Section 1 Introduction to and brief history of FTD

Chapter 1

Historical introduction to FTD

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Introduction

Over the two past decades there have been considerable advances in our understanding of the major neurodegenerative diseases producing focal cognitive deficits, most commonly referred to collectively as either Pick's disease or, more recently, frontotemporal dementia (FTD). These advances have come from the fields of neuropsychology, neuropsychiatry, neuroimaging, neuropathology, and molecular genetics. Unfortunately, most non-experts' ability to follow these developments has been hindered by the confusing plethora of terms which have been used. Central to the problem is a lack of clarity concerning the level of description (clinical syndrome versus clinicopathologic entity versus specific histologic diagnosis) and the poor concordance between these levels. In other words, while some labels denote a clinical syndrome without specific histologic implications (e.g., progressive aphasia, semantic dementia, or dementia of frontal type), others denote specific neuropathologic entities (e.g., Pick's disease, familial tauopathy, ubiquitin-inclusion disease), hybrid clinicopathologic entities (frontotemporal dementia), or even specific genetic disorders (e.g., chromosome 17-linked frontotemporal dementia with parkinsonism [FTDP-17]). The resurgence of interest in these disorders and the differences in opinion over terminology are well illustrated by the titles of the previous books published on the topic: *Pick's Disease and Pick's Complex* (Kertesz and Munoz, 1998), *Frontotemporal Dementia* (Pasquier *et al.*, 1996), and *Frontotemporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia* (Snowden *et al.*, 1996b).

The aims of this introductory chapter are to review the evolution of the terms used to describe this spectrum of disorders, to highlight recent advances and areas of continuing controversy, and to set the scene for the rest of the book. While my own preference has always been to use the term Pick's disease for this group of disorders – partly because this term is more readily understood by carers and parallels our use of the label Alzheimer's disease – the tide of medical opinion turned in favor of FTD in the late 1990s. We have, therefore, adopted this general label within which we distinguish two main clinical variants: behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA) with further subclassification of the aphasic cases. The sections that follow describe the meandering route that led to the adoption of these terms. The chapter draws heavily upon my own experience of more than 500 patients assessed in Cambridge and in Sydney over the past 20 years and has been updated since the first edition of the book to reflect areas of evolution and change.

What did Arnold Pick actually describe?

In 1892 Arnold Pick (Girling and Berrios, 1994), working in Prague, reported a 71-year-old man with progressive mental deterioration and unusually severe aphasia who at post-mortem had marked atrophy of the left temporal lobe. Twelve years later in 1904 he published his landmark paper ("On the symptomatology of left-sided temporal lobe atrophy") in which he described three further cases (Girling and Berrios, 1997). The first, a 58-year-old woman (Josephina) had a two-year history characterized by a striking loss of memory for names (amnesic aphasia) culminating in almost complete loss of speech and accompanied by changes in personality. She deteriorated rapidly and at post-mortem, two years after presentation, Pick observed asymmetric temporal lobe atrophy involving

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particularly the inferior and middle gyri (i.e., not Wernicke's area). Methods of staining brain sections were not available at that time and Pick was able to make observations on the macroscopic pathology only. The other two cases were clinically similar, except that case three had the complication of cerebral syphilis, preventing firm conclusions about the cause of the focal brain atrophy. Pick wanted to draw attention to the fact that progressive brain atrophy may lead to symptoms of focal disturbance (in this instance aphasia) through local accentuation of the disease process. He also made specific and, as we will see below, highly perceptive predictions regarding the role of the mid temporal region of the left hemisphere in the representation of word meaning. It was only in his later publication that Pick turned his attention to bilateral frontal atrophy with resultant behavioral disturbance.

Pick made major contributions which have sadly been rather overlooked in recent years. Current classifications have also relegated him to a minor role but several points should be emphasized: (1) Pick's primary interest was the language and behavioral disorder, particularly the clinico-anatomical correlates of aphasia; (2) he did not claim to have discovered a new disease, merely novel phenomena arising from asymmetric degeneration; (3) two of the major syndromes now included under the rubric of FTD (bvFTD and semantic dementia) were clearly described by Pick; (4) he did not describe distinct histopathologic changes in his patients with focal atrophy.

