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Neuroimaging across the FTD spectrum

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Abstract

Frontotemporal dementia is a complex and heterogeneous neurodegenerative disease that encompasses many clinical syndromes, pathological diseases, and genetic mutations. Neuroimaging has played a critical role in our understanding of the underlying pathophysiology of frontotemporal dementia and provided biomarkers to aid diagnosis. Early studies defined patterns of neurodegeneration and hypometabolism associated with the clinical, pathological and genetic aspects of frontotemporal dementia, with more recent studies highlighting how the breakdown of structural and functional brain networks define frontotemporal dementia. Molecular positron emission tomography ligands allowing the in vivo imaging of tau proteins have also provided important insights, although more work is needed to understand the biology of the currently available ligands.

Keywords

semantic; agrammatic; apraxia of speech; tau; TDP-43; progranulin; C9ORF72; MRI; neurodegeneration; connectivity

Introduction

Clinical classification of FTD

Frontotemporal dementia (FTD) is a clinical term for a group of neurodegenerative syndromes which are associated with degeneration of the frontal and temporal lobes of the brain. Clinical diagnostic criteria for FTD published in 1998 recognized three clinical FTD syndromes, termed behavioral variant FTD (bvFTD), semantic dementia (SD) and progressive non-fluent aphasia¹. Behavioral variant FTD was characterized by changes in personality and behavioral abnormalities, such as apathy, disinhibition and obsessive-compulsive behaviors, and loss of insight. Patients with bvFTD can develop language abnormalities as the disease progresses, and patients can also develop parkinsonism and features of motor neuron disease (MND). Updated consensus criteria for bvFTD have since been published². Semantic dementia was characterized by word finding problems (i.e. anomia) and loss of semantic knowledge (such as loss of word, object or face knowledge)³. Lastly, progressive non-fluent aphasia was characterized predominantly by the presence of non-fluent spontaneous speech output. Since this time, it has been recognized that many

patients with progressive non-fluent aphasia display combinations of two clinical features: agrammatic aphasia which is characterized by agrammatic written or spoken output and apraxia of speech which is a motor speech disorder affecting the ability to produce words, typically characterized by sound distortions and segmentations^{4,5}. Diagnostic criteria for primary progressive aphasia published in 2011 recognized an agrammatic non-fluent variant of primary progressive aphasia (agPPA) which is defined by the presence of either agrammatism or apraxia of speech⁶, although the language deficits should be the earliest and dominant feature⁷. Furthermore, a clinical entity was described in 2012 in which apraxia of speech is the sole presenting symptom, in the absence of agrammatism or any other evidence or aphasia⁸. This entity was termed primary progressive apraxia of speech (PPAOS)⁸. Patients with both agPPA and PPAOS often develop an atypical parkinsonian syndrome over time, characterized by limb apraxia, postural instability and eye movement abnormalities^{9–12}. The PPA criteria also defined a semantic variant of PPA which specifically classifies patients with anomia and loss of word knowledge, and hence includes some, although not all, patients that were originally classified as SD⁶.

Pathological classification of FTD

The pathologies underlying the FTD syndromes are heterogeneous, but are typically defined by the abnormal deposition of one of three proteins: the microtubule-associated protein tau, the TAR DNA binding protein of 43kDa (TDP-43)^{14, 15} or, less commonly, the tumor associated protein fused in sarcoma (FUS)¹³. Therefore, the majority of cases can be sub-classified into FTLD-tau, FTLD-TDP and FTLD-FUS (Figure 1), based on the biochemical signature of the abnormally deposited protein^{14,15}. Each of these three groups is also sub-classified based on inclusion morphology and lesion distribution. Hence, FTLD-tau includes specific pathologies such as Pick's disease¹⁶, progressive supranuclear palsy¹⁷ and corticobasal degeneration^{18,19}; FTLD-TDP includes four different types (A-D)^{20–22}, and FTLD-FUS includes the specific pathologies of neuronal intermediate filament inclusion disease^{23,24}, basophilic inclusion body disease^{25,26} and atypical FTLD with ubiquitin-only immunoreactive changes^{27,28}. The syndrome of bvFTD can be associated with many different FTLD pathologies, and can result from FTLD-tau, FTLD-TDP or FTLD-FUS pathology (Figure 1)¹⁵. There may be some clinical signs that suggest one specific pathology over another, although generally it is very difficult to predict the underlying pathology in bvFTD. The syndrome of SD has a more homogeneous pathology and typically results from FTLD-TDP pathology (Figure 1), particularly FTLD-TDP type C¹⁵. The syndrome PPAOS also has a relatively homogeneous pathology, with most cases resulting from FTLD-tau (Figure 1) characterized by deposition of 4-repeat tau, i.e. progressive supranuclear palsy or corticobasal degeneration¹⁰. In fact, the presence of apraxia of speech has been shown to be predictive of an underlying FTLD-tau pathology, even when it co-occurs with agrammatic aphasia¹⁰. Hence, patients with agPPA, that often have co-occurring apraxia of speech, also often have an underlying FTLD-tau pathology^{10,29}. Cases of aPPA have been reported with FTLD-TDP, although this pathology is rarer than FTLD-tau in these patients²⁹. Furthermore, patients with the clinical syndromes of FTD have been reported to have the pathology of Alzheimer's disease which is characterized by deposition of 3R+4R tau and beta-amyloid³⁰.

