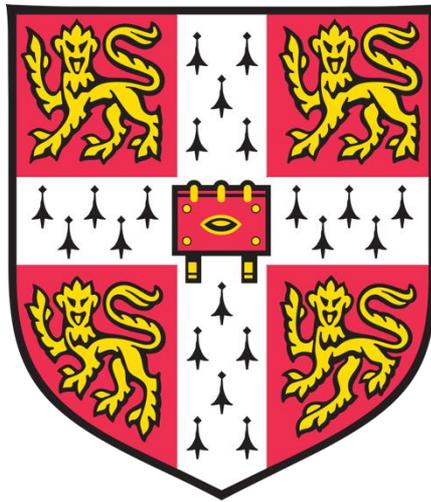


Apathy and Impulsivity in Frontotemporal Lobar
Degeneration Syndromes



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Doctor of Philosophy

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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 where declared in the text.

This work 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. 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.

The word count of 40,500 does not exceed the prescribed word limit.

Preface

The patient and control data used throughout this thesis were collected by myself and a team of researchers and clinicians at the Department of Clinical Neurosciences.

Chapter 3 and Chapter 4 have been published (see Lansdall et al., *Brain* 2017).

Chapter 5 and Chapter 6 have been submitted.

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Abstract

There has been considerable progress in the clinical, pathological and genetic fractionation of frontotemporal lobar degeneration syndromes in recent years, driving the development of novel diagnostic criteria. However, phenotypic boundaries are not always distinct and syndromes converge with disease progression, limiting the insights available from traditional diagnostic classification. Alternative *transdiagnostic* approaches may provide novel insights into the neurobiological underpinnings of symptom commonalities across the frontotemporal lobar degeneration spectrum.

In this thesis, I illustrate the use of transdiagnostic methods to investigate apathy and impulsivity. These two multifaceted constructs are observed across all frontotemporal lobar degeneration syndromes, including frontotemporal dementia, progressive supranuclear palsy and corticobasal syndrome. They cause substantial patient morbidity and carer distress, often coexist and are undertreated. Using data from the Pick's disease and Progressive supranuclear palsy Prevalence and INcidence (PiPPIN) Study, I examine the frequency, characteristics and components of apathy and impulsivity across the frontotemporal lobar degeneration spectrum.

A principal component analysis of the neuropsychological data identified eight distinct components of apathy and impulsivity, separating patient ratings, carer ratings and behavioural tasks. Apathy and impulsivity measures were positively correlated, frequently loading onto the same components and providing evidence of their overlap. The data confirmed that apathy and impulsivity are common across the spectrum of frontotemporal lobar degeneration syndromes.

Voxel based morphometry revealed distinct neural correlates for the components of apathy and impulsivity. Patient ratings correlated with white matter changes in the corticospinal tracts, which may reflect retained insight into their physical impairments. Carer ratings correlated with grey and white matter changes in frontostriatal, frontotemporal and brainstem systems, which have previously been implicated in motivation, arousal and goal directed behaviour. Response inhibition deficits on behavioural tasks correlated with focal frontal cortical atrophy in areas implicated in goal-directed behaviour and cognitive control.

Diffusion tensor imaging was highly sensitive to the white matter changes underlying apathy and impulsivity in frontotemporal lobar degeneration syndromes. Diffusion tensor imaging findings were largely consistent with voxel-based morphometry, with carer ratings reflecting widespread changes while objective measures showed changes in focal, task-specific brain regions. White matter abnormalities often extended beyond observed grey matter

changes, providing supportive evidence that white matter dysfunction represents a core pathophysiology in frontotemporal lobar degeneration.

Apathy was a significant predictor of death within two and a half years from assessment, consistent with studies linking apathy to poor outcomes. The prognostic importance of apathy warrants more accurate measurement tools to facilitate clinical trials. Although causality remains unclear, the influence of apathy on survival suggests effective symptomatic treatments may also prove disease-modifying.

These findings have several implications. First, clinical studies for apathy/impulsivity in frontotemporal lobar degeneration syndromes should target patients who present with these symptoms, irrespective of their diagnostic category. Second, data-driven approaches can inform the choice of assessment tools for clinical trials, and their link to neural drivers of apathy and impulsivity. Third, the components and their neural correlates provide a principled means to measure (and interpret) the effects of novel treatments in the context of frontotemporal lobar degeneration.

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Abbreviations

ACE-R	Addenbrooke's Cognitive Examination Revised
AES	Apathy Evaluation Scale
AD	Alzheimer's Disease
BIS	Barrett Impulsiveness Scale
BIS/BAS	Behavioural Inhibition System and Behavioural Activation System
bv-FTD	Behavioural-variant Frontotemporal Dementia
CBS/D	Corticobasal Syndrome/Degeneration
CBI-R	Cambridge Behavioural Inventory – Revised
CRRT	Cued Reinforcement Reaction Time Task
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
FAB	Frontal Assessment Battery
FPCA	Final Principal Component Analysis
FRS	Frontotemporal dementia Rating Scale
FTD	Frontotemporal Dementia
FTLD	Frontotemporal Lobar Degeneration
HD	Huntington's disease
ICD	International Classification of Diseases
ICD	Impulse Control Disorder
IST	Information Sampling Task
LPCA	Local Principal Component Analysis
lvPPA	Logopenic variant Primary Progressive Aphasia
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
nvPPA	Non-fluent Primary Progressive Aphasia
NPI	Neuropsychiatric Inventory
PCA	Principal Component Analysis
PD	Parkinson's Disease
PiPPIN	Pick's Disease and Progressive Supranuclear Palsy Prevalence and Incidence
PPA	Primary Progressive Aphasia
PSP	Progressive Supranuclear Palsy
PSP-RS	Progressive Supranuclear Palsy Rating Scale
RDoC	Research Domain Criteria
svPPA	Semantic variant Primary Progressive Aphasia
SST	Stop Signal Task
TBSS	Tract Based Spatial Statistics
VBM	Voxel Based Morphometry

Chapter 1 | Introduction

1.1 The Frontotemporal Lobar Degeneration Spectrum

Frontotemporal lobar degeneration causes a range of clinically, genetically and pathologically heterogeneous clinical syndromes¹⁻³. These include the behavioural and language variants of frontotemporal dementia (FTD), progressive supranuclear palsy (PSP) and the corticobasal syndrome (CBS, which is often but not exclusively associated with corticobasal degeneration pathology, CBD).

In this chapter, I outline the clinical features, pathological underpinnings and genetic mutations associated with each of the FTLN spectrum syndromes. Despite recent progress in pathological and genetic fractionation of these disorders⁴⁻⁶, the soft boundaries between phenotypes and convergence of syndromes with disease progression calls for an alternative transdiagnostic approach, embracing symptom commonalities across the spectrum of disorders.

The thesis focusses on apathy and impulsivity in FTLN; both are common, multifaceted constructs that cause substantial patient morbidity and carer distress across the spectrum of disorders. Apathy includes loss of interest, motivation, activity and ‘energisation’ of behaviours, and reduced spontaneous or voluntary behaviour. Impulsivity includes poor choices (risk-taking), impaired response inhibition (disinhibition), delay intolerance (delay discounting), and reflection impulsivity in humans and analogous animal models.

I first discuss the evolving theoretical framework associated with apathy; including suggested definitions, diagnostic criteria and assessment tools. I then consider the proposed underlying mechanisms associated with apathy and the limitations to currently available symptomatic therapies. Subsequently, I discuss the proposed definitions, theoretical frameworks, available assessment tools, underlying neurobiology and available treatments associated with impulsivity. I then examine the relationship between apathy and impulsivity and the underlying mechanisms that may be responsible for their coexistence in neurodegenerative diseases.

I will illustrate the advantages of transdiagnostic techniques to understand symptom commonalities across the FTLN spectrum and facilitate identification of novel treatment targets. Such approaches remain sensitive to the heterogeneity both within and across syndromes, and increase power to examine complex behavioural changes.

1.1.1 History

The illness now known as frontotemporal dementia was described in 1892 by Arnold Pick, and was for many years known as Pick's Disease⁷. Pick related the clinical features of aphasia, apraxia and behavioural change to atrophy of the frontal and temporal lobes. Neuronal inclusion bodies were identified by Alois Alzheimer in 1911⁸. Later, a spectrum of related pathologies, known collectively as frontotemporal lobar degeneration⁹, came to be recognised, underlying a group of clinically and pathologically heterogeneous progressive syndromes that combined cognitive and motor disorders¹⁰. These include the behavioural and language variants of frontotemporal dementia⁹, and two related disorders; progressive supranuclear palsy and corticobasal syndrome^{11,12}.

1.1.2 Clinical Presentation

The clinical syndromes associated with frontotemporal lobar degeneration include behavioural variant frontotemporal dementia (bvFTD)⁴, which can present with or without features of motor neuron disease (FTD-MND)¹³; the language variants of FTD, known as primary progressive aphasia (PPA), including semantic variant (svPPA), nonfluent variant (nvPPA) and logopenic variant (lvPPA)⁶; progressive supranuclear palsy (PSP)^{14,15} and the corticobasal syndrome (CBS)⁵.

1.1.2.1 Behavioural Variant Frontotemporal Dementia

Changes in personality, social conduct, emotion and cognition are characteristic of bvFTD^{2,4}, reflecting the progressive disintegration of the neuronal circuits involved in emotion regulation, social cognition, decision making and motivation¹⁶. Approximately 10% of patients also develop clinical and neurophysiological evidence of motor neurone disease (FTD-MND)^{2,13,17}. Recently proposed criteria for 'possible bvFTD' reflect the widespread behavioural changes associated with this syndrome; three of six clinically discriminating features are required to be present, including disinhibition (socially embarrassing behaviours, tactless or suggestive remarks, overspending), apathy (often paradoxically coexisting with disinhibition), loss of empathy, perseverative/compulsive behaviours, hyperorality and dysexecutive neuropsychological profile⁴. Changes in eating behaviours, mental rigidity, irritability, agitation, loss of insight and blunting of affect are also common features of bvFTD^{17,18} and many cases may develop language impairments later in the disease course¹⁹. Psychosis is uncommon, except in cases caused by the C9orf72 mutation²⁰. A diagnosis of 'probable bvFTD' requires additional functional decline and supportive neuroimaging⁴, while 'definite

bvFTD' requires pathological confirmation post mortem and/or underlying genetic mutations, despite advances in *in vivo* techniques providing evidence of the underlying cause of disease⁴.

1.1.2.2 Primary Progressive Aphasias

Pick and Serieux^{7,21} described a progressive language disorder reflecting atrophy of the frontal and temporal regions of the left hemisphere, which was later coined "progressive aphasia"^{22,23}. For many years PPAs were subtyped as "fluent/semantic" variant (svPPA)²⁴⁻²⁶ and "non-fluent variant"(nvPPA)²⁷. A third subtype was defined in 2004, termed logopenic variant aphasia (lvPPA)²⁸. Current criteria classify these variants into 3 categories of diagnostic certainty; clinical, imaging-supported and pathologically confirmed⁶.

Progressive semantic loss is a hallmark of svPPA, over and above the language changes, and the term Semantic Dementia is widely used^{24-26,29}. Semantic dementia includes a 'right-dominant' variant which is not captured fully by the criteria for svPPA⁶. Non-verbal domains include visual, tactile, olfactory and gustatory systems, and many patients develop behavioural changes similar to bvFTD^{19,24,30}.

The non-fluent variant, nvPPA, a speech output disorder, presents as apraxia of speech and/or agrammatism, with literacy deficits, effortful speech^{6,22,27} and in some cases mutism³¹. Progressively telegraphic speech/writing and deterioration of sentence comprehension reflects cortical dysfunction in the left hemisphere²⁷. Gorno-Tempini criteria require one of the two core features to be present; agrammatism or effortful speech, and at least two of three additional features including impaired syntax comprehension, spared single-word comprehension and/or spared object knowledge. Many patients develop motor abnormalities consistent with CBS or PSP³², whereas memory and visual functioning are largely preserved.

Logopenic aphasia is characterised by hesitant but grammatically correct speech²⁸, with core deficits in word retrieval (spontaneous speech and confrontation naming) and sentence repetition. Common features include word finding pauses, anomia, and impaired phonological working memory, resulting in the inability to repeat spoken phrases. In contrast to svPPA cases, single word repetition can be spared and in contrast to nvPPA patients, lvPPA does not cause dysprosodic speech output with motor speech errors and agrammatism^{6,28}.

1.1.2.3 The Corticobasal Syndrome

Corticobasal degeneration (initially termed “corticobasal ganglionic degeneration”) and the closely related “corticobasal syndrome” exhibit complex motor and cognitive changes^{33–35}. The term CBD is now used mainly to refer to the distinctive pathology, while CBS refers to the clinical syndrome. This distinction has not always been recognised^{36–38} but CBS/CBD have poor clinicopathological correlations: AD, PSP, and FTD pathologies can mimic the corticobasal syndrome^{39,40}. I use CBS to refer to the clinical syndrome and CBD to refer to the pathology.

Although previous criteria for CBD excluded “early dementia” in an attempt to increase diagnostic specificity³³, cognitive decline is a common and early feature^{38,41–43}. Despite the lack of gold standard diagnostic criteria, definitions have required the presence of an asymmetric, progressive motor syndrome with features including dystonia, myoclonus, bradykinesia, limb apraxia and levodopa-resistant parkinsonism. Higher cortical features include apraxia, alien limb phenomena, cortical sensory loss, cognitive and behavioural impairment and aphasia⁵. Language impairments and behavioural changes, including apathy, antisocial behaviour, personality changes, irritability and disinhibition, are common. Over half of CBS cases have significant behavioural changes^{5,19}.

Current consensus diagnostic criteria for CBD/CBS recognise four presenting phenotypes, including corticobasal syndrome (CBS), frontal behavioural-spatial syndrome (FBS), nonfluent variant of primary progressive aphasia (nvPPA) and a progressive supranuclear palsy syndrome (PSPS)⁵, with categories of “possible” and “probable” CBD. However, Alexander et al (2014) showed that even the Armstrong criteria lead to misdiagnosis in up to a third of CBD cases, and that no singular clinical features distinguish CBD from non-CBD cases of CBS.

1.1.2.4 Progressive Supranuclear Palsy

First described by Drs Steele, Richardson and Olszewski in 1964, progressive supranuclear palsy (PSP) is characterised by ocular, motor (akinesia and axial rigidity), cognitive and behavioural changes. Diagnostic criteria developed by Litvan (1996) required >40 years of age, progression, falls (often backwards) within a year of onset and vertical supranuclear gaze palsy or slowing of vertical saccades¹⁴. Patients meeting this criteria are generally considered to have “classical PSP”, increasingly referred to as PSP-Richardson syndrome (PSP-RS)¹⁵, which has strong clinicopathological correlations to PSP pathology in up to 95% of cases⁴⁴. While the

Litvan criteria have good specificity, they have limited sensitivity for common clinical variants of PSP¹⁵. PSP pathology causes other syndromes and shows phenotypic overlap, leading to new intermediate diagnostic terms such as CBS-PSP⁵. The new diagnostic criteria proposed by the Movement Disorders Society recognise a number of distinct PSP variants which differ in their clinical presentation: oculomotor dysfunction (PSP-OM), postural instability (PSP-PI), Parkinsonism resembling idiopathic Parkinson's Disease (PSP-P), frontal lobe cognitive or behavioural presentation (PSP-F), corticobasal syndrome (PSP-CBS), and speech/language disorders (PSP-SL)¹⁵.

Most relevant for this thesis is the acknowledgement of PSP presenting with predominant cognitive and behavioural features including changes in personality, irritability, obsessive behaviours, and executive dysfunction^{15,45,46}. Early reports suggested that approximately 10-25% of cases will present with cognitive symptoms and 70% develop dementia^{47,48}. However, cognitive presentations (including speech, language, personality) may account for the majority of cases⁴⁹. Memory, visuospatial and language functions may also be impaired⁵⁰. Apathy is common and profound in PSP⁵¹⁻⁵³, affecting over 80% of patients^{54,55}, and is included in the diagnostic criteria alongside impulsivity¹⁵. Loss of empathy and lack of insight are also recognised as features of PSP, overlapping with behavioural variant FTD¹⁸. Gilchrist et al., (2016) reported that 60% of PSP patients met criteria for bvFTD in terms of cognitive and behavioural changes. Many of these patients would likely now meet criteria for PSP-F.

1.1.3 Epidemiology

Frontotemporal dementia is a common cause of young-onset dementia⁵⁶, generating disproportionate social and economic costs. Although considered rare disorders, FTD, PSP and CBS collectively account for a substantial burden of disease. The Pick's Disease and Progressive supranuclear palsy Prevalence and INcidence Study (PiPPIN) study reported prevalence of 10.8/100,000 for all FTLT syndromes, with a similar prevalence of bvFTD, PPA, CBS and PSP¹⁹. This is consistent with previous epidemiological studies of FTD^{56,57}.

The inclusive PiPPIN study design, considering FTD, PSP and CBS together, aimed to capture transitional and intermediate clinical phenotypes. Despite significant progress in the development of novel syndrome-specific diagnostic criteria, the overlap and evolution of syndromes limits their use in epidemiological studies. Previous studies have been hindered by lack of gold standard consensus criteria and diagnostic uncertainty, restrictive age ranges, phenotypic variability and poor clinicopathological correlations, assessment in a single FTLT

syndrome and inclusion of “phenocopy” cases (non-progressive bvFTD cases, negative for C9orf72)⁵⁸. Inclusive epidemiological studies using novel diagnostic criteria such as the Movement Disorder Society NINDS-SPSP criteria for PSP¹⁵, which increasingly recognise multiple clinical phenotypes^{49,59}, are warranted. Poor clinicopathological correlations suggest the true prevalence of FTLD pathology is unclear.

For this thesis, it is advantageous to draw on an epidemiological sample to assess apathy and impulsivity, minimising bias towards a subset of patients who are able to regularly attend tertiary clinics. Therefore, unless otherwise stated, all data from this thesis are derived from the PiPPIN study.

1.1.4 Pathology

Frontotemporal lobar degeneration (FTLD) is an umbrella term for the underlying pathologies associated with FTD (with or without motor neurone disease features), PSP and CBS. FTLD is characterised by abnormally aggregated proteins in neurons and/or glia, neuronal loss, microvacuolation and a variable degree of astrocytic gliosis⁹, which I discuss in relation to each syndrome in the next sections.

1.1.4.1 Frontotemporal Dementia

FTD can be defined by the pattern of accumulated proteins. Approximately half have phosphorylated tau (“Tau”) and half have transactive response DNA-binding protein 43-kDA (“TDP43”). A small minority of patients are both tau- and TDP-43-negative, many of whom present with fused in sarcoma protein inclusions (FUS)^{60,61}. The clinic-anatomical profiles of some FTD types are consistently associated with a particular pathology. For example, svPPA and FTD-MND are closely associated with TDP pathology, with svPPA most linked to TDP of Type C specifically and FTD-MND with Type B^{10,40}. Very young onset bvFTD is characteristic of underlying FUS pathology, while logopenic aphasia is commonly caused by Alzheimer type pathology rather than FTLD⁶. A progressively smaller minority are negative for these protein inclusions, termed dementia lacking distinctive histology (DLDH)⁶².

