In the past decade there have been enormous advances in our understanding of frontotemporal dementia and related syndromes. The impetus for these advances has come from a number of directions including genetic discoveries, new approaches to neuroimaging and improved neuropsychological understanding of the cognitive aspects of the condition. This book provides a much needed review of the current status of our knowledge of these syndromes.

The book starts with chapters reviewing the history of the condition and describes the presenting clinical, neuropsychiatric and neuropsychological features, before reviewing, in detail, the areas of greatest recent research progress: brain imaging, histopathology and molecular genetics. The book concludes with a chapter proposing a multidisciplinary approach to patient management, with illustrative case studies.

Frontotemporal Dementia Syndromes will be essential reading for neurologists, psychologists, psychiatrists and other clinicians interested in cognitive and behavioural disorders, as well as to basic scientists working in the area of neurodegeneration.

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Frontotemporal Dementia Syndromes

Edited by

John R. Hodges
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Preface

In the past decade there have been enormous advances in our understanding of frontotemporal dementia (FTD). The impetus for these advances has come from a number of directions. First, the discovery in the late 1980s of tau gene mutations in some familial cases of FTD revolutionised the field and led to a huge surge in research related to the genetics and molecular pathology of FTD leading to further genetic discoveries in the past year. Second, the development of neuroimaging techniques – both structural (magnetic resonance imaging; MRI) and functional (18F)-fluorodeoxyglucose-positron emission tomography; FDG-PET) – has contributed to our understanding of the structural and functional changes in FTD syndromes. Third, increasing sophistication of neuropsychological methods has led to many insights into the cognitive aspects of the FTD syndromes. Cambridge has been at the forefront of this research effort with contributions to all major areas. Central to these developments was the specialist FTD clinic at Addenbrooke’s Hospital, which evolved out of the memory disorders clinics, and was established as a formal multidisciplinary service in 1997. This has enabled us to study large cohorts of patients in life with a range of cognitive and neuroimaging methods. We have also been able to collect over 100 brains of patients with young-onset and atypical dementias which has enabled the pathological and molecular work.

Although there have been three books dedicated to FTD (Kertesz and Munoz, 1998; Pasquier et al., 1996; Snowden et al., 1996) these were all completed before the revolutions in molecular pathology and in neuroimaging. Now seems an ideal time to survey the literature. The current multi-contributor book, written entirely by past and present collaborators in Cambridge, has the advantage of coherence but could be criticised for portraying a biased view of the topic. We have attempted to counter this by surveying thoroughly the published literature, a task which is still not too daunting given that there are some 2000 articles (compared with 30 000 on Alzheimer’s disease).

The book is aimed at neurologists, particularly those with an interest in cognitive and behavioural disorders, psychologists and psychiatrists. It should also be of interest to basic scientists working in the area of neurodegeneration.
The first chapter serves as a general introduction, highlighting the original descriptions of these syndromes by Arnold Pick, the evolving terminologies that have been applied by various research groups culminating in the recent consensus criteria and the molecular discoveries, and areas of continuing controversy. The second chapter, by Andrew Graham, covers basic epidemiological aspects of FTD such as prevalence, age of presentation, sex differences, risk factors and survival.

The third chapter forms in many ways the core of the book. Chris Kipps, Jonathan Knibb and I have attempted to describe the presenting clinical and neuropsychiatric features of the three main variants of FTD: frontal or behavioural variant (bv-FTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA). It draws upon our own clinical experience over the past decade of over 300 cases. We have also dealt with features which help to separate these syndromes from other forms of dementia, particularly Alzheimer’s disease, as well as psychiatric disorders.

My colleague Thomas Bak has developed a special interest and expertise in what might be termed “overlap syndromes”, notably corticobasal degeneration, progressive supranuclear palsy and motor neuron disease associated with FTD, which are covered in Chapter 4.

The neuropsychology of FTD has been a topic of major interest in Cambridge and has been at the centre of a research programme led by Karalyn Patterson and myself since the early 1990s. Together we have written Chapter 5, that deals with the clinical aspects of neuropsychology in bv-FTD and the two language variants, SD and PNFA. We have also covered some of the theoretical work based on patients with SD which has been directed towards understanding normal cognitive processes but a full discussion of this extensive body of research seemed beyond the scope of the present book.