Neuroimaging in FTD

Neuroimaging research has been critical in increasing our understanding of FTD. Structural magnetic resonance imaging (MRI) and (18F)-fluorodeoxyglucose positron emission tomography (FDG-PET) studies have characterized patterns of neurodegeneration and hypometabolism that define the different clinical and pathological variants of FTD, while diffusion tensor imaging (DTI) and resting-state fMRI have improved our understanding of the structural and functional connectivity breakdowns associated with FTD. The recent availability of molecular PET ligands that bind to beta-amyloid or tau proteins has also allowed the in vivo investigation of brain pathology. The knowledge we have gained from these neuroimaging modalities concerning the pathophysiology of FTD will be discussed in this review.

Imaging in the clinical syndromes of FTD

Behavioral variant FTD

Behavioral variant FTD is typically associated with atrophy on structural MRI and hypometabolism on FDG-PET in the prefrontal cortex and anterior temporal lobes, with relative sparing of more posterior regions of the brain, such as the occipital lobe^{31–39} (Figure 2). Regions in the frontal lobe that are commonly affected in bvFTD include the orbitofrontal cortex, medial and lateral prefrontal cortex and anterior cingulate, along with atrophy of the adjacent insula cortex. Imaging studies have demonstrated that atrophy of these frontal and anterior temporal regions is related to the behavioral symptoms observed in bvFTD, including apathy, disinhibition, loss of empathy, and aggression^{40–50}. Atrophy of subcortical structures, such as caudate, putamen, globus pallidus, thalamus and nucleus accumbens, are also observed, reflecting dysfunction of cortico-striato-thalamic circuits⁵¹ which have also been associated with behavioral abnormalities in bvFTD^{52–61}. Neurodegeneration in bvFTD is progressive, with decline in brain volume observed over time. Rates of whole brain volume loss can be as fast as 3% per year^{34, 35}, with greatest rates of decline observed in the frontal lobes^{62–68}. Frontotemporal and subcortical atrophy is observed in the mildest stages of the disease⁶⁹ and even before patients meet criteria for bvFTD⁷⁰, and is observed to spread as the disease progresses⁶⁹.

However, a great deal of heterogeneity in patterns of neurodegeneration has been observed within cohorts of bvFTD patients on both MRI and FDG-PET^{71–75}. Some patients tend to have more predominant frontal abnormalities^{71,72,75}, others have predominant temporal abnormalities^{71,72,75}, and some show involvement of temporal and parietal structures^{71,73,75}. A predominantly subcortical subtype has also been identified^{71,72}. Importantly, clinical characteristics differ across these different anatomical phenotypes, with the frontal phenotype showing worse executive performance and the temporal phenotype showing worse episodic memory impairment^{73,75}. Furthermore, the patients with frontal dominant patterns of atrophy tend to show faster clinical decline⁷⁶, while the subcortical subtype shows relatively slow disease progression⁷¹. Recognizing the different phenotypes of bvFTD could, therefore, be important to help improve prognostic estimates for patients. The phenotypes did not differ in terms of behavioral abnormalities, reflecting the fact that behavioral abnormalities are the key features of a bvFTD diagnosis. Heterogeneity is also

observed in the degree of asymmetry in brain atrophy^{42,73} with most patients showing symmetric patterns of atrophy, although patients also show right and left-sided patterns of atrophy⁴². In addition, some bvFTD patients have been reported that showed very little atrophy on MRI, despite fulfilling clinical criteria for bvFTD, and show slow rates of clinical decline^{77–79}. Some of these patients have been shown to display FTD pathology⁸⁰ and are occasionally associated with the presence of a *C9ORF72* genetic mutation⁷⁹ (see genetic FTD section). Those patients with additional MND, i.e. FTD-MND, show shorter disease duration than typical bvFTD patients and have been shown to have very similar patterns of atrophy to bvFTD, particularly with involvement of the frontal lobes^{81–83}. The degree of atrophy is however typically less than that observed in patients with bvFTD^{81,83}, although these patients show greater involvement of the frontal and temporal lobes compared to patients with MND in the absence of FTD⁸³.

Structural MRI and FDG-PET findings have been shown to be diagnostically useful in differentiating bvFTD from healthy individuals and patients with other neurodegenerative diseases. In particular, the relative pattern of involvement of anterior brain structures nicely differentiates patients with bvFTD from those with typical Alzheimer's dementia which typically targets posterior regions of the brain, including the posterior temporal and parietal lobes⁸⁴. Studies that have utilized pattern classification techniques have found that structural MRI can differentiate bvFTD from controls with an accuracy of 85%^{85,86}, and differentiate bvFTD from Alzheimer's dementia with an accuracy of 82%⁸⁶. Diagnostic accuracy has also been shown to be excellent with pattern analysis of FDG-PET, with discriminatory power of 92.2% to differentiate bvFTD from Alzheimer's dementia and 87.6% to differentiate bvFTD from the other language variants of FTD⁸⁷. In fact, simple visual assessments of FDG-PET looking for frontal, anterior cingulate and anterior temporal hypometabolism have excellent specificity (97.6%) and sensitivity (86%) in differentiating bvFTD from Alzheimer's dementia, and can improve differentiation based on clinical features alone⁸⁸. There is also evidence that FDG-PET can improve diagnosis over structural MRI^{89–91}, with FDG-PET being more sensitive to underlying dysfunction than structural MRI which can be normal at baseline in bvFTD patients⁹².