There are 6 tau isoforms in human brain tissue, which contain either three (3R-tau) or four (4R-tau) microtubule-binding repeats, located at the carboxy-terminal of the protein^{10,60,63}. Under normal conditions, tau isoforms are generated through alternate splicing of the tau gene MAPT, located on chromosome 17. Misfolding of tau renders it insoluble, causing it to aggregate. Mutations in the MAPT gene occur either in the coding region outside of exon 10, leading to

accumulation of 3R and 4R tau in neurons, or within the coding region of exon 10, leading to 4R tau in neurons and glia. Sporadic tauopathies, such as CBD and PSP, are often associated with 4R tau⁶⁴, whereas Pick Bodies are predominantly associated with 3R tau⁶⁵. Pick's pathology includes silver-positive rounded inclusions of 3R tau and balloon neurons known as "Pick Cells"³. Hyper-phosphorylated, ubiquitinated TDP-43 pathology can be subdivided into type A-D, each of which is associated with particular phenotypes and some of which have been linked to specific genetic mutations⁶⁶.

1.1.4.2 Corticobasal Syndrome and Progressive Supranuclear Palsy

CBS and PSP are referred to as primary tauopathies, reflecting their association with a specific 4R tau pathology¹². The distribution and composition of neuroglial inclusions differ between disorders; CBD is characterised by astrocytic plaques while PSP is associated with tuft-shaped astrocytes⁶⁷. CBD tau-positive neuronal and glial inclusions contain astrocytic plaques of 4R tau and threadlike lesions in cardinal regions³. CBS is particularly heterogeneous and has poor clinicopathological correlations^{5,39}. CBD pathology can mimic AD or PSP clinically, while CBS only reflects CBD pathology in 60% of cases³⁹.

PSP tau-positive neuronal and glial inclusions contain 4 repeat neurofibrillary tangles and tufted astrocytes³. Hyperphosphorylation and aggregation of tau occurs predominantly in the pallidum, subthalamic nucleus, red nucleus, substantia nigra, pontine tegmentum, striatum, oculomotor nucleus, medulla and dentate nucleus⁵¹. "Classical" PSP or PSP-Richardson's Syndrome has high clinicopathological correlations^{44,68} (including in our Cambridge cohorts). A recent study identified clinical features that were predictive of PSP pathology, including ocular motor dysfunction (supranuclear gaze palsy), postural instability, akinesia and cognitive dysfunction⁵⁹.

In general, clinicopathological correlates remain uncertain in FTLD syndromes^{2,17} and post mortem studies are required for diagnostic confirmation.

1.1.5 Genetics

Although FTLD syndromes are mostly sporadic, a number of genetic mutations have been identified. SvPPA, PSP and CBS/D are essentially sporadic diseases, with only rare family case reports of mutations causing syndromes similar to PSP and CBD. However, under current consensus criteria¹⁵, mutations in for example MAPT are an exclusion criterion for PSP.

Behavioural variant FTD has high rates of disease causing mutations. Up to 30-40% of patients report a family history indicative of an autosomal dominant mutation⁶⁹ and of these, half will have a recognised mutation⁷⁰. The common mutations are: progranulin (GRN), microtubule-associated protein tau (MAPT) or chromosome 9 open reading frame 72 (C9orf72; frequently associated with FTD-MND^{13,71,72})^{1,3,63,70}. Additional rare genes, including TBK1⁷³, CHMP2B⁶⁰, and FUS⁷⁴ have been identified as causing FTD syndromes.

1.1.6 A new dimensional approach to the FTLD spectrum

Classifying patients using proposed diagnostic criteria can be useful for patients and their families, but phenotypic boundaries are not distinct. Despite discrete clinical presentation at diagnosis, syndromes may converge with disease progression, such that a patient can transition to eventually meet inclusion criteria for multiple variants^{19,75}. This limits the relevance of diagnostic labels, prevents accurate epidemiological estimates and complicates treatment. It also speaks to the biological basis of phenotypic expression of neurodegeneration.

In this thesis, I consider an alternative transdiagnostic approach, moving away from a classical categorical framework for diagnosing FTLD to embrace symptom commonalities across the spectrum of disorders (Figure 1). Considering FTLD syndromes together remains sensitive to the heterogeneity both within and across groups. For example, two bvFTD patients can meet diagnostic criteria without sharing a single core clinical feature. In contrast, although svPPA patients meet different diagnostic criteria to bvFTD, patients often develop similar behavioural changes. Stratifying patients based on the presence and severity of specific symptoms/signs provides a basis for examining their underlying neural correlates and may identify targets for symptomatic treatment.

This *dimensional* approach to examine changes across neurodegenerative diseases is consistent with the recent Research Domain Criteria (RDoc), developed by the National Institute of Mental Health. RDoc is a research framework to classify mental disorders based on dimensions of observable behaviour and neurobiological measures. It considers the relevant symptom domains spanning a number of disorders, in contrast to categorical diagnostic criteria such as the International Classification of Diseases (ICD-10) (World Health Organisation, 1993) or Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th Edition (American Psychiatric Association, 2013). By integrating information spanning from genes, molecules and cells to physiology, behaviour and self-report, RDoc aims to understand the full range of human behaviour from normal to abnormal (example provided in Figure 2). By adopting this approach,

a “neurological” RDoc⁷⁶ would provide the necessary framework to examine the relationship between neurodegenerative diseases and their heterogeneity, by identifying overlapping domains of motor, cognitive and behavioural change.

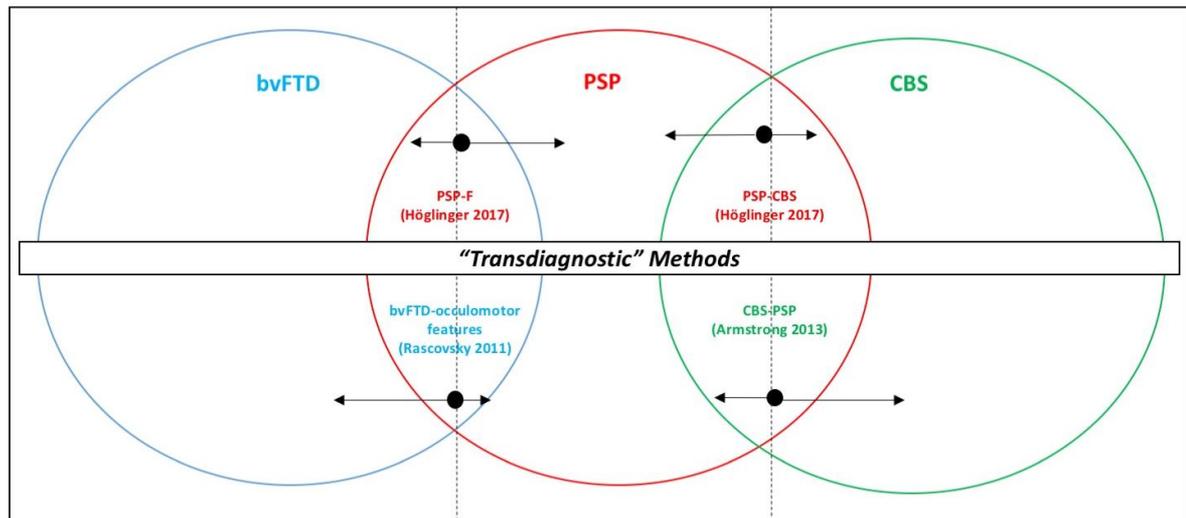


Figure 1: Transdiagnostic Methods.

Patients often meet criteria for multiple variants, effectively sitting on the border between diagnostic groups. For example, an individual may meet criteria for both PSP-F under the Höglinger criteria or bvFTD with oculomotor features under the Rascovsky criteria, PSP-CBS under the Höglinger criteria or CBS-PSP under the Armstrong criteria. Under these circumstances, clinicians may argue for or against a particular diagnosis. This categorisation has implications for clinical studies targeting specific disease groups, which may exclude patients meeting alternative diagnostic criteria. Transdiagnostic methods, such as those employed by the PiPPIN study, are inclusive of all patients irrespective of their diagnostic label. This approach is particularly relevant for assessing symptom commonalities that span the entire FTLD spectrum, including apathy and impulsivity.

1.1.7 Treatment

There are currently no proven disease modifying treatments for FTLD and pharmacotherapy focuses primarily on management of distressing and disabling symptoms. Neurotransmitter replacement or augmentation therapy is the focus of symptomatic treatments, with evidence of syndrome-specific serotonergic, dopaminergic and/or noradrenergic deficits^{77,78}.

Symptomatic treatments may improve akinetic-rigidity, dystonia, sleep disturbance, affective disorders, mood, anxiety, aggression, psychosis, myoclonus, and bowel and bladder dysfunction, but are largely prescribed based on small case studies, ‘expert opinion’ or analogous effects in other psychiatric or neurological disorders. There are limited randomised-controlled clinical trials (RCTs), and those available are restricted by small sample sizes due to low prevalence of specific FTLD subtypes^{79,80}.

Efforts to develop a disease-modifying treatment for FTLD primarily target the abnormal aggregation of proteins, with current studies focusing on the accumulation of hyperphosphorylated tau. However, the lack of suitable, FDA approved, disease-specific outcome measures is problematic for clinical trials, and novel biomarkers are warranted to accurately track disease progression. Delayed diagnosis has also hindered trials of disease modifying treatments; the repeated failure of clinical trials in Alzheimer's Disease may reflect irreversible neuropathology and neurodegeneration at the time of intervention, emphasizing the need for early diagnosis and treatment. Insights from genetically predisposed individuals suggest brain changes may occur 5-10 years prior to clinical onset⁸¹. Identifying biomarkers of early or presymptomatic disease has become a major research priority. In the absence of an effective disease-modifying therapy, the emphasis on quality of life rather than quantity is apparent, highlighting the need to treat disabling and distressing symptoms more effectively.

Furthermore, symptomatic treatment may potentially also alter the disease trajectory. Apathy, a common feature observed across FTLD syndromes, is reported to cause rapid cognitive and functional decline towards AD dementia in MCI patients⁸²⁻⁸⁴, suggesting that effective intervention targeting the underlying neurobiology of apathy may improve outcome for patients (see 2.0 Apathy section below and Chapter 6). Effective treatment of these complex disorders will almost certainly require a personalised combination of pathology-targeting, disease-modifying treatments and symptomatic therapies.

1.1.8 Interim Summary

Advances in the clinical, pathological and genetic fractionation of FTLD associated disorders has supported new diagnostic criteria⁴⁻⁶, although accuracy in the face of widening phenotypic variation remains limited. The overlap and convergence of syndromes with disease progression suggests that transdiagnostic approaches may be more appropriate for the development of novel symptomatic treatments, embracing symptom commonalities. In the following sections, I discuss the applicability of such approaches to apathy and impulsivity, two common, multifaceted and often coexisting syndromes which occur across the FTLD spectrum.

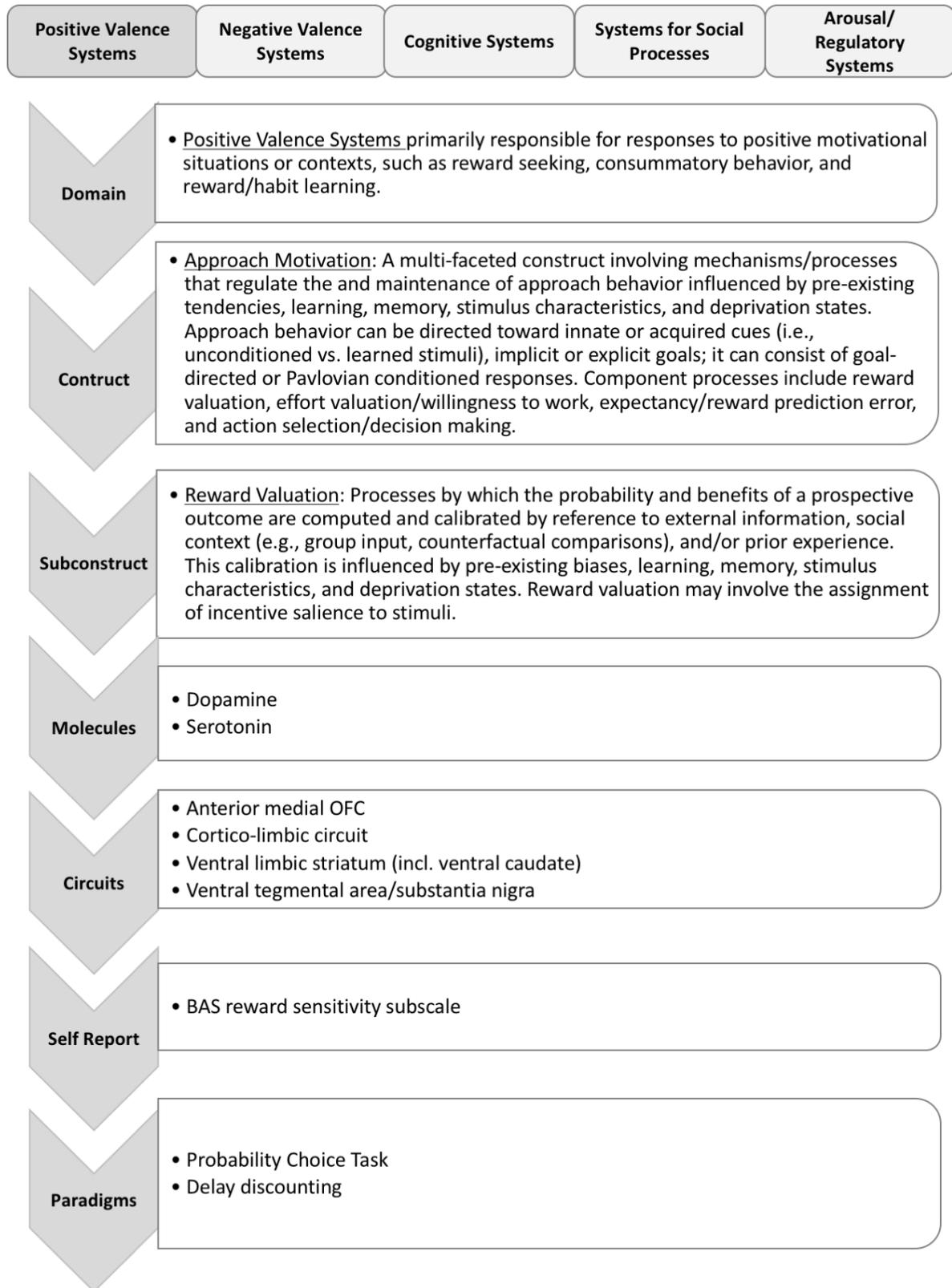


Figure 2: The Research Domain criteria (RDoc).

Developed by the National Institute of Mental Health to classify mental disorders, the RDoc includes five domains or systems, which can be categorized into constructs, sub-constructs, molecules, circuits, self-report measures, and paradigms. Above is an example relevant to motivation.

1.2 Apathy

Apathy is a common, multifaceted and highly debilitating construct spanning multiple neurological and neuropsychiatric diseases^{85–89}. Apathy is increasingly recognised to negatively impact patient outcomes⁹⁰ in Alzheimer’s Disease^{91,92}, Huntington’s Disease⁹³, Parkinson’s Disease^{83,88,91}, stroke^{87,94–97}, head injury⁹⁸, pre-dementia states^{82–84} and FTLD syndromes^{92,99–103}. Apathy has been linked to decreased functioning^{84,94}, increased caregiver distress¹⁰⁴, rapid cognitive and functional decline^{83,105,106}, poor response to treatment/rehabilitation^{94,107}, reduced quality of life⁹⁷ and poor prognosis¹⁰⁸. Crucially, apathy may represent a risk factor for conversion to dementia^{82,84}. Despite awareness of its negative impact, apathy remains poorly understood and further investigations into its components and neural correlates are warranted. Apathy may represent a biomarker for early brain changes, a predictor of individual patient trajectories/outcomes and a target for treatment.

1.2.1 Definition

There remains no consensus regarding a definition for apathy. Apathy originates from the Greek word “apatheia” meaning ‘without passion’ and is defined in the Oxford English Dictionary as a ‘lack of interest, enthusiasm or concern’. Apathy may be a primary syndrome or a secondary symptom¹⁰⁹, according to ones attribution of causality; the syndrome of apathy has been defined as a lack of motivation that is “not attributable to diminished level of consciousness, cognitive impairment (intellect), or emotional distress”, in contrast to reduced motivation as a consequence of these factors¹⁰⁹.

1.2.2 Proposed Diagnostic Criteria

A gold standard clinical diagnostic criteria for apathy is lacking. Apathy is not referenced in the *International Classification of Diseases (ICD-10)* (World Health Organisation, 1993) and is mentioned in the *Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th Edition* (American Psychiatric Association, 2013) only as a symptom (eg. of Schizophrenia and Major Depression) rather than independent syndrome. Several criteria exist, including DSM-like criteria proposed by Marin (1991), but lack of a consensus definition for apathy limit their applicability and they are rarely used in clinical practice. Stuss et al. (2000), emphasized that apathy should be defined as an absence of responsiveness to stimuli indicated by a lack of self-initiated affective, behavioural or cognitive action. Similarly, Starkstein (2000) and Robert et al., (2009) define apathy in terms of loss of motivation, loss of goal directed behaviour, cognitive activities and/or emotions, and functional impairment in the absence of physical disability. Despite efforts to develop standardised criteria, diagnosis of apathy in the clinic is

often made either based on clinical interview or by employing currently available assessment tools developed for research purposes.

1.2.3 Cognitive and Behavioural Framework

Since Marin's initial description, other proposed cognitive and behavioural frameworks for apathy remain largely descriptive and allusive. Apathy is increasingly recognised as a complex, multifaceted construct and its components and mechanisms remain controversial.

The framework by Levy & Dubois (2006) has been highly influential. They defined apathy in terms of "quantitative reductions in self-generated voluntary and purposeful behaviour", representing a behavioural and quantifiable construct rather than an emotional psychological state. The multifactorial nature of apathy has been highlighted by attempts to define subtypes relating to distinct underlying mechanisms of altered "goal-directed behaviour" (GDB) processing. The "goal" can be immediate and physical, such as relieving thirst, or long-term and abstract, such as having a family or being successful in one's job¹¹⁰. Achieving GDB depends on a number of internal and external factors that determine intention to act, plan, initiate and execute actions and provide feedback regarding the completed action^{110,111}.

