Ageing Research Reviews 87 (2023) 101916

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

The unique neuropathological vulnerability of the human brain to aging

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ARTICLE INFO

Keywords:
Human brain aging
Alzheimer
Argyrophiic grain disease
Aging-related tau astrogliopathy
Limbic predominant TDP-43 proteinopathy
Amygdale predominant Lewy body disease
Hippocampal sclerosis
Archicortex
Paleocortex
Seeding

ABSTRACT

Alzheimer's disease (AD)-related neurofibrillary tangles (NFT), argyrophilic grain disease (AGD), aging-related tau astrogliopathy (ARTAG), limbic predominant TDP-43 proteinopathy (LATE), and amygdala-predominant Lewy body disease (LBD) are proteinopathies that, together with hippocampal sclerosis, progressively appear in the elderly affecting from 50% to 99% of individuals aged 80 years, depending on the disease. These disorders usually converge on the same subject and associate with additive cognitive impairment. Abnormal Tau, TDP-43, and α-synuclein pathologies progress following a pattern consistent with an active cell-to-cell transmission and abnormal protein processing in the host cell. However, cell vulnerability and transmission pathways are specific for each disorder, albeit abnormal proteins may co-localize in particular neurons. All these alterations are unique or highly prevalent in humans. They all affect, at first, the archicortex and paleocortex to extend at later stages to the neocortex and other regions of the telencephalon. These observations show that the phylogenetically oldest areas of the human cerebral cortex and amygdala are not designed to cope with the lifespan of actual humans. New strategies aimed at reducing the functional overload of the human telencephalon, including optimization of dream repair mechanisms and implementation of artificial circuit devices to surrogate specific brain functions, appear promising.

1. Introduction

Heterogeneous pathologies are now known to contribute to cognitive impairment, behavioural and psychological deterioration, neuropsychiatric symptoms such as depression, and dementia in the elderly. For several decades, neuropathological and clinical studies have identified two main biological processes in human brain aging. On the one hand, there is the primary degeneration of nerve cells, mainly represented by neurofibrillary tangles and senile plaques culminating in Alzheimer's disease dementia. On the other, there is then the degenerative alteration of cerebral blood vessels, often occurring in parallel with the systemic degeneration of large and medium size arteries, arterioles, venules, and capillaries that may result in various vascular deficits, including cognitive impairment and dementia of vascular origin. The two biological processes may occur with variable intensity in the same individual. In recent decades, several age-related neurodegenerative diseases have been newly identified in humans such as frontotemporal lobar degeneration (FTLD), now covering several separate entities, and dementia with Lewy bodies (DLB), along with others.

In addition, several brain neuropathological changes are linked to human brain aging, including argyrophlic grain disease (AGD), aging-related tau astrogliopathy (ARTAG), Lewy body disease (LBD), TDP-43

Abbreviations: ADD, Alzheimer's disease dementia; ADNC, Alzheimer disease neuropathological change; AGD, argyrophilic grain disease; APP, amyloid precursor protein; ARTAG, Aging-related tau astrogliopathy; CBD, corticobasal degeneration; CERAD, Consortium to Establish a Registry for Alzheimer's disease; DLB, dementia with Lewy bodies; ERK, extracellular regulated MAP kinase; fAD, familial Alzheimer's disease; FTLD, Frontotemporal lobe degeneration; GSK, glycogen synthase kinase; GVD, Granulovacuolar degeneration; LATE, Limbic age-related TDP-43 encephalopathy; LBD, Lewy body disease; MCI, mild cognitive impairment; NFT, neurofibrillary tangle; PART, Primary age-related tauopathy; PD, Parkinson's disease; PHF, paired helical filament; PiD, Pick's disease; PMCA, protein misfolding cyclic amplification; PS1, PSEN1, presenilin 1; PSP, progressive supranuclear palsy; RT-QuIC, real-time quaking-induced conversion; sAD, sporadic Alzheimer's disease; SAPK/JNK, stress-activated protein kinase/c-Jun N-terminal kinase; SP, senile plaque; TDP-43, TARDBP, TAR DNA-binding protein 43; TREM, triggering receptor expressed in myeloid cells; TSA, thorn-shaped astrocyte.

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https://doi.org/10.1016/j.arr.2023.101916
Received 27 February 2023; Received in revised form 19 March 2023; Accepted 21 March 2023
Available online 28 March 2023

encephalopathy (LATE), and hippocampal sclerosis. Due to the high prevalence of Alzheimer's disease-neuropathological change (ADNC), all of them are common in patients with sAD and may contribute to worsening the clinical symptoms of AD, but they may also occur as separate neuropathological neurodegenerative changes. Most occur in combination as co-morbidities.

ADNC, AGD, ARTAG, limbic α-synucleinopathy, LATE neuropathological change (LATE-NC), and hippocampal sclerosis will be discussed in this paper. Other age-related alterations such as lipofuscin accumulation, granulovacuolar degeneration, Hirano bodies, and corpora amylacea are not considered here in detail.

All these alterations are manifestations of brain aging, although none of them per se can be considered the only expression of brain aging. Currently, these alterations reflect the complexity of brain aging neuropathology. Moreover, all these neuropathological changes are prevalent in humans and poorly represented or absent in other species. The uniqueness of the neuropathological characteristics of human brain aging points to the specific vulnerability of the human brain to aging compared with other species. Efforts are needed to dissect and identify the mechanisms leading to such vulnerability in humans as well as to discern the mechanisms preventing neurodegenerative changes in old individuals of other species.

2. Neurofibrillary tangles and senile plaques: Alzheimer's disease-neuropathological change (ADNC)

Neurofibrillary tangles (NFTs) and senile plaques (SPs) composed of a central core surrounded by dystrophic neurites, as first described by Alois Alzheimer and Oskar Fisher (Alzheimer, 1907; Fischer, 1907, 1910, 1912), are hallmark neuropathological lesions in human brain aging and AD, and named Alzheimer's disease neuropathological change (ADNC) (Fig. 1).

β-amyloid is the main component of cerebral amyloid in β-amyloid angiopathy and SPs (Glenner and Wong, 1984; Glenner et al., 1984; Masters et al., 1985; Iwatsubo et al., 1994; Masters and Beyreuther, 2006a). β-amyloid derives from the amyloid precursor protein (APP) which is a transmembrane protein that modulates brain cell adhesion, synaptic plasticity, and multiple intracellular signaling. Cleavage of APP through α- and δ-secretases leads to the non-amyloidogenic pathway of APP degradation, whereas the combined action of β- and δ-secretases

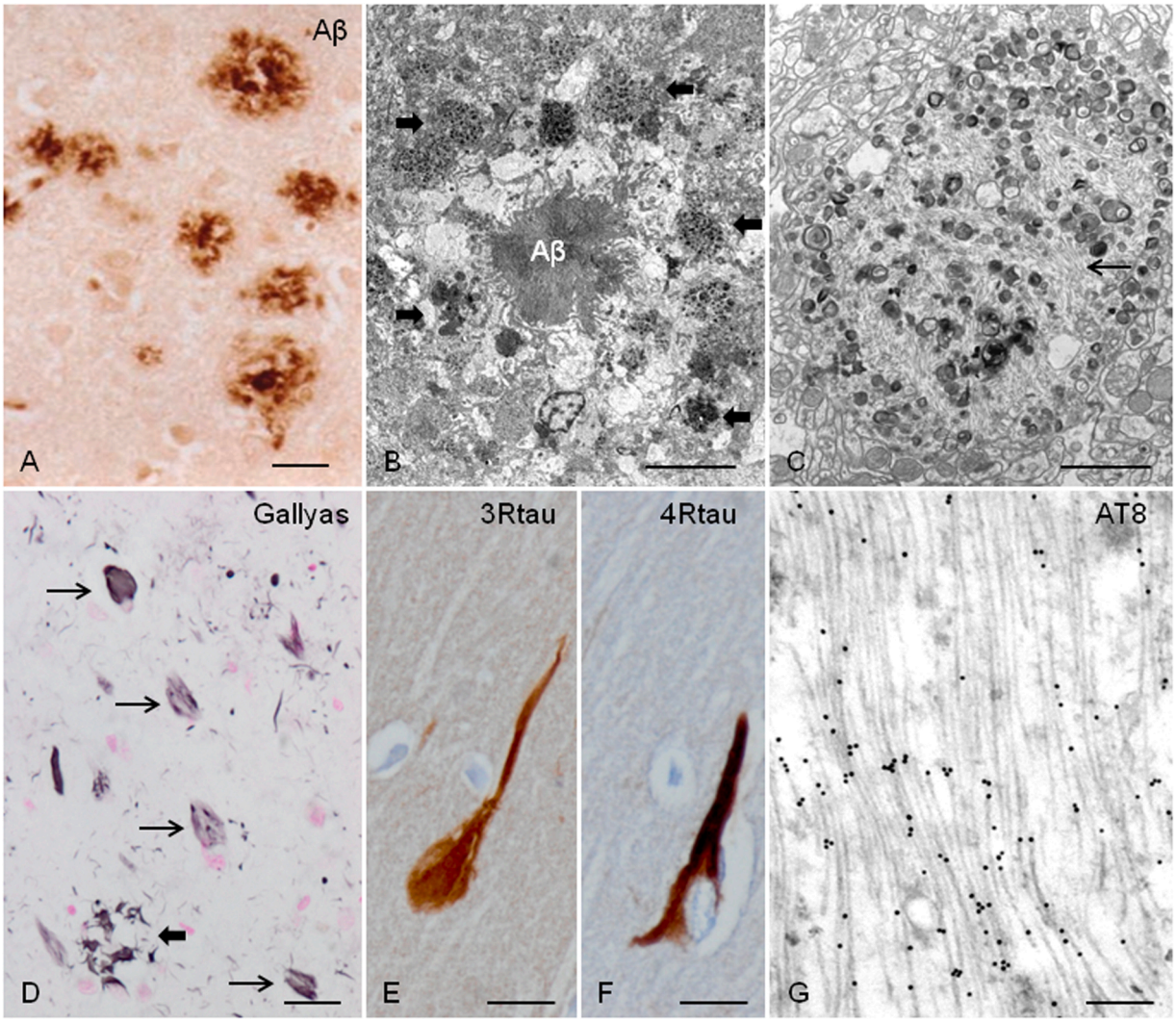

Fig. 1. Alzheimer's disease neuropathological change. A: senile plaques in the temporal cortex as seen with β-amyloid (Aβ) immunohistochemistry; B: senile plaque with a central corre of β-amyloid (surrounded by dystrophic neurites (thick arrows); C: Dystrophic neurite containing paired helical filaments (thin arrow), abnormal mitochondria, and large numbers of polymorphic and dense inclusions and vesicles; D: Neurofibrillary tangles (NFT) (thin arrows) and one senile plaque (thick arrow) as seen with the Gallyas method in the temporal cortex; E: 3Rtau immunohistochemistry of a NFT; F: 4Rtau immunohistochemistry of a NFT; G: immunoelectronmicroscopy of paired helical filaments stained with the antibody AT8 showing the localization of phospho-tau deposition (black dots). A, D-F: paraffin sections; B, C, G: transmission elecron microscopy. A, bar = 50 μm; B, bar = 10 μm; C, bar = 2 μm; D, bar = 50 μm; E, F, bar = 25 μm; G, bar = 0.2 μm.

generates truncated C-terminal peptides $A\beta_{42}$ or $A\beta_{40}$, and many other small forms (Beyreuther and Masters, 1991; Masters and Beyreuther, 2006b; Masters and Beyreuther, 2011; Masters and Selkoe, 2012; Chen et al., 2017). Seen under electron microscopy, β-amyloid is composed of fibrils with a high degree of conformational variability: α-helical intermediate conformation on the membrane, and structural transition to the β-conformation of amyloid fibrils. Cryo-electron microscopy reveals that $A\beta_{42}$ fibril is composed of two intertwined protofilaments with specific morphology (Gremer et al., 2017; Yang et al., 2022a, 2022b) (Fig. 1A-C).

The main constituent of NFTs, dystrophic neurites of SPs, and neuropil threads is abnormal tau (Delacourte and Defossez, 1986; Goedert et al., 1988; Kosik et al., 1986; Grundke-Iqbal et al., 1986a; Iqbal et al., 1986; Wischik et al., 1988; Buée et al., 2000; Iqbal et al., 2005; Mandelkow and Mandelkow, 2012; Spillantini et al., 2013; Arendt et al., 2016; Iqbal et al., 2016; Goedert and Spillantini, 2019). A combination of all six hyper-phosphorylated brain tau isoforms (3Rtau and 4Rtau expressed in brain), generated from alternative *MAPT* exon 10 splicing, is characteristic of AD tau with a ratio 1/1 (Goedert et al., 1982; Goedert et al., 1992; Delacourte et al., 1999). Western blots of sarkosyl-insoluble fractions show main bands of phospho-tau of 68 kDa, 64 kDa, and 60 kDa, an upper band of about 73 kDa, and several lower bands and smears of about 50 kDa and 30 kDa, as well as bands of lower molecular weight corresponding to truncated tau. Abnormal tau in sAD is characterized by various post-translational modifications including hyper-phosphorylation at different sites, glycosylation, acetylation, truncation at glutamic acid 391 and at aspartic acid 421, altered conformation, oligomerization, and β-sheet-rich fibril aggregation, among others (Grundke-Iqbal et al., 1986b; Weaver et al., 2000; García-Sierra et al., 2003; Hyman et al., 2005; Avila, 2006; Zilka et al., 2006; Luna-Muñoz et al., 2007; Mondragón-Rodríguez et al., 2008; Arendt et al., 2016; Avila, 2016; Iqbal et al., 2016; Goedert and Spillantini, 2019; Hernández et al., 2022). Tau hyper-phosphorylation is mediated by specific kinases accompanied by inhibition of phosphatases (Hanger et al., 2009; Wang et al., 2013; Arendt et al., 2016). Selected active kinases such as ERK1/2, p38, SAPK/JNK, and GSK3β co-localize with abnormal tau deposits in brain tissue (Ferrer et al., 2001a, b; Ferrer et al., 2005).

Under electron microscopy NFTs are seen to be composed of paired helical filaments (PHF), whereas straight filaments occur in pre-tangles, and granular tau is composed of oligomers. Cryo-electron microscopy reveals a particular conformation profile of AD-tau (Fitzpatrick et al., 2017; Shi et al., 2021a, 2021b; Kametani and Hasegawa, 2022) (Fig. 1D-G).

Mechanisms of protein degradation and debris removal are also altered in human brain aging and sAD. The ubiquitin-proteasome system is defective, and ubiquitin and p62 are accumulated in tau-positive deposits (Riederer et al., 2011; Salminen et al., 2012; Lee et al., 2013; Weng and He, 2021). Moreover, misframed ubiquitin is expressed in abnormal tau-protein aggregates (Chadwick et al., 2012; Gentier and van Leeuwen, 2015), and the immunoproteasome is activated in sAD and APP/PS1 double-transgenic mice (Ferrer et al., 2004; Aso et al., 2012).

Autophagy, including mitophagy, is impaired in brain aging and sAD (Nixon et al., 2005; Lipinski et al., 2010; Pradeepkiran and Reddy, 2020).

Although the localization and distribution of NFTs progresses following a stereotyped pattern, the pace varies from one individual to another. NFTs have been identified in selected nuclei of the brain stem in young people in their twenties (subcortical stages a-c) (Braak and Del Tredici, 2011; Braak and Del Tredici, 2015; Arnsten et al., 2021). Later on, NFTs extend to the entorhinal and transentorhinal cortices (stages I-II), hippocampus, amygdala, inferior part of the temporal lobe and limbic system (stages III-IV), and finally to the diencephalon and most parts of the telencephalon (stages V-VI). Thus, the number of NFTs increases with age and affects about 85% of human beings at the age of 65, at least involving the entorhinal and transentorhinal cortex, and the hippocampus, temporal cortex, and limbic system nuclei. About 98% of individuals have NFTs in the telencephalon at 80 (Braak and Braak, 1991; Braak and Braak, 1997; Braak et al., 2011; Ferrer, 2012; Arnsten et al., 2021; Ferrer, 2022a). However, SPs appear later, and their regional distribution also differs from NFT progression (Thal et al., 2002).

About 30% of people have SPs at age 65, and around 60% over 80. NFTs without SPs are detected in about 35% of individuals older than 90 (Braak et al., 2011; Ferrer, 2012; Arnsten et al., 2021; Ferrer, 2022).

Genetic factors modulate ADNC. The rarer familial forms of AD (fAD), which have an earlier onset, are linked to mutations in three genes which encode membrane proteins associated with membrane protein proteolysis and, in particular, with the amyloidogenic pathway: the gene encoding β-amyloid precursor protein named *APP*, presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*); increased APP dosage is also causative of fAD and β-amyloid angiopathy (Goate et al., 1991; Chartier-Harlin et al., 1991; Murrell et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995; Rogaev et al., 1995; Bertram and Tanzi, 2011).

Sporadic AD (sAD) is the most common cause of dementia in the elderly. The prevalence of dementia in 65–69 years olds is about 1–5:100 individuals; over the age of 85, between 25% and 30% of individuals suffer from dementia (Knopman et al., 2011). Between 50% and 80% of cases with dementia have sAD (Knopman et al., 2011). AD dementia (ADD) is preceded by mild cognitive impairment (MCI), and by pre-clinical AD that is characterized by the presence of ADNC and positive biological markers without apparent cognitive impairment (Knopman, 2011; Sperling et al., 2011; Knopman et al., 2012). Dementia in AD occurs at advanced stages of NFT pathology (stages V-VI) accompanied by β-amyloid deposition at advanced Thal's phases (Hyman et al., 2012; Montine det al, 2012).

Individuals with Down syndrome, caused by the presence of all or part of the third copy of chromosome 21, have large numbers of SPs and NFTs at the age of 40 (Gomez et al., 2020; Fortea et al., 2021).

Apolipoprotein E epsilon 4 (ApoEε4) was the first low-penetrating genetic risk factor of sAD identified (Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993; Jun et al., 2010). More than seventy genetic risk factors have been identified in cases with AD dementia. These include HLDL receptor related protein 1 (*LRP1*), low density lipoprotein protein receptor 1 (*LDLR*), interleukin 1a (*IL1A*), clusterin (*CLU*), phosphatidylinositol binding clathrin assembly protein (*PICALM*), complement component (3b/4b) receptor 1 (*CR1*), bridging integrator 1 (BIN1*),* triggering receptor expressed on myeloid cells 2 (*TREM2),* sortilin-related receptor 1 *(SORL1),* ADAM metallopeptidase domain 10 (*ADAM10),* ATP binding cassette subfamily A member 7 (*ABCA7),* Spi-1 proto-oncogene (*SPI1*), paired immunoglobin like type 2 receptor alpha (*PILRA),* membrane-spanning 4-domains subfamily A (*MSA4*), CD2-associated protein (*CD2AP*), and ephrin receptor A1 (*EPHA1*) (Harold et al., 2009; Lambert et al., 2009; Seshadri et al., 2010; Jun et al., 2010; Jones et al., 2010; Hollingworth, Lambert et al., 2011, 2013; Naj et al., 2014; Sims et al., 2017; Pimenova et al., 2018; Jansen et al., 2019; Kunkle et al., 2019; Andrews et al., 2020; Jansen et al., 2019; Tansey et al., 2018; Bellenguez et al., 2022).

However, individuals with NFT stages I-IV with absent β-amyloid burden, suffering from the so called primary age-related tauopathy (PART), show a lower prevalence of *ApoEε4*, rs28834970 *PTK2B*, rs6733839 in the *BIN1*, and *CR1* genes, and a higher prevalence of *ApoEε2* (Bell et al., 2019; McMillan, 2018; Robinson et al., 2020a, 2020b).

Clinical and post-mortem neuropathological changes during human brain aging and sAD progression are similar although with augmented intensity and amplified distribution of ADNC in parallel with the cognitive and mental impairment (Hubbard et al., 1990; Crystal et al., 1988; Braak and Braak, 1991; Braak and Braak, 1997; Hulette et al., 1998; Price and Morris, 1999; Knopman et al., 2003; Bennett et al., 2006; Braak and Del Tredici, 2011; Braak et al., 2011; Ferrer, 2012;

Tsartsalis et al., 2018; Arnsten et al., 2021). For this reason, a continuum of brain aging with ADNC, and sAD has been proposed (Ferrer, 2022, 2023). The present comments should not be taken to imply that sAD pathology is synonymous with brain aging, as brain aging is manifested by additional neuropathological changes (and molecular modifications) not linked to ADNC. Moreover, progeric syndromes are not manifested with ADNC (Nelson et al., 2011a, 2011b).

Altered protestasis in brain aging AD is not restricted to tau and β-amyloid. Whole proteomics studies have shown progressive deregulation of protein expression in the elderly, with marked individual variations and regional differences within the same age range; moreover, altered expression levels affect multiple structures and metabolic pathways (Musunuri et al., 2014; Hondius et al., 2016; Yu et al., 2018; McKetney et al., 2019; Wingo et al., 2019; Mendonça et al., 2019; Ping et al., 2020; Wingo et al., 2021; Velásquez et al., 2021; Gao et al., 2022).

Phosphoproteomics analyses in cases with MCI and AD dementia have identified deregulated protein phosphorylation of multiple proteins involved in a variety of molecular pathways (Tan et al., 2015; Triplett et al., 2016; Dammer et al., 2015; Sathe et al., 2020; Ping et al., 2020; Bai et al., 2020; Ferrer et al., 2021). Importantly, deregulated phosphorylation occurs in cases at early stages of ADNC (Braak stages I-II) in the frontal cortex in which NFTs and SPs are absent (Ferrer et al., 2021). Phosphoproteins deregulated in sAD are structural components of cell membranes and membrane signaling, cytoskeleton, synapses (including neurotransmitter receptors), serine-threonine kinases, proteins involved in energy metabolism, and RNA processing and splicing. Although deregulated protein phosphorylation is more pronounced at stages III and IV, and it is maintained at advanced stages of sAD, deregulated phosphorylation precedes tau and β-amyloid deposition in human brain aging (Ferrer et al., 2021).

β-amyloid plaques and β-amyloid angiopathy may be found in old dogs, bears, pinniped species, dolphins and other cetaceans, monkeys, and higher non-human primates. β-amyloid plaques are usually diffuse whereas SPs are exceptional (Price et al., 1991; Giannakopoulos et al., 1997; Borràs et al., 1999; Head, 2011; Morelli et al., 1996; Yu et al., 2011; Languille et al., 2012; Pérez et al., 2013; Uchihara et al., 2016; Edler et al., 2017; Takaichi et al., 2021; Schultz et al., 2021a, 2021b).

Phosphorylated-tau deposits in neurons are rarely encountered in most aged mammals; tau deposits have the characteristics of pre-tangles rather than NFTs, as in aged dogs (Borràs et al., 1999) and mouse lemurs (Giannakopoulos et al., 1997). Intracytoplasmic tau inclusions in neurons, astrocytes, and oligodendrocytes are found in aged baboons (Schultz et al., 2000a,2000b), but only rarely in aged gorillas (Pérez et al., 2013) and chimpanzees (Edler et al., 2017). In baboons, a combination of neuronal and glial tau pathology preferentially affects limbic brain areas, including the hippocampal formation; no apparent relationship was noted between the density and distribution of tau pathology and β-amyloid deposits (Schultz et al., 2021a and b). Tau accumulation in the brain of old sea lions, seals, and walruses forms argyrophilic fibrillar 3Rtau and 4Rtau aggregates in the neuronal somata and neurites; few tau aggregates are found in oligodendrocytes and microglia; their abundance and distribution largely differs from that seen in AD (Takaichi et al., 2021). A unique 4Rtauopathy without β-amyloid deposits mainly involving neurons of the neocortex but not the hippocampus, accompanied by widespread coiled bodies in the cerebral white matter, has been reported in aged domestic cats (Poncelet et al., 2019). *Octodon degus* is proposed as a valuable natural model of sAD (Hurley et al., 2018). However, ADNC largely differs in *O. degus* when compared with sAD; moreover, ADNC has not been identified in *O. degus* bred in captivity (Steffen et al., 2016).

Rather than discussing whether AD is restricted to humans, the available information points to a link between brain aging and abnormal tau and APP metabolism in many species, including dogs, bears, pinnipeds, primates, and cetaceans. Yet, in none of them (excepting baboons) do SPs, and more precisely NFTs, show the prevalence, localization, and widespread distribution they manifest in human beings culminating in a clinical and neuropathological state consistent with AD dementia.

Several transgenic animal models are used to mimic AD, most of them transgenic mice bearing simple, double, or triple mutations of genes involved in the β-amyloid pathway. All of them replicate some aspects of β-amyloidopathy including the development of β-amyloid plaques and β-amyloid angiopathy. Yet the addition of mutations in the tau gene is needed to generate both SPs and NFTs. Although mice bearing multiple mutations covering the β-amyloid pathway and tau resemble fAD, the translation of most beneficial therapeutic strategies in these models fail to prove effective in humans (Drummond and Wisniewski, 2017; Gotz et al., 2018; Mckean et al., 2021; Takeuchi et al., 2011; Vitek et al., 2021). The TgF344-AD rat expresses human APP with the Swedish mutation and human presenilin 1 with the ΔE9 mutation on the Fischer 344 background. These rats show Aβ plaques, NFTs, cognitive deficits, neuronal loss, reactive astrocytosis, chronic neuroinflammation, and reduced expression of triggering receptor expressed on myeloid cells-2 (TREM2) (Cohen et al., 2013; Bac et al., 2022). Further studies are needed to learn whether transgenic rats are suitable models to be used to test new therapies for AD.

3. Associated proteinopathies

Since sAD is a prevalent human age-related disorder, it is not uncommon for sAD to be associated with other age-related proteinopathies which have and additive effect on cognitive and neuropsychiatric impairment in old age (Higashi et al., 2007; Brayne et al., 2009; Kovacs et al., 2013; Kovacs et al., 2015; Elobeid et al., 2016; Spires-Jones et al., 2017; Robinson et al., 2018a, 2018b; Wennberg et al., 2019; Robinson et al., 2021; Montine et al., 2022). Co-morbidities are also common in the younger-old (Beach and Malek-Ahmadi, 2021).

3.1. *Argyrophilic grain disease (AGD)*

AGD is an age-related tauopathy characterized by argyrophilic granules or comma-shaped dendritic protrusions that contain phosphorylated 4Rtau, which are accompanied by pre-tangles, in the entorhinal cortex, hippocampus, amygdala, and neighbouring temporal cortex (Braak and Braak, 1987, 1989; Tolnay et al., 1997a; Tolnay and Clavaguera, 2004; Jellinger, 1998; Tolnay and Probst, 2008; Grinberg and Heinsen, 2009; Ferrer et al., 2008).

The frequency of AGD increases with age; it is present in about 20% and 40% of individuals at the age of 90 and 100, respectively (Braak and Braak, 1998; Ding et al., 2006; Rodriguez and Grinberg, 2015; Rodriguez et al., 2016). AGD occurs in about 25% of AD cases (Yokota et al., 2018). Other studies go further: tau-positive grains are always present in centenarians' hippocampus (Pham et al., 2011).

Argyrophilic grains are dendritic protrusions usually containing tau, and lacking spines, as revealed with combined tau immunohistochemistry and the Golgi method (Tolnay et al., 1998; Ferrer et al., 2008). In addition, tau-positive coiled bodies in oligodendrocytes and thorn-shaped astrocytes are found in the temporal white matter (Botez et al., 1999; Ikeda et al., 2018) (Fig. 2).

Ballooned neurons containing neurofilaments and αB-crystallin in the amygdala are constant features in AGD (Tolnay and Probst, 1998), but they may also occur in AD (Fujino et al., 2004).

Tau pathology in AGD has a particular phospho-tau pattern characterized by two bands of 68 kDa and 64 kDa that can be modified by the presence of additional bands in cases with concomitant AD pathology, with a ratio 3 R/4 R = 1/2 (Togo et al., 2002a, 2002b; Tolnay et al., 2002; Zhukareva et al., 2002; Ferrer et al., 2008). Tau deposits in AGD may be recognized by different antibodies directed to phospho-tau sites, including Ser262, conformational modifications, and truncated tau (Ferrer et al., 2002; Ferrer et al., 2014). Tau filament AGD-fold differs from tau filament AD-fold but resembles the four-layered fold of corticobasal degeneration (CBD) identified by cryo-electron microscopy (Shi et al., 2021a, 2021b; Kametani and Hasegawa, 2022).

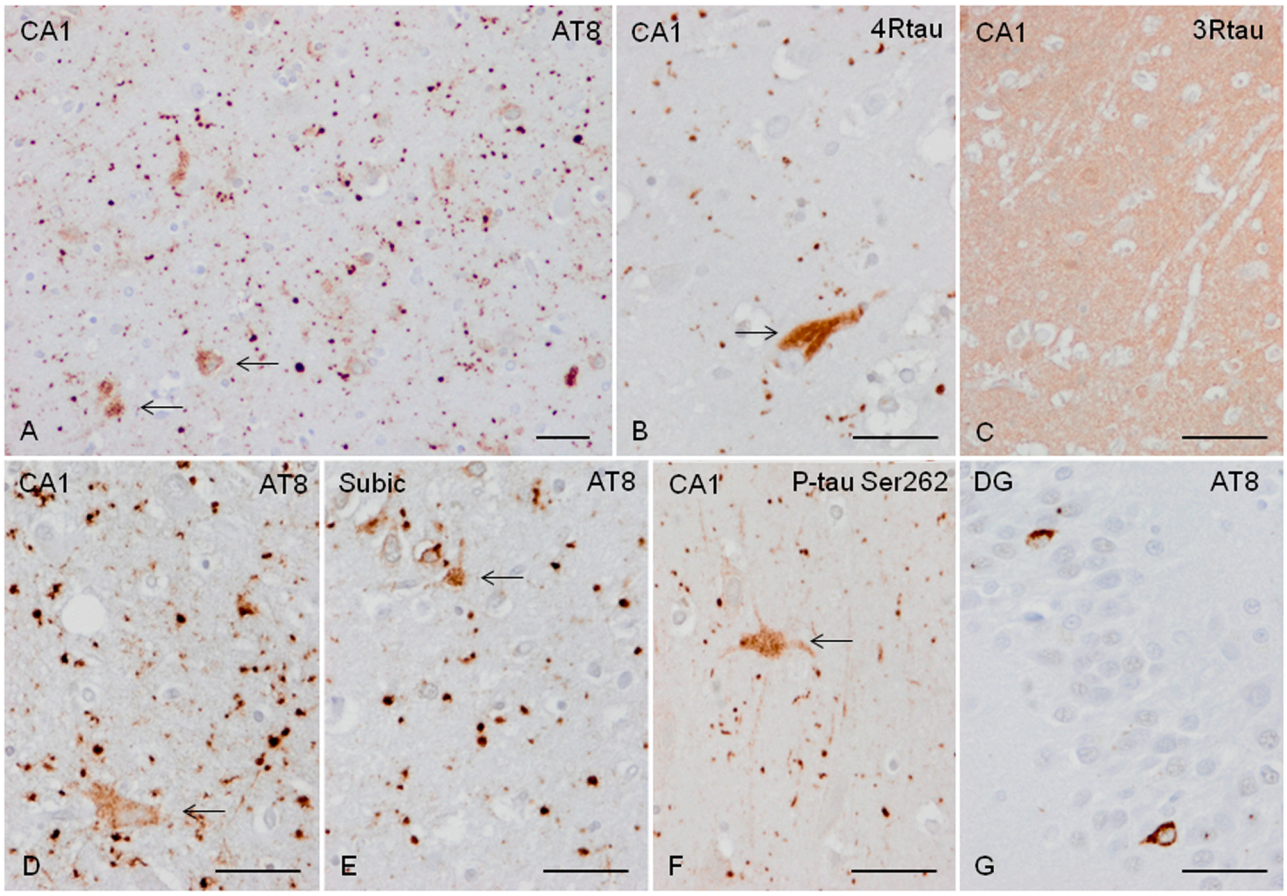

Fig. 2. Argyrophilic grain disease (AGD). A: Argyrophilic grains and neurons with pre-tangles (thin arrows) in the CA1 region of the hippocampus, as seen with AT8 immunohistochemistry; B: 4Rtau immunohistochemistry showing positivity of grains and pre-tangles (thin arrow); C: grains and pretangles are not stained with anti-3Rtau antibodies; D and E: phospho-tau-immunoreactive grains and pre-tangles in CA1 and subiculum (subic) seen with the AT8 antibody; F: grains and pre-tangles (thin arrow) stained with anti-phospho-tau Ser262 antibody; G: phospho-tau containing neurons and absence of grains in the dentate gyrus (DG). Paraffin sections slightly counterstained with haematoxylin, A, bar = 50 μm; B-G, bar = 50 μm.

Phospho-tau and active tau kinases co-localize in grains, pre-tangles, and ballooned neurons (Leroy et al., 2007; Ferrer et al., 2003; Ferrer, 2004; Ferrer et al., 2005), thus linking kinase activation and tau hyper-phosphorylation. The presence of acetylated tau in AGD is controversial (Grinberg et al., 2013; Irwin et al., 2013). Grains also contain markers of the sequestosome/p62, ubiquitin, and mutant ubiquitin (Fischer et al., 2003; Scott and Lowe, 2007; Ferrer et al., 2008). Mitochondrial dysfunction, oxidative and endoplasmic reticulum stress, and reduced neuronal haemoglobin also occur in AGD (Ilieva et al., 2011; Ferrer et al., 2011).

AGD is associated with apolipoprotein E epsilon 2 allele (*ApoEε2*), but not with *ApoEε4* allele (Ghebremedhin et al., 1998; Togo et al., 2002a, 2002b). Curiously, *ApoEε2* allele is protective against sAD. AGD is also associated with polymorphisms in α2-macroglobulin and low-density lipoprotein receptor-related protein genes (Ghebremedhin et al., 2002). Although AGD is currently viewed as sporadic, AGD-like neuropathology has been reported in cases carrying *MAPT* S305S and *MAPT* S305I mutations (Kovacs et al., 2008; Rönnbäck et al., 2014).

AGD may follow successive stages of local and regional progression: stage I: anterior entorhinal cortex, mild involvement of the cortical and basolateral nuclei of the amygdala, and mild involvement of the hypothalamic lateral tuberal nucleus; stage II: entorhinal cortex, anterior CA1, transentorhinal cortex, cortical and basolateral nuclei of the amygdala, presubiculum, hypothalamic lateral tuberal nucleus, and dentate gyrus; stage III: entorhinal cortex, CA1, perirhinal cortex, presubiculum, amygdala, dentate gyrus, hypothalamic lateral tuberal nucleus, mild involvement of CA2 and CA3, mild involvement of the subiculum, mild involvement of other nuclei of the hypothalamus (e.g. mammillary bodies), mild involvement of the anterior temporal cortex, insular cortex, anterior cingulate gyrus, orbitofrontal cortex, nucleus accumbens, and septal nuclei, and rare grains in the midbrain; and stage IV: moderate to severe additional involvement of the neocortex and brainstem (Saito et al., 2004; Ferrer et al., 2008). The gyrus ambiens is severely affected in cases with dementia (Saito et al., 2002). The involvement is asymmetric (Adachi et al., 2010; Sakurai et al., 2019).

AGD may occur as an isolated condition (Braak et al., 1987; 1989; Rodriguez et al., 2016; Wurm et al., 2020), but it is often accompanied by NFT pathology and advanced AD, and may occur in combination with other tauopathies like progressive supranuclear palsy (PSP), CBD, and Pick's disease (PiD), as well as α-synucleinopathies (Martinez-Lage and Munoz, 1997; Sabbagh et al., 2009; Nelson et al., 2010; Rodriguez et al., 2016;Yokota et al., 2018). AGD can occur as an incidental post-mortem neuropathological lesion, but it is frequently associated with cognitive impairment and dementia. When present in combination with early stages of NFT pathology of AD type, cognitive impairment and dementia are more prevalent than in cases with the same stage of NFT pathology alone (Tolnay et al., 1997b; Thal et al., 2005).

It has been suggested that there is no support for independent association between cognitive impairment linked to aging and AGs (Sabbagh et al., 2009; Nelson et al., 2010). However, dementia has been reported in AGD without co-morbidities, and the degeree of cognitive impairment depends on the extension of lesions in the limbic system and neocortex (Braak and Braak, 1987; Braak and Braak, 1989; Tolnay et al., 1997; Ikeda et al., 2000; Probst and Tolnay, 2002; Tolnay and

Clavaguera, 2004).

