Frontotemporal dementia

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Purpose of review

The syndromes of frontotemporal lobar degeneration are increasingly recognized as an important cause of early-onset dementia. Diagnostic consensus criteria have now been established for almost a decade, and form the framework for its clinical classification. While these criteria remain useful, a growing body of evidence suggests that revisions may be necessary to improve their validity and applicability.

Recent findings

In each individual syndrome, the core features are not uniformly present, and criteria that are currently used to exclude a condition, such as impaired episodic memory, are often present. Imaging, however, may warrant increased diagnostic prominence, particularly for diagnosis in semantic dementia and prognosis in behavioural syndromes. There is clinical and pathological overlap between the syndromes, but the clinical distinction between progressive nonfluent aphasia and semantic dementia is strengthening. Several series have refined our understanding of the correspondence between clinical syndromes and histopathological subtype: strong for tau-negative, ubiquitin-positive forms and more variable for tau-positive forms, yet prospective studies are still rare. The influence of genetic factors varies substantially across the syndromes.

Summary

Further research should aim to integrate detailed clinical, radiological, pathological and genetic information.

Keywords

aphasia, behaviour, clinical diagnosis, imaging, pathology

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Abbreviations

AoS	apraxia of speech
bvFTD	behavioural-variant frontotemporal dementia
CBD	corticobasal degeneration
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
FTLD-U	FTLD with ubiquitin-positive, tau-negative inclusions
MND	motor neurone disease (amyotrophic lateral sclerosis)
MTL	medial temporal lobe
PiD	Pick body disease
PNFA	progressive nonfluent aphasia
PSP	progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome)

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Introduction

There is a group of related neurodegenerative conditions which present as a disturbance of behaviour or language. This has been named frontotemporal dementia (FTD) [1] or frontotemporal lobar degeneration (FTLD) [2]. A division of FTLD into three subgroups is now widely accepted, particularly since the publication 8 years ago of diagnostic consensus criteria [2]. The first subgroup is frontal-variant or behavioural-variant FTD (fvFTD or bvFTD, or confusingly sometimes just FTD), which accounts for about half of FTLD cases [3•]. The others are progressive nonfluent aphasia (PNFA), and semantic dementia, which often presents as a fluent progressive aphasia, but is due to a deficit of conceptual knowledge rather than of language. The motor syndromes of corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and motor neurone disease (MND) may also be associated with FTLD features and pathology, and some authorities see these as part of the same spectrum [4••].

The pathology of FTLD is heterogeneous. While there are common features (cortical gliosis and laminar spongiosis), a range of histological changes are recognized, most of which are characterized either by intracellular inclusion bodies containing either abnormal forms of the microtubule-associated protein tau, notably familial FTD, Pick body disease (PiD) and the pathologies of CBD and PSP, or by tau-negative, ubiquitin-positive inclusions (FTLD-U).

In this review, we discuss the recent literature in terms of its relevance to four main areas: the current clinical and imaging criteria for diagnosis; our understanding of progressive aphasic syndromes; the relationship between clinical syndrome and pathological diagnosis; and the aetiological role of genetic factors.

Clinical diagnosis

In this section we examine the current clinical and imaging criteria for diagnosis.

Core criteria

A number of recent studies have examined the applicability of the widely used consensus diagnostic criteria [2]. For instance, of 74 patients who eventually met criteria for bvFTD, only one-third showed all five core features at first presentation [5•]. By contrast, apathy and stereotypic behaviour (which are supportive features) were among the most common initial symptoms, together with impairments of social behaviour, affection and activities of daily living. Another study also found that several of the supportive criteria show strong associations with regional single photon emission computed tomography (SPECT) hypoperfusion on first assessment [6•]. The joint Sydney–Cambridge studies have highlighted the overlap between behavioural and language variants [7].

In keeping with this, Shinagawa *et al.* [6•] found that although anomia and word comprehension difficulty are the most frequent initial features in semantic dementia, social-behavioural changes are frequently present very early. To add further confusion, two groups have emphasized that patients who present with any of the FTLD syndromes – behavioural, semantic, aphasic or extrapyramidal – frequently develop at least one other of these syndromes later in their disease [4••,8•].

