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Neuroimaging in frontotemporal dementia

JONATHAN D. ROHRER[1] & HOWARD J. ROSEN[2]

[1]*Dementia Research Centre, Department of Neurodegenerative Diseases, Institute of Neurology, University College London, UK, and* [2]*Department of Neurology, Memory and Aging Center, University of California, San Francisco, California, USA*

Abstract

The term frontotemporal dementia (FTD) refers to a group of neurodegenerative disorders that are associated with atrophy of the frontal and temporal lobes, and present clinically with impairments of behaviour or language. Three main subtypes are described, behavioural variant FTD (bvFTD) and two subtypes of the language presentation (known as primary progressive aphasia or PPA) called semantic variant of PPA and non-fluent variant of PPA. Most imaging studies of FTD have used volumetric T1 magnetic resonance imaging (MRI) or positron emissions tomography imaging to identify patterns of grey matter atrophy or hypometabolism in these different subtypes, but more recently newer imaging techniques have been used to help define abnormalities in structural connectivity (white matter tract integrity using diffusion tensor imaging), functional connectivity (resting state networks using resting state functional MRI) and perfusion (using arterial spin labelling perfusion MRI) in FTD. These techniques have the potential to improve the differential diagnosis of FTD from other disorders and to provide more informative imaging signatures of FTD syndromes.

Introduction

Frontotemporal dementia (FTD) is a clinically, genetically and pathologically heterogeneous neurodegenerative disorder (Gorno-Tempini et al., 2011; Rascovsky et al., 2011; Seelaar et al., 2011) (Figure 1). The major clinical subtypes of FTD are known as behavioural variant FTD (bvFTD) which presents with a change in personality, and primary progressive aphasia (PPA) which presents with language impairment. PPA has a number of subtypes which include the non-fluent and semantic variants (Gorno-Tempini et al., 2011), also known as progressive non-fluent aphasia (PNFA) and semantic dementia (SD). As all of these conditions progress they can overlap with each other and also with other conditions, namely amyotrophic lateral sclerosis (FTD-ALS) and the atypical Parkinsonian syndromes corticobasal syndrome (CBS) and the progressive supranuclear palsy syndrome (PSPS).

Around a third of FTD is familial with mutations in the progranulin (GRN) and microtubule-associated protein tau (MAPT) genes and hexanucleotide expansions in the C9ORF72 gene the most common causes (Rohrer & Warren, 2011) (Figure 1). MAPT mutations are associated clinically with bvFTD although the atypical Parkinsonian syndromes can be seen more rarely. GRN mutations are associated with bvFTD, PPA and also CBS, whilst expansions in C9ORF72 are associated with bvFTD, FTD-ALS and less commonly PPA. Rarer genetic causes include mutations in the valosin-containing protein (VCP) gene.

Pathologically in FTD, neuronal inclusions are found containing abnormal forms of one of three different proteins, tau, TDP-43 or fused in sarcoma (FUS) (Rohrer et al., 2011b) (Figure 1). Each of these proteinopathies has a number of further subtypes:

- *Tauopathies* include corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Pick's disease and the pathology associated with MAPT mutations. (Note that the term Pick's disease here refers to a specific pathology and not to FTD in general as it was previously used.)
- *TDP-43 proteinopathies* include four separate subtypes, named A, B, C and D. Patients with GRN mutations have type A pathology whilst patients with expansions in C9ORF72 have either Type A or B pathology. Semantic variant of PPA is usually associated with TDP-C whilst FTD-ALS is usually associated with TDP-B.
- *FUSopathies* include atypical frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U), neuronal intermediate filament inclusion disease and basophilic inclusion body disease.

