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The central role of tau in Alzheimer's disease: From neurofibrillary tangle maturation to the induction of cell death

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Abstract

The tau protein (τ) is one of the two hallmark proteins of Alzheimer's disease (AD) together with the amyloid β protein (Aβ). In contrast to Aβ, abnormal phosphorylated τ (p-τ) can also be found in non-AD tauopathies. In AD, p-τ is the main component of intraneuronal neurofibrillary tangles, which result from aggregation of abnormal phosphorylated and folded τ. In this review, we discuss the role of p-τ pathology in Alzheimer's disease considering neuropathological, biochemical, cellular, animal model, and clinical findings. We discuss the relationship between p-τ and other AD-related proteins such as Aβ and transactive response DNA-binding protein 43 (TDP-43). In light of the current state of knowledge, we conclude that p-τ aggregation known as primary age-related tauopathy (PART) may represent a prerequisite for the development of AD rather that a downstream effect of Aβ toxicity. However, Aβ as well as TDP-43 pathology appear to accelerate accumulation and propagation of p-τ pathology once initiated, ultimately leading to the full-blown picture in AD. τ seeds can induce granulovacuolar degeneration (GVD), AD-typical lesions in which the activated necrosome – required for the execution of necroptosis, a programmed form of cell death - can be found. GVD is associated with a decreasing neuronal density. Thus, we speculate that p-τ pathology is a major driver for neuron loss in AD via GVD-mediated necroptosis. Accordingly, p-τ seems to play a central role in AD as it appears to constitute a prerequisite for AD development which can then be accelerated by co-factors. This would fit in a probabilistic model of AD, related to the presence and severity of the respective co-factors such as Aβ, TDP-43, and others.

Key words: tau protein; Alzheimer's disease; amyloid β protein; TDP-43; primary age-related tauopathy; necroptosis; granulovacuolar degeneration

1. Introduction

Alzheimer's disease (AD) is the most common dementing disorder in the elderly (Association, 2021). It is characterized by its hallmark lesions, amyloid plaques and neurofibrillary tangles (NFTs) (Alzheimer, 1907). Amyloid plaques consist of extracellular aggregates of the amyloid β-protein (Aβ) (Masters et al., 1985) which is a cleavage product of the amyloid precursor protein (APP) (Kang et al., 1987). The cleavage of APP by the β- and γ-secretase releases Aβ (Haass et al., 1992; Haass and Selkoe, 2007). The active center of γ-secretase is represented by either presenilin 1 or 2 (De Strooper et al., 1998; Herreman et al., 2000; Wolfe et al., 1999). NFTs are intraneuronal aggregates of abnormal phosphorylated tau (τ)-protein (Grundke-Iqbal et al., 1986). Given that mutations in the *APP* gene, the presenilin 1 (*PSEN1*) and 2 (*PSEN2*) genes lead to familial forms of AD (Goate et al., 1991; Rogaev et al., 1995; Sherrington et al., 1995; St George-Hyslop et al., 1992; St George-Hyslop et al., 1987; Tanzi et al., 1987) whereas mutation in the τ gene (*MAPT*) cause frontotemporal lobar degeneration but not AD (Hutton et al., 1998), the amyloid hypothesis was formulated predicting that Aβ is the driver of AD whereas τ pathology was considered as a downstream effect (Hardy and Higgins, 1992; Selkoe and Hardy, 2016). Unfortunately, clinical trials using antibodies against Aβ, active vaccination strategies, or secretase inhibitors did not lead to a major modification of the course of the disease although amyloid plaques were reduced (Cummings et al., 2020; Liu and Howard, 2021; Plowey et al., 2022). This raised the question whether the amyloid hypothesis needs to be replaced by a pathogenetic concept that can explain the failure of the anti-amyloid trials. Moreover, NFT pathology correlates better with clinical dementia scores than Aβ pathology (Arriagada et al., 1992). However, none of the τ-targeting therapies developed so far was successfully tested in a clinical trial: one was ineffective whereas other studies are still ongoing (Asher and Priefer, 2022). Recently, a probabilistic concept was suggested in which the genetic drivers of familial AD as well as apolipoprotein E still have a significant weight but are

supplemented by multiple other factors that contribute to the development of AD (Frisoni et al., 2022). In this review article, we will describe the basic biochemical/biophysical and neuropathological features of τ and its roles in AD as a prerequisite for disease development as well as a critical player in the execution of neurodegeneration.

2. The τ protein: Aggregation, phosphorylation and maturation

τ protein is a microtubule associated protein that stabilizes the microtubules in the axon and regulates axonal transport (Scholz and Mandelkow, 2014). Alternative splicing of exon 10 of the τ gene (*MAPT*) leads to 6 different τ isoforms (D'Souza and Schellenberg, 2005). Three of them carry three repeats (3-repeat τ (3R τ)) in the repeat region of the protein, whereas the remaining three isoforms have four repeats (4-repeat τ (4R τ)). Accumulation of τ protein forms protofibrils which are then converted to fibrils by forming straight and paired helical filaments (PHFs). Protofibrils exhibit disease specific folding architectures at the cryo electron microscopy level that allow to distinguish an "Alzheimer fold" from τ folds seen in chronic traumatic encephalopathy, Pick's disease and corticobasal degeneration (Fitzpatrick et al., 2017; Goedert, 2021). In AD, τ lesions are composed of 3R and 4R τ (Goedert et al., 1989). However, the extracellular "ghost" tangles are enriched in 3R τ (Uchihara et al., 2012).

Phosphorylation of τ protein is a physiological process and is required for the regulation of the axonal transport by maintaining microtubule integrity (Scholz and Mandelkow, 2014). The physiological phosphorylation of τ occurs in normal processes such as neural development (Brion et al., 1993; Kenessey and Yen, 1993) and hibernation (Arendt et al., 2003; Leon-Espinosa et al., 2013).

Abnormal phosphorylation of τ, on the other hand, leads to its mislocalization into the somatodendritic compartment of neurons (Bancher et al., 1989; Braak et al., 1994). Different τ phosphorylation sites are involved in the abnormal phosphorylation of τ (**Fig. 1**). First,

phospho-threonine 231 (pT231, detected with the AT180 antibody) occurs in somatodendritic compartment as "initial cytoplasmic τ". Nearly simultaneously, phospho-serines 396 and 404 (pS396/pS404, detected with the PHF1 antibody) are found in axonal/synaptic compartments of neurons, referred to as "initial neuropil τ" (Aragao Gomes et al., 2021). This is followed by the formation of pretangles exhibiting also pS202/pT205-τ (detected with the AT8 antibody). Subsequently, an abnormal conformation of the τ protein, called the "paperclip conformation" or "MC1" conformation, is detected prior to formation of argyrophilic and ubiquitin/p62 immunoreactive NFTs (**Figs. 1, 2**) (Aragao Gomes et al., 2021; Bancher et al., 1989; Moloney et al., 2021). The p-τ forms that are measured in blood and cerebrospinal fluid (CSF) as AD biomarkers, pT181-τ and pT217-τ, have been reported to occur in p-τ lesions also exhibiting pS202/pT205-τ, pT231-τ, and pS396/pS404-τ (Aragao Gomes et al., 2021; Goedert et al., 1994; Wennstrom et al., 2022).

Although it is well known that abnormal phosphorylation often leads to τ aggregation and results in neurotoxicity, τ phosphorylation can also have beneficial effects. Specifically, the phosphorylation at T18 promotes normal axonal trafficking (Stern et al., 2017). Another study has also observed that the phosphorylation at sites S214, and S262 prevents τ fibrillization into PHFs, suggesting that τ phosphorylation in AD may not necessarily result in τ aggregation (Schneider et al., 1999). Corroborating these data, Strang and colleagues reported that S305 phosphorylation also inhibited aggregation in vitro (Strang et al., 2019). Additionally, a protective effect of site-specific τ phosphorylation by kinase p38γ was observed *in vivo*, precluding Aβ toxicity (Ittner et al., 2016). Finally, there are reports of τ phosphorylation constituting a protective mechanism against oxidative stress in AD (Nunomura et al., 2001). A recent review suggested that in advanced disease stages, aberrant phosphorylation of τ may overwhelm protective phosphorylation mechanisms and promotes neuronal demise (Xia et al., 2021). These studies highlight that τ phosphorylation in the brain is a highly complex process

involving multiple possible phosphorylation sites. AD-related p-τ formation in this context involves tauopathy related phosphorylation sites presumably destabilizing the physiological balance of aggregation-prone and aggregation-inhibiting τ phosphorylation sites.