Disruption in the structural connectivity of the brain, measured using DTI, is also a feature of bvFTD. Degeneration is observed in white matter tracts that have reciprocal projections into the frontal and temporal lobes, such as the superior longitudinal fasciculus, anterior cingulum, genu of the corpus callosum, uncinate fasciculus and the inferior longitudinal fasciculus^{45,93–98} (Figure 3). Degeneration of these tracts is associated with behavioral severity in bvFTD^{45,96}. Degeneration is also observed in fronto-striatal and fronto-thalamic pathways⁵¹. Less severe degeneration is also observed in tracts that connect into posterior regions of the brain, including the posterior cingulate and posterior aspects of the superior longitudinal fasciculus. Longitudinal studies have observed progressive degeneration of the same set of tracts that show abnormalities in cross-sectional studies, particularly the uncinate fasciculus, genu of the corpus callosum, paracallosal cingulum and frontal white matter^{99–101}, with additional progression to involve more posterior white matter tracts located in the posterior temporal and occipital lobe¹⁰². This demonstrates a spreading of disease from anterior to more posterior brain regions. DTI measures from the anterior corpus callosum are particularly promising in bvFTD since they provide good differentiation of

bvFTD patients from other clinical variants of FTD^{93,95}, perform well as a longitudinal marker to differentiate bvFTD from controls¹⁰⁰, and are associated with longitudinal decline in executive function in bvFTD¹⁰³. There is also a suggestion that DTI can pick up abnormalities in patients in which the MRI and FDG-PET scans are normal¹⁰⁴ and DTI findings can show more widespread findings than structural MRI^{98,105}, suggesting good sensitivity of DTI. The value of DTI compared to other modalities is less clear. A couple of studies have found that DTI performed better than regional volumes in differentiating bvFTD from controls¹⁰⁶ or from other FTD syndromes¹⁰⁷, although another found that DTI measures do not perform as well as FDG-PET for diagnosis at the individual-patient level¹⁰⁴. DTI does, however, appear to add complementary information to structural MRI when differentiating bvFTD from controls and Alzheimer's dementia, and hence a combination of markers from different modalities may be the best approach to differential diagnosis¹⁰⁸.

Functional brain connectivity in bvFTD has also been assessed using resting-state fMRI analyses. Studies that have focused on assessing specific brain networks have shown that one of the characteristic changes observed in bvFTD is decreased functional connectivity within the salience network^{109–114}. The salience network is involved in processing socially relevant information and involves anterior cingulate and fronto-insular regions. Similarly, other studies have found bilateral disconnection between frontal and limbic regions of the brain^{114–116}. Disruptions in connectivity in frontolimbic regions appears to be central to the disease process in bvFTD and has been shown to correlate to the degree of behavioral and executive impairment observed in bvFTD^{111,116–118}. Connectivity from the frontal lobe also appears to decrease with disease progression in bvFTD¹¹⁹. However, decreased connectivity has also been observed in the basal ganglia¹¹⁵, insula¹¹⁵ and dorsal attention network¹¹⁴, and disconnection between the frontal lobes and posterior regions of the brain, including occipital lobe^{115,120,121}, also appear to occur in bvFTD. Increases in connectivity have also been observed in other networks, such as the medial parietal components of the default mode network^{109–112} and attention/working memory network¹¹⁴, with posterior hubs relatively preserved in bvFTD¹²⁰. This pattern of connectivity changes may be useful to differentiate bvFTD patients from patients with Alzheimer's dementia, which typically show reduced connectivity in the default mode network and posterior brain nodes^{110,114,122}. Studies have started to analyze and compare resting state fMRI to other neuroimaging metrics in terms of diagnostic utility. In one study, optimum differentiation of bvFTD and controls was obtained with a combination of structural MRI, DTI and resting state measures¹²³. Similarly, optimum differentiation of bvFTD and Alzheimer's dementia was obtained with a combination of DTI and resting state fMRI measures¹²³ - combining functional and structural measures improved differentiation

Tau PET imaging has been assessed in patients with bvFTD, particularly using the THK-5351 and 18F-flortaucipir ligands. These studies have typically observed elevated uptake in the white matter of the frontal lobe^{124–127}, as well as anterior cingulate, temporal lobe, insula, and striatum^{125,127} in bvFTD patients compared to controls (Figure 4). However, results across bvFTD patients are variable, with only 50% of sporadic bvFTD patients in one study demonstrating elevated 18F-flortaucipir uptake compared to controls¹²⁶. Consistent with structural MRI, the patterns of uptake in bvFTD differ from the

more temporoparietal and occipital patterns of uptake observed in Alzheimer's dementia¹²⁴. One study found that frontal white matter uptake using THK-5351 was higher in bvFTD compared to Alzheimer's dementia, although in another study the degree of 18F-flortaucipir uptake in bvFTD was less than the binding range typically seen in Alzheimer's dementia¹²⁶. However, it is very difficult to interpret tau PET findings in bvFTD given the pathological heterogeneity and the fact that a large proportion of cases will likely have an underlying TDP-43 proteinopathy rather than a tauopathy. It is currently unclear what the ligands are binding to in the white matter and basal ganglia and whether it reflects off-target binding to a non-tau target¹²⁸. Furthermore, the tau isoforms present in bvFTD patients with genetic mutations can vary and hence influence tau-PET findings (see pathological section below) and many of these bvFTD studies have not screened cases for genetic mutations^{124,125,127}. In addition, approximately 50% of bvFTD cases can show amyloid deposition on PET scanning¹²⁹ suggesting the possibility of underlying AD pathology which may influence tau-PET findings in bvFTD¹²⁶. The value of tau-PET in bvFTD is therefore currently low until we have a better understanding of the biological underpinnings of ligand binding.