Correspondence: Dr Howard J. Rosen, Memory and Aging Center, University of California, San Francisco, 94143, CA, USA. Tel: 415-476-5567. E-mail: hrosen@memory.ucsf.edu

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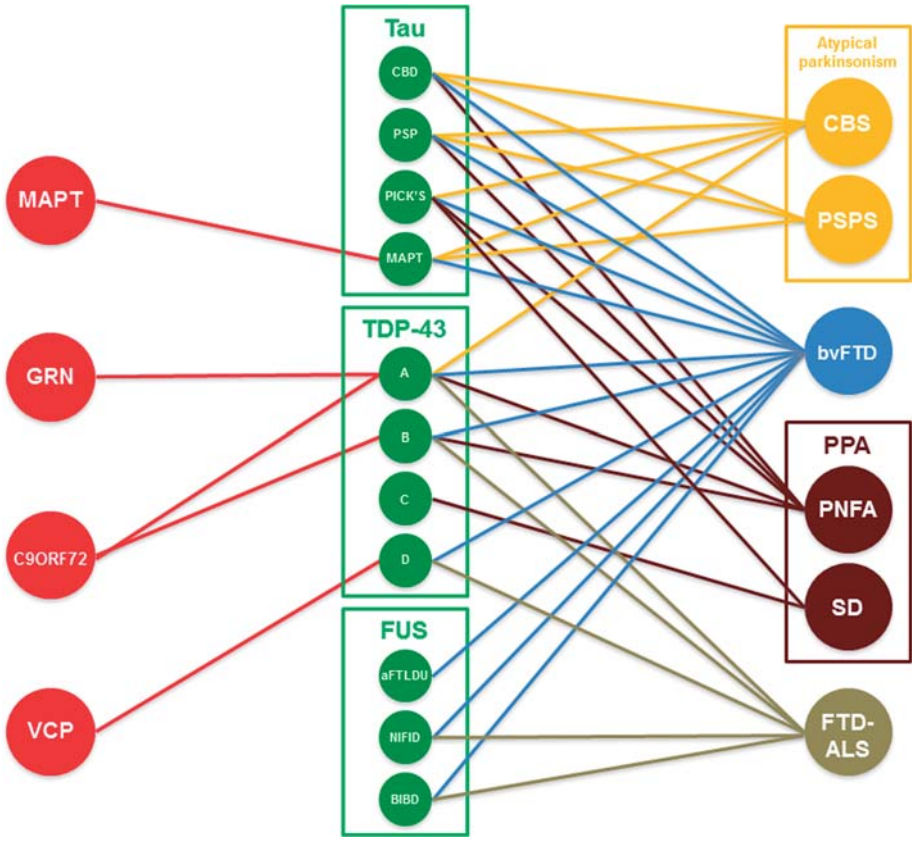

Figure 1. The clinical, pathological and genetic heterogeneity of frontotemporal dementia. This diagram highlights the complex clinico-patho-genetic relationships between the clinical syndromes within the FTD spectrum (on the right), the different pathological causes (in the centre) and the genetic causes (on the left).

This heterogeneity makes diagnosis difficult during life, particularly of the underlying pathological cause. Neuroimaging studies have been used in FTD to identify neuroanatomical signatures associated with particular clinical syndromes, genetic mutations and pathologies, but these associations have been far from perfect, particularly with respect to pathology. Until recently the majority of these studies have looked at structural imaging features using volumetric T1 MR imaging (reviewed in Agosta et al., 2012a; Rohrer, 2012; Seelaar et al., 2011). This review will concentrate on recent advances in the neuroimaging of FTD including novel imaging techniques that have provided further information about the disorder beyond that seen in structural T1 MR imaging.

What are the patterns of grey matter atrophy in FTD?

Clinical syndromes

In meta-analyses bvFTD is associated with grey matter atrophy in the frontal and temporal lobes as well as the anterior cingulate, anterior insula and subcortical structures such as the thalamus (Schroeter et al., 2007, 2008). Atrophy is often asymmetrical, affecting the right hemisphere more than the left, although this is not the case for all patients with bvFTD. However, this does not take into account the heterogeneity of bvFTD, and one study using a cluster analysis has suggested there are four different neuroanatomical groups: two with predominant frontal lobe atrophy (either restricted to the frontal lobe or involving both frontal and temporal lobes), and two with predominant temporal lobe atrophy (either restricted to the temporal lobes or affecting temporal, frontal and parietal lobes) (Whitwell et al., 2009c).

