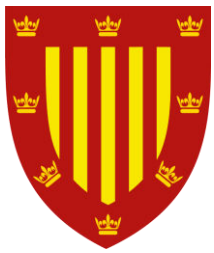
# Apathy and Impulsivity in Frontotemporal Lobar Degeneration

Ian Trevor Stuart Coyle-Gilchrist



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# Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the relevant Degree Committee.

# Apathy and Impulsivity in Frontotemporal Lobar Degeneration

**Ian Coyle-Gilchrist**

Frontotemporal Lobar Degeneration (FTLD) is pathologically heterogeneous group of degenerative diseases of the brain. While there are distinct and highly recognisable clinical syndromes associated with FTLD there is also a wider and more diverse spectrum of progressive changes in movement, coordination, language and behaviour. Correlation between clinical syndrome and pathology is variable. Furthermore, over the course of an individual's illness their syndrome may change, or they may present with features of more than one syndrome at a given time. Apathy and Impulsivity are common, distressing and disabling across the entire spectrum of FTLD and may be particularly prominent compared to other neurodegenerative diseases.

In this thesis I outline the current classification of syndromes associated with FTLD and how this has undergone expansion, refinement and fragmentation over time. Despite changes in nosology and advances in understanding of pathological heterogeneity, I argue that the clinical syndrome of FTLD is highly recognisable and has been described for centuries. I suggest that a more unifying transdiagnostic approach to FTLD may provide useful insights into an increasingly fragmented spectrum of disease.

Using this approach I conducted a large epidemiological study of FTLD and report prevalence, incidence and lifetime risk estimates. From this cohort of recruits I then surveyed patients and their carers and used a range of assessments of cognition and behaviour. I showed that while reports of apathy and impulsivity are common in FTLD, patient and carer based reports do not correlate well with each other or predict performance on a range of behavioural measures of decision making or goal directed cognition. I conclude that in FTLD, apathy and impulsivity are overlapping and multidimensional constructs and that no single testing modality used in isolation represents them completely, hence a multimodal approach to their assessment is required.

This thesis is dedicated to my father, Nicholas John Coyle-Gilchrist who I think would have been both proud and amused to have his name in Cambridge University Library, and to Coney who wouldn't have cared a jot.

# Preface

The work presented is my own, as are any mistakes or omissions. However I am grateful for the contribution of:

Chapter One. Jack Eckert of Havard Medical School for assistance tracing the author of the original article by S. Pinel as translated by W. Costello.

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Chapter Four. Eileen Wehmann recruited healthy control subjects and collected data from them. Patricia Vázquez Rodríquez, Alicia Wilcox, Katrina Dick, Claire Lansdall, Julie Wiggins and Eileen Wehmann assisted in data collection and entry from patient subjects.

Chapter Five. Eileen Wehmann recruited healthy control subjects and collected data from them. Patricia Vázquez Rodríquez, Alicia Wilcox, Katrina Dick, Claire Lansdall, Julie Wiggins and Eileen Wehmann assisted in data collection and entry from patient subjects.

The work from Chapter Two on the epidemiology of Frontotemporal Lobar Degeneration has been published:

Coyle-Gilchrist ITS, Dick KM, Patterson K, Vázquez Rodríquez P, Wehmann E, Wilcox A, et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology. 2016 May 3;86(18):1736–43.

The data I collected in this study have been used in further research which has been published:

Zhang J, Rittman T, Nombela C, Fois A, Coyle-Gilchrist I, Barker RA, et al. Different decision deficits impair response inhibition in progressive supranuclear palsy and Parkinson's disease. Brain. 2016 Jan;139(1):161–73.

Lansdall CJ, Coyle-Gilchrist ITS, Jones PS, Vázquez Rodríguez P, Wilcox A, Wehmann E, et al. Apathy and impulsivity in frontotemporal lobar degeneration syndromes. Brain. 2017 Jun 1;140(6):1792–807.

Lansdall CJ, Coyle-Gilchrist ITS, Jones PS, Vázquez Rodríguez P, Wilcox A, Wehmann E, et al. White matter change with apathy and impulsivity in frontotemporal lobar degeneration syndromes. Neurology. 2018 Mar 20;90(12):e1066–76.

Lansdall CJ, Coyle-Gilchrist ITS, Vázquez Rodríguez P, Wilcox A, Wehmann E, Robbins TW, et al. Prognostic importance of apathy in syndromes associated with frontotemporal lobar degeneration. Neurology. 2019 Apr 2;92(14):e1547–57.

Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain. 2019 Jun 1;142(6):1503–27.

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The PSP Association, FTD Support Group and local patient support groups have all helped raising the profile of the PiPPIN study and supported recruitment. This work was made possible through funding from the NIHR Cambridge Dementia Biomedical Research Centre and Biomedical Research Unit in Dementia; the Wellcome Trust, the PSP Association; Alzheimer Research UK; The Evelyn Trust for which I am extremely grateful.

I owe great thanks to my mother, Elizabeth, brothers Matthew and Alasdair and my wife Lorraine.

None of this work would be possible without the great contribution of the patients and their families who volunteered for this study. I continue to be in awe of their stoicism and dignity when faced with these ghastly diseases.

# Contents

# Abbreviations

| | |
|---|---|
| **ACE-R** | Addenbrooke's Cognitive Examination –Revised |
| **AD** | Alzheimer's Disease |
| **AES-C** | Apathy Evaluation Scale, Clinician version |
| **AES-I** | Apathy Evaluation Scale, Informant version |
| **AES-S** | Apathy Evaluation Scale, Subject version |
| **bvFTD** | behavioural variant Frontotemporal Dementia |
| **BDI-II** | Beck Depressive Inventory II |
| **BIS** | Barratt Impulsiveness Scale |
| **BIS/BAS** | Behavioural Inhibition System/Behavioural Activation System |
| **CBD** | Corticobasal Degeneration |
| **CBI-R** | Cambridge Behavioural Inventory –Revised |
| **CBS** | Corticobasal syndrome |
| **CBS-NAV** | Corticobasal Syndrome -Nonfluent/Agrammatic Variant |
| **CBS-FBS** | Corticobasal Syndrome -Frontal Behavioural-spatial Syndrome |
| **CBS-PSPS** | Corticobasal Syndrome–Progressive Supranuclear Palsy Syndrome |
| **CGT** | Cambridge Gambling Task |
| **CRRT** | Cued Reinforcement Reaction Time task |
| **C9ORF72** | Chromosome 9 Open Reading Frame 72 |
| **ESP2013** | The 2013 European Standard Population |
| **FAB** | Frontal Assessment Battery |
| **FRS** | Frontotemporal Dementia Rating Scale |
| **FTD** | Frontotemporal Dementia |
| **FTD-MND** | Frontotemporal Dementia with Motor Neuron Disease |
| **FTLD** | Frontotemporal Lobar Degeneration |
| **FUS** | Fused in Sarcoma |
| **GCRD** | Go Correct Right Direction |
| **GCWD** | Go Correct Wrong Direction |
| **GIRD** | Go Incorrect Right Direction |
| **GIWD** | Go Incorrect Wrong Direction |
| **GPI** | Generalised Paresis of the Insane |
| **IMCA** | Independent Mental Capacity Advocate |
| **IST** | Information Sampling Task |
| **LPA** | Logopenic Progressive Aphasia |
| **lvPPA** | logopenic variant Primary Progressive Aphasia |

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|---|---|
| **MAPT** | Micotubule-associated protein Tau |
| **MEI** | Motivation and Energy Inventory |
| **MND** | Motor Neuron Disease |
| **navPPA** | nonfluent/agrammatic variant Primary Progressive Aphasia |
| **NC** | Nogo Correct |
| **NI** | Nogo Incorrect |
| **NINDS-SPSP** | National Institute of Neurological Disorders and Stroke neuropathologic criteria for the diagnosis of PSP |
| **NNIPPS** | Neuroprotection and Natural History in Parkinson Plus Syndromes |
| **NPI-Q** | Neuropsychiatric Inventory –Questionnaire |
| **OCI-R** | Obsessive Compulsive Inventory-Revised |
| **ONS** | Office for National Statistics |
| **PAGF** | Pure Akinesia with Gait Freezing |
| **PD** | Parkinson's Disease |
| **PDSS** | Parkinson's Disease Sleep Scale |
| **PNFA** | Progressive Non Fluent Aphasia |
| **PPA** | Primary Progressive Aphasia |
| **PPAOS** | Primary Progressive Apraxia of Speech |
| **PGRN** | Progranulin |
| **PSP** | Progressive Supranuclear Palsy |
| **PSP-C** | Progressive Supranuclear Palsy-Cerebellar Ataxia, |
| **PSP-CBS** | Progressive Supranuclear Palsy with predominant Corticobasal Syndrome |
| **PSP-F** | Progressive Supranuclear Palsy with predominant Frontal presentation |
| **PSP-OM** | Progressive Supranuclear Palsy with predominant Ocular Motor dysfunction |
| **PSP-P** | Progressive Supranuclear Palsy with predominant Parkinsonism |
| **PSP-PAGF** | Progressive Supranuclear Palsy –Pure Akinesia with Gait Freezing |
| **PSP-PGF** | Progressive Supranuclear Palsy with Progressive Gait Freezing |
| **PSP-PLS** | Progressive Supranuclear Palsy-Primary Lateral Sclerosis, |
| **PSP-PI** | Progressive Supranuclear Palsy with predominant postural instability |
| **PSP-PNFA** | Progressive Supranuclear Palsy –Progressive Non Fluent Aphasia |
| **PSP-RS** | Progressive Supranuclear Palsy Rating Scale |
| **PSP-RS** | Progressive Supranuclear Palsy –Richardson's Syndrome |
| **PSP-SL** | Progressive Supranuclear Palsy with predominant Speech/Language disorder |
| **SHAPS** | Snaith Hamilton Anhedonia Pleasure Scale |
| **SSD** | Stop Signal Delay |
| **SSRT** | Stop Signal Reaction Time |

| | |
|---|---|
| **SST** | Stop Signal Task |
| **svPPA** | semantic variant Primary Progressive Aphasia |
| **TARDBP** | Transactive response DNA binding protein |
| **TDP-43** | Transactive Response Deoxyribonucleic acid binding Protein 43kDA. |
| **TREM2** | Triggering Receptor Expressed on Myeloid Cells 2. |
| **VAS** | Visual Analogue Scales |
| **VBM** | Voxel Based Morphometry |

# Chapter One

# The Syndromes of Frontotemporal Lobar Degeneration

## 1.1 Summary

In this chapter I describe the spectrum of clinical syndromes associated with Frontotemporal Lobar Degeneration (FTLD). Using a historical perspective I describe how the nosology associated with progressive frontotemporal syndromes has undergone expansion, refinement and fragmentation over time as clinical, pathological and genetic discoveries have been made. I outline the current diagnostic criteria for individual syndromes and argue that a more unifying transdiagnostic approach to FTLD-associated syndromes may provide useful insights into an increasingly fragmented spectrum of disease. I then outline how in subsequent chapters I have done this in the PiPPIN study of both the epidemiology of syndromes associated with FTLD and of neuropsychiatric aspects of FTLD, namely apathy and impulsivity.

## 1.2 Frontotemporal Lobar Degeneration

Frontotemporal Lobar Degeneration (FTLD) is a heterogeneous group of pathologically defined neurodegenerative disorders where progressive changes in language, behaviour and movement are accompanied by relatively selective degeneration of the frontal and temporal lobes(1), neuronal loss and abnormal accumulation of proteins, such as microtubule-associated protein Tau, Transactive response DNA-binding Protein with molecular weight 43 kDA (TDP-43) and Fused in Sarcoma protein (FUS)(2). The clinical syndromes associated with FTLD include cognitive disorders, where progressive deterioration in language and behaviour dominate the clinical picture (Frontotemporal dementia, FTD) and those where additional movement disorders such as dystonia, Parkinsonism, instability and apraxia are present (Progressive Supranuclear Palsy, PSP and Corticobasal Syndromes/Degeneration, CBS/CBD)(3).

A minority of cases can be attributed to highly penetrant inherited genetic mutations allowing confident molecular diagnosis in the absence of pathological examination of the brain. However, the majority of cases are diagnosed clinically based on clinical symptoms and neuroimaging correlates(4). In those cases that reach post mortem brain examination, clinico-pathological correlates are highly variable both within the spectrum of FTLD and beyond, where other non-FTLD pathologies (such as Alzheimer's Disease, AD) can mimic the clinical features of

FTLD(5–7). In addition to this advances in clinical genetics, improved access to genetic testing and post mortem brain examination have identified patients with FTLD pathology who presented in an atypical fashion with clinical syndromes less typically associated with FTLD(7–9).

In order to facilitate accurate clinical diagnosis and a framework for research into FTLD (and associated clinical syndromes) a number of different clinical diagnostic criteria have been devised and subsequently revised(10–13). The terminology and nosology of these disorders has changed several times (and continues to do so) resulting in somewhat fragmented classification systems based on clinical, genetic or pathological approaches with highly variable correlations between them(14). Despite this the syndromes associated with FTLD share distinctive traits that have been recognised for centuries.

Behavioural changes, particularly apathy and impulsivity, are common across the entire spectrum of FTLD and a significant source of distress and morbidity(15,16). While these symptoms are also seen in other more common conditions (such as typical AD) the prevalence and prominence of apathy and impulsivity in FTLD makes this an attractive cohort in which to study them, recognising that any insights gained within FTLD may translate to advances in a much wider range of disorders. Apathy and impulsivity are not however simple unitary entities but are complex and multifaceted constructs(17). The causes of apathetic behaviour in one subject may be quite different from another. Rather than studying these symptoms in a small subgroups of subjects with similar clinical phenotypes, by taking a transdiagnostic approach and exploring apathy/impulsivity within the entire spectrum of syndromes associated with FTLD it may be possible to exploit syndromic heterogeneity to facilitate exploration of the multiple mechanisms of common behavioural symptoms.

### 1.3 Historical Descriptions of Progressive Frontotemporal Syndromes

The first descriptions of degenerative conditions affecting frontotemporal areas are often attributed to Arnold Pick. In 1892 he described a 71 year old man who presented with two years' progressive deterioration in language, movement and behaviour which he attributed to 'senile' shrinkage of frontal and temporal lobes(18). He also described a deterioration in memory and shaking of the patient's hand that prevented writing. At postmortem, in addition to meningeal thickening and oedema there was left sided cerebral atrophy, particularly of the temporal lobe. The main emphasis of Pick's report was of the occurrence of language dysfunction in senile atrophy. He makes the distinction between senile atrophy and cases of progressive paresis of the insane where he notes similar clinical features may exist.

Pick also makes reference to a previous report of language disruption in senile atrophy by William Bevan-Lewis(18,19). Bevan-Lewis described a 52-year-old man who developed progressive deterioration in language and behaviour with abnormal eye movements and progressive paralysis who had a strong family history of behavioural disorders (two twin sisters were also resident in the same asylum as the patient where their paternal aunt had also cut her own throat). Jerky movements of the arms, head and neck were noted prior to and during his admission and partial and secondary generalised seizures occurred until his death around two years after first seeking medical attention. At postmortem asymmetric frontal brain atrophy was noted extending posteriorly to involve the parietal lobe. Like Pick, Bevan-Lewis attributes his case to senile atrophy, which he considers distinct to Generalised Paresis of the Insane(19).

The term Generalised Paresis of the Insane (GPI) is now reserved for cases of neurosyphilis. However, in the early 19th century, GPI was also used to describe a range of different syndromes and pathologies. While Bevan-Lewis and Pick are careful to consider senile atrophy a distinct pathological process this may not have been the case in earlier literature.

In 1846 in the Medical Times(20) there is a report of a case of generalized paresis of the insane with similar clinical features and brain atrophy at post mortem: A 37-year-old woman who was admitted to the Salpêtrière hospital in 1834 in a 'state of manical agitation'. Having previously led 'an exemplary and religious life' she is described as abandoning herself to 'dissolute and disorderly habits, and to drinking'. Her syndrome evolved over months into a 'paralytic numbness', which gave an 'expression of stupidity to her countenance'. Her language was affected such that her speech was slow, inarticulate, with a stuttering quality and mild anomia. Emotional lability was described with 'frequent fits of passion' but she is otherwise described as 'unconscious of her state, and 'continually sitting'. In just over a year she died. At postmortem an area of acute cerebral haemorrhage was identified as the terminal event but the author also notes atrophy of the frontal lobes.

The most remarkable aspect of this report is the final statement "This local atrophy of certain convolutions coinciding with the progression of the general paralysis and demency is of considerable interest". This case report, translated by William Costello (1800-1867) was attributed to Philippe Pinel (1745-1826) but it was almost certainly the work of his son Scipion (1795-1859). Remarkably he makes the connection between focal brain atrophy and a syndrome of progressive behavioural changes and speech disturbance.

In 1834 GPI was a relatively new diagnostic entity. Antoine Bayle compiled descriptions of a number of cases and used them to support his 1822 thesis that insanity and paresis may be

caused by an organic lesion of the brain. Although prior descriptions of the syndrome exist, Bayle's contribution consolidated it as a distinct clinical entity(21). Over the subsequent century further descriptions of GPI led to a broadening of the clinical syndrome (phenotype) and the associated aetiology such that by 1912 a wide range of causes of GPI had been described including; sexual excess, syphilis, isolation, trauma, post infectious, alcoholism, pellagra and inherited causes(22). A year later, in 1913 Hideyo Noguchi and Joseph Moore demonstrated the presence of spirochaetes in 12 of 70 paretic brains(23). From then on syphilis was considered the major underlying cause of GPI and now GPI is used exclusively to describe specific forms of neurosyphilis. Prior to this whilst the prevalence of syphilis in the general population was so high that syphilis was a common cause of the clinical syndrome, not all those diagnosed as having GPI would not necessarily have been suffering from neurosyphilis and other conditions (including FTLD) may have been the cause.

The progressive changes in behaviour, language and motor function are similar in Pick, Bevan-Lewis, and Pinel's cases. All three make the connection between the clinical syndrome and brain atrophy and in all three cases, atrophy is most marked in frontotemporal regions. It is difficult to make firm conclusions as to the underlying pathological aetiology of their cases on the basis of the limited post mortem information they provide. It seems likely that Pick and Bevan-Lewis's would have had sufficient experience with GPI caused by neurosyphilis (despite the underlying aetiology not being established at time) to recognise that their cases were different. Meningeal thickening in Pick's case does suggest that an infectious or inflammatory pathology (such as neurosyphilis) may have been a factor. The strong family history in Bevan-Lewis's case is suggestive of an inherited cause but not definitive. Spontaneous intracerebral bleeding in Pinel's case is unusual in a woman in her 30's and is highly suggestive of a vascular pathology. Given the prevalence of syphilis at the time a syphilitic vasculopathy in the setting of typical features of GPI seems likely. Frontotemporal lobar atrophy alone does not discriminate between a degenerative cause or neurosyphilis and has been reported in modern cases of microbiologically proven neurosyphilis with atrophy of frontotemporal lobes demonstrated on neuroimaging(24).

### 1.4 Pick's Disease, Frontotemporal Dementia and FTLD

Alois Alzheimer demonstrated the first positive evidence of a neurodegenerative disease (as opposed to absence of features of an alternative aetiology) in progressive frontotemporal syndromes. He described microscopic inclusions (that would later be known as 'Pick bodies') in the brains of some patients with a similar syndrome to those in Pick's reports who also had frontotemporal brain atrophy. Hence the condition became known as 'Pick's Disease'.

Subsequently it became apparent that not all cases of the syndrome Pick described had the same histopathological changes and hence when interest in these conditions resurfaced in the 1980s the term 'Frontotemporal Dementia (FTD)' was adopted with 'Pick's disease' being redefined to describe only those cases in which Pick bodies are present (25).

Just as with 'Generalised Paresis of the Insane' and 'Pick's disease', the aetiological and phenotypic associations of the term 'Frontotemporal Dementia' are evolving. Renewed interest in the cognitive syndromes associated with FTLD has led to syndromic subdivisions of behavioural variant FTD (bvFTD), where behavioural changes are the dominant early clinical features and the Primary Progressive Aphasias (PPA), where language disruption predominates(25). The Primary Progressive Aphasias have been subject to further subdivision based on the particular presentation of language dysfunction(11). While initially the emphasis of early work was focused on the cognitive aspects of FTD, the motor aspects alluded to in Pick and Bevan-Lewis's descriptions are now being incorporated in descriptions of FTD, including the overlap with Motor Neuron Disease (MND) and also with extrapyramidal syndromes such as Progressive Supranuclear Palsy (PSP) and Corticobasal Syndrome/Degeneration (CBS/D) which may share the language and behavioural aspects along with additional movement disorders(26).

Pick's disease remains a recognised neuropathological entity but other neuropathological diagnoses have also been described within the brains of patients with these clinical syndromes. Inclusions of various forms of hyperphosporylated Tau (including Pick's disease), TDP-43, and rarer pathologies e.g. FUS, have been grouped together under the 'umbrella' term Frontotemporal Lobar Degeneration (FTLD)(27). It is also recognised that non-FTLD pathology, such as AD, can produce similar clinical syndromes(7).

While such cases may be diagnosed clinically as having an FTLD-associated syndrome during life (e.g. CBS or PPA), the term FTLD is usually reserved to describe particular non-AD forms of neurodegeneration most typically associated with FTD, PSP or CBS (i.e. as a description of a pathologically, rather than syndromically, defined entity). The relationships between clinical phenotype and the underlying pathology are complex. For example less than two thirds of cases of Corticobasal Syndrome (CBS) are related to Corticobasal Degeneration at post-mortem (CBD, a specific neuropathological pattern of cellular changes and Tau deposition) (7) Conversely less than two thirds of people with CBD pathology at post mortem have CBS during life, the others having a clinical syndrome more commonly associated with a another form of FTLD(7).

### 1.5 Genetic Forms of FTLD and the Problem of Pleiotropy

While most cases of FTLD occur sporadically a significant minority can be attributed to genetic mutations that are inherited in an autosomal dominant fashion (usually with high penetrance) allowing confidence in pathological diagnosis even in the absence of pathological examination of brain tissue. However, even when a genetic mutation is identified its relevance and relationship to clinical syndrome is not always straightforward – a single genetic mutation may be associated with widely different clinical syndromes, a phenomenon known as pleiotropy.

For example, C9ORF72, a hexanucleotide expansion that can cause FTD, MND, or both, within a single family was first reported in two papers in 2011(28,29). How the same mutation may result in very different phenotypes even within a single pedigree is unclear. Variability and instability of expansion length, other genetic and environmental modifiers or the presence of comorbidities/pathological processes affecting neurodegeneration and inflammation have all been proposed as potentially contributing to clinical phenotype (30). Some studies suggest C9ORF72 may exhibit anticipation over generations(31) but this, and the penetrance of the mutation remains unclear(32).

The discovery of C9ORF72 is also contributing to our understanding of the wider spectrum of FTLD and other disease entities previously thought separate to FTLD. Amongst patients with FTD (or MND) there appears to be increased rates of psychosis amongst carriers of C9ORF72 expansions (33). This has led to some groups screening cohorts of patients with psychiatric diagnoses for C9ORF72 finding large expansions in (for example) patients diagnosed with schizophrenia(34). What role C9ORF72 has in these patients is not clear but this challenges the distinction between neurodegenerative and psychiatric diagnoses (at least in some patients) and also raises the possibility that some cases of bvFTD may be missed in the early symptomatic stages particularly as current bvFTD criteria exclude cases where psychiatric diagnoses are thought more likely to account for behavioural disturbance(35).

### 1.6 The FTD-Phenocopy Syndrome

When interest in FTD resurged in the 1980s a number of people (mainly men) were diagnosed as having FTD but who did not develop typical brain atrophy on imaging and subsequent did not deteriorate in the rapid fashion of more typical FTD(36). When this became apparent these patients were reclassified as 'phenocopies' the presumption being that they did not have FTD but an acute psychiatric episode or decompensation of premorbid psychosocial factors. As these cases remained relatively well for a long period of time they may have been overrepresented in previous studies of FTD. As a consequence the clinical research criteria for FTD were changed so

such cases are excluded(35). However, recently some slowly progressive cases of FTD have been tested and found to carry extremely large repeats in the C9ORF72 gene(37). Only one of 16 phenocopy patients in a very long term follow up study of the genotyped Cambridge phenocopy cohort had a C9ORF72 expansion(38). It is no longer clear how such cases should be classified. It is conceivable that C9ORF72 may produce changes in personality long before the more florid appearance of clinical FTD or that progression in some cases is particularly slow but it also entirely possible for people carrying C9ORF72 to acquire psychiatric or behavioural disorders quite independently. Also, where there is a family history of FTD, the effects of living with a parent with FTD on a child's upbringing and subsequent psychological state in adulthood can not be completely ignored regardless of whether they have inherited the gene or not. In addition eleven of 7,579 (0.15%) of the UK 1958 birth cohort who do not have a clinical diagnosis of neurodegenerative disease were found to have large expansions in C9ORF72(39) raising the possibility of incomplete penetrance by this age.

### 1.7 Current Classification of FTLD Associated Syndromes

The major syndromes commonly associated with FTLD type pathology are shown in Figure 1.1. Not all syndromes are encompassed fully by the current consensus diagnostic criteria. In the following sections I outline the main characteristics of these syndromes with reference to current diagnostic criteria when applicable.

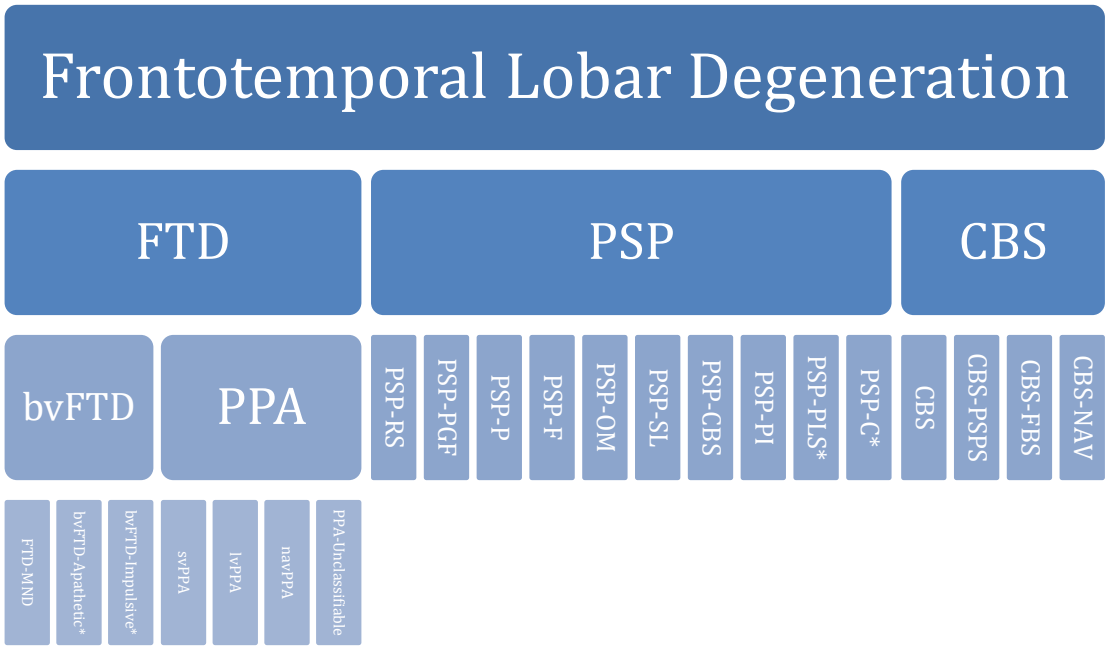



**Figure 1.1 The Clinical Syndromes Associated With Frontotemporal Lobar Degeneration.** FTD=Frontotemporal Dementia, FTD-MND=Frontotemporal Dementia-Motor Neurone Disease, bvFTD=behavioural variant Frontotemporal Dementia, PPA=Primary Progressive Aphasia, svPPA=sematic variant Primary Progressive Aphasia, lvPPA=logopenic variant Primary Progressive Aphasia, navPPA=non fluent agrammatic variant Primary Progressive Aphasia, PSP=Progressive Supranuclear Palsy, PSP-RS=Progressive Supranuclear Palsy with Richardson's Syndrome, PSP-PGF=Progressive Supranuclear Palsy with Progressive Gait Freezing, PSP-P= Progressive Supranuclear Palsy with predominant Parkinsonism, PSP-F= Progressive Supranuclear Palsy with predominant Frontal presentation , PSP-OM=Progressive Supranuclear Palsy with predominant Ocular Motor dysfunction, PSP-SL=Progressive Supranuclear Palsy with predominant Speech/Language disorder, PSP-CBS= Progressive Supranuclear Palsy with predominant Corticobasal Syndrome, PSP-PI= Progressive Supranuclear Palsy with predominant postural instability, PSP-PLS=Progressive Supranuclear Palsy-Primary Lateral Sclerosis*, PSP-C=Progressive Supranuclear Palsy-Cerebellar Ataxia*, CBS=Corticobasal Syndrome, CBS-PSPS=Corticobasal Syndrome-Progressive Supranuclear Palsy Syndrome, CBS-FBS= Corticobasal Syndrome-Frontal Behavioural-spatial Syndrome, CBS-NAV= Corticobasal Syndrome-Nonfluent/Agrammatic Variant.

*Not currently encompassed in current diagnostic criteria.

### 1.7.1 Subclassification of FTD by Clinical Syndrome

Behavioural variant Frontotemporal dementia (bvFTD) is characterised by a progressive change in personality and/or behaviour associated with neurodegeneration of the frontal and temporal lobes. Snowden et al separate bvFTD into those who present with predominantly disinhibited, impulsive and perseverative behaviour and those who show more apathetic and demotivated behavioural changes(40). While both groups of symptoms are encompassed by the recently revised diagnostic criteria(10) the current criteria have not sought to define distinct subtypes on the basis of syndrome alone.

Consensus criteria have recently been proposed for PPA(11). These firstly establish a core set of criteria required for PPA stating that language dysfunction and aphasia should be the dominant clinical features and cause of day-to-day impairment. A second set of criteria is proposed to separate PPA into nonfluent/agrammatic variant (navPPA, also known as Progressive Non Fluent Aphasia, PNFA and PPA-agrammatic) characterised by slow effortful speech and agrammatism, semantic variant (svPPA, also known as Semantic Dementia, SD, and PPA-semantic) where semantic knowledge, word and object recognition are impaired, and logopenic variant (lvPPA, also known as Logopenic Progressive Aphasia, LPA and logopenic PPA) where word retrieval and sentence repetition deficits dominate. They recognise that it is not possible to sub classify every case of PPA and suggest the term PPA-unclassifiable is used.

A fourth group of progressive speech disorder, Primary Progressive Apraxia of Speech (PPAOS) has been proposed(41) where the dominant problem is of a progressive disorder of the motor planning of speech. Josephs et al argue that as the dominant problem in PPAOS is one of a progressive disorder of motor planning as opposed to an aphasia *per s*e(42) such cases do not meet inclusion under the core consensus criteria for PPA and therefore PPAOS should be considered a distinct neurodegenerative syndrome. While this is a convincing argument, by the same reasoning svPPA could be considered separate as the dominant deficit appears to be a disorder of concepts(43) where the patient's processing of semantic information is selectively impaired. While such deficits may be most apparent initially during speech and communication they are not limited to language and a patient may not, for example, recognise a spoon either when trying to name it or when trying to use it. Such deficits have a profound effect on language and communication but by Josephs et al's reasoning also do not necessarily meet criteria for PPA. Interestingly the same group have subsequently reported that all cases of PPAOS that they have followed up have subsequently progressed to develop an extrapyramidal syndrome with features reminiscent of PSP and CBS(42).

FTD may occur in isolation or in association with Motor Neuron Disease (MND). Typically when FTD is associated with MND (FTD-MND) the cognitive syndrome is associated with more behavioural than language change but the particular subtype of MND varies (for example whether it presents initially with limb or bulbar features) (44).

### 1.7.2 Subclassification of PSP Syndromes

Progressive Supranuclear Palsy in its classic form is a predominantly axial akinetic rigid syndrome, with prominent postural instability, supranuclear upgaze palsy, falls and without tremor or responsiveness to Levodopa. This is sometimes referred to as Steele-Richardson-Olzewski syndrome (or PSP-Richardson's Syndrome, PSP-RS). Seven of the original nine cases described had major cognitive and behavioural problems, although for many years, PSP has been regarded as primarily a movement disorder. This position is changing.

The 1996 National Institute of Neurological Disorders and Stroke neuropathologic criteria for the diagnosis of PSP (NINDS-SPSP) are a set of criteria devised for the diagnosis of PSP-RS(45) separating possible and probable cases on the basis of the clinical features and time from disease onset taken to develop them. Falls within the first year of onset were required for a probable diagnosis although this has subsequently been relaxed to postural instability or falls within three years in the subsequent NNIPPS (Neuroprotection and Natural History in Parkinson Plus Syndromes) criteria(13). Marked asymmetry or features of CBS are considered mandatory exclusion criteria under both sets for a diagnosis of PSP.

However, additional syndromic variants of PSP pathology were later described including; Pure Akinesia with Gait Freezing (PAGF, PSP-PAGF), where during the initial course of the illness akinesia and freezing of gait are the dominant features without necessarily those associated with PSP-RS; PSP-Parkinsonism (PSP-P), where features are more reminiscent of idiopathic Parkinson's disease; PSP-Corticobasal Syndrome (PSP-CBS) and PSP-Progressive Non Fluent Aphasia (PSP-PNFA), which combine features of PSP-RS with features of CBS and navPPA respectively(46). Indeed, cognitive and behavioural phenotypes make up half of the presentations of PSP pathology(47).

Most recently consensus criteria (the 2017 Movement Disorder Society PSP Criteria, MDS-PSP(48)) have been proposed. There are three principal features of these criteria. First, they introduce four levels of certainty – from definite pathology proven, to probable, possible and finally 'suggestive of'. Second, they introduce clearer operational definitions for the clinical features and adjunctive investigations, supporting diagnosis. Third, and most importantly for my

work, they introduce a set of criteria for PSP associated phenotypes other than Richardson's syndrome.

The 2017 MDS-PSP criteria incorporate clinical features described amongst subjects with PSP with at post mortem into four clinical domains (ocular motor dysfunction, postural instability, akinesia and cognitive dysfunction) and describe eight clinical syndromes associated with PSP type pathology (Progressive Supranuclear Palsy with Richardson's Syndrome PSP-RS, Progressive Supranuclear Palsy with Progressive Gait Freezing PSP-PGF, Progressive Supranuclear Palsy with predominant Parkinsonism PSP-P, Progressive Supranuclear Palsy with predominant Frontal presentation PSP-F, Progressive Supranuclear Palsy with predominant Ocular Motor dysfunction PSP-OM, Progressive Supranuclear Palsy with predominant Speech/Language disorder PSP-SL, Progressive Supranuclear Palsy with predominant Corticobasal Syndrome PSP-CBS, Progressive Supranuclear Palsy with predominant postural instability PSP-PI) each with different levels of diagnostic certainty and likely association with PSP type pathology. In these criteria the concept of '4R-tauopathy' is introduced whereby no attempt is made to distinguish between pathologically defined PSP and CBD clinically for some syndromes (such as PSP-SL and PSP-CBS).

### 1.7.3 Subclassification of CBS Syndromes

Corticobasal Syndrome is a term used to describe an asymmetric syndrome of progressive limb rigidity, akinesia and apraxia which may be accompanied by cortical sensory deficits, dystonia and alien limb phenomena(12). Corticobasal Degeneration (CBD) (and the obsolete term Cortico-basal-ganglionic-Degeneration) were once synonymous with CBS but is increasingly used as a neuropathological diagnosis only - characterised by tau pathology with specific glial and neuronal distribution(7) – leaving CBS for the clinical disorder. CBS/CBD are highly heterogeneous, with early criteria sometimes incompatible with each other. For example, Lang(49) vs. Kumar(50), on whether Dementia was an exclusion criterion, or was the most common clinical presentation.

Like the criteria for PPA a recent set of criteria for CBS(12) has proposed a core set of clinical features (limb rigidity, akinesia, apraxia, cortical sensory loss myoclonus and alien limb phenomena) at least some of which are required for the diagnosis of either Probable CBS or Possible CBS. Syndromic variants are then defined by the presence of additional features: Where features of navPPA are present in addition to core CBS features the term Nonfluent/Agrammatic variant of PPA (CBS-NAV) is used; The term Corticobasal Syndrome - Frontal Behavioural-Spatial syndrome (CBS-FBS) defines cases where CBS features are present

with additional executive dysfunction, behavioural or personality changes and/or visuospatial deficits; Corticobasal Syndrome –Progressive Supranuclear Palsy syndrome (CBS-PSPS) is used to describe those case of CBS where the extrapyramidal syndrome is axial or symmetrical and additional features associated with PSP-RS are also present. In addition to diagnostic criteria for CBS, Armstrong et al(12) include an additional set of criteria designed to classify clinical syndrome by probability of underlying CBD pathology.

### 1.8 Role of Neuroimaging in the Classification of FTLD Associated Syndromes

Neuroimaging is commonly used in the diagnosis of neurodegenerative conditions. Most commonly it is used to exclude other pathological processes (e.g. demyelination or a space occupying lesion) however it has been used to subclassify FTLD associated syndromes.

#### 1.8.1 Role of Neuroimaging in the Classification of FTD

Imaging has three roles in the diagnostic criteria of FTD. Firstly, in the exclusion of other pathologies (such as infarcts or space-occupying lesions) that may mimic FTD. Second, in the criteria for bvFTD, frontotemporal imaging changes (either atrophy, hypoperfusion or hypometabolism) are required in order to make a diagnosis of probable bvFTD (in addition to (i) meeting criteria for possible bvFTD on the basis of the clinical syndrome and (ii) exhibiting significant functional decline)(10). Third amongst PPA regional atrophy, hypoperfusion or hypometabolism is used to classify the clinical syndromes as 'imaging supported' if the area affected is predominantly left posterior perisylvian or parietal for lvPPA, left posterior frontoinsular for navPPA, or anterior temporal lobe for svPPA(11).

Prior to the current criteria FTD was often previously divided into 'frontal' and 'temporal' variants(51,52) on the basis of clinical symptoms and imaging correlates (including SPECT perfusion). Frontal variant FTD implied more frontal lobe involvement and typically behavioural changes as the dominant clinical features. Temporal FTD (also known as Semantic Dementia) was characterised by markedly asymmetric anterior temporal lobe atrophy and TDP-43 pathology in the majority of cases. When semantic dementia affects the left temporal lobe the clinical syndrome is typically of impaired semantic knowledge exhibited by fluent speech lacking in meaning and impaired object recognition. This can be considered synonymous with svPPA. However a right temporal variant of semantic dementia exists where behavioural changes and prosopagnosia predominate(53). Both forms are recognised in the current criteria for PPA but the emphasis is on left temporal variants where spoken communication is more clearly affected(11). Right temporal variant FTD/right semantic dementia now often meet current

criteria for bvFTD(10) but are likely to reflect a distinct subgroup in terms of imaging, clinical and pathological profiles(43).

### 1.8.2 Role of Neuroimaging in the Classification of PSP

Previous criteria for PSP include imaging only in the exclusion of other significant pathology (such as cerebral infarcts). Focal frontal or temporoparietal atrophy was considered an exclusion criteria for PSP under the NINDS-SPSP criteria but only the term 'Significant other neurological disease on CT-scan/MRI' is used as an exclusion criteria under the NNIPPS criteria(13,54). In the most recent criteria predominant midbrain atrophy or hypometabolism or evidence of postsynaptic striatal dopaminergic degeneration allow the addition label of imaging supported diagnosis(48). This is over and above the specific but insensitive and often late classical radiological features like Hummingbird and Mickey-Mouse signs.

The 2017 MDS-PSP criteria considered the use of Tau PET imaging, but for lack of evidence of their biomarker utility, and validity, chose not to include Tau PET. MRI remains the main imaging modality in relation to PSP, while frontal and midbrain hypometabolism from SPECT/PET scanning are supportive.

### 1.8.3 Role of Neuroimaging in the Classification of CBS

Apart from aiding in the exclusion of other pathology mimicking CBD, brain imaging is not included in the current consensus criteria used in the diagnosis and classification of CBS(12).

## 1.9 Genetic and Pathological Correlates of FTLD

Not only is FTLD associated with a range of clinical syndromes but also a number of different histopathological findings at post mortem. As with the clinical syndromes these have been subject to subdivision and classification largely based on the presence and distribution of inclusions of abnormal protein aggregates within the brain(27). There a range of such proteins found within the brain of people with FTLD, most commonly Tau, Transactive Response Deoxyribonucleic acid binding Protein 43kDA (TDP-43) and Fused in Sarcoma (FUS). The exact role of these proteins in the aetiology and pathophysiology of FTLD remains unclear, however inherited genetic mutations in genes encoding many of them that appear to be sufficient (although not necessary) to produce disease in an individual. Mutations in the gene encoding Tau (MAPT), for example, can produce the clinical syndrome bvFTD with abnormal Tau deposition at post mortem(55).

Table 1.1 shows some of the gene mutations that have been associated with FTLD pathology together with the associated protein inclusions found at post mortem and commonly associated clinical syndromes. While inherited mutations are common amongst some FTLD syndromes (especially bvFTD/MND spectrum disorders) they are less common in others (such as svPPA, PSP and CBS) and even the basis for exclusion under some diagnostic criteria(12,54) . Amongst FTD up to 30% of cases may have a autosomal dominant pattern of inheritance within their family with the commonest mutations, MAPT, C9ORF72 and Progranulin (GRN) accounting for 10-20% of all cases(56). Recently loss of function mutations in TBK-1 (encoding TANK-binding kinase 1) has been shown to cause MND and FTD(57) and were the third commonest cause in a Belgian cohort (after C9ORF72 and GRN)(58). Patients with TBK-1 mutations have been described as having clinical syndromes with svPPA and spinal MND, CBS with bulbar MND, nfv-PPA (initially with apraxia of speech) followed by behavioural changes and limb weakness(59). Despite substantial advances in genetic research the majority of cases occur sporadically and without an identified underlying genetic cause.

While there are firm correlations between genetic mutations and microscopic post mortem pathology amongst those with symptomatic disease, pathological changes amongst presymptomatic mutation carriers have not yet been established. There is good evidence that structural brain changes followed by subtle impairments on formal neuropsychological testing can be identified prior to the emergence of overt symptoms amongst mutation carriers (56) but whether protein deposition and aggregation plays an active role in the process of neurodegeneration (or whether both are the consequence of some common upstream event) remains the subject of debate.

| Gene Mutation | Inclusions found at Post Mortem | Associated Syndromes |
|---|---|---|
| MAPT | Tau | bvFTD, bvFTD with Parkinsonism, PSP-RS |
| C9ORF72 | TDP-43 | MND, bvFTD, FTD-MND, nfvPPA |
| GRN | TDP-43 | bvFTD, nfvPPA, CBS |
| TBK1 | TDP-43 | bvFTD, MND, FTD-MND, PPA, bvFTD with Parkinsonism, CBS |
| VCP | TDP-43 | bvFTD, inclusion body myositis, Paget's Disease of bone, MND, FTD-MND |
| CHMP2b | FTLD-UPS* | MND, FTD-MND, bvFTD |
| TARDP | TDP-43 | MND, FTD-MND, bvFTD |
| SQSTM1 | TDP-43 | MND, FTD-MND, bvFTD |
| DCTN1 | TDP-43 | Perry Syndrome, FTD, FTD-MND, |
| FUS | FUS | MND, FTD-MND, bvFTD |

**Table 1.1 Genes associated with FTLD** *FTLD-UPS Frontotemporal lobar degeneration Ubiquitin Proteasome System. In the brains of subjects with CHMP-2B mutations ubiquitin positive inclusions are found which are negative for TDP-43, FUS and Tau stains(27).

### 1.10 Clinico-Pathological Correlation of FTLD Associated Syndromes

Within the spectrum of syndromes associated with FLTD, the strength of clinicopathological correlation varies widely. For example, sensitivity and specificity for PSP-RS using the NNIPPS criteria were 0.95 and 0.84 respectively, but only when cases with post mortem CBD were excluded and amongst a cohort already assessed as having likely PSP for entry into a clinical trial(13). Conversely by retrospectively examining clinical records for 103 consecutive cases of pathologically confirmed PSP Williams et al(60) report only 54% had the clinical 'Richardson-Syndrome' during life, although in this paper 'Richardson Syndrome' refers to a data driven classification of cases and is not synonymous with PSP-RS or PSP as defined by other clinical or research criteria.

Amongst cases of bvFTD, Tau and TDP-43 both producing similar behavioural syndromes, additional features (such as features of motor neuron disease or Steele-Richardson-Olzewski syndrome) may help increase discriminate when they are present(14). For CBS less than two thirds of cases will have CBD pathology at post mortem and conversely less than two thirds of those with CBD identified will meet criteria for CBS during life(7). Amongst cases of PPA clinic-pathological correlations are varied. svPPA is considered reasonably predictive of TDP-43 pathology; in one series 18 of 24 cases of Semantic Dementia had ubiquitin positive inclusions (confirmed as TDP-43 pathology in all of 13 cases tested) at post mortem(61). In this series the term 'Semantic Dementia' encompasses (but is not limited to) those who would classified as svPPA under current criteria(11). Conversely nfvPPA (formerly PNFA) has wide range of pathological correlates(62). Furthermore a significant number of patients who meet criteria of FTLD-associated clinical syndromes will have non FTLD-associated pathology such as Lewy Body or Alzheimer's type pathology(63). Amongst some syndromes non FTLD pathology may be the predominant underlying pathology (for example lvPPA(64)).

### 1.11 Genotype-Phenotype Correlation

With the caveat of incomplete penetrance, the presence of pathogenic genetic variants allow the diagnosis of FTLD to made in confidence in some symptomatic individuals. Table 1.1 shows clinical syndromes (phenotypes) commonly associated with genetic forms of FTLD but is by no means exhaustive. The range of clinical syndromes have been associated with each gene continues to expand. For example on 14th October 2014 (approximately three years since the first publication of C9ORF72) I performed a Pubmed search for C9ORF72. I then reviewed the titles and abstracts (where available online) of the papers identified for clinical syndromes that were proposed as associated with C9ORF72. I identified 452 papers with a total of 53 phenotypes (Figure 1.2). These ranged from the spectrum of FTLD, MND, chorea, and Parkinsonism to more diverse conditions including multiple sclerosis(65), paraneoplastic effects of lung adenocarcinoma(66), and hippocampal sclerosis(67). Since then, as of 1st January 2019, a further 807 papers have been published at an average rate of 194 papers per year (range 161-201) since the start of 2015. Despite the steady increase in published papers referencing C9ORF72 there are also a smaller number of papers reporting lack of associations with some clinical syndromes (such as DLB, idiopathic dystonia, ataxia and schizophrenia (68–71),), pathologically defined cohorts (such as DLB, MSA, PSP and CBD(72,73)) and geographically restricted cohorts of FTD/MND (such as China and Korea(74,75)).