Semantic dementia

Semantic dementia is associated with characteristic patterns of atrophy on structural MRI and hypometabolism on FDG-PET affecting the temporal lobes^{74, 107–110}. An anteroposterior gradient of atrophy is typically observed, with most marked atrophy observed in anterior temporal regions (Figure 2). Degeneration is particularly severe in the fusiform and inferior temporal gyri, although also severely affects the hippocampus, amygdala, entorhinal cortex, and middle temporal gyrus^{130–132}. The orbitofrontal cortex, medial frontal lobes, striatum and anterior insula can also be involved^{32,58,132}. Asymmetry is also a characteristic feature of SD. Patients which present with anomia and loss of word knowledge (and hence fulfill criteria for the semantic variant of PPA) typically show left-predominant patterns of atrophy and hypometabolism^{32,130–132}. However, other patients can show right-predominant patterns of atrophy and may have deficits in other types of semantic knowledge (such as recognizing familiar faces¹³³, facial emotions¹³⁴ or musical tunes^{135,136}) and behavioral abnormalities^{137–140}. Whilst the disease typically affects one hemisphere of the anterior temporal lobes early in the disease, atrophy tends to spread within both temporal lobes^{62,63,141–144} until patterns are often more symmetrical¹³⁸ and the frontal lobes become increasingly involved¹⁴⁵. The majority of studies assessing neuroimaging features of SD focus on the more common left-sided variant of SD.

The distinctive anterior temporal pattern of atrophy and hypometabolism in SD can be diagnostically useful to differentiate SD from other neurodegenerative diseases. Although anteromedial temporal structures can be involved in both SD and Alzheimer's dementia^{146,147}, the anteroposterior gradient of temporal atrophy is not observed in Alzheimer's dementia¹³⁰. One study found that an anteroposterior gradient of hypoperfusion on SPECT can help differentiate patients with SD from those with Alzheimer's dementia¹⁴⁸. Rates of atrophy of the temporal lobes are also faster in SD compared to Alzheimer's dementia⁶³. The patterns of neurodegeneration in SD can overlap with those seen in bvFTD. However, the frontal lobe is usually affected to a greater degree in bvFTD⁶⁵, and a ratio of temporal to frontal atrophy may be useful to distinguish these syndromes⁶². In addition, the

temporal pole is more atrophic in SD compared to bvFTD, with left temporal pole volume separating svPPA from bvFTD with 82% sensitivity and 80% specificity in one study⁷². Utilizing both FDG-PET and MRI measures of the temporal pole may in fact improve classification of SD from Alzheimer's dementia and other FTD syndromes better than either modality assessed in isolation¹⁴⁹.

Consistent with the temporal lobe focus of neurodegeneration, SD also shows reduced structural connectivity within the temporal lobes¹⁵⁰. White matter tract degeneration is observed in tracts that project from the temporal lobes, including the uncinate fasciculus and the inferior longitudinal fasciculus, particularly in the left hemisphere^{94,95,107,147,151–155} (Figure 3). Degeneration is also observed in frontal lobe white matter tracts, including the genu of the corpus callosum and the arcuate fasciculus, and posterior temporal lobe, although there is usually a relative sparing of tracts in parietal regions of the brain^{94,152,154}. While initial white matter degeneration in SD is limited to left temporal lobe tracts, there is evidence that degeneration spreads to bilateral frontotemporal tracts with disease progression¹⁰². Compared to bvFTD, SD patients show greater degeneration of the inferior longitudinal fasciculus^{93,94}, uncinate fasciculus¹⁵⁶ and inferior fronto-occipital fasciculus¹⁵⁶, and less degeneration of the genu of the corpus callosum, frontal white matter and parietal regions of the superior longitudinal fasciculus^{105,107}. In one study, bvFTD also tended to show greater involvement of tracts in the right hemisphere, while SD showed greater involvement of tracts in the left hemisphere¹⁵⁶. Semantic dementia appears to involve different white matter projections from the medial temporal lobe compared to Alzheimer's dementia, with SD targeting the uncinate and inferior longitudinal fasciculus and Alzheimer's dementia targeting the cingulum and corpus callosum, demonstrating vulnerability of distinct networks that both involve the medial temporal lobe¹⁴⁷ – perhaps explaining the difference clinical presentations despite...

Resting state fMRI studies have shown similarities in how neural networks are disrupted in SD compared to bvFTD, with disruptions in the salience network and frontolimbic connectivity also observed in SD patients^{111,116}. These similarities may reflect the fact that similar behavioral abnormalities can be observed in both SD and bvFTD patients¹¹⁶. However, SD appears to be specifically associated with reduced local and distinct connectivity from the anterior temporal lobe. Reduced connectivity has been observed between the left anterior temporal lobe and bilateral frontal and cingulate regions in SD compared to controls and bvFTD¹⁵⁶. In addition, SD patients show a loss of highly connected hubs in the left inferior temporal lobe, as well as in the orbitofrontal cortex and occipital lobes¹⁵⁷. These patterns of reduced functional connectivity concur with structural connectivity studies that have shown degeneration of tracts that connect the temporal pole, orbitofrontal cortex and occipital cortex, such as the uncinate fasciculus, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. The damage of these tracts could be responsible for the functional disconnections between these regions in SD. There is also evidence linking atrophy in SD to disrupted connectivity with the anterior temporal lobe, suggesting that atrophy may follow these connectional pathways¹⁵⁸.

