Biochimica et Biophysica Acta 1822 (2012) 325–332

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Structural brain imaging in frontotemporal dementia ☆

Jonathan D. Rohrer *

Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK

ARTICLE INFO

Article history:
Received 10 May 2011
Received in revised form 24 July 2011
Accepted 25 July 2011
Available online 30 July 2011

Keywords:
Frontotemporal dementia
Frontotemporal lobar degeneration
Primary progressive aphasia
Neuroimaging
MRI

ABSTRACT

Frontotemporal dementia (FTD) is the second commonest young-onset neurodegenerative dementia. The canonical clinical syndromes are a behavioural variant (bvFTD) and two language variants (progressive nonfluent aphasia, PNFA, and semantic dementia, SD) although there is overlap with motor neurone disease and the atypical parkinsonian disorders corticobasal syndrome (CBS) and progressive supranuclear palsy syndrome (PSPS). Characteristic patterns of atrophy or hypometabolism are described in each of the variants but in reality imaging studies are rather heterogeneous. This review attempts to address four key questions in the neuroimaging of FTD: 1) what are the early imaging features of the different FTD syndromes (and how do these change as the disease progresses); 2) what do studies of presymptomatic genetic cases of FTD tell us about the very early stages of the disease; 3) can neuroimaging help to differentiate the different FTD syndromes; and 4) can neuroimaging help to differentiate FTD from other neurodegenerative diseases? This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

1. Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disorder associated with atrophy of the frontal and temporal lobes. Clinically, a number of overlapping clinical syndromes are seen, with the most common being a behavioural variant (bvFTD) and two language variants (progressive nonfluent aphasia, PNFA, and semantic dementia, SD) which are often collectively called primary progressive aphasia (PPA). Motor neurone disease may occur in association with any of these (when it is known as FTD-MND), although usually with bvFTD. Although one of these clinical syndromes may predominate at the onset of the illness there is substantial overlap as the disease progresses, including with the atypical parkinsonian disorders, corticobasal syndrome (CBS) and progressive supranuclear palsy syndrome (PSPS) [1–3].

FTD is genetically and pathologically heterogeneous without a clear relationship between the clinical phenotype and the underlying pathogenetics (Fig. 1). Up to a third of patients with FTD will have an autosomal dominant family history of the disease with studies suggesting that bvFTD is more heritable than the language variants [4]. Mutations in six genes have been associated with genetic FTD although only two of these, progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*), are common causes, each accounting for around 5–10% of all FTD patients [4]. Clinically, *MAPT* mutations are usually associated with bvFTD although CBS and more rarely PSPS have been described. *GRN* mutations are also associated with bvFTD and CBS but, unlike *MAPT* mutations, a PPA syndrome can also occur. The clinical phenotypes caused by mutations in the other four genes (valosin-containing protein, *VCP*, transactive response DNA-binding protein, *TARDP*, fused-in-sarcoma, *FUS*, charged multivesicular body protein 2B, *CHMP2B*) are variable including bvFTD, FTD-MND and for *VCP* mutations a specific association with inclusion body myositis and Paget's disease of the bone (known as IBMPFD).

FTD clinical syndromes are usually associated with one of the frontotemporal lobar degeneration (FTLD) pathologies. Until recently two major pathological types of FTLD were described, those with tau-positive pathology (FTLD-tau) and those with tau-negative, ubiquitin-positive pathology (FTLD-U). However it has been shown that FTLD-U actually consists of three separate groups: those with TDP-43-positive pathology (FTLD-TDP), those with FUS-positive pathology (FTLD-FUS) and a minority of cases which are both TDP-43 and FUS-negative (now called FTLD-UPS). Each of these major pathological types also has a number of subtypes [5,6]:

- *FTLD-tau* comprises cases of corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Pick's disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with dementia (MSTD) and the pathology associated with mutations in the *MAPT* gene.
- *FTLD-TDP* has a number of pathologically distinct subtypes based on the pattern and location of protein accumulation (types A, B, C and D) and includes patients with *GRN*, *VCP* and *TARDP* mutations.
- *FTLD-FUS* subtypes include atypical FTLD with ubiquitin-inclusions (aFTLD-U), neuronal intermediate filament inclusion disease (NIFID), and basophilic inclusion body disease (BIBD).
- *FTLD-UPS* cases are a very small minority but include the patients with *CHMP2B* mutations.

☆ This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

* Corresponding author at: Dementia Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK. Tel.: +44 207 829 8773; fax: +44 207 676 2066.
E-mail address: rohrer@dementia.ion.ucl.ac.uk.

0925-4439/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbadis.2011.07.014

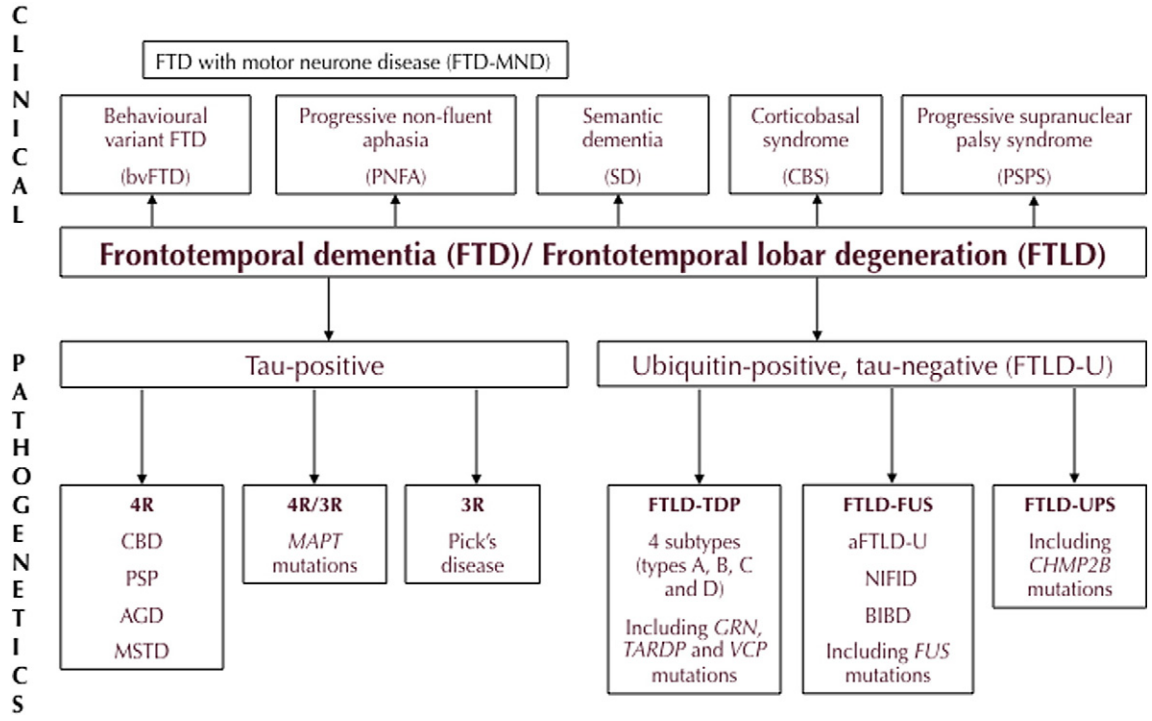

Fig. 1. The clinical, genetic and pathological heterogeneity of frontotemporal dementia. Legend: corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), argyrophilic grain disease (AGD), multiple system tauopathy with dementia (MSTD), *GRN* (progranulin), *TARDP* (transactive response DNA-binding protein), *VCP* (valosin-containing protein), atypical FTLD with ubiquitin-inclusions (aFTLD-U), neuronal intermediate filament inclusion disease (NIFID), basophilic inclusion body disease (BIBD), *CHMP2B* (charged multivesicular body protein 2B).