The histologic abnormalities associated with Pick's disease were, in fact, described a few years later by Alzheimer (1911) who recognized changes distinct from those found in the form of cerebral degeneration later associated with his name. Alzheimer recognized both argyrophilic intracytoplasmic inclusions (Pick bodies), and diffusely staining ballooned neurons (Pick cells) in association with focal lobar atrophy. It is interesting to note that a comprehensive review of 20 patients from the literature with aphasia due to focal lobar atrophy written soon after Alzheimer's description (Mingazzini, 1913) did not use the label Pick's disease. Onari and Spatz (1926) were among the first to use the eponym Pick's disease but Carl Schneider (1927, 1929) is probably most responsible for its introduction. Unfortunately, however, he concentrated on the frontal lobe component of the syndrome and began the neglect of the temporal lobe syndromes associated with focal atrophy that continued for at least half a century. He distinguished three clinical phases – the first characterized by impaired judgment and behavior, the second by focal symptoms, and the third by generalized dementia. Many papers describing similar cases appeared in the 1930s and 1940s (e.g., Ferraro and Jervis, 1940; Löwenberg and Arbor, 1936; Löwenberg *et al.*, 1939; Neumann, 1949; Nichols and Weigner 1938) which mainly focused on the frontal lobe aspects of the disorder. Given the more recent genetic discoveries related to the gene for tau protein, special mention should be made of the large Dutch family first reported by Sanders *et al.* (1939) and then again by Schenk (1951). These families were central to developments in the 1990s when linkage to the tau gene region on chromosome 17 was established by workers in the USA (Wilhelmsen *et al.*, 1994) and Europe (Heutink *et al.*, 1997).

With the general waning of interest in the cognitive aspects of neurology in the English-speaking world, interest in focal dementia syndromes faded, as reflected by the dearth of clinical papers in the neurologic literature after the Second World War. Indeed, many authors went as far as to claim that Alzheimer's and Pick's disease were clinically indistinguishable in life (Kamo *et al.*, 1987; Katzman, 1986). The focus of interest in English language publications became the neuropathology, and latterly the genetics, of these conditions. This resulted in a gradual change in the criteria for Pick's disease, which evolved to include the necessity for specific pathologic changes (i.e., focal atrophy with Pick cells and/or Pick bodies). In continental Europe, however, there remained a strong interest in the clinical phenomena of the dementias; Pick's remained an in vivo diagnosis based on a combination of clinical features suggestive of frontal and/or temporal lobe dysfunction and focal lobar atrophy (e.g., Mansvelt, 1954; Tissot *et al.*, 1975, 1985).

This controversy continues and has contributed to the adoption of the many labels to describe patients with the clinical syndrome of progressive frontal or temporal lobe degeneration.

Rediscovering Pick's disease: from dementia of the frontal type and progressive aphasia to frontotemporal dementia

A renaissance of interest in the focal dementias began in the 1980s. Workers from Lund, Sweden (Brun, 1987; Gustafson, 1987) reported on a large series of patients

with dementia and found that of 158 patients studied prospectively who came to post-mortem, 26 had evidence of frontal lobe degeneration. Since only a small proportion had Pick cells and Pick bodies – the remainder had very similar findings but without specific inclusions (i.e., focal lobar atrophy with severe neuronal loss and spongiosis) – the Lund group preferred to adopt the term "frontal degeneration of non-Alzheimer type." At approximately the same time, Neary and co-workers in Manchester (Neary *et al.*, 1986) began a series of important clinicopathologic studies of patients with presenile dementia. They, likewise, found a high proportion of cases with a progressive frontal lobe syndrome who had neither specific changes of Alzheimer's disease (plaques and tangles) nor specific inclusion pathology. They introduced the term "dementia of frontal type." Over the next few years other groups described very similar cases under the labels "frontal lobe degeneration" (Miller *et al.*, 1991) and "dementia lacking distinct histologic features" (Knopman *et al.*, 1990). These papers were important in defining the key clinical features associated with progressive frontal lobe degeneration, notably: alterations in social conduct, inhibitory control, sexual behavior, appetite; ritualized and stereotypic behaviors; reduced empathy; and apathy.