Subtypes of apathy have been proposed, and largely recognise three components of emotional, behavioural and cognitive processing. Stuss (2000), categorised apathy as a lack of response to stimuli in terms of either 'affective', 'behavioural' or 'cognitive' self-initiated actions, while Levy and Dubois (2006) proposed similar classification subtypes of 'emotional-affective', 'cognitive' and 'auto-activation'. Levy & DuBois (2006) related these subtypes to prefrontal-basal ganglia circuits¹¹², linking each to dissociable mechanisms of disrupted GDB processing (see figure 3). They proposed that 'emotional-affective' apathy results from changes in the orbital-medial prefrontal cortex or connected regions of the basal ganglia (ventral striatum). Disruptions in dorsolateral prefrontal cortex and its connections to the dorsal caudate nucleus were considered to cause executive dysfunction and 'cognitive' apathy. The auto-activation subtype was attributed to bilateral lesions of the associative and limbic territories of the globus pallidus, akin to akinetic mutism¹¹³.

Apathy exists to varying degrees in healthy people, as part of a behavioural trait within the general population. Using the recently developed Apathy Motivation Index¹¹⁴, the healthy population showed three domains of apathy: (i) 'behavioural activation' reflecting self-generated goal-directed behaviour and closely resembling the 'cognitive' and auto-activation'

aspects of Levy & Dubois' conceptualization of apathy; (ii) 'emotional sensitivity' quantifying responses to positive and negative affection, consistent with the 'emotional-effective' subtype; and (iii) 'social motivation' pertaining to an individual's personal engagement in social interactions. Dissecting the components of motivation in the healthy population¹¹⁵⁻¹¹⁷ will provide critical insights into the underlying causes of apathy in disease populations.

1.2.4 Assessment of Apathy

There are several assessment tools to measure apathy, many of which attempt to quantify apathy in terms of the proposed subtypes described above¹¹⁸. The majority of available measures are questionnaires including the Apathy Evaluation Scale (AES; patient, informant and clinician versions¹⁰⁹), Apathy Inventory¹¹⁹, Lille Apathy Rating Scale¹²⁰, NPI apathy subscore¹²¹, AES-10¹²², the Dementia Apathy Interview and Rating for apathy in Alzheimer's Disease¹²³ and the Apathy Motivation Index¹¹⁴. Assessment tools largely recognise apathy as a multifaceted construct, with typical sub-scores quantifying the "emotional-affective", "cognitive" and "auto-activation" domains of apathy. Clarke et al., (2011) examined 15 apathy scales and subscales and reported that the AES and the apathy subscale of the Neuropsychiatric Inventory were the most psychometrically robust measures for assessing apathy across any disease population. However, special considerations apply to apathy in FTLN.

Assessment of apathy in dementia often requires multiple perspectives (eg. patient vs carer), due to cognitive impairment^{38,45,46,50,124,125} and loss of insight¹⁸. Development of analogous assessment tools for the patient, carer and clinician, such as the Apathy Evaluation Scale, have facilitated studies assessing consistency across raters, and revealed disagreement between assessors¹²⁶, likely reflecting loss of patient insight and emotion recognition¹⁸ or increased carer distress^{127,128}. In conditions characterised by cognitive impairment, behavioural measures of motivation may be more appropriate to quantify apathy objectively. Behavioural tasks minimize the influence of the rater and may more effectively capture the behavioural construct of apathy¹¹¹.

Furthermore, the identification of behavioural tasks to study apathy, linked to homologous tasks in preclinical models, can facilitate translational studies of novel treatments¹²⁹⁻¹³¹. However, behavioural measures are not without their own limitations. First, some tasks developed to assess apathy in the healthy population are too complex for dementia patients, relying heavily on sequential decisions, physical effort and executive demands. Other tasks may be confounded by motor impairments in FTLN syndromes^{115,117,132,133}. Second, the relationship between

objective measures, used in preclinical and research populations, and subjective questionnaires, often the choice of assessment for large clinical trials, is unknown. A better understanding of the translational ability of these tasks, and their relevance to the behaviours reported as most problematic by patients and/or carers is needed to clarify the most appropriate outcome measures for future treatment trials.

Tools designed for and validated in specific disease areas should only be used in the intended target population¹³⁴. A recent systematic review assessing the validity and reliability of available apathy scales in neurodegenerative conditions concluded that validation studies were of average methodological quality and yielded inconsistent psychometric properties¹³⁵, highlighting the need for more accurate assessment tools for the FTLD population.

1.2.5 Prevalence

Table 1: Prevalence of Apathy among Neurological Conditions

Disease	Prevalence
Frontotemporal Dementia	89-100%
Progressive Supranuclear Palsy	22-91%
Corticobasal Syndrome	40%
Mild Cognitive Impairment	14.7-39.8%
Parkinson's Disease	17.0-45.7%
Huntington's Disease	59-82%
Stroke	15.2-42%
Vascular Dementia	22.6-93.6%
Traumatic Brain Injury	20-70%
Amyotrophic Lateral Sclerosis	55.6%
HIV	12%
Cardiovascular Disease	29%

(after Ishii et al., 2009)

Apathy is a common neuropsychiatric feature of neurological disease, including FTLD syndromes (Table 1)^{102,136-138}. Apathy is included in the diagnostic criteria for bvFTD, accounting for the high prevalence¹³⁹. However, similar prevalence occurs in the language variants, particularly svPPA¹³⁶, suggesting overlapping neurobiological changes. Litvan et al.,

(1998) reported apathy prevalence of 40% in CBS, and over 90% in PSP⁶⁸. However, efforts to estimate the prevalence of apathy among disease groups have been hindered by the lack of a gold standard clinical diagnostic criteria for apathy. Limitations to the available assessment tools and their use in unsuitable populations, may also lead to false prevalence estimates.

1.2.6 Confounds in the Assessment of Apathy

Estimating the prevalence of apathy is further complicated by its frequent overlap with depression, akinesia, anhedonia and fatigue^{107,140–143}. Particular emphasis has been placed on dissociating apathy from depression^{82,107,141,142}. Starkstein et al., (1992) reported that apathetic PD patients had slow but accurate responses on executive function (Trials Making Test, Part B) whereas depressed PD patients had inaccurate but consistent response speed, suggesting apathy and depression were dissociable. Apathy can also be clearly dissociated from depression in disorders such as PSP, where there is a high incidence of apathy but low incidence of a low mood disorder¹⁴. Indeed, a lack of correlation between apathy and depression has been reported in a combined sample of AD, FTD, PD, HD and PSP¹⁴¹. Recent findings have further demonstrated dissociable neurobiology for apathy and depression; Hollocks et al., (2015) reported that apathy, but not depression, was related to damage to cortical-subcortical networks associated with emotion regulation, reward and goal-directed behaviour in small vessel disease. These effects may relate to distinct subtypes of apathy. Using the Apathy Motivation Index, Ang et al., (2017) reported four subtypes of apathy-motivation in the healthy population, each of which differed in their association with depression, anhedonia and fatigue.

The relationship between apathy and cognitive decline is unclear. Some suggest that apathy is associated with greater cognitive impairment^{68,84} while others fail to replicate this finding⁸⁹. Mega et al., 1996 reported increased apathy with increased dementia severity, reporting 42% affected in MCI, 80% in moderate and 92% in severe cognitive impairment. However, apathy is also frequently reported in pre- and early dementia states, where its presence is predictive of a more aggressive dementia, characterised by rapid cognitive and functional decline^{82–84,109}. Whether apathy precedes cognitive impairment warrants investigation and may be clarified through ongoing studies of presymptomatic genetically predisposed individuals.

A major limitation of many studies of apathy is the bias towards recruitment of less apathetic individuals. Intuitively, those who present to clinic and take part in research studies are likely to be less apathetic than those who do not. Previous studies have also reported differences in apathy prevalence depending on one's environment; Van Reekum et al., (2005) reported a

higher prevalence of apathy in AD nursing home residents, suggesting either that certain environments may prompt increased apathy or that individuals with increased apathy are more likely to reside in a home^{82–84,104,127}, highlighting the need to embed studies of apathy in epidemiological studies rather than tertiary care settings.

1.2.7 Neurobiology

Apathy is proposed to reflect disrupted connections between the pre-frontal cortex and basal ganglia structures involved in controlling self-generated, goal-directed behaviour^{111,113,144–147}. Apathy often occurs following direct focal lesions to the frontal lobe^{113,148,149}, and is a common feature of neurodegenerative diseases affecting the prefrontal cortex, including bvFTD^{150,151}. Apathy is also frequently reported following damage to the associative and limbic territories of the basal ganglia through focal lesions to the caudate nuclei, internal pallidum and thalamic nuclei^{152–154} or neurodegenerative diseases primarily affecting the basal ganglia such as PSP^{53,68}, HD⁹³ and PD^{53,88,91}.

The similarities in behavioural disturbances that occur as a consequence of either focal basal ganglia lesions/diseases or damage to the prefrontal cortex highlight their anatomical relationship and functional dependence. Physiological, anatomical and lesion studies in monkeys show these regions to be highly interconnected^{155–157}. Alexander et al., (1986, 1990) suggested that connections between the PFC and BG formed a series of heterogeneous frontal-subcortical loops^{112,158,159}, organized into several structurally and functionally distinct circuits. Each pathway was proposed to influence, through direct and indirect pathways, distinct areas of the frontal lobe and involve dissociable parts of the striatum, globus pallidus, substantia nigra and thalamus. Three to five parallel and contiguous pathways are generally considered, but the number is arbitrary, with a functional gradient rather than discrete circuits^{160,161}. The archetypal circuits include a motor circuit originating in the supplementary motor area, an oculomotor circuit originating in the frontal eye fields and three behaviourally relevant circuits originating in the prefrontal cortex¹¹². The three prefrontal circuits originate in the dorsolateral prefrontal cortex, lateral orbitofrontal cortex and anterior cingulate¹¹² and project to the dorsolateral caudate nucleus, ventromedial region of the caudate and ventral striatum/nucleus accumbens respectively (Figure 3). The cortico-striatal pathways do not work in isolation but converge along the circuit, forming interactive networks^{162,163}. Successful goal-directed behaviour requires efficient reward evaluation, learning and flexibility to develop appropriate plans of action and inhibit inappropriate choices¹⁶².

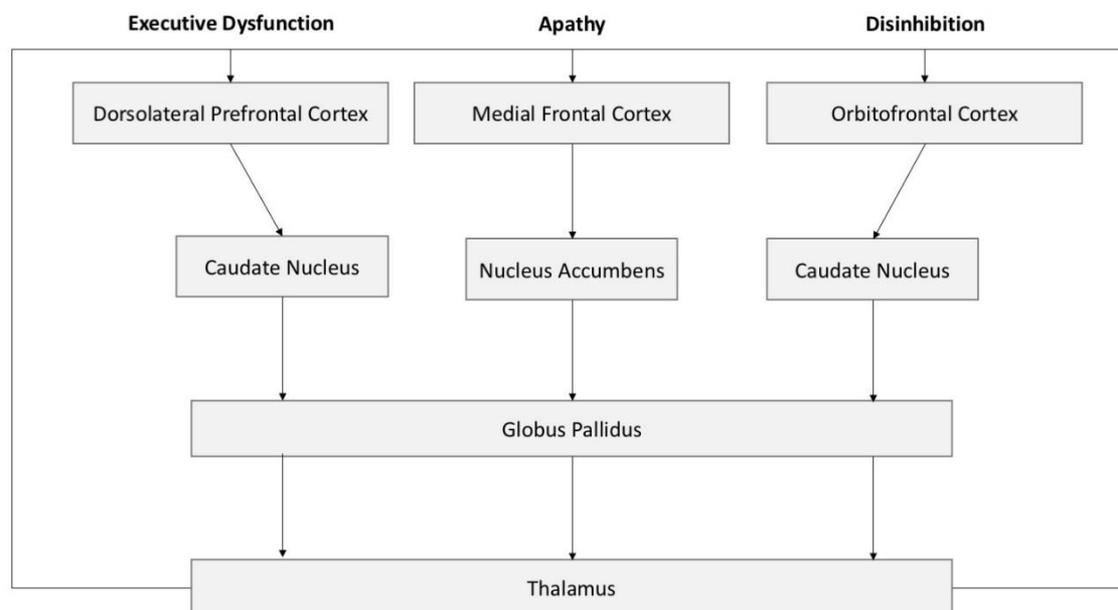


Figure 3: Parallel fronto-subcortical circuitry underlying executive dysfunction, apathy and disinhibition (after Bonelli and Cummings, 2007; Chudasama and Robbins, 2006)

Neuroimaging supports the fronto-subcortical circuitry underlying apathy. Structural magnetic resonance imaging studies of apathy have implicated the medial prefrontal cortex¹³⁸, dorsolateral prefrontal cortex^{100,102}, anterior cingulate¹⁰², temporal lobe and caudate¹⁰¹ and their connections. Indeed, substantial white matter abnormalities are increasingly recognised to accompany apathy^{97,164–167}. Hollocks et al., 2015 directly measured the white matter changes in apathetic individuals with small vessel disease and reported damage to cortical-subcortical networks associated with emotion regulation, reward and goal-directed behaviour. Reduced median fractional anisotropy (FA; a marker of white matter tract integrity) was significantly associated with apathy with strongest effects in limbic tracts including anterior cingulum, fornix and uncinate fasciculus. Hahn et al, (2013) reported a negative correlation between apathy scores and FA in the genu, body, and splenium of the corpus callosum, the left anterior and posterior cingulum, the right superior longitudinal fasciculus, and bilateral uncinate fasciculi in Alzheimer's Disease. Reduced FA in the uncinate fasciculus has also been linked to apathy in bvFTD¹⁶⁴.

Positron emission tomography (PET) studies using ¹⁸F-fluorodeoxyglucose have reported glucose hypometabolism in the dorsolateral and frontal medial cortex bilaterally in association with apathy¹⁶⁸, in addition to the ventral polar frontal cortex^{168,169}, while post mortem studies report a correlation between NPI apathy and neurofibrillary tangles in the anterior cingulate in AD¹⁷⁰.

1.2.8 Neuropharmacology

A number of neurotransmitters have been implicated in modulating the fronto-subcortical circuits discussed above, including dopamine (DA), serotonin (5-HT) and noradrenaline (NA)^{77,171}. Dysfunction of these neurotransmitter systems is recognised in FTLD syndromes, and may contribute to apathy.

Treatment of apathy has focused largely on dopaminergic intervention, which is widely implicated in the brain's reward and motivational circuitry (incentive salience) in both human and animal studies^{162,172–178}. In PD, the severity of apathy differs between 'on' and 'off' dopaminergic medication states^{116,179}, suggesting apathy is at least in part a dopamine-dependent syndrome. Apathy following lesions to the basal ganglia is also responsive to dopamine treatment, leading to increased reward sensitivity, reduced apathy, greater motivation and increased social interactions¹⁸⁰. There is evidence of nigrostriatal and mesocortical dopamine disruption in FTD and PSP, with low levels of dopamine in the striatum, substantia nigra and frontal lobes^{77,181,182}. Apathy may therefore arise from disruption of mesocortical pathways due to degeneration of dopaminergic neurons in ventral tegmental area^{51,183} and reduced D2 receptor binding in the frontal lobes in FTD¹⁸⁴ and PSP¹⁵.

Apathy often does not respond to dopamine treatment¹⁴⁰ suggesting additional neurotransmitter involvement. There is increased interest in the influence of noradrenaline, which is proposed to control the effects of the mesolimbic DA system on mediating reward¹⁸⁵. Dopamine and noradrenaline systems have mutual connections to the prefrontal cortex, which may account for their coexisting influence on motivation¹⁸⁶. Noradrenaline modulates cortical and subcortical structures (Figure 4), influencing arousal and behaviour¹⁸⁷. It also facilitates attentional shifting and behavioural flexibility by regulating exploratory behaviour and promoting focus onto behaviourally relevant stimuli¹⁸⁸. Dysfunction of NA projections from the locus coeruleus (LC) to the ventral striatum has been associated with increased apathy in PD patients¹⁸⁹. The LC is also affected in PSP, and there is accumulating evidence of an early noradrenergic deficit, with significant neuronal loss and tau pathology in the LC¹⁹⁰. Studies assessing the influence of noradrenaline for the treatment of apathy in FTLD syndromes are warranted.

1.2.9 Treatment

There are no formally approved drugs for apathy and a recent review concluded that there was limited and inconsistent evidence for the efficacy of any drug¹⁹¹, highlighting the urgent need

to identify novel treatment targets. Pharmacological efforts have targeted the dopaminergic, cholinergic, serotonergic and noradrenergic systems.

Dopaminergic therapies have controversial results. For example, levodopa therapy in PD had a positive influence on the subjective evaluation of motivation, but contrasting effects on reward sensitivity¹⁷⁹. Despite dopaminergic cell loss, PSP patients are generally unresponsive to dopamine therapy¹⁸², likely reflecting the multi-focal nature of structural brain changes, including loss of postsynaptic receptors¹⁵, which are relatively preserved in PD¹⁸³. Small case studies of dopamine agonists including selegiline¹⁹² and amantadine¹⁹³ have reported some benefit in treating apathy following traumatic brain injury and following stroke¹⁸⁰. Ropinirole, a dopamine agonist, reduces apathy following prefrontal cortex lesions¹⁹⁴ and following subthalamic nucleus stimulation in PD¹⁹⁵. Bromocriptine has shown some benefit in treating apathy following TBI¹⁹⁶ and akinetic mutism¹⁹⁷. There have been some case reports of improved apathy and amotivation with bupropion treatment¹⁹⁸, a non-selective catecholamine and indolamine reuptake inhibitor. Dopamine-resistant apathy is increasingly recognised¹⁹⁹, providing supportive evidence against DA being the sole underlying cause.

Serotonergic deficits in FTLN syndromes suggests serotonin reuptake inhibitors may be useful for treating apathy^{80,200}. However, evidence supporting their use in FTLN syndromes is limited²⁰¹ and they may even cause apathy by altering the balance between serotonin and dopamine⁸⁹.

A modest effect of acetylcholinesterase inhibitors on improving apathy has been reported in Alzheimer's Disease²⁰², PD²⁰³ and TBI²⁰⁴. However, a recent review suggested the small effect sizes made the clinical relevance of cholinesterase inhibitors doubtful, and concluded that there was insufficient evidence to determine their efficacy for the treatment of apathy in neurodegenerative diseases¹⁹¹.

There is increased interest in the potential use of noradrenergic therapies for apathy⁷⁸, although studies have so far been inconclusive. Atomoxetine is reported to improve cognitive functions in PD, including attention, decision-making and response control^{130,205}, but its effect on apathy specifically are unknown. Randomised controlled trials of methylphenidate (acting on NA and DA) for apathy in AD have reported contrasting results^{206,207}.

