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Glial cells and adaptive immunity in frontotemporal dementia with tau pathology.

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Abstract

Neuroinflammation is involved in the aetiology of many neurodegenerative disorders including Alzheimer's Disease, Parkinson's Disease and Motor Neuron Disease. Whether neuroinflammation also plays an important role in the pathophysiology of frontotemporal dementia is less well known. Frontotemportal dementia is a heterogeneous classification which covers many subtypes, with the main pathology known as frontotemporal lobar degeneration. The disease can be categorised with respect to the identity of the protein that causes the frontotemporal lobar degeneration in the brain. The most common subgroup describes diseases caused by frontotemporal lobar degeneration associated with tau aggregation, also known as primary tauopathies. Evidence suggests that neuroinflammation may play a role in primary tauopathies with genome-wide association studies finding enrichment of genetic variants associated with specific inflammation-related gene loci. These loci are related to both the innate immune system, including brain resident microglia, and the adaptive immune system through possible peripheral T cell involvement. This review discusses the genetic evidence and relates it to findings in animal models expressing pathogenic tau as well as to *post-mortem* and positron emission tomography studies in human disease. Across experimental paradigms, there appears to be a consensus regarding the involvement of innate immunity in primary tauopathies, with increased microglia and astrocyte density and/or activation, as well as increases in pro-inflammatory markers. Whilst it is less clear as to whether inflammation precedes tau aggregation or *vice-versa;* there is strong evidence to support a microglial contribution to the propagation of hyperphosphorylated in tau frontotemporal lobar degeneration associated with tau aggregation. Experimental evidence - albeit limited – also corroborates genetic data pointing to the involvement of cellular adaptive immunity in primary tauopathies. However, it is still unclear whether brain recruitment of peripheral immune cells is an aberrant result of pathological changes or a physiological aspect of the neuroinflammatory response to the tau pathology.

Keywords

Frontotemporal Dementia, Microglia, Astrocytes, Tau, Adaptive Immunity

Short title

Immunity in frontotemporal dementia

Abbreviations

AGD = argyrophilic grain disease

BBB = blood brain barrier

bvFTD = behavioural variant FTD

CBD = corticobasal degeneration

CBS = corticobasal syndrome

DAMP = damage associated molecular patterns

GGT = globular glial tauopathy

FTD = frontotemporal dementia

FTLD = frontotemporal lobar degeneration

NfT = neurofibrillary tangle

PAMP = Pathogen associated molecular patterns

PHF = Paired helical filament

PiD = Pick's disease

PNFA = progressive non-fluent aphasia

PSP = progressive supranuclear palsy

PSPS = progressive supranuclear palsy syndrome

SD = semantic dementia

WT = wildtype

Introduction

Frontotemporal dementia (FTD) is a clinically and neuropathologically diverse group of progressive neurodegenerative disorders characterized by disturbances in behaviour, impulse control, personality and language. This is due to atrophy of the frontal and temporal lobes, known as frontotemporal lobar degeneration (FTLD). FTD is a common form of early onset dementia, occurring at a similar frequency to Alzheimer's disease in patients younger than 65 years. FTD has been reported to account for 5% of all dementia cases (Barker *et al.*, 2002); although it is typically considered an early-onset dementia and as such has been shown to account for closer to 10-12% of dementia cases in a cohort of patients under 65 years old (Fig. 1A) (Harvey *et al.*, 2003; Hogan *et al.*, 2016). Indeed, a Swedish population study found the mean age of diagnosis to be 69.6, with 30% of diagnoses occurring in patients younger than 65 (Nilsson *et al.*, 2014). Epidemiological studies show a varied point prevalence for FTD of 1 – 461 cases per 100,000 and 2.7-30 people per 100,000 are diagnosed with FTD each year (Onyike and Diehl-Schmid, 2013; Hogan *et al.*, 2016). In terms of progression, FTD patients were found to have a 33% shorter survival compared to Alzheimer's disease patients, with a faster decline in their cognitive abilities (Rascovsky *et al.*, 2005).

The clinical diagnosis of FTD is based on behavioural symptoms, neuropsychological examination and brain imaging (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011), and separate from the *post-mortem* pathological diagnosis which is based on the nature of the protein that aggregates to cause FTLD (FTLD-TDP, FTLD-FUS or FTLD-tau) (Fig. 1B). The proteins that aggregate (TDP43, Fused in Sarcoma protein, or tau) form characteristic cytoplasmic or nuclear inclusions that are observed histopathologically. Among the FTLD sub-classifications, the FTLD-tau represents 50% of all FTLD cases (Boxer *et al.*, 2013) and can be further subdivided by the specific identity of tau inclusions that occur in neurons, neurites, and glia (including astrocytes and oligodendrocytes) (Fig. 3) (Kovacs, 2015). "FTLD-tau" encompasses sporadic and inherited primary tauopathies including progressive supranuclear palsy (PSP), Pick's disease (PiD), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), FTLD with genetic mutations in the gene encoding Tau, *MAPT* (FTLD-MAPT) and globular glial tauopathy (GGT).

The FTLD-tau diseases are characterised by a specific neuropathological phenotype defined by the particular tau isoforms expressed (Kovacs, 2015). The alternative splicing of the tau encoding gene (*MAPT*) can create proteins that have either three or four repeats in their C-terminal amino acid sequences, known as 3R tau and 4R tau (Sergeant *et al.*, 2008; Snowden

et al., 2011). 3R tau is expressed in the brain from foetal development to adulthood; whereas 4R tau is expressed only in adulthood (Kosik *et al.*, 1989). Changes to the 3R:4R tau ratio in tau inclusions define the various forms of FTLD-tau. Interestingly, it was observed that the pattern of phosphorylation between genetic and sporadic FTLD-tau cases was similar, and position of the mutation in FTLD-MAPT patients has no effect on the amount of tau deposition (Shiarli *et al.*, 2006). Notably, there is not always a direct association between the clinical and neuropathological diagnosis. Indeed, in a survey of 125 patients split by clinical diagnosis into five categories, only the patients with semantic dementia (SD) had the same underlying neuropathological diagnosis (PiD, n = 3). Also, 90% of patients with a clinical PSP syndrome (PSPS) had the corresponding PSP pathology. Of the other three clinical diagnoses (behavioural variant FTD = bvFTD, progressive non-fluent aphasia = PNFA, and corticobasal syndrome = CBS), the underlying pathology was variable between AGD, CBD, PSP and PiD (Josephs *et al.*, 2011; Perry *et al.*, 2017). This heterogeneity has been shown across several studies and is most prevalent in bvFTD and PNFA (Fig. 2). This is important when comparing studies assessing clinical, genetic and biological findings in FTD patients.

Genetic risk for FTLD-tau

There is a direct genetic component to FTLD-tau with 53 genetic mutations in the MAPT gene known to cause an inherited form of the disease (Ghetti *et al.*, 2015). Although the tau pathology is heterogeneous across these mutations (Shiarli *et al.*, 2006), there is evidence of neuroinflammation in patients with MAPT mutations (Lant *et al.*, 2014; Bevan-Jones *et al.*, 2019).

This section will focus specifically on genome-wide association studies (GWAS) that have highlighted genetic risk related to genes that are involved in innate and adaptive immunity, many of which are related to inflammatory signalling pathways and/or functions of mononuclear phagocytes, including microglia (Table 1). Since neurodegeneration and neuroinflammation are highly interlinked, it is not surprising that some of these risk variants are common across neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and unspecified FTD (Ferrari *et al.*, 2017). Gene variations identified as risk factors for FTD include:

Triggering Receptor Expressed on Myeloid cells 2 (TREM2)

One genetic risk factor for FTD is in the gene encoding the innate immune receptor TREM2. One set of variants in *TREM2* and its ligand TYRO protein tyrosine kinase binding protein (*TYROBP*) have been implicated in a rare autosomal recessive disorder known as Nasu-Hakola disease (NHD), which causes a progressive FTD-like dementia due to white matter degeneration and with presence of tau pathology (Paloneva *et al.*, 2000; Kaneko *et al.*, 2010) (Satoh *et al.*, 2018). In addition, description of *TREM2* mutations in patients presenting with FTD-like dementia (Chouery *et al.*, 2008; Guerreiro *et al.*, 2013) suggests that *TREM2* mutations can cause dementia associated with tau pathology and thus they may have relevance for FTD.

Mutations in *TREM2* are known to increase Alzheimer's disease risk. One of these, the R47H *TREM2* mutation, is also associated with behavioural variant (bv)FTD (Giraldo *et al.*, 2013), combined FTD (Rayaprolu *et al.*, 2013) and unspecified FTD - along with three other *TREM2* mutations (Q33X, T66M and S116C) (Borroni *et al.*, 2014). Two studies detected enrichment of other Alzheimer's disease-related *TREM2* mutations including R62H, T96K, L221P, R47H and Q33X in unspecified FTD patients (Lattante *et al.*, 2013; Cuyvers *et al.*, 2014). However, no significant association was detected for any individual variant, despite a three-fold increase in the R47H mutation in FTD in the latter study (Cuyvers *et al.*, 2014). Interestingly, another study confirmed the R47H variant association with Alzheimer's disease but not in a cohort of 682 FTD patients (Ruiz *et al.*, 2014).

The discrepancies between these studies might be explained by the difficulty in recruiting patients with a low prevalence disease and the heterogeneity of the FTD often referred to as 'unspecified'. It may also be due to the background populations of the patients included in each study. It must be noted that from these GWAS studies, a relationship between *TREM2* variants and FTLD-tau is impossible to conclude as these studies only look at clinical FTD as a whole. Also, the lack of association with PSP may rule out TREM2 as the common source of innate immune dysfunction across FTLD-tau subtypes (Rayaprolu *et al.*, 2013). Conversely, no association was found between FTLD-TDP and the *TREM2* R47H mutation (Lill *et al.*, 2015), suggesting associations in mixed cohorts may due to FTLD-tau subtypes. In support of this contention, Alzheimer's disease and mild cognitive impairment (MCI) patients that carried the risk allele had increased tau in their cerebrospinal fluid (CSF) compared to Alzheimer's disease and MCI non-carriers, suggesting a link between TREM2 and tau pathology (Lill *et al.*, 2015). This link is also relevant to FTD as although *TREM2* expression was not found to be

significantly increased in clinically diagnosed FTD patients, CSF soluble TREM2 was significantly positively correlated to CSF total tau and phosphorylated tau across all FTD subtypes (Woollacott *et al.*, 2018). However, another study did not find alterations of TREM2 levels in FTD patients' CSF (Kleinberger *et al.*, 2014). Consequently, despite conflicting evidence, the R47H *TREM2* mutation may be the most important of the *TREM2* variants for FTD risk, but it must be noted that this variant is rare, affecting about 4% of FTD patients (Borroni *et al.*, 2014).

Physiologically, TREM2 facilitates the phagocytosis of apoptotic neurons whilst also dampening the pro-inflammatory response (Takahashi *et al.*, 2005). The balance of these two functions of TREM2 is important in mediating an appropriate inflammatory response. *TREM2* mutations in FTD have been associated with a loss of function of the TREM2 protein (Kober *et al.*, 2016).