In more recent classifications these patients have been given either the general label of FTD (as distinct from progressive aphasia and semantic dementia) or alternatively frontal variant FTD and more recently bvFTD. Key advances have been the development of carer-based interview schedules or questionnaires such as the Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994), the Frontal Behavioral Inventory (FBI; Kertesz *et al.*, 2000), and the Cambridge Behavioural Inventory (CBI; Bozeat *et al.*, 2000). It has become apparent that conventional frontal lobe tests based largely on executive abilities (planning, set-shifting, problem-solving) are not very sensitive to the beginnings of this behavioral form of FTD. A range of exciting recent research has focused on ways of measuring the alterations in social conduct, theory of mind, emotion processing, and complex decision-making (Bertoux *et al.*, 2012; Gregory *et al.*, 2002; Keane *et al.*, 2002; Kumfor and Piguet, 2012; Kumfor *et al.*, 2013; Lough *et al.*, 2006; Rahman *et al.*, 1999; Rankin *et al.*, 2003; Torralva *et al.*, 2007). It had been long assumed that the orbital cortex bears the brunt, particularly in the early stages of the disease, but recent quantitative imaging work has emphasized rather the role of the mesial surface. Moreover, some of the symptoms typically regarded as "frontal" in nature may, in fact, be secondary to amygdala or insula damage. Studies attempting to relate individual clinical features to site(s) of brain dysfunction using structural or functional imaging are in their infancy (Hornberger *et al.*, 2011; Kloeters *et al.*, 2013; Rankin *et al.*, 2003; Rosen *et al.*, 2002a, 2005; Williams *et al.*, 2005) and it is certain that there will be considerable advances over the next few years.

Of relevance to the story of bvFTD was the realization a few years ago that a proportion of patients with this clinical label, bvFTD, failed to progress even over many years of follow-up. Such patients typically lacked atrophy on MRI (Davies *et al.*, 2006). Subsequent work showed that these non-progressors or "phenocopy cases," who were virtually all men, could be identified by their lack of executive (Hornberger *et al.*, 2008) or memory deficits (Hornberger *et al.*, 2010) and preservation of activities of daily living. (Piguet *et al.*, 2011). The etiology of the phenocopy syndrome remains unclear. A proportion of cases may have the *C9orf72* (chromosome 9 open reading frame 72) mutation (discussed below). Others have long-standing personality disorders and decompensate in later life. These findings contributed to the revision of criteria for bvFTD with much more clearly defined symptoms and the need for brain imaging changes, plus evidence of progression, to qualify for a diagnosis of probable, rather than possible, bvFTD (Rascovsky *et al.*, 2011).

Progressive aphasia and semantic dementia

The other strand of the story concerns the rediscovery of the syndrome of progressive aphasia in association with focal left temporal lobe or perisylvian atrophy. In 1982 Mesulam reported six patients with a history of insidiously worsening aphasia in the absence of signs of more generalized cognitive failure. One of these patients underwent a brain biopsy, which revealed non-specific histology without specific markers of either Alzheimer's or Pick's disease. Following Mesulam's seminal paper, approximately 100 patients with so-called PPA were reported over the next decade (for reviews, see Hodges and Patterson, 1996; Mesulam and Weintraub, 1992; Snowden *et al.*, 1996a). It became gradually clear that, although the term PPA was being applied to a range of very different cases, within this spectrum there were two

identifiable and distinct aphasic syndromes: progressive non-fluent aphasia (PNFA) and semantic dementia (SD), sometimes referred to as progressive fluent aphasia. In the former syndrome, speech is halting and distorted with frank articulatory and syntactic errors. Comprehension mirrors output in that single-word (semantic) comprehension is relatively intact but patients have difficulty understanding syntactically complex sentences. Oro-buccal apraxia commonly accompanies the language disorder. In the latter syndrome, speech remains fluent and well-articulated but becomes progressively devoid of content words. The language and other non-verbal cognitive deficits observed in these fluent-aphasic patients reflect a breakdown in semantic memory, which has led many authors to apply the label of "semantic dementia" first coined by Snowden et al., in 1989 (Hodges and Patterson, 1996; Hodges *et al.*, 1992, 1994; Snowden *et al.*, 1989).