In addition to phosphorylation, proteomic studies revealed a wide range of additional post-transitional modifications of τ, including ubiquitylation, acetylation and truncation in AD (Dujardin et al., 2020). Colocalization with the transactive response DNA-binding protein 43 (TDP-43) in a large subset of AD cases (Amador-Ortiz et al., 2007; Higashi et al., 2007; Tome et al., 2021) may indicate the contribution of TDP-43 in the maturation process of AD τ pathology at least in a subset of AD cases (**Fig. 2**) with NFT-like TDP-43 aggregates indicative for the type β subtype of TDP-43 pathology in non-FTLD-TDP (frontotemporal lobar degeneration with TDP-43 pathology) brains (Josephs et al., 2019). TDP-43 accumulation in this context can be seen as early as in the pretangle stage (**Fig. 3**).

3. τ pathology: Lesions, distribution and propagation

3.1. Neuropathological aspects

Neuropathologically, we distinguish NFTs, pretangles and neuropil threads in the AD brain (**Fig. 3**) (Braak and Braak, 1991). Inclusions in non-neuronal cells, i.e., astrocytes and oligodendrocytes, are restricted to non-AD tauopathies (Dickson et al., 2011; Kovacs et al., 2016) and will not be in the focus of this article. In addition to NFTs, pretangles, and neuropil threads, initial τ aggregates in the cytoplasm of neurons and in the neurites exhibiting only single phosphoepitopes of τ have been described as precursor lesions for pretangles. Initial cytoplasmic τ aggregates exhibit pT231-τ (**Fig. 3**) while initial neuropil τ show the phosphoepitopes pS396/pS404 (Aragao Gomes et al., 2021).

The first region in the human brain that exhibits p-τ pathology is the locus coeruleus. Here, only neuropil threads occur first (Braak NFT stage “a”), being later accompanied by pretangles

(Braak NFT stage "b") (Braak et al., 2011). Next, pretangle pathology extends into other subcortical nuclei, namely the raphe nuclei and the basal nucleus of Meynert (Braak NFT-stage "c") (Braak et al., 2011; Rub et al., 2000; Sassin et al., 2000). The cortical involvement in p-τ pathology starts with the transentorhinal cortex (Braak NFT stages "1a, 1b", I), followed by the entorhinal cortex (Braak NFT stage II), the hippocampus and basal temporal neocortex (Braak NFT stage III), the entire temporal cortex (Braak NFT stage IV), the rest of the neocortex with exception of the primary cortical fields (e.g., primary visual cortex). Finally, the primary cortical fields become involved as well (Braak NFT stage VI) (Braak et al., 2011). This pattern was described by first Heiko and Eva Braak (Braak and Braak, 1991; Braak et al., 2011) **(Fig. 4)** whose guidelines are recommended for determining the degree of NFT pathology in the brain of people with AD pathology (Hyman et al., 2012).

NFT pathology is by definition currently considered as AD neuropathological change (ADNC) when Aβ plaques are present as well (Hyman et al., 2012). In the event that NFTs are seen in the absence of Aβ plaque pathology they are considered to represent a primary age-related tauopathy (PART) (Crary et al., 2014). However, emerging evidence points out that PART may represent in most cases an early, pre-amyloid stage of the pathogenesis of AD. This evidence is related to the clear sequence of events of p-τ pathology evolution (a) based on the topographical expansion pattern according to the Braak NFT stages (Crary et al., 2014; Duyckaerts et al., 2015), and (b) based on the maturation processes that are the same in early affected brain regions in the absence of Aβ plaques and in later stages with definite ADNCs (Aragao Gomes et al., 2021). Another argument for PART being part of the AD pathological continuum is the seeding potential similarity of p-τ aggregates from PART and ADNC patient-derived brain homogenates (Kaufman et al., 2018). Moreover, most PART patients (≥52%) exhibited clinical signs of AD (Teylan et al., 2019) and some AD-risk factors are shared (Farrell et al., 2022). However, at the moment that PART is diagnosed as PART, one cannot exclude

that it does not develop in a different tauopathy than AD, such as NFT-predominant dementia (equals PART with clinical symptoms), argyrophilic grain disease and other form of frontotemporal lobar degeneration with τ pathology (FTLD-tau) (Crary et al., 2014; Jellinger et al., 2015). The presence of genetic risk factors for tauopathies other than AD in PART cases (Farrell et al., 2022) argues in favor of the hypothesis that PART can principally lead to the development of non-AD tauopathies as well. In approx. 40 % of the PART cases clinical symptoms do not fit well with that of AD (Teylan et al., 2019). Interestingly, symptomatic cases with PART usually exhibited co-pathologies (best cerebrovascular pathology) that better correlated with cognitive function than the Braak NFT-stage (Iida et al., 2021). Other researchers showed that PART cases only show language deficits correlating with anterior temporal atrophy whereas atrophy and the spectrum of cognitive deficits was more widespread in AD than in PART (Quintas-Neves et al., 2022). This difference may be explained by the limited distribution of p-τ pathology in PART cases, most frequently representing Braak NFT stages I and II whereas AD spectrum cases had usually high Braak stages (IV-VI) in this study (Quintas-Neves et al., 2022). Accordingly, this study does in our opinion not argue against the hypothesis that AD develops from PART as initiating pathology. In this context, less frequently other tauopathies may also arise from the "precursor" lesion PART as proposed earlier (Spires-Jones et al., 2017), especially when considering that demented cases fulfilling the PART criteria equal NFT-predominant dementia. This indicates in our opinion that PART is a "precursor" lesion for a number of tauopathies with AD being the by far biggest player among them.

Interestingly, when accepting the locus coeruleus, the raphe nuclei and the basal nucleus of Meynert as initiating foci kicking off the evolution of AD pathology, one can explain the spread towards later affected brain regions by anterograde transmission of pathology (**Fig. 4**) (Braak and Del Tredici, 2011a). This hypothesis is supported by the finding that p-τ accumulation in pre-α neurons of the entorhinal cortex is first restricted to dendrites and the cytoplasm before

p-τ can be visualized in the axonal region of these neurons in the outer molecular layer of the dentate gyrus in a later stage (Thal et al., 2000a). Thus, p-τ may be transported within the neuron from the somatodendritic compartment to the axon terminals via regular anterograde axonal transport as a prerequisite for anterograde neuron-to-neuron spreading. This has been confirmed *in-vitro* in a three-chamber neuron culture system. Here, it was also shown that synaptic and non-synaptic mechanisms were involved in the neuron-to-neuron transmission of p-τ pathology (Calafate et al., 2015). Alternatively, nanotubes between neurons have also been discussed to contribute to the transmission of p-τ pathology (Chastagner et al., 2020). In-vivo spreading of p-τ has been demonstrated after injecting seeds into mouse brains (Clavaguera et al., 2009; Iba et al., 2015), further supporting the hypothesis of the neuron-to-neuron transmission of p-τ pathology.