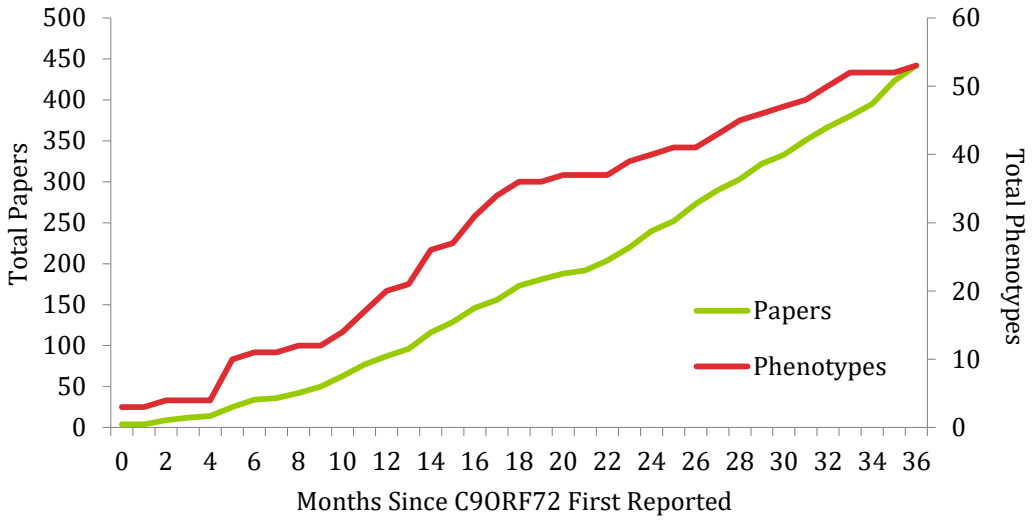



**Figure 1.2 Published Phenotypes Associated With C9ORF72 in the First Three Years Since Discovery**.

### 11.12 Rationale for a Transdiagnostic Approach to FTLD

The criteria for the syndromes associated with FTLD have each emerged as the result of attempts to provide a common framework to facilitate uniformity in diagnosis between centres(11) and also to relate the clinical syndrome to underlying pathological processes(10,12,13,54). They seek to define particular clinical features and group these into clinical syndromes. Many use different levels of probability when relating to underlying pathology (e.g. possible or probable CBD(12)).

While they define a set of clinical syndromes the current criteria do not encompass the entire spectrum of syndromes associated with FTLD. There is also considerable overlap between FTLD associated syndromes. For example there is no clear distinction between PSP-CBS and CBS-PSP on the grounds of clinical presentation or on pathological descriptions. Intermediate phenotypes where features of more than one of the 'classical' syndromes are present are common and an individual's clinical syndrome may evolve and change over time(3). While each set of criteria provides a useful framework for particular aspects of FTLD-associated syndromes they do not currently give sufficient consideration to the entire spectrum FTLD associated disorders.

A more unifying transdiagnostic approach that emphasises commonalities rather than differences between FTLD associated syndromes(26) may provide fresh insights into FTLD, its clinical syndromes and their underlying neural basis. This approach may also have the

advantage of capturing mixed or intermediate clinical syndromes that clearly fall within the spectrum of FTLD but fall between syndromes and are unclassifiable by current criteria. Consider (for example) a patient with severe semantic deficits but also behavioural changes. The behavioural changes would normally be considered exclusion criteria for a diagnosis of PPA but are a well-recognised feature of semantic dementia. Another subject with progressive language dysfunction but features of more than one subtype of PPA, clearly should be defined as PPA but forcing subcategorisation beyond this seems counterintuitive. By using current criteria for FTLD together simultaneously, disregarding those exclusion criteria for one syndrome which are inclusion criteria for others and not forcing subcategorisation where the syndrome sits within FTLD but between syndromic labels, it may be possible to capture a more representative cohort of subjects with FTLD.

While the clinical syndromes associated with frontotemporal dysfunction have been recognised for centuries, over time the clinical syndromes associated with individual diagnostic entities such as GPI or Pick's disease have been subject to progressive expansion and subsequent refinement as further discoveries as to their underlying pathology are made. More recently as genetic and histopathological advances have been made the syndromes associated with pathologically defined disease entities such as FTLD has been subject to similar phenotypic expansion. In line with advances in our understanding of these conditions the terminology used to describe these conditions has also changed and will undoubtedly continue to do so.

In both the clinical and research settings continuously evolving knowledge and nosology presents particular challenges. A clinician may be faced with a patient with a genetically defined illness and uncertainty with regard to their prognosis and what clinical consequences of their genetic diagnosis may be. More commonly a patient may present with clinical features of a syndrome associated with FTLD and uncertainty as to the underlying pathological process, prognosis, or when to test for genetic changes. As trials of disease modifying treatments are beginning to emerge the question of who to recruit for trials aimed at particular pathological processes is a particular challenge to researchers. Restricting trials to only those subjects with a genetic or pathologically defined illness risks restricting trials to a narrow subset of patients who may not be truly representative of the disease as a whole. Such restrictions also make recruitment to such studies challenging given the rarity of FTLD.

Taking a broader more inclusive approach however will lead to inclusion of multiple pathological processes and substantially reduce the power of a particular study to evaluate therapies aimed at particular pathologies. For other researchers investigating the syndromic consequences of FTLD (such as particular behavioural or cognitive syndromes) the underlying

pathology may be less important. The structural and functional brain changes caused by FTLD may be more relevant to our understanding of the neural mechanisms responsible for particular symptoms than the underlying pathology causing neurodegeneration. Better understanding of these processes may lead to better symptomatic therapies independent of the underlying pathological diagnosis and is the basis on which almost all currently licensed treatments for neurodegenerative disease in the U.K. exist.

Irrespective of pathology frontotemporal dysfunction leads to significant symptomatology, cognitive and behavioural changes and associated morbidity, which are in themselves, attractive targets for therapeutic interventions. While FTLD, and its associated syndromes, may be subdivided in a number of different ways, clinically and symptomatically they present as spectrum of disorders of language, behaviour and motor function which while diverse are also highly recognisable, sharing very particular problems and morbidity. Dissociating pathological subtypes on the basis of clinical features and current criteria is imprecise and fragments this group of disorders, leading to a potential underestimation of their impact as a whole and also limiting our ability to explore the features that are common between syndromes. As such I argue it remains valid and useful to consider these conditions together.

While there are clear advantages to a transdiagnostic approach, FTLD (and its associated clinical syndromes) are heterogeneous. There remain important genetic, pathological and syndromic differences between patients, which have important clinical and scientific implications. For example patients with bvFTD and some forms of TDP-43 are at greater risk of developing MND or of passing a C9ORF72 genetic mutation onto subsequent generations than those with PSP-RS. A potential treatment targeting Tau would be easier to evaluate in PSP-RS than in PPA or CBS where Alzheimer's and TDP-43 type pathologies are also commonly found. A transdiagnostic approach is not simply 'lumping' all patients together but accepts that each method of 'splitting' FTLD also has its own limitations. Clinicopathological correlations are variable, clinical syndromes evolve and vary over time, gene penetrance varies and pleitropy increasingly recognised, mixed pathology is common in all neurodegenerative disease. A transdiagnostic approach neither lumps nor splits FTLD but simultaneously recognises the importance of both individual differences and commonalities between patients and also that our current criteria and understanding of these conditions is incomplete and imperfect.

### 1.13 Conclusions and Thesis Outline

In this chapter I outlined the spectrum of clinical syndromes associated with FTLD. Using a historical perspective I first described how syndromes associated with disruption of frontotemporal function have been described over centuries. I then discussed how as our understanding of underlying pathology associated with these syndromes has developed, the nosology we use to described them has evolved to reflect initial phenotypic expansion and subsequent refinement. Next I discussed the current concept of FTLD as a heterogeneous group of disorders defined by a range of neuropathological findings and associated with a wide spectrum of clinical syndromes. I then discussed the diagnostic criteria and recognised syndromes associated with FTLD and how they have been developed to serve multiple functions; to provide a framework to describe clinical features and to predict disease progression, prognosis and underlying pathology. These criteria are not comprehensive and do not encompass the entire spectrum of clinical syndromes associated with FTLD. There is also overlap between criteria, clinicopathological correlation is variable and non-FTLD type pathology may also present with clinical syndromes that meet current criteria. I have argued that while FTLD is a diverse and heterogeneous group of disorders there is merit in considering these conditions together as a spectrum of syndromes associated with Frontotemporal Lobar Degeneration both in terms of exploring the impact of these conditions and in the study of particular syndromic aspects.

In the subsequent chapters I will present the results of the PiPPIN study (Pick's disease and Progressive supranuclear palsy Prevalence and INcidence) of both the epidemiology of syndromes associated with FTLD and of some neuropsychiatric aspects of FTLD (namely apathy and impulsivity). I will demonstrate how this transdiagnostic approach can provide useful data and insights into the impact of FTLD and the underlying neuropsychological basis of common and disabling neuropsychiatric symptoms in dementia.

The diagnostic criteria are heuristic, and with limitations. The criteria used in the diagnosis of FTLD associated syndromes had been recently updated before the PiPPIN study and my PhD began. However the criteria remain fragmented and each limited to a particular subset of clinical syndromes. There was also considerable overlap between them (for example a patient may meet criteria for navPPA and CBS-NAV simultaneously). Similarly over the course of an individual's illness as their disease progresses they may acquire additional clinical features and move between clinical syndromes (such as a patient meeting criteria for bvFTD and subsequently developing the movement disorder required for a clinical diagnosis of PSP-RS). Some patients may fall between criteria, meeting neither by strict application but clearly having

a clinical syndrome most likely associated with FTLD type pathology (such as a patient with profound semantic deficits who also has behavioural impairments precluding a diagnosis of PPA).

For these reasons there was a need to revisit the epidemiology of FTLD associated syndromes using the updated criteria and an inclusive approach whereby transitional and intermediate clinical phenotypes are counted, but only once. I did this in the PiPPIN study, a comprehensive clinical study of the epidemiology of FTLD associated syndromes using multiple sources of referral to recruit all clinical syndromes, transitional and intermediate cases, without age restrictions. From the cohort I recruited I then went on to focus on a major transdiagnostic problem, apathy and impulsivity, symptoms which are particularly prominent, common, distressing and disabling across the entire spectrum of FTLD associated syndromes and relevant to a far wider, range of neurological disorders. Despite their importance apathy and impulsivity remain poorly understood. Rather than single one-dimensional syndromes they appear to be multidimensional and frequently coexist in disease states. Similarly methods used in their assessment vary widely. It was not clear whether apathy and impulsivity in FTLD associated clinical syndromes represents disruption of a single common cognitive process or multiple different processes. Neither was it clear which of these are of clinical relevance and the best methods by which to assess and measure them. Before we can move to clinical trials of symptomatic therapies aimed at treating these important symptoms we need to better understand their cognitive and neural correlates and how best to assess them. With this in mind, as part of the PiPPIN study I used a variety of methods to assess apathetic and impulsive symptomatology from a range of perspectives. I demonstrate that apathetic and impulsive syndromes are common in FLTD, multidimensional and that a multimodal approach to their assessment is required.

In Chapter Two I first review previous epidemiological studies of FTLD associated syndromes and discuss some of the methodological differences between them that limit comparisons between studies, syndromes and cohorts. Many of these studies used older criteria and are limited to particular syndromes within the spectrum of FTLD. I argue that a more inclusive transdiagnostic approach may give a better and more representative estimate of the true epidemiology of FTLD associated syndromes whereby transitional and borderline cases moving between clinical syndromes are included but only counted once. I then discuss the methods used to recruit subjects to the PiPPIN study recruiting from multiple sources subjects with FTLD associated syndromes resident within the counties of Norfolk and Cambridgeshire in the UK without restriction to a particular age group or subset of clinical syndromes. Using current criteria for FTLD associated syndromes applied simultaneously so that subjects with

clinical features of one FTLD associated syndrome are not excluded from the study because they also have features of another, but are only counted once. While using this approach does not dramatically change previous epidemiological estimates of the Prevalence or Incidence of FTLD, by doing so I am able to present such estimates in a more robust fashion and in a manner that will allow easier comparison between similar cohorts in the future.

In Chapter Three, I discuss neuropsychiatric symptoms in dementia with a particular emphasis on apathy and impulsivity which I discuss in terms of disruption of goal directed cognition and behaviour. I hypothesise that apathetic and impulsive states within the syndromes associated with FTLD are due to dissociable neural and psychological mechanisms and that different apathetic and impulsive states may in some instances coexist and correlate with each other. First, using informant reports (mainly from a spouse or carer) of patients with FTLD associated syndromes in the PiPPIN study I show that neuropsychiatric symptoms, including apathy and impulsivity are commonly reported in FTLD. Second using a range of questionnaires and paper and pencil tests, I demonstrate that despite impairments across a range of cognitive domains, subjects with FTLD are able to give meaningful insights into their own cognitive and emotional states. I show that, consistent with the reports of their carers, when compared to a similarly aged group of healthy volunteers, subjects with FTLD associated syndromes report increased negative emotional feelings, more symptoms of apathy, depression and decreased motivation and hedonic tone. Finally I suggest that the underlying neuropsychological basis of these patient and carer reports is complex and multifaceted.

In Chapter Four, I discuss the limitations of a questionnaire based approach and suggest a number of ways that these might be overcome by using more objective behavioural assessments of goal directed cognition and behaviour. Across a number of different tasks aimed at assessing aspects of decision-making and reflection impulsivity, perception and responsiveness to reward, and response inhibition, patients with FTLD associated syndromes performed differently to healthy older controls; their responses are typically slower and less accurate. While subjects with FTLD remain responsive to reward and are able to detect and adapt their responses to changes in perceived reward, they do so differently to healthy older controls. I suggest that neural and cognitive mechanisms responsible for these changes in performance on tasks may also contribute to the observed increase in both apathetic and impulsive behaviour observed by carers in this patient group.

In Chapter Five, I take a multidimensional approach to apathy and impulsivity. First by performing multiple Principal Component Analyses on different versions of the Apathy Evaluation Scale (AES) I show the resulting extracted components vary depending on the person

completing the AES (the subject, an informant who knows them well, or a clinician) and the subject of the AES (a subject with FTLD, a healthy older controls, or both combined). I then show that while some extracted components can be related back to previous descriptions of the component structure of the AES, others appear more related to the manner in which items in the AES are presented. Also, while both subject and informant versions of the AES correlated with clinician based assessments, they do not correlate significantly with each other supporting the hypothesis that the results of questionnaire based assessments vary depending on who is asked, and how they are asked. Next I quantify discrepancies between subject and informant reporting of symptoms and show that some, but not all, of these correlate with subject cognition and mood.

I then examine the relationship between performance on behavioural tasks and whether subjects are considered apathetic, impulsive, or not by their carers. I show no significant differences between these groups. By performing another Principal Component Analysis, this time combining subject, informant, and clinician questionnaire based assessments with the results of behavioural testing; I show that different testing modalities load onto different extracted components with very little overlap. These extracted components show significant (but different) correlations with ratings of mood, cognition and discrepancy scores between subject and informant reports. Taken together these results support a multidimensional approach to apathy and impulsivity where different testing modalities and sources of information each contribute to the assessment of these symptoms but none in isolation give a true reflection of these complex multidimensional symptoms.

Finally, in Chapter Six, I review these results together and reflect on how using this transdiagnostic approach to the syndromes associated with FTLD has provided robust support for epidemiological estimates of these syndromes even in light of the continued evolution of the classification and associated nosology that I have discussed in this first chapter. I suggest these results provide insights into the nature of decision-making and the manner in which it is disrupted in FTLD which leads to disabling and distressing neuropsychiatric symptoms. I also discuss the limitations of this study and future directions that might overcome some of these and in turn lead to therapeutic trials that ultimately translate to effective symptomatic therapies for apathy and impulsivity, improving the lives of not only those affected by FTLD but potentially a far wider range of neuropsychiatric disorders.

# Chapter Two

# The Epidemiology of Frontotemporal Lobar Degeneration and the PiPPIN Study

## 2.1 Summary

In this chapter I discuss the epidemiology of syndromes associated with FTLD and the principles underlying systematic epidemiological study of neurodegenerative diseases. I review previous epidemiological studies of FTLD and associated syndromes and outline the methods of the PiPPIN study (Pick's disease and Progressive Supranuclear palsy Prevalence and INcidence study) a novel epidemiological study of FTLD associated syndromes in the English counties of Norfolk and Cambridgeshire (population 1.69 million). Using multisource referral over two years and clinical revalidation using current diagnostic criteria, I aimed to identify every diagnosed or suspected case of FTLD resident in these two counties secondary. A subgroup of 47 subjects were screened for known genetic causes of dementia.

Using this approach I calculated age and sex standardized prevalence and incidence rates of FTLD associated syndromes as 10.84/100,000 persons and 1.61/100,000 person-years respectively. Mortality amongst those with FTLD associated syndromes was 1.56/100,000 person-years. The lifetime risk of a diagnosis of FTLD is 1 in 742. Prevalence rates were similar between individual syndromes (Progressive Supranuclear Palsy, Corticobasal Syndrome, Behavioural Variant Frontotemporal Dementia and Primary Progressive Aphasia) as was mean survival from symptom onset however time to reach a diagnosis varied between syndromes. Peak prevalence was between 65-79 years and the prevalence in the over 65s more than double that amongst 45-64 year olds. 14.9% of those screened had a possible genetic cause of their dementia identified.

## 2.2 Introduction

The diverse clinical syndromes associated with FTLD discussed in Chapter One are often described as a common cause of young-onset dementia(76,77,78). While such statistics appear commonly in the literature and media seeking to raise the profile of FTLD, estimates of the true epidemiology of FTLD vary widely. This is largely due to methodological variations between

studies and changes to the understanding of FTLD and the criteria by which FTLD (and its associated clinical syndromes) has been defined(77).

Some studies have suggested FTD is the commonest form of young onset dementia, or second commonest after Alzheimer's disease(76,79), others suggest it is the third (behind Alzheimer's and vascular dementia)(80). Such simple, memorable and provocative statistics may be effective in promoting a particular cause or raising awareness; whether FTD is the first, second or third commonest cause of dementia is less relevant than the fact that it is an important cause of young onset dementia and as such may have a disproportionate socio-economic effect compared to other diseases in more elderly cohorts. Despite this, young onset dementia of any cause is rare. By emphasising the relatively high prevalence of FTLD amongst younger cohorts of people with dementia there is the risk of simultaneously underrepresenting FTLD amongst the elderly, and reducing awareness or correct diagnosis of FTLD associated disorders among older patients.

Beyond contextualising or raising the public profile of a particular disease, epidemiological research serves several other important purposes. Firstly, accurate epidemiological research is essential for estimating the burden of disease, for priority setting, resource allocation and public health planning(81). Secondly, studies of prevalence and incidence between different cohorts have the potential to provide insights into causation or the natural history of disease by identifying variation between populations(81). In order to do this epidemiological research needs to be accurate, with robust methodology and importantly allow comparison between studies of different cohorts. While there have been a number of previous studies of syndromes associated with FTLD several methodological aspects limit their usefulness when considering the epidemiology of FTLD associated syndromes as a whole.

In these next sections I first review the previous literature on the epidemiology of FTLD and discuss methodological differences between them. I then discuss the rationale for a new study of the epidemiology of FTLD associated syndromes using current diagnostic criteria and a reproducible and standardised approach to epidemiological estimates that allows comparison between different populations and the calculation of lifetime risk, a more easily understood statistic that reflects the impact of a disease and takes account of onset at any age.

### 2.3 Previous Epidemiological Studies of FTLD Associated Syndromes

Tables 2.1.1-2.2.2 summarise previous epidemiological studies of FTLD associated syndromes. While there have been a number of previous studies several frequent methodological issues

limit their usefulness when considering the wider spectrum of FTLD and its associated syndromes.

Firstly, as I discussed in Chapter One, the diagnostic criteria have each been revised significantly in recent years(10–13) with changes in their specificity and sensitivity(10). Most previous epidemiological studies of, for example, FTD, used consensus criteria published in 1994 and updated in 1998(82,83) these have since been revised in light of further understanding of the pathology and clinical phenotypes of bvFTD and subjected to pathological validation(35).

Second most studies have restricted themselves to particular subgroups of FTLD associated syndromes (such as bvFTD, PSP etc.). Intermediate phenotypes of uncertain nosological status lay outside former diagnostic categories, e.g. the overlap between PSP and CBS (CBS-PSP)(12,84). Patients may also evolve from one syndrome to another(46,85). As a consequence, the sum of former prevalence estimates of single disorders might not accurately reflect the prevalence of the syndromes when considered together.

In addition most studies of CBS/PSP have identified patients based on their movement disorder (for example by screening records for 'Parkinsonism' or screening incident Parkinson's cohorts), some have explicitly excluded those subjects with dementia (e.g. (86)).

Finally, previous studies used widely varying methods, age-ranges and standardisation hindering comparisons across studies(77). For these reasons there remains a need for further epidemiological study of the syndromes associated with FTLD considered together and taking account of revised diagnostic criteria.

Key principles in epidemiological research are that the entity under investigation (for example FTLD associated syndromes) and the population in which it is studied are both clearly defined. In addition to this the methods for identification of the entity should be sufficient to accurately identify a meaningful proportion of cases but also practical for the research to be conducted effectively. For example, where screening for a condition is not time consuming, expensive or invasive it will be possible to screen a much larger population than when case identification requires more involved procedures. While it may be possible to investigate the epidemiology of more common conditions within a small population, rarer conditions will require a larger population to reach the same level of accuracy. Population based studies of FTLD and its associated syndromes are particularly challenging. As the frequency of disease is low, the population at risk large and diagnosis requires expert proficiency(87). Previous studies have investigated the epidemiology (specifically the incidence and prevalence) of FTLD associated syndromes individually but differences exist between studies of the same syndrome.

For example one study in Japan estimated the prevalence of FTD at 2 per 100,000 while another in Italy estimated the prevalence fifteen times higher at 30 per 100,000(88,89). Such differences might allude to important aetiological aspects of FTLD (such as environmental or genetic factors) but differences between the methods used in these studies limit comparison between them.

The Japanese study focussed on young onset dementia (i.e. onset less than 65 years) and subsequently evaluated for FTLD as a potential cause. Subjects were only included if age at onset and age at census date were less than 65, they were identified via postal survey over a short period of time (although they do also appear to have identified some cases from local services). In contrast the Italian study focussed specifically on FTLD screening through a large database for cases identified over a period of around 10 years. They used different criteria for inclusion that also includes syndromes associated with PSP and CBD within the definition of FTLD. Second the Italian study identified subjects through a registry held for over 10 years. Subjects were included based on age of onset and survival to the census day and hence represent a cumulative prevalence of young onset dementia. While the Japanese study recruits from the Ibaraki Prefecture, one of the most highly developed, urban areas of Japan with close links to several similar immediately adjacent Prefectures, the Italian study recruited from Vallecamonica, a large valley in Northern Italy that was relatively isolated until the second World War and at the time of the study had only a single neurology unit(89). Hence the dramatically different results may reflect differences in the studies entry criteria, sources of subject identification or alternatively reflect a true difference between the rates of FTLD amongst the two populations studied. The differences may indicate important genetic or environmental risk factors for developing FTLD or differences in service provision, rates of diagnosis or survival for patients with FTLD in the two areas, all of which could have important implications for our understanding of FTLD, its diagnosis and treatment. Alternatively the differences may simply reflect methodological differences between the two studies.

While it is not possible to standardise methods for all epidemiological research, in order for epidemiological studies to be comparable specific aspects must be clearly defined namely:

1. The population under study
2. The definition of disease under study
3. The definition of a prevalent, or incident case
4. The methods used to identify these cases

| Reference | Sample Population | Age range | Syndromes Studied | Case identification | Age at onset | M:F | Cases | Criteria for confirmation | Standardisation | Prevalence per 100,000 |
|---|---|---|---|---|---|---|---|---|---|---|
| Ratnavalli 2002(76) | Cambridgeshire, UK 72,815 | 45-64 | FTD, PPA | Regional centre with coded records, contact with regional specialist services | 52.8 | 14:3 | 11 (3 CBS cases 6.9 (2.9-16.1) no cases of PSP) | 1994 Lund Manchester and 'local' criteria, specialist review either by clinical or research team | None | 15.1 (8.4-27.0) |
| Feldman 2003(90) | Canada. Individuals referred to specialist dementia clinics in Canada over 19 months | <70 | FTD | National cohort; cross section of subjects | NR | NR | 36 FTD, 16 mixed FTD/AD | 1994 Lund Manchester criteria, clinical assessment | NA | 12.1% of 670 cases of dementia |
| Harvey 2003(80) | 3 Boroughs of London, UK 117,236 | 45-64 | FTD | Hospital coding, case reporting, regional network coded records | 57 | NR | 18 | 1994 Lund Manchester criteria, Clinical record review Subset reviewed in person | None | 15.4 (9.1-24.3) |
| Rosso 2003(79) | Zuid-Holland, Netherlands 2,043,949 | 30-79 | FTD | Regional network coded records, postal survey | 58 | 1:1 | 55 | 1994 Lund Manchester crieria | None | 2.7 (2.1-3.5) |
| Ikejima 2009(88) | Ibaraki, Japan 852,889 | 45-64 | FTD | Regional network coded records, postal survey | 60 | 1.5:1 | 17 | 1994 Lund Manchester criteria. Case reporting. | Adjusted for response rate. | 2.0 (1.3-3.2) |

**Table 2.1.1 Prevalence Studies of Syndromes Associated with Frontotemporal Lobar Degeneration.** Note the restricted age-ranges and variation in case identification methods.

| Reference | Sample Population | Age range | Syndromes Studied | Case identification | Age at onset | M:F | Cases | Criteria for confirmation | Standardisation | Prevalence per 100,000 |
|---|---|---|---|---|---|---|---|---|---|---|
| Borroni 2010(91) | Brescia, Italy 531,249 | >45 | FTD, PPA | Regional network, surveillance registry over 8 years with census day point prevalence. | 65.6 | 1:1.2 | 213 | 1998 Neary Criteria and McKhann criteria. Clinical case review. | None. 95% CI using Poisson distribution. | 40 (35-45) |
| Bernardi 2012(92) | Community of Biv. Reggio Calabria, Italy, 509 | >50 | FTD | Active case ascertainment by invitation of all residents to dementia screening. | 75.9 | 1:3 | 18 | 1998 Neary Criteria and McKhann criteria. Clinician case review | None | 3.5% of population |
| Borroni 2011(93) | Brescia, Italy 322,334 | 45-65 at onset | FTD, PPA | Regional network, surveillance registry over 8 years | 59.0 | 24:23 | 94 | 1998 Neary Criteria and McKhann criteria. Clinical case review. | None. 95% CI using Poisson distribution. | 29.6 (23.7-35.6) |
| Gilberti 2012(89) | Vallecamonica, Italy 119,647 | 45-65 at onset | FTD, PPA | Regional centre, surveillance registry over 9 years. | 66.1 | 1:2 | 42 | 1998 Neary Criteria and McKhann criteria. Clinician case review | None. 95% CI using Poisson distribution. | 35 (26-46) |
| Wada-Isoe 2012(94) | Tottori Prefecture, Japan 587,772 | None | FTD, PPA | Survey of Regional Centres | NR | NR | 66 | 1998 Neary, 2011 Rascovsky, clinician review of some cases | None. | 11.2 (8.5-14.)) |

**Table 2.1.2 Prevalence Studies of Syndromes Associated with Frontotemporal Lobar Degeneration**

| Reference | Sample Population | Age range | Syndromes Studied | Case identification | Age at onset | M:F | Cases | Criteria for confirmation | Standardisation | Prevalence per 100,000 |
|---|---|---|---|---|---|---|---|---|---|---|
| Luukkainen 2015(95) | Nothern Ostrobothnia, Finland 107,516 | 45-65 | FTD, PPA | Regional centre registry over 5 years | 61.7 | | 22 | 1998 Neary and Rascovsky 2011/Gorno-Tempini 2011 (applied retrospectively) | | 20.5 Incidience over 5 years5.54 (1.9-11.3) |
| Nath 2001(96) | UK National study 59,236,500 | None | PSP-RS | Passive case identification: case reporting, charity registries UK mortality reporting | 66 | 91:96 | 577 | PSP-RS defined by NINDS-SPSP | None. | 1 (0.9-1.1) |
| Nath 2001(96) | North of England Regional study 2,589,240 | None | PSP-RS | Case referral, correspondence review from 14 months, survey,database screening | 69 | 60:47 | 80 | PSP-RS defined by NINDS-SPSP (Litvan), reviewed clinical records and personally examined where possible | Age to 1994 European standard population | 2.4 (1.9-3) |
| Nath 2001(96) | Participating General Practices in Newcastle Upon Tyne 259,998 | None | PSP-RS | Screening of GP records for features relating to Parkinsonism | 67 | 31:49 | 17 | Screened patients invited for assessment in person | Age to 1994 European standard population | 5 (2.5-7.5) |
| Golbe 1988(97) | New Jersey USA, 799,022 | None | PSP-RS | Survey of local services | NR | NR | 50 | Local criteria, clinical examination | None | 1.39 |

**Table 2.1.3 Prevalence Studies of Syndromes Associated with Frontotemporal Lobar Degeneration**

| Reference | Sample Population | Age range | Syndromes Studied | Case identification | Age at onset | M:F | Cases | Criteria for confirmation | Standardisation | Prevalence per 100,000 |
|---|---|---|---|---|---|---|---|---|---|---|
| De Rijk 1997(98) | Europe 17,205 subjects from 5 studies | >65 | Parkinsonism with associated features (e.g. PSP, MSA) | Door to door screening of older population for Parkinsonism | NR | NR | NR | Clinician review | Age standardised | 23 (1% of Parkinsonism) |
| Wermuth 1997(99) | Faroe Islands 43,709 | None | PSP-RS | GP, Hospital and Nursing Home survey, Pharmacy PD drugs search database search | NR | NR | 2 | NR | None | 4.6 |
| Chiò 1998(100) | Cossato, Italy 61,830 | None | PSP-RS | Postal survey of GP, clinical records search, pharmacy flagging of PD medication | NR | NR | 2 | Clinician review | None | 3.2 |
| Schrag 1999(86) | London and Kent UK 121 608 | None | PSP-RS | Screened GP records for terms related to Parkinsonism, MSA or PSP. Followed by notes review and clinical reevaluation Note excluded those with preceding dementia | | | | 5 probable 1 possible PSP | Age to European standard population | 6.4 (2.3 -10.6) |
| Trenkwalder 1995(101) | Two Bavarian villages, Germany | >65 | PSP-RS | Door to Door assessment of 1190 people aged >65 years | NA | NA | NA | No cases identified | NA | NA |

**Table 2.1.4 Prevalence Studies of Syndromes Associated with Frontotemporal Lobar Degeneration**

| Reference | Sample Population | Age range | Syndromes Studied | Case identification | Age at onset | M:F | Cases | Criteria for confirmation | Standardisation | Prevalence per 100,000 |
|---|---|---|---|---|---|---|---|---|---|---|
| Takigawa 2016(102) | Yonago city, Japan 139683 | None | PSP-RS, PSP-P, PSP-PAGF | 6 Yearly surveys of local databases and clinical referrals to regional centre | 72.5 | 12:13 | 25 | NINDS-SPSP criteria with local criteria for PAGF and PSP-P, clinical review of suspected cases | Sex and age adjustment to Japanese population | 17.26 (17.03-17.48) |
| Kawashima 2004(103) | Yonago, Japan 137,420 | | PSP-RS | Survey, visiting nursing homes, medical records search | 74.0 | 2:1 | 8 | NINDS-SPSP | None | 5.82 (1.78-9.86) |

**Table 2.1.5 Prevalence Studies of Syndromes Associated with Frontotemporal Lobar Degeneration**

| Reference | Sample Population | Age range | Syndromes Studied | Case identification | Age at onset | M:F | Cases | Criteria for confirmation | Standardisation | Incidence per 100,000 person years |
|---|---|---|---|---|---|---|---|---|---|---|
| Mercy 2008(104) | Cambridgeshire, UK 75,600 | 45-64 years at diagnosis | FTD | Referrals to tertiary centre, tertiary centre records (including prevalence study) over 6 years | NR | 9:7 | 16 | 1998 Neary criteria but explicitly also report SD and PNFA | None | 3.5 (2.0-5.7) Separately report of 5 incident cases of Parkinsonian disorders (PD, DLB, PSP,CBS, MSA) |
| Knopman 2004(105) | Rochester Minnesota | 40-69 | FTD+PPA | Database review and medical records review over 4 years | 48 | 0:4 | 4 | 1998 Neary, McKhann criteria. Clinical case review. | None | 4.1 (1.1-10.4) |
| Luukkainen 2015(95) | Nothern Ostrobothnia, Finland 107,516 | 45-65 | FTD, PPA | Regional centre registry over 5 years | 61.7 | NR | 29 | 1998 Neary and Rascovsky 2011/Gorno-Tempini 2011 (applied retrospectively) | None | .54 (1.9-11.3) |
| Garre-Olmo 2010(106) | Girona, Spain | 30-64 | FTD+SD | Clinical dementia registry over 3 years | NR | NR | 14 | Clinical diagnosis | None | 1.3 (0.7-2.2) |
| Linder 2010(107) | Umea region Sweden 141,950 | None | PSP, CBD | Incident cases of Parkinsonism over 4 years | 75.8 | 1:1 | 6 (0 CBD) | NINDS-SPSP | Age to Swedish Population | 1.2 (0.4-2.6) |

**Table 2.2.1 Incidence Studies of Syndromes Associated with Frontotemporal Lobar Degeneration**

| Reference | Sample Population | Age range | Syndromes Studied | Case identification | Age at onset | M:F | Cases | Criteria for confirmation | Standardisation | Incidence per 100,000 person years |
|---|---|---|---|---|---|---|---|---|---|---|
| Winter 2010(108) | District of Moscow 1,237,900 | None | PSP, CBS | Incident Parkinsonism cases Over 2.5 years | PSP 67.5, CBS 61 | 3:2 (PSP) 1 woman with CBS | 5 PSP, 1 CBS | NINDS-SPSP (PSP), Lang 1994 (CBS) | Age to general population | PSP 0.14 (0.08-0.21) CBS 0.02 (0.01-0.12) |
| Savica 2013(109) | Olmstead County Minnesota US approx. 141,000 | None | PSP, CBS | Records linkage search for incident Parkinsonism from Rochester Epidemiology Project over 15 years | NR | CBS 1:3 PSP 5:3 | 20 tauopathies (16 PSP, 4 CBS) | Specialist records review, Maraganore criteria 1992 (CBS) Collins1995 criteria (PSP) | None | Tauopathies 1.1 PSP 0.9 CBS 0.2 |
| Bower 1997(110) | Olmstead County Minnesota 1976-1990 | 50-99 | PSP-RS | Medical records linking from 1976-1990 | 72.5 | 9:7 | 16 | Clinician record review using Collins (1995) criteria | None | 5.3 |
| Schrag 1999(86) | London and Kent UK 121 608 | None | PSP-RS | Screened GP records for terms related to Parkinsonism, MSA or PSP. | NR | 1:1 | 5 probable 1 possible PSP | Notes review and clinical reevaluation | None. Indirect calculation based on reported survival of 5.6 years | 1.21 |

**Table 2.2.2 Incidence Studies of Syndromes Associated with Frontotemporal Lobar Degeneration**

### 2.3.1 Populations Under Study

In order to estimate either prevalence or incidence the total size of the population under study must be known. In the developed world reasonable estimates may be obtained from government census data but such data may be less reliable in the developing world. For geographically restricted studies, boundaries of the area under study should be clearly defined. In the United Kingdom census data with estimates of population size and demographics are freely available for the mid point of each year based on national census data. This is divided into Local Authority, Middle and Lower Super Output Areas. Groups of adjacent Local Authorities form Counties. The boundaries of these areas are subject periodic revision and are also freely available. While most changes to boundaries are relatively minor there is still potential for inaccuracy if the population estimates are not used with the correct geographic boundaries. A particular potential error is use of UK postcodes alone to identify case location by county as these are subject to change separately. For example the postcode prefix NR usually denotes residence within the County of Norfolk but also encompasses areas of the adjacent county of Suffolk.

The size of the population under study is important. Insufficient population size may lead to inaccurate estimates (particularly for rare diseases) while screen an excessively large population for a common condition is wasteful. If a smaller sample population is used to approximate the epidemiology of a much larger population then care should be taken to ensure that the sample size is sufficient and that the sample is representative of the larger population. The choice of geographic region may also influence epidemiological research. While identifying how the incidence and prevalence of disease changes between groups (where for example genetic or environmental factors may also vary and speak to the underlying disease aetiology) is a fundamental aim of epidemiological research, regional differences in healthcare organisation and social factors may also affect case identification (for example by variation in referral pathways and access to diagnostic services) or distribution (for example for more debilitating conditions the distribution of regional residential or nursing care facilities may lead to concentration of cases in particular areas).

Most studies of FTLD restrict the population under study to specific age groups. This focuses study resources on those assumed to be at highest risk but also to inflates the final estimate and hinders comparison between studies. While unrestricted age boundaries has the advantage of allowing easy comparison between studies the variety between demographics of different populations may be a confounding factor. Areas with an older population may be

expected to have a higher prevalence of age related disorders (including neurodegenerative diseases) than areas with a younger population. Similarly differences in sex distribution or other demographic variation may affect epidemiological estimates of some conditions. In order to address such issues many studies now standardise their results to a 'standard' population. Two standard populations are commonly used, the European Standard Population (which was revised in 2013) and the US Standard Population. The lack of a single standard population accepted by all groups remains a barrier to comparison between studies (particularly between the US and Europe).

### 2.3.2 Definitions of Disease Under Study

The evolution and terminology used to describe FTLD and its associated syndromes is discussed in Chapter One. A disease entity can be described by a range of factors; histopathological features, clinical symptoms and signs or by the results of investigations such as imaging or genetic tests. For research purposes most diseases are defined by a set of clinical criteria. While specific criteria are particularly important for research into disease pathology or trials of diseases modifying therapy, for epidemiological research overly specific criteria (at the expense of sensitivity) will lead to an underestimation of the frequency of disease. Furthermore, when considering syndromes associated with FTLD, a range of different pathological processes produce overlapping clinical syndromes. Specific criteria aimed at identifying a particular pathology will underestimate the frequency of the syndromic spectrum and may require a different approach.

### 2.3.3 Incident Cases

The incidence of a disease is the number of new occurrences of that disease within a given population and time. A known time of onset is therefore necessary to define an incident case. For neurodegenerative conditions this is problematic as symptomatic onset is insidious without a clear starting point; the symptomatic onset of disease may be predated by years of subclinical structural or functional brain changes and cognitive changes may be demonstrable on formal neuropyschometry years before disease becomes symptomatically evident(56). An alternative approach is to use the time of diagnosis. The advantage of this method is that it provides a definitive point in time. In less heterogeneous disorders it may also be reasonable to assume that the point at diagnosis is a reasonable estimate of the time at which symptoms had reached a particular level of severity (sufficient to allow diagnosis) but not far beyond (assuming rapid and uniform access to diagnostic services). When considering FTLD associated syndromes there are disadvantages to either method. As with other conditions, time of onset is difficult to clearly

define but also may vary between syndromes. While a predominantly language or movement disorder may have a point where normal function is clearly interrupted (a hand becomes clumsy or words are first mispronounced) the distinction between normality and symptomatic disease is less clear for behavioural changes. Time of diagnosis is also problematic with many patients acquiring several diagnostic labels over the course of their symptomatic disease both as they see different specialists with varying levels of expertise and also as their progressive disorders change over time. Someone with Tau pathology may, for example, present with a dysexecutive, apathetic syndrome and be diagnosed with depression before developing an expressive language disorder, acquiring a label of PPA or PPAOS, then developing additional extrapyramidal features typical of CBS. bvFTD may commonly be initially diagnosed as depression or Alzheimer's type dementia before the diagnosis is made. Even after the 'correct' diagnosis of bvFTD, a proportion of subjects will subsequently develop features of PSP-RS(111). More commonly PSP-RS is initially diagnosed as idiopathic Parkinson's disease and only when initial dopaminergic therapy proves ineffective is the diagnosis revised.

While time of onset has been used for some studies the majority of incident studies have used time of diagnosis. While this is a pragmatic solution when addressing an individual syndrome when considering multiple FTLD associated syndromes, transitional and intermediate clinical phenotypes it is unclear whether one particular definition of incidence is sufficient for all syndromes.

### 2.3.4 Prevalent Cases

Prevalence is usually defined as the proportion of individuals within a defined population with a particular condition at a specified time. Point prevalence is the proportion of cases at a single point in time. A prevalent case should therefore, by definition be alive, with the disease under study and resident within the catchment area at the time of prevalence estimation ('census date').

Most studies run over a particular time frame during which subjects will be identified by the study team but some will also develop symptoms, be diagnosed clinically, and migrate to and from the area in which the population under study resides, move between age groups and die. To avoid confounding estimates of prevalence it is necessary to confirm that prevalent cases identified are alive, within the population under study (by both geographical and age boundaries) and meet the definition of a prevalent case (e.g. having symptomatic disease, meeting research diagnostic criteria or having a formal diagnosis).

The methods by which prevalent cases are identified can greatly influence prevalence estimates. For example two Italian studies from Brescia(91) and Vallemonica(92) report cases identified over eight and ten years respectively. Both studies ensured patients were alive and resident within the catchment area on the census date (and hence report point prevalence) but by a longer period of effective recruitment and case ascertainment have a greater potential to identify cases. It is also possible that some cases initially meeting criteria for inclusion will develop further diagnostic features that would (if re-examined) preclude them from inclusion in a particular study especially where the study is restricted to particular subtypes of FTLD associated syndromes (for example a case of bvFTD that develops features of PSP, or alternatively a CBS that develops more florid features of Dementia with Lewy Bodies). Hence differences in the period of case ascertainment and the definition of a prevalent case may at least partially explain differences in reported prevalence.

### 2.3.5 Case Identification

The methods used for case identification will affect the results of any epidemiological study. Where it is appropriate to use a small sample population, or identification of the disease entity is simple and non invasive it may be possible to test every individual within the sample population. When identification of the disease is more involved an alternative is to use a two step approach; screening all of the population with a relatively quick and sensitive screening, followed by more specific confirmation testing in those screened as positive by screening.

Studies of individual FTLD associated syndromes have used several approaches to identify cases for example: case referrals to a specialist centre (e.g. (104)), screening of medical records for relevant diagnosis (e.g. (102)), screening of medical records for associated keywords(e.g. (86)), disease registries (e.g.(96)), door to door assessment (e.g.(98)).

Because the syndromes associated with FTLD occur infrequently within a large at risk population a large sample size is required. Screening tests for dementia mainly focus on memory and are insensitive for FTD(112). In addition to this, heterogeneity amongst the syndromes associated with FTLD are such that a test that is sensitive to (for example) the predominantly language disorders may well be insensitive for those cases where movement disorders or behavioural change dominate the clinical picture. Other potential biomarkers of FTLD such as structural or functional neuroimaging or cerebrospinal fluid analysis are time consuming, insensitive and invasive and hence not appropriate for screening purposes.

Healthcare record systems are a potentially useful method of case identification. Electronic clinical coding, billing and discharge records have been used to identify cases.

However for less common conditions such as FTLD associated syndromes their accuracy remains untested. Misreporting and under reporting is common(113). Also, in the U.K., access to healthcare records is restricted by data protection legislation to preserve patient confidentially.

With a few exceptions (such as Bernardi (92) who used door-to-door screening within set age boundaries) most epidemiological studies of FTLD studies of FTLD associated syndromes have required a suspected diagnosis of either FTLD or another neurodegenerative condition (e.g. Parkinson's disease) or documented clinical features that strongly imply such a diagnosis (e.g. treatment with dopaminergic therapy, a clinical label of 'dementia' or 'parkinsonism'). In the U.K. the diagnosis of such disorders is almost exclusively made in secondary care. Even for comparatively common neurodegenerative conditions, such as Parkinson's disease, specialist review is recommended prior to a formal diagnosis. For FTLD associated syndromes it is extremely unlikely that the diagnosis would be made exclusively in the primary care setting.

Nath et al's study(96) demonstrates how differences in the approach used to identify cases changes epidemiological estimates. In order to identify the prevalence of PSP in the UK they sought to identify cases of PSP nationally (from a population of 60m), regionally (from a subpopulation of 2.58m of the national study) and at a community level (from a subpopulation of 260,000 of the regional study). Case identification at the national level was by passive reporting from specialists with an interest in movement disorders and the British Neurological Surveillance Unit (a national register of neurologists who are asked to report cases of rare neurological disease on a monthly basis), mortality data from the Office of National Statistics (all patients where PSP was included on the death certificate). The regional study included case reporting from local specialists but also regional database review and screening of unselected correspondence from all neurologists, geriatricians and GPs who agreed to participate. The community study screened GP records for key words associated with PSP or Parkinsonism and then review for features of PSP. Where possible patients were seen in person or case records reviewed for diagnostic validation. Crude prevalence rates increased as the population size decreased (from 1.0/100,000 for the national population of 29m and 6.5/100,000 for community population of 129,000) demonstrating that epidemiological estimates are influenced by methods of case ascertainment and also that more involved active case ascertainment has the potential to identify a greater number of cases than more passive referral methods.

## 2.4 Rationale for a New Study of FTLD Associated Syndromes: The PiPPIN Study.

Previous studies of the epidemiology of FTLD associated syndromes have considered syndromes individually but not the entire spectrum of syndromes associated with FTLD. For each study the 'disease under study' has been defined with reference to clinical diagnostic criteria for individual or subgroups of syndromes associated with FTLD. This raises a number of issues. Firstly the clinical criteria used to diagnose FTLD associated syndromes have been subject to revision over recent years(11–13,35) reflecting advances in our understanding of the underlying pathology and expansion of recognised phenotypic associations. Second, patients may move between clinical syndromes as their condition progresses and the associated syndrome evolves(85). For example, a patient with Tau pathology may initially present with subtle cognitive or behavioural changes before developing a more marked language disorder, sufficient for a diagnosis of PPA, then later acquiring a movement disorder sufficient for a diagnosis of CBS or PSP. Such a patient may at some stages of their condition meet criteria for several FTLD associated diagnoses, or non-at-all. Such transitional and intermediate cases should be included in studies of the epidemiology of FTLD but illustrate that when considering the entire spectrum of FTLD associated syndromes the sum of prevalence/incidence estimates for individual syndromes may overestimate the true extent of some syndromes (by counting some overlap cases more than once) and underestimate others (by disregarding intermediate cases that fall between criteria). Finally different epidemiological studies of FTLD associated syndromes used different methods. As discussed earlier this may have significant effects on the resulting epidemiological estimates. Methodological limitations are, to some extent, unavoidable but are particularly problematic when attempting to compare between studies and make an assessment relative prevalence of particular FTLD associated syndromes difficult.

