Evolving concepts in progressive supranuclear palsy and other 4-repeat tauopathies

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Abstract | Tauopathies are classified according to whether tau deposits predominantly contain tau isoforms with three or four repeats of the microtubule-binding domain. Those in which four-repeat (4R) tau predominates are known as 4R-tauopathies, and include progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, globular glial tauopathies and conditions associated with specific *MAPT* mutations. In these diseases, 4R-tau deposits are found in various cell types and anatomical regions of the brain and the conditions share pathological, pathophysiological and clinical characteristics. Despite being considered 'prototype' tauopathies and, therefore, ideal for studying neuroprotective agents, 4R-tauopathies are still severe and untreatable diseases for which no validated biomarkers exist. However, advances in research have addressed the issues of phenotypic overlap, early clinical diagnosis, pathophysiology and identification of biomarkers, setting a road map towards development of treatments. New clinical criteria have been developed and large cohorts with early disease are being followed up in prospective studies. New clinical trial readouts are emerging and biomarker research is focused on molecular pathways that have been identified. Lessons learned from failed trials of neuroprotective drugs are being used to design new trials. In this Review, we present an overview of the latest research in 4R-tauopathies, with a focus on progressive supranuclear palsy, and discuss how current evidence dictates ongoing and future research goals.

Tauopathies are a group of neurodegenerative diseases characterized by the deposition of abnormal forms of microtubule-associated protein tau, more commonly referred to as tau, in brain cells[1]. The term was first used in 1997 to describe a syndrome of dementia and parkinsonism, which was subsequently attributed to a mutation in the *MAPT* gene, which encodes tau[2]. Tauopathies are currently classified on the basis of their histopathological features and whether the tau isoform that predominates in the pathological aggregates contains three repeats of the microtubule-binding domain (3R-tau) or four repeats (4R-tau)[3]. Progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), globular glial tauopathies (GGT) and conditions associated with specific *MAPT* mutations are characterized by the predominance of 4R-tau deposition in various cell types and anatomical regions of the brain, and are therefore referred to as 4R-tauopathies. Pathology with 4R-tau immunoreactivity has also been described in various conditions that are not classified as 4R-tauopathies, such as ageing-related tau astrogliopathy (ARTAG), tau immunoreactive pathology reported in geographical clusters[1,4], and diseases unrelated to the *MAPT* gene[5] (BOX 1).

Without exception, 4R-tauopathies are severe, untreatable diseases for which no validated biomarker exists[6]. However, these conditions have come under the spotlight of scientific research because their pathology is relatively 'pure', which facilitates testing of potential treatments[7]. Here, we review evolving concepts in 4R-tauopathies, with a focus on PSP, and discuss how these concepts could be helpful in the identification of neuroprotective treatments.

Tau physiology and pathophysiology

Structure and function

Tau was first described as a protein that promotes tubulin polymerization into microtubules in vitro[8]. In the adult human brain, six isoforms of tau are expressed[9]. These isoforms are classified as 3R-tau or 4R-tau on the basis of whether they contain three or four repeats of the microtubule-binding domain in the carboxy-terminal

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Key points

- Several lines of evidence substantiate the concept that 4-repeat tauopathies form an aetiologically coherent disease continuum, including progressive supranuclear palsy, corticobasal degeneration, globular glial tauopathy and argyrophilic grain disease.
- Neurobiological, neuroimaging and neuropathological data suggest that the spread of 4-repeat tau isoforms can induce neurodegeneration and propagation of tau pathology in a unifying disease mechanism.
- 4-repeat tauopathies are increasingly recognized in clinical settings by their characteristic clinical manifestations, spanning from predominantly movement disorders and overlap syndromes to predominantly cognitive syndromes.
- Biomarkers, such as tau PET ligands, are being developed to substantiate the diagnosis of 4-repeat tauopathies in living patients.
- Currently, symptomatic therapeutic options for 4-repeat tauopathies are limited, but the available options must not be overlooked.
- A broad spectrum of 4-repeat tau treatments are currently being developed, making the field of 4-repeat tauopathies an important testbed for precision medicine in neurodegenerative disorders.

part of the molecule. They are further classified on the basis of whether they include no inserts, or one or two inserts (29 or 58 amino acids) in the amino-terminal region, and the isoforms are referred to as 0N, 1N and 2N. The six isoforms result from alternative splicing of exons two and three (which encode the N-terminal inserts) and of exon 10 (which encodes the second of the four possible microtubule-binding domains) in the *MAPT* gene. No isoforms include the insert encoded by exon 3 without that encoded by exon 2. Thus, the six isoforms are: 0N3R, 1N3R, 2N3R, 0N4R, 1N4R and 2N4R[10]. In the healthy adult brain, levels of 3R and 4R isoforms are balanced, but in primary tauopathies, either 3R-tau or 4R-tau predominates in the pathological lesions[11,12].

Tau is mainly present in axons and its most studied function is microtubule stabilization, which promotes the integrity of neuronal processes[13]. Tau also has a regulatory effect on axonal transport[14]. The N-terminal, C-terminal and the proline-rich regions all contribute to the regulation of tau's function[15], influence the distribution of tau in cell compartments, and affect its interactions with other proteins and microtubules. In addition to its role in microtubule stabilization, tau might have other functions in other parts of the neuron, such as in dendrites and nuclei. For example, some evidence suggests that tau is involved in synaptic plasticity, promoting the integrity of nucleic acids in the nucleus and cytoplasm, export of iron from neurons, excitotoxicity and neurogenesis[10].

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Post-translational modification of tau is the main mechanism by which its function is regulated, and phosphorylation is the most widely studied of these post-translational modifications. Under normal conditions, tau is phosphorylated at various residues[16] and the degree of phosphorylation is determined by the net activity of tau kinases and phosphatases. The extent of tau phosphorylation influences its propensity to interact with microtubules; greater phosphorylation increases the dissociation of tau from microtubules[16].

An array of additional post-translational modifications can influence the phosphorylation profile of tau, compete with phosphorylation or with each other, and exert independent effects. For example, *O*-GlcNAcylation — the attachment of β-*N*-acetylglucosamine — of tau is usually associated with a decrease in phosphorylation[17,18]. Acetylation of tau also occurs and can promote or jeopardize tau function through different mechanisms at different sites[19,20]. Methylation has also been detected in normal tau. Tau methylation has an indirect effect on tau phosphorylation and might, therefore, have an important role in modulating the propensity of tau to aggregate[21].

Mechanisms of tau-related neurodegeneration

The exact mechanisms that underlie tau-related neurodegeneration have not been elucidated. However, two broad processes are thought to be central to the pathogenesis: the failure of tau in its normal function (loss of function) and the acquisition of abnormal tau functions (gain of function). Epidemiological and genetic studies have provided insights into the exact pathophysiological processes involved.

Most pathogenic mutations in *MAPT* cluster in the exons that encode the four repeats (exons 9–12) and in the intron that follows exon 10 (REF.[22]). The exonic mutations interfere with the ability of tau to bind to microtubules. Intronic mutations lead to overproduction of 4R-tau isoforms relative to 3R-tau. Mutations in exon 10 can have both effects[22]. In addition, rare *MAPT* duplications have been associated with 4R-tau pathology, suggesting that tau overexpression is an additional pathogenic factor[23].

In vitro experiments have shown that inclusion of exons 2 and 10 increases the potential for tau to aggregate, whereas inclusion of exon 3 decreases this potential[24]. However, the inclusion of exon 10 has the greatest influence, as this increases the ratio of 4R-tau to 3R-tau and the propensity for aggregation is greatest when 4R-tau predominates[24,25]. In mice that express human tau, a higher ratio of 4R-tau to 3R-tau is associated with more phosphorylation and aggregation, lower tau solubility, and a greater degree of dysfunction[26]. Unexpectedly, 4R-tau stabilizes microtubules to a greater extent than 3R-tau, suggesting that both over-stabilization of microtubules as well as under-stabilization can lead to dysfunction[27]. The exact mechanisms by which *MAPT* mutations and exon 10 inclusion increase the propensity of tau to aggregate are unclear. A recent study published in 2019 suggests that disease-associated mutations, isomerization of a critical proline or alternative splicing are all sufficient to trigger spontaneous aggregation[28].

Aetiology and pathophysiology of 4R-tauopathies

Environmental risk factors

Various environmental exposures have been associated with an increased risk of 4R-tauopathies. A large case–control study conducted in North America revealed that drinking water from a well is a risk factor for PSP, and indicated that exposure to pesticides might be involved in the pathogenesis of this disease[29]. The mitochondrial complex I inhibitor annonacin, which occurs naturally in some fruit in some parts of the world, has also been implicated in the pathogenesis of 4R-tauopathies; its consumption was associated with a PSP-like cluster in Guadeloupe[30,31] and its administration to rats caused basal ganglia and brainstem pathology[32,33]. In cultured neurons, it led to ATP depletion and a shift of tau and mitochondria from axons to somata[34–38].

Heavy metals have also been associated with a risk of 4R-tauopathies. A cluster of non-familial cases of PSP was identified in an industrialized area of Northern France that is contaminated with cadmium, chromium and nickel[39,40]. When chromium and nickel were added to human neurons derived from induced pluripotent stem cells, they induced cell death at lower concentrations in cells with *MAPT* mutations than in isogenic controls[38]. Even in isogenic control cells, tau levels and tau phosphorylation increased upon exposure to levels of chromium and nickel that killed mutant neurons, indicating that the mutations lowered the threshold for toxicity. Use of dopaminergic neuron-like cells showed that cell death was mediated by mitochondrial apoptotic mechanisms and that increased levels of tau were not associated with increased levels of tau mRNA, suggesting an impairment of tau degradation[39]. The implications of these results for sporadic PSP remain unknown.