Braak NFT stage "a" changes may occur as early as with six years of age, at least in a small amount of autopsied cases with this age (Braak et al., 2011). With increasing age, the frequency of p-τ pathology in the brain also increases. At 40 years, all investigated cases in a cohort with 2332 cases exhibited at least Braak NFT stage "a" (Braak et al., 2011). High Braak NFT stages (V and VI) become apparent in single cases with 40 years of age and increase with age. In the age group 90-100 years approx. 25% of the cases exhibited Braak NFT stages V and VI (Braak et al., 2011). This increase in p-τ pathology is accompanied by the deposition of Aβ plaques and its spreading in the whole brain (Braak et al., 2011). Interestingly, Aβ pathology usually occurs slightly later than p-τ lesions, around 17 years of age at the earliest (Braak et al., 2011). **Fig. 5** shows a similar distribution of Braak NFT stages I-VI as shown by Braak et al. (Braak et al., 2011). The Braak NFT stages "a-1b" were not determined in this cohort.

3.2. Biomarker-related aspects

During life, histopathological analysis of different brain regions is not possible without serious side effects for patients and is, therefore, not a diagnostic option. Accordingly, it is essential to estimate p-τ pathology with the help of biomarkers. Currently, the measurement of total τ and p-τ levels is possible in the blood and the cerebrospinal fluid (CSF) (Andreasen et al., 1999; Janelidze et al., 2020; Sjogren et al., 2001; Skoog et al., 1995; Thijssen et al., 2021) and the distribution and amount of τ pathology in the brain can be estimated by τ positron emission tomography (PET) (Pontecorvo et al., 2017; Schwarz et al., 2016). In this context the fluid biomarkers for pT181-τ, pT217-τ, and pT231-τ are remarkably specific for AD and correlate also with Aβ levels (Andreasen et al., 1999; Janelidze et al., 2020; Karikari et al., 2020; Mila-Aloma et al., 2022; Palmqvist et al., 2020; Sjogren et al., 2001; Skoog et al., 1995; Thijssen et al., 2021; Vanmechelen et al., 2000; Wennstrom et al., 2022). In contrast to the neuropathological detection of p-τ accumulation neurons, which precedes Aβ pathology in most cases **(Fig. 6)**, τ biomarkers exhibit AD-related changes after Aβ biomarkers become positive (Hanseeuw et al., 2019; Jack et al., 2013). That the detection of p-τ and Aβ biomarkers is different from the neuropathological sequence of events is related to a lower sensitivity of the biomarkers compared to the identification of single NFTs or Aβ plaques by microscopic examination in the brain. In this context p-τ biomarkers appear to be less sensitive than Aβ-related biomarkers. For example, the sensitivity of the flortaucipir τ PET had been investigated in an end-of-life study (Fleisher et al., 2020; Pontecorvo et al., 2020). Here, detection of τ pathology was restricted to Braak NFT-stages V and VI, i.e., the end stages of AD. Braak stage I and II cases were detected in less than 75% of the investigated cases (Fleisher et al., 2020). Likewise, blood p-τ showed an increase with Braak NFT stages using assays detecting p-τ^{181} with Braak stages I-III showing levels not significantly different from p-τ negative cases (Morrison et al., 2022). Thus, it is difficult to detect preclinical AD cases with τ biomarkers. Amyloid PET, on the other hand, can identify Aβ phase 3-5 cases covering usually non-

demented individuals with Aβ phase 3 (La Joie et al., 2018; Thal et al., 2018), i.e., being more sensitive than the τ biomarkers.

Moreover, one study did not find a correlation between CSF p-τ and the post-mortem Braak NFT stage (Engelborghs et al., 2007) whereas recently other authors reported a correlation of plasma pT181-τ, pT218-τ and pT231-τ with amyloid PET tracer retention. pT231-τ was in this context the most sensitive marker (Mila-Aloma et al., 2022).

4. Interplay between τ, Aβ, TDP-43, α-synuclein, and noradrenalin metabolites

4.1 Interplay with Aβ

In AD cases, p-τ pathology is accompanied with Aβ plaque pathology. Both pathologies increase in parallel in amount and distribution among the brain regions (Braak and Braak, 1997; Braak et al., 2011; Spires-Jones et al., 2017; Thal et al., 2002). However, a significant number of Braak NFT-stage I and II cases exhibit no Aβ plaque pathology, indicating that p-τ precedes Aβ plaque pathology (Braak et al., 2011). Cases showing Aβ plaques in the absence of p-τ pathology are, on the other hand, very rare (Braak et al., 2011) **(Fig. 6)**. Since the current recommendations of the National Institute of Aging and the Alzheimer Association (NIA-AA) for the assessment of AD neuropathological changes define Alzheimer pathology by the presence of Aβ plaques, those cases with p-τ pathology in the absence of Aβ do not fall under this definition of AD and have been referred to as cases having a primary age-related tauopathy (PART) (Crary et al., 2014), which in most instances represents a precursor pathology of AD τ pathology, i.e., is part of the AD spectrum (Aragao Gomes et al., 2021; Duyckaerts et al., 2015; Kaufman et al., 2018). Interestingly, the increase of p-τ towards Braak NFT stages V and VI is always accompanied with an increase in Aβ plaque pathology (Braak et al., 2011; Spires-Jones et al., 2017; Thal et al., 2019). This parallel increase of p-τ and Aβ pathology was also seen in cases with severe p-τ pathology in a recent longitudinal amyloid and τ imaging study (Therriault

et al., 2022) as well as in several blood biomarker studies (Janelidze et al., 2020; Lantero Rodriguez et al., 2020). Thus, if PART proceeds in the absence of Aβ it will lead to a non-AD tauopathy, e.g., NFT-predominant dementia.

P-τ and Aβ pathology do not only accumulate in parallel during the preclinical and symptomatic stages of AD, but also interact with one another as indirectly shown in animal models and imaging studies (Gotz et al., 2001; Lee et al., 2022; Lewis et al., 2001). This interaction of Aβ and τ is best documented in mouse models. In single (τ P301L) and double-transgenic mouse models (τ JNPL3/APPTg2576; APP23xTAU58), Aβ accelerated p-τ pathology (Gotz et al., 2001; Lewis et al., 2001) and promoted accelerated propagation of p-τ pathology throughout the brain (Gomes et al., 2019). On a cellular and biochemical level, there is evidence that the cellular prion protein (PrP^C) plays an important role in the interaction between Aβ and p-τ because both proteins bind to PrP^C in APP23xTAU58 mouse and in human AD brain (Gomes et al., 2019). Moreover, functional analysis of the role of PrP^C in this context revealed that PrP^C is essential for this pathological interaction. In the absence of PrP^C, Aβ had no major pathological impact on τ and neuronal function in iPSC-derived neuronal cell cultures (Corbett et al., 2020). An explanation for the role of PrP^C in the interplay between Aβ and p-τ could be the fact that PrP^C has been described to act as a receptor for soluble, oligomeric Aβ species responsible for synaptic impairment (Lauren et al., 2009). This hypothesis is supported by the fact that APP-transgenic mice show no synaptic impairment when bred on a *Prnp*-knockout background (Gimbel et al., 2010). Other authors did not find such a protection when crossing APP-transgenic and *Prnp*-knockout mice (Balducci et al., 2010; Calella et al., 2010). Moreover, a possible mechanism for PrP^C to accelerate p-τ pathology is being an interaction partner of soluble Aβ oligomers activating Fyn (Chen et al., 2013; De Mario et al., 2015), which itself increases the levels of p-τ via Pyk2-related phosphorylation of τ (Li and Gotz, 2018; Salazar et al., 2019).

These interactions between Aβ and p-τ are mainly related to soluble Aβ species and can be observed even in the absence of amyloid plaque pathology in APP23xTAU58 mice (Gomes et al., 2019). This means that soluble Aβ aggregates can accelerate p-τ pathology in the absence of Aβ plaques. Accordingly, one cannot exclude that even early p-τ lesions occurring in the absence of Aβ plaques in the human brain can likewise be interacting with soluble Aβ aggregates. On the other hand, the presence of Aβ plaques in the absence of significant p-τ pathology in neocortical brain regions of non-demented individuals with AD neuropathological changes (Thal et al., 2002; Thal et al., 2000b) or in APP-transgenic mouse lines (Games et al., 1995; Sturchler-Pierrat et al., 1997) indicates that Aβ alone is not sufficient to kick off full blown AD pathology since APP transgenic mice do not develop significant p-τ pathology. τ-pathology, e.g., PART, as a precursor lesion appears to be essential for Aβ to accelerate it (Gotz et al., 2001; Lewis et al., 2001). This hypothesis is supported by the finding that APP-transgenic mice on a τ knockout background did not develop cognitive deficits that were usually seen in APP-transgenic mice (Roberson et al., 2007).