There are at least three subtypes of PPA, the semantic variant, the non-fluent variant and the logopenic variant (Gorno-Tempini et al., 2011). The last of these is usually associated with Alzheimer's disease pathology and is not discussed in detail in this review. The semantic variant presents with a fluent aphasia, anomia and single word comprehension difficulties. It is associated with a characteristic pattern of asymmetrical, usually left greater than right, atrophy of the temporal lobes affecting particularly the anterior and inferior regions (Davies et al., 2009; Gorno-Tempini et al., 2004a; Hodges & Patterson, 2007; Rohrer et al., 2009). Over time more posterior

temporal regions become affected as well as the orbitofrontal lobe, insula and anterior cingulate, as well as homologous areas in the opposite hemisphere (Brambati et al., 2009; Rohrer et al., 2009). The non-fluent variant presents with speech production impairment secondary to agrammatism and apraxia of speech. Imaging studies show areas of atrophy mostly in the left inferior frontal lobe, insula and premotor cortex (Gorno-Tempini et al., 2004a; Josephs et al., 2006; Rogalski et al., 2011; Rohrer et al., 2009). With disease progression other areas in the frontal lobe become affected as well as the temporal lobe, anterior parietal lobe and subcortical structures including the caudate (Gorno-Tempini et al., 2004b; Rogalski et al., 2011; Rohrer et al., 2009). In contrast to the semantic and non-fluent variants, the logopenic variant of PPA tends to have more posterior cortical atrophy, with asymmetrical (left more than right) temporo-parietal atrophy predominating early in the disease (Gorno-Tempini et al., 2004a; Rogalski et al., 2011).

Genetic syndromes

Studies of genetic FTD have shown different patterns of atrophy associated with the different genes (Figure 1). MAPT mutations are associated with relatively symmetrical anterior temporal lobe atrophy with lesser involvement of the orbitofrontal cortices (Rohrer et al., 2010b; Whitwell et al., 2009b). One small study has shown that there may be differences between patients with MAPT mutations that affect splicing (which have more medial temporal lobe involvement) and mutations that affect the structure of the tau protein (which have more lateral temporal lobe involvement) (Whitwell et al., 2009a). In contrast GRN mutations are associated with strongly asymmetrical atrophy affecting either the left or right hemispheres maximally and involving the temporal, inferior frontal and inferior parietal lobes (Rohrer et al., 2010b; Whitwell et al., 2009b). More recently there have been a number of studies of patients with expansions in the C9ORF72 gene. These have shown relatively symmetrical involvement of the frontal and temporal lobes but also with more posterior cortical involvement and in contrast to other causes of genetic FTD some studies have shown involvement of the thalamus and cerebellum (Mahoney et al., 2012a, 2012b; Sha et al., 2012; Whitwell et al., 2012).

Pathological syndromes

Initial studies investigating imaging signatures of tau or TDP-43 pathology did not show a clear picture, but with increasing knowledge of the different subtypes of FTD pathology, more recent studies have refined the associations (Figure 2). Two studies of the TDP-43 proteinopathies showed similar findings, with TDP-A pathology being associated with asymmetrical fronto-temporo-parietal atrophy, TDP-B with more symmetrical atrophy affecting the frontal lobe but also the insula and anteromedial temporal lobe, and TDP-C showing asymmetrical anteroinferior temporal lobe atrophy (Rohrer et al., 2010a; Whitwell et al., 2010c).

FUS pathology is relatively rare in FTD but a number of studies have now shown a pattern of atrophy affecting the orbitofrontal lobe, anterior cingulate, insula, anterior temporal lobe and particularly severely the caudate (Josephs et al., 2010; Lee et al., 2012b; Rohrer et al., 2011a; Seelaar et al., 2010).

In the tauopathies, Pick's disease is associated with asymmetrical frontal lobe (particularly dorsolateral and orbitofrontal), insula and anterior temporal lobe atrophy (Rohrer et al., 2011b; Whitwell et al., 2011a), whilst CBD is associated with less distributed atrophy affecting mostly frontal and to a lesser extent the parietal lobe in a slightly asymmetrical pattern (Josephs et al., 2008; Rohrer et al., 2011b; Whitwell et al., 2010b).

Some work has suggested that the absence of imaging findings characteristic of FTD in a given patient has prognostic significance. Recent publications have described a series of patients with normal structural brain imaging as well as normal neuropsychological performance who do not appear to worsen over time. Such cases have been designated 'FTD phenocopies' (Kipps et al., 2009). While it has been shown that some cases with these features are associated with FTD mutations (Khan et al., 2012), many of these cases still remain a mystery, and it is likely that some do not have a neurodegenerative aetiology.