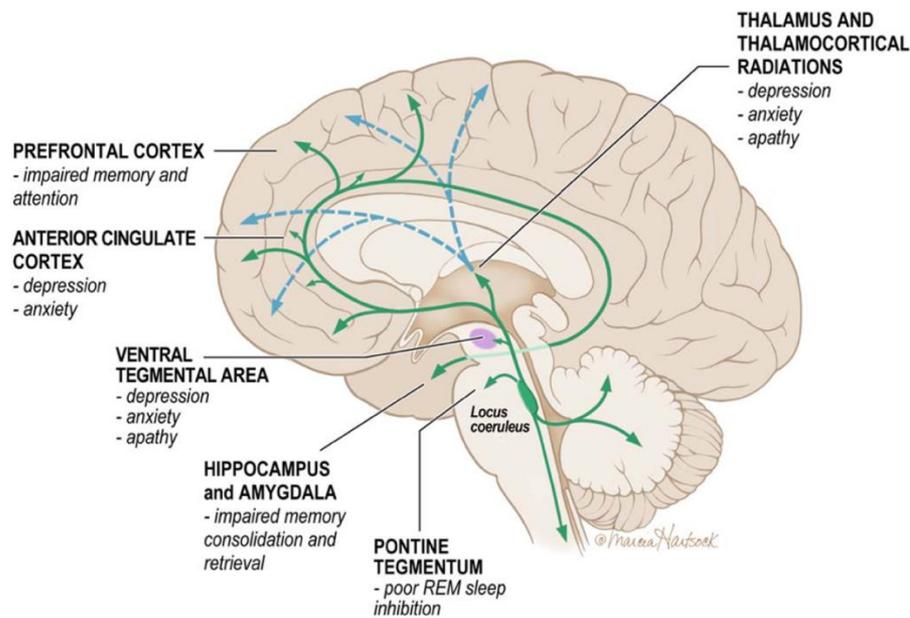


Figure 4: The Noradrenergic System (from Espay et al., 2014)

In order to clarify the impact of these neurotransmitter systems on apathy, randomised, placebo-controlled clinical trials in larger samples with apathy as the primary target and outcome variable are warranted. Studies would likely benefit from stratifying patients based on the presence and severity of apathy, rather than using categorical diagnostic criteria. Apathy symptoms and subtypes should be carefully defined. Advances in neuroimaging and biomarkers may help to clarify the relationship between apathy and treatment response, and explain why some patients may respond, while others do not¹²⁹.

1.2.10 Interim Summary

Numerous assessment tools for apathy exist, but the number of options limits comparisons between studies, without yet resolving the optimal choice of tool for any given condition. Focus has been on the development of subjective self-rated questionnaires, which may be inappropriate for FTLD syndromes. Objective measures that have been developed in the healthy population may not be readily applicable to patients. Nonetheless, apathy is highly prevalent in FTLD and is associated with negative outcomes. Improved knowledge of the neurobiological basis of apathy is needed, which I propose will benefit from dimensional and transdiagnostic approaches to assess brain-behaviour relationships and identify novel treatment targets.

1.3 Impulsivity

1.3.1 Definition

Impulsivity is a multifaceted construct, reflecting actions that are poorly conceived or without foresight, prematurely executed, unduly risky or inappropriate to the situation, often with undesirable consequences²⁰⁸. There remains no single definition that encapsulates the range of behaviours associated with impulsivity. Instead, research efforts have focused on fractionating impulsivity into its major components, each of which are considered to reflect aspects of poor cognitive control that differ in their biological basis. These include a failure to inhibit actions (“disinhibition”), inability to wait for higher but delayed rewards (“delay intolerance or impulsive choice”), sampling insufficient information before making a decision (“reflection impulsivity”) and poor responses to reward values (“reward responsiveness/risk taking”).

Impulsive actions are not always pathological, and many aspects of daily life require rapid decision making to achieve goals, and may consequently result in poor decisions with associated negative outcomes. Adolescents are also recognised as more impulsive than older adults²⁰⁹, which some suggest reflects immature development of the inferior frontal cortex in children²¹⁰, a brain region consistently implicated in studies of response inhibition²¹¹. Impulsivity can therefore be viewed as part of a normal personality trait. But, problematic and excessive impulsivity is common in psychiatric^{154,212–214} and neurological diseases^{144,215–217}.

1.3.2 Diagnostic Criteria

Impulsivity is recognised in the Diagnostic and Statistical Manual (DSM-IV) as a symptom under the criteria for impulse control disorders (ICDs) such as Pathological Gambling. However, there remains no specific criteria for impulsivity, despite its frequent occurrence in the absence of impulse control disorders²¹⁸. Some argue that the DSM-IV lacks biological footing and suggest an alternative approach to classifying impulsive “endophenotypes” by assessing behavioural and cognitive processes that reflect deficits in specific neural systems²¹⁹. This would avoid common limitations to the classical categorical approach to diagnosis of complex neurocognitive behavioural constructs including: patients with the same diagnosis having very different symptoms (for example, PSP is now recognised to have multiple different clinical presentations under newly proposed diagnostic criteria¹⁵), and patients with different diagnoses but presenting with the same symptoms (for example, FTLN disorders such as bvFTD and PSP, which can both present with profound apathy and impulsivity^{4,164,201,220}).

A dimensional approach would facilitate reporting of impulsivity constructs across diagnostic groups, and target individuals who are impulsive irrespective of other confounds. This in turn, may identify common neurobiological changes associated with impulsivity across disease groups. For example, despite differences between the clinical syndromes of Parkinson's disease and bvFTD, both disorders are characterised by impulsivity and reflect dysfunctional frontal cortico-striatal pathways²²¹.

1.3.3 Prevalence

Impulsivity is commonly reported across a number of psychiatric disorders, including attention deficit hyperactivity disorder (ADHD)^{213,214,222}, schizophrenia²¹², obsessive compulsive disorder (OCD)²²³, and neurological diseases, including PD^{86,130,216,224,225}, PSP^{15,50,201,205,226}, and FTD, where disinhibition is a diagnostic criterion for bvFTD^{5,102,137,138,144,164,217}. Impulsivity is also common in populations of substance abuse including heroin²²⁷, cocaine^{227,228}, and alcohol^{229,230}.

Similar to the apathy literature, studies commonly evaluate impulsivity within diagnostic groups, rather than across all individuals presenting with impulsivity. Transdiagnostic approaches assessing impulsivity constructs across disorders may provide more accurate estimates of its frequency within the population²¹⁹. Chamorro et al., (2012) assessed impulsivity in the general population by analysing data from 34,653 face-to-face surveys in adults aged 18+ between 2004 and 2005. They reported impulsivity in 17% of the sample, as determined by endorsement of the following question: "Most of the times throughout your life, regardless of the situation or whom you were with, have you often done things impulsively?"²³¹. Impulsivity was common among males and younger individuals and associated with drug dependence, dependent and schizotypal personality disorders, bipolar disorder and ADHD, in addition to negative outcomes such as dangerous behaviours such as reckless driving, shoplifting, domestic violence and suicide. The term "impulsivity" covers a broad range of components and this study did not clarify which component(s) of impulsivity were observed. Indeed, conflicting and unclear definitions of impulsivity complicate consistent reporting, and likely arise from distinct manifestations of impulsive behaviour across conditions²³². Furthermore, studies often select different assessment tools to measure impulsivity without clarifying or understanding which aspects of impulsivity they measure. For example, the Go/NoGo and stop signal tasks were initially used interchangeably to measure response inhibition, but they are now recognised to reflect distinct pharmacological changes²³³. As our understanding of the components of

impulsivity and their associated neurobiology improves, appropriate tasks to measure and manipulate them should be clarified.

1.3.4 Assessment of Impulsivity

A range of assessment tools are available to quantify impulsivity; including questionnaire based and behavioural based measures. Impulsivity can be assessed in humans using self-report measures including the Barratt Impulsiveness Scale (BIS)²³⁴ and Behavioural Activation System/Behavioural Inhibition system (BIS/BAS) scale²³⁵. The BIS and BIS/BAS include several subscores that recognise the multifactorial nature of impulsivity. For example, the BIS includes subscores of attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability and the BIS/BAS includes a Behavioural Inhibition score and Behavioural Activation subscores of drive, funseeking and reward responsiveness.

However, differences in terminology across questionnaires hinder direct comparisons. How do the BIS subscores relate to the BIS/BAS subscores? Furthermore, questionnaires developed within the healthy or psychiatric population may not be appropriate for neurological conditions, particularly where cognitive and functional decline is severe. For example, the BIS includes a question: “I often squirm at plays or lectures”, to which patients are often either unable to understand (‘squirm’) and require prompting, or are too functionally impaired to be able to attend such events and/or lack the ability to project themselves into an unfamiliar situation.

Carer-rated questionnaires assessing a range of behaviours relating to disinhibition are more commonly used in neurodegenerative populations. These include the Neuropsychiatric Inventory²³⁶, Cambridge Behavioural Inventory^{237,238} and Frontal Systems Behaviour Scale²³⁹, all of which contain subscales related to disinhibition. Although these questionnaires show good discrimination of frontotemporal dementia from other diseases, such as Alzheimer’s Disease^{150,237,238}, they are inherently subjective and vulnerable to caregiver distress^{104,240}. Carer ratings may therefore vary greatly, and objective measures of disinhibition may be more appropriate.

Fractionation of impulsivity into multiple components has enabled development of behavioural tasks and paradigms targeting distinct aspects of impulsivity and facilitating comparisons between animal to human studies. Impulsivity can be measured in terms of: response inhibition, including action restraint on the Go/NoGo task and action cancellation on the Stop Signal Task (SST)²³³; reflection impulsivity as measured by information sampling tasks²⁴¹, delay

intolerance or impulsive choice on delayed discounting paradigms^{242,243} and reward responsiveness/risk taking as measured by the Cued Reinforcement Reaction Time Task¹⁴⁷ or Gambling Tasks²⁴⁴.

Response inhibition can be measured in terms of action restraint on the Go/NoGo task and action cancellation on the stop signal task, which are widely recognised as dissociable components with distinct sub processes and psychopharmacology (see section 1.3.6). Action restraint reflects the inhibition of a motor response **before** the response has been initiated, while action cancellation describes the inhibition of a motor response **during** its execution. The tasks require subjects to repeatedly respond to visual stimuli by making a motor “Go” responses (often a button press, lever or touch screen). On a subset of trials, a ‘stop’ signal in the form of a visual or auditory signal informs the subject to inhibit the ‘Go’ response. The tasks are similar in format, and were previously used interchangeably to describe dysfunctional action inhibition²³³. However, the Go/NoGo contains a decision making component which is eliminated from the stop signal task. Another key difference is the positioning of the stop signal relative to the go response, which is close to the endpoint of the go response in the SST, allowing calculation of the stop signal reaction time – the major outcome measure (which cannot be calculated from the Go/NoGo task)²³³. Poor performance on tasks of response inhibition are reported across a number of psychiatric and neurological conditions, and in substance abuse populations^{131,205,214,220,228,245}.

Individuals select responses based on sensitivity to expected rewards, biased by discounting of future outcomes according to their availability and effort costs. Impulsive people tend to choose immediate gains, with discounting of future outcomes of their choices²²⁷. Delayed discounting paradigms measure this type of impulsive choice^{208,242,246}, often in the context of hypothetical monetary rewards on questionnaire-based tasks²⁴².

Incentive motivation can also be measured on tasks such as the Cued Reinforcement Reaction Time task¹⁴⁷. This task measures the ability of an individual to adapt performance in response to a change in reward probability (see Chapter 2 for details). Healthy controls decrease reaction times in response to increased probability of reward, known as reward-related speeding.

Gambling also reflects choice impulsivity. It is often assessed using gambling tasks such as the Cambridge Gambling Task²⁴⁴ and Iowa Gambling Task²⁴⁷. The Cambridge Gambling task requires subjects to determine the probability of a yellow token being placed under a red or green box, and place a bet according to their certainty. Bets are presented in ascending or

descending order, in order to dissociate motor impulsivity from risk-taking behaviour. Unlike other gambling tasks, the CGT examines decision making, without confounds of learning and working memory, by clearly presenting all information needed to make a decision throughout the task. Patients with frontal lobe lesions place high bets in both ascending and descending conditions, reflecting risky behaviours²⁴⁸. Compared to healthy controls, bvFTD patients fail to inhibit prepotent responses on the IOWA, favoring short-term gains which lead to long term losses². Despite the inclusion of disinhibition in the criteria for PSP and bvFTD, pathological gambling is uncommon in FTLT syndromes²⁴⁹, in contrast to PD^{225,250}.

Reflection impulsivity, often measured by the Information Sampling Task (see Chapter 2 for details), is less widely studied and reflects the tendency to gather and evaluate information before making a decision²⁴¹. Inaccurate or inadequate reflection will consequently lead to ill-informed or risky decisions²³². ADHD and AD patients gather less information and make riskier and less accurate decisions than healthy controls²⁵¹. Impulsive individuals therefore obtain insufficient information before reaching a decision, leading to risky behaviours and negative consequences.

Critically, the relationship between questionnaire based and behavioural based measures of impulsivity are unclear. Whether they relate to a unitary construct of impulsivity is controversial²¹⁹. Indeed, questionnaires may not reflect behavioural measurements in either humans or experimental animals¹⁹⁶, with direct implications for translational studies. For example, Clark et al., (2006) suggested their definition of reflection impulsivity corresponded somewhat to the construct of non-planning impulsivity on the BIS²³⁴, but found no correlation between performance on the information sampling task and these ratings²⁴¹. Although correlations between different questionnaires are reported²⁵², questionnaires and behavioural tasks are poorly correlated and rarely exceed $r=0.4$, with significant correlations only observed in large studies¹⁹⁶. When measuring impulsivity in FTLT therefore, one should perhaps not focus on which type of FTLT, but which type of impulsivity, and choose outcome measures accordingly.

1.3.5 Neurobiology

There is considerable evidence to suggest that different types of impulsivity can be dissociated in terms of their underlying neural substrates, providing support for a multifaceted rather than unitary construct. For example, lesions of the subthalamic nucleus cause impairments in action cancellation (SSRT), but do not affect premature responding/impulsive choice on delayed

discounting tasks, which are instead sensitive to lesions of the nucleus accumbens core region²³³. Dalley et al, (2011) proposed distinct neuronal circuitry underlying “waiting” and “stopping” impulsivity, implicating both cortical and subcortical regions. “Waiting” impulsivity reflects “limbic” fronto-striatal circuits including the ventromedial prefrontal cortex and ventral striatal regions, and regulates reward anticipation and discounting^{253,254}, while “stopping” impulsivity is associated with the inferior frontal cortex and dorsal striatum, and mediates response inhibition. Within this “stopping” network, the right inferior frontal gyrus (RIFG) in particular is considered critical for inhibitory control, specifically action cancellation, through top-down response control processes^{208,211,255}, while the basal ganglia are implicated in both action cancellation and action inhibition²³³.

Neuroimaging and lesion studies in FTD predominantly associate disinhibition with the orbitofrontal and ventromedial prefrontal cortex, temporal pole regions and their white matter connections^{102,138,144,148}. Reports of alternative neural correlates¹⁰⁰ likely reflect use of different outcome measures. In PSP, impulsivity may arise from striatal or frontal lobe dysfunction; loss of subthalamic inhibition may disinhibit thalamocortical projections and cause a bias towards action rather than restraint^{215,220}, or alternatively cortical neuropathology/degeneration in prefrontal and premotor circuits may impair correct responding by preventing accumulation of evidence^{166,183,220,256,257}. The importance of cortico-striatal circuits in disinhibited behaviours is apparent, with studies implicating both frontal (OFC and IFC) and striatal (nucleus accumbens) regions^{111,221}.

1.3.6 Neuropharmacology

The neuropharmacology of impulsive behaviours are often studied in terms of impulsive action on the Go/NoGo and SSRT tasks, impulsive choice/reward processing on gambling tasks and delay intolerance on temporal discounting tasks. Psychopharmacological dissociations in terms of dopaminergic, serotonergic and noradrenergic influence between types of impulsivity and associated tasks are reported^{233,258}. For example, serotonin influences action restraint (Go/NoGo) while having no effect on action cancellation (SST), which is sensitive to noradrenergic modulation²⁵⁹. Impulsive behaviours common to FTLD syndromes likely arise from deficits in multiple processes reflecting dysfunctional neurotransmitter systems.

Dopamine is critical to reward processing and cognitive performance, and dopamine dysregulation has been linked to impulsivity. Dopamine replacement therapy may cause impulsive behaviours (increased risk-taking²⁶⁰), delay aversion²⁶¹ and impulsive control

disorders^{225,250,262}, depending on basal level of dopamine function in underlying cortico-striatal circuitry²⁶¹. The emergence of impulse control disorders (ICDs) in PD patients on medication are proposed to reflect “overdosing” of the ventral striatum, which remains relatively intact in early PD^{225,263,264}. Whether dysregulation of dopamine in FTL^{51,77,181–183} influences impulsivity is unclear.

Serotonin is widely implicated in action restraint response inhibition^{233,258,265} and may mediate the motivational properties of reward¹⁴⁷ through interactions with the mesolimbic DA system^{178,196,266}. Serotonergic deficits are reported in bvFTD and PSP^{51,77,168,181–183} and there is accumulating evidence to suggest these deficits contribute to characteristic behavioural disturbances, including impulsivity²⁶⁷. In bvFTD, increased serotonergic neurotransmission following citalopram (a serotonin reuptake inhibitor) improved action restraint on the Go/NoGo task and caused partial restoration of corticostriatal circuitry¹³¹. These findings were consistent with a study in PD, which also reported increased prefrontal activation²⁶⁸. Serotonin depletion is also implicated in incentive motivation and decision-making, although reported effects are inconsistent^{147,233,269}. While the influence of serotonin on response inhibition is clear, its impact on the remaining components of impulsivity requires clarification¹⁹⁶.

Noradrenaline has been implicated in multiple types of impulsivity, including action cancellation, reflection impulsivity, risk taking and reward processes^{78,130,270}. Noradrenergic influences underlying impulsivity have largely been studied in the context of PD, although there is increased evidence of an early noradrenergic deficit in PSP. Atomoxetine, a selective noradrenaline reuptake inhibitor, improves response inhibition in PD^{130,205,271}, reducing SSRT²⁰⁵, increasing activation of the right inferior frontal gyrus and improving connectivity between the IFG and pre-supplementary motor cortex^{205,245,271}, consistent with reports in healthy volunteers²⁷² and ADHD²¹⁴. These findings in humans are broadly consistent with animal studies of atomoxetine, which report a dose-dependent speeding of SSRT and decrease in premature responding on the 5-choice serial reaction time task^{222,233}. Together, these findings suggest loss of NA neurons and their projections to the cortex²⁷³ may contribute to impulsivity²⁷⁴.

1.3.7 Prognosis and Treatment

Impulsivity is associated with negative outcomes and impulsive behaviours such as excessive gambling, hyper-sexuality, inappropriate social conduct and binge eating are difficult to manage and cause significant carer distress^{102,104}. An impulsive personality trait may also be a

risk factor for substance abuse and other addictions. Individuals who strongly discount future outcomes, a component of impulsivity, generally lack self-control and engage in addictive disorders such as pathological gambling, cigarette smoking and substance abuse²⁵⁴.