Genetically altering *Trem2* expression levels in mice has been shown to alter microglia activity alone and in the context of tau pathology (Fig. 4). *Trem2* knockdown causes decreased microglial phagocytotic ability and increased microglial pro-inflammatory signalling in wildtype (WT) mice (Takahashi *et al.*, 2005) and *in vitro* (Jiang *et al.*, 2018). The effect of *Trem2* knockdown on tau pathology is controversial with studies showing that TREM2 deficiency leads to exacerbated levels of phosphorylated tau in P301S mice (Jiang *et al.*, 2015), APP mice (Leyns *et al.*, 2019) and human tau expressing mice (Bemiller *et al.*, 2017). Whereas other studies also using P301S mice (Sayed *et al.*, 2018) or PS19 mice (Leyns *et al.*, 2017) found that *Trem2*-/- had no effect on phosphorylated tau levels. Interestingly the former studies used mice with 2-6 months of induced phosphorylated tau expression, compared to 8-9 months in the latter studies. This suggests that the initial loss of function in *Trem2* may prevent microglia from responding to tau pathology, but later the reduced activation of microglia may reduce neurodegeneration and atrophy (Sayed *et al.*, 2018).

In humans, there was a stronger relationship between sporadic FTD and the heterozygous R47H mutation than with the homozygous mutation that causes NHD, implying different effect of partial or complete loss of *TREM2*. Indeed *Trem2* -/+ Tau P301S mice had increased tau pathology and microglial activation compared to controls and to *Trem2* -/- P301S mice (Sayed *et al.*, 2018). Interestingly, expression of mutant *Trem2* fails to stimulate phagocytosis (Kleinberger *et al.*, 2014) with effects more in line with the *Trem2* knockout (Leyns *et al.*, 2019).

Whilst the genetic evidence in humans does suggest that *TREM2* plays a role in FTD, it should be considered carefully when comparing to animal data. Experimental animal studies

have shown TREM2 expression in microglia (Schmid *et al.*, 2002; Kiialainen *et al.*, 2005; Takahashi *et al.*, 2005), but there is scant evidence as to whether its expression is matched in humans (Sessa *et al.*, 2004), with one study showing TREM2 expression restricted to intravascular monocytes and monocytes recruited into the brain parenchyma as a consequence of blood-brain barrier breakdown following acute infarction (Fahrenhold *et al.*, 2018). Despite our lack of knowledge on TREM2 protein in humans, the genetic evidence supports a role for TREM2 mutations in FTD that might be driven by myeloid cells including macrophages and microglia.

TYRO protein tyrosine kinase binding (TYROBP)

TYROBP (also known as DAP12) is a TREM2 adapter protein encoded by the *TYROBP* gene. The activation of TREM2 leads to TYROBP phosphorylation which causes downstream changes to the cytoskeleton of microglia to allow phagocytosis (Linnartz *et al.*, 2010). This process allows for the clearance of neurons undergoing apoptosis in a non-inflammatory environment (Takahashi *et al.*, 2005). Like *TREM2, TYROBP* mutations were first found in Alzheimer's disease patients (Pottier *et al.*, 2016). A study across Alzheimer's Disease, unspecified FTD and other dementias found two patients with variants of *TYROBP*, but these were deemed to be non-pathogenic (Darwent *et al.*, 2017), suggesting that mutations in *TYROBP* do not present a risk for neurodegenerative disorders. Whilst the relevant literature is sparse, it seems that TREM2 has a clearer effect than TYROBP on neurodegenerative diseases such as FTD. However, loss of function mutations in TYROBP have been shown to cause NHD (Paloneva *et al.*, 2000), and in TYROBP$^{-/-}$ P301S mice, a reduction in microglial numbers and cell body size (associated with decreased phagocytic state) was seen compared to TYROBP$^{+/+}$ P301S mice, with increased spread and phosphorylation of tau (Audrain *et al.*, 2019).

Leucine-rich repeat kinase 2 (LRRK2)

LRRK2 is the primary cause of early-onset familial Parkinson's disease. The discovery of a genetic relationship between LRRK2 and FTD (Ferrari *et al.*, 2017) is supported by the presence of *LRRK2* mutations in patients with FTLD pathology with (Ling *et al.*, 2013) and without tau mutations (Dachsel *et al.*, 2007). Since LRRK2 is involved in modulating TNFα expression which can, in turn, alter microglial activity, an inflammatory role for LRRK2 in FTD can be proposed (Moehle *et al.*, 2012). It is known that hyperphosphorylated tau is present in Parkinson's disease patients with LRRK2 mutations (Henderson *et al.*, 2019). However,

whether LRRK2 is associated with tau pathology in FTLD-tau is less well known. A screen of 1039 PSP and 145 CBD patients for *LRRK2* found three mutations in two PSP patients (G2019S, R1441C and A1413T) and one in a CBD patient (R1707K) (Sanchez-Contreras *et al.*, 2017). Of note, in P301S mice, tau pathology develops independently of LRRK2 mutations, although the *LRRK2* G2019S mutation does promote the neuronal spread of normal tau (Nguyen *et al.*, 2018).

TBK1 binding protein 1 (TBKBP1)

TBKBP1 is another gene determined by GWAS to be related to FTD (Broce *et al.*, 2018). Like LRRK2, TBKBP1 plays a part in the signal transduction cascade that modulates TNFα signalling (Bouwmeester *et al.*, 2004). Interestingly, the link between genes that control TNFα expression and FTD are supported by evidence of increased TNFα in the CSF of FTD patients (Sjogren *et al.*, 2004) and the brains of animal models of chronic neurodegenerative diseases (Krabbe *et al.*, 2017), but the role of the protein in the disease remains to be explored.

Apolipoprotein (APOE):

APOE has long been known as the most important risk factor in Alzheimer's disease with the ε4 allele genotype conveying a significant risk (Corder *et al.*, 1993; Farrer *et al.*, 1997). Initially, *APOE* ε4 was not considered as a risk factor for FTD (Geschwind *et al.*, 1998), but recent studies have found, as for Alzheimer's disease, that the ε4 allele increases risk whereas ε2 was protective in unspecified FTD (Ferrari *et al.*, 2017) and bvFTD (Mishra *et al.*, 2017). The *APOE* ε4 association with FTD was confirmed in a meta-analysis of 28 studies, but the study failed to confirm a protective role for APOE ε2 (Rubino *et al.*, 2013).

Neuropathological differences have been detected in bvFTD *APOE* ε4 carriers, who have enhanced atrophy in the frontal lobe and ventral striatum (Boccardi *et al.*, 2004; Agosta *et al.*, 2009). This suggests that ε4 might accelerate the thinning in areas susceptible to ageing, as the effect is also observed in ε4 carrying healthy subjects (Espeseth *et al.*, 2008; Fennema-Notestine *et al.*, 2011). So not only does *APOE* affect the risk of developing FTD, but it also alters the severity and progression of neurodegeneration. *APOE* ε4 was shown to lead to increased phosphorylated tau levels in Aβ accumulating mice (Inbar *et al.*, 2010) and P301S tauopathy mice (Shi *et al.*, 2017). Therefore, apoE may impact on phosphorylated tau expression which may further contribute to FTD development. However, the mechanism by which apoE increases FTD risk remains unknown.

APOE ε4 is also linked with inflammatory signalling and repair (Rubino *et al.*, 2013). In the brain, APOE is mostly produced by microglia and astrocytes (Liao *et al.*, 2017). The ε4 allele is associated with increased expression of the pro-inflammatory Toll-like (TLR)-4 receptor and decreased expression of the anti-inflammatory signalling IL4 receptor (Tai *et al.*, 2015). A study reported that *APOE* ε4 allele increases cortical thinning and microgliosis and stimulated a three-fold increase in IL1α/β and TNFα compared to ε3 allele carrying tauopathy mice (Shi *et al.*, 2017). It has since been discovered that the microglial activation (facilitated by *APOE* ε4) is largely responsible for neurodegeneration in tauopathy mouse models, rather than tau mediated neurotoxicity (Shi *et al.*, 2019).

C-X-C chemokine receptor type 4 (CXCR4)

A variant in the gene encoding the chemokine receptor CXCR4 has been highlighted as an inflammatory-related gene which conveys a risk associated with PSP and PiD (Bonham *et al.*, 2018). This was supported by the detection of increased CXCR4 expression and activated microglia in human FTD cases and P301L tau mouse model (Bonham *et al.*, 2018).

Human leukocyte antigen (HLA)

One study found an overlap in genetic risk between FTD (excluding CBD and PSP) and immune-mediated diseases (Bonham *et al.*, 2018). The genes in question centre around loci on Chromosome 6 that correspond to the Human Leucocyte Antigen (HLA) region (which is rich in genes associated with microglial functions) - these included HLA-A, -C, -F, -DRA, and –DRQ. Expression of several of these genes is particularly enriched in microglia compared to other cells of the brain. In addition to HLA region genes, FTD susceptibility associations were found at *LRRK2*, *TBKBP1*, *TGBDP5* and *MAPT* loci, which are all co-expressed with the HLA genes (Broce *et al.*, 2018). Another study corroborated the interaction of *LRRK2* and *TBKBP1* with HLA region genes, as well as interactions between MAPT and HLA regions (Taskesen *et al.*, 2017), suggesting a genetic link between tau expression and a reactive microglial phenotype. Another study found a single nucleotide polymorphism (rs9268877), in an intergenic region between the HLA-DRA and HLA-DRB5 genes, to be a risk factor for both FTD and Parkinson's disease leading to the changed expression of several HLA genes (Ferrari *et al.*, 2017), with roles in clearing extracellular debris (Sokolowski and Mandell, 2011).

A meta-analysis comparing FTD (grouping bvFTD, SD, PNFA and FTD with motor neuron disease) and controls identified 29 single nucleotide polymorphisms in the HLA region

significantly associated with the disease. This included genes encoding for the human major histocompatibility complex (MHC) associated genes *BTNL2*, *HLA-DRA* and *HLA-DRB5* (Ferrari *et al.*, 2014), emphasising the link between FTD and HLA and thus the role of the innate (but also potentially for the adaptive) immune system in FTD.

HLA-DR expression, reflecting microglial activation, was reported increased in PSP (Ishizawa and Dickson, 2001), furthermore, increased neuronal expression of HLA-DR was found in two out of 14 cases of PiD (Hollister *et al.*, 1997). The key function of MHC molecules is to present antigen-derived peptides to T cells, and these data further support that an intricate interplay between T cells, microglia and/or neurons may play an instrumental role in FTD pathophysiology.

RAB38/Cathepsin C (CTSC)

Two other gene variants associated with FTD, with relevance for cellular adaptive immunity, were found at the *RAB38* and *CTSC* loci. Both genes have roles in lysosomal function, signalling in immune cells and aid pathogenic phagocytosis (Ferrari *et al.*, 2014). This is of particular interest considering two FTD causing genes (*CHMMP2B* and *GRN*) are related to dysfunctions in lysosomal biology and may suggest a similar occurrence in tau-related FTD (Hardy and Rogaeva, 2014).

Overall, the genetic data pertaining to inflammation-related genes and FTD highlights multiple genes that convey risk for the development of the disease. Often, these genes do not usually provide risk for just one single neurodegenerative disorder but share risk between various disease phenotypes. Thus, the expression of disease-related gene variants in different parts of the brain may lead to the development of different disorders (Ferrari *et al.*, 2016). When comparing FTD, Alzheimer's disease and Parkinson's disease for genetic risk overlap, FTD shares variants on loci for *MAPT* and *HLA* regions with Parkinson's disease, and on loci for *APOE* with Alzheimer's disease (Ferrari *et al.*, 2017). This genetic overlap implies that various mutant loci summate to increase the disease risk for sporadic FTD rather than any single gene being solely responsible for risk (with the exception of FTLD-MAPT cases). Despite the identification of FTD risk factors associated with both innate and adaptive immunity, our knowledge of the immune responses associated with primary tauopathies remains scarce.