Less commonly FTD clinical syndromes can be caused by Alzheimer's pathology e.g. in one study it was seen in 7% of bvFTD cases and 10% of SD cases [7].

From a neuroimaging perspective, FTD is classically associated with frontal and temporal lobe atrophy with sparing of posterior cortical areas [3]. BvFTD is most commonly described as having asymmetrical (often right-sided predominant) fronto-temporal atrophy whilst the language variants are said to have specific imaging patterns of asymmetrical anteroinferior temporal lobe involvement in SD and asymmetrical left-sided predominant inferior frontal lobe and insula involvement in PNFA [8–10] (Fig. 2). However, in reality there is much heterogeneity within the FTD neuroimaging literature. This is likely to reflect a number of different issues, including the variability within a particular clinical phenotype, the fact that patients are being studied at different stages of a progressive illness and that different pathological causes of the same clinical phenotype may affect distinct (although overlapping) brain networks. With these factors in mind, this review attempts to address a number of key questions in the neuroimaging of FTD:

1) What are the early imaging features of the different FTD syndromes (and how do these change as the disease progresses)?
2) What do studies of presymptomatic genetic cases of FTD tell us about the very early stages of the disease?
3) Can neuroimaging help to differentiate the different FTD syndromes (either clinically or pathologically)?
4) Can neuroimaging help to differentiate FTD from other neurodegenerative diseases?

2. What are the early imaging features of the different FTD syndromes (and how do these change as the disease progresses)?

2.1. Behavioural variant frontotemporal dementia

BvFTD is characterized by a change in personality and progressive impairment of behaviour. Symptoms include disinhibition, apathy, loss of empathy, obsessive–compulsive behaviour and a change in appetite, particularly the development of a sweet tooth [3]. However early in the disease symptoms may be subtle and can be mistaken for psychiatric problems such as depression, or even dismissed completely. At this early stage diagnosis can therefore be difficult and neuroimaging can be helpful in supporting a positive diagnosis of bvFTD.

A meta-analysis of neuroimaging studies in bvFTD identified a network of (mostly right hemisphere) areas including parts of the frontal lobe (anterior medial frontal, gyrus rectus and superior frontal) as well as anterior cingulate, anterior insula and thalamus [8,9]. However, this study did not attempt to separate patients by severity or stage of the disease — mean MMSE in the included studies varied between 14 and 25, with mean disease duration between 2 and 4 years [8,9]. One study that attempted to look at patients at different stages of bvFTD separated them into three groups according to their Clinical Dementia Rating (CDR), an early group with CDR 0.5 and two other groups with CDR 1 and CDR2-3 [11]. In the early group atrophy involved areas in the frontal lobe (rostromedial frontal, frontal pole, dorsolateral frontal and orbitofrontal) as well as anterior cingulate, anterior insula, hippocampus and subcortical areas (ventral striatum and dorsomedial thalamus). Atrophy was bilateral but right hemisphere involvement was greater than left. With greater CDR score atrophy became more extensive in the same areas, particularly within the frontal lobe, with spread to more posterior areas including posterior insula, temporal and anterior parietal lobes [11]. A further study of pathologically-confirmed bvFTD patients separated by CDR found very similar results [12]. Further studies have suggested that these areas affected in early disease (frontal-insula-anterior cingulate) are part of a structurally and functionally connected neural network (a 'salience network') that is particularly vulnerable in bvFTD and that has a histopathological correlate in the form of von Economo neurons [13–15]. In one resting-state fMRI study loss of right frontoinsular salience network connectivity correlated with bvFTD disease severity [16].

However, bvFTD is pathologically heterogeneous and it is unclear whether this same "salience network" is affected in all groups independent of the underlying pathology. One recent study

performed a cluster analysis which suggested that bvFTD can be divided into four separate neuroanatomical groups: frontal-dominant, temporal-dominant, frontotemporal and temporofrontoparietal [17]. In a subgroup of patients in this study who had come to post-mortem there were no clear correlations between imaging features and pathological subtype apart from the temporal-dominant group who all had mutations in *MAPT*[17]. Further work needs to be done to see whether these four groups map on to separate brain networks (or subsystems within the same network).

Although atrophy is commonly seen at an early stage in bvFTD there are a number of patients who have been given the diagnosis on a clinical basis but who have normal scans at presentation — recently it has been suggested that many (if not most) of these patients have a 'benign' or 'nonprogressive' form of bvFTD [18–22]. These patients are difficult to distinguish from typical progressive bvFTD on the basis of clinical symptoms but they have no supportive imaging abnormalities including having normal FDG-PET imaging as well [20].

2.2. Semantic dementia

SD is probably the most homogeneous of the FTD syndromes with characteristic clinical and neuroimaging features, and a clear correlation with FTLD-TDP type C pathology. Clinically, patients present with fluent aphasia, anomia, single word comprehension difficulties and a surface dyslexia secondary to a verbal semantic impairment. Visual, auditory, olfactory and gustatory semantic impairment can develop later on in the disease. Behavioural symptoms similar to bvFTD may be present, occurring later in the disease process in those with left hemisphere predominant atrophy