There are no treatments for impulsivity that are specifically licensed for FTLD syndromes. The multifaceted nature of impulsivity, reflecting involvement of multiple cortico-striatal pathways and neurotransmitter systems, makes it unlikely that a single treatment will benefit impulsivity as a whole. Instead, treatments targeting the dopaminergic, serotonergic and noradrenergic systems may differentially benefit distinct aspects of impulsivity as discussed above.

Drugs targeting the noradrenergic, dopaminergic and serotonergic systems, such as atomoxetine, citalopram and methylphenidate have been approved for the treatment of psychiatric illnesses including depression, ADHD, schizophrenia and obsessive compulsive disorder. Recent studies have highlighted the potential of these drugs to treat impulsivity in FTLD syndromes^{115,130,131,205,245,268,271,275}, and warrant further investigation. Effective measurement of impulsivity components and clarification of their associated neurobiology will facilitate personalised treatment targeting the underlying neural systems involved.

1.3.8 Interim Summary

Fractionation of impulsivity into multiple components has enabled development of numerous assessment tools to target distinct aspects of this multifaceted behavioural construct. The neural correlates of response inhibition are well established, but the systems regulating the remaining components of impulsivity are less clear and warrant further investigation to inform future treatment studies.

1.4 The Relationship between Apathy and Impulsivity in FTLD Syndromes

An important aim for this thesis is to examine whether apathy and impulsivity coexist in FTLD syndromes, although this may at first glance seem paradoxical^{2,86,100,104,201,224}. They are both included in the diagnostic criteria for behavioural variant FTD⁴, and in newly proposed criteria for PSP¹⁵, but also occur frequently across the full spectrum of disorders associated with frontotemporal lobar degeneration^{19,50,276}. Apathy and impulsivity may be concurrent in an individual patient^{75,150}, contradicting the notion that they represent opposite ends of a dopamine-dependent behavioural spectrum⁸⁶. Indeed, the co-existence of apathy and impulsivity suggests either that there is a coinciding neurobiological basis for these behavioural

changes²²⁰, or that the widespread pathology in FTLD syndromes leads to simultaneous deficits in anatomically and pharmacologically different networks.

Both apathy and impulsivity are recognised as multifaceted constructs (described above and by ^{111,208,216}), with multiple contributory factors. These factors may be expressed in terms of common brain network pathology^{86,100,101,216,268,275,277}, overlapping cognitive processes of motivation, reward and decision making^{111,220,224,278}, and pharmacology^{147,208,233}, as discussed in previous sections.

The presence of both apathy and impulsivity in FTLD syndromes creates a major challenge for the development of new therapeutic strategies. There are common limitations to previous studies of apathy and impulsivity, including:

- i) The assessment of either apathy or impulsivity alone, despite their frequent co-existence.
- ii) The assessment of behavioural changes within single diagnostic groups.
- iii) The use of limited sets of tasks or questions which relate to just one aspect of these multifactorial constructs.

In this thesis, I adopt an alternative dimensional approach to assess apathy and impulsivity transdiagnostically, across the behavioural and language variants of frontotemporal dementia, progressive supranuclear palsy and the corticobasal syndrome. Similar approaches have been proposed by the National Institute of Mental Health in their Research Domain Criteria Framework^{279,280}, and by Robbins et al., (2012). Such methods accommodate the commonalities of apathy and impulsivity across disorders and reveal their cognitive and anatomical bases. The ability to measure the components of apathy and impulsivity and their associated neural correlates across diagnostic groups would provide better targets for pharmacological manipulations, and facilitate new treatment strategies and strengthen translational models.

1.5 A Transdiagnostic Approach to Apathy and Impulsivity in FTLD Syndromes.

1.5.1 Thesis Overview

To elucidate the physiological, pharmacological and genetic causes of apathy and impulsivity, and to design appropriately stratified and powered clinical trials of candidate treatments, one needs four critical items. First, a clear definition of the cognitive and behavioural components of apathy and impulsivity, from which to develop robust and targeted assessment tools. Second,

one needs knowledge of how these different components are represented transdiagnostically, across disorders associated with frontotemporal lobar degeneration. Third, one requires evidence for the neural basis of the components, both to generate surrogate markers in experimental medicines studies and to validate preclinical models of behavioural disorders. And finally, one requires knowledge of the prognostic implications associated with these components.

This thesis employs data from the Picks Disease and Progressive Supranuclear Palsy Prevalence and INcidence (PiPPIN) study, an epidemiological study of FTLN syndromes in Cambridgeshire and Norfolk, in an attempt to address these outstanding issues. The PiPPIN study combined detailed neuropsychiatric and behavioural assessment of apathy and impulsivity from multiple perspectives (patient, carer, clinician, objective tests), with MRI imaging, genetic analysis and pathological post mortem diagnostic confirmatory analysis. Taken together, this assessment battery aimed to capture the major domains of apathy and its principal confounds, including motivation, anhedonia, depression/mood and akinesia and the major domains of impulsivity, including reward sensitivity, response inhibition and information sampling (see Chapter 2 for full details).

1.5.2 Thesis Aims

The aims of my thesis are as follows:

To:

- 1) Determine the frequency and characteristics of apathy and impulsivity in FTLN syndromes (Chapter 3), as measured by different tools.
- 2) Examine the neurocognitive components of apathy and impulsivity in FTLN syndromes by employing data reduction techniques, specifically principal component analysis (Chapter 3).
- 3) Determine the neural correlates of the components of apathy and impulsivity, using voxel based morphometry for volumetric analysis of grey and white matter (Chapter 4) and diffusion tensor imaging tract based spatial statistics (Chapter 5) for analysis of white matter tract integrity.
- 4) Investigate the impact of the identified apathy and impulsivity components on patient prognosis and survival (Chapter 6), drawing on previous studies which link apathy to negative outcomes. In the event of a strong link between apathy/impulsivity and disease progression, it remains elusive whether effective symptomatic treatment could prove disease-modifying.

1.5.3 Thesis Hypotheses

The hypotheses of my thesis, developed in the experimental chapters 3-6, are as follows:

- 1) Apathy and impulsivity in FTLD syndromes are multifactorial constructs, but with common and overlapping features across diagnostic groups.
- 2) Subjective and objective measures of apathy and impulsivity relate to the same components, consistent with previous translational studies.
- 3) Distinct frontostriatal, frontotemporal and brainstem circuits support the components of apathy and impulsivity.
- 4) Components of apathy have significant implications for prognosis, warranting further investigation into effective symptomatic treatments which may also prove disease-modifying.

Chapter 2 | The Pick's disease and Progressive supranuclear palsy Prevalence and Incidence (PiPPIN) Study Methods.

The Pick's disease and Progressive supranuclear palsy: Prevalence and Incidence study was an epidemiological study of FTLD syndromes in Cambridgeshire and Norfolk, aiming to a) provide more accurate estimates of prevalence and incidence of the FTLD spectrum disorders based on newly proposed diagnostic criteria and b) enable deep phenotyping of FTLD disorders in terms of neuropsychiatric, behavioural, imaging and genetic analysis.

Accurate epidemiological estimates of these conditions will have direct implications for treatment studies (both disease modifying and symptomatic), healthcare planning and policy, research design and carer and patient support. The extensive neuropsychiatric and behavioural assessment battery, MRI imaging and serum collection for genetic analysis included in the PiPPIN study protocol provides a long-term resource for studies evaluating the impact of behavioural changes on disease. The value of this information is increased if the cohort studied is representative of the full spectrum of disorders. Improved knowledge of disease characteristics and their underlying neurobiology may also provide a means to validate preclinical models and inform future clinical studies.

In the introduction, I highlighted the importance of effective measurement and improved symptomatic treatment of apathy and impulsivity in FTLD syndromes. Achieving these goals requires a detailed understanding of the components and neural correlates of apathy and impulsivity across the FTLD spectrum.

The PiPPIN study provided the ideal arena for such an analysis, employing a broad range of assessment tools to capture the major domains of apathy and its principal confounds, including motivation, anhedonia, depression/mood and akinesia and the major domains of impulsivity, including reward sensitivity, response inhibition and information sampling. Importantly, the study gained insight from various perspectives through carer, patient and clinician ratings, objective tasks and neuroimaging. Patient and carer perspectives were measured by questionnaires of the type commonly used in clinical trials, enabling assessment of potential discrepancies between carer and patient perspectives. Objective neuropsychological and

behavioural tests were employed to bridge between preclinical and clinical studies, supporting translational models.

In the following chapter I describe the methods of the PiPPIN study in detail, focusing on the cohort (patient demographics), assessment tools and acquisition methods. I also outline the analytical methods employed to examine the data, the results of which are discussed throughout chapters 3-6, including basic statistical techniques (chapter 3), multivariate principal component analysis (chapter 3), voxel-based morphometry (chapter 4), diffusion tensor imaging (chapter 5), and logistical regression (chapter 6). Detailed imaging-specific analysis methods are provided in the relevant chapters.

2.1 The PiPPIN Study Objectives

The PiPPIN study was designed to address the following major objectives:

1. To apply revised and validated diagnostic criteria for each disorder to estimate the lifetime risk, prevalence, incidence and mortality of the principal syndromes of the FTLD spectrum. The epidemiology of PiPPIN is addressed elsewhere¹⁹.
2. To acquire detailed neuropsychological and behavioural tests, combining patient, carer and clinician based assessments with objective behavioural and neuropsychological measures, in order to determine the multifactorial basis of behavioural change in FTLD associated syndromes, focussing on apathy and impulsivity.
3. To enable long term evaluation of clinicopathological correlations and genetic factors associated with the FTLD spectrum diseases.

My work addresses aim 2 detailed above, with the following additional objectives:

1. To determine the components of apathy and impulsivity transdiagnostically, across the FTLD spectrum, using data-reduction techniques, specifically principal component analysis.
2. To examine the neural correlates of apathy and impulsivity components across FTLD syndromes, in terms of volumetric grey and white matter change (voxel based morphometry and diffusion tensor imaging).
3. To evaluate the impact of apathy and impulsivity on prognosis and survival in the PiPPIN cohort.

2.2 Patient Demographics

Diagnosis was based on current diagnostic criteria for behavioural variant frontotemporal dementia [bvFTD]⁴, Primary Progressive Aphasia syndromes [PPA]⁶, Progressive Supranuclear Palsy [PSP] (Litvan et al., 1996, with variation in falls extending from 1 to 3 years, as in Bensimon et al., 2009) and the Corticobasal Syndrome [CBS]⁵, following clinical interview, physical examination, relevant exclusionary tests and brain imaging. The study was undertaken prior to the revised MDS criteria for PSP¹⁵. The primary progressive aphasias were subtyped⁶ to the non-fluent agrammatic variant (nvPPA), the semantic variant (svPPA), and a third group that included logopenic variant (lvPPA) and mixed aphasia (primary progressive aphasia as the prominent syndrome but not fitting criteria for one of the 3 defined subtypes, termed PPA). Diagnostic criteria were applied by a trained neurologist and included clinical interview, neurological and physical examination, cognitive and functional tests and brain imaging. Where there was diagnostic ambiguity a second neurologist reviewed the case and a consensus was reached. For cases that were unable or unwilling to be assessed in person, including because of death, diagnosis was based on available clinical records.

Two-hundred and four patients were identified, 167 of whom were assessed in person by a member of the study team. Eighteen either died before neuropsychological assessment or were unable to undertake testing over and above diagnostic confirmation, leaving 149 patient datasets for analysis. Fifty healthy age-/sex-matched controls were recruited from the Medical Research Council's Cognition and Brain Sciences Unit volunteer panel, with no significant neurological or psychiatric history.

2.3 Ethical Approval & Sponsorship

The PiPPIN study was approved by the Cambridge 2 Research Ethics Committee. The study was jointly sponsored by the University of Cambridge and Cambridge University Hospitals Foundation NHS Trust.

2.4 Locations

The investigators were based in the Herchel-Smith Building at the University of Cambridge where regional National Health Service clinics for PSP, FTD and CBD are held. MRI scans were performed at the Wolfson Brain Imaging Centre (WBIC) at the University of Cambridge on the Cambridge Biomedical Campus. Neuropsychological and behavioural assessments were conducted at the Herchel Smith Building or in participants own homes, or in the case of healthy volunteers the Medical Research Council's Cognition and Brain Sciences Unit.

2.5 Recruitment

Patients were recruited from the counties of Cambridgeshire and Norfolk (combined population 1.69 million (2013 UK Office for National Statistics mid-year estimate)). The study aimed to identify all cases with a reference diagnosis between January 1st 2013 and December 31st 2014. Recruitment relied on multi-source identification from primary, secondary and tertiary care, self-referral and relevant patient charities. Patients were recruited from regional specialist clinics for FTD; for disorders of movement, memory and cognition; and early dementia. Additional contact through person, letter and email was made before and during the study, to maintain raised awareness. Direct referrals from neurological and psychiatric services were also accepted, with help from the National Institute for Health Research Clinical Research Network Dementias and Neurodegeneration Speciality (DeNDRoN) and the West Anglia Clinical Research Network. Patients were also recruited through self- or carer-referral, local newspaper advertisements for the PiPPIN study, and letters of invitation to members of the local and national charities (including the UK FTD support group and the PSP Association). Patients were not required to travel to the study center, as home or nursing home assessment by the study team was available.

A personal consultee process was employed to assess the potential participation of patients who lacked mental capacity, in accordance with UK law. Firstly, their willingness to consider research participation at a level compatible with their cognitive abilities was evaluated. Secondly, a nominated individual was consulted, which included the spouse, holder of Lasting Power of Attorney, IMCA, an appropriate next of kin or chosen personal consultee as outlined in the Mental Capacity Act (2005).

2.6 Protocol Overview

The study was comprised of three tiers (see Figure 5). Tier 1 included participants with a FTLD diagnosis but who were unwilling to participate in further assessments, to enable upper estimates of prevalence and incidence in Cambridgeshire and Norfolk to be calculated. Tier 2 participants were invited to undergo multiple neuropsychiatric and behavioural assessments, focusing on apathy, impulsivity and related behavioural changes. Tier 3 included deep phenotyping of patients in terms of imaging, genetics and neuropathology. Reasons for participant drop out included; death, severe cognitive impairment, and contraindication to MRI scan (see inclusion and exclusion criteria below). Other samples within PiPPIN that lie outside of this thesis include DNA (EDTA), RNA (PAXgene), serum and plasma markers. These are

not analysed further as part of my thesis. Genetic screening results (17 known genetic causes of FTLD and non-FTLD) in forty-six patients are presented by Gilchrist et al., (2016).

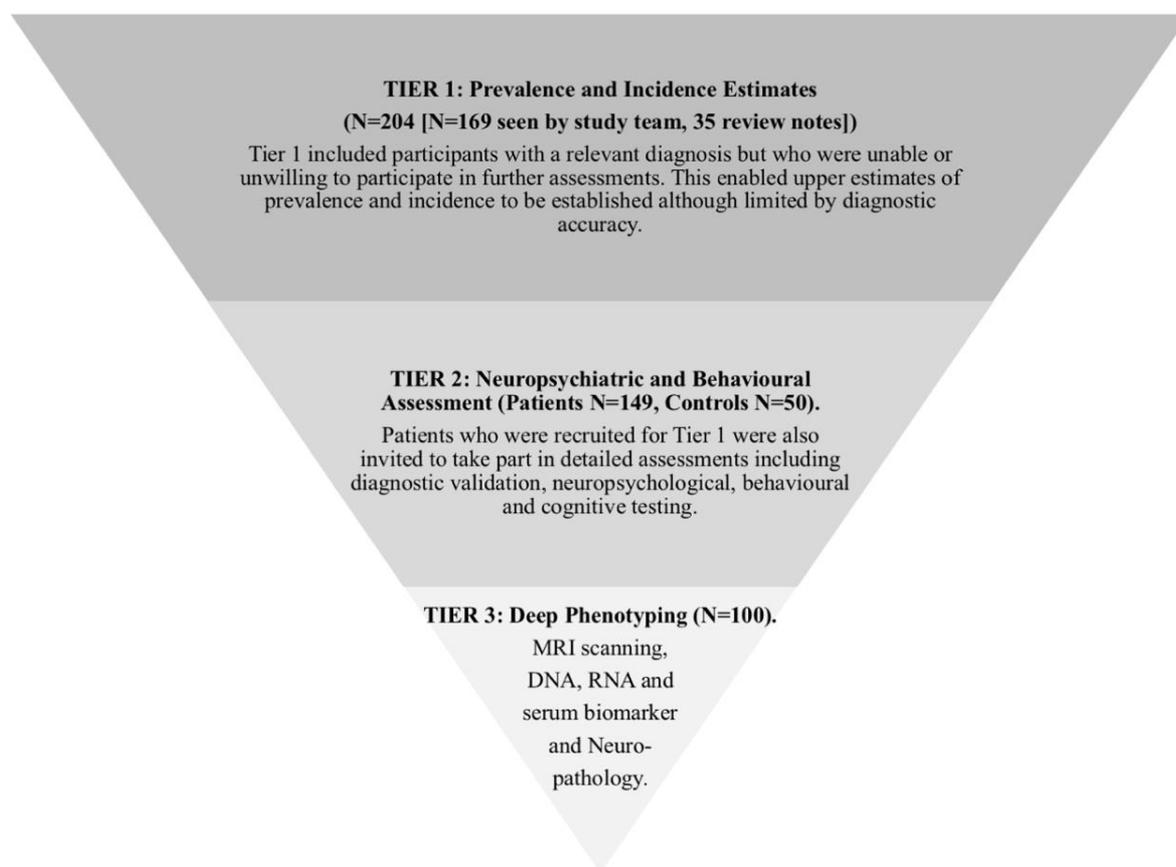


Figure 5: Overview of the Three PiPPIN Study Tiers.

2.7 Inclusion and Exclusion criteria

Inclusion and exclusion criteria differed depending on the Tier and are detailed in Table 2.

Table 2: Inclusion and Exclusion Criteria for the PiPPIN Study

TIER	INCLUSION	EXCLUSION
1	Subjects greater than 18 years old with relevant diagnoses.	NONE
2	Subjects included in tier one who are willing to participate in tier two and have either provided informed consent (if they have mental capacity to do so) or where participation is agreed after consultation with a nominated Consultee.	End stage disease. Visual, hearing and language impairment would lead to a pragmatic reduction in the protocol, but participation would still be possible.
3	Subjects included in tier two who have capacity to consent to individual elements of tier three.	Contraindication to MRI.

2.8 Power and Group Size Calculations

Based on previous epidemiological studies⁵⁶ we expected that half of the regional cases of FTD, PSP and CBD were already known to our specialist clinics at the CUHT. We anticipated around 30-40 new cases reported from the region each year. We proposed to estimate age-adjusted prevalence, separately for tier one and tier two, using census data and with statistical support from the Cambridge Institute of Public Health. Tier one was most inclusive, but lacked standardised diagnostics. Tier two provided higher diagnostic accuracy. The prevalence data was used to estimate incidence with well-known epidemiological caveats for a recruitment phase. Tier one (c. 250) and tier two (c. 150) are powered (>0.8) to detect small to medium ($d = 0.2 - 0.3$) group effects and medium transdiagnostic correlations, and to identify >4 neurobiologically distinct components of apathy and impulsivity (GPower software), but the sample sizes were driven by epidemiological recruitment rather than target sample sizes.