Dementia and other neurodegenerative diseases are amongst the greatest health and social challenges in the developed world(114). Key to addressing these challenges are accurate and up to date epidemiological estimates that reflect the true spectrum of disease and the manner in which it presents. Over the last few decades our understanding of FTLD has evolved. While prior studies of the epidemiology of FTLD have demonstrated that it is an important cause of dementia and disability, methodological limitations restrict comparability between studies and our ability to estimate the true impact and spread of FTLD associated syndromes. There is a clear need for further epidemiological studies of FTLD associated syndromes that takes account of the revised criteria, uses a standardised population and takes an inclusive and transdiagnostic approach to the syndromes associated with FTLD that takes account of intermediate and transitional syndromes.

I devised and conducted a new study of FTLD associated syndromes entitled PiPPIN (Pick's disease and Progressive supranuclear palsy Prevalence and INcidence). Over two years I aimed to collect a representative cohort of patients with FTLD associated syndromes and in view of the limitations of previous epidemiological studies of individual syndromes associated with FTLD I aimed to simultaneously address these firstly by considering all major FTLD associated syndromes together and without particular age restrictions and secondly by using the recently revised diagnostic criteria with additional consideration of intermediate clinical syndromes.

## 2.5 Methods

### 2.5.1 Ethical Approval and Consent

The PiPPIN study was approved by the Cambridge 2 Research Ethics Committee. Referring local services were required to record consent for case notification, and those patients who underwent assessment within the study (including notes review) provided additional written informed consent. Where patients lack capacity to consent, I gauged their willingness to consider research participation at a level compatible with their cognitive abilities, but also consulted an appropriate nominated person. This consultee is usually the spouse, but may include a holder of Lasting Power of Attorney, IMCA, an appropriate next of kin or nominated consultee as outlined in the Mental Capacity Act (2005).

### 2.5.2 Study Population

The catchment area included the counties of Cambridgeshire and Norfolk in the East of England. I used geographic boundaries as defined by the Office for National Statistics (ONS) which is freely available online. Boundaries used were as per 2011 census boundaries(115). The counties contain three cities, Cambridge, Peterborough and Norwich, two of which contain tertiary referral centres (Addenbrooke's hospital in Cambridge and the Norfolk and Norwich University Hospital in Norwich). Peterborough has a large secondary care Hospital, and two other medium sized district general hospitals (the Queen Elizabeth Hospital and James Paget University Hospital) are situated in Norfolk. Additional smaller healthcare units are situated in the area and several mental health trusts, residential and nursing care homes.

Demographic data for both counties are available from the ONS. The 2013 UK Office for National Statistics mid-year estimates(115) were used as the denominator for estimates of prevalence, incidence and mortality. The combined population of the catchment area was 1.69 million. This area is further subdivided into 13 local authority districts with populations of 85,398-188,373(115).

### 2.5.3 Definition of Disease Under Study

The disease entity under study was FTLD associated syndromes. Specifically bvFTD, PSP, CBS, PPA. These were as defined by the contemporary diagnostic criteria for bvFTD(10), PPA syndromes(11), PSP(13) and CBS(12), noting that the PSP criteria changed soon after PiPPIN.

In order to be inclusive of all cases within the spectrum of FTLD-associated disorders, special consideration is required when applying the criteria to cases that lie at a boundary

between two categories, or who present with an overlap of clinical features. For example, a hypothetical patient may present with an atypical semantic variant of PPA, with their principal complaint being the language disorder, and typical in respect of the language examination but with predominant behavioural disturbance under observation. Such a patient may lie outside of the svPPA criteria(11) but also not meet bvFTD criteria in view of the level of semantic deficits and absence of other bvFTD features. Excluding such a patient would underestimate prevalence of the aggregated FTLD-associated syndromes.

Conversely, another patient might meet criteria for CBS-NAV(12) but also nfvPPA(11). Such a patient should clearly only be counted once when estimating the aggregated epidemiology of FTLD-associated syndromes, even if they might be counted twice in separate studies of PPA and CBS. I did not consider exclusion criteria for one particular syndrome absolute where they would be considered inclusion criteria for another FTLD associated syndrome. For example behavioural disturbance did not automatically result in an otherwise typical case of svPPA being excluded. However exclusion criteria that do not form inclusion criteria for other FTLD associated syndromes (for example biomarkers strongly predictive of Alzheimer's disease) remained as exclusion criteria for this study. Where I refer to individual syndromes within the spectrum of FTLD I refer to the dominant clinical syndrome at the time of assessment. Where there was diagnostic ambiguity a second clinician (my supervisor Professor Rowe) reviewed the case and a consensus was reached, based on the major syndromic features and with the principle that each subject counts only once.

### 2.5.4 Prevalent Cases

In line with most previous studies I defined prevalence as point prevalence such that a prevalent case was defined as: A subject alive and resident within the catchment area on 1st January 2014 with a diagnosis of neurodegenerative disease and with a FTLD associated syndrome.

The date 1st January 2014 was used as it was the midpoint of the two years that the study ran for. Place of residence was defined as the subject's home address. Postcodes were checked against the ONS boundary data to ensure that the subject was resident within the catchment area.

### 2.5.5. Incident Cases

Incident cases were defined as those subjects with an FTLD associated syndromes who were diagnosed with a neurodegenerative disease between 1st 2013 and December 31st 2014. In order to maximise case referral I encouraged clinicians to refer cases who did not have a formal

diagnosis of an FTLD associated syndrome (but where it was a considered a possibility). The date of diagnosis was defined as that date at which a neurodegenerative disorder was first considered as a likely cause of the patient's symptoms by a clinician experienced in their diagnosis (this was a Neurologist, Psychiatrist, Geriatrician or Registrar working within these specialities). I also recorded the date at which a specific FTLD-associated diagnosis was first considered and the date which the earliest symptom of dementia was noted by the patient or carers. From these I was able to calculate age at onset, diagnosis and FTLD-associated diagnosis.

### 2.5.6 Methods for Case Identification

I sought to identify all prevalent and incident cases between January 1st 2013 and December 31st 2014. A major source of recruitment were specialist regional services for FTLD associated syndromes and the regional memory clinic namely:

1. The Cambridge Memory Clinic. This is a specialist clinic for disorders of memory, cognition and dementia. Held weekly in Addenbrooke's Hospital in Cambridge.

2. The Cambridge Early Dementia Clinic. Despite its name this is a clinic set up primarily for the diagnosis, treatment and follow up of atypical dementia occurring in all age groups but with a particular focus on FTD. It is the only specialist clinic of it's kind in East Anglia. Approximately two clinics are held each month at Addenbrooke's hospital in Cambridge.

3. The Cambridge Disorders of Movement and Cognition Clinic. This is a specialist clinic for the diagnosis, treatment and follow up of neurodegenerative movement disorders, particularly PSP and CBS. Approximately two clinics are held each month at Addenbrooke's hospital in Cambridge.

All three clinics receive referrals from primary, secondary and tertiary care services for dementia, Parkinson's disease and related disorders, MND, adult neurology, medicine for the elderly, adult- and old-age psychiatry; memory clinics; and regional community based specialist nurses for Parkinson's disease, Young Onset Dementia and Dementia. These potential referral sources were additionally contacted in person, letter and email before and during the study. Case notification was encouraged even for cases who were not referred to the specialist clinics.

All three clinics routinely ask for consent to collect and store patient details for research purposes. They have detailed databases of patients seen over many years for either clinical or research purposes (including prior epidemiological estimates of FTD and young onset dementia(76)). To identify people who were alive but no longer under regular follow-up I

searched these databases for all cases with a relevant diagnosis seen between 2003 and 2013. I then confirmed survival and residence in the catchment area by clinical records.

I also accepted direct referrals from clinical research networks including the National Institute for Health Research Clinical Research Network Dementias and Neurodegeneration Speciality and the West Anglia Clinical Research Network. I also assessed patients notified by self-referral.

To raise and maintain awareness of PiPPIN and promote case notification of patients with a diagnosed or suspected FTLD associated syndrome, I made frequent presentations to relevant national and regional conferences, meetings, research groups, support groups and charities. It was emphasised that travel to Cambridge was not a prerequisite to inclusion in the study, nor was participation in more in depth research.

To encourage self referral I placed adverts in local newspapers for the PiPPIN study, was interviewed for a national newspaper (that placed a link to the PiPPIN study on its website) and sent letters of invitation to all members of the local and national charities (including the UK FTD support group and the PSP Association) resident within the PiPPIN area.

After the two-year recruitment period I continued to recruit for a further four month period (until 31st April 2015) to allow for late case notification of patients who were alive and had a relevant diagnosis between 1st 2013 and December 31st 2014. The definitions of prevalent and incident cases still applied.

### 2.5.7 Case confirmation

For all patients who were willing to be reviewed by the PiPPIN study team applied the revised diagnostic criteria, based on clinical interview, physical examination and review of relevant tests including brain imaging. I personally reviewed the majority of cases, those who were not seen by me were seen by Professor Rowe. These assessments included:

(i) Semi-structured interview of subject and carer for clinical history and demographic data.

(ii) Structured patient and carer assessment of relevant symptoms and severity.

(iii) Structured assessment of speech, language and cognition;

(iv) Neurological examination

(v) Results of investigations during clinical diagnosis were accessed from the patient's medical records including neuropsychological assessments, neuroimaging and genetic testing.

(vi) Genetic screening for 17 known genetic causes of FTLD and non-FTLD dementia(116).

(vii) MRI of the brain

(viii) Detailed multimodal assessment of decision making and behaviour

I did not expect that all participants could complete all steps. I took a pragmatic approach and where physical or cognitive disability limited the assessment possible I took a pragmatic approach restricting assessments to those the participant could reasonably undertake and prioritising diagnostic validation. For cases that were unable or unwilling to be assessed in person I accessed existing medical records.

### 2.5.8 Epidemiological Estimates

Incidence per 100,000 person-years was calculated using the formula:

$$\frac{i}{aP}100{,}000$$

Where i=number of incident cases, P=total population under study, a =number of years cases identified over (for the PiPPIN study a=2.0).

Crude prevalence per 100,000 persons was calculated using the formula:

$$\frac{p}{P}100{,}000$$

Where p= number of prevalent cases, P=total population

To identify any regional differences in case identification, I also calculated crude prevalence rates for each local authority.

To allow comparison with other studies I also calculated standardised rates were calculated using the Revised European Standard Population 2013 (ESP2013). This is a hypothetical population that assumes equal age structure between sexes. It was recently revised to account for changes in the age structure of European member states since the 1970s.

| Age | Population | Age | Population |
|---|---|---|---|
| <1 | 1,000 | 50-54 | 7,000 |
| 01-04 | 4,000 | 55-59 | 6,500 |
| 05-09 | 5,500 | 60-64 | 6,000 |
| 10-14 | 5,500 | 65-69 | 5,500 |
| 15-19 | 5,500 | 70-74 | 5,000 |
| 20-24 | 6,000 | 75-79 | 4,000 |
| 25-29 | 6,000 | 80-84 | 2,500 |
| 30-34 | 6,500 | 85-89 | 1,500 |
| 35-39 | 7,000 | 90-94 | 800 |
| 40-44 | 7,000 | 95+ | 200 |
| 45-49 | 7,000 | | |
| | | **Total** | **100,000** |

**Table 2.3 The 2013 European Standard Population**

Standardisation is performed using the following formula

$$\frac{\sum a_i A_i}{\sum A_i}$$

Where $a_i$=observed frequency of cases (prevalence, incidence or mortality) within age/sex range I, and $A_i$=standard population in age/sex group i.

Confidence intervals for standardisation were generated using the formula:

$$1.96 \pm \frac{r}{\sqrt{\Sigma n_i}}$$

Where r=standardised rate and $n_i$=number of observed cases in age/sex group i.

### 2.5.9 Lifetime Risk

While prevalence and incidence figures, expressed per 100,000 persons or person-years are useful for comparison between groups and diseases, it can be difficult to appreciate how they relate to an individual's risk or a real world perspective. Because of this alternative calculations are commonly used in literature especially that aimed at the general public or which seeks to raise awareness or the profile of a particular disease group. A commonly used figure is lifetime risk the probability of an individual developing a disease or condition during their life, adjusted for the risk of dying from other causes first. This has been used effectively in cancer(117), dementia(118) and MND(119).

I calculated age- and sex-standardised lifetime risk using the current probability method(120,121). Note that unlike population estimates ONS mortality rates are reported in ten-year age bands (with the exception of the oldest age band and the 0-5 year youngest age band) so I combined adjacent five-year age bands from the ONS population estimates, and observed prevalence and death rates from my data to form corresponding ten year age bands. First, for each ten year age band the number of incident cases and cases of FTLD who had died over the two years the study ran were divided by two to give average yearly FTLD associated incident and mortality cases within the catchment area. Males and female cases were calculated separately before standardising to the ESP2013 to give age and sex standardised rates. The ONS mortality figures for each age band were also standardised to the ESP2013.

Next I calculated the current probability of being diagnosed with FTLD (adjusting for the risk of dying of other causes) for each age band using a life table approach(122,123). First the probability of dying, $p(D_i)$, is calculated for each age band, i, is calculated:

$$p(D_i) = \frac{2Y_{i-1}\frac{M_{i-1}}{P_{i-1}}}{2 + Y_{i-1}\frac{M_{i-1}}{P_{i-1}}}$$

Where $M_i$=all cause deaths in age band I; $P_i$=total population in age band I; $Y_i$=years in age band i

Then the percentage alive at each age band, $N_i$, is calculated:

$$N_i = N_{i-1} - (N_{i-1}.p(D_i))$$

Where $N_0$=100

Next the age specific incidence $A_i$ and person-years in the age band $B_i$:

$$A_i = \frac{I_i}{P_i}$$

$$B_i = Y_i(N_i + N_{i+1})/2$$

Where $I_i$=FTLD incident cases in age band i

Allowing the current probability, $C_i$, to be calculated for the age band:

$$C_i = A_i.B_i$$

This method assumes equally sized age bands. Special consideration is required for the youngest and oldest age bands. ONS Mortality data reports deaths in the first 5 years of life separately leading to a smaller age band of five years for $i_0$. The oldest age group, $i_9$, begins at 85 years and has no upper limit.

To account for these I adjusted the formula for $B_0$ and $B_9$:

$$B_0 = \frac{(5N_o + 10N_1)}{3}$$

$$B_9 = \frac{N_9}{\left(\frac{M_9}{P_9}\right)}$$

The lifetime risk, R, for a diagnosis of FTLD can be calculated as a percentage:

$$R = \sum_{i=0}^{i=9} C_i$$

Which can be expressed as a particular risk (i.e. 1 out of every X people) by the inverse of R.

**2.6 Results**

Two hundred and thirty four patients were assessed: 176 from specialist clinical services, 52 from clinical and research databases and six subjects were referred directly to the study team and not seen in a clinical service at the study centre. Thirty patients were rejected after review (15 with non FTLD associated diagnoses, 14 out of catchment area and 1 with onset after the recruitment window). The non FTLD diagnoses were; phenocopy syndrome (3), AD (2), Bipolar disorder (1), Obsessive Compulsive Disorder (1), Parkinson's Disease (1), Parkinson's Disease Dementia (1), Dementia with Lewy Bodies (1), Dystonia (1), Stroke (1), Multi Systems Atrophy (1). The two hundred and four remaining cases of FTLD-associated syndromes were identified in the catchment area over the study period of which 167 (81.7%) were seen in person by the study team. Clinical records of consultant neurologist or psychiatrist assessments were available in all of the remaining cases and detailed information sufficient to apply the diagnostic criteria available for 200 (90%) cases. Two patients with PSP and two with FTD-MND had only limited information.

### 2.6.1 Demographics and Symptom Profile

Table 2.4 shows the age, clinical features and years since symptom onset at assessment date.

| Dominant Clinical Syndrome | All | bvFTD | PSP | CBS | nfvPPA | svPPA | PPA (Other) |
|---|---|---|---|---|---|---|---|
| Total cases | 200 | 42 | 48 | 48 | 28 | 23 | 11 |
| M:F | 93:107 | 19:23 | 29:19 | 17:31 | 11:17 | 12:11 | 5:6 |
| Mean Age at assessment (SD) | 69.4 (8.7) | 63.7 (7.9) | 72.6 (7.8) | 70.8 (8.5) | 70.6 (9.8) | 66.7 (6.7) | 72.6 (7.8) |
| Mean years from onset to assessment (SD) | 4.3 (2.9) | 4.4 (3.0) | 4.7 (3.5) | 4.4 (2.7) | 3.7 (2.5) | 4.4 (2.7) | 4.2 (2.3) |
| Behavioural changes (%) | 158 (79) | 42 (100.0) | 40 (83.3) | 36 (75.0) | 13 (46.4) | 22 (95.7) | 5 (45.5) |
| Apathy (%) | 107 (53.5) | 34 (81.0) | 29 (60.4) | 25 (52.1) | 7 (25.0) | 9 (39.1) | 3 (27.3) |
| Impulsivity/Disinhibition (%) | 92 (46.0) | 37 (88.1) | 24 (50.0) | 14 (29.2) | 6 (21.4) | 10 (43.5) | 1 (9.1) |
| Language impairment (%) | 138 (69.0) | 31 (73.8) | 13 (27.1) | 32 (66.7) | 28 (100.0) | 23 (100.0) | 11 (100.0) |
| Impaired naming/Semantic knowledge (%) | 82 (41.0) | 24 (57.1) | 3 (6.3) | 10 (20.8) | 12 (42.9) | 23 (100.0) | 10 (90.9) |
| Agrammatism/Impaired comprehension of syntactically complex sentences (%) | 86 (43.0) | 14 (33.3) | 9 (18.8) | 25 (52.1) | 24 (85.7) | 5 (21.7) | 9 (81.8) |
| Expressive errors (phonological errors, apraxia of speech, impaired sentence repetition) (%) | 75 (37.5) | 9 (21.4) | 9 (18.8) | 23 (47.9) | 24 (85.7) | 1 (4.3) | 9 (81.8) |
| Akinesia (%) | 110 (55.0) | 27 (64.3) | 43 (89.6) | 30 (62.5) | 5 (17.9) | 3 (13.0) | 2 (18.2) |
| Rigidity (%) | 85 (42.5) | 9 (21.4) | 41 (85.4) | 33 (68.8) | 1 (3.6) | 0 (0.0) | 1 (9.1) |
| Dystonia (%) | 58 (29.0) | 4 (9.5) | 28 (58.3) | 26 (54.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Apraxia (%) | 108 (54.0) | 12 (28.6) | 25 (52.1) | 45 (93.8) | 16 (57.1) | 2 (8.7) | 8 (72.7) |
| Cortical sensory loss (%) | 43 (21.5) | 1 (2.4) | 12 (25.0) | 27 (56.3) | 2 (7.1) | 0 (0.0) | 1 (9.1) |
| Slowed vertical saccades/Supranuclear gaze paresis (%) | 76 (38.0) | 3 (7.1) | 47 (97.9) | 22 (45.8) | 2 (7.1) | 0 (0.0) | 2 (18.2) |
| Postural instability/falls (%) | 89 (44.5) | 7 (16.7) | 47 (97.9) | 32 (66.7) | 2 (7.1) | 0 (0.0) | 1 (9.1) |
| Features of Motor Neuron Disease (%) | 9 (4.5) | 8 (19.0) | 0 (0.0) | 1 (2.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Myoclonus (%) | 44 (22.0) | 6 (14.3) | 4 (8.3) | 26 (54.2) | 5 (17.9) | 0 (0.0) | 3 (27.3) |

**Table 2.4. Clinical features by dominant clinical syndrome at the time of detailed clinical assessment for 200 of 204 cases identified during the PiPPIN study.** Assignment to each syndrome was made on the basis of the primary aspect(s) of the disorder at presentation; additional features may develop overtime and are indicated at the time of PiPPIN participation to indicate the deficits in prevalent cases, not limited to incident cases.

### 2.6.2 Prevalence

One hundred and eighty two cases were alive on 1st January 2014 (89 men, 93 women) giving a crude prevalence of 10.77/100,000, The European-standardised prevalence (95% confidence intervals) were: men 10.93/100,000 (8.66-13.20), women 10.76/100,000 (8.57-12.95) and sex-standardised 10.84 (9.27-12.42).

Figure 2.1 shows crude prevalence rates by local authority boundaries, age of diagnosis and syndrome. Prevalence rates by local authority ranged from 4.09-21.7/100,000 and did not appear to be affected by proximity to the major urban centres (marked by asterisks) or the study centre.

The youngest case was 41 years at diagnosis. The ESP2013 age- and sex-standardised prevalence for the age range 40-64 was 13.05 (10.01-16.08) and 33.20 (27.02-39.37) for those over 65 years.

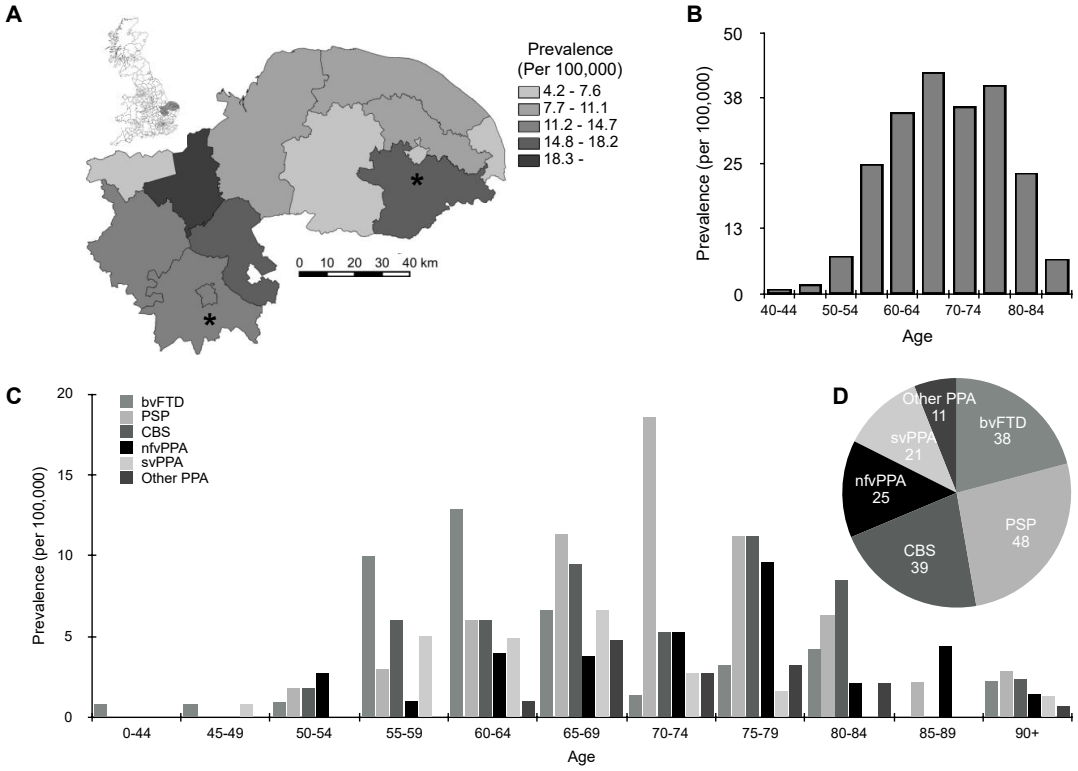



**Figure 2.1 The Prevalence of Frontotemporal Lobar Degeneration Associated Syndromes.** **A** Shows the prevalence by local authorities within Norfolk and Cambridgeshire, *denote the two tertiary referral centres. Contains National Statistics and Ordinance survey Data © Crown copyright and database right (2013). **B** Shows prevalence by age band. **C** Shows prevalence of individual syndromes by age band and **D** shows the distribution of syndromes amongst prevalent cases.

### 2.6.3 Incidence and Lifetime Risk

Fifty-three Incident cases were identified (24 men, 29 women) over 3,381,228 person-years giving crude and standardised incidence rates of 1.57 and 1.61 (1.14-1.99) per 100,000 person-years respectively. Figure 2.2 shows the crude incidence rates by age at onset and neurodegenerative diagnosis across all syndromes by age group. The lifetime risk (standardised for age and sex) was 1-in-742.

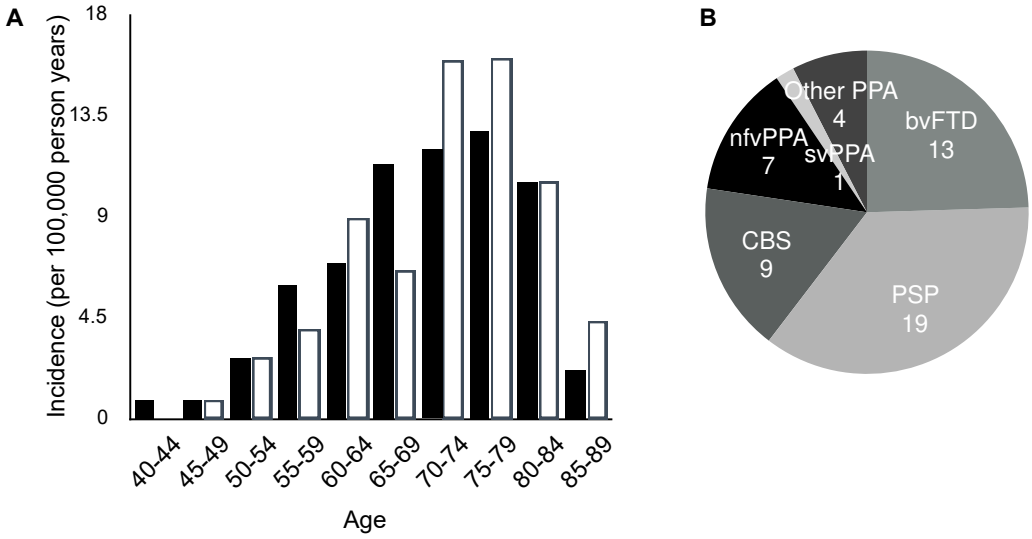



**Figure 2.2 The Incidence of FTLD Associated Syndromes.** **A.** The incidence of Frontotemporal Lobar Degeneration associated syndromes by age of onset (black bars) and by age at diagnosis (white). **B.** The distribution of incident cases by clinical syndrome.

### 2.6.4 Survival

Dates of birth, symptom onset, neurodegenerative and FTLD-associated syndrome diagnoses were available for 193 (95%) cases. Missing data were substituted by the mean within syndrome. Fifty-four cases (23 men, 31 women) died during the assessment period giving an age-adjusted all-cause mortality amongst those with FTLD of 1.57 (1.15-1.99) per 100,000 person-years. As of 31st April 2015, 6 further cases have died. Figure 2.3 shows the mean length of symptomatic disease split by time prior to a neurodegenerative diagnosis, FTLD diagnosis and death for all 60 cases that have died.

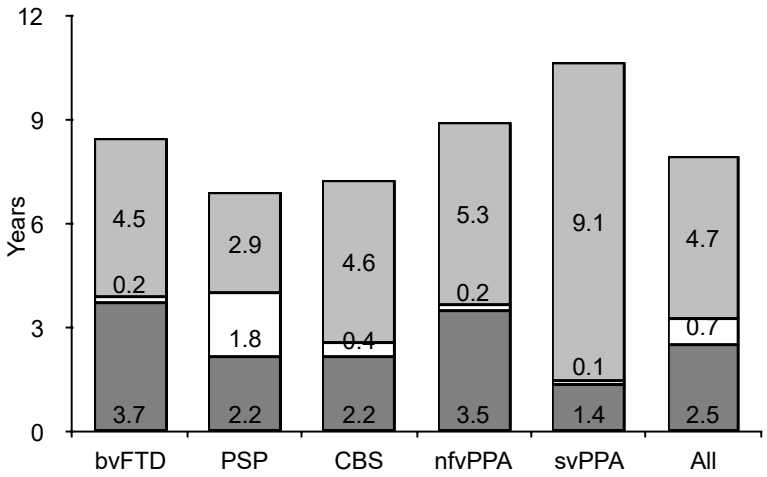



**Figure 2.3 The Survival With FTLD Associated Syndromes.** Mean duration from the onset of symptoms to the diagnosis of a neurodegenerative disorder (dark grey); to the specific diagnosis of a FTLD associated syndrome (white); and to death (light grey) for all 60 cases who have died since the start of the PiPPIN study. Inserted figures indicate the mean duration of each phase for each syndrome (years).

### 2.6.5 Genetic Screening

Forty-seven subjects (23%) underwent genetic screening (5 svPPA, 11 nfvPPA, 4 PPA(Other), 17 bvFTD, 3 CBS, 1 PSP). Seven (14.9%) subjects carried a relevant mutation (Table 2.5).

| Mutation | Clinical Syndrome | Age at Onset | Age at Diagnosis | Age at PiPPIN Assessment | Presenting Clinical Features | Additional Features at PiPPIN Assessment |
|---|---|---|---|---|---|---|
| PGRN c.385_388 delAGTC | navPPA | 55 | 57 | 60 | Progressive speech disturbance, word substitutions, impaired repetition, phonological errors, impaired comprehension of complex tasks, orobuccal apraxia. MRI: Marked left frontotemporal atrophy. | Rigid fixed routine, inappropriate giggling, jargon aphasia with phonological errors |
| MAPT c.-46G>A | lvPPA | 69 | 71 | 72 | Progressive speech difficulty, non fluent stuttering speech, phonological errors, length dependent impaired repetition. MRI: Global atrophy worst left temporo-parietally. | Mild episodic memory, visuospatial deficits, mild limb dyspraxia, myoclonus |
| TARDBP c.1147A>G | bvFTD | 49 | 56 | 58 | Insidiously progressive behavioural change, apathy, reduced empathy, fixed daily routine. MRI: Bilateral anterior temporal atrophy. | Semantic deficits, weakness and wasting of leg and paraspinal muscles, EMG confirmation of MND |
| MAPT c.1007A>G | svPPA | 62 | 63 | 67 | Isolated difficulty reading and understanding meaning of words. MRI: Bilateral anterior temporal atrophy worst on left. | Behavioural changes, disinhibition, apathy, fixed routine and loss of empathy |
| C9ORF72 | bvFTD | 57 | 57 | 60 | Dysexecutive, apathetic syndrome, social withdrawal reduced empathy. MRI: global atrophy, worst frontally | Marked apathy, mute, mobile but with falls, no signs of motor neuron disease. |
| TREM2 c.140G>A | CBS-NAV | 61 | 63 | N/A* | Word finding and articulatory impairments. Agrammatic non fluent speech, equivocal apraxia visuospatial impairment, mild asymmetric bradykinesia, MRI: biparietal atrophy, worst on right, right temporal atrophy | *Marked behavioural disturbance, aggression, dyskinesia, dystonia, grasping behaviour, supranuclear gaze palsy, myoclonus. |
| C9ORF72 | bvFTD | 64 | 65 | N/A* | Prominent behavioural change, disinhibition, dysexecutive cognitive profile. MRI: Within normal limits. | *Extrapyramidal syndrome (attributable to medication), falls. Normal DAT scan. MRI: Mild generalized atrophy |

**Table 2.5 Clinical and imaging features of the seven subjects with an identified relevant mutation.** *These two subjects were not re assessed in person as part of the PiPPIN study. The clinical features are based on their clinical records subsequent to first presentation. PGRN-Progranulin, MAPT-Microtubule Associated Protein Tau, TARDBP –Transactive response DNA binding protein, C9ORF72 –Chromosome 9 Open Reading Frame 72, TREM2-Triggering Receptor Expressed on Myeloid Cells 2.

## 2.7 Discussion

In this chapter I combined point-prevalence with an unrestricted age-range and the 2011/2013 revised diagnostic criteria for major FTLD-associated clinical syndromes. By not restricting analysis to either young-onset cases or tertiary referral centres I show that the prevalence of all disorders taken together is 10.84/100,000 with similar prevalence of bvFTD, PSP and CBS and PPA (all subtypes). The estimated lifetime risk of one of these disorders is 1-in-742.

Many previous epidemiological studies restricted assessment of the under 65 population (76,79,80,88,89,91). My data indicate that prevalence increases beyond 65, such that the prevalence amongst those 65 years and older is more than double that of the 40-64 year age group. While FTLD is one of the commonest causes of young onset dementia(80,92) it is more common in absolute terms as age increases. Previous studies emphasising the relative prevalence amongst all causes of dementia in younger cohorts may have the unintended effect giving the impression that FTLD is a disease of middle age, reducing the index of suspicion in older cohorts and hence reducing rates of diagnosis in the elderly. This may in part explain the decease in incidence and prevalence rates I observed in the very elderly. Rather than a true decline in the incidence of FTLD in old age it may be that as other forms of dementia, such as Alzheimer's and vascular disease, become more common, FTLD becomes overshadowed. As a consequence it is not considered and not diagnosed.

To illustrate this point, one of the more elderly cases of PSP I identified in this study had previously been referred to our clinical services by a clinician who suspected PSP. The patient's general practitioner had subsequently written to question whether a referral was necessary as the patient already had an established diagnosis of Alzheimer's dementia and it was not clear what another neurodegenerative diagnosis (if present) would add to their care. The patient was reviewed on a research basis and had clear features of PSP-RS. In retrospect all of the cognitive and speech impairments that had been attributed to Alzheimer's disease were more typical of FTLD (namely a non-fluent, dysexecutive syndrome, bradyphrenia and dysarthria). While rising rates of non-FTLD neurodegeneration (e.g. Alzheimer's disease) may overshadow less common conditions, such as FTLD, another potential explanation for the decrease in prevalence and incidence rates in the very elderly is that additional pathology alters the clinical phenotype such that FTLD is not simply under-recognised but also not recognisable. As rates of vascular and Alzheimer's pathology increase it is possible that these change the clinical phenotype of FTLD when it is present such that patients with FTLD do not resemble FTLD in younger cohorts and do not meet current criteria. One study showed neuropathologically defined Alzheimer's

disease in a third of people over 85 years(124) half of these had clinically diagnosed Alzheimer's disease which would preclude a diagnosis of FTLD by current criteria and also very likely change the clinical presentation and severity of FTLD pathology when it does occur.

Previously, many studies have been restricted to individual syndromes. For example some studies of the prevalence of FTD have included behavioural and language variants(76,89,91) while others are restricted to just bvFTD(79,80,88). This limits comparability between studies. Also the diagnostic criteria used in these studies may have included non progressive 'phenocopies'(36). During the PiPPIN studies I identified (and excluded) three such cases (all men, two within the catchment area, one outside). The discovery of C9ORF72 has renewed interest in phenocopies. Both cases within the catchment area that I excluded were negative for C9ORF72. One slowly progressive cases case was identified (and included) who at initial presentation had normal neuroimaging and would not have met current criteria for probable bvFTD. They subsequently developed generalised atrophy and were found to carry a pathological expansion in C9ORF72.

Epidemiological studies of PSP have mainly used case-notification to specialist centres, or reviewed cases of Parkinsonism. For example, Golbe et al.(97) surveyed neurologists for cases of suspected PSP, re-examining suspected cases. They estimated a prevalence of 0.15/100,000 and incidence of 0.3-0.4/100,000. In contrast, Schrag et al.(86) used a computerised search of terms relating to Parkinsonism and clinical re-evaluation to estimate prevalence of 6.4/100,000 (2.3-10.6). Nath et al.(96) used both methods to estimate prevalence of 0.3 and 5.0/100,000. These studies focused on the motor aspects of PSP, whereas non-motor features are common in PSP, suggesting that previous studies may not have identified the significant proportion of cases (up to 30%) who present initially with cognitive or behavioural features of PSP(111).

There are limited data on the epidemiology of CBS. From 534 incident cases of Parkinsonism, Winter et al.(108) identified one case of CBS. Schrag et al.(86) identified no cases amongst a population of 121,628. A limiting factor for studies of CBS is diagnostic uncertainty. Fewer than 2/3 of cases with a diagnosis of CBS have pathological features of Corticobasal Degeneration and vice versa(7). This is the first epidemiological study of CBS to use the revised diagnostic criteria(12) which aim to improve sensitivity. I also did not restrict the cohort to movement disorder clinics or incident cases of Parkinsonism. By selecting cases based on both motor and non-motor aspects of their illness, we were able to identify substantially more cases than previous studies(86,108).

I have estimated the prevalence for FTLD associated syndromes for each of the local authority areas within the catchment area for the PiPPIN study (Figure 2.1 A). The population size for these areas ranges from approximately 85,000 to 190,000 with small numbers of individual cases in each area. It is therefore unsurprising to see large variation in the prevalence estimates for these small groups. The area with the highest prevalence (Fenland) is relatively small in population terms but does have a high number of nursing homes that provide specialist dementia care for a wider area which may explain the high number of prevalent cases resident there. This demonstrates the importance of a large catchment area/population of study when estimating the epidemiology of rarer diseases.

Despite improved criteria, diagnostic difficulties remain that will impact on epidemiological research, especially for studies that focus on one syndrome rather than the broader spectrum of FTLD-associated syndromes. Categorical decisions are required for diagnosis; however, the boundaries between FTLD-associated syndromes are not always distinct. 95% of the cases of svPPA identified here developed behavioural changes within a mean of 4.35 years from onset. Conversely, nearly three quarters of bvFTD subsequently developed language impairment. Similarly language impairments were common in CBS (66.7%), behavioural changes in PSP (83.3%) and motor features commonly emerged in all FTD subtypes. This inclusive approach does not undermine the importance of diagnostic classification but emphasises the heterogeneous and progressive nature of these disorders. Without an inclusive approach to the FTLD spectrum, borderline or intermediate phenotypes reduce the precision of prevalence estimates of individual disorders. Furthermore the nosology and nomenclature of FTLD syndromes have changed many times(85) and will no doubt continue to do so.

Within the spectrum of FTLD, the pathological subtypes of FTLD are each associated with more than one clinical syndrome and vice versa. I cannot speak to the pathology of these cases (except in the genetic cases), and instead reference published studies of clinicopathological correlation(7,25,125–128).

Whilst I sought to identify and examine all cases where FTLD was considered, those cases in which it was not will have been missed. To overcome this fundamental limitation of an epidemiological study of diagnosed cases, systematic neuropathology in a population cohort would be required.

In a brain bank series from a community based study of the elderly(129), three out of 456 post-mortem cases had evidence of PSP. All had symptoms that could be retrospectively

attributed to PSP but none were diagnosed during life (Brayne C. et al, Unpublished data, 2014). Recruitment to brain banking in this study was disproportionately weighted to those with symptoms of dementia so while these data can not be used to draw firm conclusions regarding the actual prevalence of FTLD they do suggest that the prevalence of FTLD *pathology* may be higher than that of diagnosed cases that we report here.

It is also inevitable that pre- or oligosymptomatic subjects who nevertheless have FTLD pathology will not acquire a diagnosis of FTLD until sufficient neural disruption/degeneration has developed to produce symptoms sufficient to establish a diagnosis. By examining presymptomatic carriers of pathogenic gene mutations causing FTLD Rohrer et al.(56) showed that imaging and cognitive changes can be demonstrated 5-10 years before the expected onset of symptoms (calculated using the average age of onset within families). How these results relate to sporadic cases is unclear. I would argue that truly presymptomatic cases should be considered differently to symptomatic disease for the purposes of epidemiological research. The inclusion of presymptomatic disease in epidemiological studies would inflate epidemiological estimates and potentially overestimate the true burden of (symptomatic) disease. It is less clear how one should consider oligosymptomatic cases i.e. people who have FTLD type pathology and exhibit symptoms that are related to it but who do not yet have sufficient symptoms to establish a diagnosis. Such people have symptomatic FTLD and associated morbidity but with current criteria cannot be reliably diagnosed or differentiated from other conditions.

FTLD presents insidiously and as such time of onset can be difficult to establish. Current criteria provide a threshold of disease burden that must be reached and a surrogate for incident/prevalent cases but when using several sets of criteria for different clinical syndromes it is not necessarily the case that all patients are at the same stage of disease (in terms of life expectancy, disability burden, amount of neurodegeneration, or any other measure) at the point at which they first meet criteria. This is illustrated by the cases who have died (Figure 2.3). Although accepting that the numbers of patients are small, compared to other FTLD associated syndromes those patients with svPPA were diagnosed with a neurodegenerative illness relatively soon after symptoms first emerged and quickly with an FTLD associated diagnosis which they then lived with for a long time before death. Subjects with other syndromes had symptoms for longer before reaching a diagnosis and died sooner. Hence it may be that a patient who has accrued sufficient symptomatic disease to acquire a diagnosis by current criteria of svPPA may not be at the same stage of their illness as another who just meets criteria for PSP.

Since undertaking the PiPPIN study a new set of criteria have been published for

PSP(130). These criteria expand the range of clinical syndromes associated with PSP pathology and suggest (for example) subjects with predominantly oculomotor dysfunction without other features of PSP-RS should be included in epidemiological studies of PSP. PAGF (PSP-PGF) and PSP-P are also included within these new criteria as are overlap syndromes with CBS, PPA and bvFTD. These criteria have been derived from pathologically confirmed cohorts but not yet subjected to prospective pathological validation. I suggest that use of these new criteria at this point in time would be unlikely to substantially change the results and conclusions of this work. Firstly because the inclusive approach to syndromes associated with FTLD and inclusion of intermediate cases was a key feature of the PiPPIN study. Most of the 'overlap' syndromes included in the new PSP criteria would have been captured by the PiPPIN criteria. Second I suggest that the majority of cases that would fall outside of the PiPPIN criteria (e.g. PSP-PGF or PSP-P) would not have been recognised as related to PSP and referred into a study of this nature. As these new criteria are subject to further validation and become more widely adopted it may be necessary to revisit their impact on the epidemiology of PSP but how this should be reconciled with the negative effects on other syndromes (such as CBS, almost all of whom could now meet PSP criteria) is yet to be established. The data presented here demonstrate high frequency of shared clinical characteristics of both motor and non motor features across all syndromes associated with FTLD again emphasising the importance of a transdiagnostic approach to clinical syndromes within this spectrum of disorders.

Time from onset to diagnosis and subsequent survival varied widely between syndromes. The time from onset to neurodegenerative, and subsequent FTLD, diagnosis for those people presenting with language disorders was shorter than those with predominantly motor (PSP, CBS) or behavioural syndromes (bvFTD). This may reflect different indices of suspicion for an underlying neurological condition for different presentations, or common misdiagnosis as a primary psychiatric disorder.

I confirmed all identified cases were alive and resident within the catchment area during the study. By liaising with national charities and clinical services beyond the PiPPIN catchment area we aimed to identify any cases not have been previously known to our services that migrated into the area. I did not include cases of MND without FTD but only those that also met FTD criteria. Whilst some MND cases will have mild cognitive impairments, MND is a commoner illness with a lifetime risk of approximately 1-in-400(119). Including those cases with milder cognitive impairment or screening all regional MND would overestimate the prevalence of symptomatic FTD syndromes. Eight (19%) of the bvFTD cases identified in this study had clinical features of MND. The case of CBS with MND features is notable, possibly reflecting the range of pathological correlates of CBS; but I could not exclude other causes of denervation.

The frequency of genetic mutations identified is similar to previous studies since the discovery of C9ORF72(1); however most subjects screened had predominantly non-motor syndromes (PPA or bvFTD). The finding of relevant mutations in two subjects with typically sporadic syndromes (svPPA and CBS) further illustrates the challenges to clinical segregation of FTLD.

The incidence of 1.61/100,000 person-years is similar to the mortality (1.56/100,000 person-years). Assuming constant prevalence, mortality serves as an additional surrogate estimate of incidence, suggesting that the study achieved 'steady state' of referrals of incident cases. I report standardised prevalence and incidence estimates across all ages rather than report peak rates in the highest risk groups to allow comparison with other studies and other conditions.

## 2.8 Conclusions

In conclusion, I have shown that the revised diagnostic criteria for FTLD associated syndromes can be applied jointly in a multi-source epidemiological study without restriction to young onset cases or single syndromes. The resulting prevalence, incidence and survival data will allow better generalisation of results from clinical, genetic and pathological studies of FTLD and also enable unbiased interventional studies with reference to the whole population of affected patients including sporadic cases and those over 65 years.

# Chapter 3

# Neuropsychiatric Symptoms in FTLD

## 3.1 Summary

In this chapter I discuss neuropsychological symptoms in FTLD with a particular emphasis on apathy and impulsivity. I consider the methods by which these symptoms may be assessed and then outline the approach taken in the PiPPIN study. I show that a wide range of cognitive assessments and questionnaire based assessments of mood and motivation can be applied to a group of subjects with syndromes associated with FTLD. Compared with healthy older controls, such individuals have significant cognitive impairment across multiple cognitive domains and exhibit a range of behavioural and neuropsychiatric symptoms which are often severe and a source of distress to their carers. Using a number of assessments I show that subjects with FTLD associated syndromes have higher levels of apathetic and impulsive behaviours than healthy older controls and that in a number of subjects apathetic and impulsive behaviours coexist.

## 3.2 Introduction

Neuropsychiatric symptoms such as anxiety, depression, psychosis and aggression are common in dementia. While considered 'non cognitive' symptoms they have associations with other measures of cognition(131) and may reflect more rapid decline(132,133), higher treatment costs and poorer outcome(134–136).

Neuropsychiatric symptoms contribute to both patient and carer distress and are associated with lower quality of life measures amongst patients, have a negative impact on interpersonal relationships(137), and are associated with increased rates carer burden, distress and depression(134,138–141). Neuropsychiatric and behavioural symptoms are described across the entire spectrum of FTLD. They are a defining characteristic of bvFTD and while prominent initial behavioural disturbance is considered an exclusion criterion for PPA(11), neuropsychiatric symptoms are prevalent amongst those with PPA and may evolve over the course of their illness(142). Most historical emphasis has been on the motor aspects of PSP and CBS, but neuropsychiatric symptoms are again common and may be the dominant clinical feature. For example, amongst 62 subjects with PSP Kobylecki et al (111) found that cognitive and behavioural features were the predominant presenting feature in 58% of cases. Other

studies have also demonstrated that neuropsychiatric symptoms are commonly reported in PSP (143–145) and CBS(146).

As these symptoms are common in dementia and associated with significant morbidity they are attractive targets for the development of symptomatic therapies. In order to facilitate effective trials of future therapies there is a clear need for a better understanding of the underlying neuropsychological mechanisms that lead to these symptoms and how they can be quantifiably measured in disease states. Two such symptoms are apathy and impulsivity, which are both particularly prominent across the entire spectrum of FTLD associated syndromes making this a particularly well-suited group in which to study them. A variety of other neuropsychiatric symptoms are observed in FTLD, for example obsessive, disinhibited and compulsive symptoms (especially in bvFTD) and social withdrawal, depression and feelings of isolation. Many of these symptoms may result from disruption of goal directed behaviour, response selection, motivation and suppression which may also result in apathetic or impulsive symptomatology. Hence it seems likely that the mechanisms underlying apathetic and impulsive symptoms may also contribute to the wider range of neuropsychiatric symptoms in FTLD.

In the following sections I discuss the neuropsychiatric symptoms in the syndromes associated with FTLD with a particular emphasis on apathy and impulsivity and then outline the methods and results of a neuropsychological battery of assessments used to assess them amongst the PiPPIN cohort of subjects with FTLD associated syndromes.