What are the structural connectivity abnormalities in FTD?

Diffusion tensor imaging (DTI) allows characterization of abnormalities in the structure of white matter tracts in the brain. It evaluates the diffusion of water in each of the three main directions (right/left, front/back, up/down) and so allows quantification of the degree of anisotropy and local fibre direction on a voxel-by-voxel basis. Diffusion of water is anisotropic (directionally dependent) in white matter fibre tracts because axons and myelin sheaths act as barriers; consequently, in axons the diffusion of water (diffusivity) is significantly greater along the axis of those fibres, thereby providing a tensor measurement. Fractional anisotropy (FA) is a measure of the degree of anisotropy of a diffusion process and ranges from zero, when diffusion is isotropic (i.e. unrestricted in

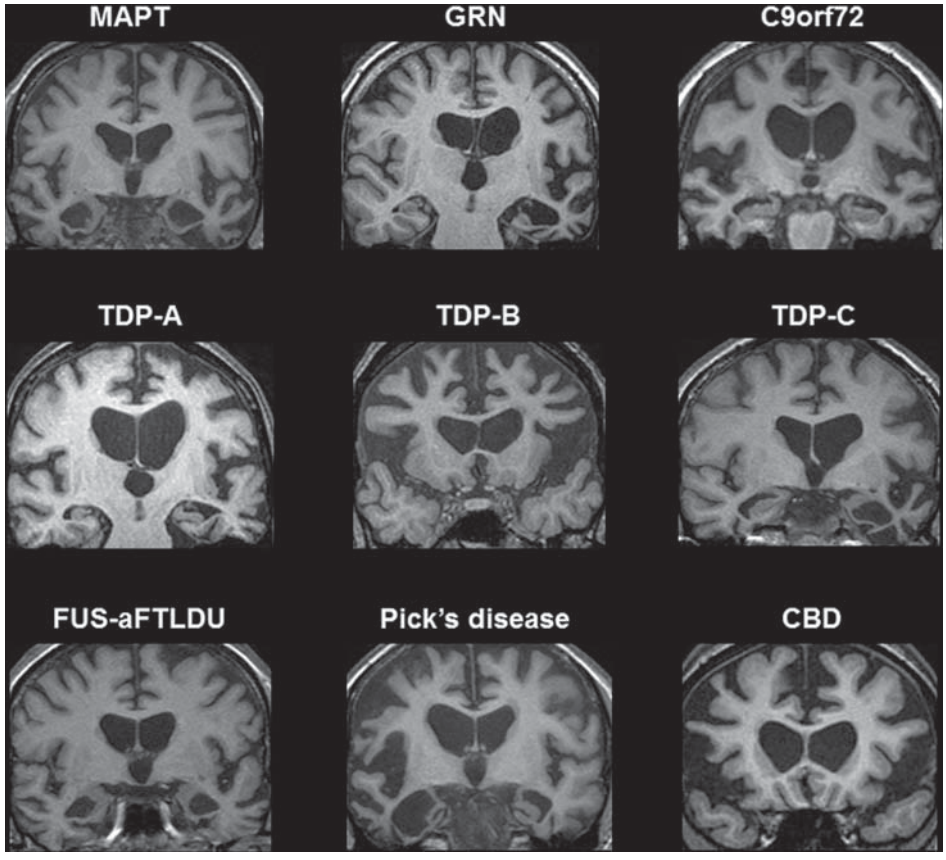

Figure 2. Coronal T1 MR images showing examples of patterns of grey matter atrophy in genetically and pathologically defined frontotemporal dementia. In MAPT mutations there is relatively symmetrical medial temporal atrophy; in GRN mutations there is asymmetrical temporo-fronto-parietal atrophy (affecting the left hemisphere here but can affect either hemisphere); in C9ORF72 expansions there is relatively symmetrical fronto-temporal atrophy. In TDP-A pathology there is asymmetrical temporo-fronto-parietal atrophy (here left-sided predominant but can affect either hemisphere). In TDP-B pathology there is more symmetrical atrophy affecting the frontal lobe, insula and anteromedial temporal lobe. In TDP-C pathology there is asymmetrical anteroinferior temporal lobe atrophy (here left-sided predominant but can affect either hemisphere). In FUS pathology there is caudate and anterior temporal lobe atrophy (and also orbitofrontal lobe and anterior cingulate involvement). In Pick's disease there is asymmetrical fronto-insula-temporal atrophy (here right-sided predominant but can affect either hemisphere); in CBD there is fronto-parietal atrophy.