Neuroinflammation in tauopathy mouse models

Microglia: Physiological roles

Microglia, the resident mononuclear phagocytes of the brain, are responsible for coordinating and enacting responses to pathogenic and damaging material in the CNS. Microglia are originally differentiated from myeloid progenitor cells in the embryonic yolk sac and enter the CNS during early embryonic development (Ginhoux *et al.*, 2010). They express a unique pattern of genes that distinguishes them from other myeloid cells or other cell types in the brain (Butovsky *et al.*, 2014), driven by the expression of the anti-inflammatory cytokine, transforming growth factor (TGF-β1) (Butovsky *et al.*, 2013). In humans, microglia represent 0.5 to 16% of the total brain cells depending on the brain area (Mittelbronn *et al.*, 2001), with significantly more cells in the white than in grey matter. The microglial population remains stable over the lifetime with a slow turn-over (Askew *et al.*, 2017) as the average microglial lifespan is ~4 years in humans (based on ^{14}C dating) (Reu *et al.*, 2017). Despite this, they are still the main identified proliferating cells in the human brain from the age of 3 years old (Dennis *et al.*, 2016).

In the healthy brain, microglia display a homeostatic phenotype (Butovsky *et al.*, 2014) with ramified morphology, small cell bodies and fine processes. Homeostatic microglia are highly dynamic and motile cells, which help regulate synaptic plasticity and communication (Salter and Stevens, 2017). They also continually survey their microenvironment for potential pathogen- or damage-associated molecular patterns (PAMPs and DAMPs), through pattern recognition receptors on their processes (Nimmerjahn *et al.*, 2005). Upon discovery of PAMPs/DAMPs, pro-inflammatory protein complexes known as inflammasomes are subsequently activated. The microglial inflammasome NLRP3 (NOD-, LRR- and pyrin domain-containing 3) responds to activation through two pathways: (i) the MyD88 (MYD88)–nuclear factor-κB (NF-κB) pathway and (ii) through heterodimerisation and aggregation with apoptosis-associated speck protein (ASC), which then activates caspase-1. The MYD88 pathway leads to the production of pro-IL1β and the caspase-1 pathway cleaves pro-IL1β to IL1β, which then exerts its pro-inflammatory response on microglia (Amin *et al.*, 2017; Heneka *et al.*, 2018). Once activated, microglia undergo a range of morphological changes as well as increasing motility and proliferation, and altering their signalling patterns (Franco Bocanegra *et al.*, 2018; Franco-Bocanegra *et al.*, 2019). They withdraw many of their branches and their cell bodies take on a more ameboid shape. The cells can also migrate down a concentration gradient of certain signalling molecules to the site of injury to phagocytose any debris. They

also signal to other cells by releasing pro-inflammatory cytokines and chemokines such as TNFα, IL1α, IL1β, IL6 and CCL2 (Wang *et al.*, 2015) which propagate the immune response to the injury. The homeostatic environment is re-established by negative feedback signalling through anti-inflammatory cytokines including IL4, IL10 and IL13 (Lively and Schlichter, 2018), which inhibits the production of inflammatory cytokines (Lobo-Silva *et al.*, 2016; Mori *et al.*, 2016) and decreases astrocytic activation (Brodie *et al.*, 1998). Although the inflammatory condition occurs naturally to prevent damage, it can become exacerbated and/or protracted with microglia becoming chronically activated (Godbout *et al.*, 2005). This means that the inflammatory mechanism may become damaging rather than restorative, contributing to the neurodegeneration observed in several diseases.

As part of the ageing process, microglia become more reactive with the upregulation of genes coding for inflammasome signalling, Fcγ receptors and HLA (Cribbs *et al.*, 2012). Morphologically, microglia change from highly ramified cells towards a more ameboid shape with reduced branching and arborization of their processes (Davies *et al.*, 2017). These changes suggest a loss of the microglial neuroprotective functions (Streit *et al.*, 2014). This is consistent with microglia acquiring a primed or trained phenotype as part of the disease process (Neher and Cunningham, 2019). A transcriptomic study in aged human microglia showed that ageing causes loss- and gain-of-function changes to provide a unique age-related microglia phenotype (Olah *et al.*, 2018). It is also now recognised that microglia will adopt different profiles partly driven by their environment (Boche *et al.*, 2013).

Contribution to the spread of tau

To understand the impact of microglia on tau pathology, depletion of the microglial population was performed by blocking the microglial specific Colony Stimulating Factor 1 receptor (CSF1R). CSFR1 inhibition by PLX3397 treatment (290mg/kg in chow, for 3 months in 12-month-old mice) decreased microglia by ~30%, but this was insufficient to modify tau pathology, astrocyte activation or neuronal loss in 15 months old Tg4510 mice (Bennett *et al.*, 2018). This may be due to a compensatory mechanism by the remaining microglia, which showed increased CD68 and CX3CR1 expression, suggesting increased microglial phagocytosis and migration (Bennett *et al.*, 2018). Another study used a lower dose in younger mice (45mg/kg, in 3.5-month-old mice) and showed an 80% loss of microglial population, resulting in decreased tau propagation in the hippocampus by ~50% in Tau P301S mutant mice and ~66% in an adenovirus P301L vector model (Asai *et al.*, 2015). These findings were

confirmed in P301S mice with the CSFR1 inhibitor JNJ-527 that reduced the microgliosis to control microglial numbers, with the consequence of also reducing the number of neurofibrillary tangles (NfTs) and tau oligomers as well as decreasing the ratio of aggregated: total tau (Mancuso *et al.*, 2019). The manipulation of microglia in the context of tau pathology supports the idea that they are central to the spread of tau from the early stages of the disease when pathology develops.

The 'spreading' of tau describes the process by which pathological tau moves from cell to cell. However, another form of tau propagation is 'seeding', where pathological tau formations causing the aggregation and misfolding of normal monomeric tau (DeVos *et al.*, 2018). Although tau mRNA is not expressed by microglia, tau seeds were isolated and released from microglia derived from Tg4510 mice and human tauopathies (Hopp *et al.*, 2018). The NLRP3-ASC inflammasome may be involved in this microglial propagation, with the inhibition of NLRP3 or a deficiency in ASC, reducing the seeding of exogenous and endogenous tau in PS19 mice (Stancu *et al.*, 2019). A similar reduction in phosphorylated tau was shown in THY-Tau22 mice with either ASC or NLRP3 knockouts.

Since pathological tau accumulates in neurons in FTLD-tau, the mechanism(s) by which it enters microglia are uncertain. It is acknowledged that physiological tau is secreted from neurons as shown *in vitro* (Karch *et al.*, 2012; Pooler *et al.*, 2013) and in the extracellular compartment of mouse brains *in vivo* (Yamada *et al.*, 2014). The degree to which neurons secrete pathological tau is harder to ascertain. *In vitro* experiments showed phosphorylated tau release from neurons in exosomes which were then taken up by other neurons and microglia, but not astrocytes (Wang *et al.*, 2017). The propagation of tau from microglia to other microglia/neurons is also hypothesised via the secretion of microglial exosomes (Asai *et al.*, 2015). Other pathways include microglia phagocytosing ghost tangles (which remain after the death of the neuron) (Gendreau and Hall, 2013) or inactive synapses (Vogels *et al.*, 2019) (reported to contain tau (Zhou *et al.*, 2017)) or through phagoptosis - the phagocytosis of live cells (Brown and Neher, 2014).

Whilst microglia are known to participate in the spread of tau pathology, they can also participate in its clearance following passive immunisation against tau (Luo *et al.*, 2015). Then questions arise of the factors involved in the switch of microglia from clearing tau to spreading it. It may be that microglia are less able to process hyperphosphorylated tau or that microglia themselves become dysfunctional in their ability to breakdown internalised material. The latter suggestion is supported by the genetic evidence which identifies lysosomal related gene mutations as risk factors for FTD.

Neuroinflammatory environment

Links between phosphorylated tau and neuroinflammation have been observed in experimental models. Mice overexpressing phosphorylated human tau (P301S) exhibit a proinflammatory phenotype in the brain and spinal cord, particularly in close proximity to tau+ cells. This was characterised by high expression of IL1β and cyclooxygenase (COX)-2 (Bellucci *et al.*, 2004), which are inflammatory molecules involved in the induction of neuronal cell death (Andreasson *et al.*, 2001). Interestingly, these findings were not replicated in mice that overexpressed WT tau (ALZ17 mice) (Bellucci *et al.*, 2004). Mice with a different variant of phosphorylated tau (R406W) – and which develop tau inclusions primarily in neurons – also exhibit astrogliosis (by GFAP) and microgliosis (by F4/80) (Ikeda *et al.*, 2005). Similarly in the P301L Tau mouse model, increased Iba1+ and MHCII+ microglia were seen close to cells containing phosphorylated tau, as also observed in PSP and PiD cases (Sasaki *et al.*, 2008).

Tau may induce neuroinflammation through the NLRP3 inflammasome which is increased in THY-Tau22 mice and FTD patients (Ising *et al.*, 2019). Indeed, tau seeds increase IL1β release (a consequence of NLRP3-ASC activation) but not when ASC is knocked out. This suggests that tau seeds activate the NLRP3-ASC inflammasome to induce neuroinflammation (Ising *et al.*, 2019). Memory impairments are also rescued by ASC deficiency, which may point to inflammasome activation as an intermediate that activate microglia to phagocytose synapses, leading to cognitive changes.

Synaptic phagocytosis by microglia

Additional evidence for the link between synaptic phagocytosis by microglia and cognitive changes comes from experimental studies. Microglial activation was shown to coincide with the loss or impaired function of synapses in the hippocampus of PS19 mice (Yoshiyama *et al.*, 2007) and P301S mice in the cortex (Hoffmann *et al.*, 2013). In both areas, this phenomenon preceded NfT formation. Tg4510 mice also have a reduction in pre- and post-synaptic spines, leading to a positional mismatch and reduced synaptic activity (Jackson *et al.*, 2017), and the electrophysiological activity of synapses in THY-Tau22 mice was similarly reduced with decreased excitatory postsynaptic potentials (Burnouf *et al.*, 2013; Ahmed *et al.*, 2015). These early synaptic changes are known to result from inflammatory processes through the actions of glial cells (Henstridge *et al.*, 2019). Interestingly the complement system may have a role in the microglial led phagocytosis of synapses and seems to be of interest in different neurological

conditions including Alzheimer's disease and schizophrenia. In P301S mice, complement 1q (C1q) was expressed on postsynaptic densities and its levels correlated with phosphorylated tau levels, and inhibition of C1q reduced microglial synaptic removal (Dejanovic *et al.*, 2018). Upregulation of C1q in THY-Tau22 mice increased tau hyperphosphorylation and was correlated with the loss of glutamatergic synapses (Carvalho *et al.*, 2019).

Whilst microglia were found to participate in synaptic degeneration and mediate tau propagation, phosphorylated tau *per se* can be toxic to microglia, with soluble tau extracted from Alzheimer's disease patients or THY-Tau22 mice leading to ~1% of primary microglia remaining viable (Sanchez-Mejias *et al.*, 2016).