Although the term "semantic dementia" (SD) is recent, the syndrome has been recognized under different labels for many years. As emphasized above, Pick (1892, 1904) and a number of other early authors (Mingazzini, 1913; Rosenfeld, 1909; Schneider, 1927; Stertz, 1926) recognized the outstanding clinical manifestation of temporal lobe atrophy as "amnesic aphasia" or "transcortical sensory aphasia," together with a type of dementia variously described as a reduction in categorical or abstract thinking, psychic blindness, or associative agnosia (Malamud and Boyd, 1940; Mingazzini, 1913; Robertson *et al.*, 1958). These features – amnesic aphasia and associative agnosia – were united under the rubric of degraded semantic memory by Warrington (1975) who reported three patients. Drawing on the work of Tulving (1972, 1983), Warrington recognized that the progressive anomia in her patients was not simply a linguistic deficit, but reflected a fundamental loss of semantic memory (or knowledge) about objects and concepts which thereby affected naming, word comprehension, and object recognition. Semantic memory is the term applied to the component of long-term memory that represents our knowledge about things in the world and their interrelationships, facts and concepts, as well as words and their meaning (Garrard *et al.*, 1997; Hodges and Patterson, 1997; Hodges *et al.*, 1992, 1998). Cases of SD have also been recognized for many years in Japan as cases of "Gogi (word meaning) aphasia" (Imura *et al.*, 1971; Morita *et al.*, 1987; Sasanuma and Mondi, 1975; Tanabe, 1992; Tanabe *et al.*, 1992). The syndrome of SD has been particularly important from a theoretical perspective because, in contrast to Alzheimer's disease, patients have relatively good day-to-day (episodic) memory and autobiographical memory, intact immediate or working memory (at least as assessed by digit span), and good visually based problem-solving and visuoperceptual abilities (Graham and Hodges, 1997; Hodges and Graham, 1998; Hodges *et al.*, 1995, 1999, 2010; Patterson and Hodges, 2000). This relative selectivity of the semantic memory impairment in SD makes these patients ideal subjects for the study of the effects of semantic dissolution uncontaminated by other cognitive deficits. As discussed elsewhere, however, the situation is somewhat more complex than when it first appeared both in terms of the purity of the syndrome and the insights afforded into the interaction between semantic memory and other putative "cognitive modules."

The above description is, of course, an oversimplification and gives the impression that cases can be neatly divided into PNFA and SD. In practice things are much less straightforward. First of all, some authors have claimed that there is a coherent third progressive aphasic syndrome (logopenic PA), characterized by word-finding difficulty and anomia but without significant comprehension impairment, and reduced verbal span, which is associated with posterior temporal, inferior parietal, or angular gyrus pathology (Gorno-Tempini *et al.*, 2004; Sonty *et al.*, 2003), with the suggestion that such cases have underlying Alzheimer's disease pathology. In a recent study using Pittsburgh compound B (PiB) as a marker of Alzheimer's pathology we were able to confirm the presence of this third logopenic variant in association with increased PiB retention (Leyton *et al.*, 2011). Other authors have claimed that patients who fall in the middle ground between SD and PNFA have no clear defining features (Sajjadi *et al.*, 2012). The identification of this third variant was one of the major factors underlying the revision of criteria for the three subtypes of PPA (Gorno-Tempini *et al.*, 2011). Investigation of these logopenic cases is a topic of considerable current interest.

Second, although this does not affect the issue of the classification of two language variants of FTD, many patients with features of SD also have prominent behavioral changes, and semantic deficits can be seen in patients with bvFTD. Indeed in our clinics we have

often seen patients with a mixture of these two syndromes. Finally, there is the problem of how to categorize cases that have all of the classic features of PNFA or SD but have additional "exclusion" features, such as subtle, but definite, visuospatial defects, poor episodic memory, or apraxia.

Our paper in 1992 (Hodges *et al.*, 1992) defined the core cognitive aspects of SD and drew attention to the association between this cognitive profile and the relatively circumscribed and asymmetric left > right temporal lobe atrophy that has subsequently been confirmed and refined in a number of publications (Davies *et al.*, 2004; Galton *et al.*, 2001; Mummery *et al.*, 1999). This typical left > right pattern raises the issue of the cognitive and/or behavioral signatures of the less common pattern of relatively isolated right, or right > left, temporal atrophy. Although we almost certainly encountered earlier patients with the syndrome now associated with prominent right temporal atrophy, the first clearly documented patient (VH) was reported as a case of gradually progressive prosopagnosia (Evans *et al.*, 1995): VH was unable to identify from face or name even very famous people (e.g., Margaret Thatcher) yet had relatively intact general semantic and autobiographical memory (Kitchener and Hodges, 1999). Over the past few years a number of authors have reported such cases, confirming the role of the right temporal lobe in the representation of knowledge about people (Gainotti *et al.*, 2003; Gentileschi *et al.*, 1999, 2001; Thompson *et al.*, 2003). In parallel with this literature, the group led by Bruce Miller drew attention to the bizarre behaviors (including irritability, impulsiveness, alterations in dress, limited and fixed ideas, and decreased facial expression) exhibited by patients with predominantly right temporal lobe atrophy (Edwards Lee *et al.*, 1997; Miller *et al.*, 1997). A study in 2003, drawing on our experience of 80 cases of whom a quarter had right-predominant atrophy, pulled together these observations by demonstrating that the right > left group tended to present with changes in person recognition *and* alterations in personality, while the more common left > right group had the typical deterioration of semantic memory for words and objects (Thompson *et al.*, 2003).