Prospective validation of the consensus criteria is still largely lacking. In a very recent study, Knopman *et al.* [9•] reported high sensitivity and specificity for predicting FTLD pathology in a mixed dementia group. They used retrospective clinical data from patients who had come to autopsy, however, rather than prospectively assessing pathology in patients with FTLD diagnoses. Only 30 autopsies were obtained from 129 patients with a clinical FTLD diagnosis, leaving open the possibility for bias: for example, lower mortality in individuals with alternative pathology may have enriched their FTLD sample. Clearly there is a need for further clinico-pathological series.

Amnesia

Despite being an exclusion criterion for FTLD, two independent studies have documented the presence of marked anterograde amnesia as either the sole or dominant symptom in FTLD [9•,10•], albeit often joined later by a more typical FTLD syndrome. Moreover, it may be found in up to 40% of pathologically verified FTLD cases whose clinical picture is dominated by the typical behavioural disturbance [9•].

The status of episodic memory in semantic dementia is also controversial; such patients have problems recognizing words or faces, and typically perform poorly on memory tests using these materials. Scahill *et al.* [11•] have shown that laterality of atrophy is a critical factor: patients with both left and right-predominant atrophy were found to have verbal memory impairment, but those with right-predominant atrophy also had poor memory for faces and geometric figures. Autobiographical memory is also impaired in semantic dementia, with some studies showing a reversal of the typical temporal gradient seen in Alzheimer's disease (i.e. better recall of more recent events in semantic dementia) [12–14].

Medial temporal lobe (MTL), and in particular hippocampal, atrophy has now been established as a feature of semantic dementia [15•] as well as of Alzheimer's disease. Nestor *et al.* [16••] recently demonstrated both bilateral hypometabolism (on ^{18}F-fluorodeoxyglucose positron emission tomography; FDG-PET) and atrophy in the MTL of semantic dementia patients. The crucial difference was the involvement of other limbic regions beyond the MTL (notably the posterior cingulate cortex) in Alzheimer's disease, but not semantic dementia, suggesting that damage in these additional areas is necessary for episodic memory impairment.

Structural imaging

At present, imaging abnormalities are only supportive rather than necessary for a diagnosis of FTLD. In the past we have been happy to diagnose FTLD in the presence of a normal magnetic resonance imaging (MRI) scan, but a recent study casts doubt on this assumption. Using a structured rating scale, all semantic dementia patients had an abnormal scan at presentation (regardless of symptom duration). In contrast, almost half of those meeting clinical criteria for bvFTD were indistinguishable from control scans (C.M. Kipps, R.R. Davies, J. Mitchell, et al., unpublished data). These imaging-normal patients were all male, and had a strikingly better prognosis than their clinically identical but imaging-abnormal counterparts, despite equivalent disease duration at the time of scanning [17]. One possible explanation for this is that the clinical criteria are not specific for patients with a neurodegenerative disease, and are met by patients with neuropsychiatric disorders which can mimic bvFTD.

Recent structural imaging studies in semantic dementia have confirmed that the temporo-polar and perirhinal cortices are the most consistently affected brain regions, and that the degree of atrophy here is correlated with the magnitude of the semantic deficit [18,19•]. In PNFA, by contrast, the anterior insula and Broca's area appear to be key regions [20].

The difficulties in early diagnosis of bvFTD and the potential role of imaging are well illustrated by the report of a patient studied prospectively because of a strong family history of FTLD [21••]. After almost 4 years she

complained of symptoms (stammering, calculation difficulty) or began to show signs (jocularity, laughing inappropriately). At baseline assessment, she demonstrated mild cognitive deficits relative to her premorbid ability (as predicted by the National Adult Reading Test), and mild verbal fluency developed on follow up. Serial MRI scanning showed quantifiable atrophy at clinical onset, implying that underlying disease progression had begun well before any features were noticed.

