, at least to some degree [47]. Thus, the elucidation of resilience mechanisms may lead to treatment interventions that are relevant not only to AD but also to other neurodegenerative diseases.

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Author's contributions M.C.H. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.C.H., G.N.B., A.D. and T.vanE. were involved in the conception and design of the study, analysis of the data and drafting the manuscript. E.K. was involved in the conception of the study and drafting the manuscript. Ö.A.O., J.K., F.J., K.F., G.R.F. and B.N. were involved in the acquisition of the data and drafting the manuscript.

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Compliance with ethical standards

Conflicts of interest MH, GNB, ÖAO, JK, FJ, KF, and BN have no conflict of interest. GRF received honoraria for speaking engagements from Bayer, Desitin, Ergo DKV, Forum für medizinische Fortbildung FomF GmbH, GSK, Medica Academy Messe Düsseldorf, Medicbrain Healthcare, Novartis, Pfizer, and Sportärztebund NRW. EK received grants from the German Ministry of Education and Research, the German ParkinsonFonds, and the German Parkinson Society as well as honoraria from Oticon GmbH, Hamburg, Germany; Lilly Pharma GmbH, Bad Homburg, Germany; Bernafon AG, Bern, Switzerland; Desitin GmbH, Hamburg, Germany. AD reports having received consulting and speaker honoraria as well as research support from Siemens Healthcare, AVID Radiopharmaceuticals, Lilly, Piramal (now Life Molecular Imaging) and GE Healthcare. TvE reports having received consulting and speaker honoraria as well as research support from Siemens Healthcare, AVID Radiopharmaceuticals, Lilly, Shire Germany, Piramal (now Life Molecular Imaging) and GE Healthcare. Data used in preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the University Cologne and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study formal consent was not required.

Informed consent Informed consent was obtained from all individual participants included in this research project as part of the study for the scientific evaluation of the AV-1451 tracer.

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Supplementary Data

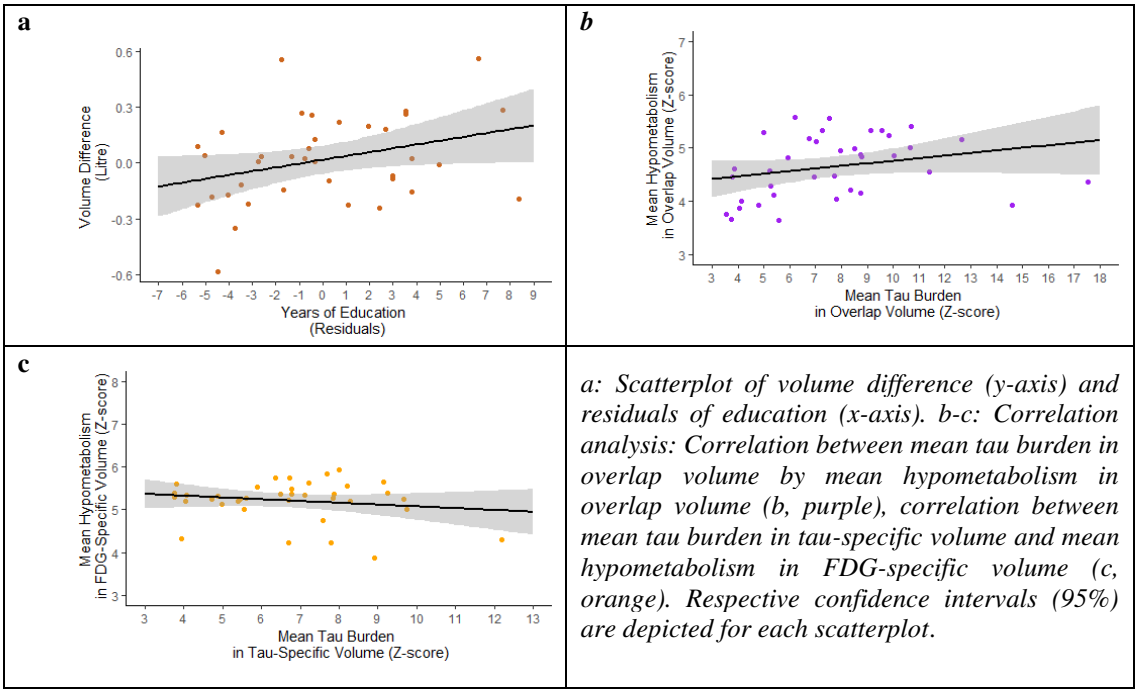
German educational system:

In Germany, there are five potential schooling-leaving qualifications: board school (8 years), main school (9 years), middle school (10 years), vocational baccalaureate diploma (12 years), A-levels (13 years). Depending on the schooling-leaving qualification, people can either start a vocational training (3 years) or go to university. A-level graduates can go to university, whereas individuals with a vocational baccalaureate diploma can study at a university of applied science (similar to a college).

Healthy control template:

The PET imaging data for the healthy control template was acquired from the ADNI platform. In ADNI, most of the cognitively normal subjects are above the age of 70 years. That it is why only a relatively small sample remained for the creation of the template in this study after age-matching the healthy control subjects to our patient sample. The respective and available co-registered, averaged images were downloaded and processed with the same pipeline as the PET imaging data of the patient sample.

Supplementary Fig. 1 – Scatterplots of difference volume and bivariate correlation analyses



a: Scatterplot of volume difference (y-axis) and residuals of education (x-axis). b-c: Correlation analysis: Correlation between mean tau burden in overlap volume by mean hypometabolism in overlap volume (b, purple), correlation between mean tau burden in tau-specific volume and mean hypometabolism in FDG-specific volume (c, orange). Respective confidence intervals (95%) are depicted for each scatterplot.