AGD has not been reported in natural conditions in species other than humans. Deafferentation of the hippocampus in rats generates phospho-tau positive grain deposits in the molecular layers of the dentate gyrus on the lesioned side, as revealed with the AT8 antibody (Mudher et al., 2001). However, the origin of the granules (dendritic or axon terminals) and the characteristics of tau deposits (argyrophilia, only 4Rtau immunoreactivity) were not described in the original paper. Therefore, deafferentation of the hippocampus is likely not the cause of AGD.

3.2. Aging-related tau astrogliopathy (ARTAG)

Thorn-shaped astrocytes (TSAs) are a subpopulation of fibrillary astrocytes containing hyper-phosphorylated tau that appear in the human aged brain in subependymal, subpial, perivascular, white matter, and grey matter locations; 4Rtau are the only tau isoforms deposited in TSAs (Ikeda et al., 1995; Schultz et al., 2004; López Gonzalez et al., 2013, Okamoto et al., 2019). In the age-range of 75–98 years, TSAs are found in approximately 50% of all individuals (Schultz et al., 2004). TSAs are prevalent in the brain of the oldest-old or supercentenarians (Takao et al., 2016; Rogalski et al., 2019).

TSAs are frequent in the brain of individuals affected by tauopathies including sAD, AGD, FTLD-tau, PSP, and chronic traumatic tauopathy (Schultz et al., 2004; Kovacs et al., 2017; Nolan et al., 2019; McCann et al., 2021; Kovacs et al., 2020; Arena et al., 2020a, 2020b; Ameen-Ali et al., 2022). In sAD, TSAs are not related to Braak neurofibrillary tangle or hippocampal tangle pathology stages (Schultz et al., 2004; Lace et al., 2012). TSAs are associated with argyrophilic grains (Lace et al., 2012), coiled bodies in oligodendrocytes (Lace et al., 2012; Forrest et al., 2022), and limbic-predominant age-related TDP-43 encephalopathy (Forrest et al., 2022). TSAs are also frequent in DLB (Liu et al., 2016). An extreme case of combined prominent ARTAG, AD, cerebral β-amyloid angiopathy, LBD, and TDP-43 proteinopathy has been reported (Klotz et al., 2021).

TSAs show deposition of phosphorylated tau at different sites, recognized with phospho-specific anti-tau antibodies Thr181, Ser202, Ser214, Thr231, Ser396, Ser422, and clones AT8 and PHF-1, and conformational changes revealed with Alz50 and MC-1 antibodies. However, TSAs are only seldom stained, or not stained at all, with phospho-specific tauSer262, and with Tau-C3 antibody directed against tau truncation at aspartic acid 421 (López-González et al., 2013; Ferrer et al., 2018). TSAs are also decorated with antibodies against tau N-terminal, C-terminal, and tau 100 (Ferrer et al., 2018). TSAs are also immunostained with antibodies to active tau kinases MAPK/ERK-P, SAPK/JNK-P, p38-P, and GSK-3β, thus suggesting a functional role of active tau kinases in the hyper-phosphorylation of tau in TSAs (López-González et al., 2013). Finally, western botting of

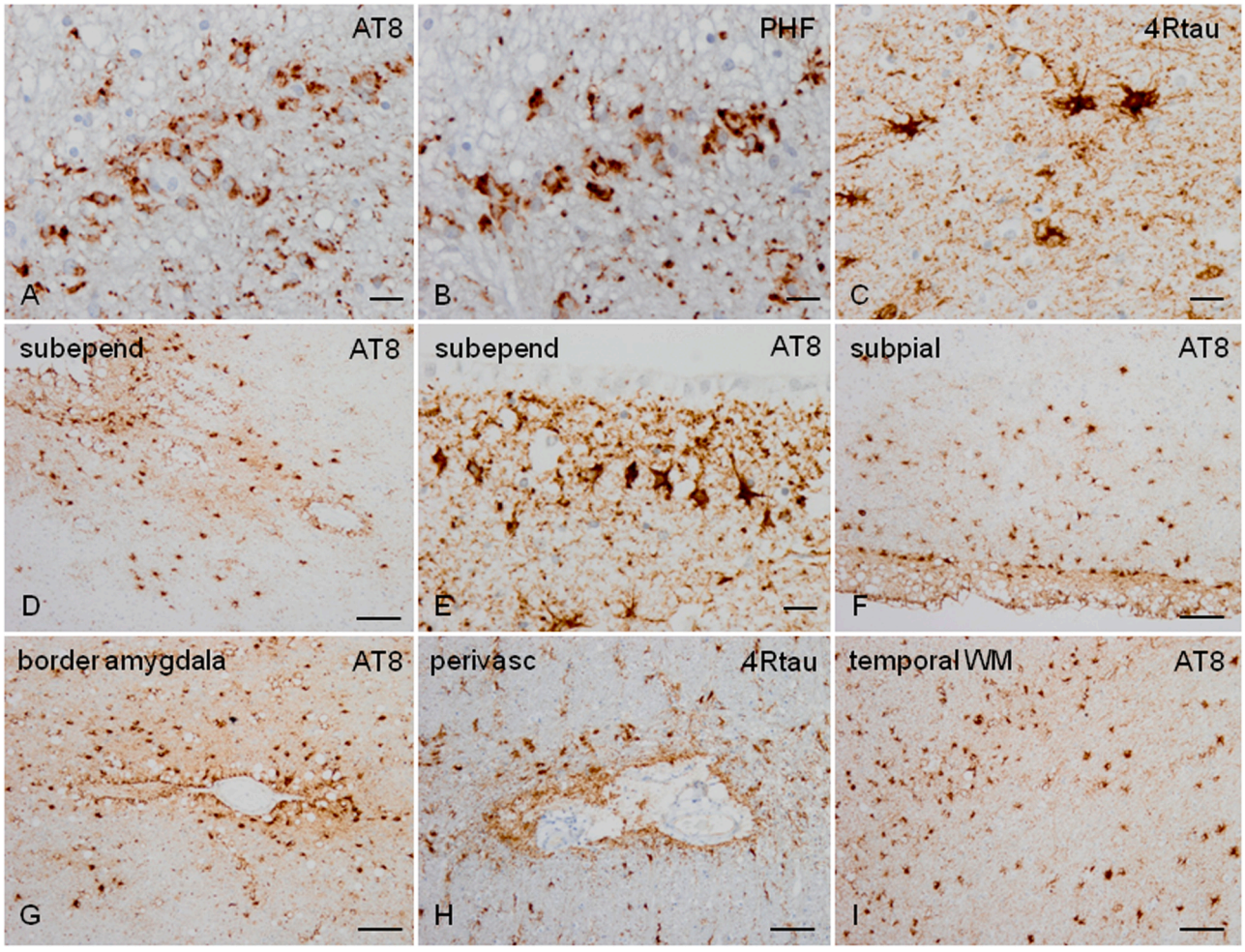

Fig. 3. Aging-related tau astrogliopathy (ARTAG); characteristics and localization of thorn-shaped astrocytes (TSAs). A-C: TSAs in the deep temporal white matter visualized with antibodies AT8 (A), PHF (B), and 4Rtau (C) showing characteristic fibrilar and short branched morphology; E: TSAs are also visualized in the subependymal region of the temporal ventricles; D, F-I: lower magnification showing TSAs in the subependyma of the temporal ventricle (D), subpial localization in the deep temporal cortex (F), border of the amygdala (G), perivascular in the white matter (H), and temporal white matter (I). Paraffin sections, slightly counterstained with haematoxylin, A-C and E, bar = 30 μm; D, F, G-I, bar = 45 μm.

sarkosyl-insoluble fractions from the temporal lobe in cases with only TSAs reveals two phospho-tau bands of 68 kDa and 64 kDa, identified with the phospho-specific tau Ser422 antibody, and several lower bands of variable molecular weight consistent with C-terminal truncated tau (Ferrer et al., 2018).

TSAs are negative for ubiquitin, mutant ubiquitin, and p62 (López-González et al., 2013).

The term aging-related tau astrogliopathy (ARTAG) was coined to describe a 4 R taupathy composed of TSAs, and solitary or clustered granular/fuzzy astrocytes (GFAs) in the gray matter (Kovacs et al., 2016). TSAs in ARTAG are localized in subpial, subependymal, perivascular, white matter, and gray matter domains, and mainly in the temporal lobe, lobar, subcortical, and brainstem (Kovacs et al., 2016). ARTAG patterns are categorized into different stages regarding the distribution of TSAs (Kovacs et al., 2018a, 2018b) (Fig. 3). The stages differ depending on the localization of of TSAs (subpial, white matter, and grey matter), and associated pathologies (for example PSP, CBD, and PiD) (Kovacs et al., 2018a, 2018b). However, TSAs in aging brain, not associated with PSP, CBD, or PiD, usually appear first in basal brain regions including subependyma of the temporal horn, temporal white matter, subpial of the entorhinal cortex, and amygdala. GFAs also occur in other tauopathies in the elderly (Ferrer et al., 2014). Whether ARTAG, or the presence of TSAs in the white matter, has any clinical manifestation is controversial (Munoz et al., 2007; Mesulam et al., 2008; Wharton et al., 2016; Resende et al., 2020). Cortical ARTAG is associated with dementia, but limbic and brainstem ARTAG is not (Robinson et al., 2018a, 2018b).

The proximity of TSAs to the subachnoidal, subventricular, and perivascular spaces prompted the suggestion that astrocytes in these areas might have a potential effect on brain-fluid interfaces; connexin-43 immunoreactivity is increased in ARTAG independently of tau pathology, and aquaporin 4 only in the white matter and grey matter, but associated with increased AT8 immunoreactivity in white matter and perivascular areas (Kovacs et al., 2018a, 2018b). However, aquaporin 4 is expressed in AT8-immunoreactive and AT8-negative astrocytes in the subependymal and perivascular regions in another study (Ferrer et al., 2018). Moreover, SOD1 and GLT1 are equally expressed in TSAs and neighboring astrocytes in ARTAG (Ferrer et al., 2018). Interestingly, TSAs express YKL40, thus pointing to an inflammatory profile for these astrocytes (Ferrer et al., 2018).

Phosphoproteomics of dissected brain regions enriched in TSAs as the only neuropathological change identifies increased phosphorylation marks in a large number of proteins in ARTAG compared with controls, including glial fibrillary acidic protein (GFAP), aquaporin 4, several serine-threonine kinases, microtubule associated proteins, and other neuronal proteins. These data reveal a hyper-phosphorylation background that affects several molecules, including many kinases and proteins that are components of various cell compartments and cell types (Ferrer et al., 2018). Therefore, deregulated protein phosphorylation is not restricted to tau hyper-phosphorylation in TSAs, but rather is a widespread altered molecular setting in ARTAG (Ferrer et al., 2018).

Several tau transgenic mice have been used as models of human tauopathies, including transgenic mice expressing either murine 3Rtau and 4Rtau, or the longest human brain 4Rtau isoform (Alz17 mice), or 1N4Rtau containing the P301S mutation, or high levels of human 3Rtau and lower 4Rtau in a KO murine tau background (hTau mice), or human 3Rtau and 4Rtau at a ratio 1:1 in a KO murine tau background (6hTau mice) (Allen et al., 2002; Andorfer et al., 2003; Yoshiyama et al., 2007; Frank et al., 2008; Takeuchi et al., 2011; Götz and Götz, 2019; Hosokawa et al., 2022). All these mice present neuronal tauopathy and variable tau deposition in glial cells resembling FTLD-tau, but none of them exhibit neuropathological patterns similar to those seen in human sporadic tauopathies including ARTAG and AGD. Transgenic rats bearing the P301S mutation also mimic human tauopathy but not AGD or ARTAG (Janice et al., 2019).

3.3. α-synuclein pathology (limbic predominant Lewy body disease)

Lewy bodies and neurites are composed of normal, misfolded, and truncated proteins, principally α-synuclein, which is abnormally phosphorylated at Ser129, nitrated and oxidized, has altered crystallographic structure and abnormal solubility, and is prone to the formation of aggregates and insoluble fibrils with predominant β-pleated sheet conformation; in addition, Lewy bodies associate proteins of the ubiquitin-protesome system and autophagy that become deficient to degrade the abnormal products (Spillantini et al., 1997; Wakabayashi et al., 1997; Arima et al., 1998; Baba et al., 1998; Hashimoto and Masliah, 1999; Duda et al., 2000; Goedert, 2001b; Giasson et al., 2002; Fujiwara et al., 2002; Iwatsubo, 2003; Saito et al., 2003; Anderson et al., 2006; Schults, 2006; Leverenz et al., 2007; Uversky, 2007; Wakabayashi et al., 2007Bandyopadhyay and Cuervo, 2007; Engelender, 2008; Xia et al., 2008; Uchihara and Giasson, 2016).

Several kinases may phosphorylate α-synuclein, including casein kinase II, leucine-rich repeat kinase 2, G-protein-coupled receptor kinase, and polo-like kinase (Kawahata et al., 2022).

Under electron microscopy, classical Lewy bodies have a central core of granular material and a peripheral halo composed of radiate fibrils. Dense Lewy bodies are composed of lipid membranes, vesicles, dysmorphic organelles, filaments interspersed between the membranes, and organelles. Clear or hyaline inclusions are mainly composed of granular material and vesicles (Roy and Wolman, 1969; Forno and Norville, 1976; Forno, 1986; Gibb et al., 1991; Galloway et al., 1992; Fukuda et al., 1993; Spillantini et al., 1998; Arima et al., 1998; Galvin et al., 1999; Schults, 2006). The use of combined methods shows a more complex structure and composition of Lewy bodies; Lewy bodies consists of vesicular structures, dysmorphic organelles, rare filaments, granules and lipid membranes (Shahmoradian et al., 2019). Cryo-electron microscopy has disclosed that α-synuclein filaments in Lewy bodies are made from two protofilaments formed by a polar fibril of staggered β-strands (Li et al., 2018; Guerrero-Ferreira et al., 2020; Yang et al., 2022a, 2022b; Kametani and Hasegawa, 2022).

Lewy bodies and neurites define Lewy body diseases (LBD), mainly represented by Parkinson's disease (PD) and DLB (Forno, 1996; Kosaka and Iseki, 1996; Goedert et al., 2001a; McKeith et al., 2004; Fujishiro et al., 2008a, 2008b; Dickson et al., 2009; Kosaka and Iseki, 2011; Ince, 2011).

LB pathology in PD progresses from the myenteric plexus and medulla oblongata (and olfactory bulb) to the midbrain, diencephalic nuclei, and neocortex (Braak et al., 2002; Braak et al., 2003; Braak et al., 2004). Stage 1 is manifested by Lewy bodies and neurites in the dorsal IX/X motor nuclei and/or intermediate reticular zone, and myentheric plexus. Stage 2 affects, in addition, the medulla oblongata and pontine tegmentum; the olfactory bulb is also involved. Stage 3 adds midbrain lesions, particularly in the substantia nigra pars compacta. Stage 4 includes basal prosencephalon and mesocortex (cortical involvement confined to the transentorhinal region and allocortex, and CA2 plexus). Stage 5 extends to sensory association areas of the neocortex and prefrontal neocortex. Stage 6 includes Lewy bodies and neurites in first-order sensory association areas of the neocortex and pre-motor areas, as well. Braak staging is well-accepted regarding typical PD progression (Dickson et al., 2010). A simplified version has been proposed for DLB, and categorized as LBD brainstem predominant, limbic, and neocortical (McKeith et al., 2017). More recently, an improved classification with higher reproducibility has been proposed based on the McKeith system, but applying a dichotomous approach for the scoring of Lewy pathology and including amygdala-predominant and olfactory-only stages (Attems et al., 2021).

Lewy pathology is frequent (about 30%−50%) in cases with mild cognitive impairment and AD dementia, and in brain aging with ADNC (Jellinger, 2004; Spina et al., 2021; Robinson et al., 2021). Conversely, the majority of patients with DLB have AD pathology, usually at NFT stages III-V, and abundant diffuse and SPs (Marui et al., 2002; Iseki et al.,

2003). Interestingly, there is an association of ApoEε4 and Lewy bodies in sAD (Tsuang et al., 2005).

An atypical but common form of LBD in the human aged brain is amygdala-predominant LBD, accompanied by Lewy bodies in the olfactory bulb, in about 30% of cases with sAD and Down syndrome (Uchikado et al., 2006) (Fig. 4A-C).

Severe Braak NFT stage, high CERAD (Consortium to Establish a Registry for Alzheimer's Disease) score, and *ApoEε4* are significantly associated with amygdala-predominant LBD, but not with the caudo-rostral progression pattern of PD. This observation suggests two distinct LBD patterns of α-synuclein pathology origin and progression in the elderly, one of them characteristic of PD and DLB, the other of amygdala-predominat LBD (Raunio et al., 2019). This observation leads to the LOC model (body-first versus brain-first model of Lewy body disorders) that proposes the enteric nervous system origin of Lewy body pathology with secondary spreading to the brain in most cases of LBD, and the central origin of Lewy body pathology in some patients with amygdala-predominant LBD with secondary spreading to the lower brainstem and peripheral autonomic nervous system (Borghammer, 2021; Borghammer et al., 2021).

Co-localization of phospho-tau and α-synuclein is not uncommon in Lewy bodies and neurites in selected neurons (Arima et al., 1999; Iseki et al., 1999; Ishizawa et al., 2003; Fujishiro et al., 2008a, 2008b; Clarimón et al., 2009). Another study in DLB shows co-localization of NFTs and Lewy bodies in the same neurons, most frequently in the subiculum-pre-CA1; phospho-tau and α-synuclein co-exist in terminal axons of the perforant pathway, and tau accumulates not in paired helical filaments but in the periphery of α-synuclein-positive components

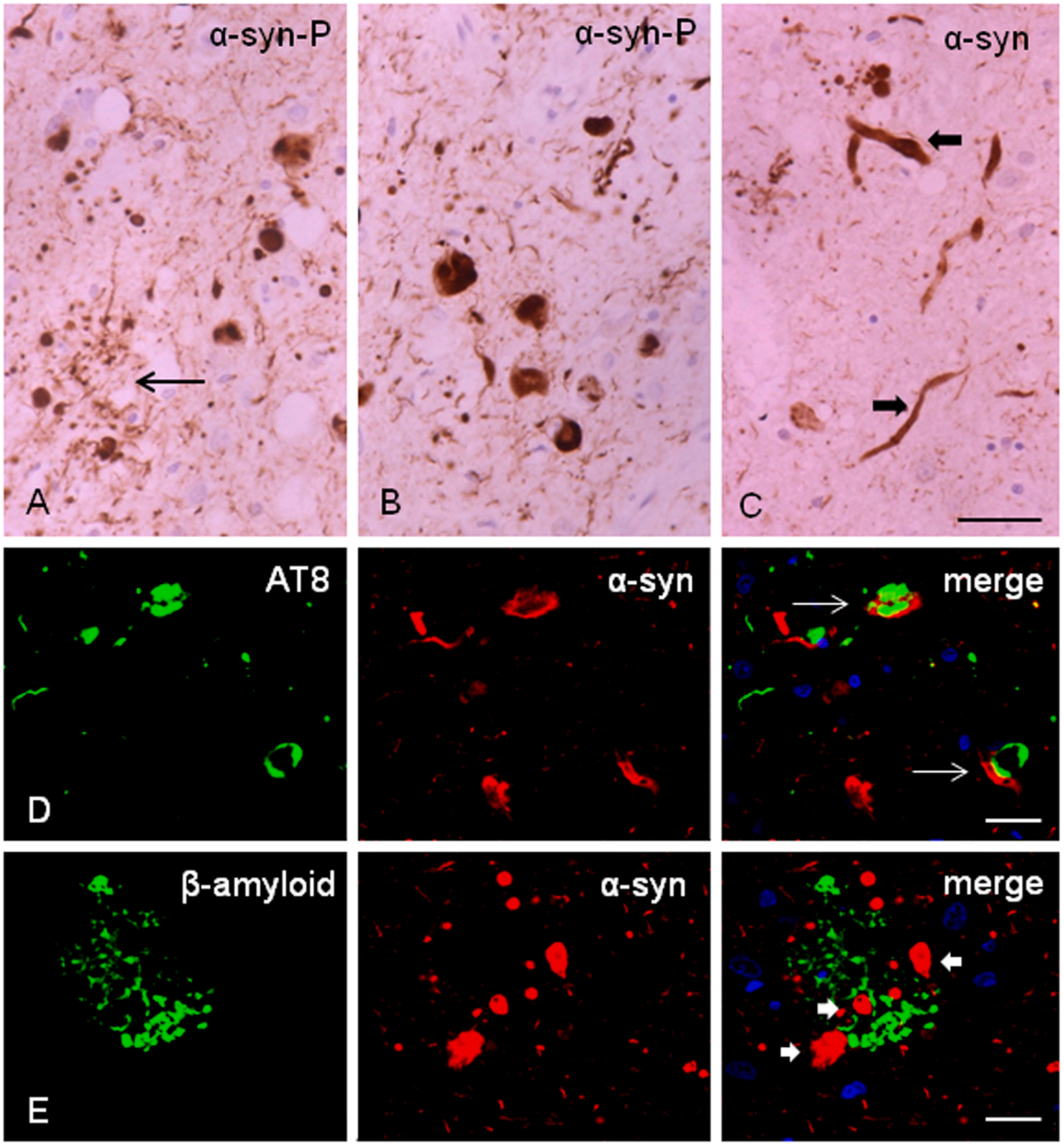

Fig. 4. Amygdala-predominant Lewy body disease. A-C: Lewy bodies, dystrophic neurites in senile plaques (thin arrow), and Lewy neurites (thick arrows) in the amygdala as seen with anti-P-α-synuclein Ser129, and non-phosphorylated α-synuclein antibodies; D: double-labelling immunofluorescence and confocal microscopy with AT8 (green) and anti-α-synuclein (red) antibodies showing co-localization of phospho-tau and α-synuclein in neurofibrillary tangles (thin arrows); E: double-labelling immunofluorescence and confocal microscopy with anti-β-amyloid (green) and anti-α-synuclein (red) antibodies showing α-synuclein-immunoreactive neurites surrounding β-amyloid deposits (thick arrows); nuclei are stained with (blue). Paraffin sections, A-C, bar = 25 μm; D, E, bar = 20 μm.

(Iseki et al., 2002) (Fig. 4D). Tau co-localizes with α-synuclein in the striatum (Wills et al., 2011) and post-synaptic spines in TgA53T mice (Teravskis et al., 2018; Singh et al., 2019). Molecular studies have also shown co-existence of phosphorylated tau and phosphorylated α-synuclein in synaptic-enriched fractions in AD, PD, and DLB (Muntané et al., 2008). *In vitro* studies have shown that tau and α-synuclein can interact and promote aggregation (Giasson, 2003) through the C-terminus of α-synuclein (Dasari et al., 2019). However, the functional consequences of tau/α-synuclein interactions in pathology remain controversial (Pan et al., 2021). β-amyloid and α-synuclein may participate in SPs, but such proteins are expressed in different compartments (Fig. 4E).

Finally, LBDs are restricted to humans. Several animal models have been generated to re-create certain aspects of PD and DLB, including drug-induced α-synuclein aggregation in the substantia nigra of baboons, as well as multiple pharmacological treatments, and transgenic mouse models bearing PD- and DLB-related human mutations. Unfortunately, none of them reproduces Lewy pathology as seen in human diseases (Kowall et al., 2000; Duty et al., 2011; Koprich et al., 2017; Hamadjida et al., 2019; Lama et al., 2021). However, overexpression of human tyrosinase in rat substantia nigra results in age-dependent production of human-like neuromelanin within nigral dopaminergic neurons which above a specific threshold is associated to an age-dependent PD phenotype, including hypokinesia, Lewy body-like formation and nigrostriatal neurodegeneration (Carballo-Carbajal et al., 2019).

3.4. TDP-43 pathology and limbic-predominant age-related TDP-43 encephalopathy (LATE)

TAR DNA-binding protein 43 (TDP-43, TARDBP) usually resides in the nucleus but can shuttle to the cytoplasm; TDP-43 acts as a transcription factor, but also exerts multiple functions such as regulation of splicing, stabilization of RNA, microRNA processing, and protein-protein interaction. TDP-43 phosphorylation on serine 379 (S379), S403, S404, S409, S410, and abnormal cleavage and formation of C-terminal fragments results in abnormal TDP-43 aggregation in the nucleus, cytoplasm, and cell processes; abnormal TDP-43 deposits are ubiquitinated as a result of dysfunctional constitutive and inducible UPS in TDP-43 proteinopathies (Neumann et al., 2006; Bendotti et al., 2012). Abnormal TDP-43 deposits in neurons and glial cells are characteristic of frontotemporal lobar degeneration with TDP-43 deposits (FTLD-TDP) and amyotrophic lateral sclerosis (ALS) (Gao et al., 2018; Prasad et al., 2019; Tziortzouda et al., 2021; Corbet et al., 2021; Liao et al., 2022; Keating et al., 2022).

TDP-43 inclusions are characterized by bundles of 10–20 nm diameter straight filaments with electron dense granular material within nuclear, cytoplasmic, and neuritic deposits, in most cases of FTLD-TDP, ALS, and AD (Lin and Dickson, 2008). Cryo-electron microscopy shows the structure of TDP-43 filaments from ALS and FTLD as a single protofilament that adopts a double-spiral-shaped fold, with no similarity to TDP-43 filaments formed in vitro (Arseni et al., 2022).

TDP-43-immunoreactive neuronal inclusions and threads are common in the hippocampus in brain aging over the age of 65, and in advanced sAD, often accompanied by hippocampal sclerosis (Geser et al., 2010; Davidson et al., 2011; Uchino et al., 2015; Josephs et al., 2015; Josephs et al., 2017; Smith et al., 2018; Nag et al., 2018; Huang et al., 2020; Gauthreaux et al., 2022). TDP-43 inclusions occur in up to 57% of sAD cases, most often in a limbic distribution, with or without hippocampal sclerosis; TDP-43 deposits can be found in neurons with NFTs (Meneses et al., 2021). Other studies estimate TDP-43 pathology to be present in up to 70% of symptomatic sAD cases (Koper et al., 2022) (Fig. 5).

TDP-43 pathology linked to sAD has been categorized into six stages: stage 1: amygdala; stage 2: entorhinal cortex and subiculum; stage 3: dentate gyrus of the hippocampus and occipitotemporal cortex; stage 4: insular cortex, ventral striatum, basal forebrain, and inferior temporal cortex; stage 5: substantia nigra, inferior olive, and midbrain tectum; and stage 6: basal ganglia and middle frontal cortex (Josephs et al., 2016). Subsequent contributions point to a simplified classification, and discriminate cases at stage 6 as FTLD-TDP (Nelson et al., 2019, see later). Similar categorization has been proposed in PART excepting for the involvement of the gyrus dentatus and the omission of advanced TDP-43 stages (Zhang et al., 2019).

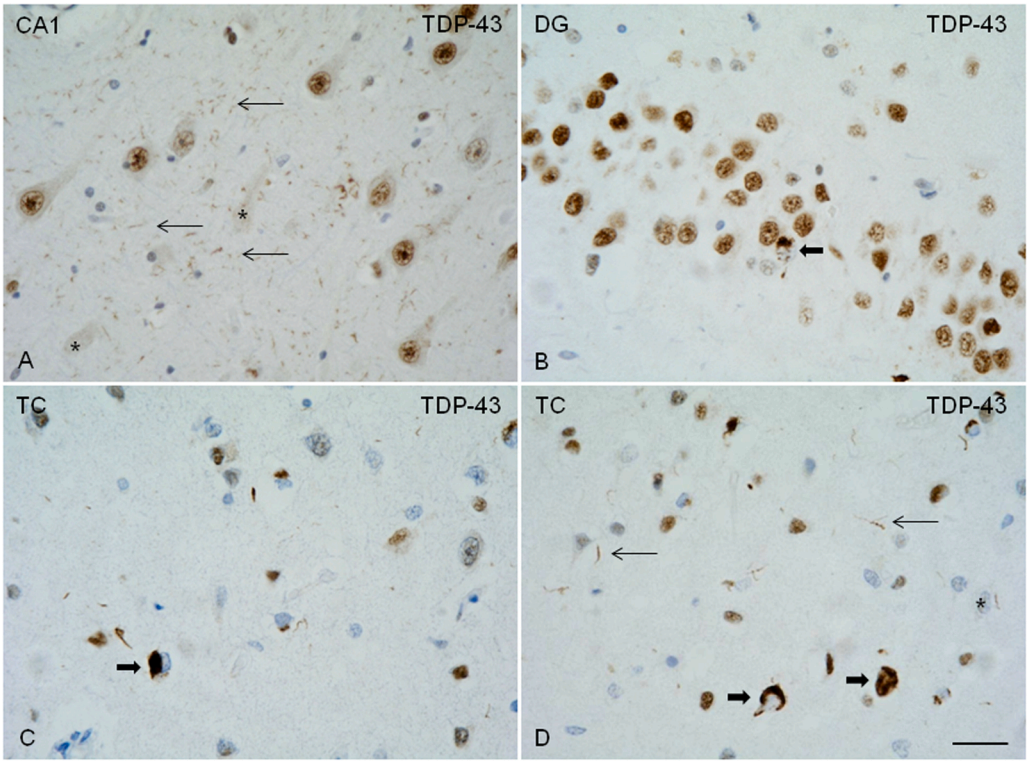

Fig. 5. Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC). TDP-43 immunoreactivity in normal nerve cells is mainly localized in the nucleus. A-D: Reduced TDP-43 expression in the nucleus (asterisk) is accompanied by abnormal localization of TDP-43 in neuropil threads (A, D, thin arrows), and in dense cytoplasmic inclusions (B, C, D) (thick arrows) in TDP-43 proteinopathy involving the hippocampus (CA1) dentate gyrus (DG) and deep regions of the temporal cortex (TC). Paraffin sections, slightly counterstained with hematoxylin, A-D, bar = 25 μm.

TDP-43 pathology in the amygdala and hippocampus also occurs in fAD and Down syndrome (Lippa et al., 2009; Davidson et al., 2011; Ichimata et al., 2022), thus linking ADNC to TDP-43 pathology in those brain regions. TDP-43 pathology co-exists with α-synuclein and tau pathology in AD and DLB (Higashi et al., 2007).

TDP-43 proteinopathy is common in AGD; phospho-TDP-43 and phospho-tau co-localize only in some but not all neuronal cytoplasmic inclusions, grain-like structures, and pre-tangles (Fujishiro et al., 2009). TDP-43 pathology in CBD and PSP is reminiscent of TDP-43 proteinopathy in ALS (Riku et al., 2022), but limbic-predominant TDP-43 encephalopathy has also been described in PSP, often in association with hippocampal sclerosis (Yokota et al., 2010). Limbic-predominant TDP-43 encephalopathy has been exceptionally reported in globular glial tauopathy (Rusina et al., 2019).

The relationship between TDP-43 and tau is puzzling (Jamerlan and An, 2020). TDP-43 and tau appear to behave independently of one another (Smith et al., 2018; Buciuc et al., 2020a; McAleese et al., 2020). Yet, combined human (h) Tau and TDP-43 expression in *C. elegans* results in severe degeneration consistent with a synergistic, rather than simply additive, interaction between hTau and hTDP-43 neurodegeneration (Latimer et al., 2019). Moreover, cytoplasmic TDP-43 accumulates in the presence of soluble human recombinant tau oligomers in cellular and murine models (Montalbano et al., 2020). Widespread co-localization of phospho-tau and phospho-TDP-43 deposits occurs in a rare form of familial astroglial predominant tauopathy (Gelpí et al., 2021).

TDP-43 proteinopathy is common in old-age hippocampal sclerosis (Nelson et al., 2016; Wang et al., 2022; Gauthreaux et al., 2022), and in cases with more severe non-β-amyloid vessel wall pathologies (Gauthreaux et al., 2022). Interestingly, neuron loss leading to old-age hippocampal sclerosis associated with TDP-43 pathology predominates in the subicular end of CA1 is more common than thye end-stage of old-age hippocampal sclerosis alone (Hokkanen et al., 2018).

The term cerebral age-related TDP-43 with (hippocampal) sclerosis (CARTS) was proposed to categorize robust TDP-43 pathology in the hippocampus of individuals older than 85 at death, and includes cases with hippocampal sclerosis in aging, and hippocampal sclerosis with sAD pathology (Nelson et al., 2016).

Later, the term limbic-predominant age-related TDP-43 encephalopathy (LATE) was coined to designate an entity characterized by the presence of TDP-43 pathology localized in the amygdala and hippocampus, and extending to the limbic system in aged individuals usually with sAD. LATE differs from FTLD-TDP. LATE is associated with hippocampal sclerosis in some cases (Nelson et al., 2019; Robinson et al., 2020a, 2020b; Nelson, 2021; Nelson et al., 2022), but may also occur in isolation (Besser et al., 2020). LATE's prevalence is very high in old-aged individuals as it occurs in about 35%− 50% of individuals over the age of 80 (Nelson, Sajjadi et al., 2019, 2022). LATE neuropathological change (LATE-NC) staging is classified as stage 1: amygdala only, stage 2 plus hippocampus, and stage 3 plus frontal cortex.

Clinically, LATE may be manifested with episodic memory loss and amnestic dementia syndrome (Nag et al., 2017; Nelson et al., 2019). No differences are apparent between black and white decedents, at least in one North American community (Nag et al., 2020). When associated with sAD, LATE-NC worsens cognitive decline in sAD and psychiatric symptoms (Vatsavayi et al., 2014; Josephs et al., 2015; Sennik et al., 2017; Nelson et al., 2019; Latimer et al., 2019; Kapasi et al., 2020; Buciuc et al., 2020b; Sajjadi et al., 2022; Gauthreaux et al., 2022). Yet TDP-43 pathology did not increase the risk of neuropsychiatric symptoms in another study (Liu et al., 2020).

Brain atrophy at early stages of sAD seems to be supported by concomitant LATE-NC (Josephs et al., 2019). This is further supported by recent MRI and PET studies showing patterns of limbic-predominant atrophy on MRI and hypometabolism on ^{18}F-fluorodeoxyglucose PET in LATE-NC plus sAD are greater than expected for levels of local sAD pathology alone (Duong and Wolk, 2022).

ApoEε4 is associated with increased risk for LATE-NC (Yang et al., 2018). Subsequent studies have identified five genes with risk alleles for LATE-NC: granulin precursor (*GRN)*, transmembrane protein 106b (*TMEM106B)*, ATP binding cassette subfamily C member 9 (*ABCC9)*, potassium calcium-activated channel subfamily M regulatory beta subunit 2 (*KCNMB2)*, and *ApoE* (Nelson et al., 2019). *TMEM106B*, *GRN*, and *ApoE* are associated with both LATE and hippocampal sclerosis, whereas *ABCC9* is associated with hippocampal sclerosis only. None of these genes except *ApoE* is associated with Alzheimer's-type pathology (Dugan et al., 2021; Meneses et al., 2021). Mutations in *GRN* are linked to FTLD-TDP (Cruts et al., 2006; Baker et al., 2006; Wauters et al., 2017), and *TMEM106B* is associated with amyloid formation in several neurodegenerative diseases (Feng et al., 2021; Schweighauser et al., 2022; Chang et al., 2022).

Abnormal TDP-43 in TDP-43 proteinopathies forms neurotoxic fibrils with variable structure depending on the origin of the fibrils, the core, C-terminal fragments, or the entire low complexity domain of TDP-43 (Chen et al., 2010; Cao et al., 2019; Li et al., 2021a, 2021b). Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP43; however, amyloid fibrils occur in combination with non-fibrillar aggregated TDP-43 (Chang et al., 2022; Jiang et al., 2022).

LATE-NC is also associated with tau pathology in glial cells. Thus, ARTAG and tau oligodendrogliopathy (mainly in the form of coiled bodies) are frequently associated with LATE (Forrest et al., 2022).

LATE-NC also occurs in combination with amygdala/limbic-predominant LBD, and more rarely with neocortical LBD (Besser et al., 2020; Agrawal et al., 2021a, 2021b; Uemura et al., 2022). Fine neurites composed of C-terminal truncated TDP-43 in CA2 mainly occur in association with LBD whereas neuronal cytoplasmic inclusions predominate in cases with combined sAD (Uemura et al., 2022). LATE-LBD also associates with the genetic risk variants of *TMEM106B* rs1990622 and *GRN* rs5848 (Uemura et al., 2022).