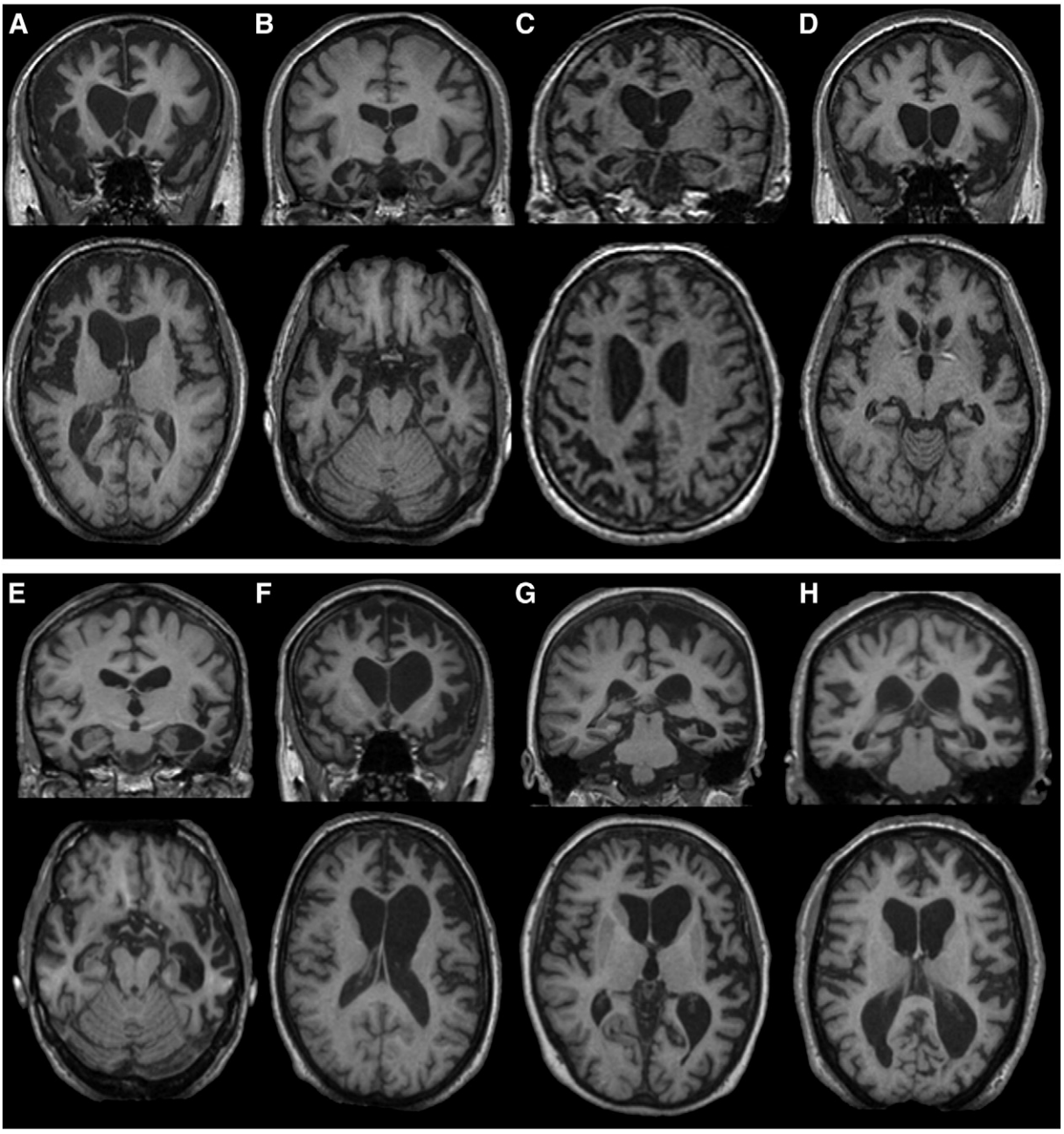

Fig. 2. Examples of structural MR imaging in pathologically-confirmed frontotemporal dementia syndromes. Legend: Images each show coronal (top) and axial (bottom) sections for bvFTD (A FTLD-tau Pick's disease, B FTLD-tau *MAPT* mutation, C FTLD-TDP type A with *GRN* mutation, D FTLD-FUS aFTLDU), SD (E FTLD-TDP type C), PNFA (F FTLD-tau Pick's disease, G *GRN* mutation) and LPA (H Alzheimer's disease).

and early in those with right hemisphere predominant atrophy (where it may be the presenting feature) [23].

Asymmetrical atrophy or hypometabolism of the temporal lobes is seen in most cases, predominantly affecting the anterior and inferior aspects of the temporal lobes, in particular the temporal pole, perirhinal cortex and anterior fusiform gyrus but also the hippocampus and amygdala, with relative sparing of the superior temporal gyrus [23–25] (Fig. 2D). In the most common variant there is left greater than right temporal lobe atrophy, with the opposite pattern seen less frequently. Patients are usually a number of years into their illness before they present and hence few studies have looked at the very early changes in the disease. One single case study followed a patient with SD from a very early period when there was only very subtle atrophy of the left anterior temporal lobe [26]. Over a follow up of 8 years there was increasing left temporal atrophy with subsequent atrophy of homologous right temporal areas. A larger study using cortical thickness measures separated patients with SD into three groups based on the severity of their anomia [27]: in the least affected group cortical thinning was limited to the anterior and inferior parts of the left temporal lobe as well as a small area of thinning in the very anterior part of the right temporal lobe affected. In the more severely affected groups there was spread to involve more posterior and superior parts of the left temporal lobe, parts of the left frontal lobe (orbitofrontal and inferior gyri), the insula and anterior cingulate. There was also increasing involvement of homologous areas in the right temporal lobe, initially affecting the anterior and inferior parts but spreading more posteriorly and superiorly in the most severely affected group. This study looked only at patients with initial left-sided predominant atrophy but studies of patients with right-sided predominant involvement suggest that a comparable mirror-image pattern of atrophy is seen both initially and with disease progression [28,29].

2.3. Progressive nonfluent aphasia

PNFA presents with speech production impairment secondary to agrammatism and apraxia of speech [1]. Other features include phonemic errors, anomia and sentence comprehension impairment. It is more clinically heterogeneous than SD and there are some suggestions that there are further clinical subtypes of PNFA e.g. cases with only agrammatism or apraxia of speech, or with a prominent anomia [30,31]. Pathologically, patients with prominent apraxia of speech often have tau pathology and may have an associated CBS or PSPS [32–34]. In contrast, patients with *GRN* mutations (and therefore FTLD-TDP type A pathology) generally do not have an apraxia of speech [31]. Of note, a third variant of PPA (distinguishable from SD and PNFA) called logopenic aphasia (LPA) has been described in recent years although this is mostly caused by Alzheimer's pathology rather than an FTLD pathology. Patients with LPA present with impaired word retrieval and sentence repetition with intact motor speech and grammar [1,35].

Neuroanatomically, the left inferior frontal lobe, insula and premotor cortex have been shown in a number of studies to be the key areas affected in early PNFA [8,14,27,32,35,36]. A single case study that followed a patient with PNFA over 4 years as she developed an associated CBS showed subsequent involvement of other areas in the frontal lobe, as well as the temporal lobe, anterior parietal lobe and subcortical structures (caudate and thalamus) [37]. The same cortical thickness study discussed above for SD also studied PNFA in a similar way, splitting patients into three groups by severity of anomia [27]: in the least affected group the areas involved were the left inferior frontal lobe, insula and premotor cortex, whilst in the more affected groups there were middle and superior frontal, superior and lateral temporal, and anterior parietal cortical thinning. Similar findings were seen in a study examining change in cortical thickness over 2 years in PNFA although with less superior temporal lobe involvement seen in this cohort as the disease progressed [38].

LPA is associated with asymmetrical left-sided predominant atrophy affecting particularly the posterior superior temporal and inferior parietal lobes as well as the posterior cingulate, precuneus and medial temporal lobe [35,39,40]. One retrospective cortical thickness study looked at a group of patients with PPA and Alzheimer's pathology all with a probable LPA syndrome and separated the patients into two groups according to severity of anomia [41]: in the less severe group the pattern of atrophy was restricted to the areas discussed above but in the more severely affected group there was also cortical thinning in more anterior left temporal lobe areas, including the superior and middle temporal gyri, as well as the left inferior frontal lobe with involvement of homologous areas to those seen in the less severely affected cases in the right hemisphere (i.e. the temporo-parietal junction, posterior cingulate, precuneus and medial temporal lobe). Similar results were found in a recent longitudinal study of cortical thickness with involvement of more anterior temporal lobe areas, inferior frontal lobe and dorsolateral frontal cortex in the left hemisphere as the disease progressed [38].