Functional imaging (metabolic)

In order to use imaging as a diagnostic marker, it is imperative to understand the distribution of changes within the brain at different stages of the disease. The findings of recent studies using SPECT or FDG-PET in bvFTD [22••,23•,24,25] have essentially mirrored those of postmortem studies [26••]. They highlight in particular the involvement of the medial prefrontal cortex, and to a variable degree the posterior orbitofrontal/subcallosal cortex, dorsolateral prefrontal regions and insula. One longitudinal PET study showed metabolic deficits progressing over 1–2 years from the lateral and medial surfaces of the frontal lobe, the caudate, insula and thalamus, to subsequently affect the inferior frontal regions, temporal lobes and inferior parietal cortex [22••].

Several studies have examined correlations between regional metabolic changes and behavioural scores [23•,24], typically focusing on apathy and disinhibition. The results suggest that damage to the orbitofrontal cortex is associated with both of these clinical features, and that the responsible regions overlap [23•]. This may explain why both apathy and disinhibition are frequently observed in the same patient depending on environmental circumstances.

Progressive aphasia

In this section we report our understanding of progressive aphasic syndromes.

Classification

It is generally agreed that progressive aphasia is not a unitary entity (though not universally [27]), but its classification is still a major area of controversy. Most published work assumes an a-priori taxonomy derived from clinical experience, but Knibb *et al.* [28••] used cluster analysis to address the question with a minimum of prior assumptions. Restricting their analysis to clinical linguistic features of the syndrome, the results provided independent evidence for the widely held view [2] in which PNFA and semantic dementia are seen as distinct conditions, within the broader rubric of progressive aphasia. Epidemiological support for this conclusion comes from Johnson *et al.*'s study [3•], where PNFA was found to begin after the age of 60 and to affect more women than men, the opposite being true for semantic dementia (and also for bvFTD). On a theoretical level, a growing body of evidence suggests that semantic dementia constitutes a distinct entity, in which neuropsychological impairments spanning various domains are all explained by a single underlying deficit in conceptual category knowledge [29••,30•,31•].

As the name 'PNFA' suggests, spontaneous speech fluency is the most clinically salient variable distinguishing PNFA and semantic dementia. The word 'fluency' is also used to describe performance in noun generation tasks, and two groups have recently investigated category fluency and initial-letter fluency in progressive aphasia [32•,33•]. They found that all patients are impaired on category fluency, but initial-letter fluency is much more abnormal in PNFA than the fluent or semantic group. Letter fluency may therefore be a useful clinical diagnostic tool in patients presenting with progressive aphasia.

Heterogeneity within progressive nonfluent aphasia

Josephs *et al.* [34••] emphasize the distinction between progressive disorders of motor speech function – apraxia of speech (AoS) [35] – and progressive aphasia proper. They describe pure progressive AoS, agrammatic progressive aphasia with AoS, and an aphasic group with neither agrammatism nor AoS. In contrast to the usual dominant hemisphere abnormalities described in aphasia, they find that AoS is associated with bilateral atrophy in prefrontal motor areas and the caudate nucleus. This paper highlights the heterogeneity within PNFA, and the clinical value that psycholinguistic expertise can bring to this underexplored field.

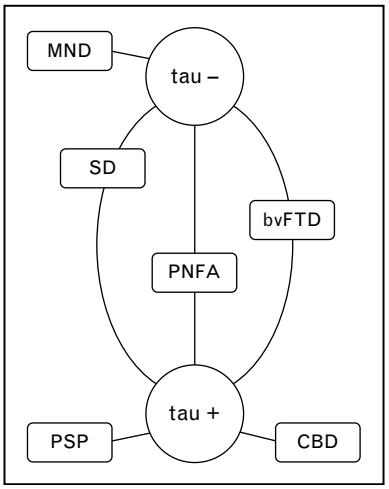
Pathology

In 2002, a systematic review by Kertesz *et al.* [36] found only 59 published cases of progressive aphasia for which pathological information was available, and no large postmortem series of FTLD were published until 2004 [7]. Since then, however, reports have appeared at an astonishing rate, and at the time of writing the total number of cases within clinico-pathological series stands at over 600, with at least nine major studies in the past year alone.