The adoption of the term semantic variant PPA to replace the label SD (Gorno-Tempini *et al.*, 2011) creates considerable difficulty in categorizing right-SD cases who do not have prominent aphasia.

Frontotemporal dementia and frontotemporal lobar degeneration

The final terms to be considered are FTD and frontotemporal lobar degeneration (FTLD). In 1994 the Lund and Manchester groups introduced the term FTD (Brun *et al.*, 1994) to describe patients with progressive changes in behavior/personality and suggested tentative criteria for the diagnosis. Then four years later a broad group of experts met and unified FTD with the progressive aphasias (Neary *et al.*, 1998). They proposed the general label FTLD with three subforms: FTD, by which was meant the predominantly behavioral variant with prominent language deficits, and the two aphasic variants, SD and PNFA. Criteria for each syndrome were proposed with major and minor inclusion features and exclusion features. This clearly represented a major advance, but did have the consequence of mixing levels of description in that FTD implies a distinct anatomical locus, whereas SD and PNFA are descriptive clinical syndromes. The use of the label FTD for those with prominent aphasia is perhaps confusing and implies that temporal lobe involvement is an invariable accompaniment of the behavioral syndrome. The "criteria" are also more akin to clinical guidelines since it is not clear how many features need to be present and whether the exclusion features are absolute. For instance, severe amnesia is said to be an exclusion feature, but it is now clear that a fairly high proportion of patients with pathologically proven FTD have significant memory impairment and in some this is of the severity seen in Alzheimer's disease (Graham *et al.*, 2005). A number of retrospective clinicopathologic studies have examined the utility of the FTLD criteria (Hodges *et al.*, 2004; Josephs *et al.*, 2006; Rosen *et al.*, 2002b).

In Cambridge we adopted a hybrid classification. The term FTD is preferred as the superordinate label applied to the whole group with a subdivision into two main variants (bvFTD and PPA). A very similar classification was proposed by Grossman (2002) who used the terms behavioral disorder and dysexecutive syndrome instead of bvFTD. An all-American group led by Guy McKhann (2001), the originator of the famous NINCDS–ADRDA criteria for Alzheimer's disease (McKhann *et al.*, 1984), have also proposed clinical criteria for FTD with a dichotomy between a behavioral presentation and a language presentation.

This has the benefit of simplicity but conflates PNFA and SD. These criteria have not stood the test of time and have been replaced by two influential international groups with proposals for criteria to diagnose bvFTD (Rascovsky *et al.*, 2011) and for three variants of PPA (Gorno-Tempini *et al.*, 2011).

One might wish to ask why these quite distinct syndromes should be regarded as variants of a single disorder in the first place. In answer to this question, three lines of evidence can be examined: (1) the degree of clinical overlap, (2) radiologic overlap, and (3) the spectrum of underlying pathology.

Clinically, patients often present with features of two (or even all three) of these seemingly distinct syndromes and, over time, the overlap typically increases. Patients with "pure" SD typically develop behavior changes, and in many bvFTD patients, aphasic features become evident on follow-up. The overlap has been emphasized by Andrew Kertesz and his colleagues from London, Ontario who have proposed the general label *Pick's complex* (Kertesz and Munoz, 2003; Kertesz *et al.*, 2005). In my experience the overlap between bvFTD and SD in terms of behavioral changes is particularly striking, whereas such changes seem less of a feature of PNFA. Indeed recent evidence has suggested that there is greater overlap between PNFA and corticobasal syndrome (CBS) at both a clinical and pathologic level (Graham *et al.*, 2003a, 2003b; Mathew *et al.*, 2012).