Differences between the experimental models

Overall, experimental models support an interaction between tau and microglial activation leading to a pro-inflammatory environment. However, one of the main questions with respect to inflammation and tau pathology is which comes first. In forms of tauopathy caused by genetic mutations in tau, and hence in mouse models, the mutation initiates the pathological process. However, in sporadic forms, the process of events is less clear. PS19 mice, seem to display microglial activation and loss of synapses in the hippocampus before tangle formation (PHF1) is found (Yoshiyama *et al.*, 2007). However, another study in P301S mice reported that phosphorylated tau (PHF6 and AT8) was present at significant levels 3.5 months before activation related changes were seen to microglial morphology or protein expression (van Olst *et al.*, 2020). These differences suggest the microglial response is triggered by the build-up of phosphorylated tau, before the formation of NfTs. Also comparing results in different models can be challenging. For example, comparing THY-Tau22 mice and P301S mice revealed that although both models had increased tau pathology, the THY-Tau22 mice had significantly less phosphorylated tau (AT8, AT100 and AT180) compared to P301S mice. In addition, the THY-Tau22 mice had significantly less expression of genes related to microglial activation compared to P301S (Romero-Molina *et al.*, 2018). Despite their difference though, microglia activation was a common feature of both models confirming the link between tau pathology and neuroinflammation.

Astrocytes: Physiological roles

Astrocytes are star-shaped glial cells that are involved in maintaining the homeostasis of the brain by providing nutrients for neurons (Prebil *et al.*, 2011), stabilising the osmolarity of the

extracellular environment and supporting synapses (Santello *et al.*, 2019). Astrocytes participate in gliotransmission at the synapse where they affect synaptic excitability through the release of ATP, D-serine and glutamate (Halassa *et al.*, 2007) or through ion, or neurotransmitter uptake (Mederos *et al.*, 2018). They also wrap end-feet around cerebral blood vessels contributing to the blood-brain barrier and participate in neurovascular coupling (Mishra *et al.*, 2016). Besides these homeostatic functions, astrocytes are key players in neuroinflammatory responses, responding to pathogens, CNS injuries, abnormal proteins and inflammatory factors including cytokines, chemokines and neurotrophic factors as well as releasing them (Farina *et al.*, 2007). This has been shown to lead to astrogliosis via pro-inflammatory cytokine signalling (Penkowa *et al.*, 1999; Herx and Yong, 2001) and the propagation of the immune response by the secretion of chemokines such as CCL2 which is involved in leukocyte recruitment (Babcock *et al.*, 2003).

It has been suggested that when astrocytes are activated, they may display one of at least two phenotypes. A1 astrocytes are thought to be harmful as they upregulate complement proteins which lead to synaptic degradation. A2 astrocytes are thought to be neuroprotective, with increased release of neurotrophic factors (Liddelow *et al.*, 2017). The importance of bidirectional communication between microglia and astrocytes (via physical contacts and secreted molecules) is also now well-acknowledged. Experimental studies imply that microglia define the functions of astrocytes. Activated microglia are important in this process as they release TNFα, IL1α and C1q which promote astrocyte activation towards the A1 phenotype (Liddelow *et al.*, 2017). Conversely, astrocytes appear to regulate microglial phenotypes and functions including motility and phagocytosis (Jha *et al.*, 2018). Ageing also seems to generate an overall activating effect on astrocytes, leading to morphological changes e.g. shortening and thickening of processes. Other age-related hallmarks include increased cell density and increased expression of the astrocytic protein GFAP (glial fibrillary acidic protein) (Jyothi *et al.*, 2015). Like for microglia, different astrocyte profiles have been identified (Zamanian *et al.*, 2012) with one driven by ageing (Clarke *et al.*, 2018), adding to the complexity of these cells.

Astrocytes in tauopathy mouse models

Knowledge on the relationship between tau and astrocytes is scarce, but astrocytes may play an important role in tauopathies with astrogliosis as a key feature in mouse models (Allen *et al.*, 2002; Laurent *et al.*, 2014; Sidoryk-Wegrzynowicz *et al.*, 2017). This is consistent with the

presence of phosphorylated tau in astrocytes being documented in several FTLD subtypes (Fig. 3) (Komori *et al.*, 1998; Kobayashi *et al.*, 1999; Dickson *et al.*, 2011). Astrocytes do not express tau endogenously but are able to take up tau. This has been observed *in vitro* (Perea *et al.*, 2019) and in the PS19 mice with increased astrocytic lysosomal activity reported (Martini-Stoica *et al.*, 2018). In addition, expression of phosphorylated tau (P301L) under the control of an astrocytic promoter led to the presence of tufted astrocytes and astrocytic plaques, as seen in FTLD-tau (Forman *et al.*, 2005).

Astrocyte dysfunction in tauopathies may have a knock-on effect on neurons. Wild-type or P301S neurons co-cultured with P301S astrocytes have reduced survival rates compared to neurons cultured with WT astrocytes (Sidoryk-Wegrzynowicz *et al.*, 2017). Also, the transplant of WT astrocytes into the cortex of P301S tau transgenic mice improved cortical neuronal cell survival (Hampton *et al.*, 2010).

Whether this points towards the loss of the neuroprotective function in P301S astrocytes or the gain of a neurotoxic phenotype in unsure. However an increase in astrocytic complement C3 gene and protein expression (as expected in neurotoxic A1 astrocytes (Liddelow *et al.*, 2017)) has been shown in P301S mice, and the knockout of C3 was shown to reduce brain atrophy and neurodegeneration (Wu *et al.*, 2019). Similarly, increased C3 levels were seen in microglia and astrocytes in PS19 mice; with the C3 knockout leading to a decrease in tau pathology as well as reduced gliosis and reduced neuronal and synaptic loss. Behaviourally the PS19 C3ar-/- mice showed improved performance in a fear learning task compared to PS19 WT mice (Litvinchuk *et al.*, 2018). These studies support a link between tau pathology, C3 expression, and the destructive A1 astrocyte phenotype. Although, this remains to be explored in human tauopathies.

Experimental models vs. human studies

Studying tauopathy and inflammation in animal models gives some insight into the relationship between tau and innate immune cells (Table 2). Animal models are particularly useful to study the earlier mechanisms of disease, as human tissue is mainly assessed *post-mortem*, although recent imaging and biomarker studies provide some insight into earlier stages of disease. However, several confounding factors separate the animal system from the human disease condition. Firstly, only half of the human genomic DNA can be aligned to the mouse one, meaning that expression profiles of both species vary considerably (Franco-Bocanegra *et al.*, 2018), which may lead to differences in the function of human and mouse microglia and

astrocytes. Secondly, exposure of humans to infection during life is suspected to modify microglia towards a primed phenotype (Neher and Cunningham, 2019) which increases their response to further infections. As experimental animals are usually pathogen-free, these inflammatory events are unlikely to occur and thus might mimic an irrelevant microglial profile, especially in relation to chronic diseases affecting people later in life. Lastly, most mouse models of tauopathies are overexpressing models which have an augmented increase in phosphorylated tau expression, leading to exacerbated tau pathology that may not be reliably reflective of the human tauopathies. For these reasons, disease mechanisms discovered through the use of animal models must be interpreted with caution and, it is important to ensure findings translate to the human.

Neuroinflammation in human FTLD-Tau

Post mortem studies

Due to the challenges of the clinical diagnosis of FTD and the availability of *post-mortem* cases, studies into neuroinflammation in FTD tend to group different subtypes of the disease into a single cohort for comparison with controls, and thus do not attempt to make distinctions between the different types of FTD, let alone the specific FTLD pathology. Most studies have used the common microglial markers Iba1 (Fig. 5a), CD68 and HLA-DR to monitor cell number and level of activation. One study looking at unspecified FTD (n = 9, with no evidence of Pick's bodies) saw two-fold increases in the number of GFAP+ astrocytes and CD68+ microglia in the frontal cortex, along with a marked decrease in neuronal density. However, this was without a significant increase in tau pathology (PHF1) suggesting that cases were not of the FTLD-tau subtype (Arnold *et al.*, 2000). However, this highlighted that activated microglia participate in the neurodegenerative process, independent of tau pathology, maybe by phagocytosing dead neurons as emphasised by the use of CD68.

The presence of brain inflammation in specific FTLD-tau subtypes has only been reported in a few *post-mortem* studies. Using semiquantitative analysis of CD68 immunohistochemistry, microglial activation was compared between different subtypes of FTLD-tau, including eight PiD, ten FTLD-MAPT and sixteen CBD/PSP cases (Lant *et al.*, 2014). In general, compared to controls, cases with FTLD had increased microglial activation in the frontal and temporal cortex, but with a different pattern of cell distribution between the FTLD-tau subtypes. CD68+ cells were more numerous in the grey vs. white matter in PiD; whereas the opposite was observed for FTLD-MAPT and PSP/CBD. Furthermore, there were increased numbers of

CD68+ microglia in FTLD-MAPT cases compared to PSP/CBD. PiD microglial numbers were between PSP/CBD and FTLD-MAPT levels but were not significantly different using a semi-quantitative assessment (Lant *et al.*, 2014).

Pick's Disease

Interestingly one study found that in six PiD cases, microglial density (using Ki-M1P antibody) was only increased in areas affected by PiD pathology. In the hippocampus, microglial density was reduced and the cells were more amoeboid (Paulus *et al.*, 1993). The pathological characteristics of FTLD-tau with and without Pick's inclusions appear to be comparable, with similar levels of cerebral atrophy, astrogliosis and an increase above control in the presence of activated microglia (particularly in the white matter). However, whilst severe astrocytosis was common between subtypes, astrocytic tau inclusions were only present in PiD.

The relationship between tau pathology and increased microglial activation was further confirmed by another study with a significant correlation between phosphorylated tau (AT8) and microglial (CD68) densities in PiD. When splitting the analysis by the microglial phenotype (ramified vs. ameboid), only amoeboid microglial density was significantly correlated with tau (Bevan-Jones *et al.*, 2020). Colocalisation between a pan-tau marker and white matter microglia (Schofield *et al.*, 2003) was reported, supporting the findings from animal experiments which implies that immune cells take up tau from synapses and axons (Burnouf *et al.*, 2013), as well as some phagocytosis of extracellular tau (Majerova *et al.*, 2014; Das *et al.*, 2020).

Progressive Supranuclear Palsy

There is an added layer of complexity with respect to PSP, as the tau pathology primarily affects subcortical (particularly motor) areas (Hauw *et al.*, 1994), with cortical pathology sometimes occurring in later stages of the disease (Bigio *et al.*, 1999; Dickson *et al.*, 2011). Early studies have found evidence of overall increased inflammatory signals in PSP brains (Kida *et al.*, 1992; Komori *et al.*, 1998), with recent studies revisiting this component of the disease.

One study looking at five PSP and four controls found that the tau load (PHF1) was only increased in PSP compared to controls in subcortical regions and not in the cortex. However, the activated microglial burden (HLA-DR) was increased in frontal, temporal and motor cortical regions as well as in several subcortical regions (particularly related to motor systems).