### 3.2.1 Apathy

Apathy is a commonly reported neuropsychiatric symptom in neurodegenerative disease(147) particularly FTLD where it is highly disabling(141,148–151); a major cause of carer distress(152); and a diagnostic criterion(10,45,82,153,154). Previous studies have linked higher rates of apathy with more severe disease, poorer prognosis and more rapid decline in Alzheimer's disease(132,133) and negative implications for treatment and long term outcome in Parkinson's disease(135,136) and the wider spectrum of dementia(147). However, most studies linking apathy to disease outcomes or patient/carer morbidity (e.g. (133)) have relied on simple questionnaire based screening tests of apathetic symptoms often using a carer or spouse as an informant and have not considered the multidimensional aspects of apathy as both a clinical and a neurocognitive syndrome(155–157).

Despite its importance, apathy is poorly understood. Authors vary in whether they define apathy as a cognitive syndrome e.g. 'a lack of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress' (158), or the resultant

behavioural syndrome e.g. 'the reduction of self-generated voluntary and purposeful behaviours' (17). Whilst the latter is a useful observable and quantifiable definition it needs to be further qualified to take into account additional factors that may reduce goal directed behaviour. If, for example, it is more difficult or painful to move a limb it requires greater motivation to move it. Simply measuring goal directed behaviour is therefore insufficient to measure apathy. Observed reduction in goal directed behaviour is multifactorial, it relies upon how one acts, interacts, feels, appears or is motivated. Similarly apathy as a cognitive syndrome must be a multifactorial construct relying upon motivation (which in turn relies on both perception of reward and responsiveness to it), decision making, ability to generate goal directed behaviour etc. Also other physical, cognitive and emotional factors may result in decreased goal directed behaviour and an 'apathetic' syndrome. For example, depression, characterised by persistent low mood, may coexist with apathetic symptoms and contribute to them. However while persistent low mood may be sufficient to produce an apathetic syndrome is not necessary and the two cognitive constructs can be dissociated amongst groups of patients with neurodegenerative disease(159). Levy et al(160) showed patients with FTD and PSP could be discriminated from patients with Alzheimer's Dementia by their more severe apathy and relatively less depression.

On the basis of previous behavioural and imaging studies in disease and animal lesional models, Levy et al(17) attempt to divide apathy into three subtypes of disrupted processing: disruption of emotional affective, cognitive and autoactivation processing. They related these to distinct anatomical correlates in the prefrontal cortex-basal ganglia circuits. Similarly, drawing from a range of studies in disease states Heron et al(161) relate deficits in self initiated goal directed behaviour to dysfunction of the anterior cingulate cortex and ventral striatum (including the nucleus accumbens) and connected structures (including the orbitofrontal cortex, ventral pallidum and ventral tegmental area). Referencing studies of Parkinson's, FTLD, AD, stroke, Huntington's and traumatic brain injury they summarise that evidence that disruption of white matter tracts, cortical volume loss and metabolism in these areas has been consistently linked to apathetic symptoms. They propose apathy should be considered a deficit in cost-benefit evaluation when choosing whether to pursue a behaviour, persist with a behaviour and evaluating and learning the costs and benefits of acting.

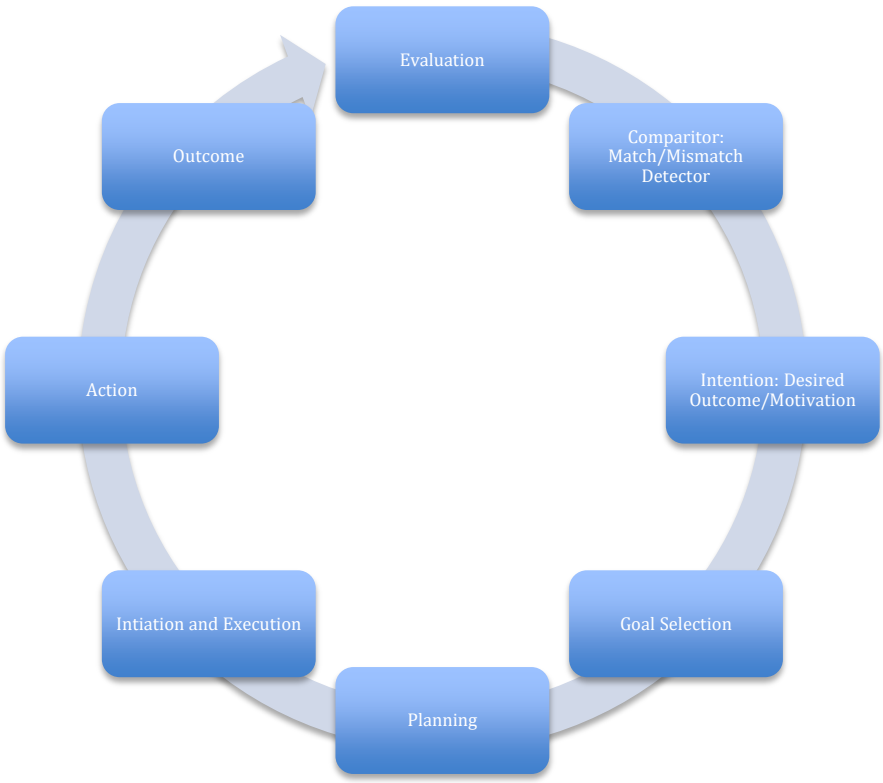



**Figure 3.1 A model of Goal Directed Behaviour.** Adapted from Levy and Dubois (2006)(17).

Figure 3.1 shows a model of organisation of goal directed behaviour. Disruption at any stage of this may result in decreased goal directed behaviour and an apathetic syndrome. While Figure 3.2 shows how dysfunction in a range of brain areas may result in reduced goal directed cognition and behaviour. Both are adapted from Levy and Dubois's paper(17) outlining a proposed model of apathy resulting from disruption of the functional anatomy of prefrontal-basal ganglia circuits. They propose three subtypes of apathetic syndrome resulting from disruption of emotional affective processing, cognitive processing and auto-activation processing. From the results of lesional and functional imaging studies in humans and lesional and electrophysiological studies in animals, they relate each cognitive sub-syndrome to disruption of prefrontal cortex-basal ganglia circuits. These are summarised in Figure 3.2 (in blue). In red additional elements of neurodegenerative disease (disorders of language, emotional distress/depression, and disruption of motor circuits) are also shown as these may also produce an apathetic syndrome even in the absence of decreased goal directed cognition. Finally carer distress as a consequence of any of these aspects of neurodegeneration or misinterpretation of behaviour and disability may also lead to identification/reporting of an apathetic syndrome even when 'true' apathy is not present or prominent.

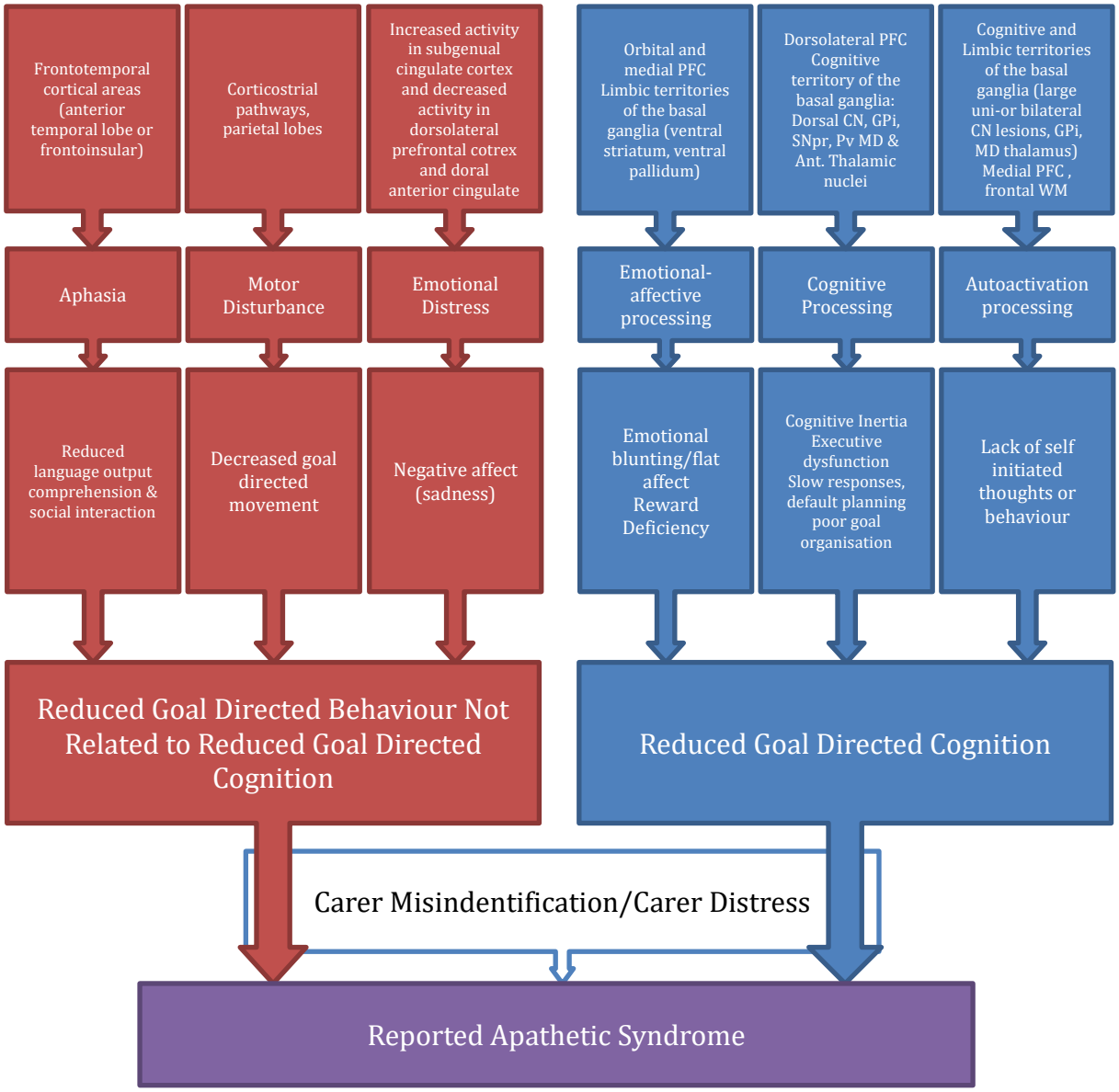



**Figure 3.2. Disruption of the Functional Anatomy of the Prefontal Cotex-Basal Ganglia Circuits leading to Apathetic Syndromes.** The top row of boxes show brain areas where dysfunction may lead to reduced goal directed cognition (in blue) and apathy (adapted from Levy and Dubois 2006(17)) while disruption of other brain areas (in red) may also lead to a similar 'apathetic' syndrome without reduced goal directed cognition. In addition carer (as opposed to subject factors) may also influence reports of an apathetic syndrome. PFC=Prefrontal Cortex, CN=Caudate Nucleus, GPi=Globus Pallidus Internus, SNpr=Substantia Nigra pars reticulata, Pv=Parvocellular, MD=Medial Dosal, Ant.=Anterior, WM=White Matter.

### 3.2.2 Impulsivity

Impulsivity, the tendency to act prematurely, at risk or without foresight(162), is a common behavioural feature of many forms of dementia and is frequently present in frontotemporal lobar degeneration (10). In contrast to apathy where goal directed behaviour is diminished, impulsivity may be associated with an increase in such activity.

In Parkinson's Disease (PD) for example, impulse control disorders such as pathological gambling, hypersexuality or hoarding are frequently observed and often associated with dopaminergic therapy, particularly dopamine agonists(163). Apathy is also commonly observed in PD but with the caveat that decreased motor function and disability (particularly at lower dopamine states where motor disturbance is worst) may lead to diminished goal directed behaviour regardless of states of goal directed cognition. It has been proposed that apathy and impulsivity may exist as opposite extremes of a single dimensional spectrum where hyperdopaminergic states within cortico-striatal circuits result in impulsivity and hypodopaminergic states within the same circuit lead to apathy(164).

There are several arguments against this unidimensional model. Firstly both apathy and impulsivity are multidimensional constructs (17,162,165) including when observed in the context of PD(166,167). There is strong evidence that there exist dissociable neural components of impulsivity(162,164). For example, lesions of the subthalamic nucleus in rats impair cancellation of planned responses without affecting premature responding in the waiting task whereas lesions in the core of the nucleus accumbens cause the opposite pattern (168). In humans, analysis of self-reported questionnaires (such as the Barrett Impulsiveness Scale) designed to assess long term personality traits relative to impulsivity reveals several potentially dissociable aspects of personality that may produce impulsiveness(169). Second impulsive and compulsive behaviour can be observed in treatment naïve patients with PD (albeit at similar rates to those observed in healthy controls) (170). Thirdly impulsive and apathetic syndromes have been observed to coexist within the same patients with PD(171). Finally both apathetic and impulsive behaviour may be attributed to reduced goal directed cognition. Impulsive behaviour may be defined by either by a reduction in foresight (planning) or by reduced 'top-down' inhibitory control(162) hence impulsive behaviour in the context of neurodegeneration is attributable to a reduction in the cognitive processes related to goal directed behaviour. Apathy may lead to diminished planning of behaviour or reduced responsiveness to negative outcomes and lead to impulsive behaviour. Put simply, reckless or impulsive behaviour is more likely if a subject is not motivated to plan out their actions or does not care about the consequences.

### 3.2.3 Apathy and Impulsivity in FTLD

Both apathy and impulsivity are common in FTLD. They are defining characteristics of bvFTD(10), supportive criteria for the diagnosis of PSP(128), and included amongst the behavioural changes used to diagnose CBS-FBS(12). Prominent behavioural features are considered exclusion criteria for the diagnosis of PPA however they can be seen as early features particularly in nfv-PPA and sv-PPA but should not be the dominant clinical features or main source of functional impairment(11). Comparison between informant reported apathy on the Neuropsychiatric Inventory (NPI) between subjects diagnosed with FTD (PPA and bvFTD) and Alzheimer's Disease (AD) showed more frequent apathetic and impulsive symptoms in FTD(172). Interestingly while the same study found similar profiles of apathetic symptoms in FTD and AD, concurrent dysphoria and apathy was unique to the AD group and the two domains were negatively correlated in FTD(172). This suggests either different mechanisms underlying apathetic syndromes in AD and FTD (where depression may have a contributory role in AD associated apathetic syndromes) or that perception and processing of negative emotional states are also impaired in FTD (so that a neurally mediated depressive state is exhibited as an apathetic syndrome without the associated dysphoria).

Zamboni et al (15) used Voxel Based Morphometry (VBM) to assess structural MRI changes in grey matter associated with informant reported apathy and disinhibition via subscales of the Frontal Systems Behaviour Scale amongst 62 patients with FTD. Apathetic profiles were associated with reduced grey matter in the dorsolateral prefrontal cortex, lateral orbitofrontal cortex, medial prefrontal cortex, striatum and temporoparietal junction. Disinhibited profiles were associated with decreased grey matter in limbic and lateral temporal lobes and the nucleus accumbens. In another study(173) disinhibition on the NPI was associated with atrophy in the left temporal pole and bilateral orbitofrontal cortex.

An association between the orbitofrontal cortex and disinhibition has also been proposed using FDG-PET imaging. Amongst 41 patients with bvFTD higher levels of disinhibition on the NPI subscale correlated with orbitofrontal hypometabolism. While no significant correlates of the apathy subscale were demonstrated, a subgroup of bvFTD with higher scores on the Neuropsychiatric Inventory (NPI) apathy subscale also had specific hypometabolism in the orbitofrontal cortex compared with healthy controls (which was not seen in the bvFTD groups without high apathy subscores)(174).

Fractional anisotropy has been used to demonstrate a relationship in FTD between disrupted white matter in the right superior longitudinal fasiculus and disinhibintion (measured

by the Frontal Behavioural Inventory)(175), the temporal portion of the left uncinate fasiculus and apathy scores (on the NPI)(176), the right corona radiata and disinhibition (on the NPI)(176).

Taken together these studies suggest that both apathy and impulsivity are frequently observed in FTLD and can be related to anatomical changes within the brain. However in the majority of cases a single measure of apathy has been relied upon, usually carer based information and views apathy and impulsivity as single unitary constructs which is in sharp contrast to neuropsychological models of apathy and impulsivity(17,165).

### 3.2.4 Measuring Apathy and Impulsivity

Measuring apathy and impulsivity has been attempted using a number of different methodologies. A range of structured questionnaires have been devised for the assessment of apathy(177). Amongst the most commonly used and best validated is the Apathy Evaluation Scale (AES)(158). Respondents are asked to rate the subject's based on the patient's thoughts feelings and activity in the past four weeks with respect to 18 items (e.g. item 4: He/She is interested in having new experiences) on a Likert type scale (Not at all, slightly, somewhat, a lot) each scoring 1 to 4 points such that the answers indicating greater levels of apathetic behaviour score more highly. Three versions are available presenting the same 18 items to either the subject/patient (AES-S), an informant/carer (AES-I) or via a clinical evaluation (AES-C) which uses the items in the AES-S as a basis for a structured interview where the patient's responses are combined with the level of detail and elaboration they are able to provide and clinical observation during the interview. In a previous study of 99 patients with Parkinson's disease the mean AES-C was 29.37 (SD 13.99) factor analysis suggested a 2 factor solution(171) termed "cognitive behavioural" and "social indifference". Another study of 45 patients with Parkinson's disease found a mean AES-C of 34.9 (11.3) compared with a mean of 23.3 (3.8) in 17 older adults with osteoarthritis (136). Marin's original paper(158) reports mean AES scores of amongst healthy older controls and amongst subjects with probable Alzheimer's disease. Using Principal Components Factor Analysis they propose a three-factor solution accounting for 50-65% of the variance supporting their view that apathy is a multidimensional construct.

Similarly a range of questionnaires designed to assess impulsivity (such as a the Barratt Impulsiveness Scale(169), Behavioural Inhibition System/Behavioural Approach System (BIS/BAS) scale(178)), anhedonia (the Snaith Hamilton Anhedonia Pleasure Scale, SHAPS(179)), depression (the Beck Depression Inventory, BDI-II (180), and sleep/arousal (Parkinson's Disease Sleep Scale, PDSS (181)). These rely on the perspective of the patient as opposed to

clinician or informant assessment *per se*. The Barrett Impulsiveness Scale (BIS-11) is one of the most widely cited instruments for the assessment of impulsive behaviour(182). It consists of 30 items where subjects are asked to grade their thoughts and actions on a four point scale (from rarely/never to almost always/always) their answers are scored out 120 of so that higher scores reflect more impulsive thoughts/behaviour. Previous Principal Component Analysis on a sample of 248 psychiatric inpatients and 412 university students revealed and 6 oblique first order factors and three second order factors (169). The BIS/BAS scales are split into the BIS scale, which is designed to measure sensitivity to anxiety provoking stimuli, and the BAS scales, which are designed to measure responsiveness to cues of reward. The concept of the two behavioural systems is based on the theory that two dimensions of personality contribute to impulsive behaviour. The Behavioural Inhibition System (BIS) is proposed as the system that controls the experience of anxiety and, in response to anxiety related cues, inhibits behaviour that may lead to negative consequences. In contrast the Behavioural Approach, or Activation, System (BAS) is sensitive to signals of reward or escape from punishment and is believed to control appetitive motivation (178). As such it is suggested that under activation of the behavioural inhibition system or over activation of the behavioural inhibition system may lead to impulsive behaviour. Some work has been done to relate both systems to distinct neural systems. For example, monoaminergic afferents from the brainstem to the frontal lobe are thought to be related to the behavioural inhibition system while dopaminergic pathways have been related to the behavioural activation systems (178).

In dementia, informant (rather than subject) based reports are often used to assess apathy and impulsivity, where by the informant (usually the patient's spouse or main carer) is asked about the presence and severity of particular symptoms. The Neuropsychiatric Inventory (NPI) is an example of this approach and features a range of neuropsychiatric symptoms (including apathy and impulsivity) and asks the informant to report whether they are present or not and to grade their severity. The Cambridge Behavioural Inventory -Revised (CBI-R) is similar except that it enquires about particular behavioural changes (such as making tactless or suggestive remarks) and asks the informant to grade the frequency (rather than a severity). Hence the CBI-R enquires about the results of neuropsychological and cognitive changes (including apathy and impulsivity) rather than explicitly about each individual symptom as in the NPI. While the NPI asks informants to make a judgement regarding severity, the CBI-R uses frequency, which while more clearly operationalised, may not always be an appropriate surrogate. Both the NPI and the CBI-R enquire about a wide range of symptoms in contrast the AES-I is an informant version of the Apathy Evaluation Scale and is designed to enquire with

specific regard to symptoms of apathy. The AES, NPI and CBI have all been extensively used in the evaluation of neuropsychiatric features of dementia including FTLD (183–185).

Questionnaire based assessments have many advantages - they are simple to administer and can relate to real world experience. However, they rely on the subject (or informant) to understand the questions posed and then be able to reflect on their experience and report accurately. Even despite clear and specific instructions a respondent may well take other aspects of their situation into account. For example when answering questions relating to the social interactivity of a subject with dysphasia a respondent is likely to take language impairments into account when responding, even if such a questionnaire is designed to assess social interest. In addition a patient's insight into their condition, or a carer's own conceptions or psychological state are likely to influence the accuracy of responses. Even if accurate reporting is assumed questionnaires are limited in their ability to dissociate individual neuropsychological constructs. For example, disruption to several neural systems may lead to reduced spontaneity in day to day behaviour (a feature of apathy) but a purely questionnaire based assessment may not be able to dissociate such underlying neural mechanisms. Finally, questionnaires often use a Likert scale and provide a quantifiable score this does not necessarily imply that all items within a questionnaire are truly of equal importance or that the final total score accurately reflects the severity of the underlying disease process either in terms of degree of neural damage or in relation to patient and carer morbidity.

To overcome some of these issues one could consider objective performance on behavioural or cognitive tasks. These may be administered via a range of methods including paper and pencil tasks (such as the Kirby delayed discounting task where subjects select options from a range of choices) or more automated computerised tasks. Computerised tests of reaction time and decision making have been used to investigate neuropsychological processes in healthy individuals(186) and those with brain disease such as FTD(187). The Cambridge Neuropsychological Test Automated Battery (CANTAB, © Cambridge Cognition Ltd) is an example of a battery of computerised tests where subjects interact with a computer via touch screen, button boxes or joysticks to interact with a customised battery of cognitive tests. The computer software allows the examiner to vary test parameters and can vary a range of test parameters (for example the time and manner of cue presentation, presentation of feedback or amount of reward) and in doing so calculate a range of outcome variables.

This approach has been used successfully to investigate goal directed behaviour including impulsivity using the stop-signal and Go/NoGo tests. The Go/NoGo paradigm consists of a series of 'Go' or 'NoGo' cues presented at the same time as arrow pointing left or right.

Subjects are instructed to make speeded motor responses depending on the direction of the arrow on 'Go' trials but withhold responses on 'NoGo' trials. Responses are rendered prepotent by including more 'Go' than 'NoGo' trials. By recording the number of inappropriate responses on 'NoGo' trials a measure of motor impulsivity can be obtained(165). By replacing the initial Go/NoGo cue with a 'stop signal', such as a beep, shortly after the directional stimulus the task become one of cancelling an already selected response rather than selecting or withholding a response at the outset. By varying the time between the initial cue and the stop signal it is possible to obtain a measure of the 'Stop Signal Reaction Time (SSRT)' i.e. the time taken by the brain to suppress prepotent motor signals (165). There appear to be overlapping but different neural correlates of the No/NoGo task and the SSRT task. Functional imaging studies have defined a 'stop circuit' including the right inferior frontal gyrus, anterior cingulate cortex presupplementary and motor cortex and basal ganglia (188). The Go/NoGo task activates the left frontal cortex more consistently than the SSRT (189). Pharmacological manipulation of serotonergic neurotransmission affects performance on the No/NoGo task but not the SSRT(168).

Performance on the Go/NoGo and SSRT tasks is impaired amongst patients with impulse control disorders including ADHD. Subjects with ADHD also tend to choose immediate smaller rewards over larger delayed reward (intolerance to delay of gratification as measured by delayed discounting paradigms). Despite impulsive behaviour on the SSRT tasks and delayed discounting tasks being highly sensitive to ADHD (identifying 90% of patients) performance on the two paradigms do not correlate with each other (190,191).

This behavioural testing approach has significant advantages over questionnaire or interview based methods as it is not asking the subject or informant to explicitly report their own perceptions of symptoms or behaviour. As such behavioural testing is not limited by the accuracy of reporting but is limited by its applicability to clinical practice. For example, apathy is known to be a frequent symptom in dementia because it is frequently reported. When reported it is associated with significant morbidity (192). Whether diminished goal directed behaviour measured on a computerised test of reaction times and the influence of various rewards relates directly to the apathetic symptoms being reported by patients and their carers is less clear. Accepting that apathy is a multidimensional construct (and reports of apathetic syndromes even more complex) it seems unlikely that a single behavioural test used in isolation would be sufficient to explore a particular neuropsychiatric symptom or syndrome. In addition particular groups of individuals may have difficulties with some methodologies that are independent of their neurodegenerative disease or cognitive impairments. For example more elderly cohorts may be less used to computers affecting performance on computerised testing

paradigms, non native English speaking subjects or subjects with dyslexia may have more difficulty with questionnaire/language based assessments.

### 3.2.5 Measuring Apathy and Impulsivity in FTLD: The PiPPIN Study

The syndromes associated with FTLD are well suited to studying apathetic and impulsive syndromes because they are particularly prominent (although not completely universal) features amongst patients with FTLD.

I hypothesised that apathetic and impulsive states within the syndromes associated with FTLD are due to dissociable neural and psychological mechanisms and that different apathetic and impulsive states may in some instances coexist and correlate with each other. Rather than choose one particular syndrome (e.g. PSP) within the spectrum of FTLD-associated disorders, I have taken a more inclusive, transdiagnostic approach.

This has several advantages: Firstly, apathy and impulsivity are common to all of the syndromes offering the possibility of identifying common underlying constructs of apathy/impulsivity. Secondly, using an alternative approach to these conditions focusing on particular behavioural syndromes may offer a novel method for patient stratification and classification, which is particularly needed in this patient group where clinico-pathologicial correlation is challenging. Thirdly, using a syndromically heterogeneous patient group allows testing procedures to be incorporated that would otherwise be impossible in certain groups because of their physical or cognitive disabilities.

Testing this hypothesis requires a method of identifying and measuring dissociable apathetic and impulsive behaviours. Previous studies have used questionnaires e.g. (133,135,136,144,158,193,194) whilst others have relied on carer observation/reports. Questionnaire based assessments have several advantages. Firstly they allow a structured and reproducible interview and assessment. They can be used to produce a quantitative score (such as the AES) based on the subject's qualitative reports of their symptoms. Perhaps most importantly they aim to address how the patient actually feels as opposed to measuring a behavioural surrogate which may, or may not, relate to goal directed behaviour or cognition. There are also clear disadvantages to a questionnaire based approach. They rely on language and accurate understanding of the items presented. This may be particularly problematic in FTLD where language disorders are common. Second they rely upon accurate reporting and insight on the part of the reporter. This may be an issue not only for the subject with FTLD (where loss of insight may be present(195)) but also when using informant/carer reports where responses will be subject to the informants interpretations of patient behaviour and also their

own psychological stress. For example lack of facial expression (hypomimia) in PSP may be mistakenly interpreted as lack of interest.

An alternative approach to assessing apathy and impulsivity is to measure a behavioural surrogate either by passive observation or by testing performance on tasks designed to address specific aspects of behaviour. Behavioural testing has been extensively used in patient groups to investigate impulsivity e.g.(190,196,197) but is less well established in apathy. One example of passive observation is actimetry. One study(198) used a wrist mounted device to record periods of activity (motion) and showed a positive correlation between carer reported apathy and periods of inactivity amongst patients with bvFTD but not semantic dementia. Behavioural tasks such the Go/NoGo task have also been used in FTLD. Hughes et al.(187) used a Go/NoGo paradigm to investigate disinhibition amongst a group of patients with bvFTD. Using magnetoencephalography and electroencephalography they showed evoked responses in the right inferior frontal gyrus and anterior temporal lobe were associated with successful response inhibition in age matched controls and that these were reduced amongst subjects bvFTD. These responses were enhanced by citalopram suggesting a serotinergic aspect to response inhibition.

Whilst this more behavioural approach to assessing apathy and impulsivity has the advantage of being a more 'objective' method of assessment, behavioural testing also has limitations, particularly in this patient group. For non-passive measures, language impairment, communication and understanding can be difficult and limit assessment. With a questionnaire based approach it may be easier to assess understanding and clarify responses. More problematic is that most non-passive assessments rely on the subject's ability to perform a task. Apraxia, which is a hallmark of CBS, limits the ability to manipulate a joystick, press buttons or write. Eye movements are severely impaired in PSP (and together with apraxia of eyelid opening this can produce a functional blindness). A more fundamental issue is whether the task actually relates to apathy or impulsivity. For example amongst bvFTD Go/NoGo performance correlates with performance on the Hayling and reports of stereotypic and motor behaviours and general disinhibition (as reported on the Cambridge Behavioural Inventory) (187). While these results support an association between a behavioural task (Go/NoGo) and reports of impulsivity in bvFTD, these data in isolation do not demonstrate a direct association between performance on the task and the reported symptoms. Performance on the task and symptom reports may both be indicative of more general cognitive or behavioural impairment or alternatively there may be another confounding element influencing both symptom reports and task performance. Furthermore, accepting the proposal that apathy and impulsivity are multidimensional, it is not clear to what extent performance on one task or questionnaire may relate to performance on another. While one study may demonstrate that (for example) a set of

apathetic symptoms relates to increased carer distress, it is not necessarily the case that the reported symptoms would also relate to impairment on behavioural testing in another study or functional imaging changes in another.

In the remainder of this chapter I outline the methods used to assess neuropsychiatric symptoms (particularly apathy and impulsivity) in the PiPPIN cohort of subjects with FTLD associated syndromes and a group of healthy older volunteers and the results obtained. Additional 'objective' behavioural testing was also performed and is discussed in more detail in Chapter Four and an integrative multimodal approach to the assessment of apathy and impulsivity in Chapter Five.

### 3.3 Methods

Patients and their carers identified with FTLD associated syndromes from the epidemiology aspect of the PiPPIN study were invited to participate in a battery of cognitive, behavioural and neuropsychological tests with particular emphasis on aspects of apathy and impulsivity (Table 3.1). Fifty healthy older people without dementia were asked to complete the same battery of tests to act as a control group. As an assessment of cognitive ability across a range of domains subjects completed the Addenbrooke's Cognitive Examination –Revised (ACE-R) and Frontal Assessment Battery (FAB) which were administered in person by either myself, a clinical research assistant or a research assistant that I had trained to administer these tasks.

Subjects completed a number of questionnaire-based assessments chosen to assess a range of symptoms and clinical features relevant to apathy and impulsivity. These included assessments of: mood and mental state (Snaith Hamilton Anhedonia Pleasure Scale, SHAPS(179), Beck Depressive Inventory II, BDI-II(180), Visual Analogue Scales, VAS, Motivation and Energy Inventory, MEI(199) , Parkinson's Disease Sleep Scale, PDSS(181); behavioural and neuropsychiatric symptoms (Neuropsychiatric Inventory –Questionnaire, NPI-Q(200), Cambridge Behavioural Inventory –Revised, CBI-R(184)); disease severity (Progressive Supranuclear Palsy Rating Scale, PSP-RS(201), Frontotemporal Dementia Rating Scale, FRS(202)); apathy (The Apathy Evaluation Scale, Informant, Clinician and Subject versions, AES-I, AES-C, AES-S(158)), compulsiveness and impulsivity (Barratt Impulsiveness Scale, BIS(169), Behavioural Inhibition System/Behavioural Activation System, BIS/BAS(178), Obsessive Compulsive Inventory-Revised, OCI-R (203)).

The assessments were administered in person in the form of a structured interview using paper and pen. For patient assessments the subjects were presented with each assessment on paper and each item of the assessment read out loud to them. With the exception of those items that are dependent on the subject physically marking the page themselves (such as drawing tasks in the ACE-R) the examiner would assist the subject with physical response entry as necessary. An informant who knew the patient well (usually a carer or the patient's partner/spouse) was asked to complete the NPI-Q, CBI-R, AES-I, FRS usually whilst the subject completed other aspects of the assessment battery so the examiner was available to clarify any particular issues. As some of these assessments are used in routine clinical practice occasionally when the patient had recently undergone an assessment and results were available (and the patient consented) these were used to avoid repetition of assessments and learning effects.

Multiple questionnaires were used. While there is some overlap between items on each instrument, the focus (target symptoms), language and scoring of each is different and each has been validated in different cohorts and disease states. Accepting that this approach does lead to some repetition it also allows clarification and corroboration of subject reports, which is of particular importance when assessing symptoms in dementia, and also explores a wider spectrum of goal directed cognition.

These questionnaire based assessments explicitly ask about relevant symptoms or behaviour in addition subjects were asked to attempt a number of behavioural tasks using a range of methodologies including the Cambridge Gambling Task (CGT), Information Sampling Task (IST), Go/NoGo task, saccadometry and actimetry monitoring, Stop Signal Reaction Time task (SSRT), Kirby delayed discounting task, the Cued Reinforcement Reaction Time task (CRRT). These behavioural tasks are discussed in Chapter Four.

| | |
|---|---|
| Informant Assessments (Questionnaires) | AES-I, NPI-Q, CBI-R, FRS |
| Patient Assessments (Questionnaires) | SHAPS, AES-S, BDI-II, BIS, BIS/BAS, OCIR, PDSS, MEI, Kirby[2], CBI-R[1], VAS |
| Clinician Assessments | AES-C, PSP-RS, clinical history and physical examination |
| Cognitive Assessments | ACE-R, FAB |
| Computerised Assessments[2] | CGT, IST, SSRT, CRRT, Go/NoGo, Saccadometry, Actimetry |

**Table 3.1 Assessments in the PiPPIN Battery.**

[1]Patients were not asked to complete all 45 items on the CBI-R but was asked to self-rate behaviours on a subset of 10 items consisting of the first item from each of the ten domains.

[2]The Kirby and Computerised assessments are discussed in Chapter Four

I expected that not all patients would be able to complete all aspects of the battery and took a pragmatic approach to the protocol limiting aspects of the protocol to those that the patient was willing and able to complete. Similarly the order in which aspects of the battery were applied was varied in order to maintain patient engagement with the tasks and maximise testing opportunities.

### 3.3.1 The Addenbrooke's Cognitive Examination Revised

The Addenbrooke's Cognitive Examination Revised (ACE-R) (204) is a 100 point bedside cognitive examination developed from the older Addenbrooke's Cognitive Examination as a screening test for dementia. Incorporating the Mini Mental State Examination (MMSE)(205) itself a bedside tool for grading the cognitive ability of patients. Widely used in clinical and research settings the ACE-R can be administered with a pen and paper and assesses several cognitive domains including attention and orientation, memory, fluency, language, visuospatial function.

### 3.3.2 The Frontal Assessment Battery

The Frontal Assessment Battery (FAB)(206) is a bedside tool designed to assess frontal executive function via six tasks including similarities (conceptualisation), lexical fluency (mental flexibility), motor series (the Luria test of programming), conflicting instructions (sensitivity to interference), go-no-go (inhibitory control) and prehension behaviour (environmental autonomy). I used letter fluency from the ACE-R to score lexical fluency (both ask subjects to as many words as they can generate words beginning with a given letter in one minute, the ACE-R version used here uses the letter P, the FAB normally uses S). Each task is scored from 0 (worst performance) to 3 (best) giving a maximum possible score of 18. A cut off of 12 differentiated between bvFTD and Alzheimer's disease with sensitivity 81% of and specificity 71% of in one study of 90 patients (64 AD and 26 FTD) with lower sensitivity (77%) but higher specificity (87%) amongst subjects with mild dementia (defined as MMSE≥24)(207).

### 3.3.3 The Apathy Evaluation Scale

The Apathy Evaluation Scale(158) consists of 18 items (e.g. item 4: He/She is interested in having new experiences) respondents are asked to grade each item based on the patient's thoughts feelings and activity in the past four weeks. Four options are given (Not at all, slightly, somewhat, a lot) and the answers scored so from 1 to 4 so that the answers indicating greater levels of apathetic behaviour score more highly.

Three versions of the scale were administered when possible. The informant/carer version (AES-I) -where a relative or carer is asked to rate the subject, a self-administered version (AES-S)–where subjects are asked to rate themselves, and a clinician version (AES-C) – where a clinician administers the scale and grades the subject based on their responses. The clinician version includes some self-evaluated questions as well as others where the clinician is

asked to grade the response based on the subjects affect whilst responding and detail of answer during a semi structured interview.

### 3.3.4 The Cambridge Behavioural Inventory –Revised

The Cambridge Behavioural Inventory –Revised (CBI-R, (184)) consists of 45 behavioural symptoms which are arranged into 10 groups (e.g. eating habits, sleep). Carers are asked to rate the frequency of each behavioural change from 0 (never) to 4 (constantly). As a surrogate marker of patient insight I asked the patients to self-evaluate their own behaviour for 10 behaviours (the first presented in each of the ten groups).

### 3.3.5 The Neuropsychiatric Inventory –Questionnaire

The Neuropsychiatric Inventory –Questionnaire (NPI-Q, (200)) is a brief questionnaire form of the Neuropsychiatric Inventory(185), designed for use in clinical practice to evaluate neuropsychiatric symptoms in dementia. An informant (usually the subject's spouse or other main carer) is asked whether specific symptoms/behaviours (such as apathy, hallucinations, night time behaviours) have been present over the last month and if so how severe they are (on a scale of 1-3, 1 being mild, 3 severe) and how much distress they cause the informant from 0 (not distressing at all) to 5 (extremely distressing).

### 3.3.6 The Frontotemporal Rating Scale

The Frontotemporal Rating Scale(202) consists of 30 behavioural changes seen in frontotemporal dementia. Carers are asked whether they are never present, sometimes present, or present all the time. A score of 1 awarded for each behavioural change that is never present (i.e. no change from premorbid function) and 0 for any other response. Hence a score of 30 would be no symptomatic change and lower scores indicative of more marked behavioural changes. The authors of the scale also suggest a percentage conversion and Logit score conversion to separate scores into very mild, mild, moderate, severe, very severe and profound categories(202).

### 3.3.7 Visual Analogue Scales

At the start of the testing protocol subjects were shown a set of 14 visual analogue scales (VAS). Each scale consists of a line 20 cm long with 'Not at all' and 'Extremely' printed above opposite ends of the scale (left and right respectively). Above this is a stimulus word printed in bold below the instruction 'Point to the appropriate point on the line to rate how closely the word below matches how you are feeling **right now**?'.

The 14 stimulus words are presented to each subject in the same randomised order. The subjects were also instructed to indicate a point on each line that was then marked with a pen by the subject (if able) or the examiner. The intersection of this mark and the line was measured from left to right and recorded (in cm).

The stimulus words used were: Stimulated, Interested, Clear Headed, Tired, Apathetic, Depressed, Happy, Calm, Alert, Motivated, Sad, Excited, Impulsive, Bored.

### 3.3.8 The BIS/BAS Scales

The Behavioural Inhibition System and Behavioural Approach System (BIS/BAS) Scales (178) are presented as a single questionnaire consisting of 30 items. Subjects state how much they agree or disagree with 24 statements (e.g. 'I go out of my way to get the things I want'). These are then scored and grouped into four scales to assess the Behavioural Inhibition System (one scale, 7 items), and Behavioural Activation System (3 scales; Reward Responsiveness -5 items, Drive -4 items, Fun Seeking -4 items). Two items are reverse scored and four items are fillers that do not contribute to any scales. The structure of the BIS and BAS subscales was derived from factor analysis of 732 college students(178).

### 3.3.9 The Barrett Impulsiveness Scale

The Barrett Impulsiveness Scale (BIS-11,(169)) is one of the most widely cited instruments for the assessment of impulsive behaviour(182). It consists of 30 items where subjects are asked to grade their thoughts and actions on a four point scale (from rarely/never to almost always/always) their answers are scored out 120 of so that higher scores reflect more impulsive thoughts/behaviour. Previous Principal Component Analysis on a sample of 248 psychiatric inpatients and 412 university students(169) revealed and 6 oblique first order factors and three second order factors. Higher scores on the BIS scale suggest more behavioural inhibition and hence a lower tendency towards impulsive actions while higher scores on BAS subscales suggests greater behavioural activation and more impulsive tendencies.

### 3.3.10 The Obsessive-Compulsive Inventory –Revised

The Obsessive-Compulsive Inventory -Revised(203) is an 18 item questionnaire where subjects are asked how much particular behaviour, thoughts or experiences related to obsessive/compulsive behaviour have distressed or bothered them during the past month on a scale of 0 (not at all) to 4 (extremely). The range of possible scores is 0-72 with a suggested cut-off of 21 where scores above this are indicative of an obsessive compulsive disorder(203).

### 3.3.11 The Snaith-Hamilton Anhedonia Pleasure Scale

The Snaith-Hamilton Anhedonia Pleasure Scale (SHAPS) is a 14 item self rated questionnaire designed to evaluate hedonic tone(179). Subjects are presented with a short statement such as ''I would enjoy my favourite television or radio programme" and asked how much they agree or disagree (strongly agree, agree, disagree, strongly disagree). The order and exact wording of responses varies between items (e.g. the word 'strongly' is sometimes replaced by 'definitely'). The scale is presented so that it may used either in a Likert-style scoring (each item being scored from one to four, with 4 being the most anhedonic) giving a range of 14-56 or alternatively simplified approach whereby either agree response scores no points and either disagree one point making the maximum (most anhedonic) score 14(179). In order to allow the greatest flexibility I chose the former method.

### 3.3.12 The Beck Depressive Inventory II

The Beck Depressive Inventory II (BDI-II)(180) is the second revision of the Beck Depressive Inventory and consists of 21 groups of statements under subheadings such as 'Pessimism' and 'Past Failure'. Subjects are asked to choose the statement that best describes how they have been feeling over the past two weeks. Responses for each statement are scored from 0 (least depressed) to 3 (most depressed) giving a range of 0-63 possible total scores. The BDI-II is amongst the most widely used tools to screen and assess depression amongst healthy populations and in disease states (including dementia)(208–210).

### 3.3.13 The Motivation and Energy Inventory

The Motivation and Energy Inventory (MEI) is a 27 item self rated questionnaire originally designed to evaluate motivation and energy in depression and hence facilitate the evaluation of treatments intended to alleviate fatigue and lassitude(199). Items are scored from 0-6 with the maximum score for each individual item varying between four, five and six. The range of possible scores is 0-144. Based on two studies of around 800 subjects diagnosed with a recurrent major depressive episode exploratory factor analysis demonstrated three factor solution (termed physical energy, mental energy and social motivation)(199).

### 3.3.14 The Parkinson's Disease Sleep Scale

The Parkinson's Disease Sleep Scale (PDSS) consists of 15 self-rated visual analogue scales assessing 15 commonly reported symptoms associated with sleep disturbance in Parkinson's disease(181). Each scale is presented as a graduated line from zero to ten with zero indicating the symptom occurs frequently/always and ten equating to never. While the scales relate to

symptoms reported in Parkinson's disease many also occur in other disease states or in the absence of disease (for example getting up to pass urine at night, unexpectedly falling asleep during the day or fidgeting in bed).

### 3.3.15 The Progressive Supranuclear Palsy Rating Scale

The Progressive Supranuclear Palsy Rating Scale(201) is a 100 point scale consisting of 28 items in six categories (daily activity, behaviour, bulbar, ocular motor, limb motor and gait/midline). It combines clinical history and examination in a well operationalized set of criteria by which the severity of PSP-RS may be assessed. In one study of 162 patients mean rate of progression was 11.3 points per year and the total score was a good independent predictor of subsequent survival(201).

### 3.3.16 Statistical Analysis

Statistical analysis was carried out using SPSS v22 (IBM 2013). Differences between groups were calculated using two tailed T-tests between groups. Where a subject was unable to complete a particular aspect of the protocol it was removed from the testing battery and analysis but the subject was still asked to attempt other tests. For carer/informant assessments most carers were able to complete the full battery of assessments. Occasional omission errors were dealt with by replacement with mean within group. For example a single omission on the CBI-R would be replaced with the mean score of the carer's responses for that particular category of behaviours.

Principal Component Analysis (PCA) was performed using orthogonal varimax rotation with Kaiser normalisation. Adequacy of sample size was assessed using Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity. The standardised correlation matrix was used for extraction of components (as opposed to the unstandardized covariance matrix) and extraction of significant components was based on Kaiser's criteria (i.e. those with Eigenvalues greater than 1).

### 3.4 Results

As expected, not all patients were able to complete the full battery of questionnaires or behavioural tests. In this, and following chapters, for each measure and exploration the number of individuals included is stated but note that different patients completed different tests and hence each correlation and analysis is performed on a different patient subgroup. The exact data pertaining to FTLD subtype and clinical characteristics for each subgroup is no longer available.

Table 3.2 summarises the results of questionnaire based testing of patients and controls with subscale scores and mean standard deviation (within subject) on VAS scales shown in Table 3.3. As expected, average patient scores across a range of cognitive tasks (FAB, ACE-R, MMSE) were lower than amongst control groups. The carers of patients with FTLD reported more symptoms associated with dementia and behavioural changes (CBI-R, NPI-Q) than partners of healthy controls and patients and their carers reported more severe symptoms of apathy, impulsivity, obsessive compulsive behaviour, depression and anhedonia (AES-S, AES-I, BIS, BIS/BAS, OCI-R, BDI-II, SHAPS) and lower levels of motivation and energy (MEI).