Recent molecular PET imaging studies have produced some interesting findings in SD. Firstly, amyloid PET studies have shown that a high proportion, in fact up to 30%, of SD

patients can have beta-amyloid deposition in their brains^{159–163}. The presence of beta-amyloid deposition does not appear to influence the clinical presentation of SD, although the patients with beta-amyloid tend to be older¹⁶³. Although Alzheimer's disease can be the pathological cause of SD in some cases^{29,164–166}, this is relatively rare. Hence, the PET findings may reflect age associated beta-amyloid deposition in SD patients where the primary pathology is still a TDP-43 proteinopathy. Second, tau-PET imaging has been performed in patients with SD and, somewhat surprisingly given the underlying pathology, elevated uptake is observed in these patients (Figure 4). Elevated uptake has been demonstrated in the anteromedial temporal lobe, as well as regions in the basal frontal lobes, insula and putamen, with elevated uptake typically observed in the white matter rather than the grey matter^{126,163,167–170}. It remains unclear what the ligand is binding to in these cases. It could reflect off-target binding, reflect low levels of binding to TDP-43 or may be binding to low levels of tau that coexists with TDP-43^{167–169}. Tau PET uptake is, in fact, higher in SD patients that show beta-amyloid deposition compared to those without beta-amyloid deposition, perhaps supporting the hypothesis that the ligand may be binding to some tau pathology present in the brain in the beta-amyloid positive patients¹⁶³. Uptake remains elevated in the patients without beta-amyloid deposition, however, suggesting a potential alternative explanation for binding in these patients^{163,170}.

Agrammatic primary progressive aphasia and primary progressive apraxia of speech

The agPPA (referred to as progressive non-fluent aphasia in many studies) is associated with relatively focal patterns of atrophy on MRI and hypometabolism on FDG-PET that target the left posterior frontal lobe, including inferior (Broca's area), middle and superior premotor gyri^{10,155,171–177}, which is accompanied by widening of the left perisylvian fissure (Figure 2). Atrophy and hypometabolism can also be observed in the insula, striatum, superior temporal lobe, and other regions in the left frontal and parietal lobes^{172,173}. In contrast to bvFTD and SD, the anterior temporal lobes are typically relatively spared in patients with agPPA. Patients diagnosed with agPPA will most commonly have some combination of agrammatic aphasia and apraxia of speech, and it has been shown that these two clinical features have distinct anatomical correlates¹⁷⁸. Apraxia of speech is associated with atrophy and hypometabolism in the superior premotor cortex^{8,75}, while agrammatic aphasia is associated with abnormalities in the left inferior frontal lobe^{178–180} and other temporal and parietal regions¹⁷⁸ within the language network¹⁸¹. In fact, patients with PPAOS, which only have apraxia of speech in the absence of aphasia, show very focal patterns of atrophy and hypometabolism involving the bilateral supplementary motor area and lateral superior premotor cortex^{8,182} (Figure 2), and show less involvement of the left inferior frontal lobe and lateral temporal lobe compared to agPPA¹⁸². As with the other FTD syndromes, atrophy and hypometabolism are progressive in both agPPA and PPAOS. In agPPA, the fastest rates of atrophy are typically observed in the frontal lobes^{143,144,183,184}, with progressive volume loss also observed in the motor cortex, temporal and parietal lobes, insula, basal ganglia, and brainstem^{11,144,184,185}. Atrophy progresses in the right hemisphere in addition to the left, although left-sided asymmetry is typically maintained over time^{144,185}. In PPAOS, bilateral patterns of progressive volume loss over time are observed in the premotor cortex, motor cortex, basal ganglia and midbrain⁹. There is, therefore, overlap in the longitudinal patterns of atrophy observed in agPPA and PPAOS, reflecting progression of common clinical

features. Degeneration of the motor cortex and brainstem, for example, are associated with the development and progression of parkinsonism and limb apraxia in these patients¹¹. However, agPPA showed faster rates of atrophy in the inferior frontal lobe compared to PPAOS, reflecting greater decline in agrammatism than the PPAOS patients¹¹. Agrammatism can develop over time in some PPAOS patients, although not all, and when it does develop it is associated with atrophy of the left inferior frontal lobe, thalamus and putamen, showing that a network of regions is responsible for the development of agrammatic aphasia¹⁸⁶.

White matter tract degeneration is associated with both agPPA and PPAOS. In agPPA, degeneration has been observed in frontotemporal and frontoparietal connections of the left superior longitudinal fasciculus^{94,154,182,187–189} (Figure 3), particularly involving the arcuate fasciculus that projects into the inferior frontal lobe¹⁰⁷. The aslant tract that projects from Broca's area to the anterior cingulate and supplementary motor cortex is also affected^{190,191}. However, degeneration is also observed in other frontal tracts, including the body of the corpus callosum, anterior cingulate, inferior frontal-occipital fasciculus, and frontostriatal pathways^{107,154,182,188,192}. White matter tract findings are typically asymmetric, with greater involvement of the left hemisphere, although tend to be more bilateral and widespread than patterns of atrophy. Degeneration in this network of white matter tracts is associated with the language deficits observed in agPPA^{188,189,192}. Temporal lobe white matter tracts can be affected^{94,153,188,193} although this is not a consistent finding¹⁸⁷, and these tracts show greater involvement in SD and bvFTD compared to agPPA^{94,153,187}. Generally there is little overlap in patterns of tract degeneration between agPPA and SD¹⁹³. The superior longitudinal fasciculus has been shown to be involved to a greater degree in agPPA compared to bvFTD⁹⁴. Patients with PPAOS show less widespread patterns of white matter tract degeneration than agPPA, with bilateral involvement of the body of the corpus callosum and premotor aspects of the superior longitudinal fasciculus that lie adjacent to regions of grey matter loss in these patients^{8,182} (Figure 5). In fact, it appears as though apraxia of speech severity is particularly associated with degeneration of white matter tracts connecting the supplementary motor area to the inferior frontal cortex, premotor cortex and striatum¹⁹². White matter tract degeneration worsens over time in agPPA^{11,100,102}, with widespread bilateral longitudinal degeneration observed in the superior longitudinal fasciculus, inferior and superior fronto-occipital fasciculus, cingulum, corticospinal tracts and white matter underlying motor cortex¹¹. Longitudinal patterns of white matter tract degeneration are more focal in PPAOS, showing progression in the superior longitudinal fasciculus and body of the corpus callosum and spread to involve the splenium of the corpus callosum and white matter underlying the motor cortex^{9,11}. It, therefore, appears that even with disease progression PPAOS remains a more focal disease compared to agPPA, although overlap between the two syndromes is observed.