One outstanding question in the study of patients with a nonfluent aphasia is whether the pattern of atrophy differs between those with different pathologies, particularly between those with tau pathology and TDP-43 pathology (including *GRN* mutations). This has yet to be clearly addressed but one small study showed more widespread asymmetrical left-sided predominant fronto-temporo-parietal atrophy affecting both the dorsal and ventral language networks in patients with *GRN* mutations in comparison to other PNFA (and LPA) patients [40].

2.4. Frontotemporal dementia with motor neurone disease/amyotrophic lateral sclerosis

FTD-MND can present initially with either an FTD syndrome (usually bvFTD, less commonly PNFA and very rarely SD) or with an MND syndrome. If it presents as bvFTD the behavioural symptoms are essentially indistinguishable from patients who do not develop MND although delusions appear more common in FTD-MND [42]. Pathologically, FTD-MND is almost always FTLD-TDP (either type B or less commonly type A) but rarely can be FTLD-FUS [28,43]. Familial FTD-MND is associated with a locus on chromosome 9 [44,45], although rare cases of patients with *GRN* mutations have been described [46].

There have been limited neuroimaging studies of patients with FTD-MND/FTD-ALS. Some cases have been described with atrophy or hypometabolism limited to the anteromedial temporal lobes in the early stages [47,48] whilst other studies have shown more frontal lobe involvement particularly in motor and premotor areas [43,49].

2.5. Corticobasal syndrome

CBS commonly presents with cortical (limb apraxia, cortical sensory loss, myoclonus) and extrapyramidal (asymmetrical akinetic-rigid syndrome) dysfunction. It can be associated with cognitive impairment (often executive dysfunction), language problems (usually PNFA) and/or behavioural symptoms [33,50,51]. Pathologically, CBS can be associated with FTLD-tau (CBD or PSP), FTLD-TDP (usually type A including *GRN* mutations) and also with Alzheimer's pathology [52,53].

CBS has traditionally been associated with asymmetrical (usually left greater than right) frontoparietal and insula atrophy [14,54]. Recent studies have compared the neuroimaging features of CBS caused by different pathologies [53,55,56]: atrophy was predominantly frontal in CBD and PSP pathologies but more widespread within the hemisphere in FTLD-TDP and Alzheimer's pathology, overlapping in all groups in the posterior frontal lobe (premotor and supplementary motor areas) and the insula. More parietal atrophy was seen in Alzheimer's pathology than in the other pathologies.

3. What do studies of presymptomatic genetic cases of FTD tell us about the very early stages of the disease?

Most imaging studies of genetic FTD have investigated symptomatic patients with *MAPT* and *GRN* mutations — these suggest differing patterns of atrophy with asymmetrical fronto-temporo-parietal atrophy in *GRN* mutations and focal (often relatively symmetrical) temporal lobe atrophy in *MAPT* mutations [57,58]. A small study has also suggested differences between different *MAPT* mutations, with more medial temporal lobe atrophy in those mutations that affect the alternative splicing of tau pre-messenger RNA, and more lateral temporal lobe atrophy in those mutations that affect the structure of the tau protein [59]. Patterns of atrophy are less clear in patients with mutations in the genes that are only rare causes of FTD i.e. *FUS*, *TARDP*, *CHMP2B* and *VCP*. One case series of a chromosome 9p-linked FTD-MND family showed bilateral frontal lobe involvement with sparing of the temporal lobes in individual cases [44].

Studying genetic FTD offers the opportunity to identify the very earliest imaging features by investigating pre-symptomatic patients who are 'at-risk' of developing FTD. However, only a few studies have so far been published that have done this. Two case reports that have followed patients from a presymptomatic period through to symptom onset have identified that cell loss occurs a number of years prior to the onset of symptoms: a patient with a *GRN* mutation and a PPA syndrome was shown to have asymmetrical atrophy at least 18 months prior to the onset of symptoms with left-sided fronto-temporo-parietal atrophy particularly affecting superior frontal and frontopolar regions, anterior cingulate, inferior temporal, middle temporal and fusiform gyri as well as the angular gyrus [60]; whilst a patient with familial FTLD-U (later shown to be FTLD-TDP type A but without a *GRN* mutation) and a PPA syndrome was shown to have very focal left frontal lobe atrophy affecting the pars opercularis around 2 years prior to the onset of symptoms [61]. Larger group studies have also been performed using a variety of imaging techniques [62–65]. A study of four pre-symptomatic *GRN* mutation carriers (in a family with a PPA clinical syndrome) showed atrophy and hypometabolism in left frontal (inferior, middle and superior), left middle temporal and left parietal lobes compared to controls. A diffusion tensor imaging (DTI) study showed abnormalities in presymptomatic *GRN* carriers in the left uncinate fasciculus and in the left inferior occipitofrontal fasciculus although with no difference from controls in a volumetric imaging analysis (voxel-based morphometry of grey and white matter) [63]. Fewer studies have been performed in *MAPT* mutation carriers but one small study of three patients showed presymptomatic hippocampal atrophy in two patients and dopaminergic dysfunction (using PET imaging) in all three. [62]. A larger study with fourteen presymptomatic *MAPT* mutation carriers showed proton MRS abnormalities several years before the onset of symptoms [65].

4. Can neuroimaging help to differentiate the different FTD syndromes (either clinically or pathologically)?

Few studies have compared the different FTD clinical syndromes [8]. One study using volumetric imaging and defined regions of interest compared FTD, SD and PNFA [66]: each of the syndromes could be discriminated from each other with relatively high sensitivity and specificity: FTD v SD (sensitivity 100%, specificity 100%), FTD v PNFA (sensitivity 92%, specificity 89%) and SD v PNFA (sensitivity 86%, specificity 100%). SD and PNFA have also been compared with LPA, using an automated structural MRI-based classification method (support vector machines) [67]. As with the first study discrimination of SD from other syndromes had a high specificity (although lower sensitivity) whilst discrimination between the non-SD syndromes was not as accurate: SD v PNFA (sensitivity 84%, specificity 94%), PNFA v LPA (sensitivity 81%, specificity 91%) and SD v LPA (sensitivity 94%, specificity 94%) [67].