all directions), to one, when diffusion occurs only along one axis and is fully restricted in the other directions. FA can therefore provide information on the orientation and integrity of fibres.

In bvFTD, studies have shown alterations in FA and diffusivity bilaterally in the majority of the frontal white matter tracts including the anterior superior longitudinal fasciculus (SLF), anterior cingulum and the genu of the corpus callosum, as well as the temporal white matter tracts including the uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF) (Agosta et al., 2012b; Avants et al., 2010; Borroni et al., 2007; Matsuo et al., 2008; Whitwell et al., 2010a; Zhang et al., 2009, 2013). Some studies do show changes (albeit to a lesser extent) more posteriorly such as in the posterior cingulate and posterior parts of the SLF consistent with studies showing more posterior grey matter involvement in some variants of FTD, particularly as the disease becomes more severe (Agosta et al., 2012b; Whitwell et al., 2010a; Zhang et al., 2009).

One study has looked at the overlap of bvFTD with ALS showing that patients with FTD-ALS have a similar pattern of involvement of the frontal and temporal white matter tracts as bvFTD but with greater corticospinal tract degeneration, in a pattern similar (although to a lesser extent) to patients with ALS alone (Lillo et al., 2012).

In the semantic variant of PPA a number of studies have shown asymmetrical alterations in diffusivity and FA in the ILF and UF with the left side more severely affected (Acosta-Cabronero et al., 2011; Agosta et al., 2010, 2012b; Borroni et al., 2007; Galantucci et al., 2011; Mahoney et al., 2013; Schwindt et al., 2011; Whitwell et al., 2010a; Zhang et al., 2013). Although some studies have shown relative sparing of the SLF (Agosta et al., 2010), others that have examined separate parts of the SLF have reported abnormalities in subcomponents,

particularly the arcuate fasciculus (Acosta-Cabronero et al., 2011; Agosta et al., 2010; Galantucci et al., 2011; Schwindt et al., 2011; Whitwell et al., 2010a). Some studies have also shown abnormalities in other tracts including the left IFOF and genu of the corpus callosum (Agosta et al., 2010; Borroni et al., 2007; Schwindt et al., 2011).

In contrast to the semantic variant, studies of the non-fluent variant of PPA have shown alterations of diffusivity and FA mostly in the dorsal language pathways i.e. the subcomponents of the left superior longitudinal fasciculus, particularly the arcuate fasciculus (Agosta et al., 2012a; Galantucci et al., 2011; Grossman et al., 2012; Mahoney et al., 2013; Schwindt et al., 2011; Whitwell et al., 2010a; Zhang et al., 2013). In patients with predominantly apraxia of speech rather than agrammatism, the premotor components of the SLF appear to be affected more than other regions (Josephs et al., 2012). Other tracts that have shown abnormalities to a lesser extent include the IFOF and UF as well as the fornix and corpus callosum, more so on the left than the right (Agosta et al., 2012b; Grossman et al., 2012; Schwindt et al., 2011).

Unlike with volumetric T1 imaging, there have been few DTI studies looking at genetically or pathologically defined FTD. One recent study of patients with expansions in the C9ORF72 gene (usually associated with bvFTD or FTD-ALS clinically) showed abnormalities in SLF, ILF, UF, anterior cingulate and corpus callosum but also corticospinal tract and anterior thalamic radiations (Mahoney et al., 2012a). Whilst there was an anterior emphasis for abnormalities, more posterior areas were also involved, consistent with the grey matter atrophy seen more posteriorly in this group.

Studies of presymptomatic subjects at-risk of developing genetic FTD have shown abnormalities a number of years before symptom onset in volumetric T1 imaging. A single study of progranulin mutation carriers showed no grey matter abnormalities on T1 imaging but did show reduced FA in the left UF and left IFOF compared to controls, suggesting that abnormalities in white matter integrity may predate grey matter atrophy (Borroni et al., 2008).