TDP-43 pathology co-exists with α-synuclein and tau pathology in AD and DLB (Higashi et al., 2007). The interaction between α-synuclein and TDP-43 is poorly understood. However, the prion-like C-terminal domain (PrLD) of TDP-43 interacts with α-synuclein to form toxic aggregates that co-localize in the cytosol of neuroblastoma cells and induce synaptic dysfunction in primary neurons (Dhakal et al., 2021a, 2021b; Dhakal et al., 2022). Moreover, electron microscopy of TDP-43 inclusions in AD and LBD shows co-localization of TDP-43-immunoreactive filaments and granular material with tau filaments in NFTs in AD, or α-synuclein filaments in Lewy bodies in LBD (Lin and Dickson, 2008).

Four LATE-NC subtypes have been identified. Pattern 1 is characterized by TDP-43-immunoreactive processes and pre-inclusion pathology in cortices of the amygdala region, and hippocampal sclerosis; pattern 2 shows neurofibrillary tangle-like TDP-43 neuronal cytoplasmic inclusions together with high AD pathology; pattern 3 is recognized by round neuronal cytoplasmic inclusions and thick neurites in amygdala, and frequent LBD; and pattern 4 is characterized by tortuous TDP-43-immunoreactive processes in subpial and white matter regions, rare AD-related pathology, and rare hippocampal sclerosis (Cykowski et al., 2022). The different morphology and distribution of TDP-43 pathology suggest molecular particularities of TDP-43 deposits among subtypes. In this line, TDP-43 aggregates in sAD vary in their composition, suggesting different molecular profiles of TDP-43 pathology (Tomé et al., 2020).

Other studies have suggested distinct clinicopathological clusters of patients with TDP-43 proteinopathy. Cluster 1 contained FTLD-TDP, clinically manifested by different frontotemporal dementia clinical phenotypes. Cluster 2 consisted of LATE-NC patients without severe neuritic amyloid plaques. Subjects in Clusters 3 and 4 had severe ADNC + LATE-NC. However, Cluster 4 was distinguished by earlier disease onset, rapid clinical course, more LBD, less neocortical TDP-43 proteinopathy, and a trend for increased C9orf72 risk SNP rs3849942 T allele (Katsumata et al., 2020). About 98% of subjects dying past age 85

years lacked clinical features of FTLD thus differentiating FTLD-TDP and LATE-NC (Katsumata et al., 2020).

Quadruple misfolded proteins (represented by NFTs, SPs, Lewy bodies and TDP-43 proteinopathy) in the same brain were detected in nearly 20% of individuals with mean age at death 86.9; triple proteinopathy in 38.1%. The prevalence of dementia was higher (89%) in cases with quadruple proteinopathy (Karanth et al., 2020; Karanth et al., 2021).

LATE-NC also commonly associates with microvascular disease including cerebral β-amyloid angiopathy (Besser et al., 2020; Agrawal et al., 2021a, 2021b; Robinson et al., 2021; Harrison et al., 2021; Wang et al., 2022).

In contrast to humans, LATE-NC has not been observed in aged macaques (Darricau et al., 2021). No evidence of hippocampal/limbic TDP-43 pathology has been identified to date in other animal species.

4. Hippocampal sclerosis

Neuron loss and reactive astrogliosis in the CA1 region of the hippocampus, subiculum, and amygdala that is out of proportion to ADNC in the same structures characterizes hippocampal sclerosis of aging (Dickson et al., 1994; Jellinger, 1994; Leverenz et al., 2011; Nelson et al., 2011a, 2011b; Montine et al., 2012). Hippocampal sclerosis in aging occurs in about 30% of nonagenarians (Dickson et al., 1994; Nelson et al., 2011a, 2011b; Zarow et al., 2012; Nelson et al., 2013). Hippocampal sclerosis is commonly assymetrical and, occasionally, segmentary (Nelson et al., 2013; Ighodaro et al., 2015). It can be presented alone or, currently, in association with AD, LBD, other tauopathies, and ALS (Dickson et al., 1994; Zarow et al., 2012; Yokota et al., 2010). The extent of hippocampal atrophy is more severe in cases with associated hippocampal sclerosis than in cases with AD alone (Zarow et al., 2012).

TDP-43 pathology is found in nearly 90% of cases with hippocampal sclerosis when compared with about 10% in cases without hippocampal sclerosis (Nelson et al., 2013), and it is usually associated with ADNC (Amador-Ortiz et al., 2007; Yokota et al., Nag et al., 2015). Aberrant TDP-43 pathology in hippocampal sclerosis is usually characterized by TDP-43 immunoreactive neurites and neuronal cytoplasmic inclusions (Nelson et al., 2011a, 2011b; Nelson et al., 2013; Gauthreaux et al., 2022a, 2022b). Usually, TDP-43 pathology is not restricted to the sclerotic regions (Nelson et al., 2013). Moreover, neuron loss leading to hippocampal sclerosis in aging starts from the subicular end of CA1 when it is associated with TDP-43 pathology; this neurodegenerative process is likely to be significantly more common than "end-stage" hippocampal sclerosis alone (Hokkanen et al., 2018).

The clinical manifestations due to hippocampal sclerosis are difficult to dissect because of the co-morbid pathology; memory impairment and dementia occur in patients with hippocampal sclerosis, an expected secondary consequence of the hippocampal circuit damage (Leverenz and Lipton, 2008; Leverenz et al., 2002; Onyike et al., 2013).

GRN, *TMEM106B, KCNMB2*, and *ABCC9* variants are identified as risk genes of hipppocampal sclerosis (Nelson et al., 2014; Nelson et al., 2015a, 2015b; Neltner et al., 2016; Katsumata et al., 2017). These are the same genetic risk factors as those identified for LATE. In contrast, there is no association between *ApoEε4* and hippocampal sclerosis dementia (Troncoso et al., 1996).

The cause of hippocampal sclerosis in aging is not known. Although there is a close association between hippocampal sclerosis and arteriolosclerosis, it is not clear whether hypoxic/ischaemic insults are the cause of hippocampal sclerosis in the elderly (Neltner et al., 2014; Walker, 2015). The possibility that altered cell cycle re-entry may play a role in the pathogenesis of hippocampal sclerosis, as happens in AD (Arendt, 2003; Arendt, 2005; Arendt et al., 2007), should be considered.

5. Centenarians/the oldest-old

Centenarians are resistant and resilient to sAD or have very low progression to advanced Braak stages of tau and β-amyloid pathology (Arenaza-Urquijo and Vemuri, 2018; Andersen, 2020; Beker et al., 2021). ADNC in the oldest-old population also shows a particular neuropathological distribution, including high densities of NFTs, mainly in the hippocampus, without apparent significant clinical deficiencies (Giannakopoulos et al., 1993; Giannakopoulos et al., 1995; Braak et al., 2011; Rogalski et al., 2019; Xuereb et al., 2000). ADNC appears to peak around 95 years of age, while other common pathologies continue to increase with age (Farfel et al., 2019). Co-morbidities, including TDP-43 proteinopathy and mesial sclerosis, reduce resilience (Aiello Bowles et al., 2019; Buciuc et al., 2020a and b). In contrast, resilient oldest-old individuals without dementia have less cerebrovascular disease, no hippocampal sclerosis, and less cortical ARTAG, TDP-43, and Lewy pathology (Latimer et al., 2022 ; Robinson et al., 2018a, 2018b).

Genetic factors participate in cognitive and neuropathological resilience (Tavana et al., 2018; Nguyen et al., 2018; Nygaard et al., 2019; Dumitrescu et al., 2020; Seto et al., 2021; Leng et al., 2021).

LYST (lysosomal trafficking regulator), *MDN1* (meiotic nuclear divisions 1), and *RBMXL1* (RNA binding motif protein X-linked (RBMX)-like 1) burden are associated with extreme aging (Nygaard et al., 2019). *ATP8B1* encodes a protein that modulates phospholipid composition within cellular membranes; a variant on chromosome 18 upstream of *ATP8B1* is associated with unimpaired cognition in the oldest-old; the top variant at this locus (rs2571244) is associated with methylation in prefrontal cortex tissue at multiple CpG sites, including one just upstream of *ATPB81* (Dumitrescu et al., 2020). A *RAB10* locus is associated with AD resilience (Tavana et al., 2018).

RORB (RAR-related Orphan Receptor B) encodes a transcription factor that drives the development of layer IV neurons in the neocortex but is also expressed in other cell layers. RORB depletion is associated with vulnerability to NFT formation in excitatory neurons of the entorhinal cortex (Leng et al., 2021). Decreased expression of genes involved in homeostasis also occurs in reactive astrocytes (Leng et al., 2021).

Non-genetic factors are differentially predictive of resilience in women and men (McDermott et al., 2017). Indeed, many genes in chromosome X predict resilience; increased expression in 19 genes is associated with slower cognitive decline in women; however, increased expression of 3 genes is associated with neuropathological tau burden in men but not women (Davis et al., 2021).

Other factors are involved in neuronal resilience in old age. Some are linked to glycolytic function and individual molecular modulators such as epigenetic regulation (Tesi et al., 2020; Zhang et al., 2021a, 2021b). Additional elements are related to neuroinflammation: expression levels of chemokines decrease, and trophic factors increase in the oldest old (Barroeta-Espar et al., 2019; Tesi et al., 2020).

Finally, there is a heterogeneous group of factors that constitute the cognitive reserve, linked to educational and occupational acquisition, social networks, and leisure activities in later life, which have a protective effect (Stern, 2012; Lesuis et al., 2018; Montine et al., 2019; Weisenbach et al., 2019; Peng et al., 2022).

6. Seeding and spreading of abnormal protein aggregates

Several studies postulate that the progression of AD, tauopathies, LBD, and other diseases with abnormal protein aggregates occurs in a similar way to prions in prion diseases (Uchihara and Giasson, 2016; Mudner er al, 2017; Volpicelli-Daley and Brundin, 2018; Fuster-Matanzo et al., 2018; Dujardin and Hyman, 2019; Tarutani and Hasegawa, 2019; Goedert et al., 2020; Peng et al., 2020; Chen and Mitchell, 2021).

Tau secretion mainly occurs trans-synaptically, but vesicular (microvesicles and exosomes) and non-vesicular transport by direct translocation across the plasma membrane may also take place; nanotubules are also implicated in tau transfer from one cell to another (Chai

et al., 2012; Dujardin et al., 2014a; Dujardin et al., 2014b; Wang et al., 2017; Katsinelos et al., 2018; Polanco et al., 2018; Merezhko et al., 2018; Ruan and Ikezu, 2019; Zhang et al., 2021a, 2021b). Tau is then internalized via endocytosis, pinocytosis, and membrane fusion, with the contribution of heparan sulfate proteoglycans, bridging integrator 1 (Bin1), LDL receptor-related protein 1 (LRP1), and muscarinic receptors (Wu et al., 2013; Holmes et al., 2013; Rauch et al., 2018; Cooper et al., 2021; Vasili et al., 2019; Rauch et al., 2020; Zhao et al., 2021).

Mechanisms of release, transfer, and uptake of α-synuclein and its aggregates are similar, and include exocytosis by exosomes/secretory vesicles, tunnelling nanotubes composed of F-actin, endocytosis, and uptake by cell surface receptors with heparan sulfate proteoglycans facilitation (Lee et al., 2005; Lee et al., 2008; Emmanouilidou et al., 2010; Danzer et al., 2012; Uchihara and Giasson, 2016; Vasili et al., 2019; Tofaris, 2022). Formation of pore-like structures may permit α-synuclein release but no similar mechanism is proved for tau (Vasili et al., 2019). Cell death also allows the transfer of tau and α-synuclein from one cell to another (Vasili et al., 2019).

In cell cultures, TDP-43 is extruded from the cytoplasm via exosomes, axon terminals, or independently of vesicles (Feiler et al., 2015; Iguchi et al., 2016; Sackmann et al., 2020). The mechanisms of TDP-43 uptake are probably linked to microvesicles; studies using microfluidic neuronal devices suggest both anterograde and retrograde trans-synaptic transmission of TDP-43 (Feiler et al., 2015).

In vitro and in vivo studies show β-amyloid transmission by axonal processes and retrogradely transported to neuronal cell bodies (Song et al., 2014). β-amyloid transmission is facilitated in regions with strong network connectivity (Pignataro et al., 2017).

6.1. *β-amyloid seeding*

The intracerebral injection of diluted extracts from AD brains or from old AD transgenic mice, and particularly soluble forms of β-amyloid, accelerates β-amyloid deposition in transgenic mice bearing *APP* and/or *PSEN1* mutations (Walker et al., 2002; Meyer-Luehmann et al., 2006; Langer et al., 2011; Rosen et al., 2012; Morales et al., 2012; Hamaguchi et al., 2012; Hérard et al., 2020). Widespread β-amyloid deposits, focal tau hyper-phosphorylation, synaptic loss, and glial reactivity occur in cynomolgus macaques following intraventricular injection of Aβ oligomers (Forny-Germano et al., 2014). Intravenous or peripheral inoculation of β-amyloid induces cerebral β-amyloidosis and β-amyloid angiopathy (Eisele et al., 2010; Burwinkel et al., 2018).

β-amyloid seeding has also been reported in humans. β-amyloid deposits are found in the brain of patients with iatrogenic Creutzfeldt-Jakob disease (CJD) contaminated with cadaveric dura mater grafts, or following treatment with human growth hormone obtained from hypophysis of CJD-affected donors (Duyckaerts et al., 2018; Lauwers et al., 2020).

6.2. *Tau seeding from AD*

Neuropathological studies in humans reveal the beginning of telencephalic tau pathology in aging and sAD in the transentorhinal and entorhinal cortex; from these regions tau spreads to the hippocampus and other regions of the limbic system, and then progresses to the whole telencephalon (Braak and Braak, 1991; Braak and Braak, 1997; Braak et al., 2011; Ferrer, 2012; Furman et al., 2017; Kaufman et al., 2018; Arnsten et al., 2021; Ferrer, 2022). Tau-PET neuroimaging studies further support tau spreading along the functional connectivity networks not only "downstream" (i.e., along the expected sequence of the established Braak stages) but also in part "upstream" or "retrograde" (Seemiller et al., 2021).

Tau seeding and then spreading is produced following the intracerebral inoculation of recombinant full-length tau or truncated tau containing four microtubule binding repeats in P301S and P301L transgenic mice overexpressing mutant human tau (Iba et al., 2013; Peeraer et al., 2015).

Tau seeding and spreading is produced following the intracerebral inoculation of fibrillar tau-enriched fractions from AD homogenates containing hyper-phosphorylated tau in wild-type (WT) mice and transgenic mice bearing murine or human tau (Ahmed et al., 2014; Clavaguera et al., 2013a, 2013b; Boluda et al., 2015; Hu et al., 2016; Guo et al., 2016; Narashiman et al., 2017; Ferrer et al., 2020a and b; Andrés-Benito et al., 2022; Ferrer et al., 2022). Tau phosphorylation is needed for tau seeding and spreading (Hu et al., 2016). Propagation in these models occurs through connectivity rather than proximity (Ahmed et al., 2014). Several studies have shown that homogenates from different tauopathies generate disease-specific patterns of seeding and spreading, and involve different cell types, thereby mimicking the original human tauopathies (Clavaguera et al., 2013a, 2013b; Boluda et al., 2016; Narashiman et al., 2017; Ferrer et al., 2022). These findings support the proposal that tau strains lie behind the different phenotypes and progression of human tauopathies (Goedert et al., 2017; Mudner et al., 2017; Goedert and Spillantini, 2017; Goedert, 2020; Vaquer-Alicea et al., 2021).

However, this assumption must be approached with caution. Oligodendroglial tau-containing inclusions (coiled bodies) are generated following the inoculation of sAD homogenates whereas coiled bodies are never seen in AD unless AD is accompanied by other tau co-morbidities. Tau seeding and spreading also occur in oligodendrocytes in WT mice following inoculation of sarcosyl-insoluble fractions in the hippocampus and corpus callosum of human brain homogenates from other tauopathies (Narasimhan et al., 2018; Ferrer et al., 2019). The inoculation of pure ARTAG homogenates generates tau deposits in neurons and oligodendroglia but rarely if present in astrocytes (see later). Since these observations are obtained in WT mice, possible by-products linked to different promoters used to deliver transgens in genetically-manipulated mice (for example, the use of *prnp* promoters that may deliver the transgen to neurons and glial cells) are not applicable. The morphology of tau deposits also depends on the site of inoculation and the characteristics of the host tau (Götz and Götz, 2019; Ferrer et al., 2020b; Andrés-Benito et al., 2022).

Different tau strains are reported in AD brains (Li et al., 2021a, 2021b); thus, different tau strains may contribute to the clinical heterogeneity in sAD and fAD (Dujardin et al., 2020; Wesseling et al., 2020; Sepulveda-Falla et al., 2021).

Finally, abnormal tau may also be transmitted to humans in parallel to iatrogenic Creutzfeldt-Jakob disease after treatment of growth hormone from a cadaveric source (Duyckaerts et al., 2018).

6.3. *Tau seeding from AGD*

Staging of tau pathology in AGD is consistent with the hypothesis of prion-like cell-to-cell transmission of abnormal tau (Clavaguera et al., 2013a, 2013b; Rábano et al., 2014). Indeed, AGD-tau has the capacity for seeding and spreading when inoculated into the hippocampus of WT mice (Ferrer et al., 2020). Abnormal hyper-phosphorylated tau deposits are found in ipsilateral hippocampal neurons, grains (dots) in the hippocampus, and threads, dots and coiled bodies in the fimbria, as well as coiled bodies and threads in the ipsilateral and contralateral corpus callosum (Ferrer et al., 2020).

6.4. *Tau seeding from ARTAG*

Brain homogenates of pure ARTAG cases unilaterally inoculated in the hippocampus and corpus callosum of WT mice have the capacity for tau seeding and spreading in the ipsilateral hippocampus and corpus callosum and distant regions such as the contraletarel corpus callosum (Ferrer et al., 2018; Ferrer et al., 2019; Ferrer et al., 2020). Hyper-phosphorylated tau deposits are found in neurons, neuronal threads, dots, and oligodendroglial cells; in contrast, astrocytes do not contain abnormal tau deposits in long-term inoculated mice. This

pattern is similar, although with variable intensity, to that following inoculation of human brain homogenates from sAD and other tauopathies in WT mice (Ferrer et al., 2018; Ferrer et al., 2019; Ferrer et al., 2020).

6.5. α-synuclein seeding from Lewy body diseases (LBD)

Recombinant α-synuclein amyloid fibrils that resemble human pathological α-synuclein have been used in a large number of α-synuclein seeding studies in cellular and animal models. Various types of α-synuclein aggregates are found in host cells, as well as in transgenic mice expressing wild-type or mutant α-synuclein and WT mice. α-synuclein aggregates in mice have been observed following intracerebral and peripheral inoculation of pre-formed fibrillar α-synuclein precursors (Luk et al., 2012; Sacino et al., 2014a, 2014b; Breid et al., 2016; Ayers et al., 2017; Gribaudo et al., 2019). The amount and type of aggregates largely depend on the type of fibrils and characteristics and age of the host (Uchihara and Giasson, 2016). Moreover, α-synuclein strains cause distinct synucleinopathies after local and systemic administration (Peelaerts et al., 2015), and have differing structural and functional effects (Bousset et al., 2013; Holec and Woerman, 2020).

Intrastriatal injection of amyloidogenic α-synuclein aggregates in human α-synuclein transgenic mice leads to widespread α-synucleinopathy independent of neuronal connectivity (Sorrentino et al., 2017). The presence of intra-astrocytic α-synuclein deposits in inoculated mice suggests that glial cells participate in α-synuclein transmission (Sorrentino et al., 2017). The inoculation of phosphorylated α-synuclein at Ser129 fibrils in the striatum of WT mice augments α-synuclein pathology in the substantia nigra and cerebral cortex when compared with mice injected with non-phosphorylated and phosphorylation-incompetent S129 fibrils (Karampetsou et al., 2017). However, the enhancer effect of phosphorylated α-synuclein at Ser129 on α-synuclein aggregation is not supported by other studies; aggregation indeed precedes α-synuclein phosphorylation (Ghanem et al., 2022).

Clinical studies have shown that Lewy bodies occur in grafted embryonic and fetal neurons in subjects with PD thus suggesting host-to-graft propagation (Kordower et al., 2008; Li et al., 2008; Chu and Kordower, 2010). Similar results have been reproduced in grafted dopaminergic neurons in cultured human cells and rats (Hansen et al., 2011; Angot et al., 2012).

The intracerebral injection of Lewy body extracts from PD patients in WT mice and macaques produced α-synuclein deposits (but not Lewy bodies) and nigrostriatal degeneration (Recasens et al., 2014). However, PD homogenates inoculated in transgenic mice expressing mutated A53T α-synuclein did not show α-synuclein conversion at one year post-inoculation (Prusiner et al., 2015). This latter observation is in striking contrast to the effective transmission of multiple system atrophy (MSA) prions to transgenic mice carried out by the same researchers (Watts et al., 2013; Prusiner et al., 2015). Other studies have shown transmission of soluble and insoluble α-synuclein from LBD brain homogenates in BDF1 transgenic mice that over-express human wild type α-synuclein under the regulatory control of the platelet-derived growth factor (PDGF-β) promoter (Jones et al., 2015); and incidental LBD (and MSA) homogenates in Tg(SNCA)1Nbm/J mice expressing human wild-type synuclein (Bernis et al., 2015). Induction of α-synuclein aggregates is also generated following intracerebral injection of brain-derived exosomes from DLB patients in wild-type mice (Ngolab et al., 2017).

Transmissible α-synuclein seeding has also been produced up to 600 days following inoculation of brain and stomach homogenates from PD patients in TgM83$^{+/-}$ mice which express the mutant human A53T α-synuclein under the direction of the mouse prion protein promoter (Thomzig et al., 2021).

Capacities for seeding and spreading of α-synuclein depend on the source (strain) from PD, incidental LBD, DLB, and MSA (Peelaerts et al., 2018). In the same line, a comparison of the seeding and spreading capacities of α-synuclein obtained from DLB cases, AD/amygdala-predominant LBD, and recombinant α-synuclein fibrils inoculated in the brain of transgenic mice overexpressing human wild-type α-synuclein, or human α-synuclein with the A53T mutation, shows differing phenotype and course of the spreading depending on the α-synuclein inoculum (Lloyd et al., 2022).

6.6. TDP-43 seeding from TDP-43 proteinopathies

Staging of TDP-43 pathology in LATE suggests the progression of abnormal TDP-43 from cell-to-cell transmission in a prion-like manner. *In vitro* and in vivo studies have shown TDP-43 transmission across axon terminals, and TDP-43-derived from FTLD-TDP and ALS spreading with sub-type specific characteristics (Nonaka et al., 2013; Feiler et al., 2015; Smethurst et al., 2015; Smethurst et al., 2016; Porta et al., 2018; De Rossi et al., 2021; Porta et al., 2021; Jo et al., 2020). To date, no similar studies assessing seeding capacities of TDP-43 from LATE cases are available.

7. *In vitro* seeding assays in clinical practice

The capacity for seeding can be analyzed in biological samples using methods that amplify abnormally conformed proteins using the corresponding natural proteins as templates. The real-time quaking-induced conversion (RT-QuIC) method shakes and breaks abnormal aggregates which are incubated with fragments of corresponding basal recombinant proteins as substrate and then amplifies the amount of misfolded abnormal protein. The protein misfolding cyclic amplification (PMCA) technique is based on the sonication of abnormally folded proteins into smaller fragments; this is followed by the incubation step in which normal proteins are recruited and converted into abnormally conformed forms. These methods, first created for the study of prion diseases, are helpful to detect small amounts of other abnormally conformed proteins in tissues and body fluids, and may be applied to the clinical diagnosis of AD, α-synucleinopathies, tauopathies, and TDP-43 proteinopathies (Saijo et al., 2019; Kraus et al., 2019; Saijo et al., 2020; Metrick et al., 2020; Tennant et al., 2020; Rossi et al., 2020; Scialò et al., 2020; Arnold et al., 2022; Yoo et al., 2022; Standke and Kraus, 2022). The PMCA method has also been helpful for detecting α-synuclein seeding in formalin-fixed post-mortem nervous system tissue (Fenyi et al., 2021). Abnormal tau seeding can also be detected in formalin-fixed tissue using a new biosensor method (Kaufman et al., 2017).

8. Role of seeding and spreading in the progression of age-related proteinopathies

Tau can propagate from one neuron to another under physiological conditions, and the process is stimulated by neuronal activity (Pooler et al., 2013; Yamada et al., 2014; Wu et al., 2016). Tau seeding and spreading is also influenced by sleep deprivation; human CSF tau increases more than 50% during sleep deprivation; and tau seeding and spreading is increased following sleep deprivation in an animal model (Holth et al., 2019). Sleep deprivation promotes AD-like pathology in another paradigm (Lv et al., 2022).

The transmission of β-amyloid is also facilitated by neuronal activity (Pignataro and Middei, 2017). Likewise, neuronal activity increases α-synuclein aggregation and spreading in organotypic cell cultures and it exacerbates α-synuclein pathology following injection of preformed α-synuclein protofibrils in the striatum of WT mice (Wu et al., 2020).

The capacity of anomalous proteins to potentiate each other's' aggregation has been contemplated in several studies. Cellular prion protein facilitates interneuronal β-amyloid transmission (Del Río et al., 2018 8), and facilitates the uptake of tau amyloid fibrils (De Cecco et al., 2020). β-amyloid enhances pathological tau seeding accompanied by increased levels of the 25 activator of CDK5 kinase in AD-tau-inoculated

4xFAD transgenic mice (Vergara et al., 2019). The inoculation of pre-formed α-synuclein fibrils in 5xFAD Tg mice, expressing mutations in *APP* (K670N/M671L [isoform 770] + I716V + V717I) and *PS1* (M146L + L286V), with abundant β-amyloid plaques promotes seeding and spreading of α-synuclein and tau hyper-phosphorylation throughout the brain (Bassil et al., 2020). Therefore, these results suggest that β-amyloid facilitates α-synuclein and tau seeding. APOE status also modulates α-synuclein's effects: α-synuclein aggregates from patients with AD plus LBD with ApoE4 are highly toxic to iPSc-derived neurons compared to aggregates from AD APOE4 − , AD APOE4 + , and AD+LB APOE4 − (Jin et al., 2022).

α-synuclein also impacts tau aggregation. Different recombinant α-synuclein fibril strains differentially promote tau inclusions in neurons (Guo et al., 2013). α-synuclein oligomers from PD cases administered to hTau mice accelerate tau oligomer formation (Castillo-Carranza et al., 2018). Intracellular tau aggregation is promoted by α-synuclein seeds in tau mouse models (Waxman and Giasson, 2011), but the opposite does not occur in α-synucleinopathy models (Williams et al., 2020).

Although mechanisms of release and uptake of abnormal aggregates are documented, the modifications of the host protein by the pathologic seed are not clearly understood. Abnormal tau triggers a series of molecular processes that include activation of several tau kinases, hyperphosphorylation, nitration, and altered tau conformation, as well as recruitment of additional substrates in tau deposits (Ferrer et al., 2018; Ferrer et al., 2019; Ferrer et al., 2020a, 2020b; 2020c; Ferrer et al., 2022). However, there is no evidence that the conformation of abnormal tau generated in the host is the same as the conformation of the inoculated tau. Indeed, hyper-phosphorylation of recruited tau appears before altered tau conformation and tau truncation, which affect a subpopulation of phospho-tau containing neurons. Thus, pathogenic aggregated tau triggers a complex response in the host that follows similar steps to those occurring during the genesis of abnormal tau in the donor. This phenomenon may explain why the characteristics of tau deposits at short time points after inoculation are similar independently of the strain. Similarly, differences in host tau may lie behind the variable pace of tau transformation following injection of similar inocula.

In vitro studies aimed at monitoring the internalization and aggregation of externally added synthetic fibrils and AD brain extracts have shown, using real-time conversion of microtubule-binding domain of tau fused to a fluorescent marker into aggregates, colocalization of ubiquitin and p62 in the aggregates (Chastagner et al., 2020). The inoculation of AD-tau into the hippocampus of THY-Tau22 transgenic mice induced tau-positive grain-like inclusion in subregions of the hippocampus at three months after injection; these inclusions were immunoreactive with the antibodies phospho-tau, 4 Rtau, misfolded tau, ubiquitin, and p62 (Audouard et al., 2016). However, no ubiquitin or p62 deposits have been observed following intracerebral inoculation of homogenates from several human tauopathies into WT mice at three and six months after injection (Ferrer et al., 2020c). These differences may be explained by differing states of abnormal tau deposition depending on the type of inoculum and characteristics of the host.

Another interesting point is the capacity to recruit 3 Rtau following injection of 4 Rtau, or 4Rtau following inoculation of 3 Rtau. PSP- and CBD-tau do not induce 3Rtau in 3Rtau-expressing mice, and PiD does not induce 3Rtau in 4 Rtau-expressing mice, whereas AD-tau induces 3Rtau and 4Rtau deposits in 3Rtau- and 4Rtau-expressing mice (He et al., 2020). However, other studies have shown small amounts of 3Rtau deposition, in addition to 4Rtau, following inoculation of homogenates from 4R-tauopathies, and a few 4Rtau deposits following inoculation of human 3Rtau homogenates; AD-tau inoculation gives rise to 3Rtau and 4Rtau deposits in WT and hTau transgenic mice (Ferrer et al., 2018; Ferrer et al., 2019; Ferrer et al., 2020a, 2020b). These results point to the possibility that foreign abnormal tau might modulate *mapt* exon 10 splicing (Ferrer et al., 2022). In this line, tau splicing modifier CKL1 is expressed in the ipsilated dentate gyrus in AD- and GGT-inoculated hTau mice but not in hTau inoculated with vehicle alone (Ferrer et al., 2022).

Another important point is the characteristics of tau spreading in the human brain that seem to skip over obligate regions on the basis of cell connectivity. The dentate gyrus does not show tau pathology in AD and other 3R+ 4R tauopathies without co-morbidities, but the dentate gyrus is commonly affected in 3R- and 4R-tauopathies. Alternatively, the following sequence has been proposed: tau pathology progresses from pre-α cells to distal dendrites in the prosubiculum and CA1; then, from CA1 or prosubicular pyramids to CA2 principal cells and CA3/CA4 mossy cells; and finally, from CA4 mossy cells to dentate granule cells (Braak and Del Tredici, 2020).

As a matter of fact, tau and α-synuclein seeding and spreading circumvent regions that should be involved according to the hypotheses of either neuronal connectivity or neuronal proximity. These observations suggest that neuronal subpopulations are able to transfer abnormal tau from one neuron to the next in the connecting pathway without recruiting host tau and forming local aggregates within themselves. In this line, tau seeding has been documented in regions with little or no apparent accumulation of phospho- tau in AD brains (Stopschinski et al., 2021).

Finally, there is no single origin of tau, β-amyloid, and α-synuclein seeding (Uchihara and Giasson, 2016; Kaufman et al., 2018). Moreover, seeding and propagation pathways of tau and α-synuclein differ in AD, other tauopathies, and α- synucleinopathies (Braak and Braak, 1991; Braak and Braak, 1995; Braak et al., 2002; Braak et al., 2003; Braak et al., 2004; McCann et al., 2016; Hoenig et al., 2018; Schwarz et al., 2018; Franzmeier et al., 2022).

Microglia and the status of neuroinflammation in brain aging and its role in the pathogenesis of AD are well documented. The involvement of microglia in tau seeding and spreading has also been assessed in animal models. Tau is internalized by microglia in vivo and in vitro (Bolós et al., 2015), but tau seeding by cultured adult microglia from AD cases and a mouse model of tauopathy is apparently not very efficient, as revealed with a sensitive fluorescence resonance energy transfer (FRET) biosensing cell line for tau seeding and aggregation (Hopp et al., 2018).

Other studies offer divergent results. Rapid tau propagation from the entorhinal cortex to the dentate gyrus was generated via an adeno-associated virus vector driving transgene expression of human P301L tau, in P301S tau transgenic mice; microglia depletion reduced tau propagation in this model (Asai et al., 2015).

TREM2 activation exacerbated β-amyloid-associated tau seeding and spreading around amyloid plaques in 5XFAD mice (overexpressing mutant human Aβ precursor protein with K670N-M671L, I716V, and V717I mutations and human PS1 harboring M146L and L286V mutations) (Jain et al., 2023). Yet TREM2 deletion and microglia ablation enhanced tau seeding and spreading around plaques in the same (5XFAD) transgenic model of β-amyloidopathy (Gratuze et al., 2021).

TREM2 deletion increased tau seeding and spreading in vivo at short time points post-inoculation of AAV-P301L tau vectors in Trem2 knockout compared with wild-type mice, and enhanced intraneuronal dispersion of tau in vitro between neuronal layers cultured in a microfluid device (Zhu et al., 2022). In contrast, TREM2 deficiency in microglia resulted in greater accumulation of tau in THY-Tau22 transgenic mice at late stages following inoculation (Vautheny et al., 2021). The study was carried out by crossing THY-Tau22 heterozygous mice expressing the 1N4Rtau and the G272V and P301S point mutations, with Trem2-/- or Trem2 + /+ littermate mice to generate two groups: Trem2 + /+ , Tau22 and Trem2-/-, Tau22 mice (Vautheny et al., 2021).

These discrepancies are difficult to explain, unless we consider the many facets of microglia as comprehensively discussed by others (Odfalk et al., 2022).

9. Human brain aging vulnerability as revealed by the regional convergence of age-related proteinopathies

The most vulnerable regions in human brain aging to sAD (including

PART), AGD, and LATE are the archicortex, followed by the paleocortex and other parts of the limbic system. TSAs in ARTAG, not associated with other tauopathies excepting sAD, chiefly appear in different locations of the temporal lobe including the subependyma of the hippocampus, subpial region of the entorhinal cortex, amygdala, and temporal white matter. Amygdala-predominant LBD in the elderly usually linked to sAD also centers on the limbic system. Other neuropathological changes associated with brain aging such as Hirano bodies and granulovacuolar degeneration (GVD) also first appear in the same regions.

Hirano bodies are eosinophilic, rod-shaped inclusions derived from an abnormal organization of the neuronal cytoskeleton mainly localized in pyramidal neurons of the hippocampus in aging and sAD (Galloway et al., 1987). Hirano bodies do not express markers of the proteasome and autophagosome, but rather ubiquilin-1, which mediates the translocation of polyubiquitinated proteins to the proteasome for degradation (Satoh et al., 2013).

GVD is characterized by the presence of vacuolar cytoplasmic lesions with a dense central core. The molecular composition of cytoplasmic granules in GVD suggests a convergence of altered proteostasis, protein hyper-phosphorylation with enhanced tau-kinase activity, altered proteolysis, an impaired ubiquitin-proteasome system, abnormal reticulum stress responses, altered endocytic and autophagic pathways, and mitophagy (Okamoto et al., 1991; Ghanevati and Miller, 2005; Barrachina et al., 2006; Hoozemans et al., 2009; Funk et al., 2011; Hu et al., 2020; Hondius et al., 2021; Andrés-Benito et al., 2021). Phospho-tau and phosphorylated TDP-43 are common components of GVD (Andrés-Benito et al., 2021; Koper et al., 2022). Moreover, LATE-NC aggravates GVD-mediated necroptosis in AD, as revealed by the increased expression of the phosphorylated necroptosis executioner mixed-lineage kinase domain-like protein (pMLKL) (Koper et al., 2022).

GVD appears in neurons of CA1 and CA2, and the subiculum in stage 1; this is followed by the entorhinal cortex, and CA4 neurons in stage 2; temporal neocortex in stage 3; amygdala and/or the hypothalamus in stage 4; and cingulate, frontal, and parietal cortices in stage 5 (Thal et al., 2011).

The particular vulnerability of the archicortex followed by the paleocortex indicates that these regions cannot cope with the physiological demands made over the whole lifespan of actual humans. Physiological failure is manifested by variable and progressive wear of neuronal and glial proteostasis with production and accumulation of abnormal protein aggregates, followed by nerve cell demise first and foremost arising in these regions. This applies to tau aggregates in NFTs, pre-tangles, and grains in neurons; TSAs in ARTAG; and coiled bodies in oligodendrocytes; as well as α-synuclein in neurons and neuritis; and TDP-43 in neurons, neurites, and glial cells.