Clinical features and pathology

The distinction between those FTLD pathologies with aggregation of tau protein, and those without, is now firmly established. From this point of view, there are two clinical syndromes which allow confident prediction of pathology. FTLD with MND is always associated with tau-negative FTLD-U [4••,37•–40•], and FTLD with the extrapyramidal features of CBD or PSP is almost always associated with tau-positive pathology [4••,37•,38•,41•]. Semantic dementia is close behind in its association with FTLD-U [37•,39•,41•,42••]. By contrast, the pathology in bvFTD and PNFA is much more heterogeneous, and unpredictable. There may be a slight excess of tau-negative pathology in bvFTD [4••,38•,39•]

Figure 1 Different clinical syndromes are associated more or less strongly with tau-positive (tau+) or tau-negative (tau−) frontotemporal lobar degeneration (FTLD) pathology, as represented by the proximity of each box to the two circles



The place of Alzheimer-type pathology is controversial and has not been represented here. bvFTD, behavioural-variant frontotemporal dementia; CBD, corticobasal degeneration; MND, motor neurone disease; PNFA, progressive nonfluent aphasia; PSP, progressive supranuclear palsy; SD, semantic dementia.

and of tau-positive pathology in PNFA [4••,28••,34••, 38•,39•], but not all studies agree [37•,41•] (Fig. 1). The place of Alzheimer's disease pathology in clinical FTLD is hotly debated; three recent papers report a significant proportion of Alzheimer's disease [4••,41•], including one [28••] in which it accounted for nearly a third of progressive aphasia cases, but other studies have found very few cases [3•,34••,37•]. The resolution of this dilemma awaits further work.

The physical signs of MND, CBD and PSP presumably allow experienced clinicians to diagnose these syndromes confidently, and semantic dementia forms a more consistent clinical syndrome [43] than either PNFA or bvFTD. This hierarchy of clinical consistency is intriguingly parallel to the degree of pathological confidence. PNFA might appear to be an exception – surely quite easy to diagnose? – but perhaps there are pathological and clinical distinctions within this group; Kertesz *et al.* [4••] found that cases of PNFA with Alzheimer pathology have more fluent speech and memory loss at onset than those with FTLD pathologies, and Josephs *et al.* [34••] hinted that the presence or absence of apraxia of speech may distinguish tau-positive from tau-negative cases.

Imaging and pathology

The prediction of pathology from imaging findings is difficult, but a small study comparing FTLD-U pathology with PiD and familial FTD (tau exons 10 and 16) suggests that there may be regionally specific radiological differences during life, albeit with substantial overlap between the affected regions. In particular, FTLD-U was associated with asymmetric temporal lobe atrophy (worse on the left), PiD had severe bifrontal volume loss and familial cases tended to have more right medial temporal lobe atrophy [44•]. The clinical usefulness of these findings remains to be tested.

Prognosis and pathology

A number of studies have compared mortality rates between the different pathological subgroups of FTLD. Patients with MND are at high risk of death from aspiration and related causes, but after excluding this group, most studies have found no difference in mortality between tau-positive and tau-negative cases [4••, 28••,37•,41•,45•]. The exception is a report by Roberson and colleagues [40•], which was designed specifically to answer this question. The clinical part of the study comprised 177 FTLD patients. Semantic dementia and Alzheimer's patients lived for the longest time from onset, followed by progressive aphasics and bvFTD patients in that order. This finding may not extend to the pathology arm of their study as they obtained only 39 FTLD autopsies. Since four of the studies previously cited are larger than this, the difference between tau-positive and tau-negative cases may be ascribed to sampling error.

Genetics

In this section we examine the aetiological role of genetic factors.

Heritability

FTLD has a strong genetic component, but only a small proportion of cases show simple Mendelian inheritance. Goldman *et al.* [46•] examine this issue in detail, by selecting FTLD pedigrees from their genetic counselling service and stratifying them according to the strength of association of the FTLD syndromes within each pedigree. They found that FTD-MND was the most heritable of the syndromes, though even here only 37% of cases occurred in pedigrees with an autosomal dominant pattern of inheritance, while 41% had no family history. Most of the responsible genes in the pedigrees with an apparent single-gene defect could not be identified on screening for recognized mutations, implying that many loci remain to be described. Semantic dementia was the least heritable syndrome, where 85% of patients lacked any relatives affected by any FTLD syndrome. Similarly, of the 29 cases of FTLD-U described by Godbolt *et al.* [39•], all seven cases with predominantly semantic features lacked a strong family history.