4.2 Interplay with TDP-43

The accumulation of TDP-43 pathology in AD cases and in elderly individuals with AD-like dementia lacking sufficient amounts of AD pathology is frequent and currently designated as limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) (Nelson et al., 2019). Up to 70% of AD cases present co-morbid LATE-NC. These AD patients have smaller hippocampal volumes and a more severe clinical phenotype, when compared to demented individuals showing LATE-NC or ADNC alone (Josephs et al., 2017; Kapasi et al., 2020; McAleese et al., 2017). Of note, phosphorylated TDP-43 protein (pTDP-43) has been shown to co-aggregate with NFTs in AD (Amador-Ortiz et al., 2007; Higashi et al., 2007; Tome et al., 2021). NFT-like aggregates containing TDP-43 have been considered to

represent a distinct morphological subtype of TDP-43 proteinopathy in non-FTLD brains, type-β, which is predominant in the limbic system (Josephs et al., 2019). Interestingly, these NFT-like material exhibiting pTDP-43 mainly contained C-terminal species, including non-phosphorylated TDP-43 and pTDP-43 (serines 409/410, but not 403/404) (Tome et al., 2020). We recently observed that τ and TDP-43 proteins interact in symptomatic AD, and that this interaction occurs between p-τ and C-terminal TDP-43 species **(Fig. 2)** (Tome et al., 2021). An impact of TDP-43 on τ expression levels was also seen in *in vitro* and in APP/PS1-transgenic mice expressing human TDP-43 (Davis et al., 2017; Gu et al., 2017). In *Caenorhabditis elegans*, it was shown that TDP-43 can increase the toxicity and accumulation of τ (Latimer et al., 2022). This is supported by findings in human cases with ADNC. Here, the absence of TDP-43 has been associated with resilience and resistance to p-τ pathology (Latimer et al., 2019), whereas the presence of TDP-43 immunoreactivity was related to higher burdens of p-τ pathology, even in cases matched by Braak NFT stages. Consistently, post-mortem AD cases with TDP-43 pathology exhibited higher Braak NFT stages, reflecting a more widespread τ distribution than those without (Josephs et al., 2014). We also observed this phenomenon in a recent study (Koper et al., 2022), in which the burden of hippocampal p-τ was increased in symptomatic AD cases with LATE-NC, when compared to cases without LATE-NC. Taken together, these studies support synergy between TDP-43 and τ. Thus, it is tempting to speculate that TDP-43 is an important player in AD worsening its clinical course.

This does not mean that TDP-43 drives p-τ pathology. Both pathologies appear to develop in parallel and TDP-43 acts as accelerator for p-τ. Accordingly, despite the interplay between τ and TDP-43 in intraneuronal aggregates, today most researchers consider TDP-43 pathology and p-τ pathology in AD cases as lesions of separate origin, TDP-43 linked to LATE and p-τ to AD/PART (Montine et al., 2022; Nelson et al., 2019).

4.3 Interplay with α-synuclein

The accumulation and aggregation of α-synuclein (α-syn) is another common co-pathology present in many AD patients (Hamilton, 2000). Its neuropathological stage is associated with younger ages at death and a faster and more aggressive progression of pathology than in AD cases lacking α-syn co-pathology (Galpern and Lang, 2006; Robinson et al., 2021; Tome and Thal, 2021).

Studies have suggested that the involvement of α-syn is relevant in early stages of the disease (Twohig et al., 2018). Consistently, an accumulating body of work postulates that α-syn contributes to AD pathophysiology (Twohig and Nielsen, 2019): first, high α-syn levels in the CSF were found to be associated with the conversion from mild cognitive impairment to dementia (Shi et al., 2018); second, there is a significant correlation between α-syn levels and both total and p-τ levels in the CSF (Mollenhauer et al., 2008; Wennstrom et al., 2012) and third, both τ and α-syn pathological expression is strongly influenced by the APOE ε4 allele (Ramanan et al., 2019; Shi et al., 2017; Zhao et al., 2020; Zhou et al., 2016).

Similarly, patients with dementia with Lewy Body (DLB) also frequently exhibit p-τ pathology together with α-syn aggregates, usually co-localizing in NFTs, neurites or Lewy bodies (Arima et al., 2000; Ishizawa et al., 2003; Spires-Jones et al., 2017). Plasma p-τ can detect ADNC in patients with Lewy body disease (Hall et al., 2021). Importantly, Parkinson's Disease patients are usually at risk for dementia and the neuropathological burden is associated with cognitive decline (Aarsland et al., 2005; Braak et al., 2005).

An interaction between p-τ and α-syn, specifically with the C-terminal domain of α-syn, has also been described (Bhasne et al., 2018; Dasari et al., 2019; Giasson et al., 2003). Specifically, α-syn was shown to increase τ phosphorylation and increase its aggregation *in vitro* (Gassowska et al., 2014; Oikawa et al., 2016; Waxman and Giasson, 2011), namely in the context of liquid-

liquid phase separation (Siegert et al., 2021). Moreover, α-synuclein was observed to modulate p-τ pathology in transgenic mice (Bassil et al., 2021; Haggerty et al., 2011).

Overall, these studies also suggest a crosstalk between τ and α-synuclein proteins in the context of AD and DLB, although the biological and clinical implications of this interaction are not yet fully elucidated (Twohig and Nielsen, 2019) it may be tempting to speculate that the accumulation of α-syn causes deleterious effects in the AD brain that ultimately contribute to neurodegeneration alike TDP-43.

4.4 Interplay with noradrenaline metabolites

Recently it was shown that τ can be modified by the monoamine oxidase A (MAO-A) metabolite of norepinephrine 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL) towards an increased aggregation and propagation throughout the brain (Kang et al., 2022). This modification is due to the reaction of DOPEGAL with the Lys353 residue of τ. Kang et al. blocked the oxidation of norepinephrine with MAO-A inhibitors and inhibited, by doing so, the spreading of pathological τ. They observed a similar effect after replacing Lys353 residue of τ by Arg353 (Kang et al., 2022). These findings may have importance because the locus coeruleus, one of the earliest sites of p-τ accumulation in the brain (Attems et al., 2012; Braak and Del Tredici, 2011b), represents the primary source of the neurotransmitter norepinephrine (= noradrenaline) (Breton-Provencher et al., 2021; Dahlstrom and Fuxe, 1964). Accordingly, it is tempting to speculate that norepinephrine oxidation by MAO-A into DOPEGAL leads to an interaction with τ that causes production and aggregation of p-τ in locus coeruleus neurons. Furthermore, chronic stress can lead to an increased production of norepinephrine in the locus coeruleus (Ross and Van Bockstaele, 2020). Therefore, it cannot be excluded that stress has impact on the amount of τ phosphorylation and aggregation. Moreover, the neurons of the locus coeruleus project in multiple different brain regions and are involved in stress and sleep-wake

regulation (Ross and Van Bockstaele, 2020; Saper and Fuller, 2017; Van Egroo et al., 2022). These widespread afferents (**Fig. 4**) warrant widespread propagation of p-τ via locus coeruleus neurons once p-τ generation may have been initiated by the norepinephrine metabolite DOPEGAL.