T-test comparisons of all differences were statistically significant with the exception of age and mean scores on VAS, BIS, Funseeking and Reward Responsiveness subscales of the BIS/BAS, average severity and distress associated with symptoms on the NPI-Q and Attention, Self control, Cognitive complexity and Cognitive instability subscales of the BIS-11.

| Variable | Controls (N, SD) | Patients (N,SD) | P value (T-test) |
|---|---|---|---|
| Age | 70.6 (50, 6.5) | 69.8 (113, 8.3) | 0.543 |
| MMSE Total score (max. 30) | 29.3 (50, 1.2) | 22.1 (85, 7.0) | 0.000 |
| ACE-R Total score (max. 100) | 95.6 (50, 4.4) | 64.3 (84, 23.2) | 0.000 |
| FAB Total score (max. 18) | 16.8 (50,1.2) | 10.0 (86, 4.5) | 0.000 |
| FRS Total score (max. 30) | 26.7 (49, 3.8) | 10.16 (106, 7.5) | 0.000 |
| FRS Per cent score (max. 100) | 92.1 (49, 10.8) | 38.1 (106, 26.8) | 0.000 |
| AES-I Total score (max. 72) | 24.2 (49, 5.7) | 48.2 (104, 12.7) | 0.000 |
| AES-S Total score (max. 72) | 25.9 (50, 7.3) | 35.7 (70, 9.5) | 0.000 |
| AES-C Total score (max. 72) | 25.9 (50, 7.3) | 43.1 (76, 10.3) | 0.000 |
| NPI-Q Total number symptoms (max. 12) | 0.3 (50, 0.7) | 4.4 (106, 2.6) | 0.000 |
| NPI-Q Mean severity[1] (max. 3) | 1.4 (5, 0.5) | 1.7 (100, 0.5) | 0.184 |
| NPI-Q Mean distress[1] (max. 5) | 0.8 (4, 1.0) | 1.9 (98, 1.2) | 0.051 |
| CBI-R Total score (max. 180) | 5.2 (49, 5.6) | 66.9 (107, 35.5) | 0.000 |
| CBI-R Self score (max. 40) | NA[2] | 17.4 (32, 9.2) | NA[2] |
| BIS-11 Total Score (max. 120) | 57.0 (50, 7.4) | 63.5 (67, 8.0) | 0.000 |
| BIS/BAS BAS Drive | 10.0 (50, 2.1) | 11.2 (66, 3.2) | 0.030 |
| BIS/BAS BAS Funseeking | 10.7 (50, 2.2) | 11.4 (66. 3.1) | 0.181 |
| BIS/BAS BAS Reward responsiveness | 15.8 (50, 2.4) | 16.7 (66, 2.7) | 0.085 |
| BIS/BAS BIS | 19.9 (50, 14.4) | 20.6 (66, 4.6) | 0.353 |
| PDSS Total score (max. 150) | 121.5 (50, 14.4) | 112.9 (64, 23.7) | 0.026 |
| MEI Total score (max. 144) | 108.9 (50, 17.2) | 81.8 (64, 25.6) | 0.000 |
| SHAPS (max. 56) | 18.7 (50, 4.4) | 22.8 (66, 4.8) | 0.000 |
| BDI-II (max. 63) | 4.4 (50, 4.0) | 12.8 (70, 9.9) | 0.000 |
| OCI-R (max. 72) | 8.5 (50, 6.4) | 14.8 (64, 11.4) | 0.001 |
| VAS mean score (max. 20) | 10.1 (50,1.3) | 9.9 (71, 2.1) | 0.615 |
| PSP-RS Total score (max. 100) | NA[2] | 31.5 (70, 20.5) | NA[2] |

**Table 3.2 Mean scores for interview/questionnaire based assessments for healthy older controls and subjects with syndromes associated with FTLD recruited in the PiPPIN study.**

[1]When completing the NPI-Q respondents are asked only to grade distress and severity only when a symptom is reported as present. Hence the average scores for severity and distress are calculated from only those subjects where symptoms have been reported and only from those where a rating for severity or distress has been recorded.

[2]Control subjects were not asked to self-rate on the CBI-R or assessed on the PSP-RS

| Variable | Controls (N, SD) | Patients (N,SD) | P-value (T-test) |
|---|---|---|---|
| ACE-R Attention & Orientation (max. 18) | 17.7 (50, 0.9) | 13.8 (85, 4.5) | 0.000 |
| ACE-R Memory (max. 26) | 24.2 (50, 2.2) | 15.4 (84, 7.9) | 0.000 |
| ACE-R Fluency (max. 14) | 12.6 (50, 2.1) | 4.5 (84, 3.7) | 0.000 |
| ACE-R Language (max. 26) | 25.4 (50, 1.0) | 19.3 (84, 6.8) | 0.000 |
| ACE-R Visuospatial (max. 16) | 15.6 (50, 0.72) | 11.2 (84,4.1) | 0.000 |
| CBI-R Memory/Orientation | 2.2 (49, 2.3) | 14.8 (107, 9.6) | 0.000 |
| CBI-R Everyday skills | 0.2 (49, 0.5) | 11.4 (107, 7.3) | 0.000 |
| CBI-R Abnormal behaviour | 0.4 (49, 1.1) | 5.7 (107, 5.4) | 0.000 |
| CBI-R Mood | 0.4 (49, 0.8) | 4.3 (107, 3.3) | 0.000 |
| CBI-R Beliefs | 0.0 (49, 0.0) | 0.6 (107, 1.3) | 0.000 |
| CBI-R Eating Habits | 0.1 (49, 0.3) | 4.6 (107, 4.2) | 0.000 |
| CBI-R Sleep | 0.9 (48, 1.0) | 3.5 (107, 2.3) | 0.000 |
| CBI-R Stereotypic behaviour | 0.3 (49, 1.0) | 5.0 (107, 5.0) | 0.000 |
| CBI-R Motivation | 0.5 (49, 1.5) | 9.8 (107, 6.9) | 0.000 |
| BIS Attention | 8.86 (50, 2.1) | 10.5 (67, 2.3) | 0.579 |
| BIS Motor | 14.0 (50, 2.7) | 14.7 (67 (4.0) | 0.003 |
| BIS Self control | 10.5 (50, 2.8) | 12.9 (67, 3.5) | 0.129 |
| BIS Cognitive complexity | 10.6 (50, 2.3) | 12.1 (67, 2.5) | 0.649 |
| BIS Perseverance | 7.4 (50, 1.4) | 8.1 (67, 2.1) | 0.007 |
| BIS Cognitive instability | 5.6 (50, 1.6) | 5.2 (67, 2.0) | 0.165 |
| VAS Mean standard deviation (within subject) | 5.5 (50, 1.2) | 4.7 (71, 1.9) | 0.007 |

**Table 3.3 Mean subscale scores for ACE-R, CBI-R, BIS assessments and mean standard deviation (within subject) on the VAS for healthy older controls and subjects with syndromes associated with FTLD recruited in the PiPPIN study.**

Figure 3.3 shows standardised subscores for the individual domains for the ACE-R and FAB. Patients performed more poorly than controls (T-tests $p<0.001$ for all) across all tested domains, the largest discrepancy is seen in fluency. Note that Fluency and Lexical Fluency are derived from the same data but scored slightly differently when included in the ACE-R or FAB.

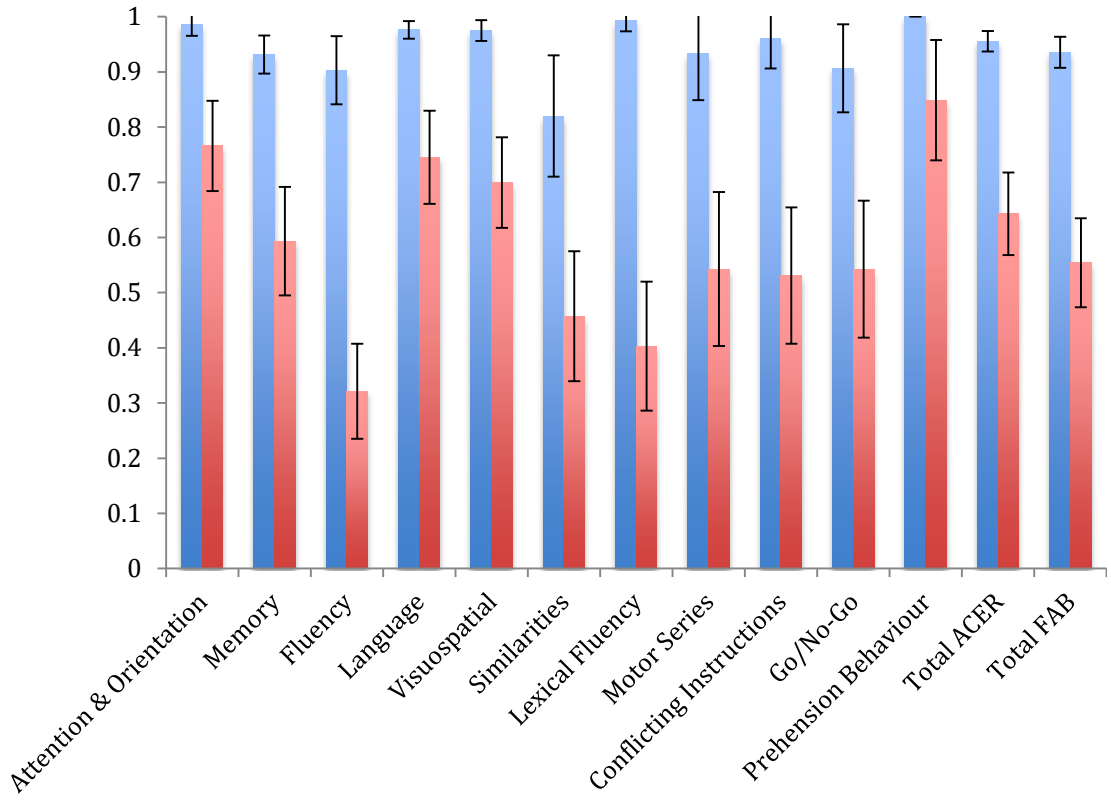



**Figure 3.3 Standardised scores for Subscales of the ACE-R and FAB for subjects with FTLD associated syndromes (red columns) and healthy older volunteers (blue).** Error bars show 95% confidence intervals.

One hundred and six carers of patients completed the NPI-Q. The commonest reported symptoms were night time behaviours (in 58.8% of cases) followed closely by apathy/indifference (57.9%), and changes in appetite/eating (56.1%). Figure 3.4 shows the frequency of symptoms reported amongst respondents, the average severity of each symptom rated by the carer and the average rating of distress it caused them (as opposed to the patient). Twenty six (24%) of informants reported both apathetic and impulsive behaviour occurring in the same subject on the NPI-Q.

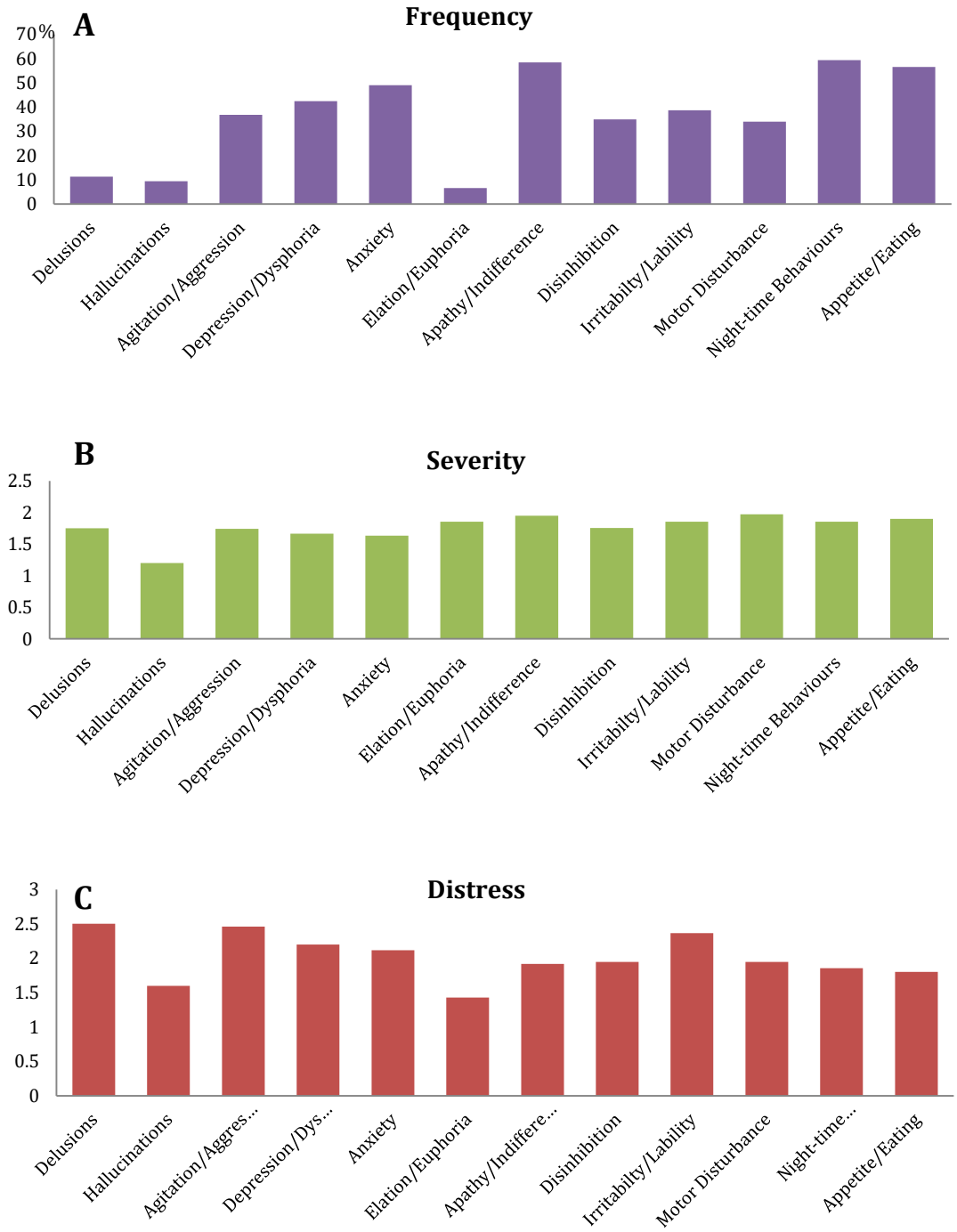



**Figure 3.4. Neuropsychiatric symptoms amongst 106 subjects with syndromes associated with FTLD as reported by informants using the Neuropsychiatric Inventory. A** shows the percentage frequency of informants who considered each symptom present. **B** shows the mean severity rating (from 1=mild to 3=severe) the informants gave each symptom (when present) and **C** the mean distress the informant experienced (from 0=not distressing at all to 5=extreme or very severe) from each symptom (when present).

One hundred and seven carers completed the CBI-R endorsing symptomatic behavioural changes across a range of activities. Standardised scores (for the total number of points available for each category) showed the highest endorsement for impairments in everyday skills, followed secondly for motivational changes (Figure 3.5). Similarly to the low frequency of reported delusions or hallucinations on the NPI-Q abnormal beliefs were the least frequently reported set of behavioural changes on the CBI-R.

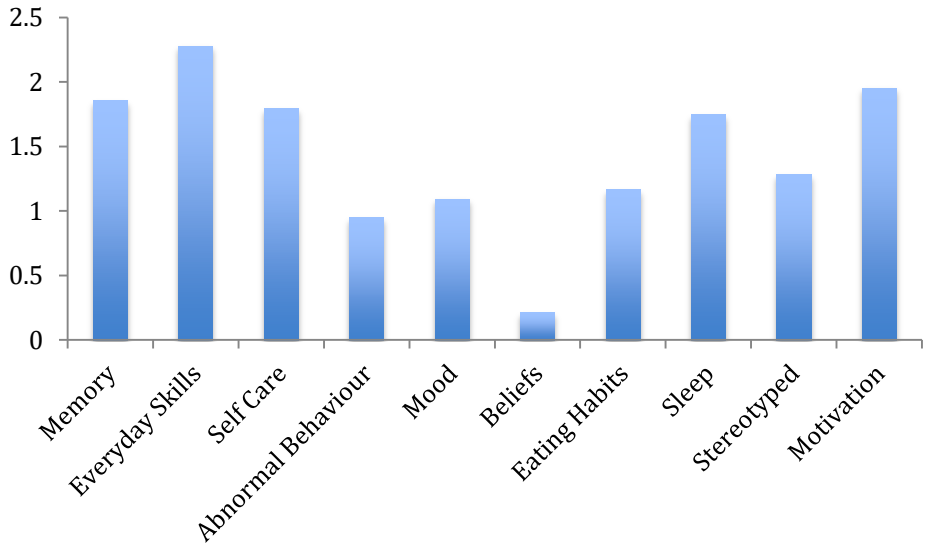
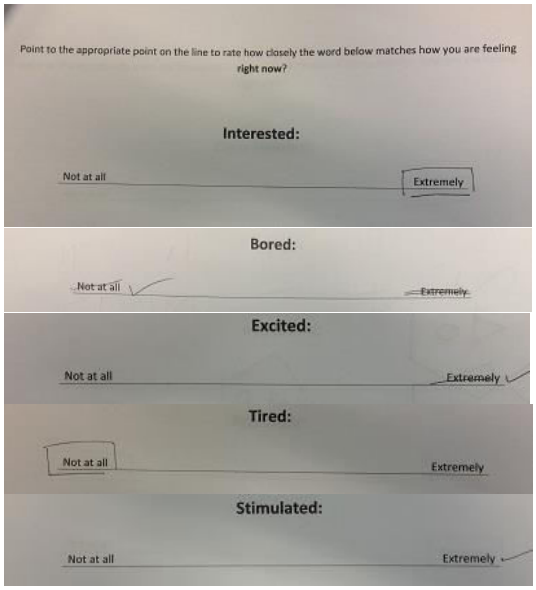
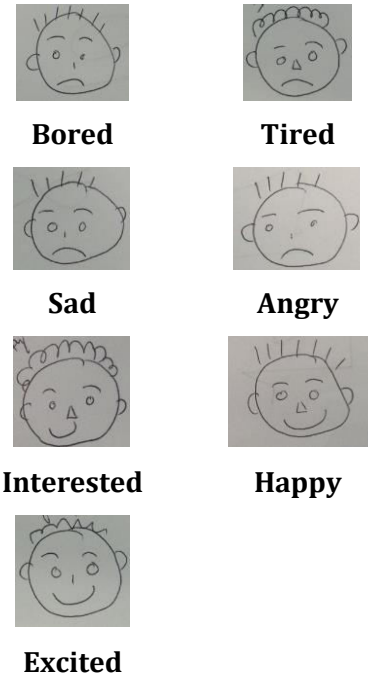



**Figure 3.5. Symptom frequency reporting by informants amongst 107 subjects with syndromes associated with FTLD using the Cambridge Behavioural Inventory-Revised (CBI-R).** Each column shows standardised frequency for each of the ten groups of symptoms in the CBI-R as reported by informants on a scale of 0=never occurs to 5=constantly occurring.

Seventy-one patients completed the visual analogue scales. Patients reported significantly higher levels of emotional and behavioural states with negative valence (e.g. sad, depressed, bored) than healthy controls and lower levels of states with positive valence (e.g. happy, stimulated, excited). On an individual level some patients appeared to have substantial difficulty on the VAS task despite their apparent simplicity. This seemed disproportionate to their functioning day-to-day or performance on some other cognitive tasks (see Figure 3.6). Mean scores for patients and controls self ratings on the scales are shown in Figure 3.7.




**A** **B**

**Figure 3.6. A**. Visual analogue scale responses from a single case. The subject was a woman in her early 60s with a recent diagnosis of bvFTD. At the time of testing she was living semi-independently in her own home and continued to manage her own financial affairs. She scored 76/100 on the ACE-R, 28/30 on the MMSE, 17/18 on the FAB and had a FRS score of 44% (classified as moderate disease). When instructed to put a mark on the line to indicate how 'interested' she felt right now she drew a box around the word extremely. She was corrected and told to draw a line on the scale to indicate how she felt. On the next scale 'bored' she drew a line through the word 'extremely' to indicate 'not at all' (the remaining response). She was corrected and asked to put the line *where* she felt and so put a line through 'not at all'. A final attempt was made asking her to put a mark on the scale at which point she ticked 'not at all'. She answered several other scales in the same manner despite repeated attempts to correct her and being shown numerous examples. **B**. To test her understanding of the cue words used in the visual analogue scales the same patient was asked to draw faces for each of the cue words. Note that while she correctly identifies the positive and negative qualities of each word, each face looks otherwise extremely similar.

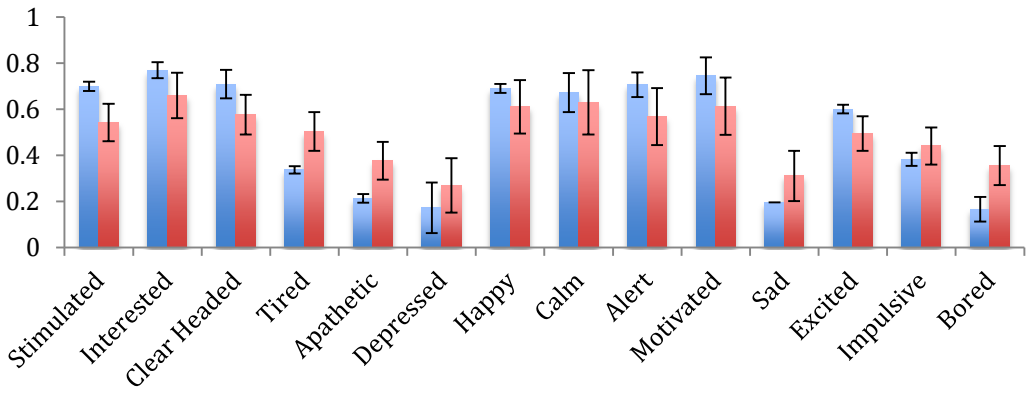



**Figure 3.7. Standardised mean scores for the visual analogue scales.** Patients with FTLD associated syndromes (red columns) and healthy control subjects (blue columns) self rated for each of the emotional states from 0 (not at all) to 1 (very). Error bars show 95% confidence intervals.

Principal Component Analysis for VAS responses for both patients and controls combined revealed a four-factor solution explaining 64% of the variance. The rotated component matrix (Table 3.4) shows the factor loading for each component.

| | Component | | | |
|---|---|---|---|---|
| **Item** | **1** | **2** | **3** | **4** |
| Excited | **0.788** | 0.161 | 0.042 | -0.03 |
| Stimulated | **0.746** | -0.092 | -0.184 | -0.124 |
| Motivated | **0.671** | 0.404 | -0.258 | -0.05 |
| Interested | **0.592** | 0.295 | -0.365 | -0.048 |
| Clear headed | **0.584** | 0.462 | -0.003 | -0.135 |
| Impulsive | **0.55** | 0.171 | **0.536** | 0.164 |
| Alert | 0.478 | **0.526** | -0.023 | -0.335 |
| Happy | 0.288 | **0.704** | -0.168 | -0.041 |
| Calm | 0.022 | **0.899** | -0.026 | -0.036 |
| Bored | -0.068 | -0.141 | **0.798** | 0.059 |
| Sad | -0.274 | -0.082 | **0.678** | 0.23 |
| Tired | 0.036 | -0.014 | -0.075 | **0.856** |
| Depressed | -0.165 | -0.15 | 0.248 | **0.705** |
| Apathetic | -0.091 | -0.044 | 0.429 | **0.657** |

**Table 3.4 Rotated component matrix for responses of seventy one patients with syndromes associated with FTLD and fifty healthy older control subjects on fourteen visual analogue scales of mood and motivational state.** Weightings >0.5 or <-0.5 highlighted and in bold.

Component One in Table 3.4 comprised of stimulus words attributable to high levels of energy and motivation (e.g. stimulated, excited, motivated). Component Two comprised of stimulus words with positive valence attributable to calm, focus and happy feelings (e.g. calm, alert, happy). Component Three comprised of stimulus words with more negative valence and low mood (e.g. sad, apathetic, bored). Component Four also comprised negative valence with possibly more emphasis on low energy, fatigue and depression (e.g. tired, apathetic, depressed). To explore the proposed factor structure further post hoc correlation analysis was performed. The rotated component matrix was used to transform the raw VAS scores to extract four new variables. Amongst patients (not controls) these extracted variables were then subjected to bivariate correlation analysis against the AES-S, MEI, SHAPS, BDI-II and PDSS. Statistically significant correlations were seen between the MEI (positive correlation), SHAPS (negative correlation) and Components One and Two (which also correlated positively with the PDSS), the BDI-II and AES-S and Component Three (which also had negative correlation with the MEI) and a negative correlation between the PDSS and Component Four (see Table 3.5). Despite strong factor loadings for the stimulus words 'apathetic' and 'depressed' onto Component Four the extracted variable did not significantly correlate with either the AES-S or BDI-II but instead correlated significantly with the PDSS which focuses more on fatigue and tiredness (note the stimulus word 'tired' also loads strongly onto Component Four). In contrast the stimulus words 'sad' and 'bored' both loaded onto Component Three with significant correlations for the extracted variable and both AES-S and BDI-II.

| Component | | MEI | SHAPS | BDI-II | AES-S | PDSS |
|---|---|---|---|---|---|---|
| 1 | Pearson Correlation | .426** | -.374** | -0.226 | -0.23 | 0.164 |
| | Sig. (2-tailed) | 0.001 | 0.002 | 0.063 | 0.062 | 0.199 |
| | N | 63 | 65 | 68 | 67 | 63 |
| 2 | Pearson Correlation | .371** | -.367** | -0.09 | -0.217 | .255* |
| | Sig. (2-tailed) | 0.003 | 0.003 | 0.464 | 0.077 | 0.043 |
| | N | 63 | 65 | 68 | 67 | 63 |
| 3 | Pearson Correlation | -.309* | 0.211 | .330** | .459** | -0.125 |
| | Sig. (2-tailed) | 0.014 | 0.092 | 0.006 | 0 | 0.331 |
| | N | 63 | 65 | 68 | 67 | 63 |
| 4 | Pearson Correlation | -0.045 | 0.057 | 0.118 | 0 | -.266* |
| | Sig. (2-tailed) | 0.728 | 0.654 | 0.338 | 0.999 | 0.035 |
| | N | 63 | 65 | 68 | 67 | 63 |

**Table 3.5 Correlation of the four components extracted from Principal Component Analysis of responses on visual analogue scales with the Motivation and Energy Inventory (MEI), Beck Depressive Inventory II, self rated version of the Apathy Evaluation Scale (AES-S) and Parkinson's Disease Sleep Scale (PDSS).** ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

### 3.5 Discussion

In this chapter I have shown that a wide range of cognitive assessments and questionnaire based assessments of mood and motivation can be applied to a group of subjects with syndromes associated with FTLD. Compared with healthy older controls, such individuals have significant cognitive impairment as measured by a range of assessments (MMSE, ACE-R, FAB) across a range of cognitive domains.

I have not presented results separated by individual clinical syndromes (such as bvFTD or PSP-RS). This is for several reasons: Clinical features overlap between individual syndromes (as I demonstrated in Chapter Two), while particular syndromes may be recognisable at a particular stage of symptomatic disease patients may transition between syndromes over the course of their illness or present with an intermediate clinical syndrome with features of multiple diagnostic criteria. I have taken an inclusive approach and recruited subjects at every stage of symptomatic disease (some at the point of clinical diagnosis, others shortly before their death). While subjects will have fulfilled criteria for a diagnosis of FTLD they may subsequently have acquired additional features beyond the limited criteria by which they were diagnosed (e.g. a subject with a diagnosis of bvFTD who later acquires additional features of CBS). How such subjects should be divided is not clear (on the basis of presenting features or on features at the time of testing). The emphasis of most of the diagnostic criteria for FTLD is placed on either the cognitive syndrome or movement disorder, not the neuropsychiatric profile. For all these reasons it seems counterintuitive to divide this cross sectional cohort on the basis of a diagnosis either at first presentation or at the time of assessment. In addition to these reasons, as I have argued previously, taking a transdiagnostic and inclusive approach to clinical syndromes associated with FTLD exploits syndromic heterogeneity providing insights into clinical features that would not otherwise be possible. This approach is central to the Research Domain Criteria (RDoC) approach to neuropsychiatry advocated by the National Institute for Mental Health(211). While individual subjects had difficulty with particular aspects of the assessments (e.g. the patient described earlier in Figure 3.6) as a group they are able to reflect on and report symptoms in a consistent manner across a range of assessment tools.

When an informant who knows the patient well was asked, they reported a range of behavioural and neuropsychiatric symptoms which, when present, are often severe and a source of distress to the informant. Apathy, night-time behaviours and changes in appetite/eating were the most commonly reported symptoms on the NPI. The least commonly reported symptoms were delusions, hallucinations and elation/euphoria. Similarly psychotic symptoms of hallucinations or delusions were also the least commonly reported symptoms on the CBI-R. The

most commonly reported behavioural symptoms on the CBI included the subject's ability to perform day-to-day tasks such as using a telephone or handling money/paying for items. Behaviours related to motivation and apathy (e.g. 'Shows less enthusiasm for his or her usual interests', 'Shows little interest in doing new things') were also amongst the most frequently reported symptoms. Changes in memory were commonly reported on the NPI and CBI-R and also seen on cognitive testing (e.g. ACE-R).

The (rare) reports of psychotic symptoms in the PiPPIN cohort and more frequent reports of memory impairments could reflect the presence of patients with non-FTLD pathology within this cohort. Psychotic symptoms are uncommonly reported in FTLD but commonly seen in Dementia with Lewy Bodies(212). Primarily psychiatric diseases may also mimic bvFTD(213). Episodic memory and visuospatial impairments are more commonly associated with Alzheimer's disease than FTLD(214,215). However I suggest the presence of these features in this cohort does not undermine the diagnosis of an FTLD related syndrome. Memory symptoms are found in FTLD(216) and were prominent in Pick's original cases. Early episodic memory impairment may indicate underlying Alzheimer's type pathology and hence is often used as an exclusion criteria for FTLD associated syndromes(35) but these criteria do not preclude memory symptoms at any stage of disease (including at onset provided they are not a prominent feature).

Similarly psychotic features were an exclusion criteria for the diagnosis of CBD (e.g. (12)) and psychiatric disease that may better account for symptoms is an exclusion criteria for bvFTD(35) but psychotic symptoms may still be seen in FTLD. In this cross sectional cohort study the presence of some psychotic features does not undermine the validity of diagnoses. It may even be that because of current diagnostic criteria, psychotic features are underrepresented in this cohort. Psychosis is a common and prominent feature amongst patients with C9ORF72(217). Prior to this discovery psychosis was considered unusual in FTLD and rarely reported. It is possible that patients with FTLD and prominent early psychosis may not have had the diagnosis considered and hence would not have been included in this study.

It is striking that across a range of different assessment tools patients consistently report higher levels of symptoms with negative valence (e.g. depression as measured by the BDI-II, Apathy as measured by the AES-S, sadness as measured by the VAS) and lower levels of symptoms with positive valence (e.g. happiness, interest on the VAS) than controls. Regardless of the version used (AES-S, AES-I or AES-C) subjects with syndromes associated with FTLD scored significantly higher on the AES than healthy older subjects, consistent with previously

reports of increased apathy in dementia(147) and specifically FTLD(183) and informant reports of apathy via the NPI and CBI-R.

Reports of both apathetic and impulsive symptoms occurring in the same subject were common on the NPI-Q, consistent with high self-rated apathetic and impulsive symptomatology on (for example) the AES and BIS. This is consistent with previous reports of co-occurrence of apathy and impulsivity in other disease states such as Parkinson's(171).

Subjects with FTLD may have diminished insight into their own disabilities, emotional or cognitive state(195), subjects with language disorders may not understand the testing material when using self reported questionnaires. I have presented the responses from one illustrative subject who despite remaining independent and living alone with reasonably well preserved cognition in most modalities had great difficulty completing visual analogue scales. While some of this difficulty appears to be her ability to comprehend the task itself her ability to dissociate distinct emotional states beyond a unipolar positive/negative valence appeared to be impaired. However, at a group level, when completing the visual analogue scales, most subjects did not use a unipolar happy/sad or positive/negative scale but instead Principal Component Analysis revealed four factors correlating with other measures of motivation, positive and negative emotional states and fatigue separately. Hence while some subjects with syndromes associated with FTLD may have diminished insight, or a simplified comprehension of emotional states, when considered at a group level they are still able to respond to questionnaire and structured interview to provide meaningful insights into how they are feeling. Consistent with the reports of their carers they report increased negative emotional feelings, symptoms of apathy and depression, decreased motivation and hedonic tone. These reports cannot be simplified into a single negative state but reflect complex and multifaceted symptomatology.

### 3.6 Conclusions

I have shown that a range of questionnaire and paper and pencil tests of cognition, emotion and motivation can be applied to a cohort of subjects with syndromes associated with FTLD. Regardless of whether the subject is asked, or an informant who knows them well, subjects with FTLD associated syndromes have higher levels of cognitive impairment and neuropsychiatric symptomatology across a range of cognitive and behavioural domains and these are a frequent source of distress for those around the subject. Apathy and impulsivity are frequently reported in FTLD and frequently coexist within a single subject. While some subjects with FTLD do have impaired ability to self report psychological symptoms and understand some aspects of this form of testing, considered together they are able to provide meaningful insights into their own emotional and motivational states. Consistent with the reports of their carers, subjects with FTLD associated syndromes report increased negative emotional feelings, symptoms of apathy and depression. They also report decreased motivation and hedonic tone. Finally I have shown that these reports cannot be simplified into a single uni-dimensional positive/negative valence state but instead reflects complex and multifaceted symptomatology.

# Chapter Four

# Behavioural Assessment of Apathy and Impulsivity in FTLD

## 4.1 Summary

In this chapter I discuss the limitations of questionnaire-based assessments of apathy and impulsivity and how an alternative approach, assessing behavioural surrogates of goal directed cognition may overcome some of these. I then present the methods by which I have done this amongst the PiPPIN cohort of patients with syndromes associated with FTLD and a group of healthy older controls. I show that the patient group perform differently to controls across the entire range of tasks and respond more slowly and less accurately. I also show that the patient group are still sensitive to changes in potential reward and adapt their responses accordingly but do so differently to healthy older controls. Compared with controls, patients demonstrated deficits in action restraint, action cancellation and higher temporal discounting rates. I suggest that these data cannot be explained by disruption of a single cognitive process and may all contribute to apathetic and impulsive behaviour in FTLD.

## 4.2 Introduction

In Chapter Three I discussed apathy and impulsivity in FTLD. As seen in other studies (e.g.(147)), within the PiPPIN cohort of subjects with FTLD associated syndromes apathetic and impulsive symptoms are common and a source of patient and carer morbidity. I have shown it is possible to quickly and simply identify problematic symptomatology by using informant questionnaires. Despite their cognitive impairments, subjects with FTLD associated syndromes are mostly able to provide insights into some aspects of their motor, functional, cognitive, emotional and motivational states using structured interviews and questionnaires (except see Figure 3.6 for some of the problems that may be encountered).

This approach is relatively straightforward and inexpensive but has limitations. Responses to informant-based assessments are influenced not only by the subject's symptoms but also by the informant's interpretation of them and the questions asked. The informant's own mental state and levels of distress may also influence their responses. Similarly subject interviews and questionnaires are limited by the subject's understanding and interpretation of the questions asked and their ability (and desire) to perform the introspective self-analysis necessary for accurate responding. While I have shown that subjects with FTLD associated

syndromes are able to provide meaningful responses, this approach when used in isolation, cannot demonstrate that their responses are entirely accurate and representative of their underlying neuropsychiatric state. I have also shown that this approach cannot be applied equally for all subjects. Language and other cognitive impairments limited some subjects' ability to accurately respond to questionnaire-based assessments. While I have argued that my results demonstrate some ability for meaningful introspection, it was clear during testing that some subjects insight into their own behaviour was limited, others found particular aspects of the testing difficult. For example some subjects with svPPA did not understand particular words or the underlying concepts in some aspects of the questionnaires. Responses to questionnaires are also dependant on the specific questions asked and how they relate to the subject's individual circumstances. Some questionnaires (such as the CBI-R) use behaviour as a surrogate for cognitive and psychological state. Asking (for example) whether the subject shows less enthusiasm for his or her usual activities may identify changes in motivation or apathy but this is a presumption, the subject may lose interest for other reasons such as physical disability or decline in visuospatial function.

Questionnaire based approaches may offer a 'score' or scale by which symptomatology may be graded but whether such as scale is an appropriate way in which to quantify symptomatology is questionable. Whether a particular score on the AES (for example) can be equated to a particular stage of disease, amount of neurodegeneration, or change in behaviour is not clear. Similarly it cannot be assumed that all items within a scale should be considered of equal value (for example suicidal feelings compared with feelings of guilt on the BDI-II). Questionnaires may have been validated by replication and psychometric properties assessment, but often only in a very different clinical context e.g. young adult depression, rather than late life dementia. As a result questionnaire based assessments may provide useful insights and effective screening tests for neuropsychiatric disease but there is also a need for more objective and quantifiable measures, particularly with a view to understanding the biology of neuropsychiatric symptoms and evaluating response to symptomatic therapies.

One approach to overcome the limitations of questionnaire/interview evaluations is to use behavioural testing. Rather than directly enquire about a particular symptom or its consequences, by instead asking the subject to perform a relevant task designed to correspond to a particular symptom it is possible to measure their performance in a more objective and quantifiable fashion. For example subject speed and accuracy on a theoretical task that requires them to make quick decisions in response to a stimulus cue may be used as a surrogate marker for aspects of attentiveness or impulsivity. A simple task may be designed to measure particular aspects of behaviour and decision-making and hence delineate aspects of behaviour that may be

preferentially impaired in disease states. This method potentially may allow the examiner to examine the underlying cognitive processes responsible for symptomatology in disease and hence the underlying neural mechanisms, offering insights which may pave the way to better symptomatic therapies and methods by which their effects can be quantified and tested.

The Go/NoGo task and Stop Signal Reaction Time (SSRT) task are two examples of behavioural testing which have been used to assess impulsivity. For the Go/NoGo task the subject is shown a randomised series of directional cues with either a 'Go' or 'NoGo' cue (e.g. a green or red light) they are instructed to make speeded responses in the direction indicated when presented with a 'Go' but not to respond when 'NoGo' is presented. The SSRT is similar in that the subject is asked to make speeded directional responses except that instead of a 'NoGo' cue on a minority of trials a beep is heard shortly after the initial cue. When this occurs the subject is instructed to inhibit their response. Hence in the Go/NoGo task the subject is asked to refrain from making a response whereas the SSRT task tests their ability to cancel their response. This subtle different in response inhibition has been shown to have dissociable neuroanatomical and neurotransmitter systems across a range of species, including humans(168). A similar approach has been used in disease states such as Parkinson's(218) to demonstrate impulsivity is not a unitary construct but has a range of underlying neural mechanisms.

Based on the hypothesis that apathy and impulsivity are multidimensional constructs related to disruption of goal directed cognition, reward responsiveness, action initiation and inhibition, I aimed to use behavioural tasks that have been designed assess these aspects of behaviour to measure selective but objective impairments in the PiPPIN cohort.

### 4.3 Methods

Patients with syndromes associated with FTLD identified in the PiPPIN study, and fifty healthy older controls, and were invited to complete a range of behavioural tasks. The tasks selected were chosen to assess particular behavioural and cognitive processes considered relevant to apathy and impulsivity after discussion with Professors James Rowe (my supervisor), Barbarah Sahakian and Trevor Robbins. The tasks were presented along with the questionnaires discussed in Chapter Three.

A pragmatic approach was taken to maximise participant inclusivity and enable subjects with significant disabilities to contribute to the study. Therefore, the order of tasks/questionnaires was not fixed and not every subject was expected to be able to complete every aspect of the testing battery. Instead where a subject had marked difficulty understanding or completing one aspect of the protocol the particular test would be terminated and they would be asked to move on to another. The assessments were varied to maintain subject interest and attentiveness. Frequent breaks were offered and on some occasions the testing would be split over a number of sessions on different days.

#### 4.3.1 The Go/NoGo Task.

Two versions of the Go/NoGo task were administered. Firstly with the patient sitting in front of a Panasonic Toughbook laptop. An initial cue of a red and a green circle is presented on the centre of the computer screen. One circle then disappears and an arrow pointing left or right appears. Subjects are asked to move a joystick in the direction of the arrow when the green circle remains but not when the red circle remains. 150 trials were administered to each subject.

The second version of the Go/NoGo task was administered using a head mounted saccadometer (Ober Consulting) a similar Go/NoGo task also administered. Instead of a computer screen lasers are projected onto a wall approximately 1.5m from the subject. A green and a red laser dot form the initial cue and then one is removed and a directional cue (another red laser) appears ten degrees to the left or right of the initial cue (replacing the arrow on the computer version). Instead of a joystick subjects simply make a saccadic eye movement to the left or right which is tracked using the reflection of an infrared bean projected onto their corneas. 300 trials are administered per subject. As the projection and recording equipment is head mounted and moves as the subject does head fixation is not required. Data was downloaded and analysed using the LatencyMeter software package (Ober Consulting Version

6.5) and automatic trials validation used to exclude non saccadic responses based on position and velocity profiles of each individual trace.

There are six possible responses for each trial; Go Correct Right Direction (GCRD), Go Correct Wrong Direction (GCWD), Go Incorrect Right Direction (GIRD), Go Incorrect Wrong Direction (GIWD), Nogo Correct (NC), Nogo Incorrect (NI). Mean reaction times (in milliseconds) were calculated for each of the Go responses and the mean number of each response type were calculated. Outliers greater than three standard deviations from the mean (within patient or control group) were excluded from each outcome variable. The sensitivity index (d'), calculated to give a measure of subject's ability to discriminate between Go and Nogo trials through their responses. First the proportion of Go trials to which the subject responded Go (in either direction) was calculated (hit rate) and the portion of incorrect Go responses for all NoGo trials (false alarm rate) were calculated. The difference between Z-transformations of hit rate and false alarm rate were calculated to give d' as follows:

$$d' = Z\left(\frac{GCRD + GCWD}{GCRD + GCWD + NI}\right) - Z\left(\frac{GIRD + GIWD}{GIRD + GIWD + NC}\right)$$

Where GCRD, GCWD, GIRD, GIWD, NI and NC represent the total number of Go Correct Right Direction, Go Correct Wrong Direction, Go Incorrect Right Direction, Go Incorrect Wrong Direction, Nogo Incorrect and Nogo Correct responses for each subject. Where either hit rate or false alarm rate were 0 or 1 values were adjusted up or down to 0.99 or 0.01 to allow Z transformation.

### 4.3.2 The Stop Signal Task

The Stop Signal Task (SST) was administered using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition). Stimuli were present on a computer screen and responses made by pressing one of two buttons (left and right) on a two buttoned press pad. The test is administered in two parts, the first is a practice session where subjects are shown an arrow pointing either left or right and asked to press the corresponding left or right button as quickly as possible. In the second part the subject is told to continue pressing buttons in response to the arrows but if they hear an auditory beep (stop signal) they should not press the button. The second part of the task was administered in five blocks of 64 trials. Stop signals were present in 25% of trials (randomly dispersed) and the delay between the arrow cue and

stop signal varied (Stop Signal Delay, SSD) to give an estimate of the stop signal reaction time (SSRT) i.e. the time it takes to internally suppress a response. Between trials the SSD varies according to previous responses. After successfully inhibited responses the SSD is increased making it more difficult, when the subject fails to inhibit a response the SSD is decreased. An estimate of SSRT is calculated by subtracting the mean SSD at which the subject is able to stop on 50% of trials (SSD (50%)) from the mean reaction time on go trials (where no stop signal is present). Total correct responses on stop and go trials, direction errors on stop and go trials, median reaction times for correct and incorrect direction responses on go trials were also recorded.

### 4.3.3 The Information Sampling Task

The Information Sampling Task (IST) was administered using the CANTAB touch screen computer. The subject is presented with a 5x5 array of grey boxes and two larger coloured panels below the boxes. They are instructed that they are playing a game for points that they can win by making a correct decision about which colour is under the majority of grey boxes. By touching the boxes one at a time they open (and remain so) to reveal one of the two colours shown at the bottom of the screen. When the subject is ready to make a decision about which colour is the majority they touch the panel of that colour. All the remaining boxes then open and a message informs the subject whether they were correct.

The colours change for each trial. After a single practice trial subjects complete 10 trials where they are awarded 100 points for a correct decision regardless of how many boxes are opened and then 10 trials where the number of points for a correct decision starts with 250 points and decreases by 10 points with each box opened. For all trials an incorrect decision costs 100 points. Errors, total correct trials, mean number of boxes opened per trial and probability of a correct decision based on the available evidence at the time of decision are automatically calculated by the Cambridge Cognition software and downloaded.

### 4.3.4 The Kirby Temporal Discounting Task

The Kirby Temporal Discounting Task is a 27-item questionnaire. For each item subjects are asked to choose between an immediate smaller monetary reward today or a larger reward in a specified number of days. Delay discounting refers to the perceptual decrease in value of an item (in this case money) as the delay to reward increases. Subjects vary in their rates of delay discounting, with more impulsive individuals less prepared to wait for larger deferred rewards and the rate of delayed discounting also varies within subject based on the size of the rewards.

The rate of delay discounting are modelled by discount curves which fit well to the hyperbolic function:

$$V = \frac{A}{1 + kD}$$

Where *V* is the present value of reward A available at delay D and k is the discount rate parameter. Their responses are grouped into those for small, medium and large rewards and an estimate of indifference factor k determined for each. By determining the value of k for each of the 27 choices it is possible to estimate the value of k for which an individual switches preference for immediate smaller rewards from the larger delayed reward. The Kirby is designed so that the items presented can be grouped into small, medium and high delayed rewards where the reward increases between items and the length of delay decreases. Calculating the geometric mean between the values of k for the two items where the subject switches from immediate to delayed reward gives an estimation of k at which the subject is indifferent for each of the three delayed reward sizes, as not every response will necessarily be entirely consistent with a single value of k and in such circumstances the value which is consistent with the most responses is used. The proportion of responses consistent with the calculated k was also calculated (from a value of zero to one, with one denoting all responses consistent with the calculated value of k) (219).

### 4.3.5 The Cambridge Gambling Task

The Cambridge Gambling Task (CGT) was administered using the CANTAB touchscreen computer (Cambridge Cognition). Subjects are shown a row of red and blue 'boxes' (presented as coloured squares on the screen) and asked to bet on whether a reward is hidden in a blue box or a red box. The ration of blue to red boxes varies between trials. The stake value (in points) varies over time allowing the subject to bet more or less points depending on when they place their bet. Increasing and decreasing stake over time conditions can be set.

### 4.3.6 The Cued Reinforcement Reaction Time Task

The Cued Reinforcement Reaction Time Task (CRRT) was based on the description from Cools et al (220). It is designed to assess the influence of cues that signal reward on motivation when completing an odd one out reaction time task. Figure 4.1 explains the paradigm which was simplified from Cools et al's original task (two colour/probability arrangements used instead of 3 and 50 trials as opposed to 100).

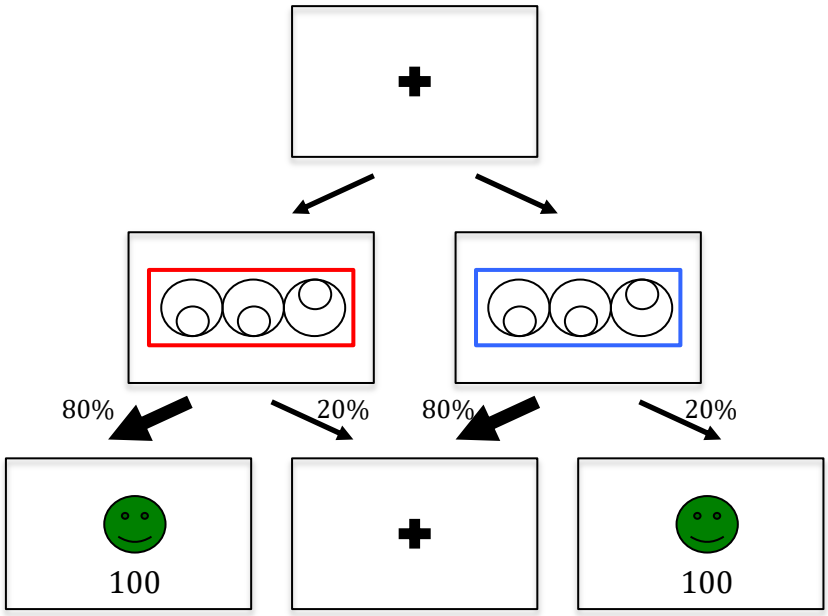



**Figure 4.1 The Modified Cued Reaction Reinforcement Time Task.** Subjects are presented 50 trials each starting with a fixation cue (first box) followed by the three circular arrangements (second row). They are instructed to select the odd one out (in this case the right circular arrangement) by pressing one of three buttons on a press pad. On half of the trials the probability of receiving feedback is 80%, on the other half the probability is 20%. The probability of receiving feedback is indicated by one of two colour boxes surrounding the circles (red or blue). The pairing colour to probabilities is varied between subjects. When feedback is given, rapid correct responses score 100 points and are shown a green smiley face together with a fanfare sound. Slow correct responses score 1 point and are accompanied by a high frequency ping sound and green smiley face. Incorrect responses score 0 points and are accompanied by a red unhappy face and a low frequency sound. The cut off for fast/slow responses is calculated from the subtracting the standard deviation from the mean response time for 20 practice trials where no feedback is given and the fixation cue is shown. Before this subjects are familiarised with the protocol with a block of 20 practice trials without feedback or recording response time.