Specific polymorphisms

Two recent studies have identified loci which may be involved in modulating the risk of developing FTLD, or

in favouring one FTLD syndrome over another. Examining allele frequencies at the apolipoprotein E locus, Acciarri *et al.* [47•] found a difference between progressive aphasic patients and controls; two previous studies [48,49] found similar results, though each in atypical clinical subgroups. Li *et al.* [50•] examined the Met-Val polymorphism of prion protein which is relevant to Creutzfeldt Jakob disease, and found an increased prevalence of the heterozygous (Met-Val) genotype in progressive aphasia.

Conclusion

The most striking area of recent progress in FTLD research is in clinico-pathological correlation, with certain syndromes being closely tied to histopathological subtypes, namely FTD-MND and semantic dementia with FTLD-U, and CBD/PSP with tau-positive inclusions. The pathological basis of bvFTD and PNFA remains unpredictable, but more detailed study of the clinical features may help here. The prognosis seems to depend on the clinical syndrome rather than on the underlying pathology. Strangely, despite the apparently similar pathological substrate, FTD-MND seems to have a strong genetic component while semantic dementia has almost none. One possible interpretation of this is that the presence of ubiquitin inclusions could be an epiphenomenon, rather than being essential to the underlying pathological process.

There appears to be a group of FTLD patients who have a deficit in semantic knowledge associated with anterior temporal lobe atrophy, and this leads to a fluent, anomic aphasia with word comprehension impairment, along with various other nonverbal deficits. In the light of the finding that there are two distinct groups of patients who present with progressive aphasia, distinguished *inter alia* by fluency, it seems likely that these semantic dementia patients account for at least the majority of fluent progressive aphasics, but this has yet to be firmly established.

The validity of the standard grouping of behavioural, aphasic and semantic syndromes together in FTLD is receiving increasing support on both clinical and pathological levels, although a small proportion of cases still turn out to have Alzheimer pathology – it is not yet clear whether these can be distinguished clinically. The argument for including extrapyramidal tau-positive syndromes such as PSP and CBD in the FTLD classification is also gaining ground. The consensus criteria for the differential diagnosis of these syndromes have been useful in clinical practice and in raising awareness, but have not been supported in detail by recent research work. In our view, the evidence suggests that the core criteria should be broadened and made more flexible, that atrophy as assessed by MRI should be given greater diagnostic weight, particularly in the case of semantic dementia, and that amnesia should no longer be considered an absolute exclusion criterion.

Several important developments have occurred in this field since the time of writing, of which two are particularly significant. Firstly, mutations in the progranulin gene (*PGRN*) have now been identified as the cause of FTLD-U pathology in a significant proportion of case [51,52]; one study suggests 25% of familial cases, and as many as 5% of sporadic case [53]. The precise characterization of individuals with this gene will be very important over the coming year, but there are preliminary suggestions that the clinical phenotype may be quite variable. Secondly, after a major effort, the target of ubiquitination in the neuronal inclusion of FTLD-U has been identified as the DNA-binding protein TDP-43 [54]. Little is known about the precise function of this protein, but that will certainly change over the coming year.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 634–636).

1 Brun A, Englund B, Gustafson L, *et al.* Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry 1994; 57:416–418.

2 Neary D, Snowden JS, Gustafson L, *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51:1546–1554.

3 • Johnson JK, Diehl J, Mendez MF, *et al.* Frontotemporal lobar degeneration: demographic characteristics of 353 patients. Arch Neurol 2005; 62:925–930.

A very large study of clinical FTLD, providing important demographic data. Also reports pathology in a proportion of cases.

4 •• Kertesz A, McMonagle P, Blair M, *et al.* The evolution and pathology of frontotemporal dementia. Brain 2005; 128:1996–2005.

A large, prospective clinico-pathological series with serial long-term follow-up. Provides a unique insight into the natural history of FTLD as well as its pathological correlations.

5 • McMurtray AM, Chen AK, Shapira JS, *et al.* Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia. Neurology 2006; 66:517–522.