Consistent with the anatomical findings, disrupted functional connectivity in agPPA has been shown to be asymmetric, predominantly affecting the left hemisphere¹¹⁵. Widespread disruptions in connectivity have been observed throughout frontal, temporal and striatal regions in the left hemisphere¹¹⁵. Within the speech-language network, agPPA patients have been shown to have a loss of functional hubs in the left fronto-temporal-parietal area and new nodes in more anterior frontal regions and the right frontal lobe compared to

controls¹⁹⁴, suggesting a reorganization of the speech-language network is occurring in agPPA. In fact, longitudinal progression of atrophy in agPPA has been shown to be spatially related to functional connectivity of the speech-language network, supporting the view that neurodegeneration in agPPA spreads through this network¹⁹¹. Patients with PPAOS also show disruption of the speech-language network, with disrupted connectivity of the right supplementary motor area and left posterior temporal gyrus to the rest of the speech-language network¹⁹⁵. The connectivity of the right supplementary motor area correlated with the severity of apraxia of speech¹⁹⁵. These results fit with MRI/FDG-PET and structural connectivity findings and point towards an important role of the supplementary motor area in apraxia of speech.

Molecular PET imaging using beta-amyloid and tau ligands have been assessed in agPPA and PPAOS patients. Beta-amyloid deposition on PET has been observed in 0–30% of agPPA patients^{162,196–198} and 8% of PPAOS patients⁸, although the MRI signatures do not seem to differ according to beta-amyloid status¹⁹⁹. Elevated 18F-flortaucipir uptake has been observed in both agPPA and PPAOS (Figure 4). Mildly increased uptake has been observed in frontal white matter and subcortical grey matter structures, including thalamus and basal ganglia, in agPPA, with greater uptake observed in the left hemisphere^{126,168,170}. Patterns within agPPA appear to differ depending on the presence of apraxia of speech, with those with apraxia of speech showing greater uptake in the motor cortex²⁰⁰. The patterns of tau PET uptake in agPPA differ from those in SD and accounting for frontal versus temporal uptake allows good separation of these two diseases¹⁶⁸. Mild tau-PET uptake, predominantly in the white matter, is also observed in PPAOS, with uptake observed in the supplementary motor area and motor cortex²⁰¹. Elevated uptake in the inferior frontal gyrus was also observed in PPAOS patients that develop agrammatic aphasia²⁰¹. Patterns of tau-PET uptake, therefore, match closely with patterns of neurodegeneration observed in both agPPA and PPAOS. Given that agPPA and PPAOS most commonly result from a 4R tauopathy, it is possible that the ligands are detecting the presence of underlying tau proteins. However, autoradiographic studies have not observed good binding of 18F-flortaucipir to 4R tau isoforms^{128,202–204}, casting doubt on the biological interpretation of findings in these diseases. It is also currently unclear why the tau-PET findings are located predominantly in the white matter in the agPPA and PPAOS, and more work is needed to understand the mechanisms of binding in these cases.

Imaging predicting pathology in FTD

The different pathologies that underlie the FTD syndromes have been shown to be associated with different neuroimaging signatures which can be helpful in allowing the prediction of underlying pathology in FTD. Since future therapeutics will likely target specific proteins or pathologies it will be necessary to provide a pathological diagnosis, rather than just a syndromic diagnosis, for FTD patients. This is particularly important in syndromes where the underlying pathology can be heterogeneous, such as bvFTD and agPPA.

There does not appear to be specific neuroimaging signatures of FTLT-tau or FTLT-TDP, but rather signatures of the specific pathologies within each of these proteinopathies^{205–208}.

Within the FTLT-tau diseases, Pick's disease has a very different neuroimaging signature compared to PSP and CBD. Pick's disease has a characteristic pattern of knife-edge atrophy of the prefrontal cortex, with additional involvement of the anterior temporal lobes, insula and anterior cingulate^{209–212} (Figure 6). The cortex appears knife-edge due to the dramatic degree of shrinkage of the frontal gyri. In contrast, PSP and CBD involve more posterior regions of the frontal lobe, including premotor cortex⁵⁹ (Figure 6). Cortical atrophy is typically more widespread in CBD compared to PSP, spreading posteriorly to involve the parietal lobe, and with greater involvement of the basal ganglia^{213,214}. Rates of brain atrophy are also typically faster in CBD compared to PSP²¹⁵. Midbrain atrophy is typically considered a diagnostic feature of PSP, although the presence of midbrain atrophy is associated with the clinical syndrome of PSP, rather than the presence of pathological PSP²¹⁶. Hence, midbrain atrophy can be observed in patients that develop the typical clinical features of PSP (postural instability and vertical supranuclear gaze palsy) but have CBD pathology²¹⁶. Cortical atrophy is often asymmetric in CBD, relating to asymmetry that is present clinically, although symmetric CBD cases are also observed^{217,218} and asymmetric cases do not always have CBD pathology^{219,220}. Different patterns of atrophy are also observed across the FTLT-TDP types. Type A is associated with widespread and asymmetric atrophy of the frontal, temporal and parietal lobes (Figure 6); type B is associated with atrophy of the frontal and medial temporal lobes; and type C is associated with asymmetric atrophy of the anteromedial temporal lobes and nearly always presents clinically with SD^{221,222}. The FTLT-FUS diseases are rarer than FTLT-tau or FTLT-TDP and are associated with frontotemporal atrophy but with additional and severe atrophy of the caudate^{223–225}. The caudate has been shown to be involved to a greater degree in FTLT-FUS compared to other FTLT-tau and FTLT-TDP diseases²²³. This caudate signature has been observed across different FTLT-FUS diseases and hence may be a useful biomarker of FTLT-FUS.