This scheme does not apply to β-amyloid deposition, as β-amyloid has no early predilection for these phylogenetically old regions, but it involves first the convexity of the telencephalon and then progresses to other brain places.

The reason for the particular vulnerability is not known but it can be linked to the advanced development of the neocortex in primates and particularly in humans when compared with other species (Crosby and Schnitzlein, 1982; Gall, 1990; Jones and Peters, 1990; Hodos and Butler, 1996; Kaas, 2017). Other gyrencephalic species such as cetaceans have highly developed and convoluted telencephalon, but they do not show the same age-related regional vulnerability seen in humans. Therefore, differences might be associated with neuron and glial cell numbers, and synapses, but more likely with the complexity of interneural connections and the variety of neuronal subpopulations in the human neocortex and subcortical nuclei, which confer unique functional activities in humans (Herculano-Houzel, 2012; Triarhou, 2017; Briscoe and Ragsdale, 2019).

Serotoninergic neurons of the raphe, noradrenergic neurons of the locus ceruleus, and dopaminergic neurons of the substantia nigra pars compacta, together with cholinergic neurons of Meynert's basal nucleus of the prosencephalon, are involved in the α-synucleinopathy at early Braak stages (mainly I-III) of Lewy body in pre-motor cases of PD; interestingly, neurons in these regions show hyperbranched axons, and they therefore support a high demand of the corresponding neurotransmitter innervation mainly to the whole telencephalon (Kanazawa et al., 2008; Sulzer and Surmeier, 2013; Uchihara and Giasson, 2016). The same types of neurons are also vulnerable at early stages of NFT pathology (stages a-c of Braak) in the elderly and in AD (Braak and Del Tredici, 2015; Arnsten et al., 2021).

10. Therapeutic implications

Current strategies to cure AD are based on the assumption that i) β-amyloid triggers tau pathology in AD and therefore, β-amyloid is the first target to combat AD; ii) tau pathology parallels cognitive impairment, and then tau is the second target to reduce AD pathology; iii) other factors, such as inflammation, membrane integrity, neurotransmitter alterations, are complementary targets to reduce neuronal damage in AD. However, all these strategies have failed to some degree as i) β-amyloid vaccination does reduce the β-amyloid burden but not tau pathology and disease progression (this is a significant point against the amyloid cascade hypothesis as the origin of sAD); ii) tau vaccination has to decide what the critical tau isoform or aggregate, among the multiple pathological tau species, is the crucial target for therapeutic intervention; iii) anti-tau phosphorylated agents (mainly anti-active kinases) act on multiple molecules that are vital to the normal cell functions; iv) other drugs directed to replace neurotransmitter deficits have transient and mild effects; v) therapies aimed at clearing abnormal proteins in the blood (i.e., plasmapheresis) are still in a preliminary phase; vi) available gene therapies in humans have demonstrated little benefit; vii) the use of shuttles including exosomes to deliver selected molecules into the cells is still at the early stages; and viii) all these procedures are implemented at the middle or advanced stages of the neurodegenerative process.

So far, no therapies have been proposed regarding AGD, LATE-NC, ARTAG, amygdala-predominant LBD, and hippocampal sclerosis.

The present scenario of human brain aging implies the need for new therapeutic attempts based on new targets altered at earlier stages of the neurodegenerative processes. One of the first points is to gain an understanding of the differential vulnerability of the human brain to aging when compared with other species based on genetic and epigenetic factors that may determine the early fragility of the human archicortex and paleocortex when compared with other species; and the dramatic progression of pathological changes, although with different individual pace, once initiated the pathological processes. Another point is to consider that NFT (and β-amyloid) pathology is not the only neurodegenerative change in the elderly, but instead that tau and β-amyloid pathology are part of a complex abnormal proteostasis; in this line, tau pathology differs in AD, ARTAG, and AGD; moreover, TDP-43 and α-synuclein pathologies are also relevant in human brain aging. Finally, alterations in other molecular pathways, including those compromising i) lipid composition of membranes, membrane proteins, and membrane signaling, ii) mitochondria and energy metabolism, iii) DNA and RNA metabolism integrity and regulation, iv) neuroinflammation, v) glial cells senescence, and vi) blood vessel dysfunction, also participate in human brain aging (Ferrer, 2022).

Another conclusion of the present review postulates that the human archicortex and paleocortex are not designed to endure a functional overload during the human lifespan. Biological cell reprogramming may cover different areas, including brain DNA editing, optimization of mitochondrial function, and pharmacological combined protection of lipid-protein interactions. Improvement in the efficiency of reparative sleep functions (program resetting during stages of sleep) may also be specifically explored. In addition to biological procedures, the rapid growth of artificial intelligence (AI) may offer excellent opportunities to use advanced technologies. Intelligent devices and "external" memories may be designed and implemented to delegate (and even expand) expensive (in terms of energy and molecular consumption) tasks of the

vulnerable phylogenetically older circuits. Implanting microdevices may facilitate cooperative human-machine function. External electrical or wave-based signals may reduce the energy consumption of essential neuronal networks.

Brain reprogramming would likely be undertaken before the beginning of the slow-pace functional decline in middle-aged adults. Improvement of brain function in aging and sAD has a chance of applying high-throughput molecular technology, AI, and robotics (Ferrer, 2022).

Funding

The project leading to these results received funding from the "la Caixa" Foundation (ID 100010434) under the agreement LCF/PR/HR19/52160007, HR18–00452. I thank the CERCA programme of the Generalitat de Catalunya for institutional support.

Declaration of Competing Interest

No competing interests to declare.

Data availability

No data was used for the research described in the article.

Acknowledgements

I wish to thank T. Yohannan for correcting the manuscript.

References

Adachi, T., Saito, Y., Hatsuta, H., Funabe, S., Tokumaru, A.M., Ishii, K., et al., 2010. Neuropathological asymmetry in argyrophilic grain disease. J. Neuropathol. Exp. Neurol. 69, 737–744. https://doi.org/10.1097/NEN.0b013e3181e5ae5c.

Agrawal, S., Yu, L., Kapasi, A., James, B.D., Arfanakis, K., Barnes, L.L., et al., 2021a. Limbic-predominant age-related TDP-43B encephalopathy neuropathologic change and microvascular pathologies in community-dwelling older persons. Brain Pathol. 31, e12939 https://doi.org/10.1111/bpa.12939.

Agrawal, S., Yu, L., Nag, S., Arfanakis, K., Barnes, L.L., Bennett, D.A., et al., 2021b. The association of Lewy bodies with limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes and their role in cognition and Alzheimer's dementia in older persons. Acta Neuropathol. Commun. 9, 156. https://doi.org/10.1186/s40478-021-01260-0.

Ahmed, Z., Cooper, J., Murray, T.K., Garn, K., McNaughton, E., Clarke, H., et al., 2014. A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. Acta Neuropathol. 127, 667–683. https://doi.org/10.1007/s00401-014-1254-6.

Aiello Bowles, E.J., Crane, P.K., Walker, R.L., Chubak, J., LaCroix, A.Z., Anderson, M.L., et al., 2019. Cognitive resilience to Alzheimer's disease pathology in the human brain. J. Alzheimers Dis. 68, 1071–1083. https://doi.org/10.3233/JAD-180942.

Allen, B., Ingram, E., Takao, M., Smith, M.J., Jakes, R., Virdee, K., et al., 2002. Abundant tau filaments and non-apoptotic neurodegeneration in transgenic mice expressing human P301S tau protein. J. Neurosci. 22, 9340–9351. https://doi.org/10.1523/JNEUROSCI.22-21-09340.2002.

Alzheimer, A., 1907. Über eine eigenartige Erkrankung der Hirnrinde. Allg. Z. Psychiat 64, 146–148.

Amador-Ortiz, C., Lin, W.L., Ahmed, Z., Personett, D., Davies, P., Duara, R., et al., 2007. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann. Neurol. 61, 435–445. https://doi.org/10.1002/ana.21154.

Ameen-Ali, K.E., Bretzin, A., Lee, E.B., Folkerth, R., Hazrati, L.N., Iacono, D., et al., 2022. Detection of astrocytic tau pathology facilitates recognition of chronic traumatic encephalopathy neuropathologic change. Acta Neuropathol. Commun. 10, 50. https://doi.org/10.1186/s40478-022-01353-4.

Andersen, S.L., 2020. Centenarians as models of resistance and resilience to Alzheimer's disease and related dementias. Adv. Geriatr. Med. Res. 2, e200018 https://doi.org/10.20900/agmr20200018.

Anderson, J.P., Walker, D.E., Goldstein, J.M., Laat, R., Banducci, K., Caccavello, R.J., et al., 2006. Phosphorylation of Ser 129 is the dominant pathological modification of synuclein in familial and sporadic Lewy body disease. J. Biol. Chem. 281, 29739–29759.

Andorfer, C., Kress, Y., Espinoza, M., de Silva, R., Tucker, K.L., Barde, Y.A., et al., 2003. Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. J. Neurochem 86, 582–590. https://doi.org/10.1046/j.1471-4159.2003.01879.x.

Andrés-Benito, P., Carmona, M., Jordán Pirla, M., Torrejón-Escribano, B., del Rio, J.A., Ferrer, I., 2021. Dysregulated protein phosphorylation as main contributor of granulovacuolar degeneration at the first stages of NFT pathology. Oct 30;S0306-4522(21)00534-0 Neuroscience. https://doi.org/10.1016/j.neuroscience.2021.10.023.

Andrés-Benito, P., Carmona, M., Jordán, M., Fernández-Irigoyen, J., Santamaría, E., del Rio, J.A., et al., 2022. Host tau genotype specifically designs and regulates tau seeding and spreading and host tau transformation following intrahippocampal injection of identical tau AD inoculum. Int J. Mol. Sci. 23, 718. https://doi.org/10.3390/ijms23020718.

Andrews, S.J., Fulton-Howard, B., Goate, A., 2020. Interpretation of risk loci from genome-wide association studies of Alzheimer's disease. Lancet Neurol. 19, 326–335. https://doi.org/10.1016/S1474-4422(19)30435-1.

Angot, E., Steiner, J.A., Lema Tomé, C.M., Ekström, P., Mattsson, B., Björklund, A., et al., 2012. Alpha-synuclein cell-to-cell transfer and seeding in grafted dopaminergic neurons in vivo. PLoS One 7, e39465. https://doi.org/10.1371/journal.pone.0039465.

Arena, J.D., Johnson, V.E., Lee, E.B., Gibbons, G.S., Smith, D.H., Trojanowski, J.Q., et al., 2020a. Astroglial tau pathology alone preferentially concentrates at sulcal depths in chronic traumatic encephalopathy neuropathologic change. Brain Commun. 2, fcaa210. https://doi.org/10.1093/braincomms/fcaa210.

Arena, J.D., Smith, D.H., Lee, E.B., Gibbons, G.S., Irwin, D.J., Robinson, J.L., et al., 2020b. Tau immunophenotypes in chronic traumatic encephalopathy recapitulate those of ageing and Alzheimer's disease. Brain 143, 1572–1587. https://doi.org/10.1093/brain/awaa071.

Arenaza-Urquijo, E.M., Vemuri, P., 2018. Resistance vs resilience to Alzheimer disease: clarifying terminology for preclinical studies. Neurology 90, 695–703. https://doi.org/10.1212/WNL.0000000000005303.

Arendt, T., 2003. Synaptic plasticity and cell cycle activation in neurons are alternative effector pathways: the "Dr. Jekyll and Mr. Hyde concept" of Alzheimer's disease or the yin and yang of neuroplasticity. Progr Neurobiol. 71, 83–248. https://doi.org/10.1016/j.pneurobio.2003.09.007.

Arendt, T., 2005. Alzheimer's disease as a disorder of dynamic brain self-organization. Prog. Brain Res. 147, 355–378. https://doi.org/10.1016/S0079-6123(04)47025-3.

Arendt, T., Brückner, M.K., 2007. Linking cell-cycle dysfunction in Alzheimer's disease to a failure of synaptic plasticity. Biochim Biophys. Acta 1772, 413–421. https://doi.org/10.1016/j.bbadis.2006.12.005.

Arendt, T., Stieler, J.T., Holzer, M., 2016. Tau and tauopathies. Brain Res. Bull. 26, 238–292. https://doi.org/10.1016/j.brainresbull.2016.08.018.

Arima, K., Uéda, K., Sunohara, N., Hirai, S., Izumiyama, Y., Tonozuka-Uehara, H., et al., 1998. Immunoelectron-microscopic demonstration of NACP/alpha-synuclein-epitopes on the filamentous component of Lewy bodies in Parkinson's disease and in dementia with Lewy bodies. Brain Res. 808, 93–100. https://doi.org/10.1016/s0006-8993(98)00734-3.

Arima, K., Hirai, S., Sunohara, N., Aoto, K., Izumiyama, Y., Ueda, K., et al., 1999. Cellular co-localization of phosphorylated tau- and NACP/alpha-synuclein-epitopes in Lewy bodies in sporadic Parkinson's disease and in dementia with Lewy bodies. Brain Res. 843, 53–61.

Arnold, M.R., Coughlin, D.G., Brumbach, B.H., Smirnov, D.S., Concha-Marambio, L., Farris, C.M., et al., 2022. Synuclein seed amplification in CSF and brain from patients with different brain distributions of pathological α-synuclein in the context of co-pathology and non-LBD diagnoses. Ann. Neurol. 92, 650–662. https://doi.org/10.1002/ana.26453.

Arnsten, A.F.T., Datta, D., Del Tredici, K., Braak, H., 2021. Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease. Alzheimers Dement 17, 115–124. https://doi.org/10.1002/alz.12192.

Arseni, D., Hasegawa, M., Murzin, A.G., Kametani, F., Arai, M., Yoshida, M., et al., 2022. Structure of pathological TDP-43 filaments from ALS with FTLD. Nature 601, 139–143. https://doi.org/10.1038/s41586-021-04199-3.

Aso, E., Lomoio, S., López-González, I., Joda, L., Carmona, M., Fernández-Yagüe, N., et al., 2012. Amyloid generation and dysfunctional immunoprotasome activation with disease progression in animal model of familial Alzheimer's disease. Brain Pathol. 22, 636–653. https://doi.org/10.1111/j.1750-3639.2011.00560.x.

Attems, J., Toledo, J.B., Walker, L., Gelpi, E., Gentleman, S., Halliday, G., et al., 2021. Neuropathological consensus criteria for the evaluation of Lewy pathology in post-mortem brains: a multi-centre study. Acta Neuropathol. 141, 159–172. https://doi.org/10.1007/s00401-020-02255-2.

Audouard, E., Houben, S., Masaracchia, C., Yilmaz, Z., Suain, V., Authelet, M., et al., 2016. High-molecular-weight paired helical filaments from Alzheimer brain induces seeding of wild-type mouse tau into an argyrophilic 4Rtau pathology in vivo. Am. J. Pathol. 186, 2709–2722. https://doi.org/10.1016/j.ajpath.2016.06.008.

Avila, J., 2006. Tau phosphorylation and aggregation in Alzheimer's disease pathology. FEBS Lett. 580, 2922–2927. https://doi.org/10.1016/j.febslet.2006.02.067.

Ayers, J.I., Brooks, M.M., Rutherford, N.J., Howard, J.K., Sorrentino, Z.A., Riffe, C.J., et al., 2017. Robust central nervous system pathology in transgenic mice following peripheral injection of α-synuclein fibrils. J. Virol. 91, e02095–e02116. https://doi.org/10.1128/jvi.02095-16.

Baba, M., Nakajo, S., Tu, P.H., Tomita, T., Lee, V.M., Trojanowski, J.Q., et al., 1998. Aggregation of α-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. Am. J. Pathol. 152, 879–884.

Bac, B., Hicheri, C., Weiss, C., Buell, A., Vilcek, N., Spaeni, C., et al., 2022. The TgF344-AD rat: behavioral and proteomic changes associated with aging and protein expression in a transgenic rat model of Alzheimer's disease. NEurobiol. Aging. https://doi.org/10.1016/j.neurobiolaging.2022.12.015.

Bai, B., Wang, X., Li, Y., Chen, P.C., Yu, K., Dey, K.K., et al., 2020. Deep multilayer brain proteomics identifies molecular networks in Alzheimer's disease progression. Neuron 105, 975–991.e7. https://doi.org/10.1016/j.neuron.2019.12.015.

Baker, M., Mackenzie, I.R., Pickering-Brown, S.M., Gass, J., Rademakers, R., Lindholm, C., et al., 2006. Mutations in progranulin cause tau-negative

frontotemporal dementia linked to chromosome 17. Nature 442, 916–919. https://doi.org/10.1038/nature05016.
Bandyopadhyay, U., Cuervo, A.M., 2007. Chaperone-mediated autophagy in aging and neurodegeneration: lessons from alpha-synuclein. Exp. Gerontol. 42, 120–128. https://doi.org/10.1016/j.exger.2006.05.019.
Barrachina, M., Maes, T., Buesa, C., Ferrer, I., 2006. Lysosome associated membrane protein 1 (LAMP-1) in Alzheimer's disease. Neuropathol. Appl. Neurobiol. 32, 505–516. https://doi.org/10.1111/j.1365-2990.2006.00756.x.
Barroeta-Espar, I., Weinstock, L.D., Perez-Nievas, B.G., Meltzer, A.C., Siao Tick Chong, M., Amaral, A.C., et al., 2019. Distinct cytokine profiles in human brains resilient to Alzheimer's disease. Neurobiol. Dis. 121, 327–337. https://doi.org/10.1016/j.nbd.2018.10.009.
Bassil, F., Brown, H.J., Pattabhiraman, S., Iwasyk, J.E., Maghames, C.M., Meymand, E.S., et al., 2020. Amyloid-beta (Aβ) plaques promote seeding and spreading of alpha-synuclein and tau in a mouse model of Lewy body disorders with Aβ pathology. Neuron 105 (260–275), e6. https://doi.org/10.1016/j.neuron.2019.10.010.
Beach, T.G., Malek-Ahmadi, M., 2021. Alzheimer's disease neuropathological comorbidities are common in the younger-old. J. Alzheimers Dis. 79, 389–400. https://doi.org/10.3233/JAD-201213.
Beker, N., Ganz, A., Hulsman, M., Klausch, T., Schmand, B.A., Scheltens, P., et al., 2021. Association of cognitive function trajectories in centenarians with postmortem neuropathology, physical health, and other risk factors for cognitive decline. JAMA 4, e2031654. https://doi.org/10.1001/jamanetworkopen.2020.31654.
Bell, W.R., An, Y., Kageyama, Y., English, C., Rudow, G.L., Pletnikova, O., et al., 2019. Neuropathologic, genetic, and longitudinal cognitive profiles in primary age-related tauopathy (PART) and Alzheimer's disease. Alzheimers Dement 15, 8–16. https://doi.org/10.1016/j.jalz.2018.07.215.
Bellenguez, C., Küçükali, F., Jansen, I.E., Kleineidam, L., Moreno-Grau, S., Amin, N., et al., 2022. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat. Genet 54, 412–436. https://doi.org/10.1038/s41588-022-01024-z.
Bendotti, C., Marino, M., Cheroni, C., Fontana, E., Crippa, V., Poletti, A., et al., 2012. Dysfunction of constitutive and inducible ubiquitin-proteasome system in amyotrophic lateral sclerosis: implication for protein aggregation and immune response. Prog. Neurobiol. 97, 101–126. https://doi.org/10.1016/j.pneurobio.2011.10.001.
Bennett, D.A., Schneider, J.A., Arvanitakis, Z., Kelly, J.F., Aggarwal, N.T., Shah, R.C., et al., 2006. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 66, 1837–1844. https://doi.org/10.1212/01.wnl.0000219668.47116.e6.
Bernis, M.E., Babila, J.T., Breid, S., Wüsten, K.A., Wüllner, U., Tamgüney, G., 2015. Prion-like propagation of human brain-derived alpha-synuclein in transgenic mice expressing human wild-type alpha-synuclein. Acta Neuropathol. Commun. 3, 75. https://doi.org/10.1186/s40478-015-0254-7.
Bertram, L., Tanzi, R.E., 2011. Genetics of Alzheimer's disease. In: Dickson, D.W., Weller, R.O. (Eds.), The molecular pathology of dementias and movement disorders, 2nd edn..,. Wiley-Blackwell, Oxford, pp. 51–61.
Besser, L.M., Teylan, M.A., Nelson, P.T., 2020. Limbic Predominant Age-Related TDP-43 Encephalopathy (LATE): Clinical and Neuropathological Associations. J. Neuropathol. Exp. Neurol. 79, 305–313. https://doi.org/10.1093/jnen/nlz126.
Beyreuther, K., Masters, C.L., 1991. Amyloid precursor protein (APP) and beta A4 amyloid in the etiology of Alzheimer's disease: precursor-product relationships in the derangement of neuronal function. Brain Pathol. 1, 241–251. https://doi.org/10.1111/j.1750-3639.1991.tb00667.x.
Bolós, M., Llorens-Martín, M., Jurado-Arjona, J., Hernández, F., Rábano, A., Avila, J., 2015. Direct evidence of internalization of tau by microglia in vitro and in vivo. J. Alzheimers Dis. 50, 77–87. https://doi.org/10.3233/JAD-150704.
Boluda, S., Iba, M., Zhang, B., Raible, K.M., Lee, V.M., Trojanowski, J.Q., 2015. Differential induction and spread of tau pathology in young PS19 tau transgenic mice following intracerebral injections of pathological tau from Alzheimer's disease or corticobasal degeneration brains. Acta Neuropathol. 129, 221–237. https://doi.org/10.1007/s00401-014-1373-0.
Borghammer, P., 2021. The α-synuclein origin and connectome model (SOC model) of Parkinson's disease: explaining motor asymmetry, non-motor phenotypes, and cognitive decline. J. Park. Dis. 11, 455–474. https://doi.org/10.3233/JPD-202481.
Borghammer, P., Horsager, J., Andersen, K., Van Den Berge, N., Raunio, A., Murayama, S., Parkkinen, L., Myllykangas, L., 2021. Neuropathological evidence of body-first vs. brain-first Lewy body disease. Neurobiol. Dis. 161, 105557 https://doi.org/10.1016/j.nbd.2021.105557.
Borràs, D., Ferrer, I., Pumarola, M., 1999. Age-related changes in the brain of the dog. Vet. Pathol. 36, 202–211. https://doi.org/10.1354/vp.36-3-202.
Botez, G., Probst, A., Ipsen, S., Tolnay, M., 1999. Astrocytes expressing hyperphosphorylated tau protein without glial fibrillary tangles in argyrophilic grain disease. Acta Neuropathol. 98, 251–256. https://doi.org/10.1007/s004010051077.
Bousset, L., Pieri, L., Ruiz-Arlandis, G., Gath, J., Jensen, P.H., Habenstein, B., et al., 2013. Structural and functional characterization of two alpha-synuclein strains. Nat. Commun. 4, 2575. https://doi.org/10.1038/ncomms3575.
Braak, H., Braak, E., 1987. Argyrophylic grains: characteristic pathology of cerebral cortex in cases of adult-onset dementia without Alzheimer changes. Neurosci. Lett. 76, 124–127. https://doi.org/10.1016/0304-3940(87)90204-7.
Braak, H., Braak, E., 1989. Cortical and subcortical argyrophylic grains characterize a disease associated with adult onset dementia. Neuropathol. Appl. Neurobiol. 15, 13–26. https://doi.org/10.1111/j.1365-2990.1989.tb01146.x.
Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259. https://doi.org/10.1007/BF00308809.
Braak, H., Braak, E., 1995. Staging of Alzheimer's disease-related neurofibrillary tangles. Neurobiol. Aging 16, 271–278. https://doi.org/10.1016/0197-4580(95)00021-6.
Braak, H., Braak, E., 1997. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol. Aging 18, 351–357. https://doi.org/10.1016/s0197-4580(97)00056.
Braak, H., Braak, E., 1998. Argyrophilic grain disease: frequency of occurrence in different age categories and neuropathological diagnostic criteria. J. Neural Transm. 105, 801–819. https://doi.org/10.1007/s007020050096.
Braak, H., Del Tredici, K., 2011. The pathological process underlying Alzheimer's disease in individuals under thirty. Acta Neuropathol. 121, 171–181. https://doi.org/10.1007/s00401-010-0789-4.
Braak, H., Del Tredici, K., 2015. The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. Brain 138, 2814–2833. https://doi.org/10.1093/brain/awv236.
Braak, H., Del Tredici, K., 2020. From the entorhinal region via the prosubiculum to the dentate fascia: Alzheimer disease-related neurofibrillary changes in the temporal allocortex. J. Neuropathol. Exp. Neurol. 79, 163–175. https://doi.org/10.1093/jnen/nlz123.
Braak, H., del Tredici, K., Bratzke, H., Hamm-Clement, J., Sandemann-Keil, D., Rub, U., 2002. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J. Neurol. 249 (suppl 3), 1–5.
Braak, H., del Tredici, K., Rüb, U., de Vos, R.A.I., Jansen Steur, E.N.H., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211.
Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., del Tredici, K., 2004. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 318, 121–134.
Braak, H., Thal, D.R., Ghebremedhin, E., Del Tredici, K., 2011. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J. Neuropathol. Exp. Neurol. 70, 960–969. https://doi.org/10.1097/NEN.0b013e318232a379.
Brayne, C., Richardson, K., Matthews, F.E., Fleming, J., Hunter, S., Xuereb, J.H., et al., 2009. Neuropathological correlates of dementia in over-80-year-old brain donors from the population-based Cambridge city over-75s cohort (CC75C) study. J. Alzheimers Dis. 18, 645–658. https://doi.org/10.3233/JAD-2009-1182.
Breid, S., Bernis, M.E., Babila, J.T., Garza, M.C., Wille, H., Tamguney, G., 2016. Neuroinvasion of α-synuclein prionoids after intraperitoneal and intraglossal inoculation. J. Virol. 90, 9182–9193. https://doi.org/10.1128/jvi.01399-16.
Briscoe, S.D., Ragsdale, C.W., 2019. Evolution of the chordate telencephalon. Curr. Biol. 29, R647–R662. https://doi.org/10.1016/j.cub.2019.05.026.
Buciuc, M., Wennberg, A.M., Weigand, S.D., Murray, M.E., Senjem, M.L., Spychalla, A.J., et al., 2020a. Effect modifiers of TDP-43-associated hippocampal atrophy rates in patients with Alzheimer's disease neuropathological changes. J. Alzheimers Dis. 73, 1511–1523. https://doi.org/10.3233/JAD-191040.
Buciuc, M., Whitwell, J.L., Tosakulwong, N., Weigand, S.D., Murray, M.E., Boeve, B.F., et al., 2020b. Association between transactive response DNA-binding protein of 43 kDa type and cognitive resilience to Alzheimer's disease: a case-control study. Neurobiol. Aging 92, 92–97. https://doi.org/10.1016/j.neurobiolaging.2020.04.001.
Buée, L., Bussière, T., Buée-Scherrer, V., Delacourte, A., Hof, P.R., 2000. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res Brain Res Rev. 33, 95–130. https://doi.org/10.1016/s0165-0173(00)00019-9.
Cao, Q., Boyer, D.R., Sawaya, M.R., Ge, P., Eisenberg, D.S., 2019. Cryo-EM structures of four polymorphic TDP-43 amyloid cores. Nat. Struct. Mol. Biol. 26, 619–627. https://doi.org/10.1038/s41594-019-0248-4.
Carballo-Carbajal, I., Laguna, A., Romero-Giménez, J., Cuadros, T., Bové, J., Martinez-Vicente, M., et al., 2019. Brain tyrosinase overexpression implicates age-dependent neuromelanin production in Parkinson's disease pathogenesis. Nat. Commun. 10, 973. https://doi.org/10.1038/s41467-019-08858-y.
Castillo-Carranza, D.L., Guerrero-Muñoz, M.J., Sengupta, U., Gerson, J.E., Kayed, R., 2018. α-synuclein oligomers induce a unique toxic tau strain. Biol. Psychiatr. 84, 499–508. https://doi.org/10.1016/j.biopsych.2017.12.018.
Chadwick, L., Gentle, L., Strachan, J., Layfield, R., 2012. Review: unchained maladie - a reassessment of the role of Ubb(+1) -capped polyubiquitin chains in Alzheimer's disease. Neuropathol. Appl. Neurobiol. 38, 118–131. https://doi.org/10.1111/j.1365-2990.2011.01236.x.
Chai, X., Dage, J.L., Citron, M., 2012. Constitutive secretion of tau protein by an unconventional mechanism. Neurobiol. Dis. 48, 356–366. https://doi.org/10.1016/j.nbd.2012.05.021.
Chang, A., Xiang, X., Wang, J., Lee, C., Arakhamia, T., Simjanoska, M., et al., 2022. Homotypic fibrillization of TMEM106B across diverse neurodegenerative diseases. Cell 185, 1346–1355.e15. https://doi.org/10.1016/j.cell.2022.02.026.
Chartier-Harlin, M.C., Crawford, F., Houlden, H., Warren, A., Hughes, D., Fidani, L., et al., 1991. Early-onset Alzheimer's disease caused by mutations at codon 717 of the β-amyloid precursor protein gene. Nature 353, 844–846. https://doi.org/10.1038/353844a0.
Chastagner, P., Loria, F., Vargas, J.Y., Tois, J., I Diamond, M., Okafo, G., et al., 2020. Fate and propagation of endogenously formed Tau aggregates in neuronal cells. EMBO Mol. Med 12, e12025. https://doi.org/10.15252/emmm.202012025.
Chen, A.K., Lin, R.Y., Hsieh, E.Z., Tu, P.H., Chen, R.P., Liao, T.Y., et al., 2010. Induction of amyloid fibrils by the C-terminal fragments of TDP-43 in amyotrophic lateral sclerosis. J. Am. Chem. Soc. 132, 1186–1187. https://doi.org/10.1021/ja9066207.
Chen, G.F., Xu, T.H., Yan, Y., Zhou, Y.R., Jiang, Y., Melcher, K., et al., 2017. Amyloid beta: structure, biology and structure-based therapeutic treatment. Acta Pharm. Sin. 38, 1205–1235. https://doi.org/10.1038/aps.2017.28.
Chen, H.J., Mitchell, J.C., 2021. Mechanisms of TDP-43 proteinopathy onset and propagation. Int J. Mol. Sci. 22, 6004. https://doi.org/10.3390/ijms22116004.