2.9 Neuropsychological and Behavioural Assessment Battery

Patients underwent a clinical assessment battery (Table 3), including a semi-structured interview for clinical history and demographic data, questionnaire based assessments of behavioural changes, focussing primarily on apathy, impulsivity and related motivational changes, and various behavioural tasks. The following principles were applied in selecting the PiPPIN test battery: to employ a variety of tests to examine the multifaceted constructs of apathy and impulsivity, to include clinically standard tests as well as experimental paradigms; to include questionnaires to be completed by patients and carers to provide complementary perspectives; to include both subjective symptom-based questionnaires and objective neuropsychological tests for both patients and controls; to measure potential confounds of apathy and impulsivity including symptoms of depression and akinesia; to prioritize untimed tests in view of likely akinesia in many participants; and to use only tasks that have been published and used with independent cohorts.

Patient self-assessment of apathy (Apathy Evaluation Scale [AES]¹⁰⁹), impulsivity (Barratt Impulsiveness Scale [BIS]²³⁴, Behavioural Inhibition System/Behavioural Activation System Scale [BIS/BAS]²³⁵), motivation (Motivation and Energy Inventory [MEI]²⁸¹), depression (Beck Depression Inventory [BDI]²⁸²), pleasure (Snaith Hamilton Pleasure Scale [SHAPS]²⁸³), sleep (Parkinsons Disease Sleep Scale [PDSS]²⁸⁴) and quality of life (Short form health survey – 36 [SF-36]²⁸⁵) were obtained. Patients also completed visual analogue scales (see Table 3 for details) and the Kirby delayed discounting paradigm²⁴².

Carer based assessments of behavioural change included the carer-rated apathy evaluation scale (AES-I¹⁰⁹), Neuropsychiatric Inventory (NPI¹²¹), Cambridge Behavioural Inventory-Revised (CBI-R²³⁷). Clinician assessments included the clinician Apathy Evaluation Scale (AES-C¹⁰⁹), and structured interview.

Cognitive and functional impairment were measured using standard cognitive (Addenbrookes Cognitive Examination Revised [ACE-R]¹²⁵, Mini Mental State Examination [MMSE], Frontal Assessment Battery [FAB]²⁸⁶) and functional rating scales (Frontotemporal Dementia Rating Scale [FRS]²⁸⁷ and Progressive Supranuclear Palsy Rating Scale [PSP-RS]¹⁴).

Computer-based behavioural tests included measures of response inhibition ('NoGo' and 'Stop-signal'(Cambridge Cognition Ltd.)), reflection impulsivity (Information Sampling Task [IST]²⁴¹), and reward responsiveness (Cued Reinforcement Reaction Time Task [CRRT]¹⁴⁷, modified Cambridge Gambling task [CGT] (Cambridge Cognition Ltd.)). In view of the motor impairments that are characteristic of some FTLD spectrum disorders, oculomotor tests of impulsivity (using a standard lightweight head mounted saccadometer) were also employed in the form of 'NoGo' saccadometry²²⁰ to enable direct comparisons with the motor Go/NoGo task.

2.9.1 Description of Questionnaires

The apathy evaluation scale (AES) is a commonly used measure for apathy assessment across several disease populations, although some of the questions are not well suited to people affected by severe physical disability, as they refer to motivation for activities that are impossible. All versions demonstrate good internal consistency, with the AES-I and AES-C also demonstrating good test-retest reliability and the AES-C reporting good inter-rater reliability^{118,134}. Consistent with the multidimensional nature of apathy, the scale assesses emotional, behavioural and cognitive constructs, with higher total scores indicating more severe symptom presentation¹⁰⁹. Disadvantages of the AES include limited convergent validity, often failing to correlate with other measures of apathy such as the NPI apathy subscore¹¹⁸. The PiPPIN study included all three versions of the Apathy Evaluation Scale, in order to assess the degree of agreement between patient (AES-P), clinician (AES-C) and carer (AES-I) ratings. Discrepancies may arise from patient loss of insight, a core feature of FTD, CBS and PSP¹⁸ or carer distress^{127,128}.

The Cambridge Behavioural Inventory-Revised (CBI-R)²³⁷ assesses behavioural change, specifically memory/orientation, everyday skills, sleep, self care, abnormal behaviours, mood, beliefs, eating habits, stereotypical behaviours and motivation. The CBI-R, an abbreviated version of the original CBI²³⁸, was developed to evaluate behavioural changes associated with various forms of dementia. Although reliability studies are lacking, the scale has demonstrated high internal consistency and is reported to effectively differentiate between disease states, including Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), svPPA and bvFTD²³⁷.

The Neuropsychiatric Inventory^{121,236} was developed to assess psychopathology in dementia patients. The scale evaluates twelve aspects of neuropsychiatric disturbance. The apathy subscale of the NPI was reported to be among the most psychometrically robust measures for assessing apathy across any disease population¹³⁴.

The self rated BIS²³⁴ and BIS/BAS²³⁵ subjectively quantified impulsivity. The BIS is a widely cited scale for the assessment of impulsivity²³⁴. Reflecting the multifactorial structure of impulsivity, it examines attention, motor and non-planning domains, with higher scores indicating a more impulsive profile.

Similarly, the BIS/BAS scale is multifaceted and follows Gray's biopsychological theory of personality that claims two general motivational systems underlie goal-directed behaviour, including the behavioural activation system regulating appetitive behaviours, and the behavioural avoidance system controlling aversive motives²³⁵. The questionnaire is internally consistent, being initially based on a principal component analysis and having gone through several cycles of item generation and testing, though in healthy college students. The motivational properties of the BIS/BAS suggest it may also be a useful measure of apathy.

The MEI²⁸¹ and SHAPS²⁸³ measure motivation and anhedonia respectively, which may relate to or influence apathetic and impulsive states and were therefore included in the analysis. Motivation may underlie clinical presentations of apathetic or impulsive behaviours, with apathy reflecting low motivation and impulsivity high motivation, although the relationship has not been fully clarified.

Table 3: Summary of PiPPIN Assessment Battery

Measurement	Test Type	Description	Rater	Outcome Measures
Addenbrooke's Cognitive Examination Revised (ACE-R)	CT	Standard assessment tool used to indicate severity of cognitive impairment. Normative values based on 63 controls aged 52-75 and 142 dementia patients aged 46-86. Cut-off <88 gives 94% sensitivity and 89% specificity for dementia Cut-off <82 gives 84% sensitivity and 100% specificity for dementia	C	ACE-R /100 Attention & Orientation /18 Memory /26 Fluency /14 Language /26 Visuospatial /16
Mini Mental State Examination (MMSE)	CT	Standard assessment tool used to indicate severity of cognitive impairment.	C	MMSE /30
Frontotemporal Dementia Rating Scale (FRS)	CT	Assessment tool used to stage disease severity in FTD based on functional dependence and behavioural changes.	I	Logit score indicating severity of disease % score/100
Frontal Assessment Battery (FAB)	CT	Sensitive to frontal lobe dysfunction. The assessment explores: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy.	C	Total score /18
Progressive Supranuclear Palsy Rating Scale (PSP-RS)	CT	Assessment tool measuring disability due to PSP. Contains six categories: daily activities (by history), behaviour, bulbar, ocular motor, limb motor and gait/midline.	C	Total /100
Apathy Evaluation Scale (AES)	Q	18 item questionnaire assessing emotional, behavioural and cognitive constructs of apathy, with higher total scores indicating more severe symptom presentation	P, I, C	Total score /72 <i>Subscores: Cognition, Emotion, Behaviour</i>
Barratt Impulsiveness Scale (BIS)	Q	30 item self-report questionnaire reflecting the multifactorial structure of impulsivity by assessing attention, motor and non-planning domains, with higher scores indicating a more impulsive profile.	P	Total score /120, <i>Subscores: Attention, Motor, Self Control, Cognitive Complexity, Perseverance, Cognitive Instability</i>
Behavioural Inhibition System Behavioural Activation System (BIS/BAS)	Q	24 item self-report questionnaire based on Gray's biopsychological theory of personality that claims two general motivational systems underlie goal-directed behaviour, including the behavioural activation system regulating appetitive behaviours, and the behavioural avoidance system controlling aversive motives.	P	Total Score <i>Subscores: BIS, BAS Drive, Funseeking, Reward Responsiveness</i>

Measurement	Test Type	Description	Rater	Outcome Measures
Cambridge Behavioural Inventory (CBI-R)	Q	45 item questionnaire developed to evaluate multiple behavioural changes associated with various forms of dementia.	C	Total Score /180 <i>Subscores: Memory/Orientation, Everyday Skills, Self Care, Abnormal, Behaviour, Mood, Beliefs, Eating Habits, Sleep, Stereotypical Behaviour, Motivation</i>
Neuropsychiatric Inventory (NPI)	Q	12 item questionnaire assessing the severity and distress of various behavioural disturbances including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, night time behaviours, appetite/eating		Total /36 Scores on each of the items can also be used as individual subscores.
Motivation and Energy Inventory (MEI)	Q	27 item questionnaire developed to evaluate reductions in motivation and energy in depression research, although commonly used in other disease areas.	P	Total Score /144
Snaith Hamilton Pleasure Scale (SHAPS)	Q	14 item questionnaire measuring hedonic capacity (anhedonia).	P	Total Score /56
Beck Depression Inventory (BDI)	Q	21 item questionnaire widely used to measure the severity of depression. The latest version, BDI-II, is designed for individuals aged 13 and over. Cut of scores are well established: 0-9: minimal depression, 10-18: mild depression, 19-29: moderate depression, 30/63: severe depression	P	Total Score /63
Visual Analogue Scales (VAS)	Q	14 words including: stimulated, interested, clear headed, tired, apathetic, depressed, happy, calm, alert, motivated, sad, excited, impulsive, bored. Each item is scored by placing an X on a horizontal line representing low to high endorsement.	P	Total score /140
Parkinson's Disease Sleep Scale (PDSS)	Q	15 item questionnaire employing a visual analogue scale to assess frequently reported symptoms associated with sleep disturbance in Parkinson's Disease.	P	Total Score /150
Obsessive Compulsive Inventory Revised (OCI-R)	Q	18 item questionnaire developed to assess behavioural changes in obsessive compulsive disorder.	P	Total Score /72
Short Form 36 health survey (SF-36)	Q	36 item questionnaire assessing quality of life. Lower scores reflect more severe disability.	P	Total Score /100

Measurement	Test Type	Description	Rater	Outcome Measures
Kirby Delayed Discounting	Q	Serial forced choice paradigm. Choice between two rewards of varying magnitude at different time delays. Delayed discounting is the tendency to prefer small immediate rewards over larger delayed rewards	P	Value of delayed discounting (k) at large, medium and small rewards. This represents the point at which individuals prefer an immediate smaller reward over a larger delayed reward.
Information Sampling Task (IST)	B	Reflection impulsivity task measuring the amount of information accumulated before making a decision.	P	Proportion of correct trials; Box Latency; Colour Latency; Boxes opened; Total Correct; Sampling error; Discrimination error (fixed and decreasing conditions)
Cued reinforcement reaction time (CRRT)	B	Reward sensitivity task measuring motivationally driven behaviour and the ability of an individual to adapt performance in response to a change in reward probability.	P	Reward related speeding (First & second half of trials); Difference in Speeding from first to second half (learning); Total Errors
Stop signal task (SST)	B	Action cancellation task, assessing the ability to inhibit a motor response during its execution. The major outcome measure is the stop signal reaction time.	P	SSRT; Median reaction time on correct GO trials; Proportion of successful stops
Motor NoGo	B	Action restraint task, testing the ability to inhibit a motor response before the response has been initiated.	P	Reaction time on GO correct; Commission/omission errors; Dprime
Saccade NoGo	S	Action restraint saccade task, testing the ability to inhibit a prepotent saccade response following a visual cue	P	Reaction time on GO correct; Commission/omission errors; Dprime
Cambridge Gambling Task (CGT)*	B	Gambling task designed to measure risk-taking and decision making behaviour.	P	Delay aversion; Deliberation time; Overall proportion bet; Quality of decision making; Risk adjustment; Risk taking; Total

Test type included questionnaires (Q), Clinical Test (CT) behavioural tasks (B) and a saccade task (S). Tests were completed by the patient (P), carer (C) or investigator (I). *Cambridge Gambling Task was discarded from further analysis after it became clear that patients could not perform the task, despite simplification.

In view of the common possibility for phenomenological confusion between apathy and depression, the BDI-II²⁸² was included to assess depression in this population. Apathy and depression are widely recognised to be dissociable constructs reflecting distinct neuronal circuitry^{107,141}. The regional clinical practice is to focus on mood (low, sad, guilty, hopeless, etc) in the diagnosis of depression, and not the physical symptoms (weight change, poor sleep, change of libido, etc), as these may arise in FTLD syndromes for reasons other than depression.

The Kirby^{227,242,288}, a delayed discounting paradigm, provided a more objective measure of impulsivity. Delayed discounting is the tendency to prefer small immediate rewards over larger delayed rewards, for example £10 today versus £12 tomorrow. This self-report questionnaire reflects everyday life decisions, whereby individuals who prefer immediate over larger deferred rewards are more likely to engage in impulsive behaviours such as pathological gambling, smoking, and drug and alcohol abuse²⁵⁴. For example, drug addicts choose to accept short-term “highs” at the cost of long-term good health²⁰⁸. A high delayed discounting rate reflects an impulsive profile²⁸⁸. Schizophrenia patients²¹², Parkinson’s disease patients²⁸⁹ and substance abusers²²⁷ have been reported to discount more steeply than healthy controls.

2.9.2 Description of Behavioural Tasks

2.9.2.1 Motor and Saccade Go/NoGo Task

The Go/NoGo task implicates response choice selection and action restraint, reflecting a key aspect of response inhibition. Response inhibition can also be measured in terms of action cancellation on the stop signal task, which involves the cancellation of an already selected response. Go/NoGo and SST are recognised to have distinct neural underpinnings, as discussed in previous chapters.

The saccadic NoGo task²²⁰ (Figure 6) used direct binocular infra-red scleral oculography, projecting laser cues from a head-mounted sacodometer (OberConsulting, Poland). Each session comprised of 300 trials, following 10 calibration trials. Participants fixated on one green dot and one red dot at 0 degrees, adjacent on a screen at approximately 1.5m distance. After 300ms, one of the central cues was removed and a red dot was presented at -10 degree or +10 degree horizontal displacement (randomised, 50:50). In 50% of trials, the green central cue remained and participants responded by making a saccade to the horizontal red cue (Go trials). In NoGo trials, the red central cue remained and participants were required to refrain from making a saccade to the target. Data were downloaded and analysed using LatencyMeter (Ober

Consulting Version 6.5), and an automatic trials validation was used to eliminate abnormal saccades based on the position and velocity profile of each individual trace.

The motor NoGo task was analogous to the saccadic task but used a joystick operated by the dominant hand (except where physical disability impaired hand use, in which case the most physically able hand was used). Stimuli were presented on a laptop screen positioned 1 meter from the subject, with the initial red and green cues presented in the top center of the screen. Subjects were instructed to initiate movement (Go trials, green central cue remaining) or inhibit movement (NoGo trials, red central cue remaining) in the direction of the presented arrow pointing left or right.

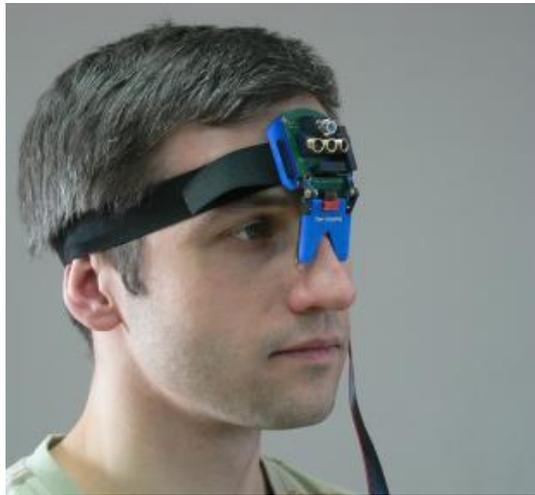


Figure 6: Saccadometer used for NoGo task (Image from Ober Consulting)

Outcome measures for the saccade and motor NoGo tasks were identical to facilitate direct comparisons, and included average reaction times for each trial type, commission and omission errors. Specifically, variables included: Go Correct Right Direction (GCRT), Go Incorrect Wrong Direction (GIWD), NoGo Correct (NC), and NoGo Incorrect (NI). Mean reaction times (in milliseconds) 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. To provide a measure of performance accuracy, the sensitivity index or d' was calculated (d'), representing the difference between the correct “hit” rate and incorrect “false-alarm” rate. The hit rate reflected the proportion of Go trials to which the subject correctly responded Go (in either direction) and the false alarm rate reflected the portion of all NoGo trials whereby the patient incorrectly responded Go. The formula for calculating d' is detailed below, 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 irrespectively 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. Higher d' reflected improved performance.

Equation 1: Formula for Calculating Dprime

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

2.9.2.2 Cued Reinforcement Reaction Time Task (CRRT)

The CRRT is an assessment of incentive motivation, designed to assess responsiveness to reward signals on an odd one out task¹⁴⁷ (Figure 7). The task was simplified from the original CRRT to 2 colour (probability) options instead of 3 and 50 trials instead of 100. The task was run on a laptop with responses recorded by a 3-button box (dominant hand). Forty practice trials without feedback were used to familiarize the participant with the task and to titrate reaction time thresholds for each individual (to ensure motivationally relevant signals were tailored to individual differences in cognitive speed)¹⁴⁷, using a cut-off value for reward feedback of mean reaction time minus one standard deviation. Participants were presented with a cue (coloured rectangle), signaling the probability of reward following a correct response, either 20% or 80%. Participants were informed that the chance of receiving feedback was dependent on the colour of the box surrounding the presented circles, but were not informed which colour was more likely to give feedback.

Participants were instructed to identify the ‘odd-one-out’ of three presented circles as quickly as possible. Feedback was; 100 points for a correct and fast response, 1 point for a correct but slow response and 0 points for an incorrect response. Participants aimed to obtain as many points as possible, for which normal controls demonstrate a “reinforcement-related speeding” effect: responding quicker under the anticipation of increased probability of reward^{147,290}. In order to assess the impact of learning, the mean reaction time at both reward probability values for the first half (FH) and second half (SH) of trials was calculated, followed by the reward-related speeding effect (First half mean RT 20% probability – First half mean RT 80% probability). The difference in reinforcement related speeding was also calculated (Speeding SH – Speeding FH). Additional outcome variables included total errors and total score.