Studies have demonstrated that these different FTD pathologies do show different neuroimaging features within groups of patients with the same clinical syndrome. Within patients with bvFTD, patterns of grey matter atrophy differ across the pathologies of Pick's disease, CBD and FTLT-TDP type A (Figure 6). While all three pathologies showed atrophy of the frontal lobes, likely related to the common clinical presentation, there are differences that may be diagnostically useful. Pick's disease has been shown to have greater atrophy in the anterior frontal lobes, insula and temporal pole compared to CBD²²⁶, while CBD has greater atrophy in the parietal lobe compared to Pick's disease²²⁶. Furthermore, FTLT-TDP type has been shown to have greater atrophy in the parietal lobe and posterior temporal lobe compared to both CBD and Pick's disease²¹². Generally, CBD showed milder patterns of atrophy compared to both Pick's disease²²⁶ and FTLT-TDP type A²¹². Imaging has also been shown to be useful in determining the underlying pathology in patients with agPPA. The agPPA patients with CBD pathology showed more widespread grey matter atrophy compared to those with PSP pathology, involving frontal, premotor and motor cortices, insula and striatum, and greater white matter atrophy in anterior parts of the frontal lobe²²⁷. However, the agPPA patients with PSP pathology developed greater atrophy of the midbrain and pons compared to those with CBD²²⁷. Furthermore, agPPA patients with FTLT-TDP pathology appear to show less white matter atrophy than agPPA patients with

either PSP or CBD pathology²²⁸. Neuroimaging, therefore, shows promise to be able to aid in the prediction of specific pathologies within bvFTD and agPPA.

Imaging in genetic FTD

A relatively large proportion of FTD patients have a family history and an autosomal dominant pattern of inheritance. A number of mutations have now been identified that account for many of these families. The most common mutations occur in the microtubule associated protein tau (*MAPT*)²²⁹ and progranulin (*GRN*)^{230,231} genes, along with an expansion of a noncoding GGGGCC hexanucleotide repeat in the *C9ORF72* gene that is genetically linked to chromosome 9p^{232,233}. Pathologically, both the *GRN* and *C9ORF72* expansion gene mutations are associated with FTLD-TDP, while *MAPT* mutations form another genetic variant of FTLD-tau. All three mutations are most commonly associated with bvFTD, although more varied clinical presentations are associated with *GRN* mutations, including agPPA^{234–238}, and *C9ORF72* repeat expansions are also associated with FTD-MND^{232,233}. Neuroimaging has proven incredibly valuable in genetic FTD to define the abnormalities associated with each mutation. This has improved our understanding of heterogeneity in FTD and provided markers that might predict the presence of a genetic mutation. Furthermore, asymptomatic family members with a genetic mutation can be followed before the development of symptoms allowing us to determine the earliest neuroimaging abnormalities in FTD; knowledge that will be crucial to allow early diagnosis.

The three main genetic mutations have been shown to have distinct neuroanatomical correlates on structural MRI. The *MAPT* mutations target the anteromedial temporal lobes, with additional atrophy observed in the frontal lobes, particularly the orbitofrontal cortex^{210,239}. Imaging findings are relatively consistent across different mutations, although some mutations tend to show predominant involvement of the medial temporal lobes and others the lateral temporal lobe²⁴⁰. The *GRN* mutations can show more variable patterns of atrophy and hypometabolism at the patient level, although they tend to typically show quite widespread and asymmetric involvement^{236,241} of the frontal, temporal and parietal lobes^{241,242}. Involvement of the parietal lobe is particularly characteristic of *GRN* mutations^{234,241,243}. The *C9ORF72* repeat expansion has been shown to be associated with symmetric patterns of atrophy involving the frontal, temporal, parietal and occipital lobes, in addition to the cerebellum^{244–247} and thalamus^{245–247}. There is evidence that imaging can help differentiate across the three mutations. Studies have found that patients with *GRN* mutations show more asymmetry²⁴⁵ and greater involvement of the posterior regions of the brain compared to *MAPT* and *C9ORF72* carriers^{234,240,244}, while *MAPT* carriers showed greater atrophy of the anterior temporal lobes than both *GRN* and *C9ORF72* carriers^{240,244,245} (Figure 7). Furthermore, the *C9ORF72* repeat expansions showing greater atrophy in parietal and occipital lobes compared to *MAPT* carriers and sporadic bvFTD²⁴⁴ (Figure 7). There is some disagreement in the field with the diagnostic utility of the thalamus for detecting *C9ORF72* mutations, with some showing the thalamus differentiates *C9ORF72* patients from sporadic FTD²⁴⁸, while others finding that the thalamus does not help to differentiate between the different FTD mutations^{244,249}. Differences across FTD mutations have also been identified in longitudinal rates of progression, with *GRN* carriers showing

faster rates of atrophy across the brain than both *MAPT*^{250,251} and *C9ORF72*^{245,252}, as well as sporadic FTD²⁵². The *GRN* mutation, therefore, appears to be particularly aggressive.