### 4.3.7 Statistical Analysis

Statistical analysis was carried out using SPSS v22. Differences between groups were calculated using two tailed T-tests between groups unless otherwise stated.

## 4.4 Results

### 4.4.1 The Go/NoGo Task

Results from 64 patients and 50 controls were included for the joystick version and 34 patients and 43 controls for the oculomotor versions of the task (Tables 4.1 and 4.2). For all trials where subjects went (Go) regardless of trial type (Go/NoGo) or direction, patients were significantly slower than controls on the joystick version of the task ($p<0.001$ for all). The only significant difference between reaction times on the oculomotor task was amongst mean GIRD response times ($p=0.03$). Omission error (NoGo response to a Go cue) rates in the Go condition were higher in patients than controls in both joystick and oculomotor versions of the task ($p<0.001$ and $p=0.002$ respectively). Commission (Go response to NoGo cue) rates in the NoGo condition were higher in controls than patients in the joystick version ($p=0.002$) and the oculomotor task ($p<0.001$). In the Go condition higher rates of direction error were seen amongst patients compared with controls for both versions of the task (joystick: $p<0.001$, oculomotor: $p=0.003$). Compared with the oculomotor version, on the joystick version of the task both patients and controls had a higher d' ($p<0.001$) and lower commission errors rate in NoGo trials ($p<0.001$). Direction error rates were lower for the joystick task amongst controls ($p=0.004$) but not significant for patients ($p=0.385$). Differences for omission error rates between tasks were not significant for patients or controls.

| | Joystick Task | | | | Oculomotor Task | | | |
|---|---|---|---|---|---|---|---|---|
| | Patients (N=64) | | Controls (N=50) | | Patients (N=34) | | Controls (N=43) | |
| Type | RT (SD) | No (SD) | RT (SD) | No (SD) | RT (SD) | No (SD) | RT (SD) | No (SD) |
| GCRD | 1126.91*** (274.95) | 52.87*** (20.75) | 757.99*** (108.54) | 68.52*** (2.61) | 459.38 (168.99) | 100.82*** (29.89) | 486.95 (66.64) | 127.49*** (12.32) |
| GCWD | 695.71*** (590.46) | 4.19*** (9.94) | 156.41*** (323.22) | 0.24*** (0.52) | 689.00 (475.16) | 6.21** (8.01) | 648.60 (418.9) | 1.81** (3.15) |
| GIRD | 699.91*** (475.69) | 3.56* (9.85) | 234.76*** (344.65) | 0.56* (0.88) | 408.82* (132.20) | 74.88*** (35.92) | 490.86* (174.30) | 40.63*** (23.67) |
| GIWD | 297.29*** (463.41) | 0.91** (1.97) | 0.00*** (0.00) | 0.00** (0.00) | 749.07 (364.22) | 9.06 (11.26) | 867.59 (240.16) | 11.70 (240.16) |
| NC | NA | 71.83** (16.74) | NA | 79.42** (0.88) | NA | 42.85*** (42.50) | NA | 83.05*** (37.49) |
| NI | NA | 10.09*** (13.62) | NA | 0.96*** (2.36) | NA | 17.79*** (24.49) | NA | 4.40*** (7.82) |

**Table 4.1 Mean Response Times (milliseconds) by response type for patients with FTLD associated syndromes and healthy older controls on the joystick and oculomotor versions of the Go/NoGo task.** GCRD=Go Correct Right Direction, GCWD=Go Correct Wrong Direction, GIRD=Go Incorrect Right Direction, GIWD=Go Incorrect Wrong Direction, Nogo Correct (NC), Nogo Incorrect (NI). No=Mean Number of Response Type, RT=Response Time, SD=Standard Deviation, NA=Not Applicable ***P≤0.001 **P≤0.01 *P≤0.05 Two tailed T-tests comparing patients and controls.

| | Joystick Task | | Oculomotor Task | |
|---|---|---|---|---|
| | Patients (SD) N=64 | Controls (SD) N=50 | Patients (SD) N=34 | Controls (SD) N=43 |
| Omission error rate in Go trials | 0.18 (0.25)*** | 0.01 (0.03)*** | 0.14 (0.17)** | 0.03 (0.06)** |
| Commission Error rate in NoGo Trials | 0.07 (0.14)** | 0.01 (0.01)** | 0.68 (0.29)*** | 0.39 (0.26)*** |
| Directional Error rate in Correct Go Trials | 0.10 (0.20)** | 0.00 (0.01)** | 0.06 (0.08)** | 0.01 (0.03)** |
| d' | 3.12 (1.31)*** | 4.42 (0.32)*** | 0.75 (1.10)*** | 2.40 (0.94)*** |

**Table 4.2 Error rates (standard deviation) by error type and sensitivity index, d', amongst patients with FTLD Associated Syndromes and healthy older controls during joystick and oculomotor versions of the Go/NoGo task** ***P≤0.001 **P≤0.01 *P≤0.05 Two tailed T-tests comparing patients and controls.

### 4.4.2 The Stop Signal Task

Sixty-three patients and all controls completed the task (Table 4.3). Controls responded more accurately than patients and made no direction errors. Median reaction times on correct Go trials were significantly faster for controls than patients, SSD(50%) and SSRT significantly were significantly shorter for controls compared with patients.

| | Patients (SD) N=63 | Controls (SD) N=50 |
|---|---|---|
| SSRT | 574.67 (1094.51)* | 181.08 (41.78)* |
| SSD (50%) | 570.10 (231.74)*** | 362.19 (125.57)*** |
| Direction errors on Go trials | 7.43 (15.77) | 0 |
| Direction errors on Stop trials | 52.00 (17.22) | 0 |
| Median Reaction Time on Go trials (correct direction) | 1144.77 (1137.86)*** | 535.88 (113.23)*** |
| Median Reaction Time on Go trials (incorrect direction) | 808.25 (1231.50) | NA |

**Table 4.3 Calculated stop signal reaction times (milliseconds), stop signal delay (milliseconds) and error rates amongst patients with FTLD associated syndromes and healthy older controls on the Stop Signal Reaction Time Task. SSRT=Stop Signal Reaction Time, SSD=Stop Signal Delay, SD=Standard Deviation.** ***P≤0.001 **P≤0.01 *P≤0.05 Two tailed T-tests comparing patients and controls.

### 4.4.3 The Information Sampling Task

Fifty controls and 61 patients completed the IST. Table 4.4 shows outcome measures for patients and controls for both fixed and decreasing reward trial types. All differences between patient and control groups were statistically significant (two tailed T-tests). Patients made decisions at lower probability thresholds (probability of being correct) for both decreasing and fixed conditions compared to controls. Both groups opened less boxes in the decreasing condition compared with fixed (repeated measure ANOVAs: Controls $F=40.39$, $df=1$, $p<0.001$; Patients $F=35.43$, $df=1$, $p<0.001$) and made decisions at a lower probability of being correct (repeated measure ANOVAs: Controls $F=14.80$, $df=1$, $P<0.001$; Patients $F=19.31$, $df=1$ $p<0.001$). Repeated measure ANOVAs for probability of being correct at the time of decision or mean number of boxes opened between condition and control vs. patient did not show a significant difference between groups ($F=1.03$, $df=1$, $p=0.313$ and $F=0.00$, $df=1$, $p=0.997$ respectively). Amongst controls box opening latency was significantly slower for decreased condition compared with fixed (repeated measure ANOVA, $F=15.61$, $df=1$, $p<0.001$) but this was not the case for patients (repeated measure ANOVA, $F=0.02$ $df=1$, $p=0.894$).

| | Patients (SD) N=61 | | Controls (SD) N=50 | |
|---|---|---|---|---|
| Condition Type | Fixed | Decreasing | Fixed | Decreasing |
| Probability of being Correct | 0.75 (0.14)*** | 0.66 (0.16)*** | 0.87 (0.11)*** | 0.81 (0.10)*** |
| Mean box opening latency | 2.11 (2.67)** | 2.07 (1.47)*** | 0.96 (0.52)** | 1.12 (0.44)*** |
| Mean colour decision latency | 29.33 (25.78)*** | 26.09 (28.57)*** | 18.74 (8.17)*** | 18.30 (9.54)*** |
| Mean boxes opened per trial | 14.39 (7.30)** | 10.36 (6.01)** | 17.84 (5.37)** | 13.80 (5.01)** |
| Sampling error | 1.25 (1.42)*** | 1.69 (1.48)** | 0.42 (0.73)*** | 0.94 (1.00)** |
| Discrimination errors | 1.50 (1.78)** | 1.92 (2.04)*** | 0.72 (0.94)** | 0.54 (0.76)*** |
| Total correct | 7.70 (1.76)*** | 6.64 (2.28)*** | 9.04 (1.12)*** | 8.68 (1.15)*** |

**Table 4.4 Performance on the Information Sampling Task of Patients with FTLD Associated Syndromes and Healthy Older controls.** Latency is in seconds. SD=Standard Deviation. ***P≤0.001 **P≤0.01 *P≤0.05 Two tailed T-tests comparing patients and controls.

### 4.4.4 The Kirby Delayed Discounting Task

Forty-nine controls and 67 patients completed the Kirby Delayed Discounting task. Values for k for small, medium and large monetary amounts were calculated and shown in Table 4.5. Mean discounting rates (k) were significantly higher in patients than controls with the highest rates observed in patients considering the smallest monetary amounts. Repeated measures ANOVA comparing values of k for high and low monetary amounts across patients and controls did not show a significant interaction (F=1.72, df=1, p=0.19). Between subjects (patients vs controls) ANOVA for k was significant (F=5.03, df=1, p=0.027).

| | Patients (SD) N=67 | Controls (SD) N=49 |
|---|---|---|
| K Mean | 0.037 (0.052)* | 0.018 (0.030)* |
| K Large | 0.031 (0.060) | 0.016 (0.050) |
| K Medium | 0.029 (0.046) | 0.016 (0.025) |
| K Small | 0.049 (0.074)* | 0.021 (0.029)* |
| Difference (K small-K large) | 0.018 (0.057) | 0.005 (0.044) |
| Consistency Large | 0.937 (0.085) | 0.984 (0.068) |
| Consistency Medium | 0.937 (0.085)*** | 0.986 (0.025)*** |
| Consistency Small | 0.932 (0.093)** | 0.982 (0.069)** |

**Table 4.5 Discounting rates, K, for patients with FTLD Associated Syndromes and Healthy older controls on the Kirby Delayed Discounting Task.** Large/Medium/Small refers to monetary value. SD=Standard Deviation. ***P≤0.001 **P≤0.01 *P≤0.05 Two tailed T-tests comparing patients and controls.

### 4.4.5 The Cambridge Gambling Task

Despite using a modified and reduced version of the CGT patients found the task overly fatiguing and difficult. So few subjects were able to complete the task that it was removed after attempting amongst 28 participants and not included in further analysis.

### 4.4.6 The Cued Reinforcement Reaction Time Task

Forty-nine controls and 51 patients completed the CRRTT (Table 4.6). Controls responded more quickly than patients throughout the task.

Repeated measures ANOVA of difference in response time by condition (0.8 probability of reward-0.2 probability of reward) between the first and second half of the trial by patient vs. control revealed a significant interaction ($F=4.86$, $df=1$, $p=0.03$). Reaction times were significantly faster in the second half of trials amongst controls for both conditions (T-test, 20% condition $t=3.14$, $df\ 48$ $p=0.003$, 80% condition $t=6.83$, $df=48$ $p<0.001$) but not patients (T-test, 20% $t=1.53$, $df=50$, $p=0.134$, 80% $t=-1.23$, $df=50$, $p=0.23$).

| | | Patients (SD) N=51 | Controls (SD) N=49 |
|---|---|---|---|
| Mean Reaction Times: First half of Trials | 20% Chance of Reward | 2359.53 (707.90)*** | 1013.12 (252.65)*** |
| | 80% Chance of Reward | 2200.47 (645.87)*** | 1029.48 (253.56)*** |
| Mean Reaction Times: Second Half of Trials | 20% Chance of Reward | 2221.58 (646.21)*** | 976.04 (242.71)*** |
| | 80% Chance of Reward | 2262.08 (627.29)*** | 948.09 (225.15)*** |

**Table 4.6 Mean Reaction Time (milliseconds) for patients with FTLD associated syndromes and healthy older controls on the Cued Reinforcement Reaction Time task.** ***P≤0.001 Two tailed T-tests comparing patients and controls.

## 4.5 Discussion

Across a range of behavioural tasks aimed at decision-making and reflection impulsivity (IST), perception and responsiveness to reward (Kirby, CRRTT, IST), and response inhibition (Go/NoGo, SSRTT), patients with FTLD associated syndromes performed differently to healthy older controls. Response times across a range of tasks were consistently slower amongst the FTLD group compared with controls with the only exception being the oculomotor task, where mean responses were marginally faster for subjects with FTLD associated syndromes compared with controls (although most not statistically significant). As the majority of patients with FTLD have some form of movement disorder it is unsurprising that limb reaction times are impaired. The relative lack of difference between patients with FTLD associated syndromes and controls when considering crude reaction times on the oculomotor task is more notable particularly when considering a significant number of subjects with FTLD have impaired saccadic eye movements. This cannot be fully explained by the automated validation process used to filter saccadic responses as the mean number of rejected responses was similar for both patients with FTLD associated syndromes 30.46 (SD, 17.57) and controls 29.77 (SD, 9.29). However, the calculated d' for subjects with FTLD associated syndromes was significantly lower on the oculomotor task compared with the joystick task demonstrating that while the subjects with FTLD associated syndromes were responding quickly, accuracy was substantially diminished.

Despite responding more slowly on most tasks the patients with FTLD associated syndromes were less accurate than controls reflected by higher omission, commission and directional errors on both forms of the Go/NoGo task, higher rates of sampling and discrimination errors on the IST and more direction errors on the SSRTT.

While reaction times *per se* may not be the most useful surrogate of goal directed cognition in this FTLD group (because of additional impairments of motor control) changes in response to anticipated reward can be interpreted in terms of motivation and goal-directness. When responding to the CRRTT, I anticipated healthy controls would respond more quickly in the second half of the test for the higher probability of reward condition (i.e. when they anticipate a greater chance of reward they respond more quickly). This is the case in the healthy older cohort but the effect is not seen amongst patients, in fact they were marginally slower in the higher probability condition in the second half of the task (although the difference was not statistically significant). In absolute terms the patient group were marginally quicker responding in the second half of the task for the lower probability condition suggesting that different susceptibility to fatigue is not sufficient to explain the lack of a significant response in terms of reaction times for the higher probability condition amongst patients in the second half

of the trial. Two alternative explanations may account for the difference between patients and controls. Firstly that controls are able to detect and respond to the difference between conditions after the first half of trials while the patients are not, or alternatively, both groups are able to detect the difference between conditions after the first half of trials but respond in a different way: Healthy controls, detecting that one condition leads to a higher probability of reward, respond more quickly when a greater probability of reward is present. Patients also detect the different probability of reward but respond more slowly either to attempt to increase accuracy or to avoid negative feedback (such risk-aversion is only relevant on those trials where feedback is given). Hence the difference between groups may be explained by; (i) decreased ability to detect the difference between conditions amongst the patients; (ii)by reduced reward responsiveness; (iii) preserved reward responsiveness but inability to increase response speed (and hence increased response time to attempt to improve accuracy); or finally (iv) increased aversion to negative feedback amongst patients with FTLD associated syndromes.

While reaction times are measured during the IST (as mean box opening latency and colour decision latency) they are not an explicit part of the task and subjects were permitted to take as long as they needed to make decisions during the task. The difference between the two conditions (where points available for a correct decision diminishes with each box opened in the diminishing condition) may serve as an alternative surrogate of responsiveness to both positive and negative feedback. Negative feedback, when the subject makes an incorrect decision and loses 100 points, remains constant between the two conditions and regardless of the number of boxes opened. Hence a subject who is more averse to negative feedback may choose to open more boxes and increase their chance of success even when this reduces the potential number of points available for a correct decision. However this was not the case. Both patients and controls opened less boxes and made decisions at a lower probability of being correct in the decreasing condition compared to the fixed condition, suggesting at least for the IST, the patient group were able to recognise the difference between the two conditions and adapt their technique in response to diminishing rewards in a similar fashion to controls.

Taken together these results suggest that compared to controls, patients with FTLD associated syndromes respond more slowly and less accurately. When potential reward or negative feedback is presented, both patients and healthy controls are responsive to feedback and adapt their response strategies. Unlike controls, patients are unable to improve response time but they still sacrifice accuracy when response time is explicitly connected to reward.

Controls, but not patients, spent significantly longer deciding whether to continue sampling or make a final decision on the IST (mean box opening latency) during the decreasing

condition compared with the fixed. While patients adapted their strategy to the change in condition (fixed vs. decreasing) deliberation time during sampling did not change significantly (in fact it was marginally shorter during the decreasing condition). Box opening latency was however substantially longer across all conditions for the patient group compared with controls. It may be that the lack of change in deliberation time between conditions amongst patients is explained by the time it takes for any response being sufficiently long to allow sufficient deliberation regardless of condition (because motor disability delays the time to make a response and hence already allows more than sufficient deliberation time) or alternatively that the patient group are unable to adapt deliberation time in response to change in condition. On average patients made a decision after opening less boxes than controls across both conditions. Hence the patient group make decisions based on less information, they are sensitive to changes in condition and reward and adapt their response strategy accordingly but do not adapt response time.

Performance on both the SSRT and Go/NoGo tasks relies on action inhibition i.e. the inhibition of a pre-planned response(168). These tasks have been used to investigate impulsivity in a range of disorders such as Attention Deficit Hyperactivity Disorder(221), Parkinson's Disease(222), PSP(223) and FTD(187). Despite their similarities there is evidence from a range of animal and human studies that performance on the two tasks depends on different neuroanatomical networks and may be modulated by different neuropharmacological interventions (with 5-HT implicated in the inhibitory control on the Go/NoGo task but not the SSRT task which is more sensitive to noradrenaline)(168). While the Go/NoGo task tests action restraint (inhibiting a response before the response is started) the additional element of the stop signal after the initial stimulus during the SSRT task tests action cancellation (the ability to inhibit a response after it has started). The highest error rate on the oculomotor task was seen amongst the patient groups' rates of commission errors. During the oculomotor task both patients and healthy controls had higher rates of commission (as opposed to omission) errors but the reverse was seen amongst patients during the joystick task and the same low rate seen for both error types amongst controls. The oculomotor version of the Go/NoGo task has the advantage of measuring the time to initiate movement as opposed to execution time and relies on the patient initiating a smaller action (initiation of a saccade) to register a response. In contrast the joystick version requires a greater movement and it is conceivable that subjects are able to inhibit a smaller response after it has been initiated (action cancellation) and not register a response by full movement of the joystick. However, compared with controls, patients also had longer SSD and SSRT on the SSRT task suggesting both action restraint and action inhibition are impaired in FTLD.

Delayed discounting refers to the tendency for more remote outcomes to have less perceived value(224). Individuals would prefer greater and more immediate rewards but when a temporal delay is introduced the perceived value diminishes such that (for example) an individual may prefer to receive £100 today rather than wait a year and receive £150. The discounting rate, k, reflects the rate at which the perceived reward diminishes with delay (such that a higher value of k reflects a more steep discounting of future rewards and a greater tendency to choose an immediate reward). Healthy controls tend to have higher discounting rates when considering smaller monetary amounts(224) and discounting rates are higher amongst groups with impulsive behaviour such as compulsive gamblers(225), heroin addicts, and patients with orbitofrontal damage(226) and schizophrenia(227).

Amongst this cohort the patient group had higher rates of temporal discounting than controls. The highest rates of temporal discounting were seen for smaller monetary amounts for both the patient group and healthy controls which was similar to previous studies (e.g. (219)). While patients had overall higher rates of temporal discounting their consistency rates were lower such that the point at which they chose to switch from higher delayed reward to smaller immediate reward was not consistent across all their responses. A similar effect has been reported in other disease groups (e.g. schizophrenia (227)) and inconsistency in response may also be a contributory factor in reported impulsivity in this disease group.

The effect of FTLD on discounting rates has been reported previously but is not clear. One study found increased discounting rates in patients with bvFTD(228) however in a another discounting rates were not significantly different compared with healthy older controls or patients with Alzheimer's Disease. This was in contrast to a group of patients with svPPA who demonstrated higher discounting rates(229). One explanation for the discrepancy is by specifically screening and excluding patients with semantic deficits from the bvFTD the second study selected less severely affected patients with bvFTD and damage to anterior temporal lobe structures related to the more pronounced semantic symptoms in svPPA may contribute to more rapid delay discounting. The authors suggest that delay discounting may be unaffected early in bvFTD but is affected as the disease progresses and spreads to involve more brain regions overlapping with svPPA(229). This serves to emphasise that using the existing diagnostic criteria used to define the syndromes associated with FTLD may inadvertently lead to misrepresentative cohorts when researching particular neurocognitive aspects of the disease as a whole.

### 4.6 Limitations

In this chapter, and also in Chapter Three, I investigated a range of neuropsychiatric features of FTLD, focussing in particular on the symptoms of apathy and impulsivity. I have recruited subjects with FTLD associated syndromes from a population based epidemiological study and using a range of techniques (including clinical assessment, carer reports, patient questionnaires and behavioural testing) demonstrated increased rates of apathetic and impulsive symptomatology. I have suggested that these data show that these are prevalent symptoms in a representative cohort of subjects.

However there are several limitations. Firstly this sub-group may not be representative of FTLD associated syndromes as a whole. I was not able to assess every subject identified in the epidemiological study in person. In Chapter Two I presented the frequency of particular symptoms across the entire cohort but in some cases I relied on specialist assessments and subsequent clinical records. It may well be in such cases the focus of the clinical encounter was directed at particular symptoms such that other features (which may have been present) were not specifically enquired about or recorded. In this chapter, and Chapter Three, I have focussed on only those subjects I was able to meet in person who were able to engage in some form of testing (even if this was limited to clinical assessment and carer interview). Whilst I travelled out to meet subjects in their own home and met subjects at every stage of disease, it is possible that those patients and carers who were willing to participate were less severely affected than those who refused any participation beyond case notification and clinical records review. In addition to this, the nature and amount of testing possible amongst those subjects I met was dependant on their physical and cognitive abilities. Some tests (such as the Cambridge Gambling Task) had to be abandoned completely as subjects with FTLD associated syndromes were so often simply not able to fully understand and complete the task. Other tests such as the Go/NoGo were only completed by a large subset of subjects who were physically able to move a joystick and had sufficient cognitive ability to understand the task. Additional elements of their clinical syndromes such as limb dystonia, myoclonus or apraxia prevented some subjects from completing the task and may have contributed to the responses recorded of others who were less severely affected and hence able to participate in the task. The oculomotor version of the Go/NoGo task overcomes any difficulties presented by limb movement disorders but other subjects had difficulty completing the task because of impairments of voluntary eye movements, blepharospasm or severe apraxia of eyelid opening. Similarly language disorders may have impaired responses to some questionnaires, visuospatial problems may affect responses on the IST and so on. As a result while I have demonstrated high levels of apathetic and impulsive symptomatology amongst patients with FTLD regardless of the testing modality used or subset

of subjects assessed I have not been able to demonstrate changes in every subject for every testing modality. Only a minority of patients with FTLD associated syndromes were able to complete every aspect of the testing protocol. Restricting analysis to only this subset of subjects would firstly have led to substantially reduced sample size but also more importantly lead to a cohort that is less representative of the syndromes associated with FTLD as a whole.

In this chapter I have demonstrated that this patient group show respond differently to healthy controls across a range of tasks that have been used to test a range of neuropsychiatric symptoms and components of decision making which have previously been used to test components of apathy and impulsivity in a range of clinical conditions (e.g. (17,165)). While patients with FTLD associated syndromes and their carers reported higher levels of apathy and impulsivity compared with controls and performed differently on these tasks, I have not attempted to demonstrate that performance on these more "objective" tests directly relates to levels of reported apathy/impulsivity per se.

Most of the justification for studying apathy and impulsivity is derived from patient and carer based reports and the correlation between these and disease morbidity (132,133,147,164). It is not certain that the specific neurocognitive processes that these behavioural tasks seek to test are directly responsible for the patient and carer based reports of apathy or impulsivity. Other factors such as patient insight, mood, fatigue or depression may relate to their own reports of symptoms. Similarly carer based interviews are limited by their own perspectives where symptoms may be misinterpreted or influenced by other factors (such as the carer's own psychological state). For example, one study comparing fitness to drive (assessed by naturalistic driving assessment and instructor based standardised road test) with carer and clinician rating of driving safety amongst patients with Alzheimer's disease found only weak associations between clinician assessment and driving performance and an inverse association between spousal ratings and naturalistic driving scores. In another study of 156 patients with Alzheimer's disease significant disagreement was found between carer and clinician assessment of neuropsychiatric symptoms, particularly those that may be related to apathy and impulsivity(230).

A questionnaire-based assessment is limited by the nature of the question asked. Simply asking whether the subject is apathetic relies on their own understanding of the concept of apathy and even a more detailed assessment based on symptoms in a range of situations may not fully apply to the respondent's particular circumstances (for example asking about social interactions or day to day conversation may not be appropriate when the respondent has expressive language difficulties). It is not clear that the symptoms that are reported by patients

or their carers are an accurate assessment of apathy or impulsivity as specific neuropsychological constructs, or that objective behavioural testing directly relates to clinically important outcome measures (something I address in more detail in subsequent chapters). By not relying on a single testing modality, using a range of testing techniques and multiple sources of information I have demonstrated that while each individual test may have limitations this patient group consistently performs differently in these tasks and have higher reported rates of apathy and impulsivity compared to a similarly aged group of healthy older people.

### 4.7 Conclusions

Using a range of behavioural tasks directed at decision-making, reward responsiveness and action inhibition I have shown that patients with FTLD associated syndromes respond differently to healthy older controls. Patients respond more slowly and are less accurate across a range of tasks. The data I have presented here suggest that subjects with FTLD associated syndromes are able to detect and adapt their responses to changes in perceived reward but do so differently than healthy older controls. Furthermore I argue that these differences cannot be explained by disruption of a single cognitive process. I suggest these data demonstrate that subjects with FTLD associated syndromes have deficits in both action restraint and action cancellation. They have higher rates of temporal discounting and different responses to the healthy group when presented with positive and negative feedback. All of these processes may be contributory to the observed increase in both apathetic and impulsive behaviour observed in this patient group.

# Chapter 5

# A Multidimensional Approach to Apathy and Impulsivity in FTLD

## 5.1 Summary

In this chapter I discuss the multidimensional nature of apathy and impulsivity and the relationship between questionnaire based and behavioural forms of assessments in the PiPPIN study of subjects with syndromes associated with FTLD. Through Principal Component Analyses I show that variation in responses on the Apathy Evaluation Scale appears to be multifactorial and while some aspects may be related to the original component structure others appear more related to the manner in which the items on the scale are presented. I also show that while multiple respondents (patient, carer, clinician) report high levels of apathetic symptomatology, patient and carer reports do not correlate well with each other and that these discrepancies may be quantified and may reflect a useful form of assessment. Next I separate patients into those rated as apathetic, impulsive or not by their carers and show that comparisons of behavioural surrogate measures of these symptoms do not show significant differences between groups. Finally I perform a further Principal Component Analysis combining assessment of apathy and impulsivity by multiple methodologies and show that these measures dissociate into a number of components. Behavioural and questionnaire based assessments largely do not overlap and appear to be measuring different things. I conclude that apathy and impulsivity are multidimensional and that while different testing modalities each have their own advantages and limitations no single method in isolation is sufficient for the assessment of apathy and impulsivity and that a multidimensional approach is necessary.

## 5.2 Introduction

In Chapter Three I demonstrated that both apathetic and impulsive behaviour are commonly reported by patients with syndromes associated with FTLD in the PiPPIN cohort and also by informants close to them. I also showed that a range of questionnaire based assessments can be used to record and quantify some of these symptoms. For example, using Apathy Evaluation Scale I demonstrated that regardless of whether the scale is completed by the patients, an informant who knows them well or by a trained assessor using a structured interview, higher

frequency of apathetic symptoms are reported amongst patients than amongst healthy subjects of a similar age.

The Apathy Evaluation Scale was derived from several hundred items designed to address apathetic symptoms based on the authors' observations and conceptualisation of apathetic subjects(158). After further consultation this was reduced to a preliminary scale of 70 items that were considered unambiguous, easily understood and representative of the domains of interest. This 70-item scale was administered to 40 subjects with a diagnosis of major depression or dementia, a further 14 items removed again on the basis of simplicity and clarity and a revised 56 item scale administered to a group of 122 subjects aged 55-85 years old and comprising of well elderly, patients with left or right hemisphere strokes, probable Alzheimer's disease or major depression. Subjects with other neurological or psychiatric diagnoses were excluded. Informant, clinician and patient versions of the scale were administered and the total number of items reduced to include only those than had item total correlations between at least three of the four versions of the scale of 0.4. The resultant 27 items were reduced to 18 on the basis of non significant correlations with the Hamilton Rating Scale for Depression (seven items, in order to differentiate apathy from depression) and using the Principal Component Analysis method(158). The resultant 18 items are classified into four types (Cognitive, Emotional, Behavioural and Other), three items are presented with negative syntax and for the Clinician version, four are self evaluated directly by the subject (as opposed to relating to the clinical impression) and four are quantifiable (based on the number of examples of a particular behaviour the subject can present). Principal Component Analysis (PCA) of the 18 item scale identified three similar factors for each version of the scale accounting for 50-65% of the variance with a single factor accounting for 32-53% of the variance(158).

This partially data driven approach has been used to design numerous scales for the assessment of psychological symptoms. These scales have many advantages; they are quick and relatively simple to administer and score and offer a degree of uniformity and inter-rater reliability that is difficult to achieve using less structured subject interviews and assessment. Using a simple points allocation for each item within a scale allows quantitative scoring of individual subjects and groups. However there are limitations to this approach. Firstly any questionnaire is limited by the subject's capacity to understand each item and apply it to their own circumstances in the manner in which the questionnaire's designer intended. Many questionnaires (for example the BIS/BAS scales) were designed and validated in healthy younger subjects (178) while others (e.g. BIS-11 and AES) used a combination of healthy subjects, psychiatric patients and patients with non-FTLD neurological disorders(158,169). Using a semi data driven approach such as PCA to gain insights into common components of

heterogeneity amongst subjects' responses potentially leads to several issues, particularly when these scales are applied to different patient groups.

Amongst a cohort consisting of patients and healthy volunteers one of the greatest differences between subjects' responses is likely to be disease state. A single factor explaining a large amount of heterogeneity between subjects may account for the majority of variance between subjects' responses and obscure subtler variance using the PCA method. Hence the concept of apathy as measured in the AES may appear more uniform than it is in reality. In Marin's original paper we see more than half the variance accounted for by PCA attributed to a single factor(158). This may be the case, but an alternative explanation is that the inclusion of healthy older volunteers introduces a single large difference between subjects that obscures more subtle factors responsible for apathetic symptoms when present in disease states. Furthermore while the component structure maybe uniform across different diseases but this is not necessarily the case. The causes and symptoms related to apathy in depressed individuals maybe very different to those seen in FTLD and hence a purely data driven set of subscales derived from one subject group with a particular set of disorders may not be directly applicable to another.

Questionnaire-based assessments rely on the respondent's understanding and interpretation of the questions set and their own insight in their condition. Some subjects (especially those with FLTD) may lack insight into their condition(195) but informant responses may also be limited by their own interpretations of the patient's cognitive state or their own psychological state and distress(231). While in other disease states Marin demonstrated good internal consistency, test-retest and interrater reliability(158) behavioural changes and anosognosia seen amongst subjects with FTLD are particularly severe compared to other diseases and distressing for carers. Hence while good interrater reliability for the AES has been demonstrated in other disease states there are good reasons that it should not be assumed that this is also the case for FTLD.

In Chapter Four I discussed some of these limitations of a questionnaire based approach and demonstrated that using a range of behavioural tasks designed to assess goal directed behaviour, patients with FTLD associated syndromes perform differently to healthy older controls. I suggested that using such a behavioural approach may overcome some of the limitations of questionnaires and provide a more objective and quantifiable method of assessing changes in cognition that could lead to apathetic or impulsive behaviour. This approach has previously been successful in demonstrating that different behavioural tasks have different neuroanatomical and neurotransmitter correlates, even when the differences between tasks

seem relatively subtle(162). Experimental modulation of these neural systems may offer further insights not only into the underlying mechanisms responsible for apathy and impulsivity but also ways into methods by which they may be treated. For example, one study used magnetoencephalopthy recording of subjects with bvFTD and healthy controls during a Go/NoGo task to show that successful response inhibition related to cortical sources in the right inferior frontal gyrus and anterior temporal lobe. These sources were significantly attenuated in bvFTD but could be partially restored using the Selective Serotonin Reuptake Inhibitor (SSRI) citalopram(187). SSRIs have been used in the treatment of behavioural symptoms amongst patients with bvFTD but despite promising reports of improvements in small open label case series, these have not been replicated in larger randomised, placebo-controlled trials(232). Similarly there is evidence that noradrenergic and dopaminergic systems have a role in goal directed behaviour. Blockade of alpha-2 adrenoreceptors in rats during the stop signal task improved attention and response inhibition while modulation of dopamine D3 receptors appears to modulate error monitoring and perseverative behaviours(233). In a human study some, but not all, subjects with Parkinson's disease showed enhanced response inhibition on the SSRT and GoNo tasks with the noradrenaline reuptake inhibitor atomoxetine and when present this was associated with increased right inferior frontal gyrus activation and frontostriatal connectivity on functional MRI(222). Another study demonstrated improvement across a range of tasks of decision making, response inhibition and goal directed behaviour(234) but there is only very limited open label data suggesting any clinically meaningful effects in Parkinson's (e.g. (235)).

Accepting that goal directed behaviour is a complex and multifaceted construct and that disruption in any stage may result in the syndromes of apathy and impulsivity, it is unsurprising that attempts to assess specific cognitive aspects using focussed behavioural tasks have not yielded immediate dramatic clinical results. Despite a predilection for specific areas of the brain, neurodegenerative diseases such as Parkinson's and FTLD have, at least by the time of diagnosis, widespread effects on multiple areas of the brain. For the same reasons it is unsurprising that subjects in the PiPPIN cohort performed differently across the whole range of behavioural tasks in a manner that cannot be easily attributed to disruption of a single simple cognitive process. In Chapter Three I demonstrated that these subjects show impairments across a range of cognitive domains and in Chapter Two that they have a range of overlapping physical and cognitive impairments, all of which may have an effect on their ability to perform behavioural tasks. It is comparatively easy to show that subjects with FTLD and their carers report apathetic and impulsive behaviour, symptoms of apathy and impulsivity and that they are impaired on

tasks of action selection, response inhibition and reward responsiveness but it is much more difficult to establish which of these are clinically relevant.

While questionnaire-based assessments are subject the limitations of the questions set and the respondent's interpretation of them, they do enquire about symptoms in 'real world' scenarios. However the validity applying of a set of questionnaires derived from one of set of clinical disorders to another (such as FTLD) can be challenged. Behavioural tasks are still limited by the subjects' understanding of the task and their other physical and cognitive abilities, but may be more objective and offer the opportunity to examine more specific, focussed areas of cognition/behaviour than is possible when using a questionnaire. However performance on behavioural tasks is less explicitly related to symptoms in everyday life. When moving beyond purely academic observation of cognitive processes and towards symptomatic therapy, clinically meaningful outcomes measures are needed and hence more than one methodology is required.

In this chapter I explore the multifaceted nature of apathy and impulsivity and the intercorrelation of different methods used in their assessment. Firstly I explore factor structure of the AES-I in relation to Marin's original three factor solution(158) and test whether PCA performed across groups and on patient's alone produce similar results. Secondly I examine the relationship between subject (AES-S), informant (AES-I) and clinician (AES-C) versions of the scale. I also examine where discrepancies exist between subject and informant reports on the AES and CBI-R and the relationship between these and other measures of mood (BDI-II) and behaviour (CBI-R) and overall cognition (FAB and ACE-R). Next using the NPI-Q I examine whether any of the behavioural measures a significantly different amongst those subjects rated by their informant as apathetic or impulsive are statistically different. Finally I demonstrate how a more integrative, mixed methodology approach may be useful to overcome some of the limitations of any single approach.

### 5.3 Methods

Subjects with syndromes associated with FTLD identified in the PiPPIN study and 50 healthy similarly aged volunteers were invited to complete a battery of questionnaires and behavioural tasks (described in Chapters Three and Four). Note that while the healthy volunteers completed all assessments not all patients completed all assessments. As a result each Principal Component Analysis was performed on a different subset of patients.

### 5.3.1 Statistical Analysis

Statistical analysis was performed in SPSS (IBM v22). Principal Component Analysis (PCA) was using orthogonal varimax rotation with Kaiser normalisation. Adequacy of sample size was assessed using Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity. The standardised correlation matrix was used for extraction of components (as opposed to the unstandardized covariance matrix) and extraction of significant components was based on Kaiser's criteria (i.e. those with Eigenvalues greater than 1).

### 5.3.2 Discrepancy Scores

In order to further explore variation between subject and information versions of the AES two additional discrepancy measures were calculated from the differences between each item within the AES-S and AES-I. Described in relation to the AES-I; AESOverscore describes the sum of differences between each item of the AES where the subject scored themselves higher on the AES-S than the informant on the equivalent item on the AES-I and AESUnderscore describes the sum of differences between each item where the patient scores themselves lower on the AES-S compared with the equivalent item on the AES-I (and both AESOverscore and AESUnderscore described as positive integers). Using exactly the same method two additional measures were derived from the CBI-R using the first item from each of the ten groups of behavioural symptoms where both subject (with FTLD associated syndrome) and informant (their carer) rated the frequency of the subject's behavioural symptoms. From the differences between subject and informant CBIUnderscore and CBIOverscore were calculated as a measure of how much the subject underestimated and over estimated symptoms in comparison with the informant's estimation.

### 5.3.3 Comparison of Behavioural Testing Performance Based on Informant Ratings of Apathy and Impulsiveness

To examine whether subjects rated by informants as apathetic or impulsive performed differently on behavioural testing subjects with syndromes associated with FTLD were divided based on informant rating of Apathy ('Does the patient seem less interesting in his/her usual activities or in the activities and plans of others?') and Disinhibition 'Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people's feelings?') on the NPI-Q. Results on behavioural testing were between the resulting groups using independent samples T-tests. The following measures were compared: From the Kirby Mean K, mean consistency and difference between K for small and large monetary amounts; From Joystick and Saccadometer Go/NoGo trials mean D', and omission and

commission error rates; From the Stop Signal Reaction Time Task the Stop Signal Reaction Time calculated from the last half of trials; From the Information Sampling Task mean probability of being correct for Fixed and Decreasing conditions and difference between conditions; From the Cued Reinforcement Reaction Time Task the difference between change in response time for higher probability of feedback in the second half of trials compared with the first.

### 5.3.4 Principal Component Analysis Across Multiple Testing Modalities

Principal Component Analysis (PCA) was performed using orthogonal varimax rotation with Kaiser normalisation. PCA was performed twice, firstly using both patient and healthy volunteers and secondly with the patient group alone. As multiple testing modalities and scoring scales were included in each PCA Z scores were calculated from each variable prior to each PCA. Missing values were replaced with the mean. While this approach has the disadvantage of reducing variance of variables and correlations between them it has the advantage of simplicity and speed. Furthermore the effects of replacing with the mean are to some extent predictable. Alternative approaches include replace missing data by imputation and statistical modelling, skipping or considering explicitly missing values. While each approach has particular advantages and limitations I chose the simplest approach to produce a set of components and extracted variables that could then be evaluated and correlated against other assessments. In doing so I sought to maximise the amount of data included in the analyses but not add a further layer of complexity and potential distortion of the results. Adequacy of sample size was assessed using Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity. The standardised correlation matrix was used for extraction of components (as opposed to the unstandardized covariance matrix) and extraction of significant components was based on Kaiser's criteria (i.e. those with Eigenvalues greater than 1). Table 5.1 shows the variables were included in the PCA:

| Task/Questionnaire | Variables used in Component Analysis |
|---|---|
| Kirby | Mean K, Mean Consistency, Difference in K between small and large values |
| Go/NoGo tasks (saccadometer and joystick versions) | D', Omission error rate, Commission error rate |
| Stop Signal Reaction Time Task | SSRT from last half of trials |
| Information Sampling Task | Prob. Being correct for fixed and decreasing conditions |
| Cued Reaction Reinforcement Time Task | Difference in speeding between first and second half of trials |
| Apathy Evaluation Scale | Total score for subject, clinician and informant versions |
| Behavioural Inhibition System/Behavioural Activation System Scales | Drive, Funseeking, Reward Responsiveness, BIS scale |
| Motivation and Energy Index | Total score |
| Snaith Hamilton Anhedonia Pleasure Scale | Total score |
| Barrett Impulsiveness Scale II | Total score |
| Obsessive Compulsive Inventory (Revised) | Total score |

**Table 5.1 Variables included in Principal Component Analysis**

To further characterise the extracted components these were expressed as variables and for the patient group Pearson's bivariate correlations were performed between these and the total scores for ACE-R (as a surrogate of global cognitive ability), the BDI-II (as a surrogate of mood/depression) and discrepancy scores for the CBI-R. Note none of these tests (ACE-R, CBI-R or BDI-II) were used in the PCA.

## 5.4 Results

### 5.4.1 Principal Component Analysis of the Apathy Evaluation Scale

The results of the PCA for each version of the AES are shown in Table 5.2. Separate analyses were performed for Controls (C), Patients (P) and both groups together (C+P). The total number of components extracted varied between 3 (AES-I (C+P)) and 6 (AES-I (C)) explaining 60.4% (AES-S (P)) and 78.6% (AES-I (C)) of the variance.

The rotated component structures are shown in graph form in Figure 5.1. On initial visual inspection of the extracted components from the PCAs, some components appeared similar in structure to others from different analyses. For example factors three from AES-S(C+P), three from AES-S (C) and two from AES-I (P) all have strong positive weightings from items 12, 13 and 14 with comparatively little contribution from other items. Rather than rely on visual inspection for the forty extracted components I took a systematic approach and attempt

to classify the extracted components in relation to the item structure proposed by Marin(158), as follows.

First I standardised component loadings by removing directionality from in each component matrix (so that negative and positive loadings were considered equally). Next I calculated mean loadings for each item type (Cognitive, Behaviour, Emotional, Other) and question type (Self Evaluated, Quantifiable and Negative syntax). I then set an arbitrary threshold of 0.499 so that if the mean standardised factor loading was above this threshold I considered the item/question type contributory to the extracted component and disregarded those that did not. As only the Clinician version of the AES includes separately self-evaluated or quantifiable items (all items are self evaluated for the other versions of the AES) I only considered these items contributory for components extracted from the AES-C. Of the 40 extracted components thirteen (33%) had at least one of Marin's item types meeting the threshold (Table 5.3). Item type did not meet the threshold for any of the fourteen components extracted from the three PCA analyses of the AES-C. Negative scoring met the threshold for six (15%) of extracted components and was the sole item/question type meeting the threshold in every case. Self evaluated or quantifiable question type met the threshold for three (21%) of the fourteen components extracted from the AES-C. For nineteen (48%) of the extracted components, no item or question type met the threshold.

| Questionnaire Assessed (Respondents) | Number of respondents | KMO | Bartlett's test of Sphericity | Components Extracted (Eigenvalues) | Variance Explained %(range) |
|---|---|---|---|---|---|
| AES-I (C+P) | 153 | 0.945 | 2289.11, p<0.001 | 3 (1.14-10.57) | 72.00 (6.36-58.71) |
| AES-I (C) | 49 | 0.650 | 454.21, p<0.001 | 6 (1.01-5.84) | 78.59 (10.65-21.32) |
| AES-I (P) | 104 | 0.913 | 1210.45, p<0.001 | 4 (1.02-8.66) | 70.17 (7.01-36.02) |
| AES-S (C+P) | 120 | 0.887 | 940.034, p<0.001 | 4 (1.10-7.09) | 61.79 (6.13-39.37) |
| AES-S (C) | 50 | 0.707 | 406.90, p<0.001 | 5 (1.29-5.57) | 68.20 (7.16-30.97) |
| AES-S (P) | 70 | 0.808 | 513.44, p<0.001 | 4 (1.20-6.61) | 60.35 (6.67-36.72) |
| AES-C (C+P) | 126 | 0.907 | 1306.17, p<0.001 | 4 (1.04-8.39) | 67.02 (5.78-46.60) |
| AES-C (C) | 50 | 0.716 | 488.27, p<0.001 | 5 (1.12-6.15) | 70.09 (6.20-34.15) |
| AES-C (P) | 76 | 0.820 | 572.96, p<0.001 | 5 (1.06-6.36) | 66.82 (5.88-35.33) |

**Table 5.2** Results of separate Principal Component Analyses for the three versions of the Apathy Evaluation Scale performed for the Informant (AES-I), Subject (AES-S) and Clinician (AES-C) versions using results from Healthy older Controls (C), Subjects with FTLD Associated Syndromes (P) and both groups combined (C+P).