Neuroimaging studies, both structural (MRI) and functional (single-photon emission computed tomography (SPECT) and PET), have played a central role in the investigation of FTD syndromes. The combination of cognitive studies with neuroimaging has also contributed significantly to understanding normal brain function. These joint aspects are described in Chapter 6 by Peter Nestor who has been working in Cambridge for the past decade.

Another field that has changed beyond all recognition over the past decade is the neuropathology of FTD. In Chapter 7 Rhys Davies and John Xuereb summarise the histological changes in subtypes of FTD emphasising the distribution of changes drawing on the extensive expertise in Cambridge. In Chapter 8 Laura Gasparini and Maria Spillantini review the fast-moving field of molecular neuropathology beginning with the discovery of tau gene mutations in the late 1990s through to recent findings related to ubiquitin-positive inclusion cases.
The management of patients with FTD requires a multidisciplinary approach. Genetic aspects are of great concern to many families. This important topic is dealt with by Jerry Brown in Chapter 9. More general management including control of problem behaviours and support of caregivers is covered by Sinclair Lough and Vanessa Garfoot in the final chapter.

The book would not have been possible without the contribution of many other colleagues and collaborations over the past 15 years. Of particular note are the series of exceptional research fellows: John Greene, Tom Esmonde, Peter Garrard, Richard Perry, Adam Zeman, Tom Bak, Cath Mummery, Clare Galton, Siân Thompson, Shibley Rahman, Peter Nestor, Rhys Davies, Andrew Graham, Chris Kipps, Jonathan Knibb, Paul McMonagle and George Pengas. We have also been blessed with overseas visitors who have contributed to the research effort, notably Pavagada Mathuranath, Ellajosyula Ratnavalli, Suvarna Alladi, Shelley Bhaskara, Facundo Manes, Joseph Spatt, Manabu Ikeda and Adrian Ivanoiu.

At the MRC–CBU Karalyn Patterson has been a constant source of inspiration and guidance. We have had the good fortune to work with outstanding cognitive neuropsychologists: Naida Graham was our first research assistant and later PhD and postdoctoral student. She was later joined by Sasha Bozeat, Raymond Knott, Karen Croot, Jon Simons, Eamon Strain, Helen Bird, Marion Kellenbach, Linda Clare, Anna Adam, Fiona Clague, Anna Woollams, Robert Dudas, Eneida Mioshi and Samrah Ahmed. We have had too many research assistants to mention them all but Sharon Davies (Erzinclioglu) has provided very long-term support and has been key in establishing our FTD carer support group. Kim Graham, Matt Lambon-Ralph and Tim Rogers deserve special recognition as long-term colleagues who have contributed a great deal to theoretical understanding of FTD.

The memory clinic was co-founded by German Berrios who has helped a great deal with an historical perspective and to realise how transient any contemporary views of medicine really are. Our clinical neuropsychologists – Kristin Breen, Diana Caine, Aidan Jones and Narinder Kapur – have continued my education on all things psychological. The FTD clinic was established with Carol Gregory and Sinclair Lough and has continued with Vanessa Garfoot. Kate Dawson has been a constant support to myself, the rest of the team and many hundreds of patients’ families. Lynne McDonald, the Cambridge early-onset dementia nurse, also strives to help local families. Alison Yorke has provided fantastic secretarial support to the clinics.

The pathological side of our work would not have been possible without John Xuereb and Angela O’Sullivan and her outstanding humanity in dealing with sufferers and their families. In addition, the neuropathological studies have benefited enormously from collaboration with colleagues in Sydney, notably Glenda Halliday and Jillian Kril. The imaging was conducted in collaboration with
members of the MRI department at Addenbrooke’s Hospital (Nagui Antoun) and the Wolfson Brain Imaging Centre (John Pickard, Adrian Carpenter and Tim Fryer).

The Medical Research Council has supported my work by means of project and programme grants and fellowships since 1991. We have also been funded by the Wellcome Trust, The Medlock Trust and the Alzheimer’s Research Trust.

Last, but not least, my secretary at the MRC–CBU Margaret Tillson has endured many re-draftings of the book with constant good grace and humour.