Provides valuable clinico-imaging correlations with the core and supportive clinical consensus criteria for bvFTD.

6 • Shinagawa S, Ikeda M, Fukuhara R, Tanabe H. Initial symptoms in frontotemporal dementia and semantic dementia compared with Alzheimer's disease. Dement Geriatr Cogn Disord 2006; 21:74–80.

Using retrospective clinical data, gives an interesting perspective on the evolution of symptoms in these conditions.

7 Hodges JR, Davies RR, Xuereb JH, *et al.* Clinicopathological correlates in frontotemporal dementia. Ann Neurol 2004; 56:399–406.

8 • Le Rhun E, Richard F, Pasquier F. Natural history of primary progressive aphasia. Neurology 2005; 65:887–891.

With a large group of patients, illustrates the progression from a pure aphasic syndrome to other features of FTLD.

9 • Knopman DS, Boeve BF, Parisi JE, *et al.* Antemortem diagnosis of frontotemporal lobar degeneration. Ann Neurol 2005; 57:480–488.

Provides pathological evidence for the validity of the FTLD diagnostic consensus criteria.

10 Graham A, Davies R, Xuereb J, *et al.* Pathologically proven frontotemporal
• dementia presenting with severe amnesia. Brain 2005; 128:597–605.
Emphasizes how amnesia may be a presenting feature of pathologically confirmed FTLD despite this being an exclusion criterion for the disease in the consensus criteria.

11 Scahill VL, Hodges JR, Graham KS. Can episodic memory tasks differentiate
• semantic dementia from Alzheimer's disease? Neurocase 2005; 11:441–451.
Highlights the possibility of true episodic memory impairment in semantic dementia, emphasizing the role of right versus left disease predominance.

12 Ivanoiu A, Cooper JM, Shanks MF, Venneri A. Patterns of impairment in autobiographical memory in the degenerative dementias constrain models of memory. Neuropsychologia 2006; 44:1936–1955.

13 Hou CE, Miller BL, Kramer JH. Patterns of autobiographical memory loss in dementia. Int J Geriatr Psychiatry 2005; 20:809–815.

14 Nestor PJ, Graham KS, Bozeat S, *et al.* Memory consolidation and the hippocampus: further evidence from studies of autobiographical memory in semantic dementia and frontal variant frontotemporal dementia. Neuropsychologia 2002; 40:633–654.

15 van de Pol LA, Hensel A, van der Flier WM, *et al.* Hippocampal atrophy on MRI
• in frontotemporal lobar degeneration and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2006; 77:439–442.
Evidence that FTLD, especially semantic dementia, patients may show medial temporal lobe atrophy comparable to that seen in Alzheimer's disease patients.

16 Nestor PJ, Fryer TD, Hodges JR. Declarative memory impairments in
•• Alzheimer's disease and semantic dementia. NeuroImage 2006; 30: 1010–1020.
Explores the role of areas within and outside the medial temporal lobe in causing amnesia, using functional imaging in carefully neuropsychologically characterized patients.

17 Davies RR, Kipps CM, Mitchell J, *et al.* Progression in frontotemporal dementia: identifying a benign behavioural variant by MRI. Arch Neurol (in press).

18 Davies RR, Graham KS, Xuereb JH, *et al.* The human perirhinal cortex and semantic memory. Eur J Neurosci 2004; 20:2441–2446.

19 Williams GB, Nestor PJ, Hodges JR. Neural correlates of semantic and
• behavioural deficits in frontotemporal dementia. NeuroImage 2005; 24:1042–1051.
Uses behavioural and volumetric data in correlational analyses, giving a valuable insight into the contributions of certain brain areas to the various features of FTLD.

20 Nestor PJ, Graham NL, Fryer TD, *et al.* Progressive nonfluent aphasia is associated with hypometabolism centred on the left anterior insula. Brain 2003; 126:2406–2418.

21 Janssen JC, Schott JM, Cipolotti L, *et al.* Mapping the onset and progression
•• of atrophy in familial frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry 2005; 76:162–168.
Importantly emphasizes that brain atrophy is established at clinical onset, and that symptoms and clinical signs are a later manifestation of pathology. It has relevance to early diagnosis and clinico-imaging correlations.