Genetic risk factors

The H1 haplotype is a shared genetic risk factor for PSP, CBD and frontotemporal dementia (FTD) syndromes, and the H1c sub-haplotype is a genetic risk factor for PSP and CBD[41,42]. Several studies have been done to investigate the underlying mechanisms of these associations. Initial studies suggested that the H1 haplotype increases 4R-tau expression but subsequent work indicates that it reduces expression of 2N isoforms[43,44]. The H1 haplotype also seems to influence the degree of methylation at the *MAPT* locus[45]. The H1c sub-haplotype has been associated with high expression of total tau and 4R-tau[46]. In 2019, new work showed that the H1d, H1g and H1o sub-haplotypes also increase the risk of PSP[47].

Studies in the past few years have indicated that *APOE* genotype influences the risk of 4R-tauopathies. Animal studies and studies of brain tissue from patients with PSP have shown that the *APOE* ε2 allele is associated with a high tau burden and that an *APOE* ε2/ε2 genotype is a risk factor for PSP[48]. Moreover, the *APOE* ε2 allele is more common among patients with AGD than among the general population, whereas the frequency of the *ApoE* ε4 allele in AGD was dependent on concurrent Alzheimer disease (AD) in one study[49–52].

Box 1 | **Classification of major tauopathies**

Major tauopathies

- 3-repeat tauopathies
  - Pick disease
  - *MAPT* mutation
- 4-repeat tauopathies
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Argyrophilic grain disease
  - Globular glial tauopathies
  - *MAPT* mutation
- Mixed 3-repeat and 4-repeat tauopathies
  - Neurofibrillary tangle dementia
  - Primary age-related tauopathy
  - Alzheimer disease (with amyloid-β)
  - MAPT mutation

Disease conditions with predominant 4-repeat tau pathology

- Ageing-related tau astrogliopathy
- Guadeloupean parkinsonism
- Tau pathology-associated mutations in genes other than *MAPT*, including *SLC9A6*, *LRRK2*, *PRKN*, *SNCA*, *TARDBP*, *C9orf72*, *ADCY5* and *ATP6AP2*

Apolipoprotein E interacts with the lipoprotein receptor LRP1, and LRP1 has been implicated in the cellular uptake and spread of tau[53], so the interaction could indicate a mechanism for the association of PSP with *APOE* genotype.

The first genome-wide association study (GWAS) of PSP identified a single nucleotide polymorphism (SNP) in the *DDB2* gene as a risk factor for PSP[54], although this finding has not been replicated in subsequent studies. In the largest independent GWAS of PSP to date, three SNPs have been associated with a risk of PSP; these SNPs are in the *STX6*, *MOBP* and *EIF2AK3* genes[55]. These findings were replicated in three subsequent studies[23,56,57]. These replication studies also identified new SNPs that influence the risk of PSP: a non-synonymous SNP in the *SLCO1A2* gene, an intergenic SNP near *DUSP10*, an intronic SNP in the *SLCO1A2* gene and an SNP associated with the *RUNX2* gene[56,57].

Further studies have identified SNPs that are risk factors for CBD, some of which are the same as those identified in PSP. A GWAS that involved patients with definite CBD showed that the SNP in *MOBP* that was previously identified in PSP is also a genetic risk factor for CBD. This study also identified two further SNPs associated with the risk of CBD: intronic SNPs in *KIF13B* and *SOS1* (REF.[58]). In addition, an analysis of published GWAS data identified five SNPs that influence the risk of both PSP and CBD: one associated with the H1 haplotype, SNPs located near *CXCR4* and inside *EGFR* and *GLDC*, and the SNP in *MOBP* already mentioned[41].

Other genetic risk factors for PSP have also been associated with other conditions. For example, a second SNP near *CXCR4*, which is in linkage disequilibrium with the first SNP mentioned above, has been identified as a shared contributor to the risk of Parkinson disease (PD) and PSP[59]. In addition, a GWAS in which

PSP–Richardson syndrome (PSP–RS), PSP with parkinsonism (PSP–P) and progressive gait freezing (PGF) were compared, an SNP in *TRIM11* was less common among people with PSP–RS than among those with the other diseases[60]. A new GWAS that included people with pathologically and clinically diagnosed PSP from two separate cohorts (stage 1) and replication data from a brain bank (stage 2), showed that genetic variation at the *LRRK2* locus was associated with survival in PSP[61]. *LRRK2* has been associated with sporadic and familial forms of PD, so this finding might indicate a genetic overlap between PD and PSP[61].

Some evidence has provided insight into the functional implications of some of the identified SNPs, including those in *MOBP*[55,62], *EIF2AK3* (REF.[63]), *TRIM11* (REF.[60]) and *STX6* (REF.[64]), but further work is needed to understand the underlying mechanisms. Another area that requires more work is the involvement of epigenetic mechanisms in PSP. Studies are in progress to compare the degree of methylation in *MAPT* and other genes between patients with PSP and healthy controls[65,66] and to assess the role of microRNAs in the pathogenesis of PSP[67,68].

Tau abnormalities and propagation

Two hallmark abnormalities of tau that occur in tauopathies are its hyperphosphorylation and the formation of soluble and insoluble tau aggregates. Hyperphosphorylation is mediated by a variety of kinases, and tau can be phosphorylated at up to 85 sites. Hyperphosphorylation can lead to dysfunction via several mechanisms[10], including aggregation. Tau acetylation and nitration also occur in 4R-tauopathies, and the sites of these modifications differ from those in health[15,20,69].

Post-translational modifications of tau also influence excretion of tau from cells, which can occur via several mechanisms, including vesicular transport and direct translocation through the plasma membrane[3]. Post-translational modifications also influence the properties of tau outside the cells[70–72]. Extracellular tau comprises various tau species that result from truncation at different sites, but most species contain the middle section of the molecule without the microtubule-binding domain[73,74]. A small percentage of extracellular tau is enclosed in vesicles[75]. Evidence suggests that fibrils, digested fibrils, fragmented fibrils, oligomers and monomers can all induce aggregation[3]. In PSP, oligomeric tau species from brain homogenates can promote tau oligomerization in vitro[76].

Studies in animals have shown that abnormal tau can act like a prion to propagate pathology. Early studies showed that brain homogenates from transgenic mice that expressed Pro301Ser human tau[77–80] and from patients with tauopathies[78] can induce the formation of tau pathology in neurons and glia in mice that overexpressed wild-type human tau. Homogenates from patients with 4R-tauopathies led to the formation of pathology with characteristics of the original disease[78]. These prion-like properties of tau are thought to be responsible for the propagation of pathology through the brain of patients with tauopathies[81].

Neuropathology of 4R-tauopathies

PSP is characterized by atrophy of the subthalamic nucleus (STN) and brainstem tegmentum, and depigmentation of the substantia nigra. Microscopic features include globose neurofibrillary tangles and neuropile threads in subcortical structures and tufted, tau-positive astrocytes[82], in which phosphorylated tau has accumulated in the proximal part of the astrocytic processes. These pathologies are often associated with oligodendroglial coiled bodies[1].

CBD pathology includes astrocytic plaques, which appear as annular clusters of stubby, tau-positive distal segments of astrocytic processes. Other characteristic features of CBD are spherical neuronal inclusions, diffuse, fine granular staining of the neuronal cytoplasm, tau accumulation in axons and oligodendrocytic cell processes in the form of threads in the white and grey matter, and coiled bodies in oligodendroglia[1,83].

AGD is characterized by atrophy of the ambient gyrus and of argyrophilic (Gallyas-positive) and 4R-tau-immunoreactive grains in medial temporal lobe structures. Pretangles, oligodendroglial coiled bodies and astroglial tau pathology, which mostly appears as granular or fuzzy astrocytes, are also characteristic[84–86]. In GGT, the main tau pathology is in oligodendrocytes and astrocytes. Neurons exhibit diffuse, fine granular cytoplasmic tau immunoreactivity, or globular or tangle-like immunoreactive structures[87]. Subtypes of GGT have characteristics that distinguish them from each other. In type I GGT, argyrophilic and 4R-tau-immunoreactive globular oligodendroglial inclusions are predominant. The morphology of these inclusions is reminiscent of those in multiple system atrophy (MSA), but the anatomical distribution and the protein (tau rather than α-synuclein) is different[88,89]. In type II GGT, corticospinal tract involvement is predominant and can be associated with PSP pathology[90]. In type III GGT, 4R-tau-immunoreactive globular astroglial inclusions are predominant[87] and peculiar horseshoe-shaped[91] tau-immunoreactive structures can be present[87].

A further 4R-tau immunoreactive pathology that can be detected in the ageing brain is ARTAG, which comprises thorn-shaped astrocytes in subpial, subependymal and/or perivascular areas and in the white and, to a lesser extent, the grey matter, and granular or fuzzy astrocytes in the grey matter[4]. ARTAG is frequently interpreted as a non-specific pathology that is most likely related to blood–brain barrier and/or cerebrospinal fluid–brain barrier dysfunction. However, some studies have suggested that, depending on the location, this pathology might reduce the threshold for decompensation of cognitive functions[92], thereby contributing to cognitive impairment.

In addition to morphological variability between 4R-tauopathies, biochemical differences are also apparent. For example, in PSP, a 33-kDa band predominates in the low molecular weight tau fragments, whereas two closely related bands of ~37 kDa predominate in CBD[93]. Some studies have also indicated differences in the fold of tau filaments. Evidence suggests that these differences are related to the protease resistance of pathological tau proteins[94] and support the concept of tau strains[78,95,96].

Pathological progression

The variability of clinical phenotypes in 4R-tauopathies and the presence of glial tau pathology make it a challenge to develop a unified staging scheme for these diseases, such as the one developed for AD[97]. A grading system for PSP was suggested in 2007 on the basis of progressive involvement of brain areas in PSP–RS[98]. A study published in 2020 emphasized that the pallidonigroluysian axis is vulnerable in early disease[99] and demonstrated the importance of glial rather than neuronal involvement in defining the phenotype. In PSP–RS, six cell-specific, sequential steps of brain region involvement have been described for different cytopathologies and translated into six neuropathological stages of diagnosis[99] (FIG. 1).