To ensure that the results were not driven by the atypical AD group, we performed a subanalysis on the typical AD group. Trend significance was reached for the main variables of interest (i.e., tau-specific volume and tau burden in the overlap volume).

Supplementary Table 1 – Results of regression analysis limited to the typical AD group

	t	β	p	F	df	p	Adj. R^2
Tau-Specific Volume				3.012	3,22	.053	.201
Education	1.943	.392	.066				
MMSE	-.912	-.186	.372				
Age	-2.280	-.424	.033				
Mean Tau Burden in Overlap Volume (Tau ∩ FDG)				7.591	3,22	.001	.452
Education	1.802	.301	.086				
MMSE	-.943	-.160	.356				
Age	-4.341	-.668	<.001				
FDG-Specific Volume				.804	3,22	.506	-.025
Education	-.345	-.079	.734				
MMSE	.323	.075	.750				
Age	1.446	.304	.163				
Volume Difference (Tau-Specific- FDG-Specific)				2.365	3,22	.100	.146
Education	1.461	.305	.159				
MMSE	-.759	-.160	.456				
Age	-2.188	-.421	.040				

The table includes the statistical model summaries of all regression analysis based on the typical AD group. CI= confidence interval; MMSE = Mini Mental State Examination.

To ensure that the results were not predominantly driven by the predefined threshold of z >= 3.0, we conducted the same analyses, but thresholding the PET scans at a more liberal z-score level of z >= 2.0, representing a one-tailed p-value of $p < .02$.

Supplementary Table 2 – Results of regression analysis using data threshold of z >= 2.0

	t	β	p	F	df	p	Adj. R^2
Tau-Specific Volume				3.062	3,33	.042	.147
Education	1.758	.284	.088				
MMSE	-1.483	-.246	.147				
Age	-1.960	-.310	.058				
Mean Tau Burden in Overlap Volume (Tau ∩ FDG)				9.320	3,33	<.001	.409
Education	2.370	.319	.024				
MMSE	-2.922	-.403	.006				
Age	-3.466	-.456	.001				
FDG-Specific Volume				2.875	3,33	.051	.135
Education	-1.771	-.288	.086				
MMSE	2.093	.349	.044				
Age	1.246	.199	.221				
Volume Difference (Tau-Specific- FDG-Specific)				3.462	3,33	.027	.170
Education	1.928	.307	.063				
MMSE	-1.974	-.323	.057				
Age	-1.727	-.270	.093				

The table includes the statistical model summaries of all regression analysis. CI= confidence interval; MMSE = Mini Mental State Examination.

Given that we observed a significant effect of age in our regression models, we further tested for the interaction effect between age and education. No significant interaction effect with age and education was found.

Supplementary Table 3 – Regression analysis (threshold: z >= 3.0) including interaction of age x education

	t	β	p	F	df	p	Adj. R^2
Tau-Specific Volume				3.941	4,32	.010	.246
Education	-.235	-.369	.816				
MMSE	-1.925	-.303	.063				
Age	-1.105	-.636	.278				
Age x Education	.467	.799	.643				
Mean Tau Burden in Overlap Volume (Tau ∩ FDG)				6.322	4,32	.001	.372
Education	1.194	1.715	.241				
MMSE	-2.682	-.385	.011				
Age	.140	.074	.889				
Age x Education	-.988	-1.543	.331				
FDG-Specific Volume				1.283	4,32	.297	.030
Education	-.522	-.932	.605				
MMSE	1.738	.310	.092				
Age	-.223	-.146	.825				
Age x Education	.388	.754	.700				
Volume Difference (Tau-Specific- FDG-Specific)				2.956	4,32	.035	.179
Education	.124	.203	.902				
MMSE	-2.048	-.336	.049				
Age	-.555	-.333	.583				
Age x Education	.085	.152	.933				

The table includes the statistical model summaries of all regression analysis including the interaction term age x education. CI= confidence interval; MMSE = Mini Mental State Examination.

ERKLÄRUNG

Ich versichere, dass ich die von mir vorgelegte Dissertation selbstständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit -einschließlich Tabellen, Karten und Abbildungen -, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen - noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen dieser Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Prof. Dr. Alexander Drzezga betreut worden.

Übersicht der Publikationen:

1. Hoenig MC, Bischof GN, Seemiller J, Hammes J, Kukolja J, Onur ÖA, Jessen F, Fliessbach K, Neumaier B, Fink GR, van Eimeren T, Drzezga A. Networks of tau distribution in Alzheimer's disease. Brain, 2018 Feb 1;141(2):568-581. doi: 10.1093/brain/awx353. PubMed PMID: 29315361.

2. Hoenig MC, Bischof GN, Hammes J, Faber J, Fliessbach K, van Eimeren T, Drzezga A. Tau pathology and cognitive reserve in Alzheimer's disease. Neurobiology of Aging, 2017 Sep;57:1-7. doi: 10.1016/j.neurobiolaging.2017.05.004. PubMed PMID: 28577411.

3. Hoenig MC, Bischof GN, Onur ÖA, Kukolja J, Jessen F, Fliessbach K, Neumaier B, Fink GR, Kalbe E, Drzezga A, van Eimeren T. Level of education mitigates the impact of tau pathology on neuronal function. European Journal of Nuclear Medicine and Molecular Imaging, 2019 Aug;46(9):1787-1795: 1787. doi: 10.1007/s00259-019-04342-3. PubMed PMID: 31183635.

Ich versichere, dass ich alle Angaben wahrheitsgemäß nach bestem Wissen und Gewissen gemacht habe und verpflichte mich, jedmögliche, die obigen Angaben betreffenden Veränderungen, dem Promotionsausschuss unverzüglich mitzuteilen.

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