Furthermore, there was a correlation between tau pathology and microglial burden in subcortical motor systems (Ishizawa and Dickson, 2001). This implies that the subcortical inflammation is related to the pathology but also that the cortical inflammation precedes and potentially participates in the propagation of the tau pathology. This is consistent with the findings from tau mice (Yoshiyama *et al.*, 2007) and PET imaging (Bevan-Jones *et al.*, 2019). Furthermore, analysis of RNA extracted from various rain regions *post mortem* showed a significant increase of IL1β in the substantia nigra in PSP (Fernandez-Botran *et al.*, 2011). Although carried out on small cohorts, these studies show an inflammatory response in the subcortical regions in PSP, which is not surprising as these regions are associated with tau pathology (basal ganglia, subthalamic nucleus and substantia nigra) (Hauw *et al.*, 1994). The cortical involvement in PSP at least remains to be further examined.

Limitations of *post mortem* studies

These neuropathology studies are usually limited in the information they provide with regards to microglia due to the use of a few inflammatory markers. This is especially important when it comes to exploring the phenotype of microglia, as it is now acknowledged that a single immunolabel is not sufficient to define their phenotype (Hopperton *et al.*, 2018). This is due to the spectrum of microglia functions and hence activation states which suggests that the historical bipartite classification (M1-like and M2-like) is an oversimplification (Boche *et al.*, 2013). In fact, using morphological characteristics or transcriptomic profiles, it was found up to 11 different classifications of microglia (Salamanca *et al.*, 2019). Due to the difficulty in attaining *post mortem* tissue, cohort sizes are often small in these studies, which limits the statistical power of the findings. The tendency to group heterogeneous subtypes of the disease also increases the likelihood of missing key features of FTLD-tau diseases. Furthermore, post-mortem studies are limited to only the end stage of the disease, so the insight they provide in terms of progression is minimal. This a limitation when addressing the role of neuroinflammation in neurodegeneration, as neuroinflammatory patterns and their impact on disease progression were suggested to vary according to disease stages. In addition, patients with neurodegenerative disorders often developed co-morbidities which may have consequences for the brain. Particularly relevant to neuroinflammation are peripheral infections such as pneumonia, a common cause of death in dementia patients (Rakic *et al.*, 2018), or sepsis which can lead to microglia activation according some studies (Lemstra *et al.*, 2007; Widmann and Heneka, 2014).

PET imaging

PET imaging is a valuable tool to monitor tau pathology and neuroinflammation in earlier stages of disease. PET uses radioligands which specifically bind to receptors or molecules and allow their abundance to be imaged and quantified *in vivo*. In this way, neuroinflammation can be investigated during the course of neurodegenerative diseases in humans to provide some insight to their aetiology. Microglial PET ligands bind to the translocator protein (TSPO) expressed on the mitochondrial membrane of activated microglia. However, some TSPO ligands also recognise macrophages, astrocytes and endothelial cells (Cosenza-Nashat *et al.*, 2009; Lavisse *et al.*, 2012). The interpretation of the TSPO signal is limited, partly due to the absence of knowledge regarding the microglial phenotypes recognised by the TSPO ligand (Boche *et al.*, 2019). As TSPO does not differentiate between functional profiles or subsets of microglia, astrocytes and/or macrophages, it may be fairer to describe a PET TSPO signal as generally indicative of the overall magnitude of neuroinflammation. TSPO PET signal has though, been associated with tau pathology in PiD and PSP patients, in a similar pattern to Iba1 microglial marker in tissue (Maeda *et al.*, 2011).

The most commonly used TSPO ligand is [11C](R)-PK11195, which has been employed in small studies of neuroinflammation in FTD. In five FTD patients (PNFA, n = 4 and bvFTD, n = 1), a significant increase in [11C](R)-PK11195 PET signal compared to controls was reported in the left prefrontal cortex, right hippocampus and parahippocampal cortices, and bilaterally in the putamen. Such an increase in cortical neuroinflammation was also partially concurrent with cerebral atrophy (Cagnin *et al.*, 2004). [11C](R)-PK11195 in combination with [^{18}F]AV-1451 (tau and TDP-43 ligand) showed a strong association between both tracers in 10 bvFTD, 11 SD and 10 PNFA patients. Furthermore, heterogeneity in the spatial distribution of [11C](R)-PK11195 was associated with different FTD syndromes and able to differentiate them better than with the differences observed in [^{18}F]AV-1451 distribution (Bevan-Jones *et al.*, 2020).

With regards to FTLD-tau, increased [11C](R)-PK11195 binding was seen in the brainstem, cerebellum and frontal lobe in four PSP patients compared to seven controls (Gerhard *et al.*, 2006). This observation was corroborated in a larger study with a significant increase of the TSPO binding in subcortical regions of 13 PSP patients *vs* controls (Passamonti *et al.*, 2018).

The PK11195 ligand presents some disadvantages such as low brain penetrance, high non-specific binding (especially to blood plasma proteins) (Venneti *et al.*, 2013) and thus other

ligands have been developed to improve the signal to noise ratio. [18F]GE180 is a third-generation ligand that has been utilised to explore neuroinflammation in PSP. Similarly to the PK11195 ligand, an increased signal was detected in structures which typically show pathology *post mortem* - midbrain, globus pallidus, and frontal lobe (Beyer *et al.*, 2018). Another TSPO ligand (11C-PBR28) confirmed the significantly increased neuroinflammation in FTD patients (three bvFTD and one PNFA) in the frontal, temporal and parietal cortex (Kim *et al.*, 2019). The TSPO [3H]DAA1106 ligand showed a higher binding affinity for activated microglia than PK11195 in *post-mortem* tissue, with the findings correlating with the CD68 immunolabelling in ten unspecified FTD cases (Venneti *et al.*, 2008). This ligand showed changes in three presymptomatic carriers of FTLD-MAPT and increased neuroinflammation in the frontal, cingulate and occipital cortex in at least one of the patients, but the pattern of activation within these three patients was different (Miyoshi *et al.*, 2010), highlighting the heterogeneity of the inflammatory response in humans and the difficulty in interpreting the PET signal.

PET imaging provides a window into the inflammatory process during FTLD-tau disease, with a recent study (using the [11C](R)-PK11195 ligand) showing that neuroinflammation precedes tau pathology (tau PET ligand [^{18}F]AV-1451) and cortical atrophy in a patient with FTLD-MAPT (Bevan-Jones *et al.*, 2019). However, small study sizes and the lack of a reliable highly specific radioligand have made it difficult to confirm the role of neuroinflammation in the early stages of the disease. However, concurrent evidence supports microglia activation as an early feature of FTLD-tau and emphasises the importance of neuroinflammation in the disease process.

Biomarkers in the CSF

Looking at other markers of neuroinflammation such as CSF levels of pro- and anti-inflammatory cytokines may also provide important information during the course of the disease. However, studies in FTD remains sparse. Analysis of the CSF of FTD patients (subtype unspecified) showed raised levels of TNFα and decreased TGFβ (Sjogren *et al.*, 2004). Interestingly, decreased levels of CCL5 (known to be neuroprotective) was seen in FTLD patients (defined as patients 'without GRN mutations' – as the study looks at the effects of GRN mutations) along with increased CSF levels of monocyte chemoattractant protein-1 (MCP-1) (Galimberti *et al.*, 2015), raising the possibility that mononuclear phagocyte recruitment into the brain parenchyma might occur as part of the disease process, as suggested in Alzheimer's disease (Hickman and El Khoury, 2010). Increased levels of the astrogliosis

marker GFAP and anti-inflammatory marker YKL-40 have also been shown in FTD patients' CSF compared to controls. Stratifying by disease protein (tau or TDP) and comorbidity with ALS, pure FTLD-tau had the lowest CSF levels of GFAP and YKL-40 of all disease groups (Abu-Rumeileh *et al.*, 2019). Looking specifically at PSP patients, elevated levels of YKL-40 and IL-8 (a neutrophil chemotactic molecule) were detected in the CSF (Hall *et al.*, 2018). However, levels of various other cytokines (IFNγ, IL10, IL18, IL1β, IL4, IL6, TGFβ1, and TNFα) were not different in the CSF of 39 PSP patients compared to 31 controls (Starhof *et al.*, 2018). Overall, these studies describe a general increase in neuroinflammation during FTLD-tau that is detectable in the CSF, but further studies are required to explore this fully.

Adaptive immunity in FTLD-tau

The role of adaptive immunity in FTLD-tau remains more elusive than innate immunity with sparse GWAS data supporting the involvement of risk genes at HLA regions and *RAB38/CTSC* loci in FTD (Ferrari *et al.*, 2014). Peripheral immune cells, particularly T cells, have been shown to infiltrate brain parenchyma in neurodegenerative diseases such as Alzheimer's disease and FTD (Togo *et al.*, 2002; Laurent *et al.*, 2017) (Fig. 5b). This infiltration was proposed to be associated with the disruption of the tight junctions between endothelial cells which increases paracellular permeability (Stamatovic *et al.*, 2008), and thus may facilitate peripheral cell recruitment. Microglia and astrocytes are known to alter the blood-brain barrier (BBB) permeability through cytokine signalling (Prat *et al.*, 2001) and along with activated peripheral T cells and macrophages, they can modify the permeability of the BBB by releasing reactive oxygen species and other inflammatory factors (Persidsky *et al.*, 1999; Hudson *et al.*, 2005). However, it is still unclear whether this cellular infiltration is mostly such a passive pathological consequence, or part of a more complex physiological immune response to brain pathology, including the specific recruitment of selected T cells.

An experimental study evaluated the expression of inflammatory markers in the hippocampus of THY-Tau22 mice, from the start of tau pathology (3 months) to a later stage (12 months) when pathology and memory deficits are established. Upregulation of mRNA and protein of T-cell-attracting chemokines (CCL3, CCL4 and CCL5) was observed and correlated with significant infiltration of CD8+ (cytotoxic) T cells in the hippocampus of THY-Tau22 mice. Unlike CD8+ T cells, parenchymal CD4+ (helper) T cells were barely observed in the hippocampus of both THY-Tau22 mice and WT littermates at all ages. Notably, such

infiltration of T cells occurred without significant alteration of the BBB in THY-Tau22 mice (Laurent *et al.*, 2017).

In a *post-mortem* study comparing T cell parenchymal infiltration across neurodegenerative disorders (including two FTD without PiD, grouped with "other dementia"), there was no difference in the number of CD3+ T cells compared to controls (Togo *et al.*, 2002). The exploration of the cerebral infiltration of CD8+ cells in three FTLD-MAPT patients (with Tau P301L mutations) and age-matched controls showed whilst CD8+ T cells were exclusively distributed along blood vessels in controls, both vascular and parenchymal CD8+ cells were found in FTLD-MAPT patients, suggesting that tau pathology is associated with selective parenchymal infiltration of CD8+ T cells (Laurent *et al.*, 2017). Of note, although not addressing tauopathies, previous studies showed a correlation between the extent of CD3+ T cell infiltration and the load of phosphorylated tau in the brain of Alzheimer's disease patients (Zotova *et al.*, 2013). Correspondingly, frequency of extravascular CD3+ T cells was correlated with tau but not amyloid pathology in the brains of Alzheimer's disease patients, suggesting that T-cell extravasation is driven by tau-related neurodegenerative changes rather than by cerebral amyloidosis (Merlini *et al.*, 2018).