In CBD, neuronal and glial tau pathology initially predominates in frontoparietal and motor cortical areas and the striatum, and later develops in other subcortical nuclei and the brainstem[100]. A study published in 2020 suggests that CBD subtypes differ in cellular tau profiles[101] and that incidental CBD (that is, CBD identified as an unexpected finding) is characterized by tau pathology predominantly in the cortical astroglia[102].

AGD can be divided into three stages[103]. In stage I, the ambient gyrus and the anterior of the hippocampus CA1 subregion are most affected. In stage II, the dentate gyrus and presubiculum become involved. In stage III, the CA2 and CA3 hypothalamic regions, the anterior temporal, cingulate, insular and orbitofrontal cortices, the accumbens nucleus and the septal nuclei are all affected. In stage IV, the neocortex and brainstem are involved.

Pathological progression of GGT type I has also been characterized to some degree. The white matter pathology involves the peri-amygdala and hippocampal white matter areas first, followed by progressive involvement of further limbic regions[88]. Progression patterns for GGT types II and III have not yet been reported.

Co-pathology

α-Synuclein deposition with Lewy body pathology has been reported in ~20% of individuals with PSP or CBD. AD-related neuropathological changes have also been identified in ~26% of people with PSP or CBD[104]. TDP-43 co-pathology has been reported in 6–16% of people with PSP and 15.4–45% of people with CBD[105,106]. AGD is commonly seen in ageing and with other proteinopathies. GGT is considered a relatively pure tauopathy[105].

Two studies published in 2020 addressed the question of whether co-pathology in PSP matters clinically. One led to the conclusion that co-pathologies do not have a substantial impact on major clinical milestones[107], and the other confirmed that tau burden is the strongest correlate of clinical severity[108]. However, further studies are needed to determine the effects of co-pathology, as it could influence the efficacy of disease-modifying treatments and might need to be taken into account when designing clinical trials to ensure that patients are appropriately stratified if necessary.

Glial pathology

In 4R-tauopathies, tau aggregates accumulate in astroglia and oligodendroglia as well as in neurons, and the shapes and structures of neuronal and glial deposits distinguish the four major 4R-tauopathies[1]. In PSP, transcripts and gene expression networks have unique patterns of association with neuronal and astroglial tau pathologies[109], indicating diverse molecular mechanisms that underlie cell-specific vulnerability and helping to understand its preferential accumulation in neurons or astroglia in different brain regions. Tau accumulation in astroglia can result from upregulation of tau expression and phosphorylation in astroglia or from tau internalization from the extracellular milieu[92].

Experimental studies have supported the concept that tau accumulation in oligodendroglia is eventually accompanied by axon degeneration and demyelination[110]. Globular oligodendroglial inclusions are predominantly associated with tract degeneration and oligodendroglial dysfunction[89]. Tau-immunoreactive oligodendroglial inclusions are observed after inoculation of CBD homogenates in experimental mouse models but are apparent only very rarely or not at all after inoculation of AD homogenates[111].

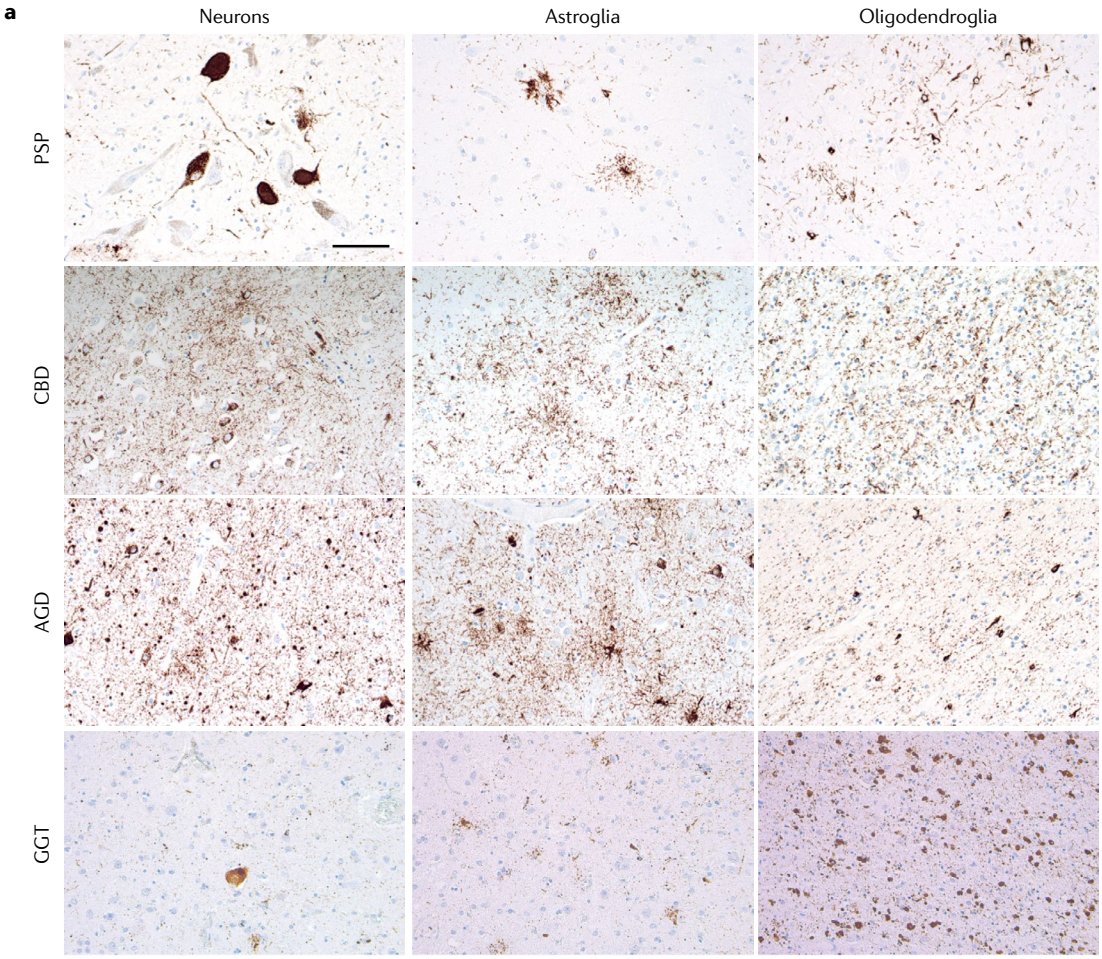
Clinical features of 4R-tauopathies

The phenotypic spectrum

4R-tauopathies cause a variety of cognitive and motor symptoms (TABLE 1) and should be thought of as a continuum rather than discrete disease subgroups[112,113]. This continuum is mainly determined by the neuroanatomical distribution and burden of neuronal and glial tau pathology[92,98,99,107,114–116].

PSP–Richardson syndrome. Patients with PSP–RS present with early postural instability and oculomotor dysfunction, including slow vertical saccades and supranuclear gaze palsy (SGP)[117–119]. Behavioural and personality changes and executive dysfunction are common, as is levodopa-resistant, axial-predominant parkinsonism. Mean survival is 6–8.5 years, although a wide range has been reported (up to 17 years) in some studies[100,112,120]. PSP–RS accounts for 24–50% of cases of PSP[98,112,120], and other PSP phenotypes eventually lead to the same clinical features as PSP–RS[112,121]. SGP with a lack of postural instability is referred to as the ocular motor dysfunction phenotype. Early postural instability and a lack of SGP is referred to as the postural instability phenotype[112]. PSP pathology is relatively specific for PSP–RS but the condition can also be associated with CBD pathology[113], TDP-43 pathology and, in rare cases, Lewy body disease[122,123] (TABLE 1).

Corticobasal syndrome. Corticobasal syndrome (CBS) is characterized by a combination of asymmetrical parkinsonian features (levodopa-resistant rigidity and akinesia, dystonia and myoclonus) and cortical features (apraxia, cognitive dysfunction, cortical sensory loss and alien-limb phenomenon)[113]. Postural instability and oculomotor dysfunction[124] frequently coexist in patients with CBS. Dysphagia and dysarthria are also very common[100]. Mean survival is 5–8 years. CBS is often caused



c Neuropathology staging scheme

Stage	1 → 2			3 → 4		5 → 6
Region	Globus pallidus	Subthalamic nucleus	Striatum	Frontal cortex	Dentale Cerebellum	Occipital cortex
Cell	Neurons Oligodendroglia	Neurons	Astroglia	Astroglia	Neurons Oligodendroglia	Astroglia

by AD pathology, PSP pathology, TDP-43 pathology and GGT pathology[125,126] (TABLE 1).

PSP with parkinsonism. PSP–P is the second most common clinical phenotype of PSP[112,120]. This condition is characterized by symmetrical or asymmetrical parkinsonism, with or without tremor, that responds to some extent to levodopa therapy. Postural instability, oculomotor dysfunction and cognitive deficits typically develop later in the disease course. PSP–P has a more benign course than PSP–RS with a mean survival of 9–13 years[112,120] (TABLE 1). PSP–P is associated with PSP,

◀ Fig. 1 | **Tau pathology and its distribution in 4R-tauopathies. a** | Pathological tau (brown) labelled with the antibody AT8 in neurons, astroglia and oligodendroglia in progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD) and globular glial tauopathy (GGT) type I. Scale bar 120 µm. **b** | The distribution of tau pathology in PSP–Richardson syndrome (PSP–RS) in neurons, astroglia and oligodendroglia. The colours indicate sequential regional involvement; darker colours indicate earlier involvement. **c** | Proposed neuropathological staging scheme for 4R-tauopathies. The scheme includes semiquantitative scoring of pathology indicated by the colours: mild (yellow), moderate (orange) and severe (red). The bottom row indicates the cell types in which pathology is present. Stages 1 and 2 require worsening pathology in the globus pallidus, subthalamic nucleus and striatum; stage 3 and 4 require worsening pathology in either or both of the frontal cortex and dentate nucleus or cerebellar white matter; and stages 5 and 6 require worsening pathology in the occipital cortex.