22 Diehl-Schmid J, Grimmer T, Drzezga A, *et al.* Decline of cerebral glucose
•• metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study. Neurobiol Aging 2006; 28 January [Epub ahead of print].
Importantly defines the topography and progression of metabolic deficits in bvFTD.

23 Peters F, Perani D, Herholz K, *et al.* Orbitofrontal dysfunction related to both
• apathy and disinhibition in frontotemporal dementia. Dement Geriatr Cogn Disord 2006; 21:373–379.
A useful study which attempts to correlate symptoms such as apathy and disinhibition with regional metabolic dysfunction.

24 Franceschi M, Anchisi D, Pelati O, *et al.* Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. Ann Neurol 2005; 57:216–225.

25 Salmon E, Kerrouche N, Herholz K, *et al.* Decomposition of metabolic brain clusters in the frontal variant of frontotemporal dementia. Neuroimage 2006; 30:871–878.

26 Kril JJ, Macdonald V, Patel S, *et al.* Distribution of brain atrophy in behavioral
•• variant frontotemporal dementia. J Neurol Sci 2005; 232:83–90.
Provides important information on regional pathology and selective vulnerability in FTD which will aid in clinicopathological correlation, particularly with respect to the progression of symptoms in early cases. Of further interest is that pathological subtype did not result in a specific pattern of regional atrophy.

27 Mesulam MM. Primary progressive aphasia. Ann Neurol 2001; 49:425–432.

28 Knibb JA, Xuereb JH, Patterson K, Hodges JR. Clinical and pathological
•• characterization of progressive aphasia. Ann Neurol 2006; 59:156–165.
Explores the syndromes of progressive aphasia using a data-driven rather than hypothesis-driven approach.

29 Patterson K, Lambon Ralph MA, Jefferies E, *et al.* 'Presemantic' cognition in
•• semantic dementia: six deficits in search of an explanation. J Cogn Neurosci 2006; 18:169–183.
Elegantly summarizes and extends the work of this group in establishing a deficit of category knowledge as the basis of both verbal and nonverbal impairments in semantic dementia.

30 Garrard P, Carroll E. Lost in semantic space: a multimodal, nonverbal
• assessment of feature knowledge in semantic dementia. Brain 2006; 129: 1152–1163.
Provides further evidence for the single-deficit view of semantic dementia using a reality decision test across various modalities.

31 Ikeda M, Patterson K, Graham KS, *et al.* A horse of a different colour:
• do patients with semantic dementia recognise different versions of the same object as the same? Neuropsychologia 2006; 44:566–575.
Provides further evidence for the single-deficit view of semantic dementia using a test of categorization ability.

32 Clark DG, Charuvastra A, Miller BL, *et al.* Fluent versus nonfluent primary
• progressive aphasia: a comparison of clinical and functional neuroimaging features. Brain Lang 2005; 94:54–60.
Provides valuable clinical, neuropsychological and metabolic imaging data on two groups of progressive aphasic patients.

33 Marczinski CA, Kertesz A. Category and letter fluency in semantic dementia,
• primary progressive aphasia, and Alzheimer's disease. Brain Lang 2006; 97:258–265.
Provides evidence for the clinical diagnostic utility of noun generation tasks in these conditions.

34 Josephs KA, Duffy JR, Strand EA, *et al.* Clinicopathological and imaging
•• correlates of progressive aphasia and apraxia of speech. Brain 2006; 129:1385–1398.
Raises the issue of clinical and pathological heterogeneity within nonfluent progressive aphasia, and provides data to suggest that apraxia of speech is an important dimension of variation.

35 Duffy JR. Motor speech disorders: substrates, differential diagnosis, and management. San Louis: Mosby; 2005.

36 Kertesz A, Munoz DG. Primary progressive aphasia: a review of the neurobiology of a common presentation of Pick complex. Am J Alzheimers Dis Other Demen 2002; 17:30–36.

37 Shi J, Shaw CL, Du Plessis D, *et al.* Histopathological changes underlying
• frontotemporal lobar degeneration with clinicopathological correlation. Acta Neuropathol (Berl) 2005; 110:501–512.
A large prospective pathological series of clinical FTLD cases, analysed by clinical syndrome and pathological subtype. Also provides important demographic data on the cases.