Studies that have assessed asymptomatic mutation carriers have found that grey matter atrophy can be detected before symptom onset in all three mutations, with regional findings typically matching those observed in symptomatic patients but to a lesser degree^{253–258}. Alterations in structural and functional connectivity have also been observed before the onset of clinical symptoms in genetic FTD^{255,259}. Degeneration of the uncinate fasciculus has been observed both in symptomatic and asymptomatic *MAPT* mutation carriers^{98,256,260}; degeneration of white matter tracts projecting into the frontal, temporal and parietal lobes, such as uncinate fasciculus, anterior corpus callosum, fronto-occipital fasciculus and superior longitudinal fasciculus have been observed in asymptomatic *GRN* mutation carriers^{255,261}; and, similarly, degeneration of white matter tracts that project into frontal and posterior brain regions, including the anterior thalamic radiations, have been observed in symptomatic and asymptomatic *C9ORF72*^{98,245,254,257,260}. In fact, one study found that diffusivity changes in patients with the *C9ORF72* repeat expansion occur 30 years before the onset of symptoms, and occur earlier than diffusivity changes in *MAPT* and *GRN* carriers²⁶⁰. Disruptions in functional connectivity in patients with the *C9ORF72* repeat expansion have been observed to overlap with those observed in sporadic bvFTD, with disruptions of the salience network and sensorimotor network in both symptomatic²⁶² and asymptomatic carriers²⁵⁴. This body of work demonstrates that measures from both structural and functional imaging have potential as early disease biomarkers in genetic FTD, although the optimum neuroimaging modality is still unclear.

Elevated uptake has been observed in patients with FTD mutations on tau-PET imaging. The distribution of uptake in the *MAPT* mutations typically mirrors the patterns of neurodegeneration, although the degree of uptake varies across the different *MAPT* mutations due to differences in the characteristic tau isoforms that are deposited in the brain (Figure 8). Hence, tau mutations, such as V337M and R406W, which deposit 3R+4R isoforms have high levels of uptake on tau-PET akin to the levels of uptake observed in Alzheimer's dementia^{126,263–265}, whereas mutations that deposit 4R isoforms of tau, such as N279K, S305N and 10+16, show milder uptake^{265–267}. Therefore, tau-PET imaging shows promise as a useful neuroimaging modality in some of the *MAPT* mutations. As discussed above, it is unclear what the ligand is binding to in the 4R *MAPT* cases. The underlying mechanism for elevated uptake in *GRN* and *C9ORF72* carriers¹²⁶ is also unclear and more work is needed to understand these findings.

Summary

The past few decades of neuroimaging research in bvFTD have provided potential disease biomarkers and taught us a lot about the breakdowns in brain structure and function, and the relationship between clinical symptoms and brain abnormalities in bvFTD. This knowledge has improved our ability to inform patients and their families, provide more targeted diagnoses and prognostic estimates, and provided outcomes measures that can be used to track disease progression for clinical treatment trials. However, we still lack definitive biomarkers of underlying pathology in FTD. Molecular PET imaging shows promise but

ligands that better target different tau isoforms, and ligands that target FTLT-DTP, will be essential for FTD.

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Figure 1: Schematic illustrating the relationship between FTD clinical syndrome and pathological diagnosis.

BvFTD = behavioral variant frontotemporal dementia, SD = semantic dementia; agPPA = agrammatic variant of primary progressive aphasia; PPAOS = primary progressive aphasia

Figure 2: Patterns of atrophy and hypometabolism associated with the FTD clinical syndromes. Group-level maps depicting grey matter atrophy compared to controls are shown on three dimensional renders of the brain. Hypometabolism on FDG-PET is shown for individual patients, represented as Z score maps depicting abnormalities compared to controls.

Figure 3: Diffusion tensor imaging findings in bvFTD, SD and agPPA.

The top panel shows color coded fractional anisotropy (FA) maps showing major white matter tracts. The bottom panel shows box-plots of FA values across the three clinical groups. The left inferior longitudinal fasciculus (ILF) is preferentially affected in SD, the uncinate fasciculus (UNC) is affected in both bvFTD and SD, and the left superior longitudinal fasciculus (SLF) is preferentially affected in agPPA. SD = semantic dementia; bvFTD = behavioral variant of FTD; agPPA = agrammatic variant of primary progressive aphasia. Reproduced with permission from *Imaging in Neurodegenerative Disorders* (Oxford University Press, 2015, edited by Luca Saba)

Figure 4: 18F-flortaucipir images from patients with different FTD clinical syndromes. Mild uptake predominantly in the white matter is observed in the frontotemporal lobes in the bvFTD patient, left temporal lobe in the SD patient, left frontal lobe of the agPPA patient and bilateral premotor cortex of the PPAOS patient.

Figure 5: Diffusion tensor imaging abnormalities in PPAOS.

Regions of reduced tract integrity are shown in red on top of a green white matter skeleton of the brain. Results were created using track-based spatial statistics comparing a PPAOS cohort to controls.

Pick's disease

FTLD-TDP

Corticobasal degeneration

Figure 6: Individual MRI scans from patients with bvFTD but different pathological diagnoses. The patient with Pick's disease shows knife-edge atrophy of the frontal lobes. The patient with FTLD-TDP shows widespread frontal, temporal and parietal atrophy. The patient with corticobasal degeneration shows atrophy predominantly of the posterior frontal lobes.

Figure 7: Three dimensional renders highlighting regional differences in patterns of atrophy amongst FTD genetic mutations.

Blue shows regions with greater atrophy in C9ORF72 compared to MAPT; green shows regions with greater atrophy in MAPT compared to C9ORF72; and red shows regions with greater atrophy in GRN compared to C9ORF72

Figure 8: Representative renderings of tau-PET uptake in MAPT mutations relative to Alzheimer's dementia.

Tau PET global distributions are displayed on individual participant's brain renderings for 3 participants: (A) patients with 4R MAPT with marginally elevated levels of tau PET signal; (B) patients with mixed 3R/4R MAPT, and (C) a representative patient with Alzheimer's dementia. Figure reproduced with permission from²⁶⁵.