Chu, Y., Kordower, J.H., 2010. Lewy body pathology in fetal grafts. Ann. NY Acad. Sci. 1184, 55–67. https://doi.org/10.1111/j.1749-6632.2009.05229.x.
Clarimón, J., Molina-Porcel, L., Gómez-Isla, T., Blesa, R., Guardia-Laguarta, C., González-Neira, A., et al., 2009. Early-onset familial lewy body dementia with extensive tauopathy: a clinical, genetic, and neuropathological study. J. Neuropathol. Exp. Neurol. 68, 73–82. https://doi.org/10.1097/NEN.0b013e3181927577.
Clavaguera, F., Akatsu, H., Fraser, G., Crowther, R.A., Frank, S., Hench, J., et al., 2013a. Brain homogenates from human tauopathies induce tau inclusions in mouse brain. Proc. Natl. Acad. Sci. USA 110, 9535–9540. https://doi.org/10.1073/pnas.1301175110.
Clavaguera, F., Lavenir, I., Falcon, B., Frank, S., Goedert, M., Tolnay, M., 2013b. "Prion-like" templated misfolding in tauopathies. Brain Pathol. 23, 342–349. https://doi.org/10.1111/bpa.12044.
Cohen, R.M., Rezai-Zadeh, K., Weitz, T.M., Rentsendorj, A., Gate, D., Spivak, I., et al., 2013. A transgenic Alzheimer rat with plaques, tau pathology, behavioral impairment, oligomeric abeta, and frank neuronal loss. J. Neurosci. 33, 6245–6256. https://doi.org/10.1523/JNEUROSCI.3672-12.2013.
Cooper, J.M., Lathuiliere, A., Migliorini, M., Arai, A.L., Wani, M.M., Dujardin, S., et al., 2021. Regulation of tau internalization, degradation, and seeding by LRP1 reveals multiple pathways for tau catabolism. J. Biol. Chem. 296, 100715 https://doi.org/10.1016/j.jbc.2021.100715.
Corbet, G.A., Wheeler, J.R., Parker, R., Weskamp, K., 2021. TDP43 ribonucleoprotein granules: physiologic function to pathologic aggregates. RNA Biol. 18, 128–138. https://doi.org/10.1080/15476286.2021.1963099.
Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G. W., et al., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923. https://doi.org/10.1126/science.8346443.
Crosby, E.C., Schnitzlein, H.N., 1982. Comparative correlative neuroanatomy of the vertebrate telencephalon. Mcmillan Pub Co,.
Cruts, M., Gijselinck, I., van der Zee, J., Engelborghs, S., Wils, H., Pirici, D., et al., 2006. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 442, 920–924. https://doi.org/10.1038/nature05017.
Crystal, H., Dickson, D., Fuld, P., Masur, D., Scott, R., Mehler, M., et al., 1988. Clinico-pathologic studies in dementia: nondemented subjects with pathologically confirmed Alzheimer's disease. Neurology 38, 1682–1687. https://doi.org/10.1212/wnl.38.11.1682.
Cykowski, M.D., Arumanayagam, A.S., Powell, S.Z., Rivera, A.L., Abner, E.L., Roman, G. C., et al., 2022. Patterns of amygdala region pathology in LATE-NC: subtypes that differ with regard to TDP-43 histopathology, genetic risk factors, and comorbid pathologies. Acta Neuropathol. 143, 531–545. https://doi.org/10.1007/s00401-022-02416-5.
Dammer, E.B., Lee, A.K., Duong, D.M., Gearing, M., Lah, J.J., Levey, A.I., et al., 2015. Quantitative phosphoproteomics of Alzheimer's disease reveals cross-talk between kinases and small heat shock proteins. Proteomics 15, 508–519. https://doi.org/10.1002/pmic.201400189.
Danzer, K.M., Kranich, L.R., Ruf, W.P., Cagsal-Getkin, O., Winslow, A.R., Zhu, L., et al., 2012. Exosomal cell-to-cell transmission of α-synuclein oligomers. Mol. Neurodegener. 7, 42. https://doi.org/10.1186/1750-1326-7-42.
Darricau, M., Canron, M.H., Bosc, M., Arotçarena, M.L., Le Quang, M., Dehay, B., et al., 2021. Planche V. Lack of limbic-predominant age-related TDP-43 encephalopathy (LATE) neuropathological changes in aged macaques with memory impairment. Neurobiol. Aging 107, 53–56. https://doi.org/10.1016/j.neurobiolaging.2021.07.009.
Dasari, A.K.R., Kayed, R., Wi, S., Lim, K.H., 2019. Tau interacts with the C-terminal region of α-Synuclein, promoting formation of toxic aggregates with distinct molecular conformations. Biochem 58, 2814–2821. https://doi.org/10.1021/acs.biochem.9b002.15.
Davidson, Y.S., Raby, S., Foulds, P.G., Robinson, A., Thompson, J.C., Sikkink, S., et al., 2011. TDP-43 pathological changes in early onset familial and sporadic Alzheimer's disease, late onset Alzheimer's disease and Down's syndrome: association with age, hippocampal sclerosis and clinical phenotype. Acta Neuropathol. 122, 703–713. https://doi.org/10.1007/s00401-011-0879-y.
Davis, E.J., CarolineW, Solsberg, C.W., Miñones-Moyano, E., Sirota, M., Chibnik, L., et al., 2021. Sex-specific association of the X chromosome with cognitive change and tau pathology in aging and Alzheimer disease. JAMA Neurol. 78, 1249–1254. https://doi.org/10.1001/jamaneurol.2021.2806.
De Cecco, E., Celauro, L., Vanni, S., Grandolfo, M., Aguzzi, A., Legname, G., 2020. The uptake of tau amyloid fibrils is facilitated by the cellular prion protein and hampers prion propagation in cultured cells. J. Neurochem 155, 577–591. https://doi.org/10.1111/jnc.15040.
De Rossi, P., Lewis, A.J., Furrer, J., De Vos, L., Demeter, T., Zbinden, A., et al., 2021. FTLD-TDP assemblies seed neoaggregates with subtype-specific features via a prion-like cascade. EMBO Rep. 22, e53877 https://doi.org/10.15252/embr.202153877.
Del Río, J.A., Ferrer, I., Gavín, R., 2018. Role of cellular prion protein in interneuronal amyloid transmission. Prog. Neurobiol. 165–167, 87–102. https://doi.org/10.1016/j.pneurobio.2018.03.001.
Delacourte, A., Defossez, A., 1986. Alzheimer's disease: Tau proteins, the promoting factors of microtubule assembly, are major components of paired helical filaments. J. Neurol. Sci. 76, 173–186. https://doi.org/10.1016/0022-510x(86)90167-x.
Delacourte, A., David, J.P., Sergeant, N., Buee, L., Wattez, A., Vermersch, P., et al., 1999. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 52, 1158–1165. https://doi.org/10.1212/wnl.52.6.1158.
Dhakal, S., Wyant, C.E., George, H.E., Morgan, S.E., Rangachari, V., 2021a. Prion-like C-terminal domain of TDP-43 and α-synuclein interact synergistically to generate neurotoxic hybrid fibrils. J. Mol. Biol. 433, 166953 https://doi.org/10.1016/j.jmb.2021.166953.E.
Dhakal, S., Wyant, C.E., George, H.E., Morgan, S.E., Rangachari, V., 2021b. Prion-like C-terminal domain of TDP-43 and α-synuclein interact synergistically to generate neurotoxic hybrid fibrils. J. Mol. Biol. 433, 166953 https://doi.org/10.1016/j.jmb.2021.166953.
Dhakal, S., Wyant, C.E., George, H.E., Morgan, S.E., Rangachari, V., 2022. Distinct neurotoxic TDP-43 fibril polymorphs are generated by heterotypic interactions with α-synuclein. J. Biol. Chem. 298, 102498 https://doi.org/10.1016/j.jbc.2022.102498.
Dickson, D.W., Davies, P., Bevona, C., Factor, S.M., Grober, E., Aronson, M.K., et al., 1994. Hippocampal sclerosis: a common pathological feature of dementia in very old (> or = 80 years of age) humans. Acta Neuropathol. 88, 212–221. https://doi.org/10.1007/BF00293396.
Dickson, D.W., Braak, H., Duda, J.E., Duyckaerts, C., Gasser, T., Halliday, G.M., et al., 2009. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. Lancet Neurol. 8, 1150–1157. https://doi.org/10.1016/S1474-4422(09)70238-8.
Dickson, D.W., Uchikado, H., Fujishiro, H., Tsuboi, Y., 2010. Evidence in favor of Braak staging of Parkinson's disease. Mov. Disord. 25 (Suppl 1), S78–S82.
Ding, Z.T., Wang, Y., Jiang, Y.P., Yoshida, M., Mimuro, M., Inagaki, T., et al., 2006. Argyrophilic grain disease: frequency and neuropathology in centenarians. Acta Neuropathol. 111, 320–328. https://doi.org/10.1007/s00401-006-0043-2.
Drummond, E., Wisniewski, T., 2017. Alzheimer's disease: experimental models and reality. Acta Neuropathol. 133, 155–175. https://doi.org/10.1007/s00401-016-1662-x.
Duda, J.E., Giasson, B.I., Chen, Q., Gur, T.L., Hurtig, H.I., Stern, M.B., et al., 2000. Widespread nitration of pathological inclusions in neurodegenerative synucleinopathies. Am. J. Pathol. 157, 1439–1445. https://doi.org/10.1016/S0002-9440(10)64781-5.
Dugan, A.J., Nelson, P.T., Katsumata, Y., Shade, L.M.P., Boehme, K.L., Teylan, M.A., et al., 2021. Analysis of genes (TMEM106B, GRN, ABCC9, KCNMB2, and APOE) implicated in risk for LATE-NC and hippocampal sclerosis provides pathogenetic insights: a retrospective genetic association study. Acta Neuropathol. Commun. 9, 152. https://doi.org/10.1186/s40478-021-01250-2.
Dujardin, S., Hyman, B.T., 2019. Tau prion-like propagation: state of the art and current challenges. Adv. Exp. Med Biol. 1184, 305–325. https://doi.org/10.1007/978-981-32-9358-8_23.
Dujardin, S., Bégard, S., Caillierez, R., Lachaud, C., Delattre, L., Carrier, S., et al., 2014a. Ectosomes: a new mechanism for non-exosomal secretion of tau protein. PLoS One 9, e100760. https://doi.org/10.1371/journal.pone.0100760.
Dujardin, S., Lécolle, K., Caillierez, R., Bégard, S., Zommer, N., Lachaud, C., et al., 2014b. Neuron-to-neuron wild-type tau protein transfer through a trans-synaptic mechanism: relevance to sporadic tauopathies. Acta Neuropathol. Commun. 2, 14. https://doi.org/10.1186/2051-5960-2-14.
Dujardin, S., Commins, C., Lathuiliere, A., Beerepoot, P., Fernandes, A.R., Kamath, T.V., et al., 2020. Med 26, 1256–1263. https://doi.org/10.1038/s41591-020-0938-9.
Dumitrescu, L., Mahoney, E.R., Mukherjee, S., Lee, M.L., Bush, W.S., Engelman, C.D., et al., 2020. Genetic variants and functional pathways associated with resilience to Alzheimer's disease. Brain 143, 2561–2575. https://doi.org/10.1093/brain/awaa209.
Duong, M.T., Wolk, D.A., 2022. Limbic-Predominant Age-Related TDP-43 Encephalopathy: LATE-breaking updates in clinicopathologic features and biomarkers. Curr. Neurol. Neurosci. Rep. 22, 689–698. https://doi.org/10.1007/s11910-022-01232-4.
Duty, S., Jenner, P., 2011. Animal models of Parkinson's disease: a source of novel treatments and clues to the cause of the disease. Br. J. Pharm. 164, 1357–1391. https://doi.org/10.1111/j.1476-5381.2011.01426.x.
Duyckaerts, C., Sazdovitch, V., Ando, K., Seilhean, D., Privat, N., Yilmaz, Z., et al., 2018. Neuropathology of iatrogenic Creutzfeldt- Jakob disease and immunoassay of French cadaver- sourced growth hormone batches suggest possible transmission of tauopathy and long incubation periods for the transmission of Aβ pathology. Acta Neuropathol. 135, 201–212. https://doi.org/10.1007/s00401-017-1791-x.
Edler, M.K., Sherwood, C.C., Meindl, R.S., Hopkins, W.D., Ely, J.J., Erwin, J.M., et al., 2017. Aged chimpanzees exhibit pathologic hallmarks of Alzheimer's disease. Neurobiol. Aging 59, 107–120. https://doi.org/10.1016/j.neurobiolaging.2017.07.006.
Eisele, Y.S., Obermüller, U., Heilbronner, G., Baumann, F., Kaeser, S.A., Wolburg, H., et al., 2010. Peripherally applied Aβ-containing inoculates induce cerebral β-amyloidosis. Science 330 (6006), 980–982. https://doi.org/10.1126/science.1194516.
Elobeid, A., Libard, S., Leino, M., Popova, S.N., Alafuzoff, I., 2016. Altered proteins in the aging brain. J. Neuropathol. Exp. Neurol. 75, 316–325. https://doi.org/10.1093/jnen/nlw002.
Emmanouilidou, E., Melachroinou, K., Roumeliotis, T., Garbis, S.D., Ntzouni, M., Margaritis, L.H., et al., 2010. Cell produced α-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. J. Neurosci. 30, 6838–6851. https://doi.org/10.1523/JNEUROSCI.5699-09.2010.
Engelender, S., 2008. Ubiquitination of alpha synuynucelin and autophay in Parkinson's disease. Autophagy 4, 372–374. https://doi.org/10.4161/auto.5604.
Farfel, J.M., Yu, L., Boyle, P.A., Leurgans, S., Shah, R.C., Schneider, J.A., Bennett, D.A., 2019. Alzheimer's disease frequency peaks in the tenth decade and is lower afterwards. Acta Neuropathol. Commun. 7, 104. https://doi.org/10.1186/s40478-019-0752-0.

Feiler, M.S., Strobel, B., Freischmidt, A., Helferich, A.M., Kappel, J., Brewer, B.M., et al., 2015. TDP-43 is intercellularly transmitted across axon terminals. J. Cell Biol. 211, 897–911. https://doi.org/10.1083/jcb.201504057.
Feng, T., Lacrampe, A., Hu, F., 2021. Physiological and pathological functions of TMEM106B: a gene associated with brain aging and multiple brain disorders. Acta Neuropathol. 141, 327–339. https://doi.org/10.1007/s00401-020-02246-3.
Fenyi, A., Duyckaerts, C., Bousset, L., Braak, H., Del Tredici, K., Melki, R., et al., 2021. Seeding propensity and characteristics of pathogenic αSyn assemblies in formalin-fixed human tissue from the enteric nervous system, olfactory bulb, and brainstem in cases staged for Parkinson's disease. Cells 10, 139. https://doi.org/10.3390/cells10010139.
Ferrer, I., 2004. Stress kinases involved in tau phosphorylation in Alzheimer's disease, tauopathies and APP transgenic mice. Neurotox. Res 6, 469–475. https://doi.org/10.1007/BF03033283.
Ferrer, I., 2012. Defining Alzheimer as a common age-related neurodegenerative process not inevitably leading to dementia. Prog. Neurobiol. 97, 38–51. https://doi.org/10.1016/j.pneurobio.2012.03.005.
Ferrer, I., 2022. Alzheimer's disease is an inherent, natural part of human brain aging: an integrated perspective. Free Neuropathol. 3, 17. https://doi.org/10.17879/freeneuropathology-2022-3806.
Ferrer, I., 2023. Hypothesis review: Alzheimer's overture guidelines. Brain Pathol. 33, 13122. https://doi.org/10.1111/bpa.13122.
Ferrer, I., Blanco, R., Carmona, M., Puig, B., 2001a. Phosphorylated mitogen-activated protein kinase (MAPK/ERK-P), protein kinase of 38 kDa (p38-P), stress-activated protein kinase (SAPK/JNK-P), and calcium/calmodulin-dependent kinase II (CaM kinase II) are differentially expressed in tau deposits in neurons and glial cells in tauopathies. J. Neural Transm. 108, 1397–1415. https://doi.org/10.1007/s007020100016.
Ferrer, I., Blanco, R., Carmona, M., Ribera, R., Goutan, E., Puig, B., et al., 2001b. Phosphorylated map kinase (ERK1, ERK2) expression is associated with early tau deposition in neurones and glial cells, but not with increased nuclear DNA vulnerability and cell death, in Alzheimer disease, Pick's disease, progressive supranuclear palsy and corticobasal degeneration. Brain Pathol. 11, 144–158. https://doi.org/10.1111/j.1750-3639.2001.tb00387.x.
Ferrer, I., Barrachina, M., Puig, B., 2002. Anti-tau phospho-specific Ser262 antibody recognizes a variety of abnormal hyper-phosphorylated tau deposits in tauopathies including Pick bodies and argyrophilic grains. Acta Neuropathol. 104, 658–664. https://doi.org/10.1007/s00401-002-0600-2.
Ferrer, I., Barrachina, M., Tolnay, M., Rey, M.J., Vidal, N., Carmona, M., et al., 2003. Phosphorylated protein kinases associated with neuronal and glial tau deposits in argyrophilic grain disease. Brain Pathol. 13, 62–78. https://doi.org/10.1111/j.1750-3639.2003.tb00007.x.
Ferrer, I., Boada Rovira, M., Sanchez Guerra, M.L., Rey, M.J., Costa-Jussá, F., 2004. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. Brain Pathol. 14, 11–20. https://doi.org/10.1111/j.1750-3639.2004.tb00493.x.
Ferrer, I., Gomez-Isla, T., Puig, B., Freixes, M., Ribé, E., Dalfó, E., et al., 2005. Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer's disease and tauopathies. Curr. Alzheimer Res 2, 3–18. https://doi.org/10.2174/1567205052772713.
Ferrer, I., Santpere, G., van Leeuwen, F.W., 2008. Argyrophilic grain disease. Brain 131, 1416–1432. https://doi.org/10.1093/brain/awm305.
Ferrer, I., Gómez, A., Carmona, M., Huesa, G., Porta, S., Riera-Codina, M., et al., 2011. Neuronal hemoglobin is reduced in Alzheimer's disease, argyrophilic grain disease, and dementia with Lewy bodies. J. Alzheimers Dis. 23, 537–550. https://doi.org/10.3233/JAD-2010-101485.
Ferrer, I., López-González, I., Carmona, M., Arregui, L., Dalfó, E., Torrejón-Escribano, B., et al., 2014. Glial and neuronal tau pathology in tauopathies: characterization of disease-specific phenotypes and tau pathology progression. J. Neuropathol. Exp. Neurol. 73, 81–97. https://doi.org/10.1097/NEN.0000000000000030.
Ferrer, I., García, M.A., González, I.L., Lucena, D.D., Villalonga, A.R., Llorens, F., et al., 2018. Aging-related tau astrogliopathy (ARTAG): not only tau phosphorylation in astrocytes. Brain Pathol. 28, 965–985. https://doi.org/10.1111/bpa.12593.
Ferrer, I., Aguiló García, M., Carmona, M., Andrés-Benito, P., Torrejón-Escribano, B., Garcia-Esparcia, P., et al., 2019. Involvement of oligodendrocytes in tau seeding and spreading in tauopathies. Front Aging Neurosci. 11, 112. https://doi.org/10.3389/fnagi.2019.00112.
Ferrer, I., Andrés-Benito, P., Sala-Jarque, J., Gil, V., Del Rio, J.A., 2020a. Capacity for seeding and spreading of argyrophilic grain disease in a wild-type murine model; comparisons with primary age-related tauopathy. Front Mol. Neurosci. 13, 101. https://doi.org/10.3389/fnmol.2020.00101.
Ferrer, I., Zelaya, M.V., Aguiló García, M., Carmona, M., López-González, I., Andrés-Benito, P., et al., 2020b. Relevance of host tau in tau seeding and spreading in tauopathies. Brain Pathol. 30, 298–318. https://doi.org/10.1111/bpa.12778.E.
Ferrer, I., Andrés-Benito, P., Ausín, K., Pamplona, R., Del Rio, J.A., Fernández-Irigoyen, J., et al., 2021. Dysregulated protein phosphorylation: A determining condition in the continuum of brain aging and Alzheimer's disease. Brain Pathol. 31, e12996 https://doi.org/10.1111/bpa.12996.
Ferrer, I., Andrés-Benito, P., Carmona, M., del Rio, J.A., 2022. Common and specific marks of different tau strains following intra-hippocampal injection of AD, PiD, and GGT inoculum in hTau transgenic mice. Int J. Mol. Sci. 23, 15940. https://doi.org/10.3390/ijms232415940.
Fischer, D.F., De Vos, R.A., Van Dijk, R., De Vrij, F.M., Proper, E.A., Sonnemans, M.A., et al., 2003. Disease-specific accumulation of mutant ubiquitin as a marker for proteasomal dysfunction in the brain. FASEB J. 17, 2014–2024. https://doi.org/10.1096/fj.03-0205com.
Fischer, O., 1907. Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz. Mon. Psychiat Neurol. 22, 361–372.
Fischer, O., 1910. Die presbyophrene Demenz, deren anatomische Grundlage und klinische Abgrenzung. Z. Ges. Neurol. Psychiat 3, 371–471.
Fischer, O., 1912. Ein weiterer Beitrag zur Klinik und Pathologie der presbyophrenen Demenz. Z. Ges. Neurol. Psychiat 12, 99–135.
Fitzpatrick, A.W.P., Falcon, B., He, S., Murzin, A.G., Murshudov, G., Garringer, H.J., et al., 2017. Cryo-EM structures of tau filaments from Alzheimer's disease. Nature 547, 185–190. https://doi.org/10.1038/nature23002.
Forno, L.S., 1986. Lewy bodies. N. Engl. J. Med. 314, 122. https://doi.org/10.1056/NEJM198601093140219.
Forno, L.S., 1996. Neuropathology of Parkinson's disease. J. Neuropathol. Exp. Neurol. 55, 259–272. https://doi.org/10.1097/00005072-199603000-00001.
Forno, L.S., Norville, R.L., 1976. Ultrastructure of Lewy bodies in the stellate ganglion. Acta Neuropathol. 34, 183–197. https://doi.org/10.1007/BF00688674.
Forny-Germano, L., Lyra e Silva, N.M., Batista, A.F., Brito-Moreira, J., Gralle, M., Boehnke, S.E., et al., 2014. Alzheimer's disease-like pathology induced by amyloid-β oligomers in nonhuman primates. J. Neurosci. 34, 13629–13643. https://doi.org/10.1523/JNEUROSCI.1353-14.2014.
Forrest, S.L., Wagner, S., Kim, A., Kovacs, G.G., 2022. Association of glial tau pathology and LATE-NC in the ageing brain. Neurobiol. Aging 119, 77–88. https://doi.org/10.1016/j.neurobiolaging.2022.07.010.
Fortea, J., Zaman, S.H., Hartley, S., Rafii, M.S., Head, E., Carmona-Iragui, M., 2021. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. Lancet Neurol. 20, 930–942. https://doi.org/10.1016/S1474-4422(21)00245-3.
Frank, S., Clavaguera, F., Tolnay, M., 2008. Tauopathy models and human neuropathology: similarities and differences. Acta Neuropathol. 115, 39–53. https://doi.org/10.1007/s00401-007-0291-9.
Franzmeier, N., Brendel, M., Beyer, L., Slemann, L., Kovacs, G.G., Arzberger, T., et al., 2022. Tau depositoion patterns are associated with functional connectivity in primary tauopathies. Nat. Commun. 13, 1362. https://doi.org/10.1038/s41467-022-28896-3.
Fujino, Y., Delucia, M.W., Davies, P., Dickson, D.W., 2004. Ballooned neurones in the limbic lobe are associated with Alzheimer type pathology and lack diagnostic specificity. Neuropathol. Appl. Neurobiol. 30, 676–682. https://doi.org/10.1111/j.1365-2990.2004.00593.x.
Fujishiro, H., Ferman, T.J., Boeve, B.F., Smith, G.E., Graff-Radford, N.R., Uitti, R.J., et al., 2008a. Validation of the neuropathologic criteria of the third consortium for dementia with Lewy bodies for prospectively diagnosed cases. J. Neuropathol. Exp. Neurol. 67, 649–656. https://doi.org/10.1097/NEN.0b013e31817d7a1d.
Fujishiro, H., Tsuboi, Y., Lin, W.L., Uchikado, H., Dickson, D.W., 2008b. Co-localization of tau and alpha-synuclein in the olfactory bulb in Alzheimer's disease with amygdala Lewy bodies. Acta Neuropathol. 116, 17–24. https://doi.org/10.1007/s00401-008-0383-1.
Fujishiro, H., Uchikado, H., Arai, T., Hasegawa, M., Akiyama, H., Yokota, O., et al., 2009. Accumulation of phosphorylated TDP-43 in brains of patients with argyrophilic grain disease. Acta Neuropathol. 117, 151–158. https://doi.org/10.1007/s00401-008-0463-2.
Fujiwara, H., Hasegawa, M., Dohmae, N., Kawashima, A., Masliah, E., Goldberg, M.S., et al., 2002. α-synuclein is phosphorylated in synucleinopathy lesions. Nat. Cell Biol. 4, 160–164. https://doi.org/10.1038/ncb748.
Fukuda, T., Tanaka, J., Watabe, K., Numoto, R.T., Minamitani, M., 1993. Immunohistochemistry of neuronal inclusions in the cerebral cortex and brain-stem in Lewy body disease. Acta Pathol. Jpn 43, 545–551. https://doi.org/10.1111/j.1440-1827.1993.tb03230.x.
Funk, K.E., Mrak, R.E., Kuret, J., 2011. Granulovacuolar degeneration (GVD) bodies of Alzheimer's disease (AD) resemble late-stage autophagic organelles. Neuropathol. Appl. Neurobiol. 37, 295–306. https://doi.org/10.1111/j.1365-2990.2010.01135.x.
Furman, J.L., Vaquer-Alicea, J., White, C.L., Cairns, N.J., Nelson, P.T., Diamond, M.I., 2017. Widespread tau seeding activity at early Braak stages. Acta Neuropathol. 133, 91–100. https://doi.org/10.1007/s00401-016-1644-z.
Fuster-Matanzo, A., Hernández, F., Ávila, J., 2018. Tau spreading mechanisms; implications for dysfunctional tauopathies. Int J. Mol. Sci. 19, 645. https://doi.org/10.3390/ijms19030645.
Gall, C., 1990. Comparative Anatomy of the Hippocampus. In: Jones, E.G., Peters, A. (Eds.), Cerebral Cortex. Cerebral Cortex. Springer, Boston, MA.
Galloway, P.G., Perry, G., Gambetti, P., 1987. Hirano body filaments contain actin and actin-associated proteins. J. Neuropathol. Exp. Neurol. 46, 185–199. https://doi.org/10.1097/00005072-198703000-00006.
Galloway, P.G., Mulvihill, P., Perry, G., 1992. Filaments of Lewy bodies contain insoluble cytoskeletal elements. Am. J. Pathol. 140, 809–822.
Galvin, J.E., Lee, V.M.Y., Schmidt, M.L., Tu, P.H., Iwatsubo, T., et al., 1999. Pathobiology of the Lewy body. Adv. Neurol. 80, 313–324.
Gao, J., Wang, L., Huntley, M.L., Perry, G., Wang, X., 2018. Pathomechanisms of TDP-43 in neurodegeneration, 10.1111/jnc.14327 J. Neurochem 27. https://doi.org/10.1111/jnc.14327.
Gao, Y., Liu, J., Wang, J., Liu, Y., Zeng, L.H., Ge, W., et al., 2022. Proteomic analysis of human hippocampal subfields provides new insights into the pathogenesis of Alzheimer's disease and the role of glial cells. Brain Pathol. 32, e13047 https://doi.org/10.1111/bpa.13047.
García-Sierra, F., Ghoshal, N., Quinn, B., Berry, R.W., Binder, L.I., 2003. Conformational changes and truncation of tau protein during tangle evolution in Alzheimer's disease. J. Alzheimers Dis. 5, 65–77. https://doi.org/10.3233/jad-2003-5201.
Gauthreaux, K., Mock, C., Teylan, M.A., Culhane, J.E., Chen, Y.C., Chan, K.C.G., et al., 2022b. Symptomatic profile and cognitive performance in autopsy-confirmed

limbic-predominant age-related TDP-43 encephalopathy with comorbid Alzheimer disease. J. Neuropathol. Exp. Neurol. 81, 975–987. https://doi.org/10.1093/jnen/nlac093.
Gauthreaux, K.M., Teylan, M.A., Katsumata, Y., Mock, C., Culhane, J.E., Chen, Y.C., et al., 2022a. Limbic-Predominant Age-Related TDP-43 Encephalopathy: Medical and pathologic factors associated with comorbid hippocampal sclerosis. Neurology 98, e1422–e1433. https://doi.org/10.1212/WNL.0000000000200001.
Gentier, R.J., van Leeuwen, F.W., 2015. Misframed ubiquitin and impaired protein quality control: an early event in Alzheimer's disease. Front Mol. Neurosci. 8, 47. https://doi.org/10.3389/fnmol.2015.00047.
Geser, F., Robinson, J.L., Malunda, J.A., Xie, S.X., Clark, C.M., et al., 2010. Pathological 43-kDa transactivation response DNA-binding protein in older adults with and without severe mental illness. Arch. Neurol. 67, 1238–1250. https://doi.org/10.1001/archneurol.2010.254.
Ghanem, S.S., Majbour, N.K., Vaikath, N.N., Ardah, M.T., Erskine, D., Jensen, N.M., et al., 2022. α-Synuclein phosphorylation at serine 129 occurs after initial protein deposition and inhibits seeded fibril formation and toxicity. Proc. Natl. Acad. Sci. USA 119, e2109617119. https://doi.org/10.1073/pnas.2109617119.
Ghanevati, M., Miller, C.A., 2005. Phospho-beta-catenin accumulation in Alzheimer's disease and in aggresomes attributable to proteasome dysfunction. J. Mol. Neurosci. 25, 79–94. https://doi.org/10.1385/JMN:25:1:079.
Ghebremedhin, E., Schultz, C., Botez, G., Rüb, U., Sassin, I., Braak, E., et al., 1998. Argyrophilic grain disease is associated with apolipoprotein E epsilon 2 allele. Acta Neuropathol. 96, 222–224. https://doi.org/10.1007/s004010050886.
Ghebremedhin, E., Schultz, C., Thal, D.R., Del Tredici, K., Rueb, U., Braak, H., 2002. Genetic association of argyrophilic grain disease with polymorphisms in alpha-2 macroglobulin and low-density lipoprotein receptor-related protein genes. Neuropathol. Appl. Neurobiol. 28, 308–313. https://doi.org/10.1046/j.1365-2990.2002.00398.x.
Giannakopoulos, P., Hof, P.R., Surini, M., Michel, J.P., Bouras, C., 1993. Quantitative immunohistochemical analysis of the distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of nonagenarians and centenarians. Acta Neuropathol. 85, 602–610. https://doi.org/10.1007/BF00334669.
Giannakopoulos, P., Hof, P.R., Giannakopoulos, A.S., Herrmann, F.R., Michel, J.P., Bouras, C., 1995. Regional distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of very old patients. Arch. Neurol. 52, 1150–1159. https://doi.org/10.1001/archneur.1995.00540360028012.
Giannakopoulos, P., Silhol, S., Jallageas, V., Mallet, J., Bons, N., Bouras, C., et al., 1997. Quantitative analysis of tau protein-immunoreactive accumulations and beta-amyloid protein deposits in the cerebral cortex of the mouse lemur, Microcebus murinus. Acta Neuropathol. 94, 131–139. https://doi.org/10.1007/s004010050684.
Giasson, B.I., 2003. Initiation and synergistic fibrillization of Tau and alpha-synuclein. Science 300, 636–640. https://doi.org/10.1126/science.10823.24.
Giasson, B.I., Duda, J.E., Murray, I.V., Chen, Q., Souza, J.M., Hurtig, H.I., et al., 2002. Oxidative damage linked to neurodegeneration by selective α-synuclein nitration in synucleinopathy lesions. Science 290, 985–989. https://doi.org/10.1126/science.290.5493.985.
Gibb, W.R., Scott, T., Lees, A.J., 1991. Neuronal inclusions of Parkinson's disease. Mov. Disord. 6, 2–11. https://doi.org/10.1002/mds.870060103.
Glenner, G.G., Wong, C.W., 1984. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys. Res Commun. 120, 885–890. https://doi.org/10.1016/j.bbrc.2012.08.020.
Glenner, G.G., Wong, C.W., Quaranta, V., Eanes, E.D., 1984. The amyloid deposits in Alzheimer's disease: their nature and pathogenesis. Appl. Pathol. 12, 357–369.
Goate, A., Chartier-Harlin, M.C., Mullan, M., Brown, J., Crawford, F., Fidani, L., et al., 1991. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 349, 704–706. https://doi.org/10.1038/349704a0.
Goedert, M., 2001a. Parkinson's disease and other α-synucleinopathies. Clin. Chem. Lab Med 39, 308–312. https://doi.org/10.1515/CCLM.2001.047.
Goedert, M., 2001b. α-synuclein and neurodegenerative diseases. Nat. Rev. Neurosci. 2, 492–501. https://doi.org/10.1038/35081564.
Goedert, M., 2020. Tau proteinopathies and the prion concept. Prog. Mol. Biol. Transl. Sci. 175, 239–259. https://doi.org/10.1016/bs.pmbts.2020.08.003.
Goedert, M., Spillantini, M.G., 2017. Propagation of tau aggregates. Mol. Brain 10, 18. https://doi.org/10.1186/s13041-017-0298-7.
Goedert, M., Spillantini, M.G., 2019. Ordered assembly of Tau protein and neurodegeneration. Adv. Exp. Med Biol. 1184, 3–21. https://doi.org/10.1007/978-981-32-9358-8_1.
Goedert, M., Wischik, C.M., Crowther, R.A., Walker, J.E., Klug, A., 1988. Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as microtubule-associated protein tau. Proc. Natl. Acad. Sci. USA 85, 4051–4055. https://doi.org/10.1073/pnas.85.11.4051.
Goedert, M., Spillantini, M.G., Cairns, N.J., Crowther, R.A., 1992. Tau proteins in Alzheimer paired helical filaments: abnormal phosphorylation of all six brain isoforms. Neuron 8, 159–168. https://doi.org/10.1016/0896-6273(92)90117-v.
Goedert, M., Eisenberg, D.S., Crowther, R.A., 2017. Propagation of tau aggregates and neurodegeneration. Annu Rev. Neurosci. 40, 189–210. https://doi.org/10.1146/annurev-neuro-072116-031153.
Gomez, W., Morales, R., Maracaja-Coutinho, V., Parra, V., Nassif, M., 2020. Down syndrome and Alzheimer's disease: common molecular traits beyond the amyloid precursor protein. Aging 12 (1), 1011–1033. https://doi.org/10.18632/aging.102677.
Gotz, J., Bodea, L.G., Goedert, M., 2018. Rodent models for Alzheimer disease. Nat. Rev. Neurosci. 9, 583–598. https://doi.org/10.1038/s41583-018-0054-8.
Götz, J.J., Götz, J., 2019. Experimental models of tauopathy–from mechanisms to therapies. Adv. Exp. Med Biol. 1184, 381–391. https://doi.org/10.1007/978-981-32-9358-8_28.
Gratuze, M., Chen, Y., Parhizkar, S., Jain, N., Strickland, M.R., Serrano, J.R., et al., 2021. Activated microglia mitigate Aβ-associated tau seeding and spreading. J. Exp. Med 218, e20210542. https://doi.org/10.1084/jem.20210542.
Gremer, L., Schölzel, D., Schenk, C., Reinartz, E., Labahn, J., Ravelli, R.B.G., et al., 2017. Fibril structure of amyloid-β(1-42) by cryo-electron microscopy. Science 358, 116–119. https://doi.org/10.1126/science.aao2825.
Gribaudo, S., Tixador, P., Bousset, L., Fenyi, A., Lino, P., Melki, R., et al., 2019. Propagation of α-synuclein strains within human reconstructed neuronal network. Stem Cell Rep. 12, 230–244. https://doi.org/10.1016/j.stemcr.2018.12.007.
Grinberg, L.T., Heinsen, H., 2009. Argyrophilic grain disease: an update about a frequent cause of dementia. Dement Neuropsychol. 3, 2–7. https://doi.org/10.1590/S1980-57642009DN30100002.
Grinberg, L.T., Wang, X., Wang, C., Sohn, P.D., Theofilas, P., Sidhu, M., et al., 2013. Argyrophilic grain disease differs from other tauopathies by lacking tau acetylation. Acta Neuropathol. 125, 581–593. https://doi.org/10.1007/s00401-013-1080-2.
Grundke-Iqbal, I., Iqbal, K., Quinlan, M., Tung, Y.C., Zaidi, M.S., Wisniewski, H.M., 1986a. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. J. Biol. Chem. 261, 6084–6089.
Grundke-Iqbal, I., Iqbal, K., Tung, Y.C., Quinlan, M., Wisniewski, H.M., Binder, L.I., 1986b. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc. Natl. Acad. Sci. USA 83, 4913–4917. https://doi.org/10.1073/pnas.83.13.4913.
Guerrero-Ferreira, R., Kovacik, L., Ni, D., Stahlberg, H., 2020. New insights on the structure of alpha-synuclein fibrils using cryo-electron microscopy. Curr. Opin. Neurobiol. 61, 89–95. https://doi.org/10.1016/j.conb.2020.01.014.
Guo, J.L., Covell, D.J., Daniels, J.P., Iba, M., Stieber, A., Zhang, B., et al., 2013. Distinct α-synuclein strains differentially promote tau inclusions in neurons. Cell 154, 103–117. https://doi.org/10.1016/j.cell.2013.05.057.
Guo, J.L., Narasimhan, S., Changolkar, L., He, Z., Stieber, A., Zhang, B., et al., 2016. Unique pathological tau conformers from Alzheimer's brains transmit tau pathology in nontransgenic mice. J. Exp. Med 213, 2635–2654. https://doi.org/10.1084/jem.20160833.
Hamadjida, A., Frouni, I., Kwan, C., Huot, P., 2019. Classic animal models of Parkinson's disease: a historical perspective. Behav. Pharm. 30, 291–310. https://doi.org/10.1097/FBP.0000000000000441.
Hamaguchi, T., Eisele, Y., Varvel, N., Lamb, B.T., Walker, L.C., Jucker, M., 2012. The presence of Aβ seeds, and not age per se, is critical to the initiation of Aβ deposition in the brain. Acta Neuropathol. 123, 31–37. https://doi.org/10.1007/s00401-011-0912-1.
Hanger, D.P., Anderton, B.H., Noble, W., 2009. Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. Trends Mol. Med 15, 112–119. https://doi.org/10.1016/j.molmed.2009.01.003.
Hansen, C., Angot, E., Bergström, A.L., Steiner, J.A., Pieri, L., Paul, G., et al., 2011. α-Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. J. Clin. Invest 121, 715–725. https://doi.org/10.1172/JCI43366.
Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M.L., et al., 2009. Genome-wide association studies identifies variants CLU and PICALM associated with Alzheimer's disease. Nat. Genet 41, 1088–1093. https://doi.org/10.1038/ng.440.
Harrison, W.T., Lusk, J.B., Liu, B., Ervin, J.F., Johnson, K.G., Green, C.L., et al., 2021. Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) is independently associated with dementia and strongly associated with arteriolosclerosis in the oldest-old. Acta Neuropathol. 142, 917–919. https://doi.org/10.1007/s00401-021-02360-w.
Hashimoto, M., Masliah, E., 1999. α-synuclein in Lewy body disease and Alzheimer's disease. Brain Pathol. 9, 707–720. https://doi.org/10.1111/j.1750-3639.1999.tb00552.x.
He, Z., McBride, J.D., Xu, H., Changolkar, L., Kim, S.J., Zhang, B., et al., 2020. Transmission of tauopathy strains is independent of their isoform composition. Nat. Commun. 11, 7. https://doi.org/10.1038/s41467-019-13787-x.
Head, E., 2011. Neurobiology of the aging dog. Age 33, 485–496. https://doi.org/10.1007/s11357-010-9183-3.
Hérard, A.S., Petit, F., Gary, C., Guillermier, M., Boluda, S., Garin, C.M., et al., 2020. Induction of amyloid-β deposits from serially transmitted, histologically silent, Aβ seeds issued from human brains. Acta Neuropathol. Commun. 8, 205. https://doi.org/10.1186/s40478-020-01081-7.
Herculano-Houzel, S., 2012. The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost. PNAS 109, 10661–10668. https://doi.org/10.1073/pnas.1201895109.
Hernández, F., Ferrer, I., Pérez, M., Zabala, J.C., Del Rio, J.A., Avila, J., 2022. Tau aggregation. May 4:S0306-4522(22)00220-2. doi Neuroscience. https://doi.org/10.1016/j.neuroscience.2022.04.024.
Higashi, S., Iseki, E., Yamamoto, R., Minegishi, M., Hino, H., Fujisawa, K., et al., 2007. Concurrence of TDP-43, tau and alpha-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies. Brain Res 1184, 284–294. https://doi.org/10.1016/j.brainres.2007.09.048.
Hodos, W., Butler, A.B., 1996. Comparative vertebrate neuroanatomy: Evolution and adaptation. Wiley and Sons Inc.
Hoenig, M.C., Bischof, G.N., Seemiller, J., Hammes, J., Kukolja, J., Onur, O.A., et al., 2018. Networks of tau distribution in Alzheimer's disease. Brain 141, 568–581. https://doi.org/10.1093/brain/awx353.

Hokkanen, S.R.K., Hunter, S., Polvikoski, T.M., Keage, H.A.D., Minett, T., Matthews, F.E., et al., 2018. Hippocampal sclerosis, hippocampal neuron loss patterns and TDP-43 in the aged population. Brain Pathol. 28, 548–559. https://doi.org/10.1111/bpa.12556.