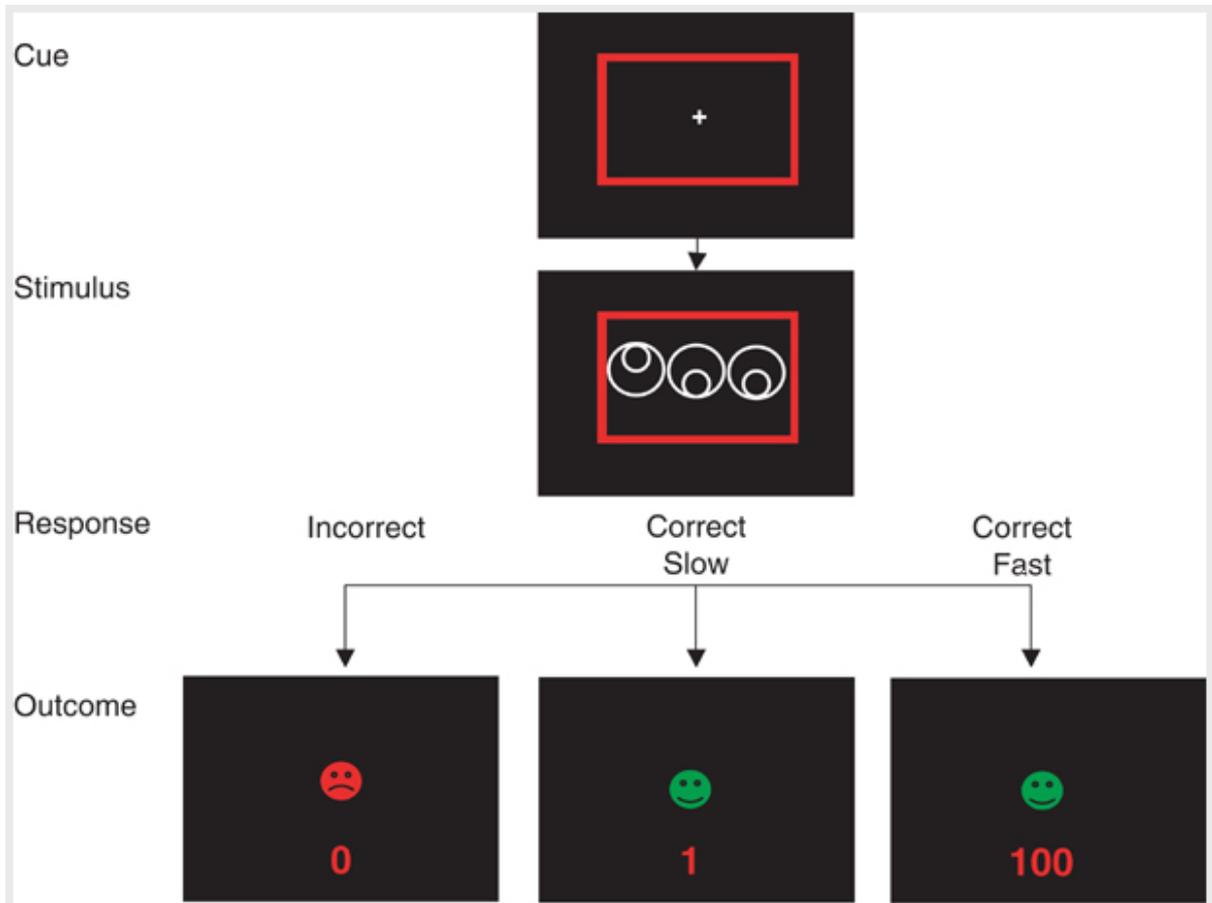


Figure 7: The Cued Reinforcement Reaction Time Task.

Outcome is indicated as incorrect (0 points), correct but slow (1 point) or correct and fast (100 points). Taken from Cools *et al.*, 2005.

2.9.2.3 Information Sampling Task (IST)

The Cambridge Neuropsychological Test Automated Battery (CANTAB) IST²⁴¹ was administered on a touch screen computer to assess reflection impulsivity using five fixed condition and five descending win condition trials. Participants were presented with a 5x5 matrix of 25 grey boxes which, when selected, turned blue/yellow (Figure 8). On fixed trials, participants were instructed to open as many boxes as they liked, before deciding whether there were mostly blue or yellow boxes. On decreasing trials, every selected box subtracted 10 points from a starting sum of 250, to encourage faster decision making based on limited information. Correct responses were rewarded by gaining 100 points and incorrect were punished by losing 100 points. Outcome measures included the time and information required to reach a decision and subsequent accuracy of that decision²³⁰(Cambridge Cognition Ltd.). Specifically, these included the probability of being correct at the time of making the decision, mean box opening latency, mean colour decision latency, mean boxes opened per trial, incorrect decisions based

on insufficient evidence (sampling error), incorrect decision based on available evidence (discrimination errors) and total correct decisions. In a study of impulsive responding, measured by decision making on the IST, chronic drug users were reported to sample less information than control subjects and respond at a lower probability of making a correct response²⁹⁰. Impulsive individuals appear to obtain insufficient information before reaching a decision, leading to risky behaviours and negative consequences²¹⁶.

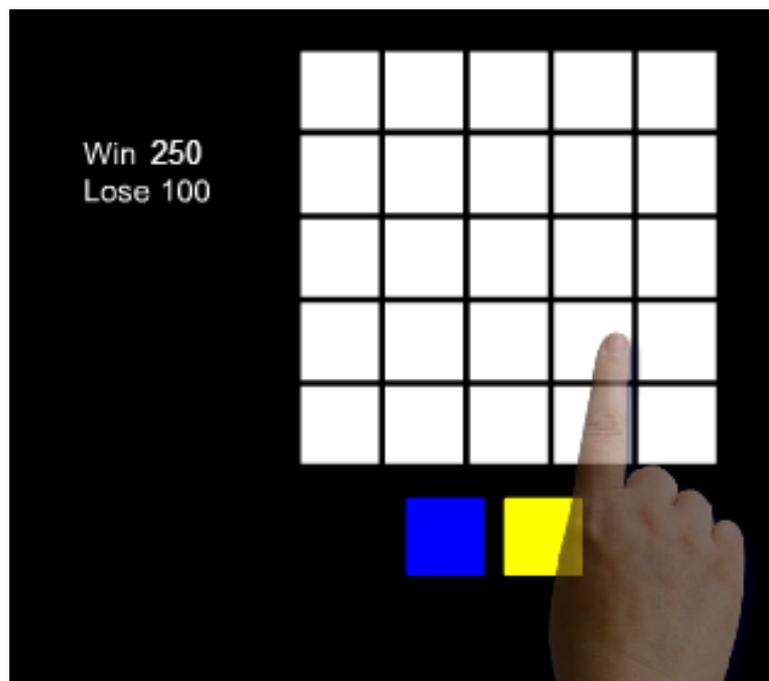


Figure 8: The Information Sampling Task (CANTAB)

2.9.2.4 *Stop Signal Task (SST)*

The SST is a response inhibition (impulse control) task focusing specifically on action cancellation²¹⁴ (Figure 9). The SST was administered using the CANTAB and a two button press pad. In the first practice session (16 trials), stimuli were presented on a computer screen and participants were instructed to press the right/left button as quickly as possible in response to the corresponding right/left arrow. The second part consisted of 64 trials, by which participants were instructed to continue responding as quickly as possible, but to refrain from responding when they heard an auditory signal (beep), presented in 25% of trials (randomly dispersed). The delay between presentation of the arrow stimuli and the stop signal varied, known as the stop signal delay), in order to give an estimate of the stop signal reaction time (SSRT; the time it takes to successfully inhibit a response). Outcome measures were generated using the CANTAB and included SSRT, total correct responses on stop and go trials, direction errors on stop and go trials, and mean/median reaction times for all go trials.

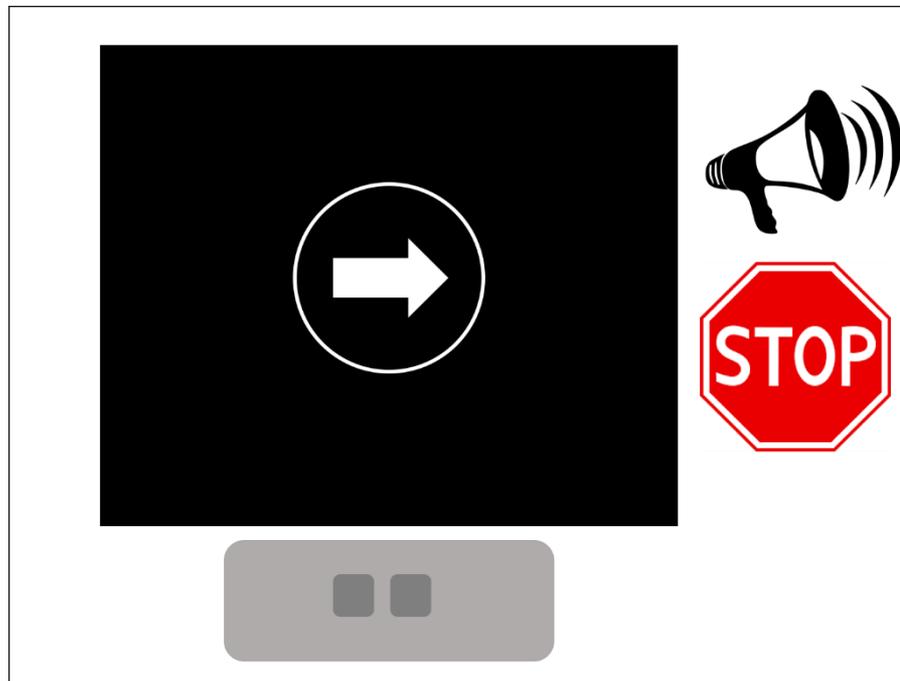


Figure 9: The Stop Signal Task (CANTAB)

2.9.2.5 Cambridge Gambling Task (CGT)

The CGT (Figure 10) is a unique task assessing decision-making and risk taking behaviour in the absence of learning or information retrieval. The CGT dissociates risk taking from impulsivity, as participants have to wait for a risky bet in the ascending condition²⁴⁸.

The task was administered using the CANTAB and consisted of a neutral part and two gambling parts. Participants were presented with a row of red and blue boxes at the top of the screen, and were instructed to guess which colour box a yellow token was placed under. Participants responded by touching the boxes containing the words 'Red' or 'Blue' at the bottom of the screen. In the gambling stages, participants started with 250 points and could select how confident they are with their decision by gambling a certain proportion of these points, which were displayed on the right hand side of the screen in either ascending (part 1) or descending (part 2) order. Participants were instructed to obtain as many points as possible, with the total accumulated points displayed on the screen throughout.

Note: The CGT was removed from the protocol after 37 participants due to floor effects and difficult task engagement by FTLD patients, even following simplification of the task. This highlights the need to develop a disease-specific task to look at gambling behaviours in FTLD syndromes.

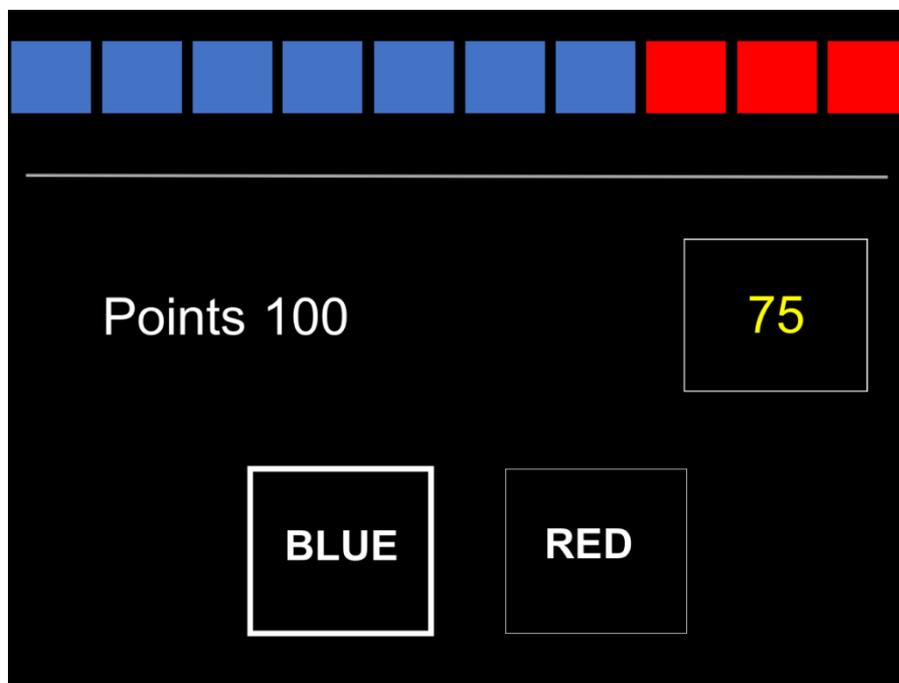


Figure 10: The Cambridge Gambling Task (CANTAB)

2.10 Imaging Methods

The imaging acquisition and sequences included in the PiPPIN protocol are provided below. Detailed voxel-based morphometry and diffusion tensor imaging analysis methods are described in chapter 4 and 5 respectively.

Magnetic resonance imaging (MRI) was performed at the Wolfson Brain Imaging Centre, using a TIM-Trio 3T scanner (Siemens, Germany <http://www.medical.siemens.com/>). Scans obtained included optimized T1 and volumetric T2, diffusion weighted imaging for analysis of white matter tracts; perfusion MRI; SWI and multi echo BOLD sensitive echoplanar fMRI. Total scanning time was <1h.

T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) images were acquired with a TR=2300ms, TE=2.86ms, matrix=192×192, in-plane resolution of 1.25x1.25mm, 144 slices of 1.25mm thickness, inversion time=900ms and flip angle =9°. Diffusion-weighted images (DWI) were acquired using a 63-direction gradient sequence with the following parameters: b value 1000s/mm²; TR 7800ms; TE 90ms; axial in-plane acquisition matrix 96×96; field of view 192×192 mm; slice thickness 2mm and a total of 63 contiguous slices with in-plane resolution 2mm isotropic. Additionally, a single b value of 0 s/mm² image with no diffusion weighting was acquired. Other sequences acquired but not used as part of this thesis include a localizer; BOLD fMRI eyes-closed resting state; axial PD-T2.

2.11 Statistical Analysis

2.11.1 Demographics and Clinical Features

Statistical analysis of behavioural data used SPSS v22.0 (IBM). Comparisons between groups were made using Student's T-tests or analysis of variance (ANOVA) followed by post hoc t-tests and correction for multiple comparisons. Pearson's correlations for parametric data were used to examine the relationship between variables. Pearson's correlation is highly robust against deviations from normality within the data. Comparisons were made for demographic data and disease characteristics, including age, gender, cognitive and functional measures, and the major outcome variables for each of the questionnaires and objective behavioural tasks employed in the principal component analysis.

2.11.2 Principal Component Analysis

Principal Components Analysis (PCA) was used to identify the components of apathy and impulsivity that best explained the data variance, reducing the dimensionality and increasing reliability by combining data from multiple tests. PCAs were run on patient and control data combined (n=199: noting that there were no major differences to the component structure if using only 149 patients' data) using varimax rotation. Varimax rotation ensures orthogonality and maximises the dispersion of loadings within components to facilitate interpretation. The correlation matrix was used for extraction of components and component scores were generated using the regression method. Kaiser-Meyer-Olkin and Bartlett's test of sphericity were used to determine the adequacy of the sample size for PCA analysis.

As many of the individual tasks give rise to multiple outcome measures (for example the Cambridge Behavioural Inventory produces 10 sub-scores, see Table 3 & 4), a hierarchical, two-step PCA approach was employed (Figure 11). First, task-specific 'local' PCAs (LPCA) with varimax rotation were performed separately on the individual questionnaires and behavioural measures. Input variables included the established outcome measures or sub-scores for each questionnaire/behavioural test (see Table 4). Selection of components used Kaiser's or Cattell's criteria, whichever was more inclusive, plus an additional criterion of explaining >10% of the initial variance. To ensure all measures were standardised, the correlation matrix was used for extraction of components. Component loadings above 0.50 were considered meaningful and component scores were computed using the regression method. Second, the components extracted from each of the local PCAs were included in a final PCA (FPCA), which also included total scores or d-prime from the tests which were not subject to local PCA (Table 4). Criteria for component selection were the same.

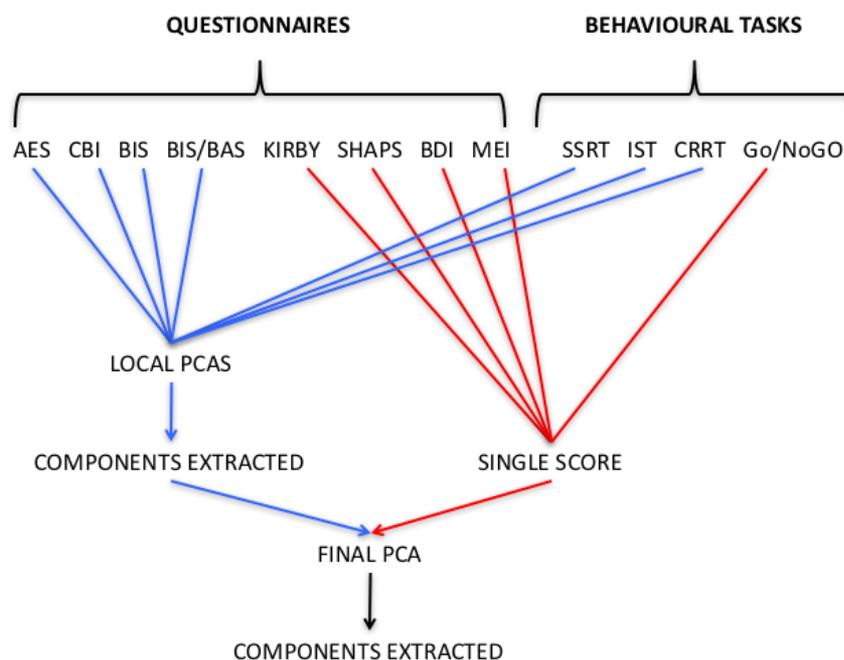


Figure 11: Principal Component Analysis Data Reduction Method.

Local PCAs were carried out on all questionnaires and behavioural tasks independently, where appropriate. Components were then extracted from a final PCA. Note: the Go/NoGo task was run as both a motor and saccade task (2 variables).

2.11.3 Tasks Excluded from the Principal Component Analysis

Some of the PiPPIN assessment battery were disease-specific for non-FTLD disorders and were therefore excluded from the PCA analysis. For example, the Obsessive Compulsive Inventory (OCI-R) is designed for obsessive compulsive disorder patients and may not be readily applicable to FTLN patients. In addition, the Parkinson's disease sleep scale (PDSS) is specific to Parkinson's disease and was developed to measure changes in sleeping behaviours rather than apathy/impulsivity. The SF-36 was also excluded as it is not specific to apathy, impulsivity or related behavioural change.