More importantly than separating FTD patients by their clinical phenotype perhaps will be the ability to separate patients by their underlying pathology, particularly as trials of targeted disease-modifying agents are developed over the next few years: unless there is a reliable and objective way of identifying patients in this way, such trials risk including patients with several different pathologies — this both reduces the chance of detecting a positive outcome and risks exposing individuals who will not benefit from treatment to potential side effects. In early studies there were conflicting results, with some showing differences between patients with FTLD-tau and FTLD-U [68] and others showing very similar patterns of atrophy [69]. However, as the pathological basis of FTLD has become increasingly stratified with the descriptions of FTLD-TDP and FTLD-FUS (and their subtypes) more recent studies have suggested specific differentiating patterns of atrophy. Two studies of FTLD-TDP subtypes showed very similar findings (although confusingly used separate numbering systems for TDP-43 pathology in the two papers) [28,43]. Using the recently described harmonised classification system for TDP-43 pathology [70], type A patients had an asymmetrical pattern of atrophy with frontal, temporal and parietal lobe as well as caudate involvement, type B patients had medial posterior frontal, insula and medial temporal lobe atrophy, and type C patients had asymmetrical anteroinferior temporal lobe atrophy with involvement of the insula (i.e. the pattern seen in patients with SD). Recent investigations of patients with FTLD-FUS pathology have shown involvement of the frontal-insula-anterior cingulate network but with particularly severe caudate atrophy compared to other FTD patients [71–73]. Whilst these studies were limited to a single type of abnormal protein inclusion (TDP-43 or FUS) one recent study has investigated imaging across FTLD-tau, FTLD-TDP and FTLD-FUS subtypes [74]. It suggests that the different FTLD pathologies are not specific for a particular brain region but rather that they target distributed brain networks in a predictable manner, segregating according to two factors: firstly, whether they show relatively symmetric versus strongly asymmetric hemispheric atrophy, and, secondly, whether they are associated with relatively localised temporal versus extra-temporal atrophy within an affected hemisphere. Patterns of atrophy seen in the study were: asymmetric, predominantly temporal lobe atrophy in TDP-C, relatively symmetric, predominantly temporal lobe atrophy in *MAPT* mutations, strongly asymmetric, distributed atrophy in PiD and TDP-A, and relatively symmetric, predominantly extratemporal atrophy in CBD and FUS [74]. However, although there are suggestive group differences in neuroimaging patterns between the pathological subtypes neither this study nor any of the other studies have quantified the specificity and sensitivity for distinguishing the different syndromes. Furthermore, it has yet to be shown whether particular imaging features described in the different pathologies (or clinical syndromes) at a group level can usefully translate into a way of diagnosing patients on a single case basis: the answer to this question is likely to require larger collaborative studies (each of the currently published studies reporting only relatively small numbers of cases).

5. Can neuroimaging help to differentiate FTD from other neurodegenerative diseases?

Clinically, FTD is usually clearly distinguishable from the typical amnestic Alzheimer's disease (AD) presentation. However, there can be a grey area with some FTD patients having prominent impairment of episodic memory and some patients with AD having more atypical presentations i.e. language variant AD (usually logopenic aphasia), frontal variant AD (i.e. a syndrome with prominent behavioural symptoms and/or executive dysfunction), posterior cortical atrophy (which often presents with visuospatial and/or visuoperceptual impairment and is therefore sometimes called the 'visual variant')

and a corticobasal syndrome presentation of AD. In reviewing imaging studies comparing FTD and AD it is therefore important to understand the groups being studied i.e. whether they are clinical or pathological phenotypes.

Studies comparing FTD with a typical AD syndrome have shown differences using voxel-based morphometry of structural MRI (atrophy in posterior parietal and occipital cortex in AD compared to atrophy in frontal insula-cingulate and striatum in FTD [75]), cortical thickness (greater parietal and precuneus thinning in AD [76]), amyloid PET imaging (positive in AD [77]), ASL (hypoperfusion in parietal regions and posterior cingulate in AD compared to hypoperfusion in the frontal lobes in FTD [78,79]), DTI (reduced fractional anisotrophy in frontal brain regions in FTD [80]) and combined FDG-PET with structural MRI [81]. Automated methods of classification using support vector machines have shown the ability to accurately differentiate AD and FTD with relatively high sensitivity and specificity [82,83].

Studies investigating more atypical phenotypes of AD have suggested that, independent of clinical phenotype, patients with underlying AD pathology have involvement of posterior cingulate, precuneus, posterior parietal and medial temporal areas [84,85]. Comparison of PPA patients with and without AD pathology suggests that differentiating factors between these two groups include greater left temporo-parietal atrophy in those with AD pathology (usually an LPA syndrome clinically) and the presence of knife-edge anterior temporal lobe atrophy in those with FTD pathology [86][87].

Less commonly, FTD can be mistaken for dementia with Lewy Bodies (DLB) — this may well be because some patients with FTD clinical syndromes can develop delusions and/or visual hallucinations [42,88]. One small study suggested that MRI was not helpful in differentiating FTD from DLB [89]. However a recent study has shown accurate differentiation using ^{123}I-MIBG scintigraphy in which uptake is markedly reduced in DLB but normal in FTD [90].

As with the studies that attempted to distinguish the different FTD syndromes it is not clear that the described group differences between FTD and AD (or FTD and DLB) can translate into an adequate diagnostic biomarker at the single case level. Two issues in particular need to be addressed more thoroughly in future studies: firstly, to what extent MR imaging adds extra diagnostic information in addition to a cognitive and behavioural assessment for individual patients; and secondly, to what extent 'difficult' or 'atypical' clinical cases can be diagnosed accurately — most comparative imaging studies have investigated typical AD and FTD cases whereas on a clinical basis it is the less typical cases which prove most difficult to diagnose.

6. The future of neuroimaging in FTD

Newer imaging techniques such as DTI, ASL and resting state fMRI (and the multimodal combination of such techniques) are likely to be increasingly used in studies of FTD. Newer PET imaging methods have recently been investigated (e.g. cholinergic imaging in FTD, PSP and CBS [91] and newer ^{18}F amyloid labelling compounds) and in the future the development of PET ligands that would bind to tau, TDP-43 or FUS would be a huge advance in the ability to make a molecular diagnosis [92]. Increased international collaboration between centres will be important in furthering our understanding of the neuroimaging of FTD, as has happened in other neurodegenerative diseases (e.g. the Alzheimer's Disease Neuroimaging Initiative, ADNI [93]), and in particular for studies of presymptomatic genetic FTD and in the development of trials of disease-modifying therapies [94].

Acknowledgements

This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer's Research Trust Co-ordinating Centre.