The second area of overlap is radiological. Although patients with bvFTD have predominantly frontal atrophy, anterior temporal involvement is common, while those with SD may have accompanying frontal atrophy, again pointing to a clinicopathologic continuation rather than distinctive syndromes (Mummery *et al.*, 2000; Rosen *et al.*, 2002a).

Neuropathology remains the gold standard of classification in neurodegenerative disease. Progress in this field has been rapid and is reviewed in detail in Chapter 13. Here I provide a brief overview highlighting some of the landmark discoveries.

The neuropathology of FTD is far more complex than that of Alzheimer's disease. Whereas patients with clinically diagnosed Alzheimer's disease, whether young or old, familial or sporadic, will have pathologically identical changes (intraneuronal tangles and extracellular amyloid plaques), the changes in FTD are heterogeneous.

What are the current facts? The majority, but not all, of patients with one of the FTD syndromes described above have non-Alzheimer's pathology. Although tau-positive inclusions (Pick bodies) were the first form of pathologic change identified in the context of FTD, these constitute a minority of cases. The more recently described transactive response DNA-binding protein 43 (TDP-43) inclusions are the most common histopathologic variant.

If this book had been written a decade ago the section on neuropathology would have stated that a minority of cases have Pick body-positive FTD while the majority have neuronal loss and gliosis, but without distinctive histopathology. The recent and ever-expanding development of more sophisticated immunohistologic staining techniques has led to the identification of an even wider range of histologic abnormalities in cases of non-Alzheimer dementia involving the frontotemporal cortex (for review see Davies *et al.*, 2005; Forman *et al.*, 2006; Hodges *et al.*, 2004; Jackson and Lowe, 1996; Josephs *et al.*, 2011; Knopman *et al.*, 2005; Mott *et al.*, 2005; Rademakers *et al.*, 2013). Three major patterns are currently recognized.

(1) Tau-positive inclusion pathology. This, in turn, encompasses a number of subforms: cases with classic intraneuronal tau-positive Pick bodies, most of whom are sporadic; patients with familial, so-called FTDP-17, pathology who typically display diffuse neuronal and glial tau-positive inclusions without discrete Pick bodies; corticobasal degeneration (CBD) which is characterized by tau-positive pathology with ballooned achromatic neurons and astrocytic plaques; and finally argyrophilic grain disease in which the tau staining is punctate and "grain"-like particularly involving the medial temporal lobe.
(2) TDP-43 pathology. In 2006, TDP-43 was identified in both FTD and motor neuron disease (MND; amyotrophic lateral sclerosis [ALS]) (Neumann *et al.*, 2006). Such pathology is found in patients with mutation of the progranulin (*GRN*) gene and with the expansion of the hexanucleotide repeat in gene *C9orf72* as well as in sporadic cases of FTD and MND. Various subforms of TDP-43 are identified.
(3) FUS or fused in sarcoma pathology. These constitute a minority of cases who are non-familial with young onset, prominent behavioral changes, and caudate atrophy.

A major topic, addressed more fully elsewhere, is the predictability of pathology in vivo. In brief, patients with PNFA typically have tau-positive pathology although a substantial minority have Alzheimer's with atypical distribution (Chare *et al.*, 2014; Knibb *et al.*, 2006). Those with clinical MND have TDP-43-positive inclusion pathology. SD is also typically associated with TDP-43-positive disease but only a minority develops clinical MND (Chare *et al.*, 2014; Davies *et al.*, 2005). The pathologic substrate of the commonest form, bvFTD, remains the least predictable. In the combined Sydney–Cambridge series of 61 cases, 26 presented with bvFTD and there were approximately equal numbers with tau-positive and tau-negative pathology (Hodges *et al.*, 2004), subsequently confirmed in a larger study involving a total of 178 cases (Chare *et al.*, 2014).