What are the functional connectivity abnormalities in FTD?

Resting state functional MRI (RS-fMRI) examines temporal synchronization of intrinsic fluctuations in signals dependent on blood oxygen level arising from neuronal and synaptic activity that is observed independent of overt cognitive information processing. RS-fMRI has been used to elucidate a variety of coherent large-scale brain networks, the best described being the default mode network, a set of regions that routinely decrease their activity during attention-demanding tasks. Other networks subserving vision, audition and motor function have also been characterized. In FTD the networks of most interest have been language and semantic networks in the left hemisphere, an executive control network linking dorsolateral frontal and parietal cortices, and a salience network centred around the ventral frontal cortex, insula and dorsal anterior cingulate (Lee et al., 2012a; Seeley et al., 2007, 2009).

An early RS-fMRI study showed that bvFTD is associated with reduced connectivity in the salience network but with increased connectivity in the default mode network (with the opposite pattern being found in Alzheimer's disease) (Zhou et al., 2010). This reduced connectivity in the salience network has been replicated in further studies of bvFTD (Farb et al., 2012; Filippi et al., 2012; Whitwell et al., 2011b) but other results from these studies are conflicting. One study showed similarly increased connectivity in the default mode network (Farb et al., 2012) whilst another study showed increased connectivity in part of the default mode network (medial parietal) but reduced connectivity in other parts (lateral temporal, medial prefrontal and dorsolateral frontal lobes) (Whitwell et al., 2011b). A third study showed a trend towards reduced connectivity in the default mode network (Filippi et al., 2012). The reason for this variability of findings is unclear but may represent differences in methodology or in different bvFTD subtypes being studied.

A single study has examined the use of RS-fMRI in presymptomatic MAPT mutation carriers. This showed no changes in the salience network but reduced connectivity in parts of the default node network (lateral temporal and medial prefrontal cortex) with increased connectivity in other parts of the default node network (medial parietal) and no abnormalities seen on T1 imaging, suggesting that, as with DTI, RS-fMRI changes may predate atrophy (Whitwell et al., 2011b).

What are the perfusion abnormalities in FTD?

Arterial spin labelling perfusion MRI (ASL) is a method for assessing brain perfusion and function in dementia. In ASL, the assumption is made that regional metabolism and perfusion are coupled; therefore, when arterial blood water is labelled as an endogenous diffusible tracer for perfusion, it can depict functional deficiencies similarly to 18-F-flourodeoxyglucose positron emission tomography (FDG-PET) and 99mTc-hexamethylpropyleneamine oxime single photon emission tomography (HMPAO-SPECT) but is non-invasive and free of exposure to

ionizing radiation, intravenous contrast agents, and radioactive isotopes.

Studies of ASL in bvFTD have shown hypoperfusion in bilateral frontal regions as well as anterior cingulate and thalamus compared to controls (Du et al., 2006; Shimizu et al., 2010; Zhang et al., 2011). A further study looking at a group of patients with frontotemporal dementia that included PPA and bvFTD found hypoperfusion compared to controls in dorsolateral prefrontal cortex bilaterally and right inferior fronto-insular areas with areas of hyperperfusion in medial parietal cortex, precuneus and posterior cingulate (Hu et al., 2010).

What are the abnormalities in FTD seen with PET and SPECT?

SPECT and PET can be used to measure the uptake of a variety of compounds that are labelled with radioactive isotopes. The most commonly studied SPECT method uses HMPAO, which crosses the blood–brain barrier and is taken up in proportion to blood flow allowing the tracking of cerebral perfusion. The PET compound most commonly used in FTD is FDG, which crosses the blood–brain barrier and is taken up by metabolically active cells thus providing a measure of brain activity.