Aside from parenchymal infiltration, changes in T cell biology have been shown in FTD. Perivascular CD3+ T cells were detected in a patient with PSP who had Alzheimer's like tau pathology and increased microglial activation (CD68+) (Dale *et al.*, 2017). Also, a significant decrease in the number of CD4+ lymphocytes expressing CTLA-4, a T-cell inhibitory receptor, has been reported in from FTD patients compared to controls (Santos *et al.*, 2014). Interestingly, a decrease in peripheral B and T cell populations in the blood of patients with unspecified FTD compared to control patient was found. Such a decrease in cell number may lead to increased activation of the remaining cell populations (Busse *et al.*, 2017). Altogether this suggests an altered homeostasis and/or activation pattern of T cells in FTD, which whilst not highlighting a direct link to the disease supports a potential instrumental role of cellular adaptive immunity in FTD pathophysiology. However, due to the overall limited number of studies and cases investigated, the role of adaptive immunity in tauopathies remains to be further investigated in both pre-clinical models and clinical studies.

Immunity in FTLD-TDP and FTLD-FUS

Tau aggregation is the most common pathology in frontotemporal lobar degeneration, with FTLD less commonly occurring due to the aggregation of TDP43 or FUS. Evidence of

microglial and astrocyte activation has been seen in animal models of TDP43 (Spiller *et al.*, 2018) and FUS proteinopathies(Huang *et al.*, 2011). Furthermore astrocytic expression of FUS has been shown to lead to increased pro-inflammatory signalling by astrocytes, leading to microglial activation and neuronal death (Ajmone-Cat *et al.*, 2019). This is also a suggested mechanism by which TDP43 proteinopathies may cause neurodegeneration (Serio *et al.*, 2013; Sloan and Barres, 2013).

In a study investigating microglial activation in human FTLD, with comparison between FTLD-tau/FUS/TDP pathologies, the authors showed increased expression (compared to controls) of microglial phagocytic activity (marker CD68) in FLTD-tau and FTLD-TDP, but not in FTLD-FUS. Of note, an increase in Iba1 burden was reported only in FTLD-tau and not in FTLD-TDP or FUS. These data suggest that microglial activation may be more pronounced in association with tau pathology, than FUS or TDP43 pathology (Woollacott *et al.*, 2020). Further studies are required to fully understand the role of neuroinflammation in FTLD-TDP and FTLD-FUS, and potential roles for adaptive immunity in FTLD-TDP or FUS still remain to be explored.

Conclusion

The studies reviewed here highlight a link between neuroinflammation and FTLD-tau. GWAS hits related to FTD include loci for genes relevant to microglial function (TREM2, TYROBP, and APOE) and TNFα signalling (LRRK2 and TBKBP1). This is supported by the (i) presence of microglial and astrocyte activation in various tau mouse models and in human tauopathies, and (ii) increased TSPO-PET signal and inflammatory biomarkers in patients. The increased neuroinflammation in response to tau pathology has been shown to lead to neurodegeneration as microglia respond to neuronal damage in an increasingly uncontrolled way, also inducing astrocytic activation. Microglia also play a role in the propagation of phosphorylated tau in the brain. Whether microglia are involved in the initiation of tau accumulation is as yet unclear, although genetics, experimental and human studies support this concept.

As for the involvement of adaptive immunity, the evidence is less strong so far with conflicting and limited human findings. However, the combination of GWAS data implicating adaptive immunity-related genes (HLA/CTSC) and tissue studies confirming the presence of recruited T cells in brain parenchyma in tauopathies, together with recent supporting studies in mouse model, does provide a compelling case for the adaptive immune system involvement in

FTLD-tau pathophysiology. Further studies in humans and preclinical models are still needed to confirm its role and mechanistic involvement in the disease.

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Competing interests

The authors report no competing interests.

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Legends

Figure 1. Diagrams showing the epidemiology and classification of FTD
A. The prevalence of dementia-related diseases in patients under the age of 65. AD = Alzheimer's Disease, VaD = vascular dementia, FTD = frontotemporal dementia, ARD = alcohol-related dementia, DLB = dementia with Lewy-Bodies, HD = Huntington's disease. Adapted from Harvey et al. (2003) (Harvey *et al.*, 2003). **B.** FTD disorders can be classified by their clinical syndrome (bvFTD, PNFA or SD), or the identity of the protein pathology that causes fronto-temporal lobar degeneration (FTLD-Tau, FTLD-TDP, and FTLD-FUS). Within these, the disorders can be further categorised (as with FTLD-TDP Type A, B, C or D) and also can be caused by genetic mutations (FTLD-TDP = PGRN, TARDBP and C9ORF72). FTLD-FUS can include NFID = Neuronal intermediate filament inclusion disease; and BIBD basophilic inclusion body disease. FTLD-Tau can be classified by the number of repeats of the chain of the tau protein that builds up (3R/4R). Pick's Disease is a 3R tauopathy whereas argyrophilic grain disease (AGD), progressive supranuclear palsy (PSP) corticobasal degeneration (CBD) are 4R tauopathies. Mutations in the MAPT gene can also cause FTLD-tau. Adapted from Rabinovici (Rabinovici and Miller, 2010) and Boxer (Boxer *et al.*, 2013).

Figure 2. The clinicopathological heterogeneity in subtypes of FTLD-tau.
Data from 12 studies, involving 262 patients showing the variety of clinical syndromes caused by each underlying neuropathology. At least some patients with each neuropathological diagnosis were clinically diagnosed with bvFTD (black). PiD patients were more often diagnosed with bvFTD (n = 56) than other syndromes (n = 19) and FTLD-MAPT was the only neuropathological diagnosis to be associated with only one clinical syndrome (bvFTD). Unsurprisingly PSPS and CBS were the most common clinical diagnoses of PSP/CBD patients n = 38/30 respectively. Although some patients were diagnosed with the other disorder (i.e. CBD patients diagnosed with PSPS) and the rest were diagnosed with other disorders (PNFA, bvFTD). SD was only diagnosed in patients with PiD, however, only four patients were included. This may be because SD is more often caused by FTLD-TDP43 rather than FTLD-tau. PSP is also relatively homogenous in underlying pathology. bvFTD = behavioural variant FTD; PNFA = progressive non-fluent aphasia; SD = semantic dementia; PSPS = progressive supranuclear palsy syndrome; CBS = corticobasal syndrome. (Data taken from: (Hodges *et al.*, 2004; Kertesz *et al.*, 2005; Knopman *et al.*, 2005; Shi *et al.*, 2005; Forman *et al.*, 2006; Josephs *et al.*, 2006; Hodges and Patterson, 2007; Lladó *et al.*, 2008; Snowden *et al.*, 2011; Xiong *et al.*, 2011; Perry *et al.*, 2017; Tacik *et al.*, 2017))

Figure 3. Features of tau pathology in human FTLD-tau.
Immunohistochemical examples of pathological hallmarks of FTLD-tau as stained by phosphorylated tau antibody AT8 (Ser202/Thr205). Scale bar = 100µm.

Figure 4. Diagram outlining the effects of Trem2 alterations in mouse models.
Under normal conditions *Trem2* facilitates microglial phagocytosis whilst dampening down pro-inflammatory signalling, to allow controlled clearance of debris (Takahashi *et al.*, 2005). In tau mice, with 2-6 months of tau pathology, the knockout of *Trem2* -/- leads to exacerbation

of the tau pathology as microglia are less able to respond (Jiang *et al.*, 2015; Bemiller *et al.*, 2017; Leyns *et al.*, 2019). With tau pathology lasting >8 months *Trem2* KO (-/-) appears to prevent excessive microglia activation and thus reduces cortical atrophy (Leyns *et al.*, 2017; Sayed *et al.*, 2018). *Trem2* -/+ appears to have a worse effect than *Trem2* -/-, leading to increased cortical atrophy and microgliosis and more tau pathology (Sayed *et al.*, 2018). The expression of mutant tau causes a loss of function of the protein and has a similar effect to the early-stage knockout (Leyns *et al.*, 2019).

Figure 5. Examples of microglia and T cells in the brain in FTLD-tau
A. Immunohistochemical examples of microglial morphologies as stained by Iba1. Ramified microglia **(i)**(arrow) have more, thinner processes whereas the processes are fewer and thicker, or even absent in activated microglia **(ii)** which have a more ameboid morphology (arrow and star). Scale bars are 100µm. Example images of parenchymal **(Bi)** and perivascular **(Bii)** T cells in the grey matter (as immunostained by CD3+ cells) in a patient with PSP. Scale bar =100µm.

Table 1. GWAS hits in frontotemporal dementia-related to innate and adaptive immunity.

	Cells/Function	Variant/Loci	Mutation Effect
TREM2	Facilitates phagocytosis of apoptotic neurons reduces pro-inflammatory response	R47H, T66M, S116C, T96K, L221P, R62H	Compromises ligand binding
		Q33X (NHD-related)	Loss of membrane incorporation
		p.T198X	Nonsense mutation
TYROBP	Microglia phagocytosis and activating natural killer cells	Gly2Glu/Val55Leu	Benign
		19q31.1 (NHD-related)	Homozygous deletion – loss of function
LRRK2	TNFα expression regulation	PSP: G2019S, R1441C, A1413T CBD: R1707K	Not reported
TBKBP1	TNFα expression regulation	rs2192493	Not reported
APOE	Transports cholesterol to neurons	Rs6857	Not reported
		E4 allele	Increased disease risk
		E2 allele	Protective
			No effect
CXCR4	Chemokine. Immune cell chemotaxis	Rs749873	Not reported. CXCR4 is increased in human FTD cases
HLA	MHC protein immune regulation	6p21.3	Altered HLA-DRA methylation levels
RAB38/CTSC	Immune-related. Lysosomal protein trafficking and proteinase activation.	11q14	Decreased function/expression

From: Borroni *et al.*, 2014; Bonham *et al.*, 2018; Broce *et al.*, 2018; Cuyvers *et al.*, 2014; Darwent *et al.*, 2017; Giraldo *et al.*, 2013; Ferrari *et al.*, 2014; Lattante *et al.*, 2013; Mishra *et al.*, 2017; Paloneva *et al.*, 2000; Rayaprolu *et al.*, 2013; Rubino *et al.*, 2013; Sanchez-Contreras *et al.*, 2017

Table 2. Summary of the most common tauopathy mouse models including tau pathology progression and neuroinflammation findings.