GGT and, in rare cases, dementia with Lewy bodies pathology (TABLE 1).

Progressive gait freezing. PGF is characterized by levodopa-resistant gait freezing in the absence of prominent parkinsonism. Postural instability, falls, dysarthria and handwriting changes can occur, and dementia and vertical gaze palsy can develop in later disease stages. The most common underlying pathologies in PGF are PSP and CBD, followed by pallidonigroluysian degeneration and Lewy body pathology[127–129] (TABLE 1).

Primary lateral sclerosis. Primary lateral sclerosis is characterized by upper motor neuron signs with spasticity, pyramidal weakness, dysarthria and dysphagia. TDP-43 pathology is the most common neuropathological basis, but underlying 4R-tauopathy, including PSP[130] and GGT[87,131] pathology, has been described in rare cases (TABLE 1).

Late-onset cerebellar ataxia. Some cases of late-onset cerebellar ataxia with underlying PSP pathology have been described, predominantly in Asian countries[132–134]. These patients presented with limb, trunk and gait ataxia and later developed parkinsonism, SGP and postural instability (TABLE 1).

Behavioural variant of frontotemporal dementia. Patients with the behavioural variant of FTD (bvFTD) predominantly exhibit behavioural and personality changes, including disinhibition, apathy, loss of empathy, perseverative behaviours and executive dysfunction[135]. The underlying pathology in bvFTD can be any of the 4R-tauopathies (PSP, CBD, GGT or AGD)[87], Pick disease, TDP-43 or AD pathology[90,136,137] (TABLE 1).

Non-fluent/agrammatic variant of primary progressive aphasia. The non-fluent/agrammatic variant of primary progressive aphasia (nfaPPA) manifests with agrammatism, simplifications and impaired syntax, though single-word comprehension and semantics are spared[138,139]. Unlike other forms of primary progressive aphasia, nfaPPA is primarily associated with 4R-tauopathies, including PSP, CBD and GGT[137,140,141]. Less commonly, nfaPPA occurs in Pick disease, tau-negative frontotemporal lobar degeneration (FTLD) and AD[138].

Primary progressive apraxia of speech. 4R-tauopathies can initially present with primary progressive apraxia of speech (PPAOS), which is a motor speech disorder that presents with effortful, halting speech with inconsistent sound errors and distortions or slow syllabically segmented prosodic speech patterns with spared single-word comprehension, object knowledge, and word retrieval during sentence repetition[118]. PPAOS can present with nfaPPA but an underlying 4R-tauopathy seems to be more specific for PPAOS than for nfaPPA[137].

Visuospatial syndrome. Visuospatial syndrome is characterized by prominent visuospatial dysfunction, which is also referred to as posterior cortical atrophy, has been described in some patients with CBD pathology[142,143] and is a common coexisting feature in patients who present with CBS[144]. Other pathologies that can underlie posterior cortical atrophy include AD pathology and Lewy body pathology[145].

Amnestic syndrome. Amnestic syndrome that involves initially mild cognitive impairment and later comes to resemble AD dementia has been associated with AGD pathology. These patients usually also have behavioural syndromes, psychosis and depression[3].

Clinical diagnostic criteria

Clinical diagnostic criteria have been defined for PSP and CBD, and are outlined in the sections below. Clinical diagnostic criteria for the other 4R-tauopathies have not yet been defined.

Diagnostic criteria for PSP. The Movement Disorders Society diagnostic criteria for PSP (MDS–PSP criteria; BOX 2; Supplementary Figure 1) include a total of 12 core clinical features in four clinical domains: ocular motor dysfunction (O), postural instability (P), akinesia (A) and cognitive dysfunction (C). Each of the four clinical domains includes three core clinical features, which are graded for their specificity from one (most specific) to three (least specific). The criteria also include four clinical clues and two imaging findings.

The combination of core clinical features and clinical clues determines the degree of diagnostic certainty — probable, possible or 'suggestive of' PSP — and the clinical type[118]. A diagnosis of probable PSP requires vertical gaze palsy (O1) or slow velocity of vertical saccades (O2) plus at least one other core feature. For a diagnosis of possible PSP or suggestive of PSP, neither postural instability nor ocular motor dysfunction need to be present. These criteria include phenotypes other than PSP–RS, and the introduction of the suggestive of PSP category is intended to enable early identification of patients[118]. The application of these criteria when phenotypes overlap has been described elsewhere[121]. An online tool for diagnosis of PSP with these criteria has been developed.

Diagnostic criteria for PSP have also been developed by the US National Institute of Neurological Disorders and Stroke and the Society for PSP (the NINDS–SPSP criteria) but three clinicopathological studies have demonstrated that the MDS–PSP criteria are more sensitive than the NINDS–SPSP criteria[146–148]. In the first

Table 1 | **Frequency of 4R-tau and non-4R-tau pathology in phenotypes of 4R-tauopathies**

Phenotype	Estimated frequency of underlying pathology							
	4R-tau pathologies				Non-4R-tau pathologies			
	PSP	CBD	GGT	AGD	PiD	TDP-43	AD	LBD
RS	Frequent	Rare	Rare	Unknown	Unknown	Unknown	Unknown	Rare
CBS	Intermediate	Intermediate	Rare	Unknown	Unknown	Intermediate	Intermediate	Unknown
bvFTD	Intermediate	Rare	Rare	Intermediate	Rare	Intermediate	Intermediate	Unknown
nfaPPA	Intermediate	Rare	Rare	Unknown	Rare	Rare	Rare	Unknown
VS	Unknown	Rare	Unknown	Unknown	Unknown	Unknown	Intermediate	Intermediate
PSP–P	Intermediate	Unknown	Rare	Unknown	Unknown	Unknown	Unknown	Intermediate
PGF	Intermediate	Rare	Unknown	Unknown	Unknown	Unknown	Unknown	Rare
PLS	Rare	Unknown	Rare	Unknown	Unknown	Intermediate	Unknown	Unknown
LOCA	Rare	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Intermediate
Amnestic syndrome	Unknown	Unknown	Unknown	Frequent	Unknown	Unknown	Frequent	Unknown

4R, four-repeat; AD, Alzheimer disease; AGD, argyrophilic grain disease; bvFTD, behavioural variant of frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; GGT, globular glial tauopathy; LBD, Lewy body disease; LOCA, late-onset cerebellar ataxia; nfaPPA, non-fluent/agrammatic variant of primary progressive aphasia; PGF, progressive gait freezing; PiD, Pick disease; PLS, primary lateral sclerosis; PSP, progressive supranuclear palsy; PSP–P, progressive supranuclear palsy with parkinsonism; RS, Richardson syndrome; TDP-43, transactive response DNA binding protein 43; VS, visuospatial syndrome.

of these studies, the sensitivity of the MDS–PSP criteria was 87.9% compared with 45.5% for the NINDS–SPSP criteria, and the specificity of the MDS–PSP criteria ranged from 39.7% for suggestive of PSP to 85.7% for probable PSP[147]. In the second study, the sensitivity of the MDS–PSP criteria was higher than that of the NINDS–SPSP criteria for suggestive of PSP (100% versus 72.2%) and for probable PSP (61.1% versus 48.1%). Specificity of the MDS–PSP criteria ranged between 53.1% for suggestive of PSP and 95.1% for probable PSP vs. 97.5% and 100% for possible PSP and probable PSP[148] with the NINDS–SPSP criteria.

In the third study, the performance of the criteria for suggestive of PSP was analysed in an autopsy cohort of 204 individuals with PSP and 216 controls with CBD, MSA, PD or 4R-tau-negative FTLD. Inclusion of the criteria for suggestive of PSP significantly increased the sensitivity for the diagnosis of PSP. The overall sensitivity of the MDS–PSP criteria was 64.2% in the first 3 years of disease and 85.8% at the final record, compared with 25% and 50%, respectively, for the NINDS–SPSP criteria. The time to first PSP diagnosis was 2.2 years with the MDS–PSP criteria compared with 4.0 years with the NINDS–SPSP criteria. The specificity of the MDS–PSP criteria in the first 3 years after disease onset was 75.9%[146].

Diagnostic criteria for CBD. Four clinical phenotypes are incorporated into the current CBD criteria: CBS, frontal behavioural and spatial syndrome, nfaPPA and PSP-like syndrome[113]. Two retrospective validation studies have indicated that the specificity and sensitivity of the criteria for the diagnosis of probable and possible CBD are low[149,150]. However, AD was not excluded in either study even though this is a requirement for the criteria. The most common misdiagnoses of CBD include AD and PSP[116,125]. Imaging and fluid biomarkers, including amyloid PET and the CSF profile of tau and amyloid-β, can help identify AD pathology in patients with apparent CBS, and these tests should be done to exclude AD.

Diagnostic criteria for 4R-tauopathy. The MDS–PSP criteria include a diagnostic category of 'probable 4R-tauopathy' to account for the undisputable phenotypic overlap of PSP and CBD. Probable 4R-tauopathy includes all probable PSP, possible PSP with speech and language dysfunction (PSP–SL) and possible PSP–CBS. These criteria proved to be specific for 4R-tauopathies in a retrospective validation study[151]. Combining the diagnosis of PSP and CBD is a reasonable approach because 4R-tauopathies share targets for disease-modifying therapies.