5. τ pathology, granulovacuolar degeneration, necroptosis and neuron loss

The presence of ghost tangles is known for decades and demonstrates that neurons with NFTs, i.e., with p-τ pathology are subject to neuronal death **(Fig. 2, 3)** (Alzheimer, 1911). Although apoptosis has been scarcely observed in AD, it may not be a major contributor for AD-related neuron death (Stadelmann et al., 1999). Multiple other programmed forms of cell death exist (Tang et al., 2019). Recently, necroptosis – a programmed form of necrosis - has been reported in AD (Caccamo et al., 2017). Necroptosis is characterized by the formation of the necrosome complex consisting of phosphorylated receptor-interacting serine/threonine-protein kinase 1 (pRIPK1), pRIPK3, and phosphorylated mixed lineage kinase domain-like protein (pMLKL). pMKLK oligomers act, in this context, as final executor of necroptosis (Grootjans et al., 2017). Recently, we described that in AD brain, the necrosome is formed in lesions that are morphologically defined as granulovacuolar degeneration (GVD) (Koper et al., 2020). GVD consists of accumulated vacuoles with granules which exhibit autophagy markers (Funk et al., 2011), casein kinase 1δ and ε (Kannanayakal et al., 2006; Schwab et al., 2000; Thal et al., 2011), and many other mostly phosphorylated proteins including p-τ (Dickson et al., 1987), pTDP-43 (Kadokura et al., 2009; Lippa et al., 2009), and phosphorylated Aβ (Köhler, 2016; Kumar et al., 2016). In these vacuoles and granules, all activated necrosome components are also found (Koper et al., 2020). Interestingly, GVD occurs in τ transgenic but not in APP transgenic mice (Kohler et al., 2014) and can be induced by τ seeds in primary neuronal cell cultures (Wiersma et al., 2019). A recent study indeed showed that p-τ induces necroptosis and inflammation *in*

vitro and in a τ-transgenic mouse model, which can be inhibited with Nec-1, a necroptosis inhibitor (Dong et al., 2022). Therefore, it is tempting to speculate that τ pathology induces GVD and, by doing so, the activation of the necroptosis pathway. Since necrosome expression in GVD was associated with a reduction of the neuronal density in AD (Koper et al., 2020), it appears to be very likely that this form of GVD-mediated necroptosis is an important form of neuronal death in AD that can be induced by τ pathology. Recently, we observed that the expression of the necroptosis executor pMLKL was augmented in AD cases with co-morbid LATE-NC (Koper et al., 2022). Given that p-τ and TDP-43 also interact in AD, it is tempting to speculate that both τ and TDP-43 contribute to the induction of GVD-mediated necrosis. Initial evidence for a TDP-43 contribution on GVD-mediated necroptosis was seen in the hippocampal formation of ALS patients. Here, necrosome activation in GVD was associated not only with p-τ but also with TDP-43 pathology (Van Schoor et al., 2021). On the other hand, brain regions showing only pTDP-43 pathology in ALS, such as the motor cortex or the spinal cord, did not show GVD or any kind of necrosome accumulation pointing to the presence of p-τ as a potential prerequisite for the accumulation of the necrosome. Overall, the road from p-τ accumulation to GVD-mediated necroptosis may deserve more attention in the future as it offers potential for therapeutic intervention probably by employing already available inhibitors such as Nec-1 that showed a rescue of neurons in τ-transgenic mice (Dong et al., 2022).

Interestingly, the GVD distribution across the brain indicates that those brain regions related to chronic stress regulation and the modulation of the sleep-wakefulness state appear to be most vulnerable for GVD (Thal et al., 2011). All these regions receive afferent fibers from locus coeruleus (Breton-Provencher et al., 2021; Ross and Van Bockstaele, 2020; Saper and Fuller, 2017), i.e., from the brain region that is most vulnerable for developing p-τ pathology very early in the disease (Braak et al., 2011). Accordingly, these regions are presumably exposed to p-τ

aggregates that can trigger GVD and necroptosis since the initiation of p-τ pathology in the brain.

6. A central role for τ in the pathogenesis of Alzheimer's disease (Fig. 7)

In light of the described neuropathological age-related prevalence of p-τ pathology, its maturation in a given region, its propagation into further brain regions, and its interaction with Aβ and other proteins/metabolites, one can conclude that p-τ pathology is a prerequisite for the development of Alzheimer's disease, even though Aβ may be necessary for the conversion from the preclinical and mild cognitive impairment stage to full-blown dementia (Therriault et al., 2022). Arguments in favor of this hypothesis are (1) all symptomatic AD cases have p-τ pathology, usually of Braak NFT stage IV and higher (Thal et al., 2010; Thal et al., 2002), (2) p-τ pathology correlates better with cognitive decline than Aβ plaque pathology (Arriagada et al., 1992; Thal et al., 1998), (3) p-τ can lead to neuronal death as indicated by the presence of ghost tangles and by inducing GVD-mediated necroptosis pathway activation (Alzheimer, 1911; Bancher et al., 1989; Koper et al., 2020; Wiersma et al., 2019), and (4) p-τ pathology is accelerated by Aβ (Gotz et al., 2001; Lewis et al., 2001), which seems to be crucial to reach fully developed p-τ pathology (Braak NFT stages V-VI) (Braak et al., 2011; Spires-Jones et al., 2017). Braak NFT stage V/VI τ pathology is usually not seen in cases with PART and NFT-predominant type of dementia (Crary et al., 2014; Yamada, 2003). Another argument favoring this hypothesis is the fact that APP overexpressing mouse models do not develop neurofibrillary pathology (Games et al., 1995; Hsiao et al., 1996; Sturchler-Pierrat et al., 1997) and GVD (Kohler et al., 2014) as long as there is no expression of mutant τ protein (Lewis et al., 2001).

Given that the noradrenergic neurons of the locus coeruleus are the first to be involved in the development of p-τ pathology (Braak and Del Tredici, 2011b) and that norepinephrine (= noradrenaline) metabolites modify τ and enhance its aggregation potential and toxicity (Kang

et al., 2022), the primary involvement of these neurons may be crucial for further propagation of τ pathology. Neuron-to-neuron propagation appears to be accelerated by Aβ probably via a PrP^C-linked mechanism (Gomes et al., 2019). Another way of accelerating p-τ pathology spreading could be related to TDP-43 aggregates, which have been shown to propagate from neuron-to-neuron as well (Feiler et al., 2015; Porta et al., 2018), and can accelerate p-τ pathology (Latimer et al., 2019; Latimer et al., 2022). Finally, τ fibrils are capable of initiating GVD-meditated activation of the necroptosis pathway (Kohler et al., 2014; Wiersma et al., 2019), which ultimately leads to neuronal death, the culprit of neurodegeneration. Accordingly, it is tempting to reject the amyloid hypothesis and to replace it with a hypothesis that gives τ a more central role employing a probabilistic model in which genetic, environmental players and co-pathologies contribute towards the development of dementia (Frisoni et al., 2022). Such a central role of τ in the pathogenesis of AD explains, in this context, the lacking or low efficiency of Aβ targeting therapeutical approaches and strongly encourages the development of τ targeting therapies including those directed against downstream execution pathways of neurodegeneration, e.g., the necroptosis pathway.

7. References

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Figures

Figure 1 – τ isoforms and important phosphorylation sites. τ protein exhibits six isoforms, (a) 4R- or (b) 3R-τ, both with 3 isoforms each, which are expressed in AD cases and are distinguished by the presence or absence of exon 10, respectively. The most important phosphorylated epitopes are represented, which relate to τ maturation seen in human AD cases: pThr231 (AT180) and pSer202/Thr205 (AT8), followed by pSer396/pSer404 (PHF1), pThr181 (AT270), pThr212/pSer214 (AT100) and finally, by the conformational paperclip modification MC1.