Model	Genetic Mutation	Tau Pathology	Neuroinflammation	Papers using the model
Tg4510	P301L mutation 0N4R human tau CaMKII promoter	MC-1 and CP13 - 1 month Tangles, PHF1, AT8- 4-5 months (Ramsden *et al.*, 2005; Santacruz *et al.*, 2005)	Gliosis seen from 2.5 months. (Helboe *et al.*, 2017)	Hopp *et al.*, 2018; Jackson *et al.*, 2017; Nash *et al.*, 2013; Ishikawa *et al.*, 2018; Bennett *et al.*, 2018
PS19 (P301S)	P301S mutation 1N4R human tau Mouse prion protein promoter	PHF1 accumulation – 6 months AT8/100/180 – 9 months (Yoshiyama *et al.*, 2007)	Activated microglia 3-4 months (Yoshiyama *et al.*, 2007)	Yoshiyama *et al.*, 2007; Dejanovic *et al.*, 2018; Wu *et al.*, 2019; Litvinchuk *et al.*, 2018
P301S	P301S mutation 1N4R human tau Thy1.2 Promoter	MC1 and CP13 from 2 months AT180 from 5/6 months (Xu *et al.*, 2014) AT8 from 5 months (Allen *et al.*, 2002)	Microgliosis from 6 months Microglial activation from 5 months (Bellucci *et al.*, 2004)	Luo *et al.*, 2015; Sidoryk-Wegrzynowicz *et al.*, 2017; Hampton *et al.*, 2010; Mancuso *et al.*, 2019; Bellucci *et al.*, 2004; van Olst *et al.*, 2020; Romero-Molina *et al.*, 2018
P301L	P301L mutation 2N4R human tau Hamster prion protein promoter.	Mild AT8 staining at 11m, stronger at 17m	Microglia increased in areas of AT8 staining	Sasaki *et al.*, 2008; Asai *et al.*, 2015; Bonham *et al.*, 2018
THY-Tau22	G272V/P301S 4R human tau Thy1.2 promotor	PHF1 – 6 months AT8 - 12 months (Schindowski *et al.*, 2006)	Glial activation – 12 months (Schindowski *et al.*, 2006)	Sanchez-Mejias *et al.*, 2016; Ahmed *et al.*, 2015; Burnouf *et al.*, 2013; Carvalho *et al.*, 2019; Laurent *et al.*, 2014; Romero-Molina *et al.*, 2018
R406W	R406W mutation 4R h-tau mutant Hamster prion protein promoter	Tau accumulation – 6 months	Microgliosis and astrogliosis correlated with tau accumulation	Ikeda *et al.*, 2005

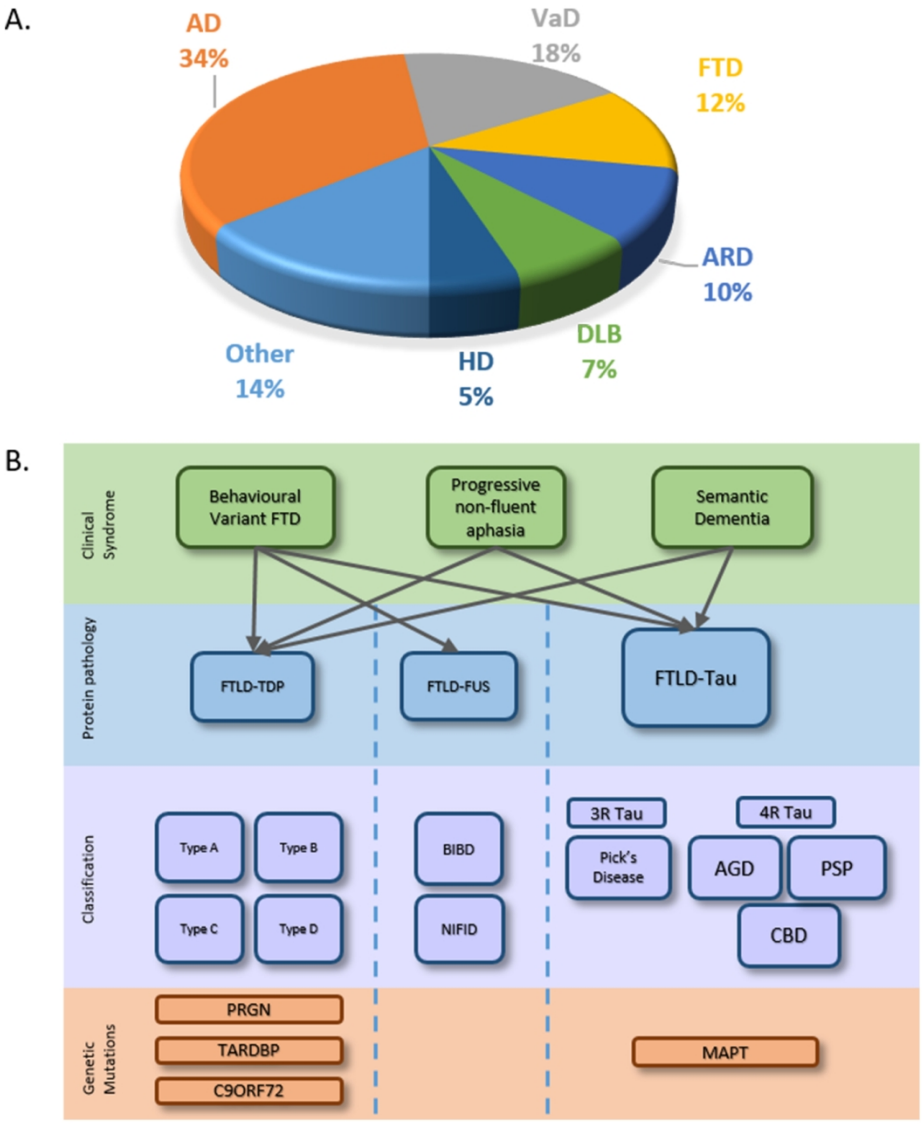

Figure 1. Diagrams showing the epidemiology and classification of FTD
A. The prevalence of dementia-related diseases in patients under the age of 65. AD = Alzheimer's Disease, VaD = vascular dementia, FTD = frontotemporal dementia, ARD = alcohol-related dementia, DLB = dementia with Lewy-Bodies, HD = Huntington's disease. Adapted from Harvey et al. (2003) (Harvey et al., 2003). B. FTD disorders can be classified by their clinical syndrome (bvFTD, PNFA or SD), or the identity of the protein pathology that causes fronto-temporal lobar degeneration (FTLD-Tau, FTLD-TDP, and FTLD-FUS). Within these, the disorders can be further categorised (as with FTLD-TDP Type A, B, C or D) and also can be caused by genetic mutations (FTLD-TDP = PGRN, TARDBP and C9ORF72). FTLD-FUS can include NFID = Neuronal intermediate filament inclusion disease; and BIBD basophilic inclusion body disease. FTLD-Tau can be classified by the number of repeats of the chain of the tau protein that builds up (3R/4R). Pick's Disease is a 3R tauopathy whereas argyrophilic grain disease (AGD), progressive supranuclear palsy (PSP) corticobasal degeneration (CBD) are 4R tauopathies. Mutations in the MAPT gene can also cause FTLD-tau. Adapted from Rabinovici (Rabinovici and Miller, 2010) and Boxer (Boxer et al., 2013).

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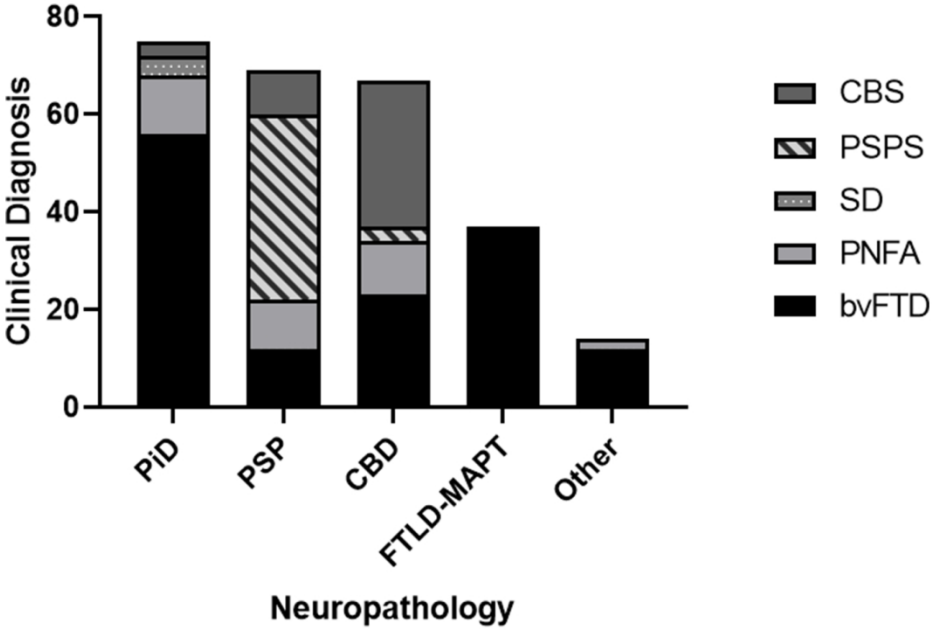

Figure 2. The clinicopathological heterogeneity in subtypes of FTLD-tau.
Data from 12 studies, involving 262 patients showing the variety of clinical syndromes caused by each underlying neuropathology. At least some patients with each neuropathological diagnosis were clinically diagnosed with bvFTD (black). PiD patients were more often diagnosed with bvFTD (n = 56) than other syndromes (n = 19) and FTLD-MAPT was the only neuropathological diagnosis to be associated with only one clinical syndrome (bvFTD). Unsurprisingly PSPS and CBS were the most common clinical diagnoses of PSP/CBD patients n = 38/30 respectively. Although some patients were diagnosed with the other disorder (i.e. CBD patients diagnosed with PSPS) and the rest were diagnosed with other disorders (PNFA, bvFTD). SD was only diagnosed in patients with PiD, however, only four patients were included. This may be because SD is more often caused by FTLD-TDP43 rather than FTLD-tau. PSP is also relatively homogenous in underlying pathology. bvFTD = behavioural variant FTD; PNFA = progressive non-fluent aphasia; SD = semantic dementia; PSPS = progressive supranuclear palsy syndrome; CBS = corticobasal syndrome. (Data taken from: Hodges et al., 2004; Kertesz et al., 2005; Knopman et al., 2005; Shi et al., 2005; Forman et al., 2006; Josephs et al., 2006; Hodges and Patterson, 2007; Lladó et al., 2008; Snowden et al., 2011; Xiong et al., 2011; Perry et al., 2017; Tacik et al., 2017).

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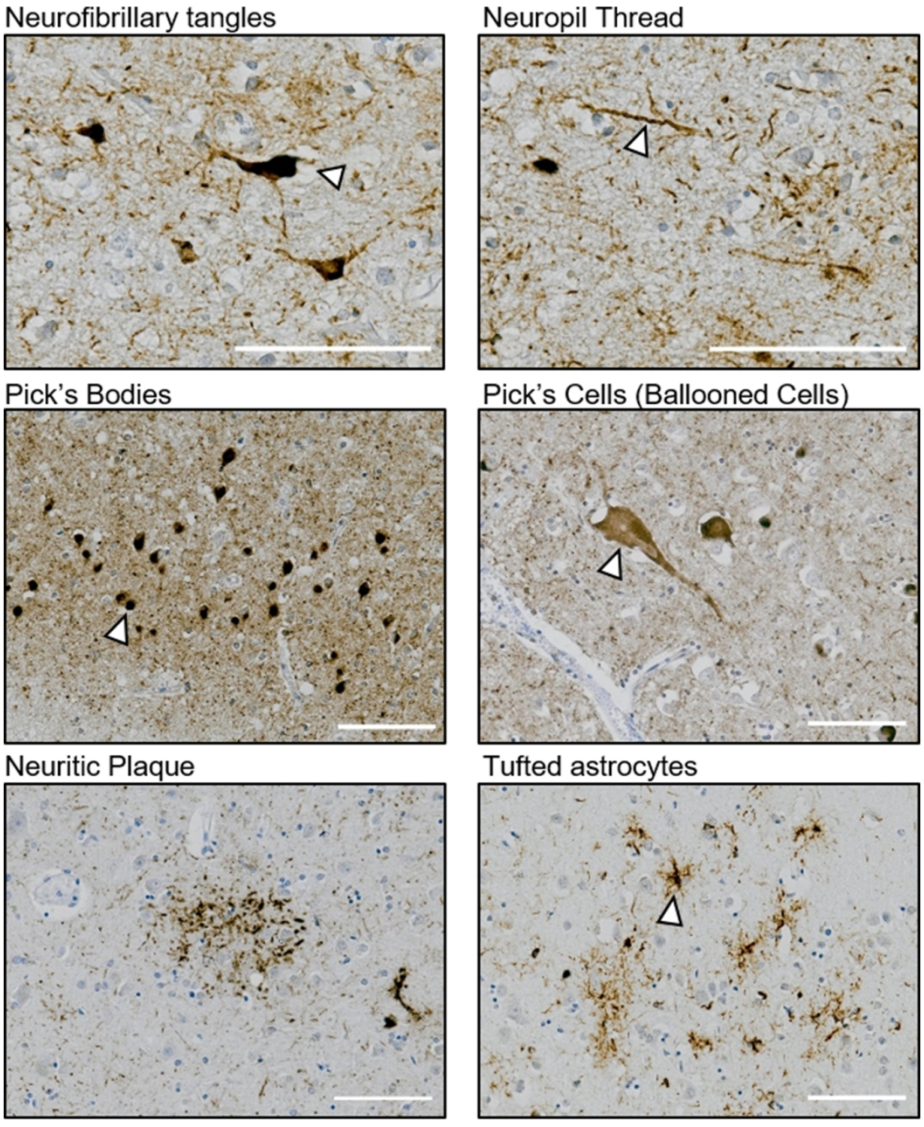

Figure 3. Features of tau pathology in human FTLD-tau.
Immunohistochemical examples of pathological hallmarks of FTLD-tau as stained by phosphorylated tau antibody AT8 (Ser202/Thr205). Scale bar = 100μm.