Imaging and fluid biomarkers

MRI

MRI reveals distinct patterns of brain atrophy in the different 4R-tauopathies. PSP–RS produces characteristic patterns of atrophy of the midbrain with relative sparing of the pons, known as the hummingbird sign or penguin sign[152,153], and atrophy in the superior cerebellar peduncle (SCP)[154], basal ganglia and frontal lobes[155] (FIG. 2). MRI measurements of the midbrain can differentiate PSP–RS from PD and MSA[156–158]. Degeneration of the dentatorubrothalamic tract is also observed in PSP–RS, along with reduced diffusivity of the SCP, body of the corpus callosum and association fibres that project to the frontal lobes[155,159–161]. Abnormalities in the dentatorubrothalamic tract are greater in PSP–RS than in PD[162–168]. Functional and structural connectivity between the midbrain and the cerebellum, basal ganglia, thalamus and cortex in PSP–RS, and between the thalamus and the premotor cortex is reduced[155,169,170]; these observations are consistent with the pattern of dentatorubrothalamic degeneration.

Imaging characteristics differ between clinical phenotypes of PSP[171]. In PSP–P, midbrain and SCP atrophy is less severe than in PSP–RS[161,171–173]. The value

of midbrain-based metrics for differentiation of PSP–P from PD and other non-PSP diseases is uncertain[174,175]. Reduced integrity of the SCP, corpus callosum and supratentorial association fibres has been observed in PSP–P but to a lesser degree than in PSP–RS[161–163,176,177]. In PGF, atrophy is predominantly subcortical and in the midbrain but is mild[171,178,179]. Midbrain metrics enable only moderate differentiation of PGF from PD[179]. In PSP–CBS, PSP–F and PSP–SL, atrophy of the frontal cortex is greater than in PSP–RS, PSP–P and PGF[171,180]. Atrophy of the premotor and motor cortices is particularly striking in PSP–SL, and midbrain atrophy can also develop over time in this condition as features of PSP–RS develop[171,181,182]. Infratentorial structures, including the midbrain and SCP, are affected in PSP–F and PSP–CBS[171].

In CBS, supratentorial patterns of degeneration can be seen, with asymmetrical atrophy in the posterior frontal lobe, superior parietal lobe[183] and the basal ganglia (FIG. 2), and degeneration of the body and splenium of the corpus callosum, middle cingulate bundle and premotor, motor and superior parietal white matter tracts[184–187]. Brain functional connectivity is reduced in right temporoparietal and insular regions and increased in frontal networks[188,189]. However, patterns of atrophy in CBS differ according to the underlying pathology[143,190–192].

PET

PET can be used to assess metabolism and tau pathology in the brain, and PET findings differ between 4R-tauopathies. ^{18}F-Fluorodeoxyglucose (FDG) PET in PSP–RS has revealed hypometabolism in the midbrain, basal ganglia, thalamus and frontal lobes, including prefrontal, anterior cingulate, premotor and motor regions[193–207] (FIG. 3). In CBS, hypometabolism is typically asymmetrical and involves the frontal and parietal lobes, basal ganglia and thalamus[206,208] (FIG. 3), although patterns of hypometabolism vary according to pathology[209,210].

Box 2 | **Core clinical features, clinical clues and imaging findings of diagnostic categories of PSP**

Characteristics are according to the Movement Disorders Society criteria for progressive supranuclear palsy (PSP)[118]. Features are stratified by presumed level of certainty that they contribute to the diagnosis of PSP, from 1 (highest) to 3 (lowest).

Ocular motor dysfunction
O1: vertical supranuclear gaze palsy
O2: slow velocity of vertical saccades
O3: frequent macro square wave jerks or 'eyelid opening apraxia'

Postural instability
P1: repeated unprovoked falls within 3 years
P2: tendency to fall on the pull test within 3 years
P3: more than two steps backward on the pull test within 3 years

Akinesia
A1: progressive gait freezing within 3 years
A2: parkinsonism, akinetic–rigid, predominantly axial and levodopa-resistant
A3: parkinsonism, with tremor and/or asymmetrical and/or levodopa-responsive

Cognitive dysfunction
C1: speech/language disorder
C2: frontal cognitive or behavioural presentation
C3: corticobasal syndrome

Clinical clues
CC1: levodopa-resistant
CC2: hypokinetic, spastic dysarthria
CC3: dysphagia
CC4: photophobia

Imaging findings
IF1: predominant midbrain atrophy or hypometabolism
IF2: postsynaptic striatal dopaminergic degeneration

The parietal lobes are affected to a greater degree in CBS than in PSP–RS, whereas the midbrain is affected to a greater degree in PSP–RS[197,199]. These patterns of hypometabolism in 4R-tauopathies[211] perform well in the differential diagnosis of PSP–RS from PD[212,213] and MSA[207,212]. In PSP–P and PGF, hypometabolism is seen in subcortical areas, particularly in the putamen in PSP–P[213,214] and the thalamus[213] and midbrain[215] in PGF. Frontal hypometabolism is seen in PSP–SL[137,216].

Studies to assess the performance of PET tracers that bind to tau have been conducted in patients with PSP (mainly PSP–RS) and CBS. Several studies in which ^{18}F-flortaucipir (formally known as ^{18}F-AV-1451) has been used in patients with PSP–RS have shown consistent patterns of elevated uptake in the midbrain, cerebellar dentate, STN, thalamus, globus pallidus (GP) and striatum[217–223]. Uptake in the GP is a particularly useful measure for differentiating PSP–RS from PD[217,223]. Some evidence suggests that uptake in these regions increases over time[224] and relates to the neurodegenerative process in PSP[225–227], although the degree of uptake does not relate to clinical disease severity[217,219,222]. ^{18}F-Flortaucipir uptake is increased in the basal ganglia in PSP–RS, PSP–P, PGF and PSP–SL, in the cerebellar dentate and midbrain in only PSP–RS, and in the frontal cortex in only PSP–SL[171] (FIG. 3). ^{18}F-Flortaucipir uptake correlates well with tau burden across brain regions in individuals with CBD or PSP[192,228,229], though how well the ^{18}F-flortaucipir signal reflects binding to 4R-tau remains unclear[230–232].

Another PET ligand called ^{18}F-PI-2620 has high affinity for 4R-tau and is more specific to this form of tau than ^{18}F-flortaucipir[233,234]. Elevated uptake of ^{18}F-PI-2620 has been observed in the GP, STN, putamen, substantia nigra and cerebellar dentate in PSP–RS, and uptake patterns can be used to correctly classify 85% of patients with PSP–RS[233]. Uptake is also increased in the GP and STN in PSP–P, PSP–F and CBS, although uptake in the GP is higher in PSP–RS than in these variants[233]. Perfusion-phase ^{18}F-PI-2620 PET images obtained early in the acquisition correlate strongly with FDG PET images, so ^{18}F-PI-2620 PET could provide images of tau uptake and neuronal injury[235].

In PSP–RS, similar patterns of uptake have been observed with the PET ligand ^{11}C-PBB3 (REFS[236,237]). However, PBB3 is relatively unstable so has been modified to improve its stability and sensitivity to tau fibrils; the modified ligand is the propanol modification of PBB3, known as ^{18}F-PM-PBB3 (REF.[238]). Uptake of PM-PBB3 is also increased in subcortical structures in PSP, but its uptake is greater than that of ^{11}C-PBB3 and its signal is more on-target[238]. Uptake of another radioligand, ^{18}F-THK-5351, is also elevated in typical PSP-related regions in patients with PSP[239,240], and enables good differentiation from PD[241], but this ligand has strong off-target binding to monoamine oxidase B, so its utility is limited[242,243].

^{18}F-Flortaucipir, ^{18}F-THK-5351 and ^{11}C-PBB3 have all been used as PET ligands in CBS, in which they are taken up asymmetrically in grey and white matter of the sensorimotor cortex, superior frontal and parietal lobes, putamen and GP[192,229,237,244–249]. However, their uptake can vary between patients, possibly as a

result of heterogeneous underlying pathology[249,250]. In a cohort of patients with autopsy-confirmed CBD, uptake of ^{18}F-flortaucipir was elevated in premotor and motor cortices and in the GP[228]. Uptake of ^{18}F-flortaucipir in the red nucleus was also elevated in PSP, and the ratio of uptake in the GP to that in the red nucleus enabled complete differentiation of autopsy-confirmed CBD and PSP[228].

Fluid biomarkers

CSF and serum components have been studied as biomarkers of 4R-tauopathies and could be helpful in identifying and distinguishing these conditions. Total tau levels and levels of phosphorylated tau-181 (p-tau) are decreased in the cerebrospinal fluid in patients with PSP compared with controls, albeit with substantial overlap between the groups[73,251].

Tau species in the CSF in PSP and AD consist of various tau fragments that are not detected by conventional assessment of t-tau and p-tau. Protein misfolding cyclic amplification and real-time quaking-induced conversion (RT-QuIC) enable the detection of tau aggregates in tauopathies. An ultrasensitive tau seed amplification assay for 4R-tauopathies (4R RT-QuIC) has been developed and the use of this approach in post-mortem CSF from people with neuropathologically confirmed PSP and CBD has enabled identification of three disease-associated classes of 4R-tau seeds. However, CSF from patients with PSP and CBD had weaker seeding activity than that from healthy controls. This method is, therefore, promising and needs further validation[252].

Another potential fluid marker of 4R-tauopathies is neurofilament light chain (NfL), release of which reflects non-specific axonal damage. NfL levels in the serum and CSF are elevated in PSP and can be used to discriminate atypical parkinsonian disorders from PD, though cannot distinguish between the atypical disorders[253–255]. Blood levels of NfL correlate well with CSF levels and also enable discrimination between atypical parkinsonian disorders and PD[256–258]. One prospective study has shown that NfL can be used to make this distinction early in the disease course, which is crucial for early diagnosis[254]. Importantly, NfL levels seem to correlate with disease severity and other clinical variables, and also predict progression[251,259–261]. Higher plasma and CSF levels of NfL predict faster clinical deterioration[256,261]. On the basis of these findings, NfL could be a useful end point in clinical trials of disease-modifying treatments[262–264].