Familial chromosome 17-linked frontotemporal dementia and the discovery of unique tau pathology

As described in more detail in Chapter 14, linkage was established in a number of families in which FTD is inherited as an autosomal dominant trait to the region of chromosome 17 (q21–22) containing the gene for the microtubule-associated protein tau (Wilhelmsen, 1997). The story of the chromosome 17 linkage is extraordinary in a number of ways. Families around the world with what has become known as FTD with parkinsonism linked to chromosome 17 or FTDP-17 (Spillantini *et al.*, 1998a) had originally been reported under a range of headings including: disinhibition–dementia–parkinsonism–amyotrophy complex (Wilhelmsen *et al.*, 1994), rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration (Wszolek *et al.*, 1992), familial progressive subclinical gliosis (Petersen *et al.*, 1995), hereditary dysphasia and dementia (Morris *et al.*, 1984), hereditary frontotemporal dementia (Heutink *et al.*, 1997), familial multiple system tauopathy with presenile dementia (Spillantini *et al.*, 1997), familial presenile dementia with psychosis (Sumi *et al.*, 1992), and Pick's disease (Schenk, 1951). In 1996 a meeting of representatives from all of the groups identifying linkage to chromosome 17 was held in Ann Arbor, Michigan (Foster *et al.*, 1997). Comparison of clinical and pathologic data revealed a great deal of similarity between the families who all shared the characteristics of predominantly frontotemporal distribution of pathology with marked behavioral changes. Extrapyramidal dysfunction was present in most. In some families psychotic symptoms were a major feature and a number had amyotrophy. It was recognized at that time that some of the families shared the common pathology with microtubule-associated protein tau-positive inclusions. Progress in the field was then rapid. It was soon discovered that most, if not all, families had diffuse neuronal and glial tau inclusions with a distinctive morphologic pattern, leading to the coining of the term "familial tauopathy" and the suggestion that the disease might reflect a mutation in the gene for tau protein known to be located in the 17q21–22 region (Spillantini *et al.*, 1998a). Within two years of the Ann Arbor meeting, several groups had identified the genetic mutation which, as predicted, was in the gene for tau protein (Dumanchin *et al.*, 1998; Hutton *et al.*, 1998; Poorkaj *et al.*, 1998; Spillantini *et al.*, 1998b).

Since 1998, more than 30 different mutations of the gene for tau protein have been identified, largely involving the coding regions, particularly the so-called microtubule-binding domains (exons 9–12) of the gene for tau. There has been an explosion of interest in the molecular pathology of tau. Although the histopathologic appearances in cases with mutations of the gene for tau are consistent, the clinical phenotypes across and even within families have varied considerably, suggesting that other factors influence the distribution of pathologic changes within the brain. It is also clear that much remains to be learnt.

Very recently, interest has shifted to cases with ubiquitin-positive pathology, particularly the growing number of familial cases which have all been linked to chromosome 17 (Mackenzie *et al.*, 2006; Van der Zee *et al.*, 2006). Just as the first edition of this book was nearing completion, two groups reported mutations in the gene encoding progranulin, close to but apparently independently of the microtubule-associated protein tau (*MAPT*) gene (Baker *et al.*, 2006; Cruts *et al.*, 2006). Moreover, it seems that progranulin mutations are relatively common as over 30 families were discovered within months of the original discovery. Another recent genetic breakthrough involves the well-known Danish kindred from Jutland. Linkage to chromosome 3 was established in 1993 (Brown *et al.*, 1993) but in 2005 a mutation in the endosomal sorting complex required for transport III (ESCRT-III) complex subunit *CHMP2B* gene was described in affected members

of the family and in one unrelated sporadic Cambridge patient (Skibinski *et al.*, 2005). A recent large-scale screen of 141 familial probands from the USA and UK suggests that in contrast to *MAPT* and progranulin this mutation is extremely rare (Cannon *et al.*, 2006).

The even more recent discovery of the *C9orf72* gene expansion is best considered after discussing the overlap between FTD and MND.

Frontotemporal dementia with motor neuron disease

Although MND has traditionally been regarded as a disorder which spares higher cognitive abilities, it has become clear since early reports from Japan (Mitsuyama and Takamiya, 1979) that the rate of dementia in MND is significantly greater than expected, and conversely a significant minority of patients with FTD develop features of MND (for reviews see Bak and Hodges, 1999; Burrell *et al.*, 2011; Caselli *et al.*, 1993; Lillo *et al.*, 2010, 2011; Neary *et al.*, 1990; Rakowicz and Hodges, 1998). Many patients with the overlap syndrome present with behavioral changes and/or progressive aphasia, which then progresses rapidly, followed by the emergence of bulbar features and mild limb amyotrophy, although the reverse sequence can be seen. Such patients were noted to have prominent neuropsychiatric features including psychosis (Lillo and Hodges, 2010), which is interesting in the context of the *C9orf72* mutation cases.