Holec, S.A.M.M., Woerman, A.L., 2020. Evidence of distinct α-synuclein strains underlying disease heterogeneity. Acta Neuropathol. 142, 73–86. https://doi.org/10.1007/s00401-020-02163-5.

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J.C., Carrasquillo, M.M., et al., 2011. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat. Genet 43, 429–435. https://doi.org/10.1038/ng.803.

Holmes, B.B., DeVos, S.L., Kfoury, N., Li, M., Jacks, R., Yanamandra, K., et al., 2013. Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. Proc. Natl. Acad. Sci. USA 110, E3138–E3147. https://doi.org/10.1073/pnas.1301440110.

Holth, J.K., Fritschi, S.K., Wang, C., Pedersen, N.P., Cirrito, J.R., Mahan, T.E., et al., 2019. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. Science 363, 880–884. https://doi.org/10.1126/science.aav2546.

Hondius, D.C., van Nierop, P., Li, K.W., Hoozemans, J.J.M., van der Schors, R.C., van Haastert, E.S., et al., 2016. Profiling the human hippocampal proteome at all pathologic stages of Alzheimer's disease. Alzheimer'S. Dement. 12, 654–668. https://doi.org/10.1016/j.jalz.2015.11.002.

Hondius, D.C., Koopmans, F., Leistner, C., 2021. Pita-Illobre D, Peferoen-Baert RM, Marbus F, et al. The proteome of granulovacuolar degeneration and neurofibrillary tangles in Alzheimer's disease. Acta Neuropathol. 141, 341–358. https://doi.org/10.1007/s00401-020-02261-4.

Hoozemans, J.J., van Haastert, E.S., Nijholt, D.A., Rozemuller, A.J., Eikelenboom, P., Scheper, W., 2009. The unfolded protein response is activated in pretangle neurons in Alzheimer's disease hippocampus. Am. J. Pathol. 174, 1241–1251. https://doi.org/10.2353/ajpath.2009.080814.

Hopp, S.C., Lin, Y., Oakley, D., Roe, A.D., DeVos, S.L., Hanlon, D., Hyman, B.T., 2018. The role of microglia in processing and spreading of bioactive tau seeds in Alzheimer's disease. J. Neuroinflamm. 15, 269. https://doi.org/10.1186/s12974-018-1309-z.

Hosokawa, M., Masuda-Suzukake, M., Shitara, H., Shimozawa, A., Suzuki, G., Kondo, H., et al., 2022. Development of a novel tau propagation mouse model endogenously expressing 3 and 4 repeat tau isoforms. Brain 145, 349–361. https://doi.org/10.1093/brain/awab289.

Hu, W., Zhang, X., Tung, Y.C., Xie, S., Liu, F., Iqbal, K., 2016. Hyperphosphorylation determines both the spread and the morphology of tau pathology. Alzheimers Dement 12, 1066–1077. https://doi.org/10.1016/j.jalz.2016.01.014.

Huang, W., Zhou, Y., Tu, L., Ba, Z., Huang, J., Huang, N., et al., 2020. TDP-43: from Alzheimer's disease to limbic-predominant age-related TDP-43 encephalopathy. Front Mol. Neurosci. 13, 26. https://doi.org/10.3389/fnmol.2020.00026.

Hubbard, B.M., Fenton, G.W., Anderson, J.M., 1990. A quantitative histological study of early clinical and preclinical Alzheimer's disease. Neuropathol. Appl. Neurobiol. 16, 111–121. https://doi.org/10.1111/j.1365-2990.1990.tb00940.x.

Hulette, C., Welsh-Bohmer, K., Murray, M., Saunders, A., Mash, D., Mcintyre, L., 1998. Neuropathological and neuropsychological changes in "normal" aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. J. Neuropathol. Exp. Neurol. 57, 1168–1274. https://doi.org/10.1097/00005072-199812000-00009.

Hurley, M.J., Deacon, R.M.J., Beyer, K., Ioannou, E., Ibáñez, A., Teeling, J.L., et al., 2018. The long-lived *Octodon degus* as a rodent drug discovery model for Alzheimer's and other age related diseases. Pharm. Ther. 188, 36–44. https://doi.org/10.1016/j.pharmthera.2018.03.001.

Hyman, B.T., Augustinack, J.C., Ingelsson, M., 2005. Transcriptional and conformational changes of the tau molecule in Alzheimer's disease. Biochim Biophys. Acta 1739, 150–157. https://doi.org/10.1016/j.bbadis.2004.06.015.

Hyman, B.T., Phelps, C.H., Beach, T.G., Bigio, E.H., Cairns, N.J., et al., 2012. National Institute on Aging-Alzheimer's Association disease guidelines for the neruropathologic assessment of Alzheimer's disease. Alzheimers Dement 8, 1–13. https://doi.org/10.1016/j.jalz.2011.10.007.

Iba, M., Guo, J.L., McBride, J.D., Zhang, B., Trojanowski, J.Q., Lee, V.M., 2013. Synthetic tau fibrils mediate transmission of neurofibrillary tangles in a transgenic mouse model of Alzheimer's-like tauopathy. J. Neurosci. 33, 1024–1037. https://doi.org/10.1523/JNEUROSCI.2642-12.2013.

Ichimata, S., Yoshida, K., Visanji, N.P., Lang, A.E., Nishida, N., Kovacs, G.G., 2022. Patterns of mixed pathologies in Down syndrome. J. Alzheimers Dis. 87, 595–607. https://doi.org/10.3233/JAD-215675.

Ighodaro, E.T., Jicha, G.A., Schmitt, F.A., Neltner, J.H., Abner, E.L., Kryscio, R.J., et al., 2015. Hippocampal sclerosis of aging can be segmental: two cases and review of the literature. J. Neuropathol. Exp. Neurol. 74, 642–652. https://doi.org/10.1097/NEN.0000000000000204.

Iguchi, Y., Eid, L., Parent, M., Soucy, G., Bareil, C., Riku, Y., et al., 2016. Exosome secretion is a key pathway for clearance of pathological TDP-43. Brain 139, 3187–3201. https://doi.org/10.1093/brain/aww237.

Ikeda, C., Yokota, O., Miki, T., Takenoshita, S., Ishizu, H., Terada, S., et al., 2018. Astrocytic tau pathologies in argyrophilic grain diseaseand related four-repeat tauopathies. Acta Med Okayama 72, 211–221. https://doi.org/10.18926/AMO/56066.

Ikeda, K., Akiyama, H., Kondo, H., Haga, C., Tanno, E., Tokuda, T., et al., 1995. Thorn-shaped astrocytes: possibly secondarily induced tau-positive glial fibrillary tangles. Acta Neuropathol. 90, 620–625. https://doi.org/10.1007/BF00318575.

Ikeda, K., Akiyama, H., Arai, T., Matsushita, M., Tsuchiya, K., Miyazaki, H., 2000. Clinical aspects of argyrophilic grain disease. Clin. Neuropathol. 19, 278–284.

Ilieva, E.V., Kichev, A., Naudí, A., Ferrer, I., Pamplona, R., Portero-Otín, M., 2011. Mitochondrial dysfunction and oxidative and endoplasmic reticulum stress in argyrophilic grain disease. J. Neuropathol. Exp. Neurol. 70, 253–263. https://doi.org/10.1097/NEN.0b013e31820f8765.

Ince, P.G., 2011. Dementia with Lewy bodies and Parkinson's disease with dementia. In: Dickson, D.W., Weller, R.O. (Eds.), Neurodegeneration, the Molecular Pathology of Dementia and Movement Disorders. Wiley-Blackwell, Oxford, pp. 224–237.

Iqbal, K., Grundke-Iqbal, I., Wisniewski, H.M., 1986. Neuronal cytoskeleton in aging and dementia. Prog. Brain Res 70, 279–288. https://doi.org/10.1016/s0079-6123(08)64310-1.

Iqbal, K., Alonso, A., del, C., Chen, S., Chohan, M.O., El-Akkad, E., et al., 2005. Tau pathology in Alzheimer disease and other tauopathies. Biochim Biophys. Acta 1739, 198–210. https://doi.org/10.1016/j.bbadis.2004.09.008.

Iqbal, K., Liu, F., Gong, C.X., 2016. Tau and neurodegenerative disease: the story so far. Nat. Rev. Neurol. 12, 15–27. https://doi.org/10.1038/nrneurol.2015.225.

Irwin, D.J., Cohen, T.J., Grossman, M., Arnold, S.E., McCarty-Wood, E., Van Deerlin, V. M., Lee, V.M., et al., 2013. Acetylated tau neuropathology in sporadic and hereditary tauopathies. Am. J. Pathol. 183, 344–351. https://doi.org/10.1016/j.ajpath.2013.04.025.

Iseki, E., et al., 1999. Frequent coexistence of Lewy bodies and neurofibrillary tangles in the same neurons of patients with diffuse Lewy body disease. Neurosci. Lett. 265, 9–12. https://doi.org/10.1016/s0304-3940(99)00178-0.

Iseki, E., Takayama, N., Marui, W., Uéda, K., Kosaka, K., 2002. Relationship in the formation process between neurofibrillary tangles and Lewy bodies in the hippocampus of dementia with Lewy bodies brains. J. Neurol. Sci. 195, 85–91. https://doi.org/10.1016/s0022-510x(01)00689-x.

Iseki, E., Togo, T., Suzuki, K., Katsuse, O., Marui, W., de Silva, R., et al., 2003. Dementia with Lewy bodies from the perspective of tauopathy. Acta Neuropathol. 105, 265–270. https://doi.org/10.1007/s00401-002-0644-3.

Ishizawa, T., Mattila, P., Davies, P., Wang, D., Dickson, D.W., 2003. Co-localization of tau and alpha-synuclein epitopes in Lewy bodies. J. Neuropathol. Exp. Neurol. 62, 389–397. https://doi.org/10.1093/jnen/62.4.389.

Iwatsubo, T., 2003. Aggregation of α-synuclein in the pathogenesis of Parkinson's disease. J. Neurol. 250 (suppl 3), 11–14. https://doi.org/10.1007/s00415-003-1303-x.

Iwatsubo, T., Odaka, A., Suzuki, N., Mizusawa, H., Nukina, N., Ihara, Y., 1994. Visualization of A beta 42(43) and A beta 40 in senile plaques with end-specific A beta monoclonals: evidence that an initially deposited species is A beta 42(43). Neuron 13, 45–53. https://doi.org/10.1016/0896-6273(94)90458-8.

Jain, N., Lewis, C.A., Ulrich, J.D., Holtzman, D.M., 2023. Chronic TREM2 activation exacerbates Aβ-associated tau seeding and spreading. J. Exp. Med 220, e20220654. https://doi.org/10.1084/jem.20220654.

Jamerlan, A., An, S.S.A., 2020. The influence of Aβ-dependent and independent pathways on TDP-43 proteinopathy in Alzheimer's disease: a possible connection to LATE-NC (Nov). Neurobiol. Aging 95, 161–167. https://doi.org/10.1016/j.neurobiolaging.2020.06.020.

Janice, C., Malcolm, J.C., Breuillau, L., Do Carmo, S., Hall, H., Welikovitch, L.A., et al., 2019. Neuropathological changes and cognitive deficits in rats transgenic for human mutant tau recapitulate human tauopathy. Neurobiol. Dis. 127, 323–338. https://doi.org/10.1016/j.nbd.2019.03.018.

Jansen, I.E., Savage, J.E., Watanabe, K., Bryois, J., Williams, D.M., Steinberg, S., et al., 2019. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat. Genet 51, 404–413. https://doi.org/10.1038/s41588-018-0311-9.

Jellinger, K.A., 1994. Hippocampal sclerosis: a common pathological feature of dementia in very old humans. Acta Neuropathol. 88, 599. https://doi.org/10.1007/BF00296500.

Jellinger, K.A., 1998. Dementia with grains (argyrophilic grain disease. Brain Pathol. 8, 377–386. https://doi.org/10.1111/j.1750-3639.1998.tb00161.x.

Jellinger, K.A., 2004. Lewy body-related synucleinopathy in the aged human brain. J. Neural Transm. 111, 1219–1235. https://doi.org/10.1007/s00702-004-0138-7.

Jiang, Y.X., Cao, Q., Sawaya, M.R., Abskharon, R., Ge, P., DeTure, M., et al., 2022. Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP-43 (May). Nature 605 (7909), 304–309. https://doi.org/10.1038/s41586-022-04670-9.

Jin, Y., Li, F., Sonoustoun, B., Kondru, N.C., Martens, Y.A., Qiao, W., et al., 2022. APOE4 exacerbates –synuclein seeding activity and contributes to neurotoxicity in Alzheimer's disease with Lewy body pathology. Acta Neuropathol. 143, 641–662. https://doi.org/10.1007/s00401-022-02421-8.

Jo, M., Lee, S., Jeon, Y.M., Kim, S., Kwon, Y., Kim, H.J., 2020. The role of TDP-43 propagation in neurodegenerative diseases: integrating insights from clinical and experimental studies. Exp. Mol. Med 52, 1652–1662. https://doi.org/10.1038/s12276-020-00513-7.

Jones, D.R., Delenclos, M., Baine, A.M.T., DeTure, M., Murray, M.E., Dickson, D.W., et al., 2015. Transmission of soluble and insoluble α-synuclein to mice. J. Neuropathol. Exp. Neurol. 74, 1158–1169. https://doi.org/10.1097/NEN.0000000000000262.

Jones, E.G., 1990. Peters. Cerebral cortex. In: Comparative structure and evolution of the cerebral cortex, vol 8. Springer.

Jones, L., Holmans, P.A., Hamshere, M.L., Harold, D., Moskvina, V., Ivanov, D., et al., 2010. Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. PLoS One 5, e13950. https://doi.org/10.1371/journal.pone.0013950.

Josephs, K.A., Whitwell, J.L., Tosakulwong, N., Weigand, S.D., Murray, M.E., Boeve, B.F., et al., 2015. TAR DNA-binding protein 43 and pathological subtype of Alzheimer's disease impact clinical features. Ann. Neurol. 78, 697–709. https://doi.org/10.1016/j.neurobiolaging.2020.04.001.

Josephs, K.A., Murray, M.E., Whitwell, J.L., Tosakulwong, N., Weigand, S.D., Petrucelli, L., et al., 2016. Updated TDP-43 in Alzheimer's disease staging scheme. Acta Neuropathol. 131, 571–585. https://doi.org/10.1007/s00401-016-1537-1.

Josephs, K.A., Dickson, D.W., Tosakulwong, N., Weigand, S.D., Murray, M.E., Petrucelli, L., et al., 2017. Rates of hippocampal atrophy and presence of post-mortem TDP-43 in patients with Alzheimer's disease: a longitudinal retrospective study. Lancet Neurol. 16, 917–924. https://doi.org/10.1016/S1474-4422(17)30284-3.

Josephs, K.A., Murray, M.E., Tosakulwong, N., Weigand, S.D., Knopman, D.S., Petersen, R.C., et al., 2019. Brain atrophy in primary age-related tauopathy is linked to transactive response DNA-binding protein of 43 kDa. Alzheimers Dement 15, 799–806. https://doi.org/10.1016/j.jalz.2019.03.003.

Jun, G., Naj, A.C., Beecham, G.W., Wang, L.S., Buros, J., Gallins, P.J., et al., 2010. Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. Arch. Neurol. 67, 1473–1484. https://doi.org/10.1001/archneurol.2010.201.

Kaas, J.H., 2017. Evolution of nervous system, second edition.,, 4 volumes. Elsevier Inc.

Kametani, F., Hasegawa, M., 2022. Structures of tau and α-synuclein filaments from brains of patients with neurodegenerative diseases. Neurochem. Int. 158, 105362 https://doi.org/10.1016/j.neuint.2022.105362.

Kanazawa, T., Uchihara, T., Takahashi, A., Nakamura, A., Orimo, S., Mizusawa, H., 2008. Three-layered structure shared between Lewy bodies and Lewy neurites—three-dimensional reconstruction of triple-labeled sections. Brain Pathol. 18, 415–422. https://doi.org/10.1111/j.1750-3639.2008.00140.x.

Kapasi, A., Yu, L., Boyle, P.A., Barnes, L.L., Bennett, D.A., Schneider, J.A., 2020. Limbic-predominant age-related TDP-43 encephalopathy. ADNC Pathol., Cogn. Decline Aging Neurol. 95, e1951–e1962. https://doi.org/10.1212/WNL.0000000000010454.

Karampetsou, M., Ardah, M.T., Semitekolou, M., Polissidis, A., Samiotaki, M., Kalomoiri, M., et al., 2017. Phosphorylated exogenous alpha-synuclein fibrils exacerbate pathology and induce neuronal dysfunction in mice. Sci. Rep. 7, 16533. https://doi.org/10.1038/s41598-017-15813-8.

Karanth, S., Nelson, P.T., Katsumata, Y., Kryscio, R.J., Schmitt, F.A., Fardo, D.W., et al., 2020. Abner EL. Prevalence and clinical phenotype of quadruple misfolded proteins in older adults. JAMA Neurol. 77, 1299–1307. https://doi.org/10.1001/jamaneurol.2020.1741.

Karanth, S.D., Schmitt, F.A., Nelson, P.T., Katsumata, Y., Kryscio, R.J., Fardo, D.W., et al., 2021. Four common late-life cognitive trajectories patterns associate with replicable underlying neuropathologies. J. Alzheimers Dis. 82, 647–659. https://doi.org/10.3233/JAD-210293.

Katsinelos, T., Zeitler, M., Dimou, E., Karakatsani, A., Müller, H.M., Nachman, E., et al., 2018. Unconventional secretion mediates the trans-cellular spreading of tau. Cell Rep. 23, 2039–2055. https://doi.org/10.1016/j.celrep.2018.04.056.

Katsumata, Y., Nelson, P.T., Ellingson, S.R., Fardo, D.W., 2017. Gene-based association study of genes linked to hippocampal sclerosis of aging neuropathology: GRN, TMEM106B, ABCC9, and KCNMB2. Neurobiol. Aging 53 (193), e117–193.e125. https://doi.org/10.1016/j.neurobiolaging.2017.01.003.

Katsumata, Y., Abner, E.L., Karanth, S., Teylan, M.A., Mock, C.N., Cykowski, M.D., et al., 2020. Distinct clinicopathologic clusters of persons with TDP-43 proteinopathy. Acta Neuropathol. 140, 659–674. https://doi.org/10.1007/s00401-020-02211-0.

Kaufman, S.K., Thomas, T.L., Del Tredici, K., Braak, H., Diamond, M.I., 2017. Characterization of tau prion seeding activity and strains from formaldehyde-fixed tissue. Acta Neuropathol. Commun. 5, 41. https://doi.org/10.1186/s40478-017-0442-8.

Kaufman, S.K., Del Tredici, K., Thomas, T.L., Braak, H., Diamond, M.I., 2018. Tau seeding activity begins in the transentorhinal/entorhinal regions and anticipates phospho-tau pathology in Alzheimer's disease and PART. Acta Neuropathol. 136, 57–67. https://doi.org/10.1007/s00401-018-1855-6.

Kawahata, I., Finkelstein, D.I., Fukunaga, K.I., 2022. Pathogenic impact of α-synuclein phosphorylation and its kinases in α-synucleinopathies. Int J. Mol. Sci. 23, 6216. https://doi.org/10.3390/ijms23116216.

Keating, S.S., San Gil, R., Swanson, M.E.V., Scotter, E.L., Walker, A.K., 2022. TDP-43 pathology: from noxious assembly to therapeutic removal. Prog. Neurobiol. 211, 102229 https://doi.org/10.1016/j.pneurobio.2022.102229.

Klotz, S., Fischer, P., Hinterberger, M., Ricken, G., Hönigschnabl, S., Gelpi, E., et al., 2021. Multiple system aging-related tau astrogliopathy with complex proteinopathy in an oligosymptomatic octogenarian. Neuropathology 41, 72–83. https://doi.org/10.1111/neup.12708.

Knopman, D., 2011. Clinical aspects of Alzheimer's disease. In: Dickson, D.W., Weller, R. O. (Eds.), Neurodegeneration, the molecular pathology of dementia and movement disorders. Wiley- Blackwell, pp. 39–50.

Knopman, D.S., Parisi, J.E., Salviati, A., Floriach-Robert, M., Boeve, B.F., Ivnik, R.J., et al., 2003. Neuropathology of cognitively normal elderly. J. Neuropathol. Exp. Neurol. 62, 1087–1095. https://doi.org/10.1093/jnen/62.11.1087.

Knopman, D.S., Jack, C.R., Wiste, H.J., Weigand, S.D., Vemuri, P., Lowe, V., et al., 2012. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. Neurology 78, 1576–1582. https://doi.org/10.1212/WNL.0b013e3182563bbe.

Koper, M.J., Tomé, S.O., Gawor, K., Belet, A., Van Schoor, E., Schaeverbeke, J., et al., 2022. LATE-NC aggravates GVD-mediated necroptosis in Alzheimer's disease. Acta Neuropathol. Commun. 10, 128. https://doi.org/10.1186/s40478-022-01432-6.

Koprich, J.B., Kalia, L.V., Brotchie, J.M., 2017. Animal models of α-synucleinopathy for Parkinson disease drug development. Nat. Rev. Neurosci. 18, 515–529. https://doi.org/10.1038/nrn.2017.75.

Kordower, J.H., Chu, Y., Hauser, R.A., Freeman, T.B., Olanow, C.W., 2008. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat. Med 14, 504–506. https://doi.org/10.1038/nm1747.

Kosaka, K., Iseki, E., 1996. Dementia with Lewy bodies. Curr. Opin. Neurol. 9, 271–275. https://doi.org/10.1097/00019052-199608000-00005.

Kosik, K.S., Joachim, C.L., Selkoe, D.J., 1986. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc. Natl. Acad. Sci. USA 83, 4044–4048. https://doi.org/10.1073/pnas.83.11.4044.

Kovacs, G., Ferrer, I., Alafuzoff, I., 2015. Concomitant pathologies II: Neurodegenerative conditions. Neuropathology of neurodegenerative diseases: a practical guide. Kovacs GG (edit). Cambridge University Press, Cambridge, pp. 292–298.

Kovacs, G.G., Pittman, A., Revesz, T., Luk, C., Lees, A., Kiss, E., 2008. MAPT S305I mutation: implications for argyrophilic grain disease. Acta Neuropathol. 116, 103–118. https://doi.org/10.1007/s00401-007-0322-6.

Kovacs, G.G., Milenkovic, I., Wöhrer, A., Höftberger, R., Gelpi, E., Haberler, C., et al., 2013. Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. Acta Neuropathol. 126, 365–384. https://doi.org/10.1007/s00401-013-1157-y.

Kovacs, G.G., Ferrer, I., Grinberg, L.T., Alafuzoff, I., Attems, J., Budka, H., et al., 2016. Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy. Acta Neuropathol. 131, 87–102. https://doi.org/10.1007/s00401-015-1509-x.

Kovacs, G.G., Robinson, J.L., Xie, S.X., Lee, E.B., Grossman, M., Wolk, D.A., et al., 2017. Evaluating the patterns of aging-related tau astrogliopathy unravels novel insights into brain aging and neurodegenerative diseases. J. Neuropathol. Exp. Neurol. 76, 270–288. https://doi.org/10.1093/jnen/nlx007.

Kovacs, G.G., Xie, S.X., Robinson, J.L., Lee, E.B., Smith, D.H., Schuck, T., et al., 2018a. Sequential stages and distribution patterns of aging-related tau astrogliopathy (ARTAG) in the human brain. Acta Neuropathol. Commun. 6, 50. https://doi.org/10.1186/s40478-018-0552-y.

Kovacs, G.G., Yousef, A., Kaindl, S., Lee, V.M., Trojanowski, J.Q., 2018b. Connexin-43 and aquaporin-4 are markers of ageing-related tau astrogliopathy (ARTAG)-related astroglial response. Neuropathol. Appl. Neurobiol. 44, 491–505. https://doi.org/10.1111/nan.12427.

Kovacs, G.G., Robinson, J.L., Perl, D.P., Lee, V.M., Trojanowski, J.Q., 2020. Thorn-shaped astrocytes in the depth of cortical sulci in Western Pacific ALS/Parkinsonism-Dementia complex. Acta Neuropathol. 140, 591–593. https://doi.org/10.1007/s00401-020-02192-0.

Kowall, N.W., Hantraye, P., Brouillet, E., Beal, M.F., McKee, A.C., Ferrante, R.J., 2000. MPTP induces alpha-synuclein aggregation in the substantia nigra of baboons. Neuroreport 11, 211–213. https://doi.org/10.1097/00001756-200001170-00041.

Kraus, A., Saijo, E., Metrick 2nd, M.A., Newell, K., Sigurdson, C.J., Zanusso, G., et al., 2019. Seeding selectivity and ultrasensitive detection of tau aggregate conformers of Alzheimer disease. Acta Neuropathol. 137, 585–598. https://doi.org/10.1007/s00401-018-1947-3.

Kunkle, B.W., Grenier-Boley, B., Sims, R., Bis, J.C., Damotte, V., Naj, A.C., et al., 2019. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat. Genet 51, 414–430. https://doi.org/10.1038/s41588-019-0358-2.

Lace, G., Ince, P.G., Brayne, C., Savva, G.M., Matthews, F.E., de Silva, R., et al., 2012. Mesial temporal astrocyte tau pathology in the MRC-CFAS ageing brain cohort. Dement Geriatr. Cogn. Disord. 34, 15–24. https://doi.org/10.1159/000341581.

Lama, J., Buhidma, Y., Fletcher, E.J.R., Duty, S., 2021. Animal models of Parkinson's disease: a guide to selecting the optimal model for your research. Neuron Signal 5, NS20210026. https://doi.org/10.1042/NS20210026.

Lambert, J.C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., et al., 2009. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat. Genet 41, 1094–1099. https://doi.org/10.1038/ng.439.

Lambert, J.C., Ibrahim-Verbaas, C.A., Harold, D., Naj, A.C., Sims, R., Bellenguez, C., et al., 2013. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat. Genet 45, 1452–1458. https://doi.org/10.1038/ng.2802.

Langer, F., Eisele, Y.S., Fritschi, S.K., Staufenbeil, M., Walker, L.C., Jucker, M., 2011. Soluble Aβ seeds are potent inducers of cerebral β-amyloid deposition. J. Neurosci. 31, 14488–14495. https://doi.org/10.1523/JNEUROSCI.3088-11.2011.

Languille, S., Blanc, S., Blin, O., Canale, C.I., Dal-Pan, A., Devau, G., et al., 2012. The grey mouse lemur: a non-human primate model for ageing studies. Ageing Res Rev. 11, 150–162. https://doi.org/10.1016/j.arr.2011.07.001.

Latimer, C.S., Burke, B.T., Liachko, N.F., Currey, H.N., Kilgore, M.D., Gibbons, L.E., et al., 2019. Resistance and resilience to Alzheimer's disease pathology are associated with reduced cortical pTau and absence of limbic-predominant age-related TDP-43 encephalopathy in a community-based cohort. Acta Neuropathol. Commun. 7, 91. https://doi.org/10.1186/s40478-019-0743-1.

Latimer, C.S., Stair, J.G., Hincks, J.C., Currey, H.N., Bird, T.D., Keene, C.D., et al., 2022. TDP-43 promotes tau accumulation and selective neurotoxicity in bigenic Caenorhabditis elegans. Dis. Model Mech. 15, dmm049323. https://doi.org/10.1242/dmm.049323.

Lauwers, E., Lalli, G., Brandner, S., Collinge, J., Compernolle, V., Duyckaerts, C., et al., 2020. Potential human transmission of amyloid-beta pathology: surveillance and risks. Lancet Neurol. 19, 872–878. https://doi.org/10.1016/S1474-4422(20)30238-6.

Lee, H.J., Patel, S., Lee, S.J., 2005. Intravesicular localization and exocytosis of α-synuclein and its aggregates. J. Neurosci. 25, 6016–6024. https://doi.org/10.1523/JNEUROSCI.0692-05.2005.

Lee, H.J., Suk, J.E., Bae, E.J., Lee, J.H., Paik, S.R., Lee, S.J., 2008. Assembly-dependent endocytosis and clearance of extracellular α-synuclein. Int J. Biochem Cell Biol. 40, 1835–1849. https://doi.org/10.1016/j.biocel.2008.01.017.

Lee, M.J., Lee, J.H., Rubinsztein, D.C., 2013. Tau degradation: the ubiquitin-proteasome system versus the autophagy-lysosome system. Prog. Neurobiol. 105, 49–59. https://doi.org/10.1016/j.pneurobio.2013.03.001.
Leng, K., Li, E., Eser, R., Piergies, A., Sit, R., Tan, M., et al., 2021. Molecular characterization of selectively vulnerable neurons in Alzheimer's disease. Nat. Neurosci. 24, 276–287. https://doi.org/10.1038/s41593-020-00764-7.
Leroy, K., Yilmaz, Z., Brion, J.P., 2007. Increased level of active GSK-3beta in Alzheimer's disease and accumulation in argyrophilic grains and in neurones at different stages of neurofibrillary degeneration. Neuropathol. Appl. Neurobiol. 33, 43–55. https://doi.org/10.1111/j.1365-2990.2006.00795.x.
Lesuis, S.L., Hoeijmakers, L., Korosi, A., de Rooij, S.R., Swaab, D.F., Kessels, H.W., et al., 2018. Vulnerability and resilience to Alzheimer's disease: early life conditions modulate neuropathology and determine cognitive reserve. Alzheimers Res Ther. 10, 95. https://doi.org/10.1186/s13195-018-0422-7.
Leverenz, J.B., Lipton, A.M., 2008. Clinical aspects of hippocampal sclerosis. Handb. Clin. Neurol. 89, 565–567 doi:S0072-9752(07)01252-3.
Leverenz, J.B., Agustin, C.M., Tsuang, D., Peskind, E.R., Edland, S.D., Nochlin, D., et al., 2002. Clinical and neuropathological characteristics of hippocampal sclerosis: a community-based study. Arch. Neurol. 59, 1099–1106. https://doi.org/10.1001/archneur.59.7.1099.
Leverenz, J.B., Umar, I., Wang, Q., Montine, T.J., McMillan, P.J., Tsuang, D.W., et al., 2007. Proteomic identification of novel proteins in cortical Lewy bodies. Brain Pathol. 17, 139–145. https://doi.org/10.1111/j.1750-3639.2007.00048.x.
Levy-Lahad, E., Wasco, W., Poorkaj, P., Romano, D.M., Oshima, J., Pettingell, W.H., et al., 1995. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 18 (269), 973–977. https://doi.org/10.1126/science.7638622.
Li, J.Y., Englund, E., Holton, J.L., Soulet, D., Hagell, P., Lees, A.J., et al., 2008. Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat. Med 14, 501–503. https://doi.org/10.1038/nm1746.
Li, L., Shi, R., Gu, J., Tung, Y.C., Zhou, Y., Zhou, D., et al., 2021a. Alzheimer's disease brain contains tau fractions with differential prion-like activities. Acta Neuropathol. Commun. 9, 28. https://doi.org/10.1186/s40478-021-01127-4.
Li, Q., Babinchak, W.M., Surewicz, W.K., 2021b. Cryo-EM structure of amyloid fibrils formed by the entire low complexity domain of TDP-43. Nat. Commun. 12, 1620. https://doi.org/10.1038/s41467-021-21912-y.
Li, Y., Zhao, C., Luo, F., Liu, Z., Gui, X., Luo, Z., et al., 2018. Amyloid fibril structure of α-synuclein determined by cryo-electron microscopy. Cell Res 28, 897–903. https://doi.org/10.1038/s41422-018-0075-x.
Liao, Y.Z., Ma, J., Dou, J.Z., 2022. The role of TDP-43 in neurodegenerative disease. Mol. Neurobiol. 59, 4223–4241. https://doi.org/10.1007/s12035-022-02847-x.
Lin, W.L., Dickson, D.W., 2008. Ultrastructural localization of TDP-43 in filamentous neuronal inclusions in various neurodegenerative diseases (Aug). Acta Neuropathol. 116 (2), 205–213. https://doi.org/10.1007/s00401-008-0408-9.
Lipinski, M.M., Zheng, B., Lu, T., Yan, Z., Py, B.F., Ng, A., et al., 2010. Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease. Proc. Natl. Acad. Sci. USA 107, 14164–14169. https://doi.org/10.1073/pnas.1009485107.
Lippa, C.F., Rosso, A.L., Stutzbach, L.D., Neumann, M., Lee, V.M.Y., Trojanowski, J.Q., 2009. Transactive response DNAbinding protein 43 burden in familial Alzheimer disease and Down syndrome. Arch. Neurol. 66, 1483–1488. https://doi.org/10.1001/archneurol.2009.277.
Liu, A.K.L., Goldfinger, M.H., Questari, H.E., Pearce, R.K.B., Gentleman, S.M., 2016. ARTAG in the basal forebrain: widening the constellation of astrocytic tau pathology. Acta Neuropathol. Commun. 4, 59. https://doi.org/10.1186/s40478-016-0330-7.
Liu, K.Y., Reeves, S., McAleese, K.E., Attems, J., Francis, P., Thomas, A., et al., 2020. Neuropsychiatric symptoms in limbic-predominant age-related TDP-43 encephalopathy and Alzheimer's disease. Brain 143, 3842–3849. https://doi.org/10.1093/brain/awaa315.
Lloyd, G.M., Sorrentino, Z.A., Quintin, S., Gorion, K.M., Bell, B.M., Paterno, G., et al., 2022. Unique seeding profiles and prion-like propagation of synucleinopathies are highly dependent on the host in human α-synuclein transgenic mice. Acta Neuropathol. 143, 663–685. https://doi.org/10.1007/s00401-022-02425-4.
López-González, I., Carmona, M., Blanco, R., Luna-Muñoz, J., Martínez-Mandonado, A., Mena, R., et al., 2013. Characterization of thorn-shaped astrocytes in white matter of temporal lobe in Alzheimer's disease brains. Brain Pathol. 23, 144–153. https://doi.org/10.1111/j.1750-3639.2012.00627.x.
Luk, K.C., Kehm, V.M., Zhang, B., O'Brien, P., Trojanowski, J.Q., Lee, V.M.Y., 2012. Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice. J. Exp. Med 209, 975–988. https://doi.org/10.1084/jem.20112.457.
Luna-Muñoz, J., Chávez-Macías, L., García-Sierra, F., Mena, R., 2007. Earliest stages of tau conformational changes are related to the appearance of a sequence of specific phospho-dependent tau epitopes in Alzheimer's disease. J. Alzheimers Dis. 12, 365–375. https://doi.org/10.3233/jad-2007-12410.
Lv, Y.N., Cui, Y., Zhang, B., Huang, S.M., 2022. Sleep deficiency promotes Alzheimer's disease development and progression. Front Neurol. 13, 1053942. https://doi.org/10.3389/fneur.2022.1053942.
Mandelkow, E.M., Mandelkow, E., 2012. Biochemistry and cell biology of tau protein in neurofibrillary degeneration. Cold Spring Harb. Perspect. Med. 2, a006247. https://doi.org/10.1101/cshperspect.a006247.
Martinez-Lage, P., Munoz, D.G., 1997. Prevalence and disease associations of argyrophilic grains of Braak. J. Neuropathol. Exp. Neurol. 56, 157–164. https://doi.org/10.1097/00005072-199702000-00006.
Marui, W., Iseki, E., Nakai, T., Miura, S., Kato, M., Uéda, K., et al., 2002. Progression and staging of Lewy pathology in brains from patients with dementia with Lewy bodies. J. Neurol. Sci. 195, 153–159. https://doi.org/10.1016/s0022-510x(02)00006-0.
Masters, C.L., Beyreuther, K., 2006a. Pathways to the discovery of the Ab-amyloid of Alzheimer's disease, 9 Suppl J. Alzheimers Dis. 3, 155–161. https://doi.org/10.3233/jad-2006-9s318.
Masters, C.L., Beyreuther, K., 2006b. Alzheimer's centennial legacy: prospects for rational therapeutic intervention targeting the Abeta amyloid pathway. Brain 129, 2823–2839. https://doi.org/10.1093/brain/awl251.
Masters, C.L., Beyreuther, K., 2011. Amyloid-β production. In: Dickson, D.W., Weller, R. O. (Eds.), Neurodegeneration: the molecular pathology of dementia and movement disorders, 2nd ed..,. Blackwell Publishing Co, pp. 92–96.
Masters, C.L., Selkoe, D.J., 2012. Biochemistry of amyloid β-protein and amyloid deposits in Alzheimer disease. Cold Spring Harb. Perspect. Med 2, a006262. https://doi.org/10.1101/cshperspect.a006262.
Masters, C.L., Simms, G., Weinman, N.A., Multhaup, G., McDonald, B.L., Beyreuther, K., 1985. Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proc. Nat. Acad. Sci. USA 82, 4245–4249. https://doi.org/10.1073/pnas.82.12.4245.
McAleese, K.E., Walker, L., Erskine, D., Johnson, M., Koss, D., Thomas, A.J., et al., 2020. Concomitant LATE-NC in Alzheimer's disease is not associated with increased tau or amyloid-β pathological burden. Neuropathol. Appl. Neurobiol. 46, 722–734. https://doi.org/10.1111/nan.12664.
McCann, H., Cartwright, H., Halliday, G.M., 2016. Neuropathology of alpha-synuclein propagation and braak hypothesis. Mov. Disord. 31, 152–160. https://doi.org/10.1002/mds.26421.
McCann, H., Durand, B., Shepherd, C.E., 2021. Aging-related tau astrogliopathy in aging and neurodegeneration. Brain Sci. 11, 927. https://doi.org/10.3390/brainsci11070927.
McDermott, K.L., McFall, G.P., Andrews, S.J., Anstey, K.J., Dixon, R.A., 2017. Memory resilience to Alzheimer's genetic risk: sex effects in predictor profiles. J. Gerontol. B Psychol. Sci. Soc. Sci. 72, 937–946. https://doi.org/10.1093/geronb/gbw161.
Mckean, N.E., Handley, R.R., Snell, R.G., 2021. A review of the current mammalian models of Alzheimer's disease and challenges that need to be overcome. Int J. Mol. Sci. 22, 13168. https://doi.org/10.3390/ijms222313168.
McKeith, I., Mintzer, J., Aarsland, D., Burn, D., Chiu, H., Cohen-Mansfield, J., et al., 2004. Dementia with Lewy bodies. Lancet Neurol. 3, 19–28. https://doi.org/10.1016/s1474-4422(03)00619-7.
McKeith, I.G., Boeve, B.F., Dickson, D.W., Halliday, G., Taylor, J.P., Weintraub, D., et al., 2017. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89, 88–100. https://doi.org/10.1212/WNL.0000000000004058.
McKetney, J., Runde, R.M., Hebert, A.S., Salamat, S., Roy, S., Coon, J.J., 2019. Proteomic atlas of the human brain in Alzheimer's disease. J. Proteome Res 18, 1380–1391. https://doi.org/10.1021/acs.jproteome.9b00004.
McMillan, C.T., Lee, E.B., Jefferson-George, K., Naj, A., Van Deerlin, V.M., Trojanowski, J.Q., et al., 2018. Alzheimer's genetic risk is reduced in primary age-related tauopathy: a potential model of resistance? Ann. Clin. Transl. Neurol. 5, 927–934. https://doi.org/10.1002/acn3.581.
Mendonça, C.F., Kuras, M., Nogueira, F.C.S., Plá, I., Hortobágyi, T., Csiba, L., et al., 2019. Proteomic signatures of brain regions affected by tau pathology in early and late stages of Alzheimer's disease. Neurobiol. Dis. 130, 104509 https://doi.org/10.1016/j.nbd.2019.104509.
Meneses, A., Koga, S., O'Leary, J., Dickson, D.W., Bu, G., Zhao, N., 2021. TDP-43 pathology in Alzheimer's disease. Mol. Neurodegener. 16, 84. https://doi.org/10.1186/s13024-021-00503-x.
Merezhko, M., Brunello, C.A., Yan, X., Vihinen, H., Jokitalo, E., Uronen, R.L., et al., 2018. Secretion of tau via an unconventional non-vesicular mechanism. Cell Rep. 25, 2027–2035. https://doi.org/10.1016/j.celrep.2018.10.078.
Mesulam, M., Wicklund, A., Johnson, N., Rogalski, E., Léger, G.C., Rademaker, A., et al., 2008. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann. Neurol. 63, 709–719. https://doi.org/10.1002/ana.21388.
Metrick 2nd, M.A., Ferreira, N.D.C., Saijo, E., Kraus, A., Newell, K., Zanusso, G., et al., 2020. A single ultrasensitive assay for detection and discrimination of tau aggregates of Alzheimer and Pick diseases. Acta Neuropathol. Commun. 8, 22. https://doi.org/10.1186/s40478-020-0887-z.
Meyer-Luehmann, M., Coomaraswamy, J., Bolmont, T., Kaeser, S., Schaefer, C., Kilger, E., et al., 2006. Exogenous induction of cerebral b-amyloidogenesis is governed by agent and host. Science 313, 1781–1784. https://doi.org/10.1126/science.1131864.
Mondragón-Rodríguez, S., Basurto-Islas, G., Santa-Maria, I., Mena, R., Binder, L.I., Avila, J., et al., 2008. Cleavage and conformational changes of tau protein follow phosphorylation during Alzheimer's disease. Int J. Exp. Pathol. 89, 81–90. https://doi.org/10.1111/j.1365-2613.2007.00568.x.
Montalbano, M., McAllen, S., Cascio, F.L., Sengupta, U., Garcia, S., Bhatt, N., et al., 2020. TDP-43 and Tau Oligomers in Alzheimer's disease, amyotrophic lateral sclerosis, and frontotemporal dementia. Neurobiol. Dis. 146, 105130 https://doi.org/10.1016/j.nbd.2020.105130.
Montine, T.J., Phelps, C.H., Beach, T.G., Bigio, E.H., Cairns, N.J., Dickson, D.W., et al., 2012. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 123, 1–11. https://doi.org/10.1007/s00401-011-0910-3.
Montine, T.J., Cholerton, B.A., Corrada, M.M., Edland, S.D., Flanagan, M.E., Hemmy, L. S., et al., 2019. Concepts for brain aging: resistance, resilience, reserve, and compensation. Alzheimers Res Ther. 11, 22. https://doi.org/10.1186/s13195-019-0479-y.