References

[1] M.L. Gorno-Tempini, A.E. Hillis, S. Weintraub, A. Kertesz, M. Mendez, S.F. Cappa, et al., Classification of primary progressive aphasia and its variants, Neurology 76 (2011) 1006–1014.
[2] O. Piguet, M. Hornberger, E. Mioshi, J.R. Hodges, Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management, Lancet Neurol. 10 (2011) 162–172.
[3] H. Seelaar, J.D. Rohrer, Y.A.L. Pijnenburg, N.C. Fox, J.C. Van Swieten, Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review, J. Neurol. Neurosurg. Psychiatry 82 (2011) 476–486.
[4] J.D. Rohrer, R. Guerreiro, J. Vandrovcova, J. Uphill, D. Reiman, J. Beck, et al., The heritability and genetics of frontotemporal lobar degeneration, Neurology 73 (2009) 1451–1456.
[5] N.J. Cairns, E.H. Bigio, I.R.A. Mackenzie, M. Neumann, V.M.-Y. Lee, K.J. Hatanpaa, et al., Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration, Acta Neuropathol. 114 (2007) 5–22.
[6] I.R.A. Mackenzie, M. Neumann, E.H. Bigio, N.J. Cairns, I. Alafuzoff, J. Kril, et al., Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update, Acta Neuropathol. 119 (2010) 1–4.
[7] S. Alladi, J.H. Xuereb, T.H. Bak, P.J. Nestor, J.A. Knibb, K. Patterson, et al., Focal cortical presentations of Alzheimer's disease, Brain 130 (2007) 2636–2645.
[8] M.L. Schroeter, K. Raczka, J. Neumann, D.Y. von Cramon, Towards a nosology for frontotemporal lobar degenerations—a meta-analysis involving 267 subjects, Neuroimage 36 (2007) 497–510.
[9] M.L. Schroeter, K. Raczka, J. Neumann, D.Y. von Cramon, Neural networks in frontotemporal dementia—a meta-analysis, Neurobiol. Aging 29 (2008) 418–426.
[10] J.D. Rohrer, N.C. Fox, Neuroimaging of primary progressive aphasia, Eur. Neurol. J. (2009) 1–9.
[11] W.W. Seeley, R.K. Crawford, K. Rascovsky, J.H. Kramer, M.W. Weiner, B.L. Miller, et al., Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia, Arch. Neurol. 65 (2008) 249–255.
[12] J.L. Whitwell, C.R. Jack, M.L. Senjem, J.E. Parisi, B.F. Boeve, D.S. Knopman, et al., MRI correlates of protein deposition and disease severity in postmortem frontotemporal lobar degeneration, Neurodegener Dis 6 (2009) 106–117.
[13] W.W. Seeley, Anterior insula degeneration in frontotemporal dementia, Brain Struct. Funct. 214 (2010) 465–475.
[14] W.W. Seeley, R.K. Crawford, J. Zhou, B.L. Miller, M.D. Greicius, Neurodegenerative diseases target large-scale human brain networks, Neuron 62 (2009) 42–52.
[15] W.W. Seeley, Selective functional, regional, and neuronal vulnerability in frontotemporal dementia, Curr. Opin. Neurol. 21 (2008) 701–707.
[16] J. Zhou, M.D. Greicius, E.D. Gennatas, M.E. Growdon, J.Y. Jang, G.D. Rabinovici, et al., Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease, Brain 133 (2010) 1352–1367.
[17] J.L. Whitwell, S.A. Przybelski, S.D. Weigand, R.J. Ivnik, P. Vemuri, J.L. Gunter, et al., Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study, Brain 132 (2009) 2932–2946.
[18] R.R. Davies, C.M. Kipps, J. Mitchell, J.J. Kril, G.M. Halliday, J.R. Hodges, Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging, Arch. Neurol. 63 (2006) 1627–1631.
[19] C.M. Kipps, P.J. Nestor, T.D. Fryer, J.R. Hodges, Behavioural variant frontotemporal dementia: not all it seems? Neurocase 13 (2007) 237–247.
[20] C.M. Kipps, J.R. Hodges, T.D. Fryer, P.J. Nestor, Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype, Brain 132 (2009) 2566–2578.
[21] M. Hornberger, B.P. Shelley, C.M. Kipps, O. Piguet, J.R. Hodges, Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation? J. Neurol. Neurosurg. Psychiatry 80 (2009) 591–593.
[22] C.M. Kipps, J.R. Hodges, M. Hornberger, Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the "bvFTD phenocopy syndrome", Curr. Opin. Neurol. 23 (2010) 628–632.
[23] J.R. Hodges, K. Patterson, Semantic dementia: a unique clinicopathological syndrome, Lancet Neurol. 6 (2007) 1004–1014.
[24] R.R. Davies, V.L. Scahill, A. Graham, G.B. Williams, K.S. Graham, J.R. Hodges, Development of an MRI rating scale for multiple brain regions: comparison with volumetrics and with voxel-based morphometry, Neuroradiology 51 (2009) 491–503.
[25] R.R. Davies, K.S. Graham, J.H. Xuereb, G.B. Williams, J.R. Hodges, The human perirhinal cortex and semantic memory, Eur. J. Neurosci. 20 (2004) 2441–2446.
[26] K. Czarnecki, J.R. Duffy, C.R. Nehl, S.A. Cross, J.R. Molano, C.R. Jack, et al., Very early semantic dementia with progressive temporal lobe atrophy: an 8-year longitudinal study, Arch. Neurol. 65 (2008) 1659–1663.
[27] J.D. Rohrer, J.D. Warren, M. Modat, G.R. Ridgway, A. Douiri, M.N. Rossor, et al., Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration, Neurology 72 (2009) 1562–1569.
[28] J.D. Rohrer, F. Geser, J. Zhou, E.D. Gennatas, M. Sidhu, J.Q. Trojanowski, et al., TDP-43 subtypes are associated with distinct atrophy patterns in frontotemporal dementia, Neurology 75 (2010) 2204–2211.
[29] S.M. Brambati, K.P. Rankin, J. Narvid, W.W. Seeley, D. Dean, H.J. Rosen, et al., Atrophy progression in semantic dementia with asymmetric temporal involvement: a tensor-based morphometry study, Neurobiol. Aging 30 (2009) 103–111.
[30] J.D. Rohrer, M.N. Rossor, J.D. Warren, Syndromes of nonfluent primary progressive aphasia: a clinical and neurolinguistic analysis, Neurology 75 (2010) 603–610.
[31] J.D. Rohrer, S.J. Crutch, E.K. Warrington, J.D. Warren, Progranulin-associated primary progressive aphasia: a distinct phenotype? Neuropsychologia 48 (2010) 288–297.