Both SPECT and PET have been used to show that FTD is associated with hypometabolism in the frontal and anterior temporal regions, with svPPA showing more temporal lobe hypometabolism and bvFTD showing more frontal hypometabolism (Edwards-Lee et al., 1997; Frisoni et al., 1995; Jagust et al., 1989; Miller et al., 1991; Salmon et al., 1994) The patterns tend to be similar to those seen with structural imaging, although they are often easier to appreciate by eye (Rabinovici et al., 2011). A recent study comparing FTD and Alzheimer's disease patients whose diagnoses were ultimately confirmed at autopsy showed that FDG-PET increases diagnostic accuracy beyond clinical features alone (Foster et al., 2007). The utility of FDG-PET in diagnosing FTD led to this technique being the first imaging technique approved by the US Medicare health insurance programme for diagnosis of FTD.

New PET-based imaging techniques will be even more important for diagnosing FTD. Pittsburgh compound B (PiB) and florbetapir are both radiolabelled compounds that bind to cerebral amyloid plaques in patients with Alzheimer's disease (Landau et al., 2012). Florbetapir has an advantage over PiB because PiB is labelled with carbon-11, which has a relatively short half-life and thus requires a cyclotron to be in close proximity to the PET scanner, whereas florbetapir is labelled with F-18, which has a half-life long enough to allow delivery to the PET scanner from a central manufacturing facility. PiB has been well demonstrated to differentiate FTD from AD, although only small numbers of pathologically verified FTD patients have been studied so far (Rabinovici et al., 2011). Although florbetapir has not yet been studied in FTD, these studies are ongoing.

Discussion

What role is imaging serving in research and care of FTD?

The growth in the last few years in our knowledge of the molecular underpinnings and the neuroanatomical signatures of each of the clinical, genetic and pathological variants of FTD has led to a much deeper understanding of the disease. Because of the reliability of the imaging findings described above, and concerns that some patients show symptoms of FTD due to non-neurodegenerative disorders, abnormalities detected with brain imaging are now accepted as a criterion for establishing a diagnosis of 'probable' FTD in the most recently published diagnostic criteria (Rascovsky et al., 2011). Structural and functional imaging abnormalities are thus used as one means of confirming that a typical sounding FTD presentation is likely due to a neurodegenerative aetiology (although radiological experience in reviewing such scans is clearly important in accurate diagnosis (Suarez et al., 2009). Furthermore, in the near future, PET imaging to detect amyloid will likely play an important role in ensuring that the degenerative aetiology is unlikely to be Alzheimer's disease.

However, imaging is still incapable of providing some very important information. First, there are no imaging features yet identified that reliably make the critical distinction between TDP-43 and tau pathology. This has vital implications for treatment. Recently developed techniques for imaging tau using PET scanning holds promise in this regard, but this is just starting to undergo clinical validation (Chien et al., 2013). In addition, although PiB and florbetapir can identify Alzheimer's-type pathology, there are no techniques yet capable of identifying other pathologies that might be confused with FTD, such as Lewy bodies.

Beyond diagnosis, imaging has other potential uses. Current research is focusing on the potential utility of imaging as a marker of disease severity that can be used to track drug effects in clinical trials or ultimately in patient care (Knopman et al., 2007). This could be particularly important for treatment that might be used in an asymptomatic phase of disease to prevent deterioration. Given that the rates of change in brain volume are twice as fast in FTD as in Alzheimer's disease (Krueger et al., 2010), imaging in FTD shows great promise for this purpose.

Lastly, the discussion above makes it clear that the majority of imaging findings in FTD have relied heavily on volumetric T1 MR and PET imaging to define patterns of grey matter atrophy and hypometabolism. The newer imaging techniques discussed in this review have the potential to supplement the more established techniques. For instance, ASL measures may be able to substitute for FDG-PET because of the strong correlation between perfusion and glucose metabolism. However, these novel MRI techniques are now just starting to be used to study FTD, and so their role in diagnosis and tracking of FTD has yet to be established.

Take home points

FTD is heterogeneous but studies of volumetric T1 imaging have provided neuroanatomical signatures of clinical, genetic and pathological syndromes.

Novel imaging techniques such as DTI, RS-fMRI and ASL have further refined the imaging findings in the clinical syndromes of FTD.

Future directions

Future studies of FTD will look at novel imaging techniques such as DTI, RS-fMRI and ASL in genetically and pathologically defined FTD.

It will also be important in the future for specialist FTD centres to work together in international consortia to increase the numbers of patients and therefore scans available for studying.

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