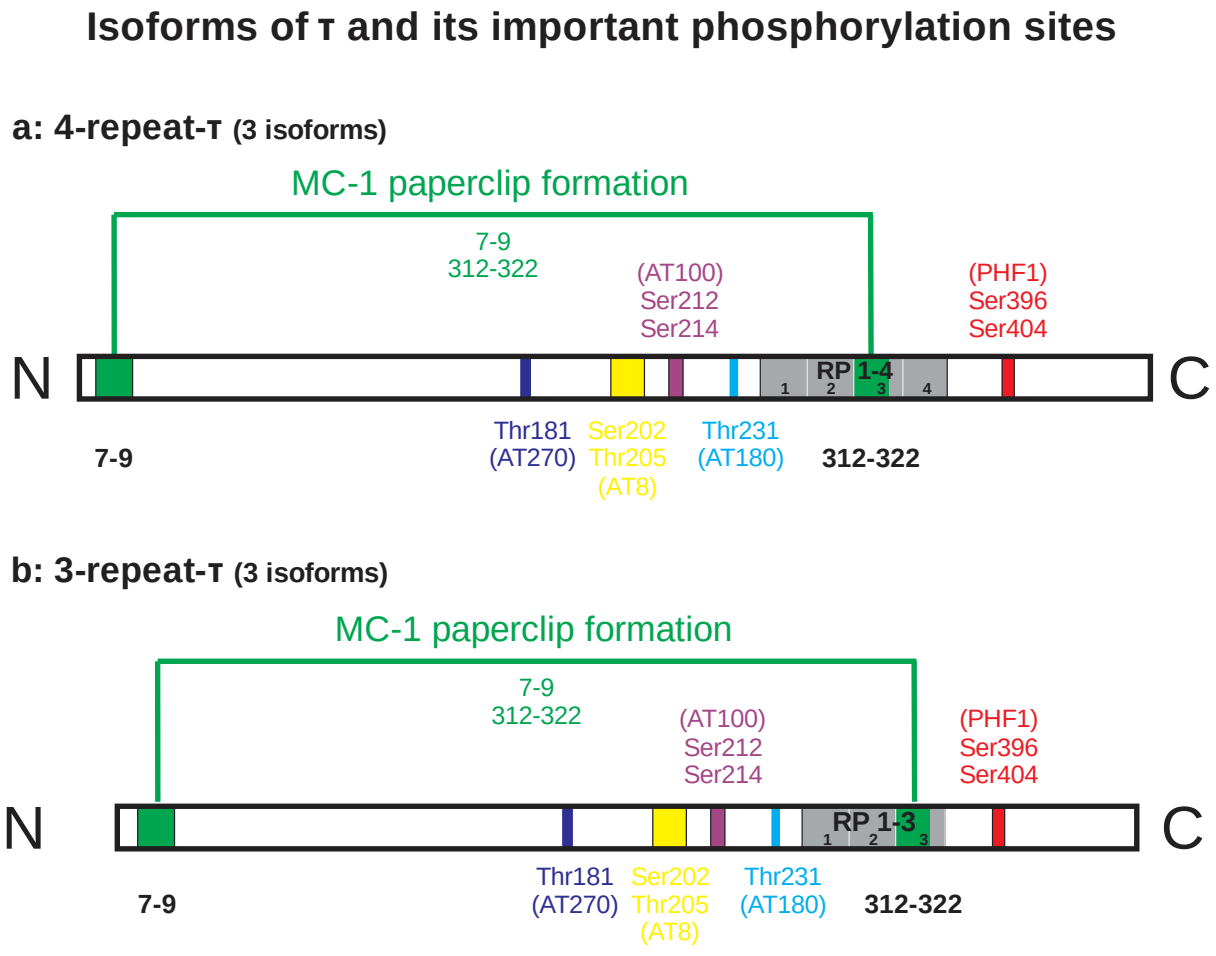

Figure 2 – Maturation and formation of τ NFTs in AD. In healthy brains, physiologically phosphorylated and non-phosphorylated τ is expressed (**a**). pThr396/pThr404-τ (PHF1) and pThr231-τ (AT180), are expressed in in the neuropil (IN-) or in the cytoplasm (IC) which precedes the formation of pretangles (**b**). Pretangles containing pSer205/pSer205 (AT8) are formed (**c1**), which can be accompanied by phosphorylated C-terminal TDP-43 species (**c2**). Conformationally-modified τ exhibiting the MC1 epitope occurs later and is found in all AD cases, with (**d1**) or without TDP-43 (**d2**). Gallyas-positive NFTs can then be detected (**e1**), co-expressing with pTDP-43 in a large subset of AD cases (**e2**). Ghost tangles can be observed in later stages of the disease, reflecting residual NFTs after the neurons have died (**f1,f2**).

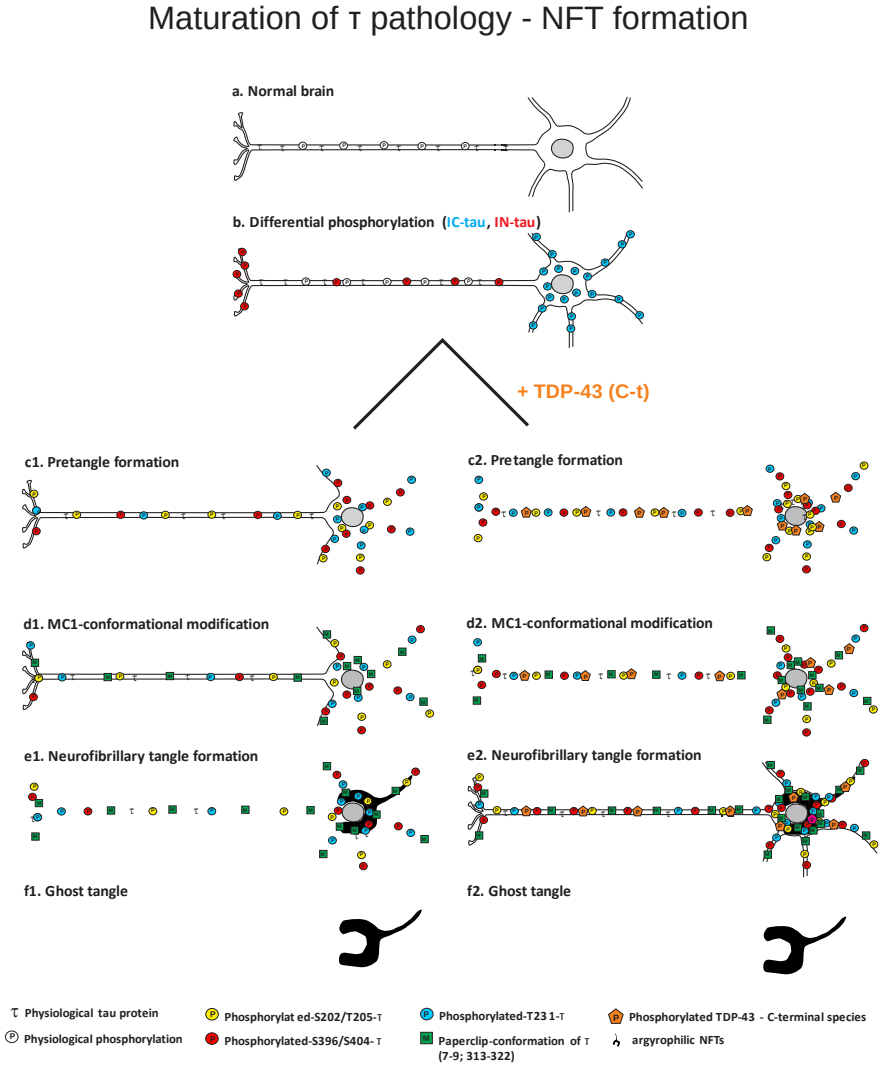

Figure 3 – τ lesions observed in post-mortem AD tissue. Neuropil threads are early lesions observed consisting of p-τ accumulation in distal dendrites (**a-b**, white arrowheads). τ protein can also be observed diffusely distributed in the cytoplasm, known as IC-τ (**a**, black arrows). Pretangles are observed in the cytoplasm and do not yet exhibit fibrillary structure (**a**, white arrow), in addition to neurons negative for τ pathology (**a**, black arrowheads). NFTs consisting of fibrillar p-τ aggregates are observed (**b**, black arrow) in later stages of p-τ pathology maturation, while "ghost" tangles remain after death of an NFT-bearing neuron (**c**). p-τ pathology in AD is commonly also seen in dystrophic neurites of neuritic plaques (**d**). In a subset of AD cases pTDP-43 can be observed in neurons with p-τ pathology, here depicted in the pretangle stage (**e**). Stainings: **a**: anti-pT^{231}-τ (AT180); **b, d**: anti-pS202/pT205-τ (AT8); **c**: Gallyas silver staining; **e**: double label immunofluorescence - anti-pS202/pT205-τ (AT8; red) and anti-pTDP43 (S409/S410).