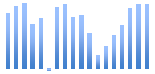
| Component | AES-I | | | AES-S | | | AES-C | | |
|---|---|---|---|---|---|---|---|---|---|
| | All Subjects (CP) | Controls (C) | Patients (P) | All Subjects (CP) | Controls (C) | Patients (P) | All Subjects (CP) | Controls (C) | Patients (P) |
| 1 |  |  |  |  |  |  |  |  |  |
| 2 |  |  |  |  |  |  |  |  |  |
| 3 |  |  |  |  |  |  |  |  |  |
| 4 | |  |  |  |  |  |  |  |  |
| 5 | |  | | |  | | |  |  |
| 6 | |  | | | | | | | |

**Figure 5.1 Component structure extracted from nine Principal Component Analyses of three versions of the Apathy Evaluation Scale (AES) using all subjects (CP), controls only (C) and patients only (P).** Each extracted component is shown in graph form with each column representing a single item from the 18 in the AES and the height of each column representing its contribution (positive or negative) to the component.

| Extracted Component* | Item Type | | | | Question Type | | |
|---|---|---|---|---|---|---|---|
| | Cognitive | Behaviour | Emotion | Other | Self Evaluated | Quantitative | Negative Syntax |
| ICP1 | 1 | | 1 | 1 | NA | NA | |
| ICP2 | | | | | NA | NA | |
| ICP3 | | | | | NA | NA | 1 |
| IC1 | | | | 1 | NA | NA | |
| IC2 | | | | | NA | NA | |
| IC3 | | | | | NA | NA | |
| IC4 | | | 1 | | NA | NA | |
| IC5 | | | | | NA | NA | |
| IC6 | | | | | NA | NA | |
| IP1 | 1 | | 1 | 1 | NA | NA | |
| IP2 | | | | | NA | NA | |
| IP3 | | | | | NA | NA | |
| IP4 | | | | | NA | NA | 1 |
| SCP1 | | | 1 | 1 | NA | NA | |
| SCP2 | | | | | NA | NA | |
| SCP3 | | | | | NA | NA | |
| SCP4 | | | | | NA | NA | 1 |
| SC1 | | | | 1 | NA | NA | |
| SC2 | | | | | NA | NA | |
| SC3 | | | 1 | | NA | NA | |
| SC4 | | | | | NA | NA | |
| SC5 | | | | | NA | NA | 1 |
| SP1 | | | 1 | | NA | NA | |
| SP2 | | | | | NA | NA | |
| SP3 | | | | 1 | NA | NA | |
| SP4 | | | | | NA | NA | 1 |
| CCP1 | | | 1 | | | 1 | |
| CCP2 | | | | | 1 | | |
| CCP3 | | | | | | | |
| CCP4 | | | | | | | |
| CC1 | | | | 1 | | | |
| CC2 | | | | | | | |
| CC3 | | | | | | | |
| CC4 | | | | | | | |
| CC5 | | | | | | | |
| CP1 | | | | | 1 | | |
| CP2 | | 1 | | | | | |
| CP3 | | | 1 | | | | |
| CP4 | | | | | | | |
| CP5 | | | | | | | 1 |

**Table 5.3.** Components meeting 'contribution threshold' for each of the forty extracted components resulting from nine PCA analysis of AES-S, AES-I, AES-C responses using subjects with FTLD, healthy other controls and subjects and controls combined. 1=Threshold met (i.e. item/question type considered contributory) blank=Threshold not met. NA=Not Applicable. *Key: First letter =AES Version (I=Informant, S=Subject, C=Clinician Version), Second (and third) letter =Subjects included in analysis (C=healthy older controls, P=subjects with FTLD associated syndromes), Number=component extracted from highest to lowest variance explained

### 5.4.2 Intercorrelation Between Versions of the Apathy Evaluation Scale

Amongst the patient group significant correlations were seen between subject and clinician, and clinician and informant versions of the AES. No significant correlation was observed between subject and informant versions of the AES (Table 5.4). Amongst the control group significant correlations were seen between subject and informant versions of the AES (Pearson 0.503, $p<0.001$) but not clinician and informant versions (0.261, $p=0.07$). Post hoc partial correlation controlling for total score on the ACE-R and BDI-II showed significant correlations between all three versions of the AES amongst controls and amongst patients between subject and clinician (Pearson 0.605, $p<0.001$), clinician and informant (0.425, $p=0.001$) but the correlation between subject and informant scores remained non significant (0.012, $p=0.926$).

| | | AES-I | AES-S | AES-C |
|---|---|---|---|---|
| AES-I | Pearson Correlation | 1 | .238 | 0.589** |
| | Sig. (2-tailed) | | 0.051 | 0.000 |
| | N | 104 | 68 | 74 |
| AES-S | Pearson Correlation | 0.238 | 1 | 0.718** |
| | Sig. (2-tailed) | 0.051 | | 0.000 |
| | N | 68 | 70 | 70 |
| AES-C | Pearson Correlation | 0.589** | 0.718** | 1 |
| | Sig. (2-tailed) | 0.000 | 0.000 | |
| | N | 74 | 70 | 76 |

**Table 5.4. Intercorrelation between three versions of the Apathy Evaluation Scale amongst patients with syndromes associated with FTLD.**

**Correlation is significant at the 0.01 level (2-tailed)(uncorrected for multiple comparisons).

### 5.4.3 Discrepancies Between Subject and Informant Ratings on the AES and CBI-R

Mean AESOverscore, AESUnderscore, CBIOverscore and CBIUnderscore are shown in Table 5.5. AESUnderscore was significantly lower amongst controls than patients (T-test, $p<0.001$) but AESOverscore was not significantly different between the two groups (T-test, $p=0.417$). Table 5.6 shows the results of correlations between Overscore and Underscore values on the AES and CBI-R. Note that only the patient group completed the CBI-R for themselves hence no CBI-R discrepancy scores were calculated for the control group. Significant negative correlations were seen between Underscore and Overscore values within and between questionnaires (AES and CBI-R) with the exception of the negative correlation between Underscore on the AES and Overscore on the CBI-R which did not reach significance. Significant positive correlations were seen between Underscore values on both questionnaires and between Overscore values.

| Score | Group | N | Mean | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| CBIOverscore | Patient | 70 | 4.3286 | 5.06114 | .60492 |
| CBIUnderscore | Patient | 70 | 6.21429 | 5.050162 | .603610 |
| AESUnderscore | Control | 49 | 1.3673 | 3.90349 | .55764 |
| | Patient | 68 | 10.2500 | 11.31948 | 1.37269 |
| AESOverscore | Control | 49 | 6.7347 | 5.19525 | .74218 |
| | Patient | 68 | 7.7794 | 8.62285 | 1.04567 |

**Table 5.5 Discrepancy scores between subject and informant rating of symptoms on the Apathy Evaluation Scale and Cambridge Behavioural Inventory for patients with FTLD associated syndromes and healthy older controls.**

| | | AESUnderscore | AESOverscore | CBIOverscore |
|---|---|---|---|---|
| AESUnderscore | Pearson Correlation | 1 | -0.492** | -0.139 |
| | Sig. (2-tailed) | | 0.000 | 0.259 |
| | N | 117 | 117 | 68 |
| AESOverscore | Pearson Correlation | -0.492** | 1 | 0.256* |
| | Sig. (2-tailed) | 0.000 | | 0.035 |
| | N | 117 | 117 | 68 |
| CBIOverscore | Pearson Correlation | -0.139 | 0.256* | 1 |
| | Sig. (2-tailed) | 0.259 | 0.035 | |
| | N | 68 | 68 | 70 |
| CBIUnderscore | Pearson Correlation | 0.598** | -0.422** | -0.420** |
| | Sig. (2-tailed) | 0.000 | 0.000 | 0.000 |
| | N | 68 | 68 | 70 |

**Table 5.6 Intercorrelation of discrepancy scores between subject and informant rating of symptoms on the Apathy Evaluation Scale and Cambridge Behavioural Inventory (Revised).** *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

Amongst patients significant correlation was observed between the total score on the BDI-II and CBIOverscore (Pearson correlation 0.419, $p<0.001$) but not AESOverscore (-0.057, $p=0.647$), Underscore on CBI (-0.035, $p=0.778$) or AES (0.079, $p=0.526$). No significant correlations were seen between any of the Underscore or Overscore values and overall performance on the ACE-R or FAB.

### 5.4.4 Comparison of Behavioural Testing Performance Based on Informant Ratings of Apathy and Impulsiveness

Of fourteen comparisons of behavioural task performance between those rated as apathetic or not and a further fourteen comparisons of those rated as impulsive or not, only one reached statistical significance without correction for multiple comparisons (Probability of being correct on the IST, decreasing condition, disinhibited vs. not groups, p=0.03), and this does not survive correction (Table 5.7).

| Test | Apathy | | | | | Disinhibition | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Yes | | No | | P Value | Yes | | No | | P Value. |
| | N | Mean (SD) | N | Mean (SD) | | N | Mean (SD) | N | Mean (SD) | |
| Kirby Mean K | 33 | 0.04 (0.05) | 31 | 0.03 (0.04) | 0.666 | 19 | 0.04 (0.06) | 45 | 0.03 (0.04) | 0.453 |
| Kirby Mean Consistency | 33 | 0.94 (0.05) | 31 | 0.93 (0.11) | 0.693 | 19 | 0.96 (0.12) | 45 | 0.02 (0.04) | 0.303 |
| Kirby Difference K | 33 | 0.02 (0.06) | 31 | 0.00 (0.04) | 0.104 | 19 | 0.00 (0.07) | 45 | 0.04 (0.01) | 0.298 |
| Joystick Go/NoGo D' | 32 | 3.12 (1.33) | 29 | 3.18 (1.31) | 0.829 | 20 | 3.26 (1.43) | 41 | 3.09 (1.26) | 0.644 |
| Saccade Go/NoGo D' | 14 | 0.70 (1.00) | 17 | 0.90 (1.24) | 0.622 | 8 | 1.26 (1.46) | 23 | 0.65 (0.98) | 0.195 |
| Joystick Go/NoGo Ommission Error Rate | 32 | 0.19 (0.24) | 29 | 0.17 (0.25) | 0.863 | 20 | 0.15 (0.19) | 41 | 0.19 (0.25) | 0.555 |
| Joystick Go/NoGo Commision Error Rate | 32 | 0.06 (0.17) | 29 | 0.07 (0.11) | 0.879 | 20 | 0.07 (0.21) | 41 | 0.19 (0.25) | 0.876 |
| Saccade Go/NoGo Ommission Error Rate | 14 | 0.09 (0.10) | 17 | 0.17 (0.21) | 0.222 | 8 | 0.08 (0.21) | 23 | 0.15 (0.19) | 0.331 |
| Saccade Go/NoGo Comission Error Rate | 14 | 0.74 (0.24) | 17 | 0.60 (0.33) | 0.206 | 8 | 0.60 (0.41) | 23 | 0.69 (0.25) | 0.505 |
| SSRT | 31 | 470.22 (276.63) | 28 | 714.46 (1616.61) | 0.411 | 20 | 449.04 (209.67) | 39 | 659.34 (1379.19) | 0.502 |
| IST P being Correct (fixed condition) | 30 | 0.77 (0.15) | 27 | 0.72 (0.14) | 0.184 | 17 | 0.80 (0.10) | 40 | 0.72 (0.15) | 0.072 |
| IST P being correct (decreasing condition) | 30 | 0.68 (0.14) | 27 | 0.63 (0.19) | 0.207 | 17 | 0.73 (0.15) | 40 | 0.63 (0.17) | 0.030 |
| IST Difference in P being correct between conditions | 30 | 0.09 (0.16) | 27 | 0.09 (0.16) | 0.937 | 17 | 0.07 (0.12) | 40 | 0.10 (0.17) | 0.571 |
| CRRT Difference in Speeding | 27 | 57.13 (506.87) | 20 | 157.97 (378.76) | 0.459 | 15 | 70.88 (384.08) | 32 | 115.61 (489.37) | 0.757 |

**Table 5.7 Comparisons of Behavioural Testing Performance of Subjects with Syndromes Associated with FTLD Based on Informant Ratings of Apathy and Impulsiveness.** P values are results of individual T-tests

### 5.4.5 Principal Component Analysis of Patients and Controls Across Testing Modalities

For the PCA of patients with FLTD associated syndromes and healthy older subjects the combined KMO measure of sampling adequacy was 0.615 and Bartlett's Test of sphericity significant ($p<0.001$). Repeating the analysis for subjects with FTLD associated syndromes alone KMO was 0.470 and Bartlett's test not significant ($p=0.999$). Note these KMO values indicate weak to poor sampling adequacy and hence the results should be interpreted with caution. Eight factors were extracted from PCA of both subject groups (Tables 5.8 and 5.9) accounting for 70% of the observed variance. For subjects with FTLD associated syndromes alone nine factors were extracted accounting for 74% of the observed variance (Tables 5.10 and 5.11).

| Component | Eigenvalue Total | % of Variance | Cumulative % |
|---|---|---|---|
| 1 | 3.956 | 16.485 | 16.485 |
| 2 | 2.496 | 10.402 | 26.886 |
| 3 | 2.446 | 10.19 | 37.076 |
| 4 | 2.003 | 8.346 | 45.422 |
| 5 | 1.895 | 7.895 | 53.317 |
| 6 | 1.433 | 5.969 | 59.286 |
| 7 | 1.395 | 5.814 | 65.1 |
| 8 | 1.223 | 5.094 | 70.195 |

**Table 5.8. Total Variance Explained: Rotation sums of Square loadings for Principal Component Analysis of subjects with FTLD associated syndromes and healthy controls.**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| AES S | **0.834** | -0.096 | -0.189 | 0.032 | -0.045 | -0.024 | -0.055 | -0.048 |
| MEI | **-0.824** | 0.071 | 0.162 | -0.027 | 0.159 | -0.015 | -0.081 | -0.031 |
| AES C | **0.791** | 0.026 | -0.097 | 0.107 | -0.161 | 0.124 | -0.171 | -0.015 |
| SHAPS | **0.756** | -0.238 | -0.097 | -0.135 | -0.036 | 0.048 | 0.122 | -0.001 |
| AES I | **0.62** | 0.124 | 0.02 | 0.202 | -0.133 | 0.115 | -0.249 | -0.029 |
| BIS-II | **0.613** | 0.31 | -0.14 | 0.187 | -0.084 | -0.196 | 0.054 | -0.109 |
| OCI-R | **0.504** | 0.333 | 0.084 | -0.001 | -0.099 | 0.133 | 0.395 | 0.298 |
| BAS Funseeking | 0.009 | **0.858** | 0.076 | 0.054 | -0.029 | -0.083 | -0.015 | -0.054 |
| BAS Drive | 0.058 | **0.852** | -0.044 | -0.005 | 0.018 | 0.065 | -0.1 | -0.033 |
| BAS Reward Responsiveness | -0.155 | **0.718** | 0.015 | 0.113 | -0.176 | 0.009 | 0.214 | -0.005 |
| Joystick Go/NoGo Omission Error Rate | 0.088 | -0.083 | **-0.783** | 0.157 | -0.215 | 0.271 | -0.11 | -0.077 |
| Joystick Go/NoGO D' | -0.213 | -0.021 | **0.717** | -0.182 | 0.127 | **-0.545** | 0.029 | 0.12 |
| Kirby Mean Consistency | -0.136 | -0.119 | **0.711** | -0.024 | 0.082 | 0.092 | -0.183 | -0.196 |
| Saccadometer Go/NoGo Omission Error Rate | 0.266 | -0.172 | **-0.604** | 0.053 | 0.004 | -0.124 | -0.138 | -0.249 |
| Saccadometer Go/NoGo Commission Error Rate | 0.025 | 0.118 | 0.01 | **0.953** | -0.08 | 0.003 | 0.025 | 0.076 |
| Go/NoGO Saccadometer D' | -0.187 | -0.016 | 0.284 | **-0.882** | 0.069 | 0.05 | 0.046 | 0.07 |
| IST Probability of being correct (decreasing condition) | -0.199 | -0.167 | 0.129 | -0.093 | **0.849** | 0.166 | 0.065 | 0.115 |
| IST Probability of being correct (fixed condition) | -0.21 | 0.195 | 0.086 | -0.144 | **0.685** | -0.114 | -0.089 | 0.3 |
| SSRT (Last half of trials) | 0.136 | 0.202 | -0.105 | -0.043 | **-0.67** | 0.082 | 0.06 | 0.275 |
| Joystick Go/NoGo Commission Error Rate | 0.119 | 0.106 | -0.278 | 0.059 | 0.099 | **0.781** | 0.077 | -0.154 |
| Kirby Difference K | 0.209 | -0.048 | 0.243 | 0.134 | -0.121 | 0.125 | **-0.592** | -0.217 |
| BIS | 0.044 | -0.007 | 0.171 | 0.086 | -0.13 | 0.125 | **0.79** | -0.173 |
| CRRT difference in speedings | -0.018 | -0.112 | 0.055 | 0.024 | 0.063 | -0.043 | -0.011 | **0.817** |
| Kirby K mean | 0.059 | 0.164 | -0.22 | 0.267 | 0.1 | -0.495 | 0.018 | -0.191 |

**Table 5.9 Rotated component matrix for PCA of subjects with FTLD associated syndromes and healthy controls.** Weightings >0.5 or <-0.5 highlighted and in bold.

| Component | Eigenvalue Total | % of Variance | Cumulative % |
|---|---|---|---|
| 1 | 3.14 | 13.083 | 13.083 |
| 2 | 2.743 | 11.43 | 24.513 |
| 3 | 2.209 | 9.206 | 33.719 |
| 4 | 1.948 | 8.118 | 41.837 |
| 5 | 1.885 | 7.855 | 49.692 |
| 6 | 1.762 | 7.34 | 57.032 |
| 7 | 1.543 | 6.429 | 63.461 |
| 8 | 1.271 | 5.297 | 68.758 |
| 9 | 1.218 | 5.076 | 73.834 |

**Table 5.10 Total Variance Explained: Rotation sums of Square loadings for Principal Component Analysis of patients with FTLD associated syndromes only.**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| AES S | **0.823** | -0.083 | -0.184 | -0.058 | 0.086 | -0.129 | 0.071 | -0.109 | -0.229 |
| MEI | **-0.82** | 0.136 | 0.064 | 0.024 | 0.111 | -0.08 | 0.053 | -0.092 | -0.058 |
| AES C | **0.726** | 0.016 | -0.003 | -0.1 | -0.049 | 0.013 | 0.385 | -0.022 | -0.218 |
| SHAPS | **0.675** | -0.336 | 0.041 | -0.145 | -0.019 | 0.143 | -0.067 | 0.237 | 0.27 |
| AES I | 0.412 | 0.058 | 0.284 | 0.07 | -0.059 | 0.085 | **0.521** | 0.066 | 0.017 |
| BIS-II | **0.601** | 0.428 | -0.18 | 0.282 | -0.096 | -0.188 | 0.071 | -0.15 | 0.089 |
| OCI-R | 0.309 | 0.337 | 0.215 | -0.189 | -0.139 | 0.15 | -0.304 | 0.485 | 0.034 |
| BAS Funseeking | 0.003 | **0.872** | 0.128 | 0.1 | -0.036 | -0.073 | -0.005 | -0.056 | 0.086 |
| BAS Drive | -0.035 | **0.86** | -0.009 | -0.045 | 0.025 | 0.075 | 0.139 | 0.01 | -0.012 |
| BAS Reward Responsiveness | -0.279 | **0.747** | 0.098 | -0.049 | -0.12 | 0.006 | -0.204 | 0.084 | 0.031 |
| Joystick Go/NoGo Omission Error Rate | -0.039 | -0.129 | **-0.723** | 0.191 | -0.163 | 0.387 | 0.082 | -0.048 | -0.16 |
| Joystick Go/NoGO D' | 0.004 | 0.065 | **0.566** | -0.115 | 0.067 | **-0.764** | -0.049 | 0.036 | 0.069 |
| Kirby Mean Consistency | -0.071 | -0.105 | **0.576** | 0.103 | 0.227 | -0.167 | 0.054 | -0.169 | -0.129 |
| Saccadometer Go/NoGo Omission Error Rate | 0.205 | -0.201 | **-0.743** | -0.084 | 0.056 | -0.089 | 0.047 | -0.164 | 0.065 |
| Saccadometer Go/NoGo Commission Error Rate | -0.136 | 0.1 | 0.309 | **0.903** | -0.036 | 0.027 | 0.023 | 0.072 | 0.006 |
| Go/NoGO Saccadometer D' | -0.01 | 0.059 | 0.214 | **-0.918** | -0.002 | 0.028 | -0.048 | 0.027 | -0.09 |
| IST Probability of being correct (decreasing condition) | 0.002 | -0.105 | 0.177 | 0.023 | **0.874** | 0.244 | -0.054 | 0.074 | -0.02 |
| IST Probability of being correct (fixed condition) | -0.024 | 0.309 | 0.045 | -0.102 | **0.624** | 0.018 | 0.047 | 0.31 | 0.302 |
| SSRT (Last half of trials) | 0.105 | 0.161 | -0.024 | 0.006 | **-0.712** | 0.137 | -0.067 | 0.221 | 0.03 |
| Joystick Go/NoGo Commission Error Rate | 0.011 | 0.041 | -0.045 | -0.076 | 0.12 | **0.849** | -0.038 | -0.102 | -0.078 |
| Kirby Difference K | 0.108 | -0.097 | 0.106 | 0.145 | -0.132 | 0.098 | **0.586** | -0.187 | 0.339 |
| BIS | 0.004 | -0.038 | 0.254 | 0.047 | -0.167 | 0.12 | **-0.754** | -0.102 | 0.045 |
| CRRT difference in speedings | -0.014 | -0.075 | -0.008 | 0.078 | 0.024 | -0.162 | 0.067 | **0.804** | -0.08 |
| Kirby K mean | -0.101 | 0.098 | -0.07 | 0.084 | 0.081 | -0.15 | 0.085 | -0.066 | **0.862** |

**Table 5.11 Rotated component matrix for Principal Component Analysis of patients with FTLD associated syndromes only.** Weightings >0.5 or <-0.5 highlighted and in bold.

### 5.4.6 Correlation Between Extracted Components and Measures of Cognition, Carer Distress, Subject Mood and Discrepancy Scores

Tables 5.12 and 5.13 show the results of Pearson correlations between the extracted components of the two multimodal PCAs. Significant correlations were seen for components one, three, five and six extracted from the PCA of patients with FTLD associated syndromes and healthy controls combined and components one, five, six and seven extracted from the PCA of patients with FTLD alone. The ACE-R significantly correlated with three of eight components when healthy controls were included in the analysis. When only subjects with FTLD associated syndromes were included correlation with the ACE-R and Component Three approaches significance (p=0.06), none of the other components correlations were significant.

| Component | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| **ACE-R** | Pearson Correlation | -0.322** | -0.055 | 0.270** | -0.118 | 0.177* | -0.099 | 0.041 | 0.049 |
| | Sig. (2-tailed) | 0 | 0.524 | 0.002 | 0.176 | 0.041 | 0.255 | 0.64 | 0.574 |
| | N | 134 | 134 | 134 | 134 | 134 | 134 | 134 | 134 |
| **Total Carer Distress (NPI-Q)** | Pearson Correlation | 0.165 | 0.06 | -0.003 | 0.084 | 0.301** | 0.458** | -0.084 | -0.015 |
| | Sig. (2-tailed) | 0.097 | 0.549 | 0.976 | 0.4 | 0.002 | 0 | 0.4 | 0.883 |
| | N | 102 | 102 | 102 | 102 | 102 | 102 | 102 | 102 |
| **CBIOverscore** | Pearson Correlation | 0.319** | -0.002 | -0.04 | -0.232 | 0.08 | -0.076 | -0.017 | 0.052 |
| | Sig. (2-tailed) | 0.007 | 0.984 | 0.74 | 0.053 | 0.509 | 0.529 | 0.886 | 0.669 |
| | N | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| **CBIUnderscore** | Pearson Correlation | 0.002 | 0.078 | 0.071 | 0.032 | 0.094 | 0.243* | -0.186 | -0.019 |
| | Sig. (2-tailed) | 0.985 | 0.523 | 0.559 | 0.794 | 0.438 | 0.042 | 0.123 | 0.878 |
| | N | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| **BDI-II** | Pearson Correlation | 0.709** | -0.004 | -0.137 | 0.104 | -0.117 | 0.099 | 0.036 | -0.073 |
| | Sig. (2-tailed) | 0 | 0.969 | 0.137 | 0.26 | 0.205 | 0.283 | 0.694 | 0.431 |
| | N | 120 | 120 | 120 | 120 | 120 | 120 | 120 | 120 |

**Table 5.12. Two tailed Pearson correlations between extracted components from PCA of Patients with FTLD associated syndromes and healthy control subjects and scores on the Addenbrooke's Cognitive Examination –Revised (ACE-R), Total Carer Distress reported on Neuropsychiatric Inventory (NPI-Q), Cambridge Behavioural Inventory Discrepancy Scores (CBIOverscore and CBIUnderscore) and Beck Depressive Inventory II (BDI-II).**

*Correlation is significant at the 0.05 level.

**Correlation is significant at the p<0.01 level.

| Component | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| **ACE-R** | Pearson Correlation | -0.054 | 0.045 | 0.206 | 0.031 | 0.119 | -0.072 | -0.056 | -0.005 |
| | Sig. (2-tailed) | 0.628 | 0.683 | 0.06 | 0.777 | 0.282 | 0.517 | 0.614 | 0.962 |
| | N | 84 | 84 | 84 | 84 | 84 | 84 | 84 | 84 |
| **Total Carer Distress (NPI-Q)** | Pearson Correlation | 0.13 | 0.01 | 0.167 | 0.078 | 0.202* | 0.484** | 0.193 | 0.047 |
| | Sig. (2-tailed) | 0.201 | 0.922 | 0.101 | 0.446 | 0.046 | 0 | 0.057 | 0.644 |
| | N | 98 | 98 | 98 | 98 | 98 | 98 | 98 | 98 |
| **CBIOverscore** | Pearson Correlation | 0.333** | 0.035 | -0.099 | -0.188 | 0.031 | -0.046 | 0.003 | -0.001 |
| | Sig. (2-tailed) | 0.005 | 0.774 | 0.417 | 0.12 | 0.8 | 0.704 | 0.978 | 0.996 |
| | N | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| **CBIUnderscore** | Pearson Correlation | -0.042 | 0.021 | 0.206 | -0.008 | 0.058 | .272* | 0.310** | 0.021 |
| | Sig. (2-tailed) | 0.732 | 0.864 | 0.087 | 0.946 | 0.633 | 0.023 | 0.009 | 0.861 |
| | N | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| **BDI-II** | Pearson Correlation | 0.676** | -0.031 | -0.031 | 0.002 | -0.082 | 0.151 | 0.039 | -0.015 |
| | Sig. (2-tailed) | 0 | 0.797 | 0.801 | 0.984 | 0.499 | 0.211 | 0.746 | 0.902 |
| | N | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |

**Table 5.13. Two tailed Pearson correlations between extracted components from PCA of patients with FTLD associated syndromes only and scores on the Addenbrooke's Cognitive Examination –Revised (ACE-R), Total Carer Distress reported on Neuropyschiatric Inventory (NPI-Q), Cambridge Behavioural Inventory Discrepancy Scores (CBIOverscore and CBIUnderscore) and Beck Depresssive Inventory II (BDI-II).**
*Correlation is significant at the 0.05 level.

**Correlation is significant at the p<0.01 level.

For both combined (patient and controls) and patient only PCA the first component comprises mainly of questionnaire-based assessments with positive weighting associated with higher scores towards states with a negative valence (e.g. the higher rates of apathetic symptoms on the AES, lower hedonic tone as measured by the SHAPS). This component correlated positively with patient Overscore on the CBI-R and higher depressive symptoms on the BDI-II suggesting negative emotional states may by a substantial aspect of this component.

Component Two comprises mainly of positive weighting from the BAS subscales. These comprise of questions aimed at assessing behavioural activation and positive motivational states (reward responsiveness, drive and fun seeking). The lack of substantial contribution from other

aspects of the testing battery or correlation with BDI-II, ACE-R or CBI-R discrepancy scores suggests that there may be particular aspects of subject response to the BAS sections of the BIS/BAS questionnaire which are not captured by the other tasks/questionnaires.

Component Three comprises of substantial weighing from the consistency scores on the Kirby, D' from the Joystick version of the Go/NoGo rates and low omission rates on both versions of the Go/NoGo rate. Cognition as measured with the ACE-R significantly correlated with this component in combined (patient and control) analysis and neared significance on the patient only analysis. Performance on the ACE-R is substantially affected by attention and diminished attention will substantially impair performance on tests of episodic memory and orientation (which feature heavily in the ACE-R and would normally be relatively preserved in FTLD associated syndromes). The Go/NoGo protocol is relatively lengthy and requires sustained concentration and attention, as does consistent performance on the Kirby. Hence this component may reflect the subjects' ability to attend to the tasks presented and maintain consistent performance and engagement.

Component Four is heavily weighted by performance on the saccadometer task particularly D' and commission error rates with very little contribution from other tasks and no significant correlations between component and ACE-R, BDI-II or CBI-R discrepancy scores. It may be such a strong weighting towards saccadometry suggests that this component is strongly influenced by the subjects ability to engage with the saccadometer task, either for technical reasons or because of impairment in ability to direct saccades which appears somewhat distinct to other testing modalities.

Component Five consists of substantial weighting from the IST and SSRT. The association between higher sampling rates on the IST (hence a higher probability of being correct) and shorter SSRT suggests that greater action cancellation may be associated with increased IST sampling.

Component Six comprises of strong positive weighting of commission error rate and negative weighting from D' for the joystick task. Again, as with Component Four (where saccadometry measures were the only major contributing factor), this may reflect a unique aspect of the manner in which the joystick task was administered such as the patient's ability to use the joystick. This component showed significant positive correlations with carer distress and patient underscore.

Component Seven showed positive weighting from the difference between values of K for different monetary amounts on the Kirby and negative weighting from BIS score. Making

this the only component with substantial weighting from behavioural and questionnaire based assessments. The BIS subscale comprises of items related to perceived anxiety, worries and sensitivity to negative feedback/criticism from others. Similarly the difference in values of K between monetary values may also reflect some aspect of reward responsiveness. It is notable that the reward responsiveness subscale of the BAS makes very little contribution to this component.

The major contribution to Component Eight was difference in speeding on the CRRTT again suggesting this measure may be relatively distinct to other measures in the analysis.

PCA for subjects with FTLD associated syndromes alone resulted in an additional component. This ninth component only met the threshold for inclusion for the PCA of the subjects with FTLD associated diagnoses. The largest contribution was mean K on the Kirby. Whether this is of any true significance is unclear given the small sampling size and low KMO.

## 5.5 Discussion

Principal Component Analysis of the three separate versions of the AES yielded different results depending on the version of the AES used and whether the analysis was restricted to patients, controls or both. The resultant component structures vary in terms of number and variance explained but without more detailed inspection it is not clear how significant these differences between analyses are. On first inspection some components do appear similar with strong loadings for the same items, but simple comparisons of forty components from nine separate analyses would be unreliable. Instead I chose to use a standardised approach to attempt to classify each component based on the item and question type as set out in the original description of the AES(158).

Using this method only a third of components, and none of the components extracted from the AES-C, could be classified by item type. Including question type allowed for a further 19% of components to be classified including 15% of all components that could only be classified by negative scoring. By this method the components extracted from PCA of different versions of the AES and different cohorts are classified differently. Some components may be classified in relation to Marin's item type but others cannot. Of the remaining components some may be classified by question type (for example negative syntax) but nearly half of the extracted components cannot be classified by this method. These results demonstrate that despite sampling adequacy for each PCA, the results of the analysis vary and are dependent upon the groups from which the data are drawn. Variation in patterns of response to the questions in the AES depend upon who is being asked (i.e. subject, informant, clinician), what they are being asked (e.g. item type), and how they are asked (e.g. question type).

The patient group scored more highly on all three versions on the AES than healthy controls. While subject and informant versions of the AES showed significant positive correlations amongst the control group this was not the case amongst the patients. Despite significant correlations between patient and clinician assessment on the AES (AES-S and AES-C) and between clinician and carer (AES-C and AES-I) there appears to be differences between the patient reports and those of their carers (AES-S and AES-I) even when the cognitive measures (ACE-R) and measures of mood disturbance (BDI-II) are controlled for. This demonstrates that while apathetic symptoms are commonly reported amongst people with FTLD associated syndromes, irrespective of whether subject, informant, or clinician is asked, the nature of these reports varies between each source and do not correlate with each other.

I quantified the discrepancies between subject and informant scores on the AES and CBI-R. The terms 'Overscore' and 'Underscore' denote the subject's (patient's) scoring relative to the informant (carer), although in reality an 'Overscore' may indicate the patient truly over reporting their symptoms (overscoring) or the carer under reporting (underscoring) the patient's symptoms. Similarly a high 'Underscore' may reflect low scoring by the patient or high scoring by the carer. While patient scores may be influenced by their own insight, mood, cognitive ability or distress, carer scores may also be affected by the carer's own conceptions of the patient behaviour or their own psychological state. For example, discrepancy between patient scores on the AES-S and carer scores on the AES-I due to a high Underscore (i.e. the patient scores lower than the carer) which may relate to lack of insight by the patient and hence underreporting of their symptoms or alternatively, by the carer's own distress and over reporting.

A significant correlation was observed between CBIOverscore and the BDI-II but this was not the case for Underscore on the CBI or AES and no significant correlations were observed between either of the discrepancy measures and performance on the ACE-R or FAB. These results suggest that subject mood and depression may influence how they report symptoms but changes in subject mood or general cognitive performance alone are insufficient to explain the full discrepancy between patient reporting and that of their carers.

Taken together these results suggest that:

1. Using a questionnaire or structured interview based approach to assess apathy, respondents report high levels of apathetic symptoms amongst subjects with syndromes associated with FTLD.
2. Reporting varies amongst respondent with subjects with syndromes associated with FTLD reporting differently to their carers/other informants.
3. These differences cannot be solely attributed subject emotional state or overall cognitive performance.
4. Variation in reporting appears to be multifactorial and may be classified at least in part, by the questions asked and also the manner in which they are presented.

Accepting that responses to questionnaire-based assessment of neuropsychiatric syndromes vary with respect multiple factors is not necessarily a limitation of this approach. Neuropsychiatric syndromes are complex multidimensional constructs with a wide range of neural, cognitive and psychological correlates. By examining the factor structure and inter- and intra-correlation of the AES between different respondents and other assessments of mood and

cognition it is clear that responses to the items that make up the AES may vary with a variety of factors and that the AES when used in isolation cannot disentangle the underlying mechanisms by which apathetic syndromes are being reported.

Behavioural testing is subject to different limitations than a questionnaire based approach and offers an alternative modality by which to examine behavioural and the underlying cognitive correlates. While there are clear advantages to this approach it is also important to ensure that the behavioural test used does relate to the reported clinical syndrome. Splitting groups into those considered apathetic or disinhibited (or not) by their carers/informants and comparing mean scores for a range of fourteen behavioural measures (selected to test aspects of decision making and response inhibition) resulted in only one measure reaching statistical significance. This was the probability of being correct at the point of decision-making on the Information Sampling Task (IST). Interestingly subjects rated as disinhibited opened more boxes before reaching a decision than those who did not on the decreasing condition (where reward decreases as more boxes are opened). The same pattern was observed for the fixed condition (where possible reward is unchanged regardless of how many boxes are opened) but did not reach significance. When considering the IST, one could have expected more impulsive and disinhibited patients to make a decision quicker with less sampling and the probability of being correct lower (as was the case when patients were compared to healthy controls in Chapter Four). This does not appear to be the case between patients who were rated impulsive or not. There are several possible interpretations of this result. It may be that disinhibited subjects are less sensitive to the perceived reward so decreasing reward is of reduced significance to them (analogous to social disinhibition where subjects make inappropriate or tactless remarks and appear indifferent to the consequences). Alternatively the IST requires subjects to sample a number of boxes then make the conscious effort to stop and evaluate the information they have obtained. In may be that more impulsive subjects are more likely to simply continue with the first aspect of the task (sampling) and not stop to evaluate and make a decision. Finally the results may be chance. One statistically significant result at the $p<0.05$ level from twenty-eight comparisons to reach significances at is within the expected rate for type one errors and this individual result does not survive correction for multiple comparisons. Regardless of a single statistically significant result the most notable results is that in all other comparisons of behavioural tests there was no significant difference between subjects when separated on the presence of apathy or disinhibition by their carers.

A similar dichotomy arises between questionnaire based and behavioural assessments when Principal Component Analyses are performed across testing modalities. For both analyses (subjects and healthy controls and subjects alone) with the exception of factor seven (where the

difference in K loads strongly in the opposite direction to the BIS) behavioural and questionnaire based assessments load onto different components suggesting distinct mechanisms for variation in performance on behavioural tasks compared with questionnaire based assessments (regardless of whether subject or carer is the completing the questionnaire).

The component structure for PCA of multiple testing modalities for patients alone for and patients and controls combined, appear very similar (Tables 5.9 and 5.11). For the first analysis (subjects with FTLD associated syndromes and controls) Bartlett's test of sphericity was significant and KMO of 0.615 implies mediocre factorial simplicity(236). However, the lack of significance for Bartlett's test and lower KMO when the analysis is repeated for subjects with FTLD alone suggests sampling is inadequate and that these data are insufficient for PCA. Hence these results should be interpreted with caution. The similarity between component structure for both analyses suggests that while sample size may be inadequate to robustly support PCA analysis of subjects with FTLD associated syndromes in isolation the component structure for PCA of results from subjects with FTLD associated syndromes and controls is likely to be applicable to the FTLD group alone.

By considering the weighting of individual variables included in the PCA for all subjects and the correlation between the extracted components and other measures not included in the analysis (e.g. ACE-R, BDI-II) it is possible to make some inferences as to what the extracted components may represent. The PCA resulted an eight-factor component structure with an additional ninth component for the patient only analysis. The first two components seem strongly influenced by patient reports of mood (Component One, which correlated strongly with the BDI-II) and motivation (Two, which did not). Note the informant version of the AES did not make a large contribution to these. The patient's ability to attend to, and maintain, consistent performance on behavioural tasks seems core to component Three and is further emphasised by significant correlation with the ACE-R. Other components such as Four and Six are heavily influenced by a single testing modality (saccadometer or joysticks tests) which raises the possibility these components relate to the methodology rather than cognitive target of these assessments.

While the tasks and variables included in the PCA have an a priori rationale for being relevant to apathy and impulsivity it does not necessarily follow that variance in performance on these tasks is related to disruption of cognitive process that result in apathy or impulsivity. It may be that rather than being related to dissociable components of clinical apathy/impulsivity, these components simply reflect the subjects' ability to make accurate voluntary saccades or physically handle and manipulate a joystick. It is possible that (for example) Component Six

reflects physical disability e.g. limb apraxia which could also account for the correlation with higher carer distress and hence the correlation with patient underscore (carers reporting higher symptom frequency relative to the patient because of their distress). While I attempted to make inferences as to the nature of structure of individual components this approach is ultimately subjective and confounding influences not directly related to apathy/impulsivity remain possible.

These results demonstrate that using a wide range of different methods subjects with syndromes associated with FTLD have higher levels of apathetic and impulsive behaviour than healthy controls. While at a group level, subjects and their carers both report high levels of apathy and impulsivity, their reports do not correlate with each other. Discrepancies between their reports cannot be easily explained by a single factor and in some subjects may be under- or over- reporting symptoms, as may be their carers. Furthermore, subjects with FTLD perform differently to healthy controls on a range of tests of apathy and impulsivity. There appears to be some underlying common factors to performance across different tasks but variance in performance does appear to be multifactorial. Emotional and general cognitive factors appear to be relevant to some factors but less clearly so for others. Some variance may not relate directly to apathy or impulsivity and the manner in which a task is presented and how the subject is able to interact and respond also appear to be relevant.

These data support the hypothesis that in FTLD apathy and impulsivity are common and that they are complex multidimensional constructs with more than one underlying factor. Subjects with FTLD associated syndromes and their carers differ in reporting symptom frequency and severity. The underlying causes of these discrepancies also appear to be multifactorial. While objective behavioural tasks overcome some of the limitations of more subjective reporting methods, performance on these tasks does not correspond to symptoms of apathy and impulsivity reported by other methods. When results of multiple testing modalities are considered together, variance appears multifactorial with physical, emotional and cognitive performance contributing differently to different factors. Despite overlap between some tasks, dissociation between behavioural and questionnaire based assessments remain.

## 5.6 Conclusions

In this chapter I have shown amongst subjects with syndromes associated with FTLD apathetic and impulsive symptomatology may be measured in a variety of ways but different methods do not correlate well with each other. While these data support the hypothesis that

apathy and impulsivity are multidimensional constructs I have also demonstrated that a statistical, data driven approach to dissociating these is subject to variation as the sample from which the data are derived changes. Behavioural surrogates of apathy and impulsivity appear to measure relatively distinct processes compared with questionnaire based assessment. The results of behavioural testing can be dissociated in a number of ways but variation amongst subjects seems at least in part to relate to the physical process of testing (e.g. through a joystick, button or eye tracker) in addition to variation in goal directed cognition. Similarly questionnaire based assessments of apathy and impulsivity vary with who is being asked and how they are asked. Because of the multidimensional nature of apathy and impulsivity and these limitations of each individual form of testing I suggest these results support a multidimensional approach to apathy and impulsivity.

# Chapter Six

# General Discussion

### 6.1 Summary

I studied a regional epidemiological cohort of patients with clinical syndromes associated with FTLD to describe the clinical features, lifetime risk, prevalence and incidence of these conditions. Using a range of assessment techniques I explored the symptoms of apathy and impulsivity in this cohort. In this final chapter I discuss my key findings with reference to the following hypotheses:

1. The clinical syndromes associated with FTLD overlap and form a dynamic spectrum of recognisable symptomatology.
2. The revised diagnostic criteria for FTLD associated syndromes can be applied jointly to estimate their epidemiology.
3. Apathy and impulsivity are commonly reported across the entire spectrum of syndromes associated with FTLD.
4. Reports of apathy and impulsivity depend on who is asked, what they are asked and how they are asked.
5. Subjects with FTLD perform differently to healthy controls on behavioural assessments of apathy and impulsivity.
6. Reports of apathy or impulsivity do not predict performance on behavioural assessments of these syndromes.
7. Apathy and impulsivity are overlapping and multidimensional constructs.
8. No single testing modality used in isolation represents these constructs completely, or overcomes motor or language confounds that arise in some of the FTLD associated syndromes.

### 6.2 The Clinical Syndromes Associated With FTLD Overlap and Form a Dynamic Spectrum of Recognisable Symptomatology.

The clinical syndromes associated with frontotemporal degeneration have been described for centuries. In Chapter One I re-presented a historical case of behavioural change associated with atrophy of frontal and temporal lobes. While the underlying aetiology is debateable, the clinical syndrome of progressive behavioural change, disinhibition and apathy is extremely recognisable and remarkably similar to that seen in modern cases of behavioural variant FTD. The patient

described by Pinel also had a movement disorder ('a paralytic numbness') and changes in language function similar to later historical descriptions attributed to 'senile' frontotemporal atrophy (such as Arnold Pick and William Bevan-Lewis' case reports).

These early descriptions of FTLD were not restricted to isolated disorders of behaviour, language or motor function but all three coexisted in a single subject. Similarly in the PiPPIN cohort while individuals have been given diagnostic labels of particular syndromes (and met criteria for such) in a cross sectional study it is clear that clinical features overlap between syndromes. Movement disorders, language deficits and behavioural changes were commonly observed amongst all clinical syndromes, similarly apathy and impulsivity were frequently reported. In Chapter Two I present the clinical features of 200 of the 204 cases of FTLD associated syndromes identified in the PiPPIN study (Table 2.4). Through assessment in person and careful review of clinical records I have shown that while behavioural and language disorders are prevalent in the syndromes of FTD they are also common in PSP and CBS. Agrammatism (for example) was seen in over half of cases of CBS and nearly a fifth of those with PSP. Apraxia and akinesia was noted in 8.7 and 13% of cases of svPPA respectively and semantic deficits noted in more than half of cases of bvFTD.

This overlap is not unexpected and does not undermine diagnostic distinctions between clinical syndromes: over the course of their illness patients will deteriorate, acquire further disability and new clinical features. Some initially prominent features will become masked as others emerge and individuals may move between diagnostic categories. For example, a patient with prominent behavioural changes may be diagnosed as having bvFTD before later motor features of PSP-RS emerge. This movement disorder and bulbar dysfunction may prevent the disinhibited actions by which behavioural change were exhibited. Similarly a patient may first develop features of nfvPPA before limb dystonia and dyspraxia emerge to suggest an alternative diagnosis of CBS.

In Chapter One I outlined the criteria that have been developed to diagnose the syndromes associated with FTLD. Over time these criteria and also the associated nosology have evolved and fragmented. For example, while Arnold Pick did not describe the first case of progressive language impairment associated with 'senile' frontotemporal atrophy(18), his name became has become associated with 'Pick's Disease'(237). Initially the term was used to describe a clinical syndrome accompanied by frontotemporal atrophy characterised by the presence of 'Pick bodies'(237), (histopathological inclusions first described by Alzheimer on the basis of their morphology and staining properties(238)) but it subsequently became clear that not all cases had Pick bodies at post mortem and 'Pick's Disease' became the term reserved for

only those cases in which Pick bodies were identified (or presumed to be present). Pick bodies are now further defined on their molecular basis by the predominance of three repeat microtubule binding repeat isoforms of Tau proteins(239)). The result is that over the course of the last century 'Pick's Disease' has been used to describe a variety of pathologically and clinically defined conditions. Similar semantic shift is seen with other terms associated with FTLD. At the same time, additional distinct clinical syndromes have recognised and defined. The term 'Pick's Disease' was superseded by 'FTD' which was divided between bvFTD and PPA and all of the associated subtypes, each with their own set of criteria which have been subsequently revised and refined by further experience and pathological validation.

Conversely pathological and genetic discoveries have also expanded the clinical phenotypes of some forms of FTLD. For example, the dramatic expansion in the clinical associations with large expansions of C9ORF72 that I discussed in Chapter One. A subset of the PiPPIN cohort were screened for genetic mutations associated with dementia. One case with lvPPA (more typically associated with Alzheimer's pathology) and one with svPPA (typically TDP-43 and not usually associated with genetic mutations) had mutations in their MAPT gene. Technology has improved speed and affordability of genetic testing and in turn access to genetic testing which in turn is increasing genotype-phenotype associations and shifting the boundaries of clinical syndromes they are used to investigate.

One issue concerning diagnostic criteria is that they serve more than a single purpose. They may be used to define a clinical syndrome (such as PPA or PSP-RS) and offer a set of descriptive terms of particular clinical features or syndromes. Alternatively they may be used to predict underlying pathology, prognosis or influence genetic testing.

In a research setting there is a clear need for criteria to define clinical syndromes and relate them to underlying pathology. This facilitates biological and treatment studies aimed at the underlying pathological basis of neurodegeneration. There is also clear need for a common framework to describe the neuropsychiatric, behavioural and cognitive aspects of these diseases, regardless of their molecular basis. Defining and subdividing cohorts on the basis of different aspects of their syndrome may also in turn lead to new criteria and expose new ways to differentiate pathology. For example, while FTD is largely considered a cognitive disorder (even though movement disorders coexist in early descriptions) the presence of features of PSP-RS or MND may be more predictive of underlying pathology than cognitive features. Similarly in CBS cognitive features may be better predictors of underlying pathology than the movement disorder.

Rather than considering individual syndromes separately I chose to consider them simultaneously thereby allowing analysis of variance across the spectrum, and inclusion of intermediate clinical phenotypes that fall between criteria or transitional cases that move between criteria as the clinical syndrome develops. In doing so I have shown that cognitive and movement disorders are common across the entire spectrum of FTLD. Furthermore by discussing FTLD associated syndromes from a historical perspective I have shown that while frontotemporal syndromes are highly recognisable distinct set of syndromes but the boundaries between syndromic subdivisions and their associated nosology are less clear and subject to shift over time -in a manner that is reminiscent of the evolution of an individual's clinical syndrome over the course of symptomatic neurodegeneration.