[32] K.A. Josephs, J.R. Duffy, E.A. Strand, J.L. Whitwell, K.F. Layton, J.E. Parisi, et al., Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech, Brain 129 (2006) 1385–1398.
[33] K.A. Josephs, J.R. Duffy, Apraxia of speech and nonfluent aphasia: a new clinical marker for corticobasal degeneration and progressive supranuclear palsy, Curr. Opin. Neurol. 21 (2008) 688–692.
[34] J.D. Rohrer, D. Paviour, A.M. Bronstein, S.S. O'Sullivan, A. Lees, J.D. Warren, Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: a neuropsychological and neuroimaging analysis, Mov. Disord. 25 (2010) 179–188.
[35] M.L. Gorno-Tempini, N.F. Dronkers, K.P. Rankin, J.M. Ogar, L. Phengrasamy, H.J. Rosen, et al., Cognition and anatomy in three variants of primary progressive aphasia, Ann. Neurol. 55 (2004) 335–346.
[36] P.J. Nestor, N.L. Graham, T.D. Fryer, G.B. Williams, K. Patterson, J.R. Hodges, Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula, Brain 126 (2003) 2406–2418.
[37] M.L. Gorno-Tempini, J.M. Ogar, S.M. Brambati, P. Wang, J.H. Jeong, K.P. Rankin, et al., Anatomical correlates of early mutism in progressive nonfluent aphasia, Neurology 67 (2006) 1849–1851.
[38] E. Rogalski, D. Cobia, T.M. Harrison, C. Wieneke, S. Weintraub, M.-M. Mesulam, Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia, Neurology 76 (2011) 1804–1810.
[39] M.L. Gorno-Tempini, S.M. Brambati, V. Ginex, J. Ogar, N.F. Dronkers, A. Marcone, et al., The logopenic/phonological variant of primary progressive aphasia, Neurology 71 (2008) 1227–1234.
[40] J.D. Rohrer, G.R. Ridgway, S.J. Crutch, J. Hailstone, J.C. Goll, M.J. Clarkson, et al., Progressive logopenic/phonological aphasia: erosion of the language network, Neuroimage 49 (2010) 984–993.
[41] J.D. Rohrer, M.N. Rossor, J.D. Warren, Alzheimer's pathology in primary progressive aphasia, Neurobiol. Aging (2010).
[42] P. Lillo, B. Garcin, M. Hornberger, T.H. Bak, J.R. Hodges, Neurobehavioral features in frontotemporal dementia with amyotrophic lateral sclerosis, Arch. Neurol. 67 (2010) 826–830.
[43] J.L. Whitwell, C.R. Jack, J.E. Parisi, M.L. Senjem, D.S. Knopman, B.F. Boeve, et al., Does TDP-43 type confer a distinct pattern of atrophy in frontotemporal lobar degeneration? Neurology 75 (2010) 2212–2220.
[44] A.L. Boxer, I.R. Mackenzie, B.F. Boeve, M. Baker, W.W. Seeley, R. Crook, et al., Clinical, neuroimaging and neuropathological features of a new chromosome 9p-linked FTD-ALS family, J. Neurol. Neurosurg. Psychiatry 82 (2011) 196–203.
[45] C. Vance, A. Al-Chalabi, D. Ruddy, B.N. Smith, X. Hu, J. Sreedharan, et al., Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2–21.3, Brain 129 (2006) 868–876.
[46] A.S. Chen-Plotkin, M. Martinez-Lage, P.M.A. Sleiman, W. Hu, R. Greene, E.M. Wood, et al., Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration, Arch. Neurol. 68 (2011) 488–497.
[47] G. Garraux, E. Salmon, C. Degueldre, C. Lemaire, G. Franck, Medial temporal lobe metabolic impairment in dementia associated with motor neuron disease, J. Neurol. Sci. 168 (1999) 145–150.
[48] H. Kuwahara, K. Tsuchiya, Y. Saito, Z. Kobayashi, H. Miyazaki, Y. Izumiyama, et al., Frontotemporal lobar degeneration with motor neuron disease showing severe and circumscribed atrophy of anterior temporal lobes, J. Neurol. Sci. 297 (2010) 92–96.
[49] B.B. Avants, A. Khan, L.F. McCluskey, L. Elman, M. Grossman, Longitudinal cortical atrophy in amyotrophic lateral sclerosis with frontotemporal dementia, Arch. Neurol. 66 (2009) 138–139.
[50] N.L. Graham, T.H. Bak, J.R. Hodges, Corticobasal degeneration as a cognitive disorder, Mov. Disord. 18 (2003) 1224–1232.
[51] R.K. Mahapatra, M.J. Edwards, J.M. Schott, K.P. Bhatia, Corticobasal degeneration, Lancet Neurol. 3 (2004) 736–743.
[52] H. Ling, S.S. O'sullivan, J.L. Holton, T. Revesz, L.A. Massey, D.R. Williams, et al., Does corticobasal degeneration exist? A clinicopathological re-evaluation, Brain 133 (2010) 2045–2057.
[53] J.L. Whitwell, C.R. Jack, B.F. Boeve, J.E. Parisi, J.E. Ahlskog, D.A. Drubach, et al., Imaging correlates of pathology in corticobasal syndrome, Neurology 75 (2010) 1879–1887.
[54] A.L. Boxer, M.D. Geschwind, N. Belfor, M.L. Gorno-Tempini, G.F. Schauer, B.L. Miller, et al., Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy, Arch. Neurol. 63 (2006) 81–86.
[55] M.C. Tartaglia, M. Sidhu, V. Laluz, C. Racine, G.D. Rabinovici, K. Creighton, et al., Sporadic corticobasal syndrome due to FTLD-TDP, Acta Neuropathol. 119 (2010) 365–374.
[56] K.A. Josephs, J.L. Whitwell, B.F. Boeve, D.S. Knopman, R.C. Petersen, W.T. Hu, et al., Anatomical differences between CBS-corticobasal degeneration and CBS-Alzheimer's disease, Mov. Disord. 25 (2010) 1246–1252.
[57] J.D. Rohrer, G.R. Ridgway, M. Modat, S. Ourselin, S. Mead, N.C. Fox, et al., Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations, Neuroimage 53 (2010) 1070–1076.
[58] J.L. Whitwell, C.R. Jack, B.F. Boeve, M.L. Senjem, M. Baker, R. Rademakers, et al., Voxel-based morphometry patterns of atrophy in FTLD with mutations in MAPT or PGRN, Neurology 72 (2009) 813–820.
[59] J.L. Whitwell, C.R. Jack, B.F. Boeve, M.L. Senjem, M. Baker, R.J. Ivnik, et al., Atrophy patterns in IVS10+16, IVS10+3, N279K, S305N, P301L, and V337M MAPT mutations, Neurology 73 (2009) 1058–1065.
[60] J.D. Rohrer, J.D. Warren, J. Barnes, S. Mead, J. Beck, T. Pepple, et al., Mapping the progression of progranulin-associated frontotemporal lobar degeneration, Nat. Clin. Pract. Neurol. 4 (2008) 455–460.
[61] J.C. Janssen, J.M. Schott, L. Cipolotti, N.C. Fox, R.I. Scahill, K.A. Josephs, et al., Mapping the onset and progression of atrophy in familial frontotemporal lobar degeneration, J. Neurol. Neurosurg. Psychiatry 76 (2005) 162–168.
[62] M. Miyoshi, H. Shinotoh, Z.K. Wszolek, A.J. Strongosky, H. Shimada, R. Arakawa, et al., In vivo detection of neuropathologic changes in presymptomatic MAPT mutation carriers: a PET and MRI study, Parkinsonism Relat. Disord. 16 (2010) 404–408.
[63] B. Borroni, A. Alberici, E. Premi, S. Archetti, V. Garibotto, C. Agosti, et al., Brain magnetic resonance imaging structural changes in a pedigree of asymptomatic progranulin mutation carriers, Rejuvenation Res. 11 (2008) 585–595.