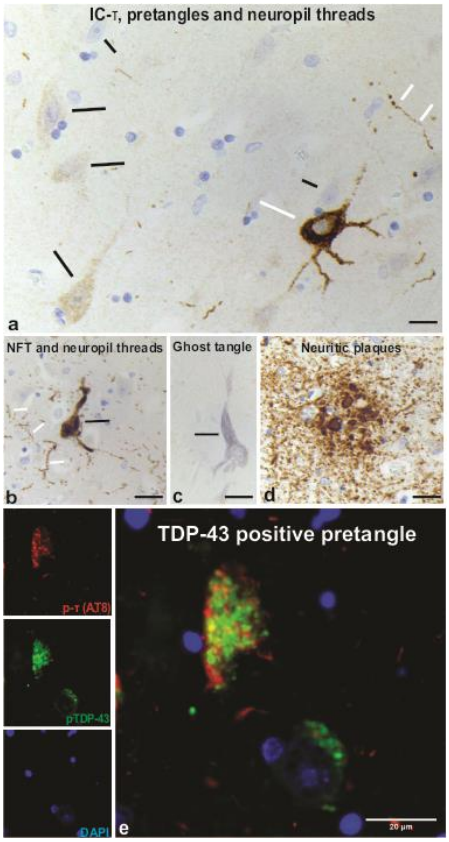

Figure 4 – Anterograde spreading of τ pathology in AD. Braak NFT stages as described by Braak et al. (Braak et al., 2011) including the brainstem stages a-1b (**a**) and anatomical spreading of τ pathology considering the anterograde neuronal transport pathways (**b**). Stages a-1b highlight the early involvement of the locus coeruleus, raphe nuclei, and the basal nucleus of Meynert, which later facilitates the spreading to the hippocampus and cortical areas by anterograde transport, resulting in a widespread distribution of τ aggregates in late stages of the disease.

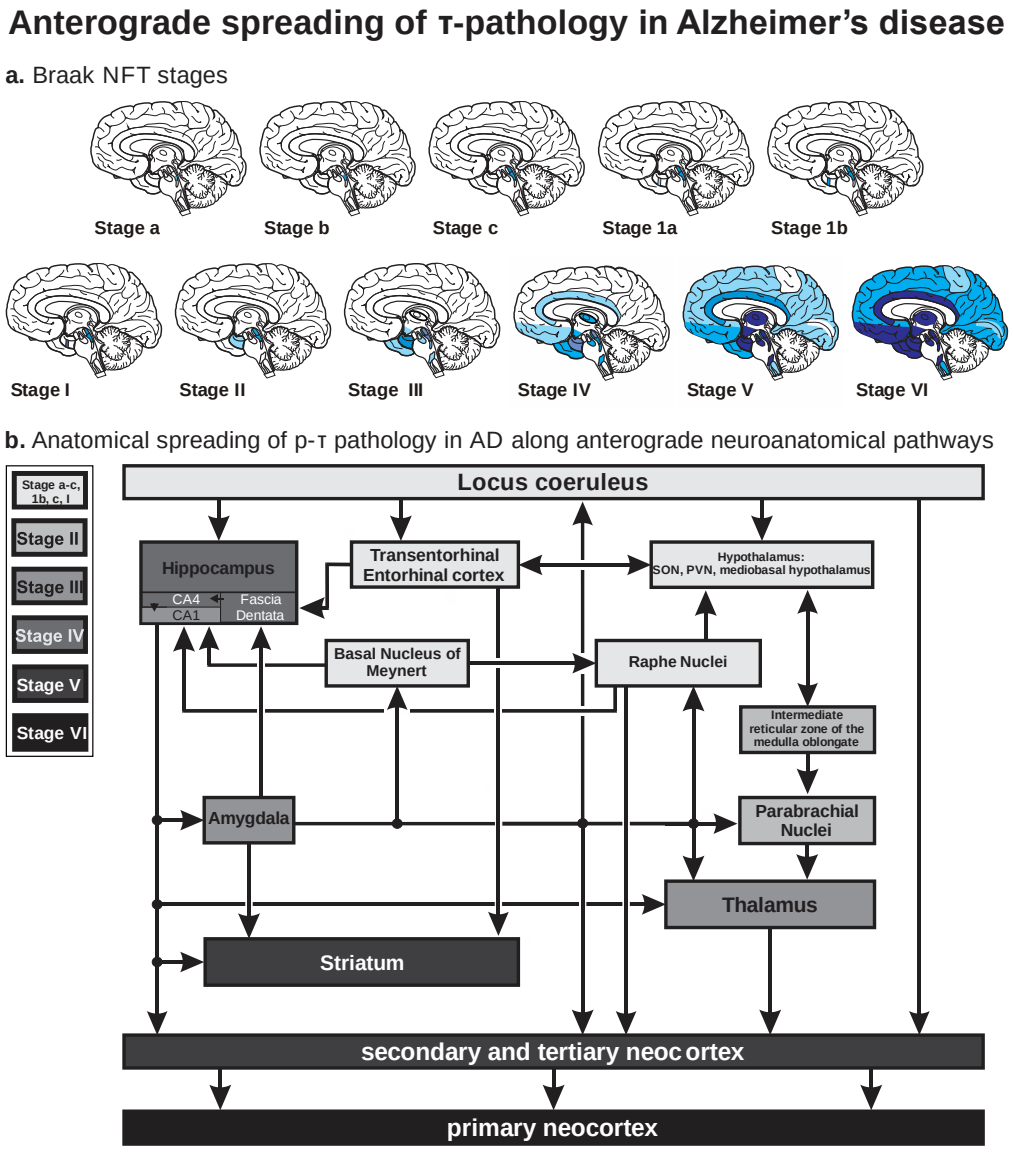

Figure 5 – Frequency of Braak NFT stages between 0-100 years. In a hospital-based cohort including 706 cases, we found only Braak NFT stage I cases until 40 years of age representing less than 20 % of the cases in the respective age groups. Between 41 and 60 years, Braak NFT stage I was observed in more than 60 % of the cases, with a few cases exhibiting higher stages. With increasing age (61-100 years), higher Braak NFT stages were more frequently seen and only a very small amount of cases remained negative for p-τ pathology.