### 6.3 The Revised Diagnostic Criteria for FTLD Associated Syndromes Can Be Applied Jointly to Estimate Their Epidemiology

I used point prevalence methods, an unrestricted age range and revised criteria for FTLD associated syndromes simultaneously to estimate their prevalence, incidence and lifetime risk. The prevalence of these disorders was 10.84/100,000, incidence 1.61/100,000 and lifetime risk 1 in 742. Prevalence rates were similar between the major syndromes associated with FTLD (PPA, PSP, CBS, bvFTD). Incidence and mortality rates were similar suggesting short-medium stability of the FTLD rates. While similar to previous epidemiological estimates of FTLD (see Tables 2.1.1-2.2.2) these estimates are not limited to individual syndromes, incorporate intermediate clinical syndromes and exclude non-progressive 'phenocopy' syndromes.

By considering all age groups I have shown that rather than diseases of middle age, these FTLD syndromes are increasingly common with advancing age. The youngest case identified in the PiPPIN study was 41 at diagnosis (with potentially 5-6 years of prior prodromal symptoms), the oldest 92 at diagnosis (with 4-5 years of prodromal symptoms). In both cases the diagnosis of an FTLD associated syndrome was delayed because of their age. In the younger case a psychiatric condition thought most likely but when a neurodegenerative condition was suspected FTLD was considered early. In the older case, Alzheimer's was considered most likely and delayed their final diagnosis of PSP (the subjects general physician wrote questioning whether further evaluation would be helpful given their age and pre-existing Alzheimer's diagnosis). On further evaluation they did not have clinical features of typical Alzheimer's dementia.

Young onset dementia is rare but FTLD accounts for a significant proportion of cases and hence is a "common" cause of young onset dementia. Conversely despite being more common as

age increases other pathologies (such as Alzheimer's) dominate and the index of suspicion for FTLD and proportion of cases correctly diagnosed may decrease.

Within the PiPPIN catchment area there are three cities, large rural areas and a total population of around 1.6m. Demographics vary widely between areas. For example North Norfolk has the second oldest median age by local authority in the UK, while Norwich has one of the youngest (Office for National Statistics mid 2015 census data (115)). The population of East Anglia is predominantly white and British including substantial historic Viking and Norman contributions while more recently the Universities (particularly Cambridge) have attracted more diverse immigration to the area and areas of very high education rates. Such demographic environmental and genetic factors may well influence rates of FTLD pathology, and also rates of diagnosis. The numbers of cases of FTLD in individual areas within the PiPPIN catchment area are too small to allow direct comparison between them. However by using geographic boundaries that coincide with the output areas for the UK census data, detailed population demographics data for this population are freely available and may be compared with other studies of FTLD associated syndromes. In order to facilitate such comparisons I have standardised these epidemiological estimates by age and sex to the European Standard Population.

### 6.4 Apathy and Impulsivity Are Commonly Reported Across The Entire Spectrum of Syndromes Associated With FTLD.

In the PiPPIN study behavioural changes were reported in all the FTLD associated syndromes, most commonly in bvFTD and svPPA (100 and 96% respectively) but also in nfvPPA and PPA(other) (46% for both). Apathy was reported in more than half of subjects and impulsivity in 46% (Table 2.4). Nearly 60% of carers of 106 subjects with FTLD reported apathy and a third of all carers reported disinhibition when asked to complete the NPI-Q (Figure 3.4). Similarly high rates of apathetic symptoms were self reported by subjects (Table 3.2) with FTLD (via the AES-S) and observed during clinical interview (e.g. the AES-C). Subjects with FTLD also reported higher rates of impulsiveness compared to similarly aged healthy controls.

### 6.5 Reports of Apathy and Impulsivity Depend on Who is Asked, What They Are Asked and How They Are Asked.

Reports of apathetic and impulsive symptomatology are common regardless of whether the subject with FTLD is asked or a carer who knows them well. However reports of symptomatology did not correlate well between patients and carers. For example, patients with FTLD score significantly higher on the AES as a measure of apathetic symptomatology regardless

of whether the AES-S (subject rated), AES-I (informant rated) or AES-C (clinician rated) questionnaire is used. While the AES-I and AES-S both correlated significantly with the AES-C (as would be expected as this version combines subject interview with observed behaviour) the AES-S and AES-I do not correlate significantly (Table 5.4).

It is tempting to favour the cognitively unimpaired carer's reports of symptomatology as more likely to be reliable than those of the patient with FTLD but despite having cognitive impairment, patients are still able to give meaningful insights into their own emotional states. When completing self rated visual analogue scales of mood and motivation subjects with FTLD reported higher levels of states with negative valence (e.g. sad, bored) and lower levels of positive valence states compared to healthy controls (Figure 3.7). However their responses were not one-dimensional, instead PCA of responses on 14 different scales revealed a four component solution with significant and separate correlation with other assessments of mood, motivation, apathy and arousal (Table 3.5).

I also compared subject and informant responses on the CBI-R. Subjects were asked to self-rate frequency for a subset of symptoms that their carer had also rated. Patients on occasion over- or underscored symptoms relative to their carer. While overscoring correlated significantly with self reported depressive symptomatology (via the BDI-II) no significant correlation was observed for underscoring or between performance on the ACE-R or FAB and either under- or overscoring. These results suggest that the subject's mood and coexisting depression may influence their reporting of symptoms but changes in their mood or general cognitive performance alone are insufficient to explain the all the discrepancies between patient reporting and that of their carers. It is possible that at least some of these relate not directly to emotional or cognitive state in the patient but instead to carer factors, whereby their own insights, interpretations and emotional state influence their reporting.

In Chapter Five I examined the components resulting from PCA of the each of the three versions of the AES performed separately for all subjects (patients and controls) and patients and controls separately. The extracted components vary in number and variance explained between the separate analyses. From nine PCAs a total of 40 components were extracted. Using a systematic approach I then sought to classify these components based on the original item structure within the AES. A third of components could be classified by the item type (e.g. cognitive, behavioural etc.) while a further 15% could not, but could be classified by negative scoring alone (where the scale the respondent is asked to complete is reversed compared to other items on the questionnaire). These together suggest that responses rating apathetic symptomatology for a single subject with FTLD (via the AES) vary depending on who is

completing the AES, the particular items that make up the AES and also the manner in which they are presented.

### 6.6 Subjects With FTLD Perform Differently to Healthy Controls on Behavioural Assessments of Apathy and Impulsivity.

Rather than rely solely on questionnaire-based assessments of behaviour and symptomatology I also used behavioural measures that seek to assess and measure specific aspects of behavioural and cognitive symptomatology in a more objective manner. Subjects with FTLD performed differently on a range of behavioural tasks designed to test goal directed behaviour, reward responsiveness, action selection, initiation and cancellation. When compared to controls across a range of tasks patients respond more slowly and less accurately. When potential reward or negative feedback are introduced (such as the IST and CRRT), subjects with FTLD and controls are both sensitive to this change and adapt their response strategies however amongst subjects with FTLD associated syndromes (and in contrast to healthy volunteers who are able to improve reaction time) I was unable to demonstrate a change in reaction time in response to the introduction of feedback or reward, despite a reduction in accuracy. For example, during the second half of trials for the CRRT task (where response time is explicitly related to reward) healthy controls respond more quickly, especially when there is a higher chance of reward, but subjects with FTLD do not.

Speed accuracy trade offs are well recognised across a number of species and tasks(240). Most subjects are able to sacrifice accuracy in exchange for better response time. It is therefore notable that during tasks where speed is related to reward, subjects with FTLD did not appear able to improve reaction time even when accuracy reduced. Conversely when reaction time is not related to reward but accuracy and sampling rates are (such as the decreasing vs. fixed conditions of the IST) healthy controls respond more slowly while subjects with FTLD did not (their box opening latency was actually marginally quicker for the decreasing condition).

During the IST subjects with FTLD opened fewer boxes across both conditions and made more errors, despite being substantially slower when completing the task. They made a final decision based on less information and took longer reaching a decision point. However, both healthy controls and subjects with FTLD adapted their strategies to the change in condition from fixed to decreasing reward, sampling less and making a final decision based on less information demonstrating that both groups were sensitive to the change in condition. Amongst controls only, I observed an increase in box opening latency when the condition switched from fixed to decreasing reward suggesting that when the number of boxes sampled has an effect on potential

reward, healthy subjects spent more time deliberating whether to continue sampling boxes or to reach a final decision. This was not the case for subjects with FTLD who in actual terms had a slightly shorter deliberation time (box latency) during the decreasing condition compared with the fixed.

Taken together these results suggest that subjects with FTLD are:

1. Slower and less accurate in their responses compared to healthy controls.
2. Sensitive to reward and change in condition.
3. Less able to slow down to make decisions, in response to new reward contingencies.
4. Inclined to make decisions based on less information than healthy controls.

This failure to slow down under conditions of uncertainty, risk or high-stakes has been demonstrates in other disorders, for example in Parkinson's disease (e.g.(223,241)). In contrast to this problem gamblers appear to be able to detect changes in reward and risk and do adapt by slowing reaction time (for example in a computerised simulation of blackjack both problem gamblers and healthy controls slowed reaction times in response to higher risk situations(242)). In one study using the SSRT, regular poker players were compared to non-gamblers; as the probability of a stop signal was increased both groups detected this and slowed reaction times(243). In a non time limited paradigm (the Matching Familiar Figures Test) Kertzman et al.(244) showed that pathological gamblers had higher error rates than healthy controls but were not significantly different in terms of response times, suggesting that mechanisms other than speed-accuracy trade-offs may underpin impulsivity in such subjects. Interestingly, in one further study subjects with both Parkinson's and a gambling disorder had significantly faster reaction times than subjects with Parkinson's alone but only in high risk situations(245) suggesting perhaps that impulsivity underpinning pathological gambling in the context of Parkinson's may differ from those with problem gambling outside of a neurodegenerative condition; that the former having a measurable surrogate in terms of the effect of risk contingency on reaction time, while the later does not. Alternatively, it may be that the combination of Parkinson's pathology modulates the effect of a gambling disorder and results in an observable effect of risk on reaction time.

A number of models have proposed for simple decision making, most assume accumulation of noisy evidence to a decision threshold, such as the drift diffusion model (Figure 6.1). In this evidence from perception or memory accumulates from a starting point to a threshold e.g. a boundary to 'go' or an opposite boundary to 'no go'(246). Accumulation is noisy and at a particular moment in time may point towards either boundary (but more often the

correct than incorrect), average rates of accumulation are called drift(246). Speed accuracy changes may be explained in this model by changes in the thresholds at which a decision is made (Figure 6.1C). Alternatively the starting point off accumulation may be shifted towards one boundary, simultaneously adding a bias and increasing the likelihood of that response (Figure 6.1D). Bias may be introduced in the relative rates of accumulation between respective thresholds(246).

It is remarkable that some subjects with FTLD, especially PSP-RS, take an inordinate amount of time to make a response and yet when they do it is frequently a poorly conceived one. Zhang et al(223) addressed this by applying a drift diffusion model to decisions in an oculomotor version of the Go/NoGo task by subjects with PSP-RS, Parkinson's and healthy controls (including some of the data from the PiPPIN study). Comparing four variants of the drift diffusion model they showed best fit for a model in which starting point and rates of drift were variable and that using this model, subjects with PSP had higher response bias to Go but slower drift rates i.e. they were strongly biased towards making a response but severely impaired at accumulating the necessary evidence to commit to it (Figure 6.1E). This reconciles the counterintuitive observation that subjects with PSP exhibit marked akinesia with motor impulsivity(223). Similarly in the larger PiPPIN cohort, impaired accumulation could explain the increased reaction time observed and a lowering of threshold for response accounting for decreased accuracy in patients vs. controls. Interestingly in Zhang et al.'s model subjects with PSP had shorter non decision time (Ter in Figure 6.1E, thought to reflect latency of early sensory encoding external to the decision process) than controls which they compare to similar EEG findings in Parkinson's and suggest of could imply a partial compensation for impaired cognition by additional processing(223).

The drift diffusion model used in this context assumes that inaction (NoGo) is an active decision not to go (as opposed to no decision and no action). A subject who is not attending to the task or unable to generate any response in time (from either cognitive or motor deficits) will have higher omission rates, as was the case for both joystick and oculomotor tasks in the PiPPIN study. In studies of the Go/NoGo task amongst healthy undergraduate students a single boundary model (a single threshold for 'Go') does not fit well(247,248) however in the PiPPIN cohort the sensitivity index (d') for patients was significantly lower than controls for both forms of the Go/NoGo task (especially the oculomotor task). This suggests lower signal detection amongst patients i.e. that their responses were noisier with less detectible signal. In Zhang et al.'s study response times amongst the patients groups with PD and PSP were not slower than controls study but they were in the PiPPIN study. Subjects in the PiPPIN study did have significantly slower mean response times on all versions of the Go/NoGo task than controls.

This difference may reflect lack of power to detect such a difference in the smaller PSP cohort used by Zhang et al. or alternatively greater variance and noise in the larger and more diverse PiPPIN cohort.

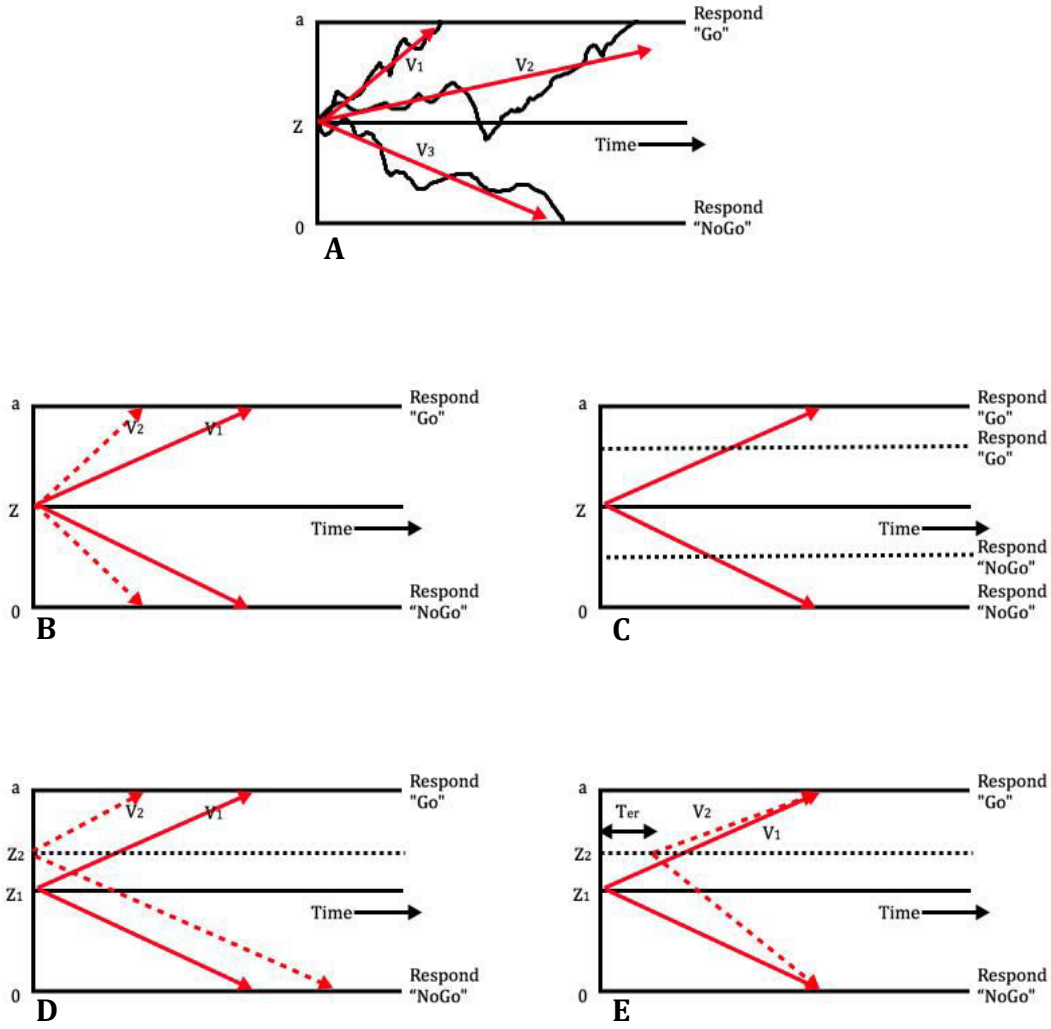



**Figure 6.1. A The Drift Diffusion Model.** Evidence for either outcome is accumulated in a noisy fashion (irregular black lines) with the rate of accumulation (drift) represented by the red arrows. Signal accumulates from starting point, Z, until it reaches a threshold level (a or 0) at which a decision ('Go' or 'NoGo') is made. Three example trajectories are shown with three rates of drift ($V_{1-3}$). Response time may be varied by changing the rate of accumulation (from $V_1$ to $V_2$ in **B**), or the threshold at which a decision is made (**C**). In **D** moving the starting point from $Z_1$ to $Z_2$ introduces bias and makes Go responses more likely and quicker for a constant rate of accumulation ($V_1$=$V_2$). Zhang et al.'s(249) model of drift diffusion is shown in **E**. Subjects with PSP (red dashed lines) start with a bias towards the Go threshold (Z2) but signal accumulation ($V_2$) is impaired compared to healthy controls (solid red arrows and $V_1$). Response rates were not significantly different between PSP and controls who had a longer non decision time ($T_{er}$).

It is possible that subjects with FTLD are unable to make an appropriate speed-accuracy tradeoff when adapting to change in condition because their response time is already as short as they are able. However subjects with FTLD do appear to have different levels of accuracy when conditions change (as in the IST).

It may be that rather than slower signal accumulation, in FTLD the accumulation of information is more stochastic and unstable. As neurodegeneration occurs connectivity and efficiency of the brain is reduced(250). In contrast to a healthy brain where responses are the result of (comparatively) steady and stable accumulation of signal, in FTLD there may be greater entropy of signal, impaired (rather than slowed) accumulation of signal and quicker signal breakdown. The result being that reaching a given signal threshold occurs less frequently and for shorter periods. Lowering a threshold for response would have little effect on reaction time and those responses that do occur would be less predictable, less accurate or consistent (Figure 6.2).

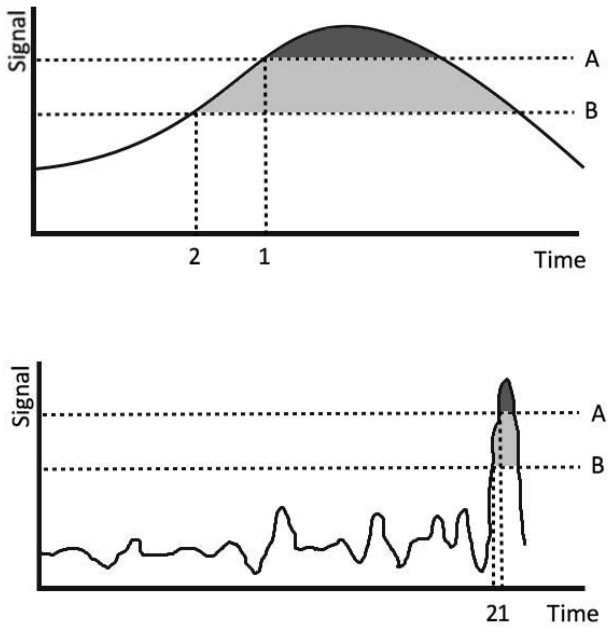



**Figure 6.2. Models of Response Initiation.** In the top panel slow accumulation of signal/information eventually reaches threshold A, at which point a response/action is initiated at time point 1. Lowering the threshold to B improves response time (2) but as less information has been accumulated, accuracy is sacrificed. In the lower panel signal accumulation is stochastic and noisy. Responses occur less frequently and suddenly. In this model lowering the threshold sacrifices accuracy but has little effect on response time.

Average discounting rates during the Kirby were higher for patients than controls (i.e. the prefer immediate reward compared to higher reward after a delay). As with the lower

sensitivity indices observed amongst patients in the Go/NoGo tasks, patient consistency when completing the Kirby temporal discounting task was significantly lower than controls (i.e. the point at which they chose to switch from higher delayed reward to smaller immediate reward was not consistent across all their responses). The Kirby is designed to assess aspects of decision making and patients may deliberate for as long as they like. Even outside of a time dependent test patient responses tend towards the more impulsive option than controls but their responses are also more erratic.

A frequent and early feature of bvFTD is emotional lability i.e. rapid switching on and off, of emotions. Despite this increase in emotionality they are also described apathetic with loss of warmth and empathy with a psychomotor slowing and dramatic reduction in spontaneity(251). This combination of hyper- and hypo-emotionality is reminiscent of the akinesia and motor impulsivity seen in PSP-RS. Compared to Alzheimer's, subjects with bvFTD and PSP have impaired emotion recognition(252,253). In Figure 3.6 I presented a dramatic example of impaired ability to differentiate between emotional states more subtle than simply positive or negative. Across all the patients, within subject variance on visual analogue scales of emotional state was higher for patients than controls i.e. they reported more extreme variation in emotional state (Table 3.3.). This was also seen on self reported questionnaires that did not rely on an analogue scale (e.g. the AES or BDI-II). Subjects with FTLD appear less emotional most of the time(251), but when they do display (or report) emotion it is more rapid and intense. I suggest subjects with FTLD are less able to generate and/or recognise an emotion in themselves. In a similar fashion to their impaired ability to accumulate signal and respond in tasks of decision making, when patients process their own emotional states, impaired ability to recognise emotion impairs their ability to accumulate evidence (signal) to support a particular response. As a result there is a compensatory lowering of threshold, partly by simplifying the range of emotionality so that emotions become more dramatic e.g. 'all or nothing' and simpler e.g. 'happy or sad'.

### 6.7 Reports of Apathy or Impulsivity Do Not Predict Performance on Behavioural Assessments of These Syndromes.

In Chapter Five I separated patients based on informant reports (via the NPI-Q) of whether they displayed apathetic behaviour or not and compared performance on a range of fourteen behavioural tasks that were selected to assess aspects of decision making and goal directed behaviour (Table 5.7). There were no significant differences between groups. Similarly splitting the patients into groups depending on whether informants reported impulsive/disinhibited behaviour and repeating the comparison yielded only one statistically significant difference (i.e.

within the frequency expected for type 1 errors at this level of significance). It is possible that the items from the NPI-Q used to define apathetic or impulsive groups (Apathy: 'Does the patient seem less interesting in his/her usual activities or in the activities and plans of others?' and Impulsivity: 'Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people's feelings?') are insensitive or not sufficiently specific to these syndromes to accurately dissociate groups. However behavioural measures and questionnaire based assessments of apathy/impulsivity reporting also loaded onto separate factors on Principal Component Analysis suggesting a similar dissociation of objective measures and a wide range of patient self assessments and informant reports.

Performance on these particular behavioural tests of decision making and goal directed behaviour could therefore have limited relevance to apathetic or impulsive behaviours observed by carers, or self-reported by patients. Against this argument is that the behavioural tasks used were selected because they directly related to models of response initiation, inhibition, decision making and goal directed cognition. They had previously been used in healthy subjects, subjects with other brain disease and in animals to assess these aspects of behaviour (e.g. (165,166,187,220,233)). In addition in the PiPPIN study subjects with FTLD demonstrated a partially preserved ability to change behaviour in response to changes in task conditions. When conditions for potential reward or perceived value change (e.g. in the IST and CRRT tasks), so do their response strategies, demonstrating that the subjects are interacting with these tasks in a manner that is dependent on, and varies with, their perceptions of the effects of their actions. As such their performance on these behavioural task does appear to be homologous to carer observed changes in motivation and goal directed cognition.

Another explanation for the dichotomy between behavioural tasks and questionnaire based assessments may be that instead of the behavioural tasks not measuring relevant aspects of apathy/impulsivity, the subject/informant reports of apathy/impulsivity are unreliable in this clinical population, and do not relate to true symptomatology. The informant based assessment tools used here been used in a wide range of clinical and research settings including dementia. For example the CBI-R has been in use for over a decade to assess symptoms in dementia (including FTD) via informant reporting(254) while individual informants may in some circumstances be unreliable it seems implausible that this would be case for the majority of the 107 informants who completed the CBI-R in PiPPIN. Similarly while patient self-reporting may be challenged on the basis of accuracy or levels of insight, I have demonstrated that these patients reports correlate with each other (e.g. Table 3.5) and on multimodal PCA load onto the same factors in an appropriate directional fashion (i.e. those questionnaires where positive valence symptoms equal positive scoring loading in the opposite direction to those with

negative scoring for positive valence). These patients are able to give some insights into their own symptomatology and emotional and motivational state, even if their responses do not significantly correlate with carers' responses. While behavioural tasks, patient self reports and informant reports do not correlate well with each other, they appear to provide complementary insights into apathetic and impulsive symptomatology in this patient group.

### 6.8 Apathy and Impulsivity Are Overlapping and Multidimensional Constructs.

The lack of correlation between different testing modalities when assessing apathy and impulsivity discussed above is perhaps unsurprising. As discussed in Chapter Three, goal directed behaviour is dependant on more than one cognitive process (e.g. see Figure 3.1) and disruption at any point in this process may result in reduced goal directed cognition and hence the syndrome of apathy. In the PiPPIN cohort reports of apathetic and impulsive symptomatology frequently coexisted within a single subject. This observation also supports a multidimensional approach to these symptoms. As I argued in Chapter Three, while poorly conceived and reckless and disinhibited behaviour may appear the direct opposite of apathy, it may also be the result of an "apathetic approach to consequences".

In support of the multiplicity of factors in apathy/impulsivity was the result of the multimodal PCA. Eight factors accounted for 70% of the variance (Table 5.8). Significant but different patterns of correlation were seen between these factors and tests of global cognition, mood, carer distress and discrepancies between patient and informant symptom reports (Table 5.12). From these data it appears that performance on these assessments of apathetic and impulsive symptomatology is not related to disruption of single one-dimensional process.

### 6.9 No Single Testing Modality Used in Isolation Represents These Constructs Completely, or Overcomes Motor or Language Confounds That Arise in Some of the FTLD Associated Syndromes

If apathy and impulsivity are complex and multidimensional then a comprehensive assessment of them will need to be similarly complex. Taking a multimodal approach to their assessment is very similar to the clinical approach to the diagnosis of dementia as a whole. A diagnosis of dementia is very rarely made on the basis of the patient's own self reported symptoms in isolation. Instead this is combined with collateral history from informants and objective tests like cognitive assessments and neuroimaging. Where over emphasis is placed on one modality there is greater risk of diagnostic error, for example the bvFTD phenocopy syndrome where collateral history of behavioural change was not accompanied by typical deterioration in cognitive testing or brain atrophy.

In the PiPPIN study I took a multimodal approach to the assessment of apathy and impulsivity. Patient and informant reports were combined with behavioural measures using a range of tasks and input methods. When the results of these assessments were combined into a single PCA different testing modalities loaded onto different components (Table 5.9). Behavioural assessments loaded onto different components than questionnaires. Interestingly while carer reports of symptoms did not predict performance on behavioural tasks, significant correlation with carer distress and discrepancy measures on the CBI-R were seen with extracted components that predominantly comprised of behavioural (rather than questionnaire based) assessments (Table 5.12) suggesting that performance on these behavioural measures may also be relevant to elements of carer morbidity and reporting which were not captured by the other assessments. Many previous studies have used individual assessment tools (such as the AES) that use a single testing modality (e.g. questionnaire based) and then extract multiple components of such a tool. My data suggests that while this may be a useful approach to assessing some aspects of apathy/impulsivity but (at least in this cohort) it does not capture the full spectrum of symptomatology and other potentially clinically relevant aspects may be overlooked. Rather than demonstrating one testing modality or assessment tool that is superior to others or more relevant, these results support a multidimensional and multimodal approach to the assessment of apathy and impulsivity.

### 6.10 Limitations

The PiPPIN study aimed to identify every subject with a diagnosis of a syndrome associated with FTLD within a geographically defined area. Despite multisource referral and using a range of approaches to raise awareness of the study it is likely that some cases will have been missed. Some subjects with a diagnosis will not have been invited and some may have been invited but refused to participate. Others with the relevant disease will not have been correctly diagnosed, or not presented for diagnosis at all.

The majority of patients with a diagnosis of FTLD are seen in our regional referral centre for these conditions and hence are seen in a clinical capacity by physicians who both work in the PiPPIN study (such as myself) or work closely alongside us. I am aware of only one subject with FTLD who initially refused participation in PiPPIN (and subsequently changed their mind to be included in the epidemiological aspects of the study) suggesting that the number of subjects with a diagnosis who refuse any participation is likely to be very small.

It is more difficult to estimate the number of patients with symptomatic FLTD who do not carry a diagnosis (or have it suspected) and hence would not have been invited to participate. This group of patients may be split into those who have symptomatic FTLD but are in an early prodromal phase whereby they would not meet criteria for a diagnosis ('pre-diagnosable'), those who have symptomatic disease that is not typical for one of the syndromes of FTLD either because of comorbidities or because of an unrecognised syndromic variant ('undiagnosable') or those who have typical syndromic disease but have not been recognised as such (missed diagnosis). While knowledge of the number of pre-diagnosable patients with prodromal disease has use from an epidemiological perspective and clear value in early intervention trials, expanding the inclusion criteria to capture such patients also limits the usefulness of such a study. Moreover, expanding the inclusion criteria is likely to reduce their specificity and hence the cohort acquired may be less reflective of FTLD pathology. Including patients with pre- or oligosymptomatic disease also reduces the level of current morbidity of the collected cohort. As a result inclusion of 'prediagnosable' subjects may both over represent the epidemiological impact of FTLD and simultaneously underrepresent its morbidity.

Those 'undiagnosable' patients, who do not fulfil current criteria for FTLD associated syndromes and do not present in a fashion that may be recognised as associated with FTLD, represent a different challenge to epidemiological estimates of FTLD. Some patients with FTLD will have additional comorbid neuro- and psychopathology that may not only serve as exclusion criteria for the diagnosis of FTLD but also change the clinical phenotype. Mixed pathology is common in dementia especially with advancing age and may account for the some of the reduction in incidence and prevalence of FTLD seen in the most elderly groups in the PiPPIN study. It is also possible that FLTD pathology may present as a syndrome not encompassed by current clinical criteria. For example Pure Akinesia with Gait Freezing (PAGF) is a syndrome associated with PSP type pathology but not included in the NINDS-SPSP or NNIPPS criteria used in the PiPPIN study. Other syndromes may exist that are not currently recognised as being associated with FTLD. Epidemiological studies of this nature cannot encompass such cases, which can only be identified via clinico-pathological studies using other biomarkers, genetics and pathological validation.

Since this study was designed and conducted, new criteria have been proposed for PSP(48). Progressive Supranuclear Palsy was originally a clinically defined entity, this is now more commonly referred to as PSP-Richardson's syndrome (formerly Steele-Richardson or Steele-Richardson-Olszewski syndrome)(255) while PSP is used to denote a particular pattern of neuronal atrophy and four repeat Tau aggregation(47). The most recent criteria for PSP attempt to reconcile the wide variety of clinical syndromes associated with PSP pathology and

by using different thresholds of ocular motor dysfunction, postural instability, akinesia and cognitive impairment, seek to operationalize criteria by which different levels of diagnostic certainty may be attributed(48,256). The authors suggest different levels of certainty may be appropriate for different purposes. Using a more inclusive and sensitive criteria for epidemiological research but restricting therapeutic and biological studies to those syndromes with the highest specificity(48).

These new criteria have taken a similar approach to the current criteria for CBD(7,12). By taking a more inclusive approach syndromes that would previously have been classified as CBS or bvFTD may now be considered within the spectrum of PSP. Patients with mutations in MAPT (who would previously have been excluded from criteria for PSP) may now be classified as PSP. While subjects recruited in the PiPPIN study were not assessed with direct reference to these criteria I suspect use of these new criteria are unlikely to change the epidemiological estimates substantially for several reasons. Firstly the new criteria broaden the clinical phenotype associated with probable or possible PSP mainly by inclusion of aspects of other FTLD associated syndromes (such as CBS or bvFTD). These are already included in the PiPPIN criteria and clinical features of another FTLD associated syndrome were not considered exclusion criteria for PiPPIN or individual syndromes. Second while some clinical syndromes that would not have been included in PiPPIN are now included in the criteria for PSP I think it is unlikely that many such cases would have been identified and referred to the PiPPIN study even if these criteria were used in the study assessments. Examples of such cases include PSP-P (where slow vertical saccadic speed plus Parkinsonism with tremor, which may be dopamine responsive and asymmetric) or progressive gait freezing. Under new criteria these would be considered possible or probable PSP pathology and the authors suggest inclusion in epidemiological studies(48). Working within general neurology clinics for over seven years, and in specialist tertiary clinics for PSP, CBS and MSA for four years, I have seen three cases of pure akinesia with gait freezing. While gait freezing in isolation is highly suggestive of PSP pathology(9) I suggest it is rare and would not necessarily be recognised as a presentation of PSP-pathology in general neurology clinics and hence would be unlikely to have been referred to a study such as PiPPIN or a tertiary service for PSP during the study. I do not anticipate that inclusion of such cases would have substantially changed the epidemiological estimates. In contrast to this inclusion of subjects meeting criteria for PSP-P may have had a more dramatic effect on the epidemiological estimates. The new criteria for PSP classify a case of typical Parkinsonism (dopa responsive asymmetric rigidity with tremor) with slowing of vertical saccades, as 'PSP-P' with probable underlying PSP pathology. This is on the basis of a retrospective review of clinical features of 437 patients (206 with PSP pathology) recruited from

nine brain banks(48,256). Accepting that subjects with a syndrome more typically associated with idiopathic Parkinson's Disease may at post mortem have PSP pathology(60) the authors of the new criteria have used the high specificity of abnormal vertical saccades in this cohort to justify use of saccades as a sensitive and specific feature of PSP type pathology(48,256). I suggest this may be open to misinterpretation. Firstly as idiopathic Parkinson's Disease is underrepresented in their brain bank cohort, and second as they consider a clinical feature that has not been recorded as one that is absent - this is not necessarily the case(256). Abnormal saccades had a sensitivity of 7.5% for Parkinson's pathology amongst a cohort of 53 pathologically defined cases(256). Hence abnormal saccades were documented in three cases of Parkinson's and presence or absence of abnormal saccades in the rest unknown. The new PSP criteria provide much better operationalized criteria for abnormal vertical saccades as a criterion for PSP but these have not been subjected to prospective pathological validation (48). Two studies have retrospectively addressed specificity and sensitivity of these new criteria: The first using subjects with Parkinsonism or pathologically confirmed PSP from the Society for Progressive Supranuclear Palsy brain bank(257) and the second by review of clinical features recorded from a brain bank cohort of subjects with FTLD(258). Neither approach can assess the sensitivity or specificity of these criteria to detect PSP pathology from a cohort of (for example) incident Parkinsonism. Recruitment into the Society for PSP brain bank is very likely to be biased towards rarer movement disorders and where PSP was already suspected (and with reference to older criteria). Cases with Parkinsonism within this cohort will therefore not be representative of all cases of incident Parkinsonism. Validation of these criteria amongst cases of FTLD demonstrates that they are useful for this purpose but does not overcome the issue of non-FTLD type pathology (such as Parkinson's disease). It has been demonstrated that subjects with Parkinson's disease may have impaired vertical saccades; even if this occurs in 7.5% of cases of Parkinson's(256), the higher prevalence of Parkinson's compared to PSP mean that Parkinson's would still be the commonest cause of PSP-P as defined by the new criteria. It may be that with further validation of these criteria, or subsequent refinement, it will become possible to include subjects with syndromes more traditionally associated with Parkinson's Disease into epidemiological studies of PSP. However given the substantially higher prevalence of Parkinson's compared to FTLD, inclusion of PSP-P into epidemiological studies may lead to substantial over estimates of PSP pathology. I suspect that (at present) even if PSP-P had been included in the PiPPIN criteria many subjects meeting the criteria for PSP-P would not have been recognised and referred, as many clinicians would diagnose idiopathic Parkinson's disease.

This issue speaks to a more fundamental one, how a disease is defined and to what purpose. Many recent classification systems have recognised that the purpose of classification

varies(11,48). Some clinicians use criteria to reflect diagnostic certainty and relate diagnosis to prognosis or treatment options, biological studies of pathogenesis or of disease modifying therapeutics require high-level clinico-pathological specificity while studies of the epidemiology of disease or of disease burden may prioritise sensitivity or specific aspects of the clinical syndrome. Other studies may not require firm pathological validation but instead a common framework to describe clinical aspects of the condition and uniformity between groups/centres(11). In some circumstances the molecular or histopathological basis of a particular syndrome may be less relevant that the syndrome itself and its neuropsychological, cognitive and functional neural basis. The syndromes of PSP-RS or bvFTD (for example) cause similar morbidity irrespective of whether they are caused by a 4 repeat tauopathy, TDP-43 or some other process and as such should be considered together in (for example) some epidemiological studies, descriptive studies of symptomatology or morbidity and some interventional trials.

Even using current criteria that have been subjected to pathological validation some of the subjects included in the PiPPIN study will not have an FLTD pathology. The specificity for these criteria is not 100% and other pathologies may mimic FTLD. Limitations of clinicopathological correlation and disease identification are common in epidemiological research. Some of this may be ameliorated by reference to cohorts with pathological correlation (e.g. (129,259)) however such 'Brain Bank' studies are also subject to their own limitations and bias(260). It is also possible to use additional biomarkers (e.g. CSF Tau and β-Amyloid or PET imaging) to increase specificity to FLTD but, as with post mortem validation, this more invasive approach would limit recruitment those who chose to participate in such a study may not be representative of the cohort as a whole.

Pathological validation may not always be necessary and in some circumstances could be unhelpful. I have shown that the syndromes of frontotemporal degeneration are well documented and recognisable across two centuries of scientific literature. The progressive destruction of personality, interpersonal relationships and motivation that are associated with these syndromes have unique effects and morbidity irrespective of whether they are caused by Tau, TDP-43 or another non-FTLD type pathology and there is merit in studying the epidemiology of these ***syndromes*** in their own right. This work aims to investigate the epidemiology of these highly recognisable syndromes, not necessarily their associated pathology. While studies directed at the pathogenesis of neurodegeneration in FLTD may require high levels of molecular and pathological validation, studies such as this that examine the pathogenesis of the syndromic aspects (such as this study of apathy and impulsivity) and associated morbidity do not necessarily require these additional molecular restrictions.

Not every subject recruited was able to complete every aspect of the protocol. I had expected this to be the case, by attempting to recruit a representative cohort I chose to include subjects whose illness was advanced to the point where they were unable to attend clinic or complete assessments themselves, and could only complete the most basic aspects of clinical verification in the PiPPIN study. Amongst this cohort were subjects who (for example) had significant language deficits such that questionnaire based assessments were not possible but they had sufficient comprehension to be able to complete aspects of the behavioural testing. Others were able to complete most questionnaires but motor aspects of their condition significantly limited behavioural testing. Within a heterogeneous spectrum of clinical syndromes it is very likely that some testing modalities will be better to suited to some subjects than others. Rather than restrict testing to specific and narrowly defined clinical syndromes I chose a more inclusive approach. Not only because this approach better represents the clinical syndromes associated with FTLD but also because it seems possible that those aspects that limit some aspects of testing may be directly relevant to the syndromes of apathy and impulsivity that I wished to study. Also this inclusive approach exploits syndromic heterogeneity and allows identification of common factors that may run throughout the spectrum of FTLD associated syndromes.

I have deliberately not separated results by clinical diagnosis because such distinctions, typically made at the point of diagnosis, often dissipate over the course of an individual's illness(26). As I have shown (in Chapter Two) and consistent with other reports of FTLD (e.g. (261) individual clinical features of each syndrome are not exclusive. A supranuclear gaze paresis (for example) is not only seen in PSP and apraxia is not exclusive to CBS. While some subjects may have met criteria for bvFTD at the diagnosis, by the time of testing in the PiPPIN study they may have acquired further features of CBS or PSP-RS. It is not clear to me how such subjects would be classified if the results here were compared by diagnostic category, accepting that the point of diagnosis is to some extent arbitrary and dependent upon when a subject meets with a suitably experienced clinician. One aspiration of this work was to set out methods by which behavioural syndromes may be quantified and operationalized within this cohort of subjects, with the eventual aim of facilitating further study of such syndromes and symptomatic treatment trials. Subdividing results by clinical syndrome would limit the opportunities to do so and restrict sample size and usefulness of these data substantially.

I have shown that performance on tasks selected to assess apathy and impulsivity may be separated into a number of distinct components, some of which relate to carer reports, others to patient or clinician assessments and others to performance on a range of behavioural tasks. I have not however demonstrated that performance on each task directly relates to apathetic or

impulsive behaviour/cognition, or assessed which relate to patient or carer morbidity. It is very likely that other factors including (for example) motor disabilities, carer distress and patient insight will all have had an effect on symptom reporting and performance on some aspects of the testing battery. While this is a limitation when drawing conclusions on disruption of goal directed cognition, this is also a limitation of any behavioural testing or interview based psychology.

By using a heterogeneous group of subjects and an array of different testing methods I have attempted to ameliorate the effects of any specific limitations in any particular syndromic group but I also suggest that some deficits may be directly relevant to a clinically based study of apathy and impulsivity. For example in a study of stroke patients language disorders and motor dysfunction strongly correlated with assessments of apathy(262).

Despite selecting a range of behavioural tasks aimed to assess aspects of decision making that have a clear relevance to apathy and impulsivity, there was very little significant difference between performance amongst those subjects with FTLD rated as apathetic or impulsive by their cares and those who were not. Similarly combining 'objective' behavioural testing with 'subjective' patient and carer based questionnaires into a single Principal Component Analysis produced very little overlap between testing modalities. Similar lack of association between questionnaire and task based assessments have been reported in other studies, for example, of inhibitory control(263)

At least some of the extracted components appear to relate to the method by which testing is performed (for example by measuring saccades, use of a joystick etc.). Motor components have previously been reported as confounding neuropsychological testing in some studies (e.g. in motor neurone disease(266)), others have suggested that associations between dysfunction of motor control and behavioural testing reflect common underlying mechanisms. One study(267) bradykinesia and chorea both had significant but opposite associations with apathy in Huntington's disease. The authors suggest this may support both motor dysfunction and apathy being manifestations of dysfunctional striatal gating in Huntington's. Hence while some extracted components in the PiPPIN study may be related to abnormal motor function they may still be relevant to the study of motivation and behaviour.

Principal Component Analyses of the various versions of the AES demonstrated that extracted component structure varied depending on who was included in the analysis (patients, controls or both), who was asked (subject, informant, clinician) and that the extracted components could be classified not only by what was being asked (item type) but also the

manner in which was asked (question type). Again while this suggests factors other than simply variation in the target symptoms may be contributory to the results. Such factors are not simply confounders but may also be contributory to apathy and impulsivity. Factors such as insight, perspective and emotional state of each interviewee are likely to be directly relevant to subject behaviour. For example the characteristics of carers of people with dementia and their premorbid relationship can contribute to aggressiveness in dementia(268), how a carer responds to their situation and their own management strategies also influence patient behaviour(137). Language considerations are also likely to be relevant to behavioural symptoms. Aphasia is associated with post stroke apathy(264) but also distinct patterns of speech and language dysfunction in FTLD have been associated with different motivational changes in FTLD. For example in one study patients with primary progressive apraxia of speech had higher rates of apathy but lower disinhibition rates than patients with other forms of primary progressive aphasia(269).

Throughout this thesis I have argued that apathetic and impulsive symptomatology is an important source of patient and carer morbidity and as such a valid subject of research. This argument is largely based on clinical observation and carer reports which are subject to the same limitations as the reports and testing used here. Rather than considering other factors such as motor disability, language disruption, patient insight and carer distress as potential confounding factors, I suggest they are directly relevant to the clinically observed syndromes of apathy and impulsivity in FTLD and as such equally valid and important.

### 6.11 Future Directions

A single epidemiological study can only provide estimates of disease state in a defined population at a defined point in time. There is a need to monitor the epidemiology of FTLD and its associated syndromes to track changes and important differences in disease rates between cohorts. Such disease monitoring is vital to identify risk factors and barriers to diagnosis and care. No single study is sufficient to do this and, as with other diseases, there is a need to periodically revisit the epidemiology using methods such as these to allow comparison between studies. As diagnostic criteria continue to change future studies will also need to consider methods by which changes in criteria may affect diagnosis rates and allow for this when comparing with previous estimates. We await the results of the second phase of PiPPIN, undertaken between 1st January 2017 and 31st December 2018.

I studied apathy and impulsivity with syndromes associated with FTLD. I have shown that these subjects perform differently on tests of these symptoms and their performance relates not to a single process but to a multitude of different components that each relate to performance on different sets of assessment tools. I have not attempted to show which of these are clinically important in terms of mortality risk – a point addressed by Lansdall et al(270). Nor have I undertaken a health-economics assessment, although others have shown the impact of apathy on healthcare cost(271,272). The anatomical, chemical and functional brain changes associated with the PiPPIN cohort have been addressed by Lansdall et al(255,256) and on going work in second phase of PiPPIN that recruited 2017-2018 in conjunction with MR-spectroscopy (Murley et al in prep).

A future treatment for apathy or impulsivity will seek to modulate these brain changes, if not by repair then by supplementing deficits. One potential further development may be studying the functional and structural correlates of individual components of apathy/impulsivity and by doing so it may be possible to make inferences from previous research as to how these processes may modulated pharmacologically and select potential treatments for further evaluation. Targets include the noradrenergic(222,234,273,274), dopaminergic(275,276) and serotonergic (220,277,278) contributors to impulsivity; and the restoration of GABA-ergic and Noradrenergic systems that are abnormal in FTLD disorders(162,168,279).

Before moving to treatment trials for apathy or impulsivity there is also a need to establish which components of these syndromes are clinically important and relate to mortality, co-morbidity and quality of life. This is not straightforward. It is not immediately clear how

they should be measured, in which patients and by whom. The effects of different components of apathy/impulsivity may be felt differently by patient or those around them (and this may account for some differences between reports in the PiPPIN study). Reports of distress or morbidity are subjective and limited by the same factors as the questionnaire based assessments of apathy/impulsivity used(280–283). More 'objective' assessments of morbidity may include assessments of financial or social cost, for example hospital admission rates or care costs, but these are influenced by a much wider range of factors than just apathy or impulsivity.

### 6.12 Conclusion

In conclusion I have shown that the syndromes associated with frontotemporal lobar degeneration have been described over centuries. The nosology and criteria used to describe them have evolved and changed over time but within this entire spectrum of disease there are recognisable and important syndromes such as apathy and impulsivity. The basis of these and how they relate to associated morbidity is complex and they reflect multifaceted and multidimensional constructs. They may be assessed by a variety of different methods but I have argued that a multidimensional approach with respect to the underlying cognitive constructs and their effects on patients and those around them has the best chance of accurate and useful results.

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