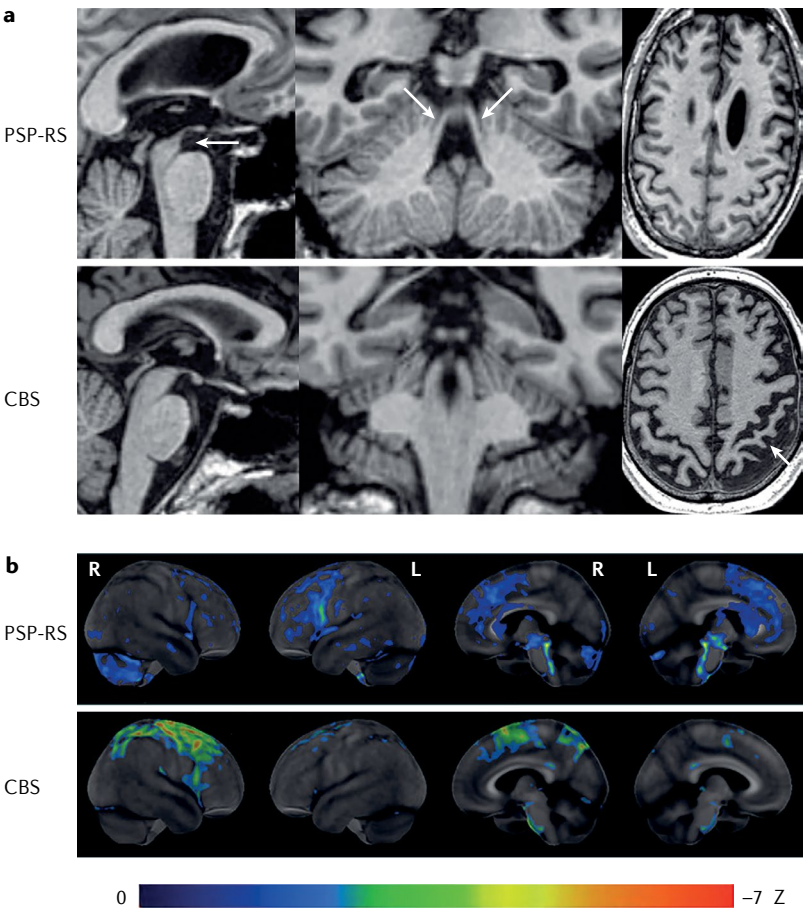


Fig. 2 | **Imaging characteristics of PSP–RS and CBS. a** | Representative MRI slices show atrophy of the midbrain (top left, arrow), superior cerebellar peduncles (top centre, arrows) and mild posterior frontal atrophy with enlargement of the ventricle (top right) in progressive supranuclear palsy–Richardson syndrome (PSP–RS). The midbrain (bottom left) and superior cerebellar peduncle (bottom centre) are spared in corticobasal syndrome (CBS), although striking asymmetrical atrophy is observed in the cortex (bottom right, arrow). **b** | FDG PET images that show regions of hypometabolism in PSP–RS and CBS. Images show CortexID Z score maps. In PSP–RS, mild hypometabolism is apparent in the brainstem, corpus callosum and frontal lobes. In CBS, more and asymmetrical hypometabolism is visible in the posterior frontal and parietal lobes.

Therapeutic approaches

Symptomatic treatment

Given that no disease-modifying treatments are available for 4R-tauopthies, the goal of current management is to alleviate symptoms and preserve the patient's performance in activities of daily living (TABLE 2). Pharmacotherapy, exercise, and occupational, physical and speech therapy are all crucial elements of the management of 4R-tauopathies. Caregiver support and advanced care planning should not be overlooked[265,266]. Use of pharmacotherapy in PSP and CBD is mostly based on experience in other neurodegenerative diseases and on case series, and no evidence exists for its use in AGD and GGT. Deep brain stimulation is not recommended in 4R-tauopathies[267–270], as the widespread neurodegeneration means there is no rationale for its use, and insufficient evidence exists to support its use[271–274].

Parkinsonism. Patients with parkinsonism are commonly prescribed levodopa (up to 1 g/day), which typically elicits a short-lived, mild to modest clinical improvement in 25–38% of patients with PSP and in 0–56% of patients with CBD[265,269,275]. Dopamine agonists and monoamine oxidase B inhibitors are not as effective as levodopa. Amantadine can be used as a second-line agent but high doses reduce tolerability owing to adverse effects[269,272]. Patients with PSP–P are likely to gain the greatest clinical benefit from dopaminergic drugs[112,119]. In addition, frequent, monitored exercise can contribute to preservation of balance and prevent falls.

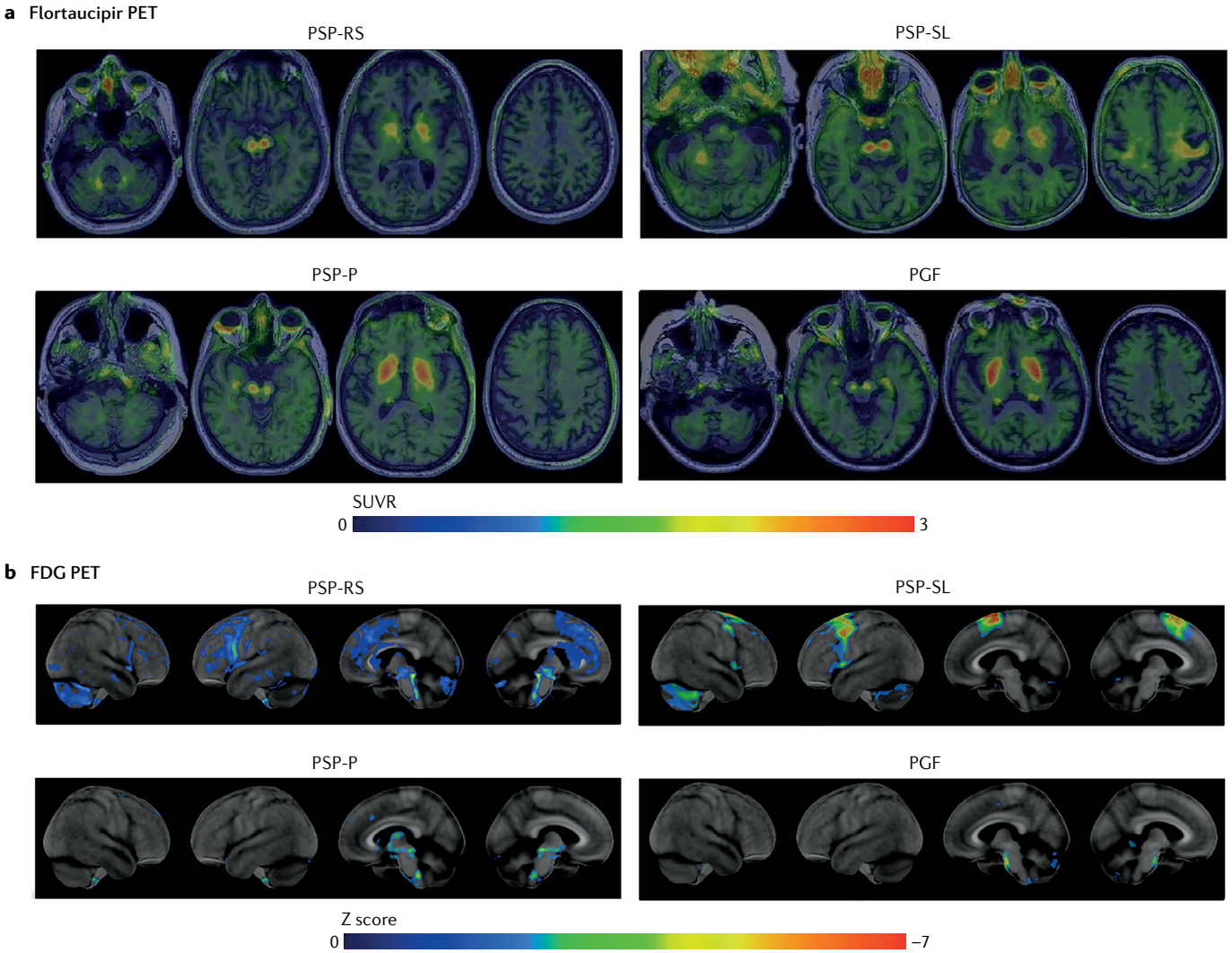


Fig. 3 | **PET findings in 4R-tauopathies. a** | Flortaucipir PET findings in representative patients with progressive supranuclear palsy–Richardson syndrome (PSP–RS), progressive supranuclear palsy with speech and language dysfunction (PSP–SL), PSP with parkinsonism (PSP–P) and progressive gait freezing (PGF). In all four patients, flortaucipir uptake is seen in the midbrain and basal ganglia. In PSP–RS and PSP–SL, uptake is seen in the cerebellar dentate. Only in PSP–SL is uptake seen in the cortex. **b** | FDG PET images in patients with PSP–RS, PSP–SL, PSP–P and PGF. Frontal hypometabolism is apparent in PSP–RS and PSP–SL. Hypometabolism is more severe in PSP–SL, particularly in the superior premotor cortex. No hypometabolism is apparent in the cortex in PSP–P or PGF, although mild hypometabolism can be seen in the brainstem in both variants.

Dystonia and myoclonus. Botulinum toxin can be tried for the management of dystonia, but caution is needed owing to adverse effects such as dysphagia. Clonazepam or levetiracetam can be used to treat myoclonus, but levetiracetam can lead to mood changes (depression and anxiety), drowsiness and agitation[264,265,268,270,276]. Pretarsal injection of botulinum toxin can be tried for eyelid opening apraxia[264,265,268,270,276].

Cognitive impairment and neuropsychiatric symptoms. Acetylcholinesterase inhibitors are not recommended for cognitive impairment in 4R-tauopathies because they can exacerbate motor manifestations[277,278]. The management of behavioural manifestations should include reducing drugs that may worsen them, such as benzodiazepines and tricyclic antidepressants[265,276]. Antipsychotic medications should be avoided if possible, as they can worsen parkinsonism[6,268,269,279,280]. Selective serotonin reuptake inhibitors are effective for the treatment of anxiety and depression and can be used also for emotional incontinence. The serotonin–norepinephrine reuptake inhibitors bupropion, trazodone and mirtazapine can also be prescribed[250–252,254,259]. Insomnia can be managed with melatonin, trazodone and zolpidem[250–252,254,259].