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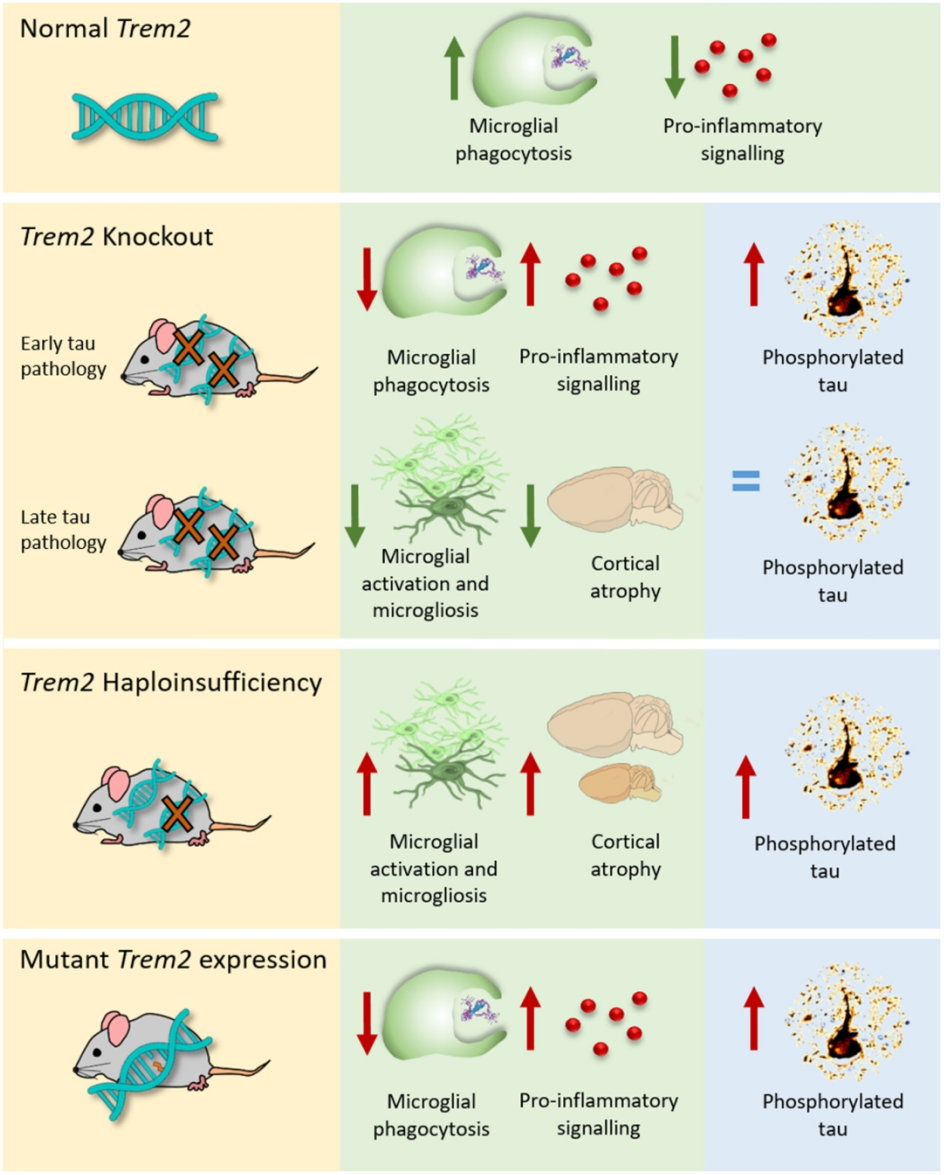

Figure 4. Diagram outlining the effects of Trem2 alterations in mouse models.
Under normal conditions Trem2 facilitates microglial phagocytosis whilst dampening down pro-inflammatory signalling, to allow controlled clearance of debris (Takahashi et al., 2005). In tau mice, with 2-6 months of tau pathology, the knockout of Trem2 -/- leads to exacerbation of the tau pathology as microglia are less able to respond (Jiang et al., 2015; Bemiller et al., 2017; Leyns et al., 2019). With tau pathology lasting >8 months Trem2 KO (-/-) appears to prevent excessive microglia activation and thus reduces cortical atrophy (Leyns et al., 2017; Sayed et al., 2018). Trem2 -/+ appears to have a worse effect than Trem2 -/-, leading to increased cortical atrophy and microgliosis and more tau pathology (Sayed et al., 2018). The expression of mutant tau causes a loss of function of the protein and has a similar effect to the early-stage knockout (Leyns et al., 2019).

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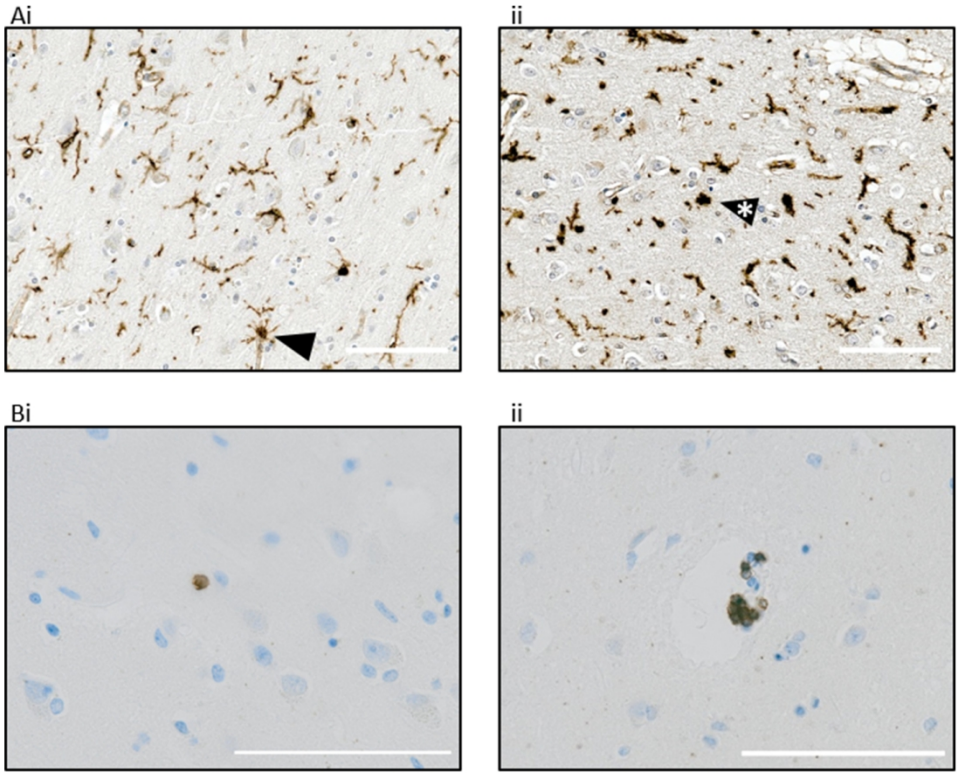
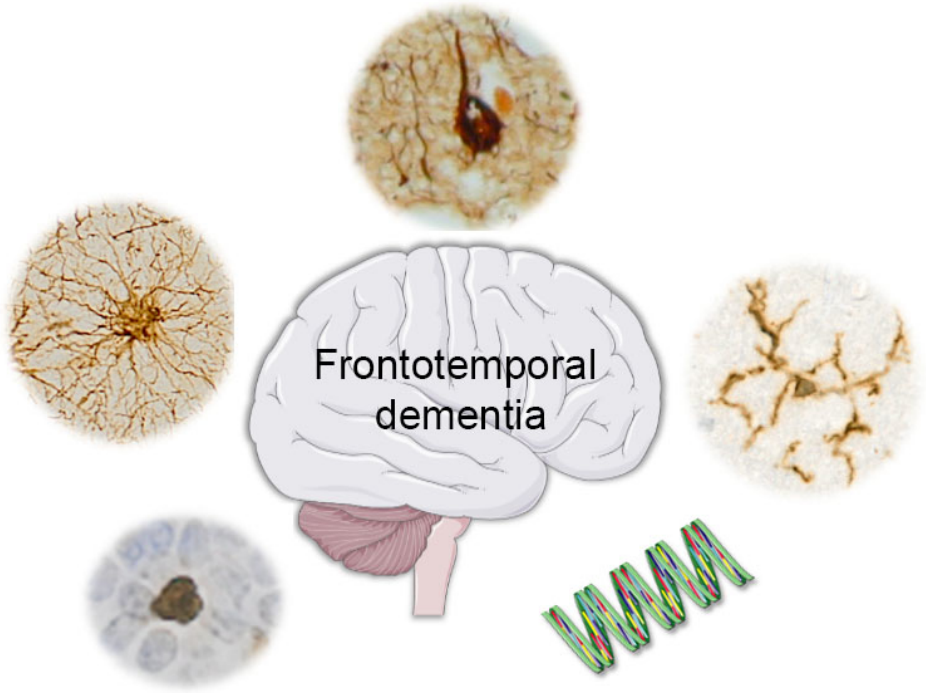


Figure 5. Examples of microglia and T cells in the brain in FTLD-tau
A. Immunohistochemical examples of microglial morphologies as stained by Iba1. Ramified microglia (i)(arrow) have more, thinner processes whereas the processes are fewer and thicker, or even absent in activated microglia (ii) which have a more ameboid morphology (arrow and star). Scale bars are 100μm. Example images of parenchymal (Bi) and perivascular (Bii) T cells in the grey matter (as immunostained by CD3+ cells) in a patient with PSP. Scale bar =100μm.



A comprehensive review on the role of neuroinflammation in Frontotemporal dementia, with a focus on frontotemporal lobar degeneration associated with tau. Evidence from genetics, experimental and human studies are presented and discussed.

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