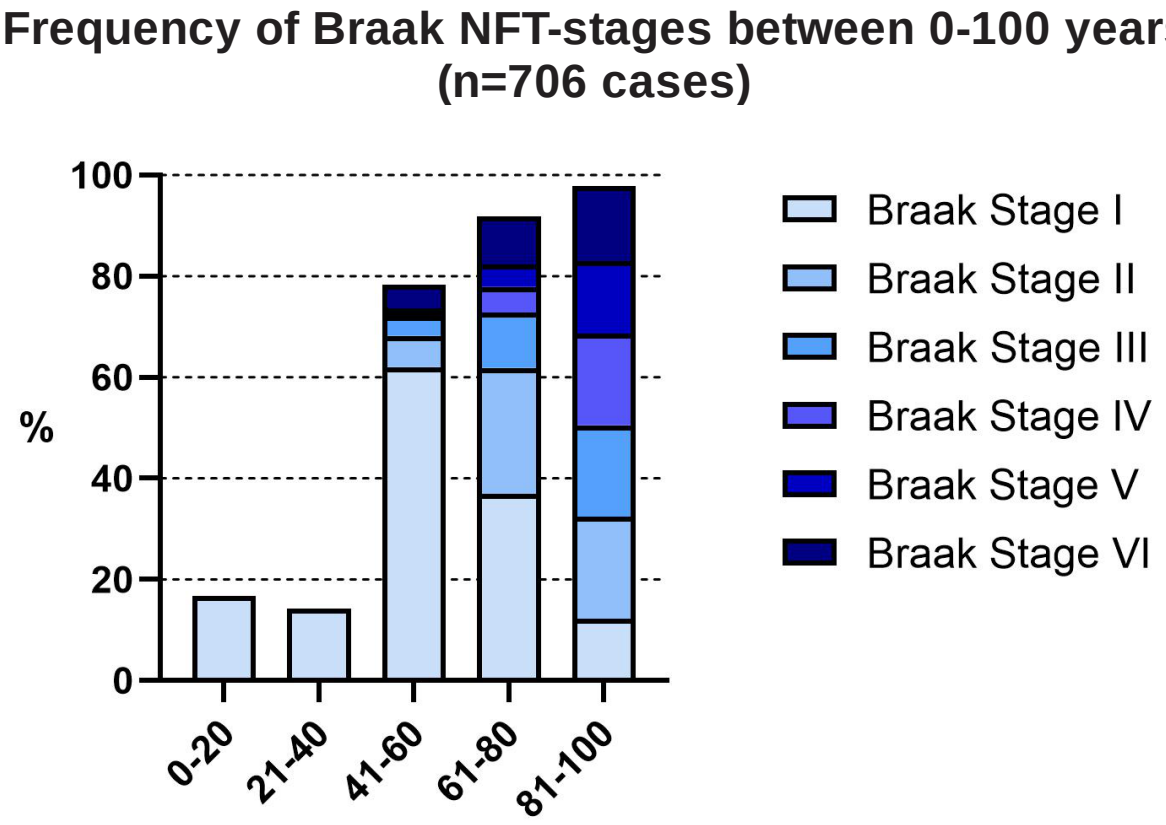

Figure 6 – Frequency of the occurrence of Aβ and τ pathologies alone and together in a hospital-based cohort (n=628). We observed that the majority of cases (n=423, 67,4%) exhibited both pathologies (AD), while 193 cases (30,7%) presented PART and only 12 (1,9%) presented only Aβ pathology (ADNC). In this analysis only cases exhibiting Aβ and/or p-τ pathology were included. Cases not fulfilling the diagnostic criteria for ADNC and/or PART were not included.

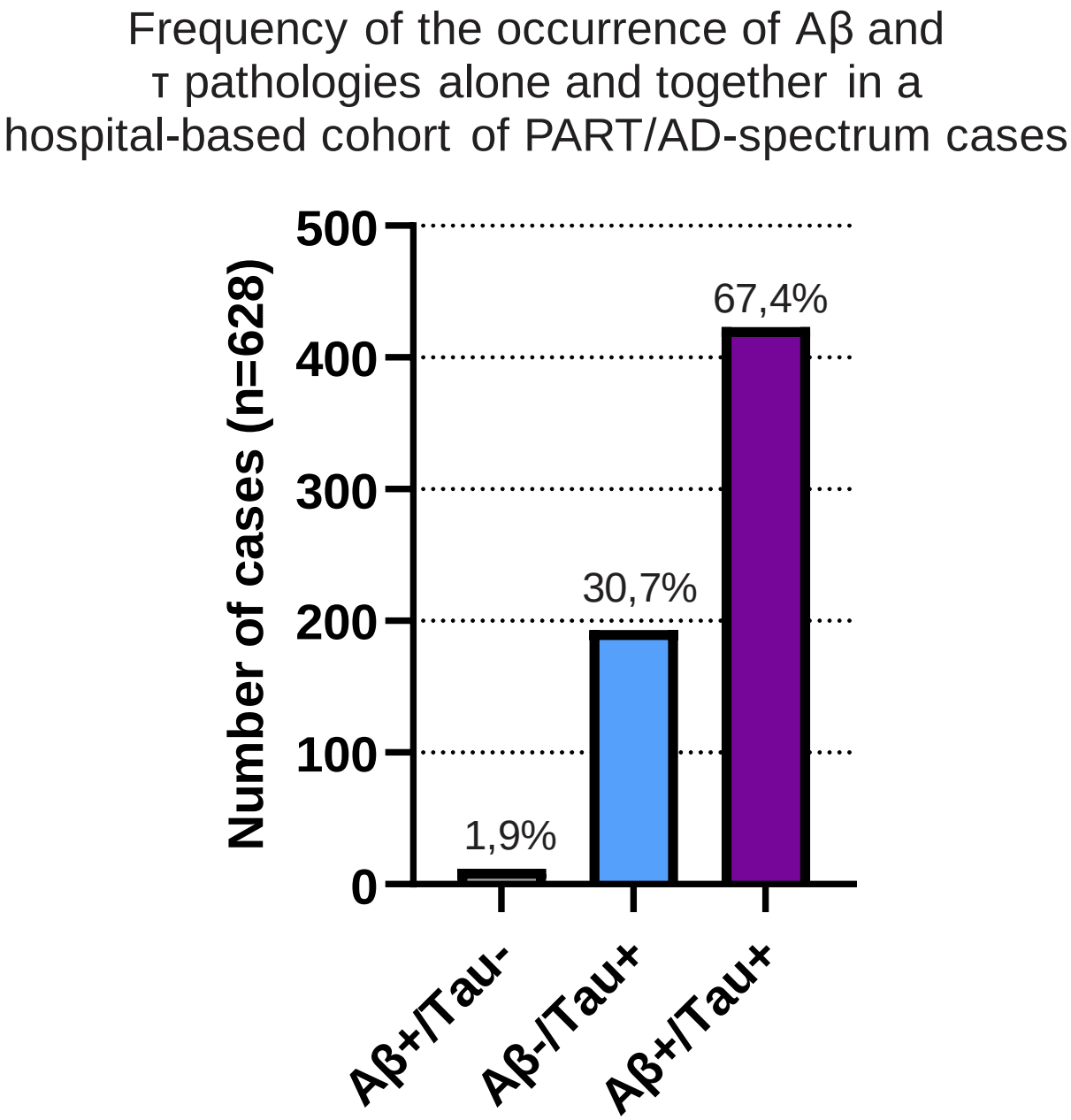

Figure 7 – Schematic representation of the hypothetical, central role of p-τ pathology in AD. ***Propagation and Acceleration***: p-τ pathology in the form of a primary tauopathy is considered to represent a prerequisite for the development of AD. This may be initiated by interaction of the norepinephrine metabolite DOPEGAL with τ leading to an accelerated phosphorylation and propagation of p-τ pathology (Kang et al., 2022). After the first seeds are available, the primary tauopathy can increase in severity and starts to spread into brain regions that become affected in later stages. In AD, this spreading and increase of τ pathology is presumably accelerated by additional factors, i.e., Aβ and, in cases with TDP-43 pathology, probably TDP-43 (Gomes et al., 2019; Gotz et al., 2001; Latimer et al., 2019; Latimer et al., 2022; Lewis et al., 2001). ***Maturation and neuron death***: In parallel, neurons with p-τ pathology undergo maturation from initial cytoplasmic/ neuropil τ (IC-τ/IN-τ) accumulation, pretangle and NFT formation in each region (Aragao Gomes et al., 2021; Bancher et al., 1989; Braak et al., 1994) before the neuron eventually exhibits the active necrosome complex in GVD bodies. This probably leads to GVD-mediated necroptosis and neuron death (Koper et al., 2020) leaving only a ghost tangle behind (Alzheimer, 1911). Whether other cell death pathways also contribute to p-τ induced neuron death is not yet fully understood.