Other symptoms. Urinary frequency, urgency and incontinence are managed with anticholinergic medications or mirabegron, a β_3-adrenoreceptor agonist[281]. Botulinum toxin injection in the detrusor muscle is an alternative. Urinary retention can be managed with α_1-adrenoreceptor antagonists or cholinergic drugs, such as pyridostigmine, that increase detrusor muscle contractility. Alternative, non-pharmacological management

approaches are intermittent self-catheterization or placement of a permanent suprapubic catheter[282,283].

Everyday management of dysphagia requires speech therapy with a goal of maintaining adequate calorie intake and minimizing the risk of aspiration. Percutaneous endoscopic gastrostomy can be used to reduce the risk of aspiration. Drooling can be managed by salivary gland injection of botulinum toxin.

Table 2 | **Symptomatic treatments in 4R-tauopathies**

Symptom	First-line treatments and doses	Second-line treatments and doses	Refs
Parkinsonism	Levodopa, gradually titrated to 300 mg four times daily (>1 g/day is rare in practice)	Amantadine, 100–200 mg three times daily (>400–450 mg/day is rare in practice)	275,316
Dystonia	Botulinum toxin (if focal)	Benzodiazepines (e.g. clonazepam, 0.5–8 mg/day)	265,317, 318
Eyelid opening apraxia – blepharospasm	Botulinum toxin	NA	319,320
Myoclonus	Clonazepam, 0.5–8 mg/day Levetiracetam, 250–3,000 mg/day	Valproic acid, 1,200–2,000 mg/day Piracetam, 2.4–21.6 g/day Gabapentin, up to 3,600 mg/day	265,267, 321,322
Cognitive impairment	Lifestyle modifications	NA	266
Behavioural manifestations	Reduce or discontinue possible offending drugs (e.g. drugs with anticholinergic action) Identify and address potential causes of distress (e.g. pain) Occupational therapy	Selective serotonin reuptake inhibitors (e.g. citalopram, 20–40 mg/day) Antipsychotics (best avoided if possible)	265,266
Apathy	Serotonin–noradrenaline reuptake inhibitors (e.g. venlafaxine, 75–375 mg/day) Bupropion, 150–300 mg/day Amantadine, 100–200 mg three times daily (>400–450 mg/day is rare in practice) Regular exercise	NA	265,266
Depression and/or anxiety	Selective serotonin reuptake inhibitors (e.g. citalopram, 20–40 mg/day)	Mirtazapine, 15–45 mg/day Trazodone, 150–300 mg/day	270,276
Emotional incontinence	Selective serotonin reuptake inhibitors at low dosage (e.g. citalopram, 10 mg/day)	NA	276
Insomnia	Melatonin, 1–12 mg/day Trazodone, 25–75 mg/day Zolpidem, 5–10 mg/day	NA	266,269
Urinary frequency, urgency and incontinence	Mirabegron, 25–50 mg/day Anticholinergics (e.g. trospium, 20 mg immediate release twice daily or 60 mg controlled release once daily; tolterodine, 2 mg immediate release twice daily or 4 mg controlled release once daily; solifenacin, 5–10 mg/day; darifenacin, 7.5–15 mg/day)	Botulinum toxin injections in the detrusor muscle	282
Urinary retention	α1-Adrenoreceptor antagonists (e.g. tamsulosin, 0.4 mg/day)	Cholinergic drugs (e.g. pyridostigmine, 60–240 mg/day) Intermittent self-catheterization Permanent suprapubic catheter	323
Dysphagia	Speech therapy	Percutaneous endoscopic gastrostomy	323
Eye dryness	Topical preparations	NA	265
Drooling	Topical preparations Botulinum toxin injections in the salivary glands	NA	324
Constipation	Dietary modifications Increased fluid intake Exercise	Laxatives	266

NA, not available.

Eye dryness is managed with topical preparations, such as artificial tears. Constipation is addressed by making dietary modifications, ensuring adequate fluid intake, maintaining physical activity and use of laxatives[280].

Neuroprotective treatments

Several drugs have been tested in clinical trials as potential disease-modifying therapies in 4R-tauopathies. However, these trials have largely failed.

Riluzole. Riluzole has a neuroprotective effect in amyotrophic lateral sclerosis. However, a multicentre randomized controlled phase III study demonstrated that riluzole has no influence on survival rates or disease progression in PSP[284].

Coenzyme Q10. Based on the assumption that mitochondrial dysfunction is one cause of tau-induced neurodegeneration[285], oral coenzyme Q10 was tested in a randomized controlled phase II trial. Administration of the drug for 6 weeks produced a small but significant symptomatic improvement on the PSP Rating Scale and the Frontal Assessment Battery[286]. By contrast, a longer-term study over 12 months showed no significant influence on disease progression[287], although this study had methodological limitations, such as a long recruitment period, a high drop-out rate and an underpowered study population.

Glycogen synthase kinase 3 inhibitors. The glycogen synthase kinase 3 (GSK3) inhibitor tideglusib reduced tau aggregation in experimental models by reducing tau phosphorylation[288]. In humans, a randomized, controlled phase II trial of tideglusib in patients with PSP showed no overall disease-modifying effect[289], although attenuated progression of brain atrophy, particularly in the temporal and parietal lobes, was seen in a subgroup that underwent imaging[290]. Similarly, a randomized controlled phase II trial of sodium valproate, which also inhibits GSK3, demonstrated no disease-modifying effect of the drug in PSP[291].

Salsalate. Acetylation of tau increases its propensity to aggregate, so inhibition of acetylation might be expected to be beneficial in 4R-tauopathies. In experimental animals, inhibition of acetylation with salsalate, a non-steroidal anti-inflammatory drug, reversed cognitive impairments[292]. However, in a single-centre phase I futility study of salsalate in PSP, the drug had no effect[293].

Microtubule stabilization. Given that tau detachment from microtubules destabilizes the microtubules and impairs axonal transport, microtubule stabilization is an attractive therapeutic target in 4R-tauopathies. Davunetide, a neurotrophic protein with microtubule-stabilizing activity, has been tested in this context in a multicentre, randomized controlled phase III trial in PSP but had no significant effects on primary or secondary end points[263].

TPI-287 is a paclitaxel derivative with microtubule-stabilizing activity and good intrathecal bioavailability, as it penetrates the blood–brain barrier. However, in a phase I study of TPI-287 in PSP and amyloid-PET-negative CBS, postural instability and dementia worsened within a 9-week treatment period[294].

Passive immunization. Passive immunization with monoclonal antibodies to the N terminus of tau has been proposed as a way to prevent the spreading of tau pathology via extracellular species. Two such antibodies have been tested in phase II studies in PSP[295,296]. The first is BIIB092 (also known as BMS-986168 or gosuranemab), which targets amino acids 15–23 of tau[297]. In a phase I study, BIIB092 reduced the concentration of free tau in the CSF in a dose-dependent manner in patients with PSP[298] but it had no disease-modifying effect in a randomized controlled phase II study[299]. The second antibody is ABBV-8E12 (also known as C2N-8E12 or tilavonemab), which targets amino acids 25–30 of tau. This antibody decreased insoluble tau and brain atrophy and improved motor and sensorimotor function in animal models, and had a good safety profile in patients with PSP in a phase I trial[295,296,300]. However, a randomized controlled phase II trial of ABBV-8E12 in PSP was terminated early owing to futility[301].