Montine, T.J., Corrada, M.M., Kawas, C., Bukhari, S., White, L., Tian, L., Cholerton, B., 2022. Association of cognition and dementia with neuropathologic changes of Alzheimer Disease and other conditions in the oldest-old. Neurology 99, e1067–e1078. https://doi.org/10.1212/WNL.0000000000200832.

Morales, R., Duran-Aniotz, C., Castilla, J., Estrada, L.D., Soto, C., 2012. De novo induction of amyloid-b deposition in vivo. Mol. Psychiatry 17, 1347–1353. https://doi.org/10.1038/mp.2011.120.

Morelli, L., Wei, L., Amorim, A., McDermid, J., Abee, C.R., Frangione, B., et al., 1996. Cerebrovascular amyloidosis in squirrel monkeys and rhesus monkeys: apolipoprotein E genotype. FEBS Lett. 379, 132–134. https://doi.org/10.1016/0014-5793(95)01491-8.

Mudher, A.K., Yee, B., Smith, A.D., Perry, V.H., 2001. Deafferentation of the hippocampus results in the induction of AT8 positive 'granules' in the rat. Neurosci. Lett. 301, 5–8. https://doi.org/10.1016/s0304-3940(01)01593-2.

Mudner, A., Colin, M., Dujardin, S., Medina, M., Dewachter, I., Naini, S.M.A., et al., 2017. What is the evidence that tau pathology spreads through prion-like propagation? Acta Neuropathol. Commun. 5, 99 doi:1186/s40478-017-0488-7.

Munoz, D.G., Woulfe, J., Kertesz, A., 2007. Argyrophilic thorny astrocyte clusters in association with Alzheimer's disease pathology in possible primary progressive aphasia. Acta Neuropathol. 114, 347–357. https://doi.org/10.1007/s00401-007-0266-x.

Muntané, G., Dalfó, E., Martinez, A., Ferrer, I., 2008. Phosphorylation of tau and α-synuclein in synaptic-enriched fractions of the frontal cortex in Alzheimer's disease, and in Parkinson's disease and related α-synucleinopathies. Neuroscience 152, 913–923. https://doi.org/10.1016/j.neuroscience.2008.01.030.

Murrell, J., Farlow, M., Ghetti, B., Benson, M.D., 1991. A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease. Science 254, 97–99. https://doi.org/10.1126/science.1925564.

Musunuri, S., Wetterhall, M., Ingelsson, M., Lannfelt, L., Artemenko, K., Bergquist, J., et al., 2014. Quantification of the brain proteome in Alzheimer's disease using multiplexed mass spectrometry. J. Proteome Res 13, 2056–2068. https://doi.org/10.1021/pr401202d.

Nag, S., Yu, L., Capuano, A.W., Wilson, R.S., Leurgans, S.E., Bennett, D.A., Schneider, J. A., 2015. Hippocampal sclerosis and TDP-43 pathology in aging and Alzheimer disease. Ann. Neurol. 77, 942–952. https://doi.org/10.1002/ana.24388.

Nag, S., Yu, L., Wilson, R.S., Chen, E.Y., Bennett, D.A., Schneider, J.A., 2017. TDP-43 pathology and memory impairment in elders without pathologic diagnoses of AD or FTLD. Neurology 88, 653–660. https://doi.org/10.1212/WNL.0000000000003610.

Nag, S., Yu, L., Boyle, P.A., Leurgans, S.E., Bennett, D.A., Julie, A., et al., 2018. TDP-43 pathology in anterior temporal pole cortex in aging and Alzheimer's disease. Acta Neuropathol. Commun. 6, 33. https://doi.org/10.1186/s40478-018-0531-3.

Nag, S., Barnes, L.L., Yu, L., Wilson, R.S., Bennett, D.A., Schneider, J.A., 2020. Limbic-predominant age-related TDP-43 encephalopathy in black and white decedents. Neurology 95, e2056–e2064. https://doi.org/10.1212/WNL.0000000000010602.

Naj, A.C., Jun, G., Reitz, C., Kunkle, B.W., Perry, W., Park, Y.S., et al., 2014. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. JAMA Neurol. 71, 1394–1404. https://doi.org/10.1001/jamaneurol.2014.1491.

Narashiman, S., Guo, J.L., Changolkar, L., Stieber, A., McBride, J.D., Silva, L.V., et al., 2017. Pathological tau strains from human brains recapitulate the diversity of tauopathies in non-transgenic mouse brain. J. Neurosci. 37, 11406–11423. https://doi.org/10.1523/JNEUROSCI.1230-17.2017.

Narasimhan, S., Changolkar, L., Riddle, D.M., Kats, A., Stieber, A., Weitzman, S.A., et al., 2018. Human tau pathology transmits glial tau aggregates in the absence of neuronal tau. J. Exp. Med 84, 499–508. https://doi.org/10.1084/jem.20190783.

Nelson, P.T., 2021. LATE neuropathologic changes with little or no Alzheimer disease is common and is associated with cognitive impairment but not frontotemporal dementia. J. Neuropathol. Exp. Neurol. 80, 649–651. https://doi.org/10.1093/jnen/nlab050.

Nelson, P.T., Abner, E.L., Schmitt, F.A., Kryscio, R.J., Jicha, G.A., Smith, C.D., Davis, D. G., Poduska, J.W., Patel, E., Mendiondo, M.S., Markesbery, W.R., 2010. Modeling the association between 43 different clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. Brain Pathol. 20, 66–79. https://doi.org/10.1111/j.1750-3639.2008.00244.x.

Nelson, P.T., Head, E., Schmitt, F.A., Davis, P.R., Neltner, J.H., Jicha, G.A., Abner, E.L., Smith, C.D., Van Eldik, L.J., Kryscio, R.J., Scheff, S.W., 2011a. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. Acta Neuropathol. 121, 571–587. https://doi.org/10.1007/s00401-011-0826-y.

Nelson, P.T., Schmitt, F.A., Lin, Y., Abner, E.L., Jicha, G.A., Patel, E., et al., 2011b. Hippocampal sclerosis in advanced age: clinical and pathological features. Brain 134, 1506–1518. https://doi.org/10.1093/brain/awr053.

Nelson, P.T., Smith, C.D., Abner, E.L., Wilfred, B.J., Wang, W.X., Neltner, J.H., et al., 2013. Hippocampal sclerosis of aging, a prevalent and high-morbidity brain disease. Acta Neuropathol. 126, 161–177. https://doi.org/10.1007/s00401-013-1154-1.

Nelson, P.T., Estus, S., Abner, E.L., Parikh, I., Malik, M., Neltner, J.H., et al., 2014. ABCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology. Acta Neuropathol. 127, 825–843. https://doi.org/10.1007/s00401-014-1282-2.

Nelson, P.T., Jicha, G.A., Wang, W.X., Ighodaro, E., Artiushin, S., Nichols, C.G., et al., 2015a. ABCC9/SUR2 in the brain: Implications for hippocampal sclerosis of aging and a potential therapeutic target. Ageing Res Rev. 24, 111–125. https://doi.org/10.1016/j.arr.2015.07.007.

Nelson, P.T., Wang, W.X., Partch, A.B., Monsell, S.E., Valladares, O., Ellingson, S.R., et al., 2015b. Reassessment of risk genotypes (GRN, TMEM106B, and ABCC9 variants) associated with hippocampal sclerosis of aging pathology. J. Neuropathol. Exp. Neurol. 74, 75–84. https://doi.org/10.1097/NEN.0000000000000151.

Nelson, P.T., Trojanowski, J.Q., Abner, E.L., Al-Janabi, O.M., Jicha, G.A., Schmitt, F.A., et al., 2016. "New Old Pathologies": AD, PART, and cerebral age-related TDP-43 with sclerosis (CARTS). J. Neuropathol. Exp. Neurol. 75, 482–498. https://doi.org/10.1093/jnen/nlw033.

Nelson, P.T., Dickson, D.W., Trojanowski, J.Q., Jack, C.R., Boyle, P.A., Arfanakis, K., et al., 2019. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain 142, 1503–1527. https://doi.org/10.1093/brain/awz099.

Nelson, P.T., Brayne, C., Flanagan, M.E., Abner, E.L., Agrawal, S., Attems, J., et al., 2022. Frequency of LATE neuropathologic change across the spectrum of Alzheimer's disease neuropathology: combined data from 13 community-based or population-based autopsy cohorts. Acta Neuropathol. 144, 27–44. https://doi.org/10.1007/s00401-022-02444-1.

Neltner, J.H., Abner, E.L., Baker, S., Schmitt, F.A., Kryscio, R.J., Jicha, G.A., et al., 2014. Arteriolosclerosis that affects multiple brain regions is linked to hippocampal sclerosis of ageing. Brain 137, 255–267. https://doi.org/10.1093/brain/awt318.

Neltner, J.H., Abner, E.L., Jicha, G.A., Schmitt, F.A., Patel, E., Poon, L.W., et al., 2016. Brain pathologies in extreme old age. Neurobiol. Aging 37, 1–11. https://doi.org/10.1016/j.neurobiolaging.2015.10.009.

Neumann, M., Sampathu, D.M., Kwong, L.K., Truax, A.C., Micsenyi, M.C., Chou, T.T., et al., 2006. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314, 130–133. https://doi.org/10.1126/science.1134108.

Ngolab, J., Trinh, I., Rockenstein, E., Mante, M., Florio, J., Trejo, M., et al., 2017. Brain-derived exosomes from dementia with Lewy bodies propagate α-synuclein pathology. Acta Neuropathol. Commun. 5, 46. https://doi.org/10.1186/s40478-017-0445-5.

Nguyen, M.T., Mattek, N., Woltjer, R., Howieson, D., Silbert, L., Hofer, S., Kaye, J., Dodge, H., Erten-Lyons, D., 2018. Pathologies underlying longitudinal cognitive decline in the oldest old. Alzheimer Dis. Assoc. Disord. 32, 265–269. https://doi.org/10.1097/WAD.0000000000000265.

Nixon, R.A., Wegiel, J., Kumar, A., Yu, W.H., Peterhoff, C., Cataldo, A., et al., 2005. Extensive involvement of autophagy in Alzheimer disease: an immunoelectron microscopy study. J. Neuropathol. Exp. Neurol. 64, 113–122. https://doi.org/10.1093/jnen/64.2.113.

Nolan, A., De Paula Franca Resende, E., Petersen, C., Neylan, K., Spina, S., Huang, E., et al., 2019. Astrocytic tau deposition is frequent in typical and atypical Alzheimer disease presentations. J. Neuropathol. Exp. Neurol. 78, 1112–1123. https://doi.org/10.1093/jnen/nlz094.

Nonaka, T., Masuda-Suzukake, M., Arai, T., Hasegawa, Y., Akatsu, H., Obi, T., et al., 2013. Prion-like properties of pathological TDP-43 aggregates from diseased brains. Cell Rep. 4, 124–134. https://doi.org/10.1016/j.celrep.2013.06.007.

Nygaard, H.B., Erson-Omay, E.Z., Wu, X., Kent, B.A., Bernales, C.Q., Evans, D.M., et al., 2019. Whole-exome sequencing of an exceptional longevity cohort. J. Gerontol. A Biol. Sci. Med Sci. 74, 1386–1390. https://doi.org/10.1093/gerona/gly098.

Odfalk, K.F., Bieniek, K.F., Hopp, S.C., 2022. Microglia: Friend and foe in tauopathy. Prog. Neurobiol. 216, 102306 https://doi.org/10.1016/j.pneurobio.2022.102306.

Okamoto, K., Hirai, S., Iizuka, T., Yanagisawa, T., Watanabe, M., 1991. Reexamination of granulovacuolar degeneration. Acta Neuropathol. 82, 340–345. https://doi.org/10.1007/BF00296544.

Okamoto, K., Amari, M., Fukuda, T., Suzuki, K., Takatama, M., 2019. Astrocytic tau pathologies in the aged human brain. Neuropathology 39, 187–193. https://doi.org/10.1111/neup.12544.

Onyike, C.U., Pletnikova, O., Sloane, K.L., Sullivan, C., Troncoso, J.C., Rabins, P.V., 2013. Hippocampal sclerosis dementia: an amnesic variant of frontotemporal degeneration. Dement Neuropsychol. 7, 83–87. https://doi.org/10.1590/S1980-57642013DN70100013.

Pan, L., Meng, L., He, M., Zhang, Z., 2021. Tau in the pathophysiology of parkinson's disease. J. Mol. Neurosci. 71, 2179–2191. https://doi.org/10.1007/s12031-020-01776-5.

Peelaerts, W., Bousset, L., Van der Perren, A., Moskalyuk, A., Pulizzi, R., Giugliano, M., et al., 2015. α-synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature 522, 340–344. https://doi.org/10.1038/nature14547.

Peelaerts, W., Bousset, L., Baekelandt, V., Melki, R., 2018. α-synuclein strains and seeding in Parkinson's disease, incidental Lewy body disease, dementia with Lewy bodies and multiple system atrophy: similarities and differences. Cell Tissue Res. 373, 195–212. https://doi.org/10.1007/s00441-018-2839-5.

Peeraer, E., Bottelbergs, A., Van Kolen, K., Stancu, I.C., Vasconcelos, B., Mahieu, M., et al., 2015. Intracerebral injection of preformed synthetic fibrils initiates widesprad tauopathy and neuronal loss in the brains of tau transgenic mice. Neurobiol. Dis. 73, 83–95. https://doi.org/10.1016/j.nbd.2014.08.032.

Peng, C., Trojanowski, J.Q., Lee, V.M.Y., 2020. Protein transmission in neurodegenerative disease. Nat. Rev. - Neurol. 16, 199. https://doi.org/10.1038/s41582-020-0333-7.

Peng, S., Roth, A.R., Apostolova, L.G., Saykin, A.J., Perry, B.L., 2022. Cognitively stimulating environments and cognitive reserve: the case of personal social networks. Neurobiol. Aging 112, 197–203. https://doi.org/10.1016/j.neurobiolaging.2022.01.004.

Pérez, S.E., Raghanti, M.A., Hof, P.R., Kramer, L., Ikonomovic, M.D., Lacor, P.N., et al., 2013. Alzheimer's disease pathology in the neocortex and hippocampus of the western lowland gorilla *(Gorilla gorilla gorilla)*. J. Comp. Neurol. 521, 4318–4338. https://doi.org/10.1002/cne.23428.

Pham, C.T., de Silva, R., Haïk, S., Verny, M., Sachet, A., Forette, B., et al., 2011. Tau-positive grains are constant in centenarians' hippocampus. Neurobiol. Aging 32, 1296–1303. https://doi.org/10.1016/j.neurobiolaging.2009.07.009.

Pignataro, A., Middei, S., 2017. Trans-synaptic spread of amyloid-β in Alzheimer's disease: paths to β-amyloidosis. Neural Plast. 2017, 5281829. https://doi.org/10.1155/2017/5281829.
Pimenova, A.A., Raj, T., Goate, A.M., 2018. Untangling genetic risk for Alzheimer's disease. Biol. Psychiat 83, 300–310. https://doi.org/10.1016/j.biopsych.2017.05.014.
Ping, L., Kundinger, S.R., Duong, D.M., Yin, L., Gearing, M., Lah, J.J., et al., 2020. Global quantitative analysis of the human brain proteome and phosphoproteome in Alzheimer's disease. Sci. Data 7, 315. https://doi.org/10.1038/s41597-020-00650-8.
Polanco, J.C., Li, C.Z., Durisic, N., Sullivan, R., Götz, J., 2018. Exosomes taken up by neurons hijack the endosomal pathway to spread to interconnected neurons. Acta Neuropathol. Commun. 6, 10. https://doi.org/10.1186/s40478-018-0514-4.
Poncelet, L., Ando, K., Vergara, C., Mansour, S., Suain, V., Yilmaz, Z., et al., 2019. A 4R tauopathy develops without amyloid deposits in aged cat brains. Neurobiol. Aging 81, 200e212. https://doi.org/10.1016/j.neurobiolaging.2019.05.024.
Pooler, A.M., Phillips, E.C., Lau, D.H.W., Noble, W., Hanger, D.P., 2013. Physiological release of endogenous tau is stimulated by neuronal activity. EMBO Rep. 14, 389–394. https://doi.org/10.1038/embor.2013.15.
Porta, S., Xu, Y., Restrepo, C.R., Kwong, L.K., Zhang, B., Brown, H.J., et al., 2018. Patient-derived frontotemporal lobar degeneration brain extracts induce formation and spreading of TDP-43 pathology in vivo. Nat. Commun. 9, 4220. https://doi.org/10.1038/s41467-018-06548-9.
Porta, S., Xu, Y., Lehr, T., Zhang, B., Meymand, E., Olufemi, M., et al., 2021. Distinct brain-derived TDP-43 strains from FTLD-TDP subtypes induce diverse morphological TDP-43 aggregates and spreading patterns in vitro and in vivo. Neuropathol. Appl. Neurobiol. 47, 1033–1049. https://doi.org/10.1111/nan.12732.
Pradeepkiran, J.A., Reddy, P.H., 2020. Defective mitophagy in Alzheimer's disease. Ageing Res Rev. 64, 101191 https://doi.org/10.1016/j.arr.2020.101191.
Prasad, A., Bharathi, V., Sivalingam, V., Girdhar, A., Patel, B.K., 2019. Molecular mechanisms of TDP-43 misfolding and pathology in amyotrophic lateral sclerosis. Front Mol. Neurosci. 12, 25. https://doi.org/10.3389/fnmol.2019.00025.
Price, D.L., Martin, L.J., Sisodia, S.S., Wagster, M.V., Koo, E.H., Walker, L.C., et al., 1991. Aged non-human primates: an animal model of age-associated neurodegenerative disease. Brain Pathol. 1, 287–296. https://doi.org/10.1111/j.1750-3639.1991.tb00672.x.
Price, J., Morris, J.C., 1999. Tangles and plaques in non demented aging and "preclinical" Alzheimer's disease. Ann. Neurol. 45, 358–368. https://doi.org/10.1002/1531-8249(199903)45:3<358::aid-ana12>3.0.co;2-x.
Probst, A., Tolnay, M., 2002. Argyrophilic grain disease (AgD), a frequent and largely underestimated cause of dementia in old patients. Rev. Neurol. (Paris) 158, 155–165.
Prusiner, S.B., Woerman, A.L., Mordes, D.A., Watts, J.C., Rampersaud, R., Berry, D.B., et al., 2015. Evidence for alpha-synuclein prions causing multiple system atrophy in humans with parkinsonism. Proc. Natl. Acad. Sci. USA 112, E5308–E5317. https://doi.org/10.1073/pnas.1514475112.
Rábano, A., Rodal, I., Cuadros, R., Calero, M., Hernández, F., Ávila, J., 2014. Argyrophilic grain pathology as a natural model of tau propagation. J. Alzheimers Dis. 40 (Suppl 1), S123–S133. https://doi.org/10.3233/JAD-132288.
Rauch, J.N., Chen, J.J., Sorum, A.W., Miller, G.M., Sharf, T., See, S.K., et al., 2018. Tau Internalization is regulated by 6-O sulfation on heparan sulfate proteoglycans (HSPGs). Sci. Rep. 8, 6382. https://doi.org/10.1038/s41598-018-24904-z.
Rauch, J.N., Luna, G., Guzman, E., Audouard, M., Challis, C., Sibih, Y.E., et al., 2020. LRP1 is a master regulator of tau uptake and spread. Nature 580, 381–385. https://doi.org/10.1038/s41586-020-2156-5.
Raunio, A., Kaivola, K., Tuimala, J., Kero, M., Oinas, M., Polvikoski, T., et al., 2019. Lewy-related pathology exhibits two anatomically and genetically distinct progression patterns: a population-based study of Finns aged 85. Acta Neuropathol. 138, 771–782. https://doi.org/10.1007/s00401-019-02071-3.
Recasens, A., Dehay, B., Bové, J., Carballo-Carbajal, I., Dovero, S., Pérez-Villalba, A., et al., 2014. Lewy body extracts from Parkinson disease brains trigger α-synuclein pathology and neurodegeneration in mice and monkeys. Ann. Neurol. 75, 351–362. https://doi.org/10.1002/ana.24066.
Resende, E.P.F., Nolan, A.L., Petersen, C., Ehrenberg, A.J., Spina, S., Allen, I.E., et al., 2020. Language and spatial dysfunction in Alzheimer disease with white matter thorn-shaped astrocytes. Neurology 94, e1353–e1364. https://doi.org/10.1212/WNL.0000000000008937.E.
Riederer, B.M., Leuba, G., Vernay, A., Riederer, I.M., 2011. The role of the ubiquitin proteasome system in Alzheimer's disease. Exp. Biol. Med 236, 268–276. https://doi.org/10.1258/ebm.2010.010327.
Riku, Y., Iwasaki, Y., Ishigaki, S., Akagi, A., Hasegawa, M., Nishioka, K., et al., 2022. Motor neuron TDP-43 proteinopathy in progressive supranuclear palsy and corticobasal degeneration. Brain 145, 2769–2784. https://doi.org/10.1093/brain/awac091.
Robinson, A.C., Davidson, Y.S., Roncaroli, F., Minshull, J., Tinkler, P., Horan, M.A., et al., 2020a. Influence of APOE genotype in primary age-related tauopathy. Acta Neuropathol. Commun. 8, 215. https://doi.org/10.1186/s40478-020-01095-1.
Robinson, J.L., Corrada, M.M., Kovacs, G.G., Dominique, M., Caswell, C., Xie, S.X., Lee, V.M., Kawas, C.H., Trojanowski, J.Q., 2018a. Non-Alzheimer's contributions to dementia and cognitive resilience in The 90+ Study. Acta Neuropathol. 136, 377–388. https://doi.org/10.1007/s00401-018-1872-5.
Robinson, J.L., Lee, E.B., Xie, S.X., Rennert, L., Suh, E., Bredenberg, C., et al., 2018b. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain 141, 2181–2193. https://doi.org/10.1093/brain/awy146.
Robinson, J.L., Porta, S., Garrett, F.G., Zhang, P., Xie, S.X., Suh, E., et al., 2020b. Limbic-predominant age-related TDP-43 encephalopathy differs from frontotemporal lobar degeneration. Brain 143 (9), 2844–2857. https://doi.org/10.1093/brain/awaa219.
Robinson, J.L., Richardson, H., Xie, S.X., Suh, E., Van Deerlin, V.M., Alfaro, B., et al., 2021. The development and convergence of co-pathologies in Alzheimer's disease. Brain 144, 953–962. https://doi.org/10.1093/brain/awaa438.
Rodriguez, R.D., Grinberg, L.T., 2015. Argyrophilic grain disease: An underestimated tauopathy. Dement Neuropsychol. 9, 2–8. https://doi.org/10.1590/S1980-57642015DN91000002.
Rodriguez, R.D., Suemoto, C.K., Molina, M., Nascimento, C.F., Leite, R.E., de Lucena Ferretti-Rebustini, R.E., et al., 2016. Argyrophilic grain disease: demographics, clinical, and neuropathological features from a large autopsy study. J. Neuropathol. Exp. Neurol. 75, 628–635. https://doi.org/10.1093/jnen/nlw034.
Rogaev, E.I., Sherrington, R., Rogaeva, E.A., Levesque, G., Ikeda, M., Liang, Y., et al., 1995. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature 376, 775–778. https://doi.org/10.1038/376775a0.
Rogalski, E., Gefen, T., Mao, Q., Connelly, M., Weintraub, S., Geula, C., et al., 2019. Cognitive trajectories and spectrum of neuropathology in SuperAgers: The first 10 cases. Hippocampus 29, 458–467. https://doi.org/10.1002/hipo.22828.
Rönnbäck, A., Nennesmo, I., Tuominen, H., Grueninger, F., Viitanen, M., Graff, C., 2014. Neuropathological characterization of two siblings carrying the MAPT S305S mutation demonstrates features resembling argyrophilic grain disease. Acta Neuropathol. 127, 297–298. https://doi.org/10.1007/s00401-013-1229-z.
Rosen, R.F., Fritz, J.J., Dooyema, J., Cintron, A.F., Hamaguchi, T., Lah, J.J., LeVine 3rd, H., et al., 2012. Exogenous seeding of cerebral β-amyloid deposition in βAPP-transgenic rats. J. Neurochem 120, 660–666. https://doi.org/10.1111/j.1471-4159.2011.07551.
Rossi, M., Candelise, N., Baiardi, S., Capellari, S., Giannini, G., Orrù, C.D., et al., 2020. Ultrasensitive RT-QuIC assay with high sensitivity and specificity for Lewy body-associated synucleinopathies. Acta Neuropathol. 140, 49–62. https://doi.org/10.1007/s00401-020-02160-8.
Roy, S., Wolman, L., 1969. Ultrastructural observations in Parkinsonism. Am. J. Pathol. 99, 39–44. https://doi.org/10.1002/path.1710990106.
Ruan, Z., Ikezu, T., 2019. Tau secretion. Adv. Exp. Med Biol. 1184, 123–135. https://doi.org/10.1016/j.nbd.2014.08.032.
Rusina, R., Csefalvay, Z., Kovacs, G.G., Keller, J., Javurkova, A., Matej, R., 2019. Globular glial tauopathy type I presenting as atypical progressive aphasia, with comorbid limbic-predominant age-related TDP-43 encephalopathy. Front Aging Neurosci. 11, 336. https://doi.org/10.3389/fnagi.2019.00336.
Sabbagh, M.N., Sandhu, S.S., Farlow, M.R., Vedders, L., Shill, H.A., Caviness, J.N., Connor, D.J., Sue, L., Adler, C.H., Beach, T.G., 2009. Correlation of clinical features with argyrophilic grains at autopsy. Alzheimer Dis. Assoc. Disord. 23, 229–233. https://doi.org/10.1097/WAD.0b013e318199d833.
Sacino, A.N., Brooks, M., McGarvey, N.H., McKinney, A.B., Thomas, M.A., Levites, Y., et al., 2014a. Induction of CNS α-synuclein pathology by fibrillar and non-amyloidogenic recombinant α-synuclein. Acta Neuropathol. Commun. 1, 38. https://doi.org/10.1186/2051-5960-1-38.
Sacino, A.N., Brooks, M., Thomas, M.A., McKinney, A.B., Lee, S., Regenhardt, R.W., et al., 2014b. Intramuscular injection of α-synuclein induces CNS α-synuclein pathology and a rapid onset motor phenotype in transgenic mice. Proc. Natl. Acad. Sci. 111, 10732–10737. https://doi.org/10.1073/pnas.13217.85111.
Sackmann, C., Sackmann, V., Hallbeck, M., 2020. TDP-43 Is efficiently transferred between neuron-like cells in a manner enhanced by preservation of its N-terminus but independent of extracellular vesicles. Front Neurosci. 14, 540. https://doi.org/10.3389/fnins.2020.00540.
Saijo, E., Groveman, B.R., Kraus, A., Metrick, M., Orrù, C.D., Hughson, A.G., et al., 2019. Ultrasensitive RT-QuIC seed amplification assays for disease-associated tau, α-synuclein, and prion aggregates. Methods Mol. Biol. 1873, 19–37. https://doi.org/10.1007/978-1-4939-8820-4_2.
Saijo, E., Metrick 2nd, M.A., Koga, S., Parchi, P., Litvan, I., Spina, S., et al., 2020. 4-Repeat tau seeds and templating subtypes as brain and CSF biomarkers of frontotemporal lobar degeneration. Acta Neuropathol. 139, 63–77. https://doi.org/10.1007/s00401-019-02080-2.
Saito, Y., Nakahara, K., Yamanouchi, H., Murayama, S., 2002. Severe involvement of ambient gyrus in dementia with grains. J. Neuropathol. Exp. Neurol. 61, 789–796. https://doi.org/10.1093/jnen/61.9.789.
Saito, Y., Kawashima, A., Ruberu, N.N., Fujiwara, H., Koyama, S., Sawabe, M., et al., 2003. Accumulation of phosphorylated α-synuclein in aging human brain. J. Neuropathol. Exp. Neurol. 62, 644–654. https://doi.org/10.1093/jnen/62.6.644.
Saito, Y., Ruberu, N.N., Sawabe, M., Arai, T., Tanaka, N., Kakuta, Y., et al., 2004. Staging of argyrophilic grains: an age-associated tauopathy. J. Neuropathol. Exp. Neurol. 63, 911–918. https://doi.org/10.1093/jnen/63.9.911.
Sajjadi, S.A., Bukhari, S., Scambray, K., Yan, R., Kawas, C., Montine, T.J., et al., 2022. Impact and risk factors of limbic predominant age-related TDP-43 encephalopathy neuropathologic change in an oldest old cohort. Neurology. Oct 27;10.1212/WNL.0000000000201345. doi: 10.1212/WNL.0000000000201345.
Sakurai, K., Tokumaru, A.M., Ikeda, T., Morimoto, S., Inui, S., Sumida, K., et al., 2019. Characteristic asymmetric limbic and anterior temporal atrophy in demented patients with pathologically confirmed argyrophilic grain disease. Neuroradiology 61, 1239–1249. https://doi.org/10.1007/s00234-019-02247-4.
Salminen, A., Kaarniranta, K., Haapasalo, A., Hiltunen, M., Soininen, H., Alafuzoff, I., 2012. Emerging role of p62/sequestosome-1 in the pathogenesis of Alzheimer's disease. Prog. Neurobiol. 96, 87–95. https://doi.org/10.1016/j.pneurobio.2011.11.005.

Sathe, G., Mangalaparthi, K.K., Jain, A., Darrow, J., Troncoso, J., Albert, M., et al., 2020. Multiplexed phosphoproteomic study of the brain in patients with Alzheimer's disease and age-matched cognitively healthy controls. OMICS 24, 2016–2227. https://doi.org/10.1089/omi.2019.0191.

Satoh, J., Tabunoki, H., Ishida, T., Saito, Y., Arima, K., 2013. Ubiquilin-1 immunoreactivity is concentrated on Hirano bodies and dystrophic neurites in Alzheimer's disease brains. Neuropathol. Appl. Neurobiol. 39, 817–830. https://doi.org/10.1111/nan.12036.

Saunders, A.M., Strittmatter, W.J., Schmechel, D., St George-Hyslop, P.H., Pericak-Vance, M.A., Joo, S.H., 1993. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43, 1467–1472. https://doi.org/10.1212/wnl.43.8.1467.

Schults, C.W., 2006. Lewy bodies. Proc. Nat. Acad. Sci. USA 103, 1661–1668. https://doi.org/10.1073/pnas.0509567103.