38 Josephs KA, Petersen RC, Knopman DS, *et al.* Clinicopathologic analysis of
• frontotemporal and corticobasal degenerations and PSP. Neurology 2006; 66:41–48.
A large retrospective series of FTLD pathology cases, reviewed for clinical characteristics.

39 Godbolt AK, Josephs KA, Revesz T, *et al.* Sporadic and familial dementia with
• ubiquitin-positive tau-negative inclusions: clinical features of one histopathological abnormality underlying frontotemporal lobar degeneration. Arch Neurol 2005; 62:1097–1101.
Retrospective clinical analysis of 29 cases with this pathology. Also provides heritability data.

40 Roberson ED, Hesse JH, Rose KD, *et al.* Frontotemporal dementia pro-
• gresses to death faster than Alzheimer disease. Neurology 2005; 65:719–725.
A large clinical series of FTLD and Alzheimer's disease patients, providing important data on mortality. Also reports pathology in a proportion of cases.

41 Forman MS, Farmer J, Johnson JK, *et al.* Frontotemporal dementia: clinico-
• pathological correlations. Ann Neurol 2006; 59:952–962.
A large retrospective series of FTLD pathology cases, reviewed for clinical characteristics and mortality data.

42 Davies RR, Hodges JR, Kril JJ, *et al.* The pathological basis of semantic
•• dementia. Brain 2005; 128:1984–1995.
The largest series to date of pathologically characterized semantic dementia cases; provides evidence for a relatively tight clinico-pathological correlation in this condition.

43 Hodges JR, Patterson K. Nonfluent progressive aphasia and semantic dementia: a comparative neuropsychological study. J Int Neuropsychol Soc 1996; 2:511–524.

44 Whitwell JL, Josephs KA, Rossor MN, *et al.* Magnetic resonance imaging
• signatures of tissue pathology in frontotemporal dementia. Arch Neurol 2005; 62:1402–1408.
An original approach, exploring the association of histopathological FTLD subtype with the distribution of regional brain atrophy.

45 Rascovsky K, Salmon DP, Lipton AM, *et al.* Rate of progression differs in
• frontotemporal dementia and Alzheimer disease. Neurology 2005; 65:397–403.
Compares disease progression and mortality between the two groups defined pathologically, and also between pathological subtypes of FTLD.

46 Goldman JS, Farmer JM, Wood EM, *et al.* Comparison of family histories in
• FTLD subtypes and related tauopathies. Neurology 2005; 65:1817–1819.
A detailed and useful study of the degree of co-segregation within families of the various clinical FTLD syndromes.

47 Acciarri A, Masullo C, Bizzarro A, *et al.* ApoE epsilon2-epsilon4 genotype is a
• possible risk factor for primary progressive aphasia. Ann Neurol 2006; 59:436–437.
Provides interesting data to support the proposal of the ApoE gene polymorphism as affecting the development of primary progressive aphasia.

48 Gorno-Tempini ML, Dronkers NF, Rankin KP, *et al.* Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol 2004; 55:335–346.

49 Short RA, Graff-Radford NR, Adamson J, *et al.* Differences in tau and apolipoprotein E polymorphism frequencies in sporadic frontotemporal lobar degeneration syndromes. Arch Neurol 2002; 59:611–615.

50 Li X, Rowland LP, Mitsumoto H, *et al.* Prion protein codon 129 genotype
• prevalence is altered in primary progressive aphasia. Ann Neurol 2005; 58:858–864.
Provides interesting data to support the prion protein gene polymorphism as affecting the development of primary progressive aphasia.

51 Baker M, Mackenzie IR, Pickering-Brown SM, *et al.* Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006; 442:916–919.

52 Cruts M, Gijselinck I, van der Zee J, *et al.* Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006; 442:920–924.

53 Gass J, Cannon A, Mackenzie IR, *et al.* Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. Hum Mol Genet 2006; September 1 [Epub ahead of print].

54 Lee VM. Data presented at: 5th International Conference on Frontotemporal Dementias, University of California, San Francisco, 2006.