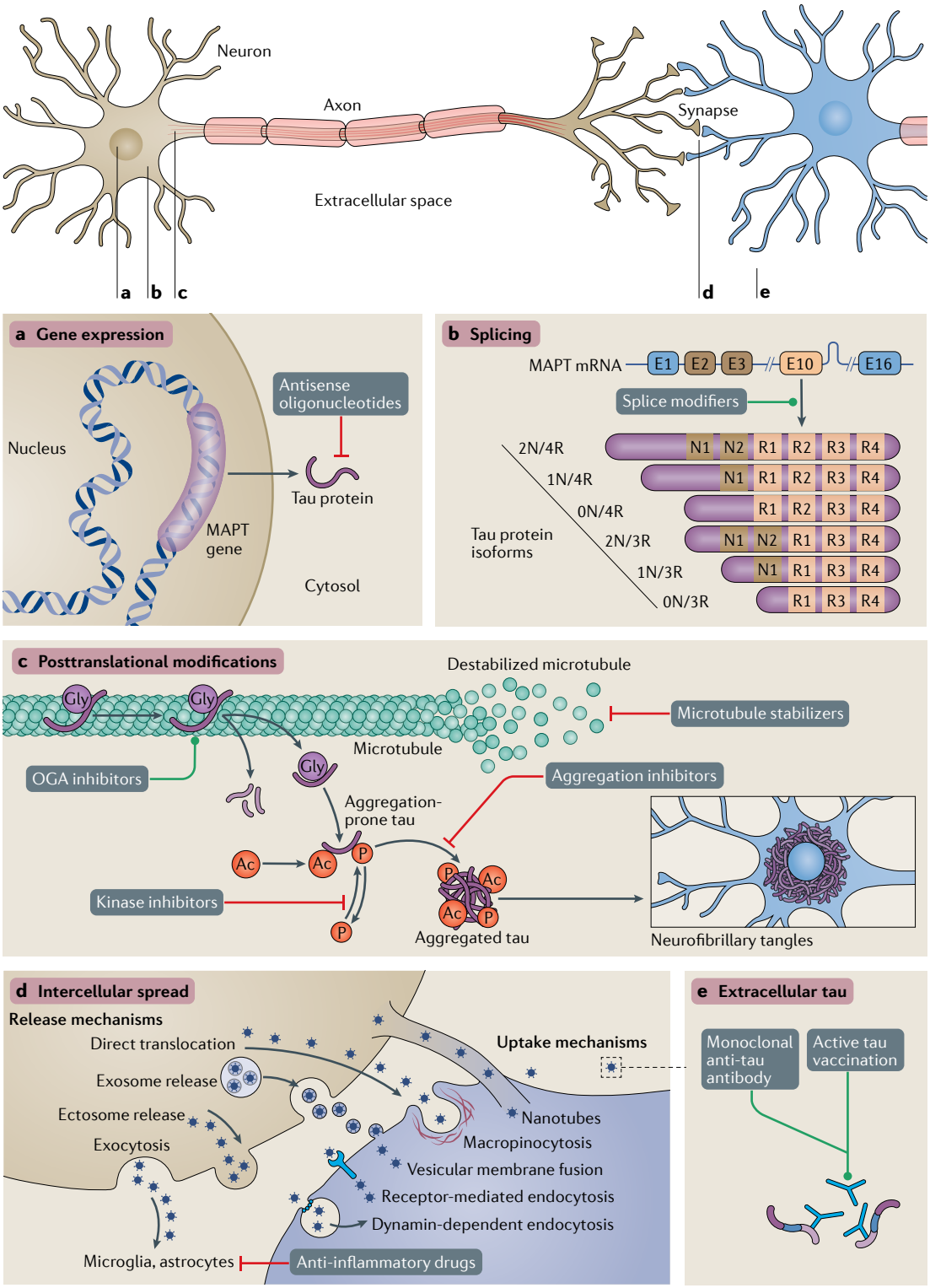
Emerging treatments

Although trials of disease-modifying drugs for 4R-tauopathies have been unsuccessful so far, they have provided insights that are being used to develop new therapeutics for PSP and related tauopathies (FIG. 4; TABLE 3). These drugs are at various stages of development.

Passive immunization. In experimental models (for example, brains of transgenic mice that had been injected with human AD brain extracts), the monoclonal antibody called UCB0107 (also known as bepranemab), which binds to amino acids 235–246 in the mid-region of tau, had better therapeutic efficacy than the N-terminal tau antibodies[302,303]. On this basis, the safety, tolerability and pharmacokinetics of UCB0107 is being tested in the PSP003 study, a participant-blind, investigator-blind, placebo-controlled phase I study, and patients will subsequently be enrolled into an open-label extension study to evaluate long-term safety and tolerability (TABLE 3).

Active immunization. Active immunization — the induction of a long-lasting antigen response against extracellular tau by stimulation of the immune system with an appropriate epitope — could help overcome the need for repeated antibody infusions and even become an option for primary prevention. AADVac1 is a vaccine that consists of tau fragments designed to trigger a B cell-mediated immune response, and a phase I study of this vaccine in patients with AD showed good tolerability and immunogenicity[304]. AADVac1 and another tau vaccine, ACI-35, are currently in phase I clinical testing for their ability to generate immune responses against extracellular tau species in tauopathies other than PSP, including AD and nfaPPA.

Small molecules. Tolfenamic acid is a non-steroidal anti-inflammatory drug that reduced tau phosphorylation in a mouse model of AD by reducing the activity of



the tau kinases cyclin-dependent kinase-5 (CDK5) and GSK3 (REF.[305]). On this basis, a 12-week, randomized controlled phase II study to assess the safety and efficacy of tolfenamic acid in patients with PSP is in progress (NCT04253132).

Previously, another small molecule called AZP2006, which is a small synthetic cationic amphiphilic compound, was claimed to block tau phosphorylation[306]. However, no further preclinical data have been published for AZP2006. Recruitment is underway for a phase II study of this molecule in PSP (NCT04008355).

Antisense oligonucleotides. Downregulation of tau expression by antisense oligonucleotides (ASO) can reduce tau aggregation in transgenic mice that express human tau[307], so the use of ASOs is a potential approach

◀ Fig. 4 | **Targets of therapeutic interventions according to aetiopathogenetic cellular and molecular mechanisms in 4R-tauopathies. a** | Genetic variants in *MAPT* affect the expression of tau protein. This expression can be modulated therapeutically with antisense oligonucleotides. **b** | Alternative splicing of *MAPT* mRNA at exon 10 generates three tau isoforms with three or four microtubule-binding repeat domains. The ratio of these isoforms can be changed by the use of therapeutic splice modifiers. **c** | Tau is a microtubule-binding protein and post-translational modifications modulate its interactions with microtubules. Inhibition of *O*-GlcNase (OGA) stabilizes *O*-linked *N*-acetylglucosamine (Gly) residues at tau. Inhibition of tau kinases reduces tau phosphorylation. Both approaches strengthen the affinity of tau for microtubules, reducing the detachment and aggregation of tau. Microtubule destabilization after tau detachment can be prevented with microtubule stabilizers. Acetylation (Ac) increases the propensity of tau to aggregate. **d** | Pathogenic tau species can spread from cell to cell via cellular release and uptake mechanisms. These species could be accessible to therapeutic interventions. Anti-inflammatory approaches might also interfere with tau spreading and neurodegeneration. **e** | Extracellular tau species are therapeutic targets for active and passive vaccination approaches. Adapted with permission from REF.[3], Elsevier.

to reducing tau pathology in humans. One phase I/II study of an ASO that targets tau (called MAPTRx) in patients with AD is ongoing, and a phase I trial of another ASO (NIO752) in PSP is ongoing (TABLE 3).

O-GlcNase inhibition. Post-translational modification of tau with the sugar molecule *O*-GlcNAc reduces binding of phosphate groups[308], so tau phosphorylation could be reduced by inhibition of *O*-GlcNase, which mediates this modification. The *O*-GlcNase inhibitor ASN120290 has been tested in a phase I study in healthy individuals, which showed that it is safe and well tolerated[309].

Conclusions and future directions

The introduction into the MDS–PSP diagnostic criteria of clinical features that are 'suggestive of' PSP puts an emphasis on early diagnosis. Prospective validation of the MDS–PSP criteria for suggestive of PSP is pending and will reveal how reliably they differentiate PSP from other neurodegenerative diseases in a prospective setting. Large, prospective cohort studies in PSP and CBD that include autopsy confirmation are ongoing worldwide[180,310,311], and high-quality natural history data are expected from these studies. These data are crucial, as disease-modifying therapies are being developed and early clinical diagnosis of PSP and CBD, as well as specific biomarkers for early disease stages, are needed.

Improvements in methodology are also needed to obtain better results from clinical trials. Clinical readouts are currently being developed to provide a more patient-centred perspective and higher sensitivity to changes; examples include the modified PSP rating scale[312] the PSP clinical disability scale[310] and the Cortical Basal Ganglia Functional Scale[313]. Other improvements being considered for future trials include longer observation periods, stratification of trial participants according to early clinical phenotype[146] or genotype[61], and consideration of mixed protein pathologies.

Imaging has been used to characterize many different aspects of brain structure and function in PSP–RS and CBS, and imaging biomarkers can differentiate 4R-tauopathies from PD and MSA. Consequently, we

Table 3 | **Clinical trials of treatments for tauopathies**

Disease	Name of drug	Mechanism	Phase	Status	Outcome	ClinicalTrials.gov
PSP	NIO752	Tau antisense oligonucleotide	I	Recruiting	NA	NCT04539041
	ABBV-8E12 (C2N-8E12, tilavonemab)	Monoclonal N-terminal human tau antibody	I	Completed	Safe	NCT02494024
	BIIB092 (BMS-986168, gosuranemab)	Monoclonal N-terminal human tau antibody	Ib	Completed	Safe, target engagement	NCT02460094
	UCB0107	Monoclonal mid-region human tau antibody	Ib	Ongoing	NA	NCT04185415 NCT04658199
	Tolfenamic acid	Reduction of tau phosphorylation	I/II	Not yet recruiting	NA	NCT04253132
	BIIB092 (BMS-986168, gosuranemab)	Monoclonal N-terminal human tau antibody	II	Completed	Safe, primary end point not met	NCT03068468
	ABBV-8E12 (C2N-8E12, tilavonemab)	Monoclonal N-terminal human tau antibody	II	Terminated due to futility	Safe, target engagement, primary end point not met	NCT02985879
	AZP2006	Increases progranulin levels, decreases tau phosphorylation	II	Recruiting	NA	NCT04008355
AD	ACI-35	Active tau immunization	I/II	Recruiting	NA	NCT04445831
	AADvac1	Active tau immunization	I	Completed	Safe, immunogenicity	NCT01850238 NCT02031198 NCT02579252 NCT03174886
	MAPTRx	Tau antisense oligonucleotide	I/II	Active, not recruiting	NA	NCT03186989
nfvPPA	AADvac1	Active tau immunization	I	Active, not recruiting	NA	NCT03174886
Healthy individuals	ASN120290 (ASN-561)	*O*-GlcNase inhibitor	I	Completed	Safe	NA

AD, Alzheimer disease; NA, not applicable; nfvPPA, non-fluent variant of primary progressive aphasia; PSP, progressive supranuclear palsy.

are starting to better understand the heterogeneity of 4R-tauopathies in terms of clinical phenotypes and underlying pathology, although more work is still needed. For example, little is known about the neuroimaging features of some of the most recently defined PSP variants[118]. Some PET ligands have promise as biomarkers of 4R-tau, but more autopsy studies are needed to better understand the biological underpinnings of ligand binding. Tau PET ligands that are specific for 4R-tau are urgently needed. Use of PET to investigate other pathophysiological aspects of disease, such as neuroinflammation[314] and synaptic loss[315], and their relationship with other neuroimaging metrics in 4R-tauopathies could also be informative.

Ultimately, a better understanding of 4R-tauopathies will lead to better biomarkers and improved targeting of treatment in future therapeutic trials. The developments discussed in this Review demonstrate the dynamic advances being made in this field with important unmet needs.

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