Schultz, C., Dehghani, F., Hubbard, G.B., Thal, D.R., Struckhoff, G., Braak, E., et al., 2000a. Filamentous tau pathology in nerve cells, astrocytes, and oligodendrocytes of aged baboons. J. Neuropathol. Exp. Neurol. 59, 39–52. https://doi.org/10.1093/jnen/59.1.39.

Schultz, C., Hubbard, G.B., Rüb, U., Braak, E., Braak, H., 2000b. Age-related progression of tau pathology in brains of baboons. Neurobiol. Aging 21, 905–912. https://doi.org/10.1016/s0197-4580(00)00176-7.

Schultz, C., Ghebremedhin, E., Del Tredici, K., Rüb, U., Braak, H., 2004. High prevalence of thorn-shaped astrocytes in the aged human medial temporal lobe. Neurobiol. Aging 25, 397–405. https://doi.org/10.1016/S0197-4580(03)00113-1.

Schwarz, A.J., Shcherbinin, S., Slieker, L.J., Risacher, S.L., Charil, A., Irizarry, M.C., et al., 2018. Topographic staging of tau positron emission tomography images. Alzheimers Dement 10, 221–231. https://doi.org/10.1016/j.dadm.2018.01.006.

Schweighauser, M., Arseni, D., Bacioglu, M., Huang, M., Lövestam, S., Shi, Y., et al., 2022. Age-dependent formation of TMEM106B amyloid filaments in human brains. Nature 605, 310–314. https://doi.org/10.1038/s41586-022-04650-z.

Scialò, C., Tran, T.H., Salzano, G., Novi, G., Caponnetto, C., Chiò, A., et al., 2020. TDP-43 real-time quaking induced conversion reaction optimization and detection of seeding activity in CSF of amyotrophic lateral sclerosis and frontotemporal dementia patients. Brain Commun. 2, fcaa142. https://doi.org/10.1093/braincomms/fcaa142.

Scott, I.S., Lowe, J.S., 2007. The ubiquitin-binding protein p62 identifies argyrophilic grain pathology with greater sensitivity than conventional silver stains. Acta Neuropathol. 113, 417–420. https://doi.org/10.1007/s00401-006-0165-6.

Seemiller, J., Bischof, G.N., Hoenig, M.C., Tahmasian, M., van Eimeren, T., Drzezga, A., et al., 2021. Indication of retrograde tau spreading along Braak stages and functional connectivity pathways. Eur. J. Nucl. Med Mol. Imaging 48, 2272–2282. https://doi.org/10.1007/s00259-020-05183-1.

Sennik, S., Schweizer, T.A., Fischer, C.E., Munoz, D.G., 2017. Risk factors and pathological substrates associated with agitation/aggression in Alzheimer's disease: a preliminary study using NACC data. J. Alzheimers Dis. 55, 1519–1528. https://doi.org/10.3233/JAD-160780.

Sepulveda-Falla, D., Chavez-Gutierrez, L., Portelius, E., Vélez, J.I., Dujardin, S., Barrera-Ocampo, A., et al., 2021. A multifactorial model of pathology for age of onset heterogeneity in familial Alzheimer's disease. Acta Neuropathol. 141, 217–233. https://doi.org/10.1007/s00401-020-02249-0.

Seshadri, S., Fitzpatrick, A.L., Ikram, M.A., DeStefano, A.L., Gudnason, V., Boada, M., et al., 2010. Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA 303, 1832–1840. https://doi.org/10.1001/jama.2010.574.

Seto, M., Weiner, R.L., Dumitrescu, L., Hohman, T.J., 2021. Protective genes and pathways in Alzheimer's disease: moving towards precision interventions. Mol. Neurodegener. 16, 29. https://doi.org/10.1186/s13024-021-00452-5.

Shahmoradian, S.H., Lewis, A.J., Genoud, C., Hench, J., Moors, T.E., Navarro, P.P., et al., 2019. Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes. Nat. Neurosci. 22, 1099–1109. https://doi.org/10.1038/s41593-019-0423-2.

Sherrington, R., Rogaev, E.I., Liang, Y., Rogaeva, E.A., Levesque, G., Ikeda, M., et al., 1995. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 375, 754–760. https://doi.org/10.1038/375754a0.

Shi, Y., Murzin, A.G., Falcon, B., Epstein, A., Machin, J., Tempest, P., et al., 2021a. Cryo-EM structures of tau filaments from Alzheimer's disease with PET ligand APN-1607. Acta Neuropathol. 141, 697–708. https://doi.org/10.1007/s00401-021-02294-3.

Shi, Y., Zhang, W., Yang, Y., Murzin, A.G., Falcon, B., Kotecha, A., et al., 2021b. Structure-based classification of tauopathies. Nature 598, 359–363. https://doi.org/10.1038/s41586-021-03911-7.

Sims, R., van der Lee, S.J., Naj, A.C., Bellenguez, C., Badarinarayan, N., Jakobsdottir, J., et al., 2017. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nat. Genet 49, 1373–1384. https://doi.org/10.1038/ng.3916.

Singh, B., Covelo, A., Martell-Martinez, H., Nanclares, C., Sherman, M.A., Okematti, E., et al., 2019. Tau is required for progressive synaptic and memory deficits in a transgenic mouse model of α-synucleinopathy. Acta Neuropathol. 138, 551–574. https://doi.org/10.1007/s00401-019-02032-w.

Smethurst, P., Sidle, K.C., Hardy, J., 2015. Review: Prion-like mechanisms of transactive response DNA binding protein of 43 kDa (TDP-43) in amyotrophic lateral sclerosis (ALS). Neuropathol. Appl. Neurobiol. 41, 578–597. https://doi.org/10.1111/nan.12206.

Smethurst, P., Newcombe, J., Troakes, C., Simone, R., Chen, Y.R., Patani, R., et al., 2016. In vitro prion-like behaviour of TDP-43 in ALS. Neurobiol. Dis. 96, 236–247. https://doi.org/10.1016/j.nbd.2016.08.007.

Smith, V.D., Bachstetter, A.D., Ighodaro, E., Roberts, K., Abner, E.L., Fardo, D.W., et al., 2018. Overlapping but distinct TDP-43 and tau pathologic patterns in aged hippocampi. Brain Pathol. 28, 264–273. https://doi.org/10.1111/bpa.12505.

Song, H.L., Shim, S., Kim, D.H., Won, S.H., Joo, S., Kim, S., et al., 2014. β-Amyloid is transmitted via neuronal connections along axonal membranes. Ann. Neurol. 75, 88–97. https://doi.org/10.1002/ana.24029.

Sorrentino, Z.A., Brooks, M.M.T., Hudson, V., Rutherford, N.J., Golde, T.E., Giasson, B.I., et al., 2017. Intrastriatal injection of α-synuclein can lead to widespread synucleinopathy independent of neuroanatomic connectivity. Mol. Neurodegener. 12, 40. https://doi.org/10.1186/s13024-017-0182-z.

Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., et al., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 280–292. https://doi.org/10.1016/j.jalz.2011.03.003.

Spillantini, M.G., Goedert, M., 2013. Tau pathology and neurodegeneration. Lancet Neurol. 12, 609–622. https://doi.org/10.1016/s0166-2236(98)01337-x.

Spillantini, M.G., Schmidt, M., Lee, V.M., Trojanowski, J.Q., Kaques, R., Goedert, M., 1997. α-synuclein in Lewy bodies. Nature 388, 839–840. https://doi.org/10.1038/42166.

Spillantini, M.G., Crowther, R.A., Jakes, R., Hasegawa, M., Goedert, M., 1998. α-synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. Proc. Natl. Acad. Sci. USA 95, 369–473. https://doi.org/10.1073/pnas.95.11.6469.

Spina, S., La Joie, R., Petersen, C., Nolan, A.L., Cuevas, D., Cosme, C., et al., 2021. Comorbid neuropathological diagnoses in early versus late-onset Alzheimer's disease. Brain 144, 2186–2198. https://doi.org/10.1093/brain/awab099.

Spires-Jones, T.L., Attems, J., Thal, D.R., 2017. Interactions of pathological proteins in neurodegenerative diseases. Acta Neuropathol. 134, 187–205. https://doi.org/10.1007/s00401-017-1709-7.

Standke, H.G., Kraus, A., 2022. Seed amplification and RT-QuIC assays to investigate protein seed structures and strains. Mar 8 Cell Tissue Res. https://doi.org/10.1007/s00441-022-03595-z.

Steffen, J., Krohn, M., Paarmann, K., Schwitlick, C., Brüning, T., Marreiros, R., et al., 2016. Revisiting rodent models: Octodon degus as Alzheimer's disease model? Acta Neuropathol. Commun. 4, 91. https://doi.org/10.1186/s40478-016-0363-y.

Stern, Y., 2012. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 11, 1006–1012. https://doi.org/10.1016/S1474-4422(12)70191-6.

Stopschinski, B.E., Del Tredici, K., Estill-Terpack, S.J., Ghebremdehin, E., Yu, F.F., Braak, H., et al., 2021. Anatomic survey of seeding in Alzheimer's disease brains reveals unexpected patterns. Acta Neuropathol. Commun. 9, 164. https://doi.org/10.1186/s40478-021-01255-x.

Strittmatter, W.J., Saunders, A.M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G.S., 1993. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc. Natl. Acad. Sci. USA 90, 1977–1981. https://doi.org/10.1073/pnas.90.5.1977.

Sulzer, D., Surmeier, D.J., 2013. Neuronal vulnerability, pathogenesis, and Parkinson's disease. Mov. Disord. 28, 41–50. https://doi.org/10.1002/mds.25095.

Takaichi, Y., Chambers, J.K., Takahashi, K., Soeda, Y., Koike, R., Katsumata, E., et al., 2021. Amyloid β and tau pathology in brains of aged pinniped species (sea lion, seal, and walrus). Amyloid β and tau pathology in brains of aged pinniped species (sea lion, seal, and walrus). Acta Neuropathol. Commun. 9, 10. https://doi.org/10.1186/s40478-020-01104-3.

Takao, M., Hirose, N., Arai, Y., Mihara, B., Mimura, M., 2016. Neuropathology of supercentenarians – four autopsy case studies. Acta Neuropathol. Commun. 4, 97. https://doi.org/10.1186/s40478-016-0368-6.

Takeuchi, H., Iba, M., Inoue, H., Higuchi, M., Takao, K., Tsukita, K., et al., 2011. P301S mutant human tau transgenic mice manifest early symptoms of human tauopathies with dementia and altered sensorimotor gating. PLoS One 6, e21050. https://doi.org/10.1371/journal.pone.0021050.

Tan, H., Wu, Z., Wang, H., Bai, B., Li, Y., Wang, X., Zhai, B., et al., 2015. Refined phosphopeptide enrichment by phosphate additive and the analysis of human brain phosphoproteome. Proteomics 15, 500–507. https://doi.org/10.1002/pmic.201400171.

Tansey, K.E., Cameron, D., Hill, M.J., 2018. Genetic risk for Alzheimer's disease is concentrated in specific macrophage and microglial transcriptional networks. Genome Med 10, 14. https://doi.org/10.1186/s13073-018-0523-8.

Tarutani, A., Hasegawa, M., 2019. Prion-like propagation of α-synuclein in neurodegenerative diseases. Prog. Mol. Biol. Transl. Sci. 168, 323–348. https://doi.org/10.1016/bs.pmbts.2019.07.005.

Tavana, J.P., Rosene, M., Jensen, N.O., Ridge, P.G., Kauwe, J.S., Karch, C.M., 2018. RAB10 an Alzheimer's disease resilience locus and potential drug target. Clin. Inter. Aging 14, 73–79. https://doi.org/10.2147/CIA.S159148.

Tennant, J.M., Henderson, D.M., Wisniewski, T.M., Hoover, E.A., 2020. RT-QuIC detection of tauopathies using full-length tau substrates. Prion 14, 249–256. https://doi.org/10.1080/19336896.2020.1832946.

Teravskis, P.J., Covelo, A., Miller, E.C., Singh, B., Martell-Martinez, H.A., Benneyworth, M.A., et al., 2018. A53T mutant alpha-synuclein induces Tau-dependent postsynaptic impairment independently of neurodegenerative changes. J. Neurosci. 38, 9754–9767. https://doi.org/10.1523/JNEUR.OSCI.0344-18.2018.

Tesi, N., van der Lee, S.J., Hulsman, M., Jansen, I.E., Stringa, N., van Schoor, N.M., et al., 2020. Immune response and endocytosis pathways are associated with the resilience against Alzheimer's disease. Transl. Psychiatry 10, 332. https://doi.org/10.1038/s41398-020-01018-7.

Thal, D.R., Rüb, U., Orantes, M., Braak, H., 2002. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. Neurology 58, 1791–1800. https://doi.org/10.1212/WNL.58.12.1791.

Thal, D.R., Schultz, C., Botez, G., Del Tredici, K., Mrak, R.E., Griffin, W.S., et al., 2005. The impact of argyrophilic grain disease on the development of dementia and its relationship to concurrent Alzheimer's disease-related pathology. Neuropathol. Appl. Neurobiol. 31, 270–279. https://doi.org/10.1111/j.1365-2990.2005.00635.x.

Thal, D.R., Del Tredici, K., Ludolph, A.C., Hoozemans, J.J., Rozemuller, A.J., Braak, H., et al., 2011. Stages of granulovacuolar degeneration: their relation to Alzheimer's disease and chronic stress response. Acta Neuropathol. 122, 577–589. https://doi.org/10.1007/s00401-011-0871-6.

Thomzig, A., Wagenführ, K., Pinder, P., Joncic, M., Schulz-Schaeffer, W.J., Beekes, M., 2021. Transmissible α-synuclein seeding activity in brain and stomach of patients with Parkinson's disease. Acta Neuropathol. 141, 861–879. https://doi.org/10.1007/s00401-021-02312-4.

Tofaris, G.K., 2022. Initiation and progression of α-synuclein pathology in Parkinson's disease. Cell Mol. Life Sci. 79, 210. https://doi.org/10.1007/s00018-022-04240-2.

Togo, T., Cookson, N., Dickson, D.W., 2002a. Argyrophilic grain disease: neuropathology, frequency in a dementia brain bank and lack of relationship with apolipoprotein E. Brain Pathol. 12, 45–52. https://doi.org/10.1111/j.1750-3639.2002.tb00421.x.

Togo, T., Sahara, N., Yen, S.H., Cookson, N., Ishizawa, T., Hutton, M., et al., 2002b. Argyrophilic grain disease is a sporadic 4-repeat tauopathy. J. Neuropathol. Exp. Neurol. 61, 547–556. https://doi.org/10.1093/jnen/61.6.547.

Tolnay, M., Clavaguera, F., 2004. Argyrophilic grain disease: a late-onset dementia with distinctive features among tauopathies. Neuropathology 24, 269–283. https://doi.org/10.1111/j.1440-1789.2004.00591.x.

Tolnay, M., Probst, A., 1998. Ballooned neurons expressing αB-crystallin as a constant feature of the amygdala in argyrophilic grain disease. Neurosci. Lett. 246, 165–168. https://doi.org/10.1016/s0304-3940(98)00250-x.

Tolnay, M., Probst, A., 2008. Argyrophilic grain disease. Handb. Clin. Neurol. 89, 553–563. https://doi.org/10.1016/S0072-9752(07)01251-1.

Tolnay, M., Spillantini, M.G., Goedert, M., Ulrich, J., Langui, D., Probst, A., 1997a. Argyrophilic grain disease: widespread hyperphosphorylation of tau protein in limbic neurons. Acta Neuropathol. 93, 477–484. https://doi.org/10.1007/s004010050642.

Tolnay, M., Schwietert, M., Monsch, A.U., Staehelin, H.B., Langui, D., Probst, A., 1997b. Argyrophilic grain disease: distribution of grains in patients with and without dementia. Acta Neuropathol. 94, 353–358. https://doi.org/10.1007/s004010050718.

Tolnay, M., Mistl, C., Ipsen, S., Probst, A., 1998. Argyrophilic grains of Braak: occurrence in dendrites of neurons containing hyperphosphorylated tau protein. Neuropathol. Appl. Neurobiol. 24, 53–59. https://doi.org/10.1046/j.1365-2990.1998.00090.x.

Tolnay, M., Sergeant, N., Ghestem, A., Chalbot, S., De Vos, R.A., Jansen Steur, E.N., et al., 2002. Argyrophilic grain disease and Alzheimer's disease are distinguished by their different distribution of tau protein isoforms. Acta Neuropathol. 104, 425–434. https://doi.org/10.1007/s00401-002-0591-z.

Tomé, S.O., Vandenberghe, R., Ospitalieri, S., Van Schoor, E., Tousseyn, T., Otto, M., et al., 2020. Distinct molecular patterns of TDP-43 pathology in Alzheimer's disease: relationship with clinical phenotypes. Acta Neuropathol. Commun. 8, 61. https://doi.org/10.1186/s40478-020-00934-5.

Triarhou, L.C., 2017. The comparative neurology of neocortical gyration and the quest for functional specialization. Front Syst. Neurosci. 11, 96. https://doi.org/10.3389/fnsys.2017.00096.

Triplett, J.C., Swomley, A.M., Cai, J., Klein, J.B., Butterfield, D.A., 2016. Quantitative phosphoproteomic analyses of the inferior parietal lobule from three different pathological stages of Alzheimer's disease. J. Alzheimer's Dis. 49, 45–62. https://doi.org/10.3233/JAD-150417.

Troncoso, J.C., Kawas, C.H., Chang, C.K., Folstein, M.F., J C Hedreen, J.C., 1996. Lack of association of the apoE4 allele with hippocampal sclerosis dementia. Neurosci. Lett. 204, 138–140. https://doi.org/10.1016/0304-3940(96)12331-4.

Tsartsalis, S., Xekardaki, A., Hof, P.R., Kövari, E., Bouras, C., 2018. Early Alzheimer-type lesions in cognitively normal subjects. Neurobiol. Aging 62, 34–44. https://doi.org/10.1016/j.neurobiolaging.2017.10.002.

Tsuang, D.W., Wilson, R.K., Lopez, O.L., Luedecking-Zimmer, E.K., Leverenz, J.B., DeKosky, S.T., et al., 2005. Genetic association between the APOEε4 allele and Lewy bodies in Alzheimer disease. Neurology 64, 509–513. https://doi.org/10.1212/01.WNL.0000150892.81839.D1.

Tziortzouda, P., Van Den Bosch, L., Hirth, F., 2021. Triad of TDP43 control in neurodegeneration: autoregulation, localization and aggregation. Nat. Rev. Neurosci. 22, 197–208. https://doi.org/10.1038/s41583-021-00431-1.

Uchihara, T., Giasson, B.I., 2016. Propagation of alpha-synuclein pathology: hypotheses, discoveries, and yet unresolved questions from experimental and human brain studies. Acta Neuropathol. 131, 49–73. https://doi.org/10.1007/s00401-015-1485-1.

Uchihara, T., Endo, K., Kondo, H., Okabayashi, S., Shimozawa, N., Yasutomi, Y., et al., 2016. Tau pathology in aged cynomolgus monkeys is progressive supranuclear palsy/corticobasal degeneration, but not Alzheimer disease-like. Ultrastructural mapping of tau by EDX. Acta Neuropathol. Commun. 4, 118. https://doi.org/10.1186/s40478-016-0385-5.

Uchikado, H., Lin, W.L., DeLucia, M.W., Dickson, D.W., 2006. Alzheimer disease with amygdala lewy bodies: A distinct form of alpha-synucleinopathy. J. Neuropathol. Exp. Neurol. 65, 685–697. https://doi.org/10.1097/01.jnen.0000225908.90052.07.

Uchino, A., Takao, M., Hatsuta, H., Sumikura, H., Nakano, Y., Nogami, A., et al., 2015. Incidence and extent of TDP-43 accumulation in aging human brain. Acta Neuropathol. Commun. 3, 35. https://doi.org/10.1186/s40478-015-0215-1.

Uemura, M.T., Robinson, J.L., Cousins, K.A.Q., Tropea, T.F., Kargilis, D.C., McBride, J.D., et al., 2022. Distinct characteristics of limbic-predominant age-related TDP-43 encephalopathy in Lewy body disease. Acta Neuropathol. 143, 15–31. https://doi.org/10.1007/s00401-021-02383-3.

Uversky, V.N., 2007. Neuropathology, biochemistry, and biophysics of synuclein aggregation. J. Neurochem 103, 17–37. https://doi.org/10.1111/j.1471-4159.2007.04764.x.

Vaquer-Alicea, J., Diamond, M.I., Joachimiak, L.A., 2021. Tau strains shape disease. Acta Neuropathol. 142, 57–71. https://doi.org/10.1007/s00401-021-02301-7.

Vasili, E., Dominguez-Meijide, A., Outeiro, T.F., 2019. Spreading of α-synuclein and tau: a systematic comparison of the mechanisms involved. Front Mol. Neurosci. 12, 107. https://doi.org/10.3389/fnmol.2019.00107.

Vatsavayi, A.V., Kofler, J., Demichele-Sweet, M.A., Murray, P.S., Lopez, O.L., Sweet, R. A., 2014. TAR DNA-binding protein 43 pathology in Alzheimer's disease with psychosis. Int Psychogeriatr. 26, 987–994. https://doi.org/10.1017/S1041610214000246.

Vautheny, A., Duwat, C., Aurégan, G., Joséphine, C., Hérard, A.S., Jan, C., et al., 2021. THY-Tau22 mouse model accumulates more tauopathy at late stage of the disease in response to microglia deactivation through TREM2 deficiency. Neurobiol. Dis. 155, 105398 https://doi.org/10.1016/j.nbd.2021.105398.

Velásquez, E., Szeitz, B., Gil, J., Rodriguez, J., Palkovits, M., Renner, É., Hortobágyi, T., et al., 2021. Topological dissection of proteomic changes linked to the limbic stage of Alzheimer's disease. Front Immunol. 12, 750665 https://doi.org/10.3389/fimmu.2021.750665.

Vergara, C., Houben, S., Suain, V., Yilmaz, Z., De Decker, R., Vanden Dries, V., et al., 2019. Amyloid-β pathology enhances pathological fibrillary tau seeding induced by Alzheimer PHF in vivo. Acta Neuropathol. 137, 397–412. https://doi.org/10.1007/s00401-018-1953-5.

Vitek, M.P., Araujo, J.A., Fossel, M., Greenberg, B.D., Howell, G.R., Rizzo, S.J.S., et al., 2021. Translational animal models for Alzheimer's disease: An Alzheimer's Association business consortium think tank. Alzheimers Dement 6, e12114. https://doi.org/10.1002/trc2.12114.

Volpicelli-Daley, L., Brundin, P., 2018. Prion-like propagation of pathology in Parkinson disease. Handb. Clin. Neurol. 153, 321–335. https://doi.org/10.1016/B978-0-444-63945-5.00017-9.

Wakabayashi, K., Matsumoto, K., Takayama, K., Yoshimoto, M., Takahashi, H., 1997. NACP, a presynaptic protein, immunoreactivity in Lewy bodies in Parkinson's disease. Neurosci. Lett. 249, 180–182. https://doi.org/10.1016/s0304-3940(97)00891-4.

Wakabayashi, K., Tanji, K., Mori, F., Takahashi, H., 2007. The Lewy body in Parkinson's disease: molecules implicated in the formation and degradation of α-synuclein aggregates. Neuropathology 27, 494–506. https://doi.org/10.1111/j.1440-1789.2007.00803.x.

Walker, L.C., Callahan, M.J., Bian, F., Durham, R.A., Roher, A.E., Lipinski, W.J., 2002. Exogenous induction of cerebral beta-amyloidosis in betaAPP-transgenic mice. Peptides 23, 1241–1247. https://doi.org/10.1016/s0196-9781(02)00059-1.

Walker, M.C., 2015. Hippocampal sclerosis: causes and prevention. Semin Neurol. 35, 193–200. https://doi.org/10.1055/s-0035-1552618.

Wang, J.Z., Xia, Y.Y., Grundke-Iqbal, I., Iqbal, K., 2013. Abnormal hyperphosphorylation of tau: sites, regulation, and molecular mechanism of neurofibrillary degeneration. J. Alzheimers Dis. 33, S123–S139. https://doi.org/10.3233/JAD-2012-129031.

Wang, S.H., Guo, Y., Ervin, J.F., Lusk, J.B., Luo, S., 2022. Neuropathological associations of limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) differ between the oldest-old and younger-old. Acta Neuropathol. 144, 45–57. https://doi.org/10.1007/s00401-022-02432-5.

Wang, Y., Balaji, V., Kaniyappan, S., Krüger, L., Irsen, S., Tepper, K., et al., 2017. The release and trans-synaptic transmission of tau via exosomes. Mol. Neurodegener. 12, 5. https://doi.org/10.1186/s13024-016-0143-y.

Watts, J.C., Giles, K., Oehler, A., Middleton, L., Dexter, D.T., Gentleman, S.M., et al., 2013. Transmission of multiple system atrophy prions to transgenic mice. Proc. Natl. Acad. Sci. USA 110, 19555–19560. https://doi.org/10.1073/pnas.1318268110.

Wauters, E., Van Mossevelde, S.V., Van der Zee, J., Cruts, M., Van Broeckhoven, C.V., 2017. Modifiers of GRN-associated frontotemporal lobar degeneration. Trends Mol. Med 23, 962–979. https://doi.org/10.1016/j.molmed.2017.08.004.

Waxman, E.A., Giasson, B.I., 2011. Induction of intracellular tau aggregation is promoted by α-synuclein seeds and provides novel insights into the hyperphosphorylation of tau. J. Neurosci. 31, 7604–7618. https://doi.org/10.1523/JNEUROSCI.0297-11.2011.

Weaver, C.L., Espinoza, M., Kress, Y., Davies, P., 2000. Conformational change as one of the earliest alterations of tau in Alzheimer's disease. Neurobiol. Aging 21, 719–727. https://doi.org/10.1016/s0197-4580(00)00157-3.

Weisenbach, S.L., Kim, J., Hammers, D., Konopacki, K., Koppelmans, V., 2019. Linking late life depression and Alzheimer's disease: mechanisms and resilience. Curr. Behav. Neurosci. Rep. 6, 103–112. https://doi.org/10.1007/s40473-019-00180-7.

Weng, F.L., He, L., 2021. Disrupted ubiquitin proteasome system underlying tau accumulation in Alzheimer's disease. Neurobiol. Aging 99, 79–85. https://doi.org/10.1016/j.neurobiolaging.2020.11.015.

Wennberg, A.M., Whitwell, J.L., Tosakulwong, N., Weigand, S.D., Murray, M.E., Machulda, M.M., et al., 2019. The influence of tau, amyloid, alpha-synuclein, TDP-43, and vascular pathology in clinically normal elderly individuals. Neurobiol. Aging 77, 26–36. https://doi.org/10.1016/j.neurobiolaging.2019.01.008.

Wesseling, H., Mair, W., Kumar, M., Schlaffner, C.N., Tang, S., Beerepoot, P., et al., 2020. Tau PTM profiles identify patient heterogeneity and stages of Alzheimer's disease. Cell 183, 1699–1713.e13. https://doi.org/10.1016/j.cell.2020.10.029.

Wharton, S.B., Minett, T., Drew, D., Forster, G., Matthews, F., Brayne, C., et al., 2016. Epidemiological pathology of Tau in the ageing brain: application of staging for

neuropil threads (BrainNet Europe protocol) to the MRC cognitive function and ageing brain study. Acta Neuropathol. Commun. 4, 11. https://doi.org/10.1186/s40478-016-0275-x.
Williams, T., Sorrentino, Z., Weinrich, M., Giasson, B.I., Chakrabarty, P., 2020. Differential cross-seeding properties of tau and α-synuclein in mouse models of tauopathy and synucleinopathy. Brain Commun. 2, fcaa090. https://doi.org/10.1093/braincomms/fcaa090.
Wills, J., Credle, J., Haggerty, T., Lee, J.-H., Oaks, A.W., Sidhu, A., 2011. Tauopathic changes in the striatum of A53T α-Synuclein mutant mouse model of Parkinson's disease. PLoS ONE 6, e17953. https://doi.org/10.1371/journal.pone.00179.53.
Wingo, A.P., Dammer, E.B., Breen, M.S., Logsdon, B.A., Duong, D.M., Troncosco, J.C., et al., 2019. Large-scale proteomic analysis of human brain identifies proteins associated with cognitive trajectory in advanced age. Nat. Commun. 10, 1619. https://doi.org/10.1038/s41467-019-09613-z.
Wingo, A.P., Liu, Y., Gerasimov, E.S., Gockley, J., Logsdon, B.A., Duong, D.M., et al., 2021. Integrating human brain proteomes with genome-wide association data implicates new proteins in Alzheimer's disease pathogenesis. Nat. Genet 53, 143–146. https://doi.org/10.1038/s41588-020-00773-z.
Wischik, C.M., Novak, M., Edwards, P.C., Klug, A., Tichelaar, W., Crowther, R.A., 1988. Structural characterization of the core of the paired helical filament of Alzheimer disease. Proc. Natl. Acad. Sci. USA 85, 4884–4888. https://doi.org/10.1073/pnas.85.13.4884.
Wu, J.W., Herman, M., Liu, L., Simoes, S., Acker, C.M., Figueroa, H., et al., 2013. Small misfolded tau species are internalized via bulk endocytosis and anterogradely and retrogradely transported in neurons. J. Biol. Chem. 288, 1856–1870. https://doi.org/10.1074/jbc.M112.394528.
Wu, J.W., Hussaini, S.A., Bastille, I.M., Rodriguez, G.A., Mrejeru, A., Rilett, K., et al., 2016. Neuronal activity enhances tau propagation and tau pathology in vivo. Nat. Neurosci. 19, 1085–1092. https://doi.org/10.1038/nn.4328.
Wu, Q., Shaikh, M.A., Meymand, E.S., Zhang, B., Luk, K.C., Trojanowski, J.Q., et al., 2020. Neuronal activity modulates alpha-synuclein aggregation and spreading in organotypic brain slice cultures and in vivo. Acta Neuropathol. 140, 831–849. https://doi.org/10.1007/s00401-020-02227-6.
Wurm, R., Klotz, S., Rahimi, J., Katzenschlager, R., Lindeck-Pozza, E., Regelsberger, G., et al., 2020. Argyrophilic grain disease in individuals younger than 75 years: clinical variability in an under-recognized limbic tauopathy. Eur. J. Neurol. 27, 1856–1866. https://doi.org/10.1111/ene.14321.
Xia, Q., Liao, L., Cheng, D., Duong, D.M., Gearing, M., Lah, J.J., et al., 2008. Proteomic identification of novel proteins associated with Lewy bodies. Front Biosci. 13, 3850–3856. https://doi.org/10.2741/2973.
Xuereb, J.H., Brayne, C., Dufouil, C., Gertz, H., Wischik, C., Harrington, C., et al., 2000. Neuropathological findings in the very old. Results from the first 101 brains of a population-based longitudinal study of dementing disorders. Ann. N. Y Acad. Sci. 903, 490–496. https://doi.org/10.1111/j.1749-6632.2000.tb06404.x.
Yamada, K., Holth, J.K., Liao, F., Stewart, F.R., Mahan, T.E., Jiang, H., et al., 2014. Neuronal activity regulates extracellular tau in vivo. J. Exp. Med 211, 387–393. https://doi.org/10.1084/jem.20131685.
Yang, H.S., Yu, L., White, C.C., Chibnik, L.B., Chhatwal, J.P., Sperling, R.A., et al., 2018. Evaluation of TDP-43 proteinopathy and hippocampal sclerosis in relation to APOE epsilon4 haplotype status: a community-based cohort study. Lancet Neurol. 17, 773–781. https://doi.org/10.1016/S1474-4422(18)30251-5.
Yang, Y., Arseni, D., Zhang, W., Huang, M., Lövestam, S., Schweighauser, M., et al., 2022a. Cryo-EM structures of amyloid-β 42 filaments from human brains. Science 375, 167–172. https://doi.org/10.1126/science.abm7285.
Yang, Y., Shi, Y., Schweighauser, M., Zhang, X., Kotecha, A., Murzin, A.G., et al., 2022b. Structures of α-synuclein filaments from human brains with Lewy pathology. Nature 610, 791–795. https://doi.org/10.1038/s41586-022-05319-3.
Yokota, O., Davidson, Y., Bigio, E.H., Ishizu, H., Terada, S., Arai, T., et al., 2010. Phosphorylated TDP-43 pathology and hippocampal sclerosis in progressive supranuclear palsy. Acta Neuropathol. 120, 55–66. https://doi.org/10.1007/s00401-010-0702-1.
Yokota, O., Miki, T., Ikeda, C., Nagao, S., Takenoshita, S., Ishizu, H., et al., 2018. Neuropathological comorbidity associated with argyrophilic grain disease. Neuropathology 38, 82–97. https://doi.org/10.1111/neup.12429.
Yoo, D., Bang, J.I., Ahn, C., Nyaga, V.N., Kim, Y.E., Kang, M.J., et al., 2022. Diagnostic value of α-synuclein seeding amplification assays in α-synucleinopathies: A systematic review and meta-analysis. Park. Relat. Disord. 104, 99–109. https://doi.org/10.1016/j.parkreldis.2022.10.007.
Yoshiyama, Y., Higuchi, M., Zhang, B., Huang, S.M., Iwata, N., Saido, T.C., et al., 2007. Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. Neuron 53, 337–351. https://doi.org/10.1016/j.neuron.2007.01.010.
Yu, C.H., Song, G.S., Yhee, J.Y., Kim, J.H., Im, K.S., Nho, W.G., et al., 2011. Histopathological and immunohistochemical comparison of the brain of human patients with Alzheimer's disease and the brain of aged dogs with cognitive dysfunction. J. Comp. Pathol. 145, 45–58. https://doi.org/10.1016/j.jcpa.2010.11.004.
Yu, L., Petyuk, V.A., Gaiteri, C., Mostafavi, S., Young-Pearse, T., Shah, R.C., et al., 2018. Targeted brain proteomics uncover multiple pathways to Alzheimer's dementia. Ann. Neurol. 84, 78–88. https://doi.org/10.1002/ana.25266.
Zarow, C., Weiner, M.W., Ellis, W.G., Chui, H.C., 2012. Prevalence, laterality, and comorbidity of hippocampal sclerosis in an autopsy sample. Brain Behav. 2, 435–442. https://doi.org/10.1002/brb3.66.
Zhang, K., Sun, Z., Chen, X., Zhang, Y., Guo, A., Zhang, Y., 2021a. Intercellular transport of Tau protein and β-amyloid mediated by tunneling nanotubes. Am. J. Transl. Res. 13, 12509–12522.
Zhang, X., Sun, B., Wang, X., Lu, H., Shao, F., Rozemuller, A.J.M., et al., 2019. Phosphorylated TDP-43 staging of primary age-related tauopathy. Neurosci. Bull. 35, 183–192. https://doi.org/10.1007/s12264-018-0300-0.
Zhang, X., Alshakhshir, N., Zhao, L., 2021b. Glycolytic metabolism, brain resilience, and Alzheimer's disease. Front Neurosci. 15, 662242 https://doi.org/10.3389/fnins.2021.662242.
Zhao, J., Wu, H., Tang, X.Q., 2021. Tau internalization: A complex step in tau propagation. Ageing Res. Rev. 67, 101272 https://doi.org/10.1016/j.arr.2021.101272.
Zhu, B., Liu, Y., Hwang, S., Archuleta, K., Huang, H., Campos, A., et al., 2022. Trem2 deletion enhances tau dispersion and pathology through microglia exosomes. Mol. Neurodegener. 17, 58. https://doi.org/10.1186/s13024-022-00562-8.
Zhukareva, V., Shah, K., Uryu, K., Braak, H., Del Tredici, K., Sundarraj, S., et al., 2002. Biochemical analysis of tau proteins in argyrophilic grain disease, Alzheimer's disease, and Pick's disease: a comparative study. Am. J. Pathol. 161, 1135–1141. https://doi.org/10.1016/s0002-9440(10)64390-8.
Zilka, N., Filipcik, P., Koson, P., Fialova, L., Skrabana, R., Zilkova, M., et al., 2006. Truncated tau from sporadic Alzheimer's disease suffices to drive neurofibrillary degeneration in vivo. FEBS Lett. 580, 3582–3588. https://doi.org/10.1016/j.febslet.2006.05.029.