There is also evidence that patients with the MND-dementia/aphasia complex have disproportionate impairment of verb, compared with noun, knowledge (Bak and Hodges, 1997; Bak *et al.*, 2001), which is pertinent to the hypothesis that some components of the widespread semantic network in the brain are located in or near corresponding sensory/motor areas.

The topic of the degree of overlap between MND and FTD has become one of active investigation. Our studies have suggested that subtle behavioral changes, particularly apathy, are very common in MND and often precede classic motor symptoms (Lillo *et al.*, 2011; Mioshi *et al.*, 2014), and that such symptoms impact significantly on caregiver burden (Lillo *et al.*, 2012). Viewed from the opposite perspective, it appears that perhaps 10–20% of patients with FTD will develop frank MND although a much higher proportion show subtle signs of motor neuron dysfunction; however, the long-term implications of the latter finding remains unclear (Burrell *et al.*, 2011). Chapter 6 provides more detail on this dimension of overlap within the FTD spectrum.

Discovery of the *C9orf72* mutation

The latest piece of the genetics puzzle links FTD to MND. It had been clear that certain families included members suffering from both of these disorders and that the responsible gene was *C9orf72*. In 2011 an exciting discovery was the expansion of a hexanucleotide repeat in the gene *C9orf72*, soon established to be the commonest genetic cause of both FTD and MND (DeJesus-Hernandez *et al.*, 2011; Renton *et al.*, 2011). As well as accounting for a high proportion of familial cases, this mutation appears to be a relatively common cause of cases (perhaps around 5–10%) of apparently sporadic bvFTD (Hodges, 2012). From a clinical perspective, such cases appear atypical in that they may have a slowly progressive or indolent course with prominent psychiatric features and relatively little in the way of brain atrophy (Devenney *et al.*, 2014). These findings beg the question of how many cases with the non-progressive or phenocopy syndrome may turn out to have this expansion.

Corticobasal syndrome

The other clinical syndrome which overlaps considerably with FTD is CBS, originally described as a movement disorder characterized by an asymmetric akinetic-rigid syndrome with prominent apraxia culminating, in some instances, in the striking feature of alien or anarchic hand (Gibb *et al.*, 1989) and associated with a characteristic pattern of tau-positive neuropathology involving basal ganglia and parietal and frontal cortices (Dickson *et al.*, 2002; Feany and Dickson, 1996). It is now clear that cognitive deficits are virtually universal in CBS (Graham *et al.*, 2003a, 2003b). The pattern of dementia fits most closely with PNFA, although frontal-executive deficits are also common (Graham *et al.*, 2003a). One relatively unique feature is the prominence of visuospatial and perceptual deficits not seen in other forms of FTD (Bak *et al.*, 2005, 2006). Another facet of the overlap is that the typical tau-positive CBD neuropathology may be found in patients presenting with FTD syndromes without motor features, at least in the earlier stages of their illness (Mathuranath *et al.*, 2000). To add further to the confusion, it is emerging that some patients with an in vivo diagnosis of CBS may have Alzheimer's disease

neuropathology at autopsy (Boeve *et al.*, 1999; Doran *et al.*, 2003; Schneider *et al.*, 1997; Shelley *et al.*, 2009). It remains unclear whether such patients can be distinguished in life from those without Alzheimer's pathology (Alexander *et al.* 2014; Burrell *et al.*, 2013). Further details on this domain of overlap within the FTD spectrum can be found in Chapter 7.

Conclusions

It should be clear from this overview that research on FTD is flourishing and that the knowledge base is expanding rapidly. Searching PubMed under the terms FTD, FTLD, or Pick's reveals a little over 4000 papers, half of which have been published since the year 2010. Many of the recent papers concern aspects of molecular pathology and genetics but, compared with Alzheimer's disease, a very high proportion of the papers still deal with the neuropsychology of FTD. One of the remarkable facts about the disorder, which makes it so interesting to study from the perspective of behavioral neurology, is the involvement of brain systems involved in social cognition, language, and semantic memory which can be strikingly selective for a number of years. The following chapters now flesh out this outline and review the current status from many different viewpoints.

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