[64] C. Cruchaga, M.A. Fernández-Seara, M. Seijo-Martínez, L. Samaranch, E. Lorenzo, A. Hinrichs, et al., Cortical atrophy and language network reorganization associated with a novel progranulin mutation, Cereb. Cortex 19 (2009) 1751–1760.
[65] K. Kantarci, B.F. Boeve, Z.K. Wszolek, R. Rademakers, J.L. Whitwell, M.C. Baker, et al., MRS in presymptomatic MAPT mutation carriers: a potential biomarker for tau-mediated pathology, Neurology 75 (2010) 771–778.
[66] O. Lindberg, P. Ostberg, B.B. Zandbelt, J. Oberg, Y. Zhang, C. Andersen, et al., Cortical morphometric subclassification of frontotemporal lobar degeneration, AJNR Am. J. Neuroradiol. 30 (2009) 1233–1239.
[67] S.M. Wilson, J.M. Ogar, V. Laluz, M. Growdon, J. Jang, S. Glenn, et al., Automated MRI-based classification of primary progressive aphasia variants, Neuroimage 47 (2009) 1558–1567.
[68] E.J. Kim, G.D. Rabinovici, W.W. Seeley, C. Halabi, H. Shu, M.W. Weiner, et al., Patterns of MRI atrophy in tau positive and ubiquitin positive frontotemporal lobar degeneration, J. Neurol. Neurosurg. Psychiatry 78 (2007) 1375–1378.
[69] J.M.S. Pereira, G.B. Williams, J. Acosta-Cabronero, G. Pengas, M.G. Spillantini, J.H. Xuereb, et al., Atrophy patterns in histologic vs clinical groupings of frontotemporal lobar degeneration, Neurology 72 (2009) 1653–1660.
[70] I.R.A. Mackenzie, M. Neumann, A. Baborie, D.M. Sampathu, D. Du Plessis, E. Jaros, et al., A harmonized classification system for FTLD-TDP pathology, Acta Neuropathol. 122 (2011) 111–113.
[71] J.D. Rohrer, T. Lashley, J. Holton, T. Revesz, H. Urwin, A.M. Isaacs, et al., The clinical and neuroanatomical phenotype of FUS associated frontotemporal lobar degeneration, J. Neurol. Neurosurg. Psychiatry (2010).
[72] K.A. Josephs, J.L. Whitwell, J.E. Parisi, R.C. Petersen, B.F. Boeve, C.R. Jack Jr., et al., Caudate atrophy on MRI is a characteristic feature of FTLD-FUS, Eur. J. Neurol. (2010).
[73] H. Seelaar, K.Y. Klijnsma, I. de Koning, A. van der Lugt, W.Z. Chiu, A. Azmani, et al., Frequency of ubiquitin and FUS-positive, TDP-43-negative frontotemporal lobar degeneration, J. Neurol. 257 (2010) 747–753.
[74] J.D. Rohrer, T. Lashley, J.M. Schott, et al., Clinical and neuroimaging signatures of tissue pathology in frontotemporal lobar degeneration, Brain 32 (2011) 1765–1773.
[75] G.D. Rabinovici, W.W. Seeley, E.J. Kim, M.L. Gorno-Tempini, K. Rascovsky, T.A. Pagliaro, et al., Distinct MRI atrophy patterns in autopsy-proven Alzheimer's disease and frontotemporal lobar degeneration, Am. J. Alzheimers Dis. Other Demen. 22 (2007) 474–488.
[76] A.-T. Du, N. Schuff, J.H. Kramer, H.J. Rosen, M.-L. Gorno-Tempini, K.P. Rankin, et al., Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia, Brain 130 (2007) 1159–1166.
[77] G.D. Rabinovici, A.J. Furst, J.P. O'Neil, C.A. Racine, E.C. Mormino, S.L. Baker, et al., 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration, Neurology 68 (2007) 1205–1212.
[78] W.T. Hu, Z. Wang, V.M.-Y. Lee, J.Q. Trojanowski, J.A. Detre, M. Grossman, Distinct cerebral perfusion patterns in FTLD and AD, Neurology 75 (2010) 881–888.
[79] A.T. Du, G.-H. Jahng, S. Hayasaka, J.H. Kramer, H.J. Rosen, M.L. Gorno-Tempini, et al., Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI, Neurology 67 (2006) 1215–1220.
[80] Y. Zhang, N. Schuff, A.-T. Du, H.J. Rosen, J.H. Kramer, M.-L. Gorno-Tempini, et al., White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI, Brain 132 (2009) 2579–2592.
[81] J. Dukart, K. Mueller, A. Horstmann, H. Barthel, H.E. Möller, A. Villringer, et al., Combined evaluation of FDG-PET and MRI improves detection and differentiation of dementia, PLoS One 6 (2011) e18111.
[82] S. Klöppel, C.M. Stonnington, C. Chu, B. Draganski, R.I. Scahill, J.D. Rohrer, et al., Automatic classification of MR scans in Alzheimer's disease, Brain 131 (2008) 681–689.
[83] J.-F. Horn, M.-O. Habert, A. Kas, Z. Malek, P. Maksud, L. Lacomblez, et al., Differential automatic diagnosis between Alzheimer's disease and frontotemporal dementia based on perfusion SPECT images, Artif. Intell. Med. 47 (2009) 147–158.
[84] R. Migliaccio, F. Agosta, K. Rascovsky, A. Karydas, S. Bonasera, G.D. Rabinovici, et al., Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum, Neurology 73 (2009) 1571–1578.
[85] M. Lehmann, J.D. Rohrer, M.J. Clarkson, G.R. Ridgway, R.I. Scahill, M. Modat, et al., Reduced cortical thickness in the posterior cingulate gyrus is characteristic of both typical and atypical Alzheimer's disease, J. Alzheimers Dis. 20 (2010) 587–598.
[86] L. Xiong, J.H. Xuereb, M.G. Spillantini, K. Patterson, J.R. Hodges, P.J. Nestor, Clinical comparison of progressive aphasia associated with Alzheimer versus FTD-spectrum pathology, J. Neurol. Neurosurg. Psychiatry 82 (2011) 254–260.
[87] W.T. Hu, C. McMillan, D. Libon, S. Leight, M. Forman, V.M.-Y. Lee, et al., Multimodal predictors for Alzheimer disease in nonfluent primary progressive aphasia, Neurology 75 (2010) 595–602.
[88] R. Omar, E.L. Sampson, C.T. Loy, C.J. Mummery, N.C. Fox, M.N. Rossor, et al., Delusions in frontotemporal lobar degeneration, J. Neurol. 256 (2009) 600–607.
[89] D.O. Claassen, J.E. Parisi, C. Giannini, B.F. Boeve, D.W. Dickson, K.A. Josephs, Frontotemporal dementia mimicking dementia with Lewy bodies, Cogn. Behav. Neurol. 21 (2008) 157–163.
[90] F. Novellino, A. Bagnato, M. Salsone, G.L. Cascini, G. Nicoletti, G. Arabia, et al., Myocardial (123)I-MIBG scintigraphy for differentiation of Lewy bodies disease from FTD, Neurobiol. Aging 31 (2010) 1903–1911.

[91] S. Hirano, H. Shinotoh, H. Shimada, A. Aotsuka, N. Tanaka, T. Ota, et al., Cholinergic imaging in corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia, Brain 133 (2010) 2058–2068.
[92] M.T. Fodero-Tavoletti, N. Okamura, S. Furumoto, R.S. Mulligan, A.R. Connor, C.A. McLean, et al., 18F-THK523: a novel in vivo tau imaging ligand for Alzheimer's disease, Brain 134 (2011) 1089–1100.
[93] S.G. Mueller, M.W. Weiner, L.J. Thal, R.C. Petersen, C.R. Jack, W. Jagust, et al., Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI), Alzheimers Dement. 1 (2005) 55–66.
[94] D.S. Knopman, J.H. Kramer, B.F. Boeve, R.J. Caselli, N. Graff-Radford, M.F. Mendez, et al., Development of methodology for conducting clinical trials in frontotemporal lobar degeneration, Brain (2008).