Cognitive and functional measures including the ACE-R, MMSE, FRS, FAB, and PSPRS were not included in the PCA and were instead used to correlate components with to determine the impact of cognitive and functional status on component scores.

In practice, it became clear that some questionnaires and behavioural tasks were inappropriate for the disease group. Both the Visual Analogue Scales (VAS) and Cambridge Gambling Task were particularly difficult for patients. It became clear through the administration of the VAS that answers were heavily confounded by patients understanding of the key words, and patients

often placed an “X” either at the extremes or elsewhere on the sheet of paper. The Cambridge Gambling Task (CGT) was removed from the protocol after 37 participants due to floor effects and difficult task engagement by FTLD patients, even following simplification of the task. This highlights the need to develop a disease-specific task to look at gambling behaviours in FTLD syndromes, which is sensitive to the cognitive and motor deficits of this cohort.

2.11.4 Relationship of Components to Other Measures

In order to examine the relationship between the extracted components of apathy/impulsivity and other confounding factors, component scores were correlated with age, measures of cognition (ACE-R, MMSE), function (FAB) and disease severity (FRS, PSP-RS) in SPSS v22 (IBM). Component scores were also compared across groups using an ANOVA with *post-hoc* t-tests and correction for multiple comparisons.

2.11.5 Imaging Analyses

The neural correlates of the extracted components were analysed through voxel based morphometry of grey and white matter (in SPM) and diffusion tensor imaging of white matter tract integrity (using tract based spatial statistics in FSL). For full details see Chapter 4 for VBM and Chapter 5 for DTI.

2.11.6 Survival Analysis using Logistic Regression

Logistic regression was used to examine the prognostic implications of the identified components. I focused on the impact of apathy on disease progression and survival, based on previous reports linking apathy to rapid cognitive and functional decline in other related neurological diseases, such as PD⁸³ and AD^{82,84}. See chapter 6 for full details.

2.12 Conclusion

The PiPPIN assessment battery measured multiple aspects of apathy and impulsivity. The following experimental chapters (3-6) employ these measures to assess the components, neural correlates and prognostic implications of these behavioural changes across FTLD syndromes.

Table 4: Variables Used for Local Principal Component Analysis

Test	Outcome Measures/Subscores	Comment
AES	Cognitive, Emotion, Behavioural	Included all sub-scores for patient, carer and clinician versions in LPCA.
BIS	Attention, Cognitive instability, Motor, Perseverance, Self-control, Cognitive complexity	Included all in LPCA
BIS/BAS	BIS, BAS-Drive, Fun-seeking, Reward-Responsiveness	Included all in LPCA
BDI	One outcome measure to give overall rating of depression. Scores indicate minimal (0-9), mild (10-18), moderate(19-29) and severe (30-63) depression.	Included directly in FPCA. Due to a single outcome measure, it was not considered useful to run a LPCA (one was attempted and revealed too many components).
SHAPS	One outcome measure to give overall rating of anhedonia. Higher scores reflect more severe symptom presentation.	Included directly in FPCA, due to a single outcome measure.
MEI	One outcome measure to give overall rating of motivation. Higher scores indicate higher motivation levels.	Included in directly in FPCA, due to a single outcome measure.
CBI_R	Memory and orientation, Everyday skills, Self-care, Abnormal behaviour, Mood, Beliefs, Eating habits, Sleep, Stereotypic and motor behaviours, Motivation	Included all in LPCA
NPI	Severity and distress of a number of psychiatric symptoms.	Included directly in FPCA. For relevance purposes, scores on the apathy and disinhibition subscores were included in FPCA.
KIRBY	K_Large, K_Medium, K_Small	Included directly in FPCA as a single outcome measure “Kirby Difference”: the difference between K_large and K_small. This variable reflects the change in delayed discounting of reward.
Go/NoGo *	Twelve outcome measures covering latency and errors of commission and omission.	Included directly in FPCA a single outcome measure “dprime”.
SST	Direction errors, Proportion of successful stops, reaction times, SSD (50%), SSRT	Included in LPCA: Proportion of successful stops, SSRT, Mean RT on Correct Go trials
IST	Eight outcome measures including errors, latency, total correct trials, mean number of boxes opened per trial, and probability of the participant’s decision being correct based on the available evidence at the time of decision.	Included all in LPCA.
CRRT	Reaction times and errors	Included in LPCA: Speeding first half (reaction time difference), Speeding second half, Difference in speeding, Error

***Saccade and Motor versions of the Go/NoGo were used.**

Chapter 3 | The Components of Apathy and Impulsivity in Frontotemporal Lobar Degeneration Syndromes.

In this Chapter, I describe the demographics and disease characteristics of the PiPPIN cohort and the associated neuropsychological and behavioural results. I then present findings from the principal component analysis, adopting a dimensional reduction technique to combine scores from multiple tests to identify components that best explain the variability within the dataset.

3.1 Key Features

The key demographics and disease characteristics, neuropsychological and behavioural features of the PiPPIN cohort are detailed below.

3.1.1 Cohort

Two hundred and four cases of frontotemporal lobar degeneration were identified within the PiPPIN catchment area over 24 months. Of these, 200 cases were used for epidemiological estimates (see¹⁹) and 167 were seen by a member of the study team. Patients met current consensus clinical diagnostic criteria for bvFTD⁴, svPPA, nvPPA, PPA other (those with a primary progressive aphasia not fitting criteria for one of the 3 defined subtypes⁶), CBS⁵ or PSP¹⁴. Datasets from 149 patients were used for neuropsychiatric and behavioural analysis and a subset of 100 underwent MRI imaging analysis (these subsets being the focus of this thesis). Thirty three patients have subsequently donated their brain for post mortem studies, allowing pathological confirmation of their diagnosis. The results are presented in Table 5 below.

Table 5: Pathologically Confirmed Cases

Clinical Diagnosis	Pathological Diagnosis				
	<i>FTD-TDP-43</i>	<i>CBD</i>	<i>PSP</i>	<i>FTD-Tau (Pick's Disease)</i>	<i>AD</i>
CBS (N=15)	1	6	1	1	6
PSP (N=9)	0	0	9	0	0
bvFTD (N=4)	3	1	0	0	0
svPPA (N=2)	2	0	0	0	0
nvPPA (N=2)	0	0	0	0	2
PPA Other (N=1)	0	0	0	0	1

Participants were tested while on their usual medication. Forty percent of patients were taking antidepressant medications (for either affective or behavioural indications), 4% were taking antipsychotic medication, and 29% were taking dopaminergic medication (for movement disorder). Thirty-seven percent were taking other medications that may act on the central nervous system including benzodiazepines (for anxiolysis, sedation or myoclonus), antiepileptic medication, analgesics (opioid, gabapentin, pregabalin) including one case on cholinesterase inhibitors.

3.1.2 Demographics, Clinical Features, Cognitive Status and Disease Severity.

Details of participant demographics, cognitive, functional and motor features by diagnosis are provided in Table 6. Patients demonstrated cognitive and functional impairment across groups compared to controls, as measured by the ACE-R, MMSE, FAB, FRS and PSPRS. Additional motor features were also present in some patients across diagnostic groups, including akinesia, rigidity, dystonia, apraxia, vertical gaze palsy, postural instability, and myoclonus. Years from symptom onset were estimated based on recall of initial relevant symptoms.

3.1.3 Neuropsychiatric and Behavioural Features of the PiPPIN cohort

The neuropsychological and behavioural performance of patients and controls are presented in Table 7 and 8. Patients and controls were matched for age and gender. Patients demonstrated cognitive and functional impairment across groups compared to controls, as measured by the ACE-R, MMSE, and FAB (Table 7 and 8). Patients had significant cognitive deficits compared to controls in addition to significantly higher apathy (AES), impulsivity (BIS), depression (BDI) and anhedonia (SHAPS) with lower levels of motivation (MEI). Patients also demonstrated significant impairments on behavioural tasks of reflection impulsivity (Information sampling task), incentive motivation (Cued reinforcement), response inhibition (limb-motor and saccade tasks) and action cancellation (Stop-Signal task). The BIS/BAS and Kirby responses did not differentiate patients and controls.

Table 6: Demographics, Cognitive, Functional and Motor Features of the PCA Sample by Diagnosis.

	PSP	CBS	svPPA	PPA	bvFTD	nvPPA	Control
N	41	37	12	11	32	16	50
Age	72.9 ±8.5	69.7±7.8	71.1±4.1	73.1±4.9	64.0±7.3	71.6±9.1	70.6±6.5
Gender (M:F)	21:20	18:19	7:5	5:6	18:14	7:9	23:27
Duration (of symptoms)	4.5±3.4	4.1±2.3	5.7±2.9	4.1±2.2	4.9±3.0	2.0±2.0	NA
ACE-R (Max 100)	75.5±14.6	65.7±21.3	29.2±14.7	58.5±20.5	59.0±26.9	64.4±21.0	95.6±4.4
MMSE (max 30)	25.0±4.8	22.0±6.6	11.8±8.7	21.0±5.1	21.4±7.6	23.0±6.3	29.3±1.2
FRS % Score (max 100)	40.9±25.1	31.4±23.3	20.9±14.6	66.3±28.4	26.8±18.0	63.7±28.4	92.1±10.8
FAB (Max 18)	10.5±4.0	10.0±4.4	9.4±3.8	10.0±4.4	9.4±5.3	9.2±4.4	16.8±1.2
PSP-RS (Max 100)	43.8±14.8	39.6±16.1	NA	5.3±4.7	16.1±10.0	8.4±6.2	NA
Akinesia (N)	35	27	2	2	22	31	0
Rigidity (N)	35	27	0	1	6	1	0
Dystonia (N)	25	24	0	0	2	0	0
Apraxia (N)	22	33	2	8	8	11	0
Vertical Gaze Palsy [†] (N)	41	19	0	2	3	1	0
Postural instability/Falls* (N)	41	24	0	1	7	2	0
Myoclonus (N)	3	22	0	3	3	5	0

[†] or slowing of vertical saccades; * or wheelchair dependence

Abbreviations: Progressive Supranuclear Palsy (PSP), Corticobasal Syndrome (CBS), semantic variant Progressive Aphasia (svPPA), other Progressive Aphasia (PPA), behavioural variant Frontotemporal Dementia (bvFTD), nonfluent variant Progressive Aphasia (nvPPA), Addenbrooke's Cognitive Examination Revised (ACE-R), Mini Mental State Examination (MMSE), Frontotemporal dementia Rating Scale (FRS), Frontal assessment battery (FAB), Progressive supranuclear palsy rating scale (PSP-RS).

Table 7: Neuropsychiatric and Behavioural Results

	Variable	Controls (n=50)	Patients (n=149)	T Stat	Group Difference
Demographics & Cognition	Age	70.6 ± 6.5	69.9 ± 8.2	0.9	NS
	Gender M:F	23:27	76:73	($\chi^2=-0.6$)	NS
	ACE-R Total (max 100)	95.6 ± 4.4	64.7 ± 22.6	12.7	**
	MMSE Total (max 30)	29.3 ± 1.2	22.3 ± 6.8	9.6	**
	PSP-RS	NA	31.5 ± 20.1	NA	NA
	FAB	16.8 ± 1.2	9.9 ± 4.4	14.4	**
	FRS % Score (max 100)	92.1 ± 10.8	37.9 ± 26.5	18.5	**
Questionnaires	Apathy Evaluation Scale (AES, max 72):				
	-carer	24.2 ± 5.7	48.1 ± 12.4	-16.7	**
	-patient	25.7 ± 5.6	36.1 ± 9.4	-7.8	**
	-clinician	25.9 ± 7.3	43.6 ± 10.0	-11.8	**
	Barratt Impulsiveness Scale (BIS, max 120)	57.0 ± 7.4	63.6 ± 8.1	-4.6	**
	Behavioural Inhibition System/Behavioural Activation System (BIS/BAS):				
	-BIS subscore	19.9 ± 3.4	20.6 ± 4.5	-1.0	NS
	-BAS drive	10.0 ± 2.1	10.9 ± 3.2	-1.9	NS
	-BAS funseeking	10.7 ± 2.2	11.3 ± 3.0	-1.2	NS
	-BAS Reward Responsivness	15.8 ± 2.4	16.6 ± 2.7	-1.7	NS
	Motivation and energy inventory (MEI, max 144)	108.9 ± 17.2	81.1 ± 26.4	7.0	**
	Beck depression inventory (BDI, max 63)	4.2 ± 4.0	13.0 ± 10.1	-6.7	**
	Snaith Hamilton pleasure scale (SHAPS, max 56)	18.6 ± 4.4	22.5 ± 4.8	-4.5	**
	Neuropsychiatric inventory (NPI, fraction with positive response):				
	-Apathy subscore	0.000 ± 0.0	0.616 ± 0.5	-13.3	**
	-Disinhibition subscore	0.020 ± 0.1	0.336 ± 0.5	-6.5	**
	Cambridge behavioural inventory (CBI-R, max 180)	5.2 ± 5.6	66.7 ± 35.2	-18.2	**
Kirby (difference)	0.005 ± 0.04	0.019 ± 0.1	-1.6	NS	
Behavioural Tasks	Information Sampling Task (IST)				
	-Probability of being correct Fixed	0.87 ± 0.1	0.75 ± 0.1	4.9	**
	-Probability of being correct Decreasing	0.81 ± 0.1	0.67 ± 0.2	5.4	**
	Cued reinforcement reaction time (CRRT)				
	-Reward related speeding	-43.4 ± 90.9	196.3 ± 739.1	-2.4	*
	-Total Errors	3.8 ± 3.4	4.2 ± 5.7	-0.5	NS
	Cambridge Gambling task				
	- Deliberation time	2240. ± 767	7053. ± 4449	1.4	**
	- Risk adjustment	1.57 ± 1.1	0.23 ± 0.9	4.1	**
	Stop Signal Task (SST)				
	-Stop signal reaction time (SSRT)	181.1 ± 41.7	439.8 ± 190.4	-3.1	**
Motor Go/NoGo Dprime	4.4 ± 3	3.2 ± 1.3	7.8	**	
Saccade Dprime	2.4 ± 9	0.75 ± 1.1	7.4	**	

Objective measures corrected for outliers +/-3SD of the mean. Independent samples t-test uncorrected for multiple comparisons are shown outside parentheses: **p<0.001, *p<0.05, NS not significant. Significance after Bonferroni correction is indicated by (**). Note that some measures are not independent, for example, MMSE is a component of the ACE-R, and NPI subscales are component of the total NPI score. CGT task data from 37 participants only.

Table 8: Summary of Patient Characteristics by Diagnostic Group

	Variable	PSP	CBS	bvFTD	PPA	
	N	41	37	32	39	
Demographics & Cognition	Age	72.1±8.3	69.4±8.2	63.9±8.0	71.0±7.3	
	Gender M:F	21:20	18:19	18:14	19:20	
	ACE-R Total (/100)	75.5±14.6	65.7±21.3	59.0±27.0	54.8±23.6	
	MMSE Total (/30)	25.0±4.8	22.0±6.6	21.4±7.6	19.9±7.8	
	FRS % Score (/100)	40.9±25.1	31.4±23.3	23.4±6.0	50.1±31.8	
Questionnaires	Apathy Evaluation Scale (AES /72):					
	- <i>carer</i>	48.4±10.9	48.6±11.2	54.3±9.4	42.6±14.9	
	- <i>patient</i>	39.1±11.2	36.1±6.8	32.3±9.6	35.2±7.8	
	- <i>clinician</i>	47.1±11.0	45.2±8.2	43.2±7.3	36.9±9.9	
	Barratt Impulsiveness Scale (BIS /120)	65.2±7.3	61.8±10.2	63.3±6.7	63.2±8.0	
	Behavioural Inhibition System/Behavioural Activation System (BIS/BAS):					
	- <i>BIS subscore</i>	19.8±3.2	21.9±3.3	19.3±3.3	21.8±7.0	
	- <i>BAS drive</i>	11.0±3.1	9.9±3.4	12.6±3.2	10.5±7.0	
	- <i>BAS funseeking</i>	10.7±2.8	10.3±3.7	12.7±3.2	11.8±2.1	
	- <i>BAS Reward Responsivness</i>	16.2±2.7	17.3±2.2	16.7±3.6	16.5±2.2	
	Motivation and energy inventory (MEI /144)	70.7±29.5	74.1±23.5	96.9±23.9	90.3±15.9	
	Beck depression inventory (BDI /63)	17.8±11.5	14.3±8.0	9.3±6.1	7.8±9.4	
	Snaith Hamilton pleasure scale (SHAPS /56)	22.3±4.3	24.1±5.1	26.8±18.0	20.25±3.5	
	Neuropsychiatric inventory (NPI, fraction with positive response):					
	- <i>Apathy subscore</i>	0.63±0.5	0.78±0.4	0.68±0.5	0.40±0.5	
	- <i>Disinhibition subscore</i>	0.23±0.4	0.19±0.4	0.56±0.5	0.40±0.5	
	Cambridge behavioural inventory (CBI-R /180)	56.0±32.4	73.5±30.6	85.6±26.2	55.7±41.1	
	Kirby (difference)	0.035±0.06	0.017±0.04	-0.0002±0.08	0.008±0.03	
	Behavioural Tasks	Information Sampling Task (IST)				
		-Probability of being correct Fixed	0.743±0.1	0.705±0.1	0.846±0.1	0.706±0.1
-Probability of being correct Decrease		0.678±0.1	0.617±0.2	0.721±0.2	0.654±0.1	
Cued reinforcement reaction time (CRRT)						
-Difference Speeding		31.6±581.3	183.4±235.1	-1.81±305.9	657.8±1230.9	
-Total errors		3.8±3.2	4.0±4.2	2.4±2.1	6.8±10.3	
Stop Signal Task (SST)						
-Stop signal reaction time (SSRT)		431.7±146.1	435.2±189.3	367.4±154.7	512.6±251.5	
Motor Go/NoGo Dprime		3.3±1.1	2.8±1.4	4.0±1.5	3.1±1.4	
Saccade Dprime		0.71±9	0.98±1.2	1.1±1.4	0.4±1.0	

Demographics and disease characteristics by diagnostic group, split into equally weighted groups of PSP, CBS, bvFTD and PPA. Note that PPA included 16 nvPPA, 12 svPPA and 11 “PPA other” cases (2 lvPPA and the remaining not meeting criteria for either svPPA or nvPPA and therefore unspecified).

3.1.4 Neuropsychiatric and Behavioural Assessment Correlations and Comparisons

3.1.4.1 Apathy and Impulsivity

The well-established measures of apathy and impulsivity were positively correlated in this cohort; the more apathetic an individual rated themselves, the more impulsive. Significant and strong positive correlations were observed between total scores on the self-rated Apathy Evaluation Scale and the Barratt Impulsiveness Scale (Pearson's $r = .495$, $p < 0.001^{**}$, see Figure 12), tools that are frequently used to measure apathy and impulsivity respectively. This provided initial supportive evidence suggesting that apathy and impulsivity are related in the PiPPIN cohort.

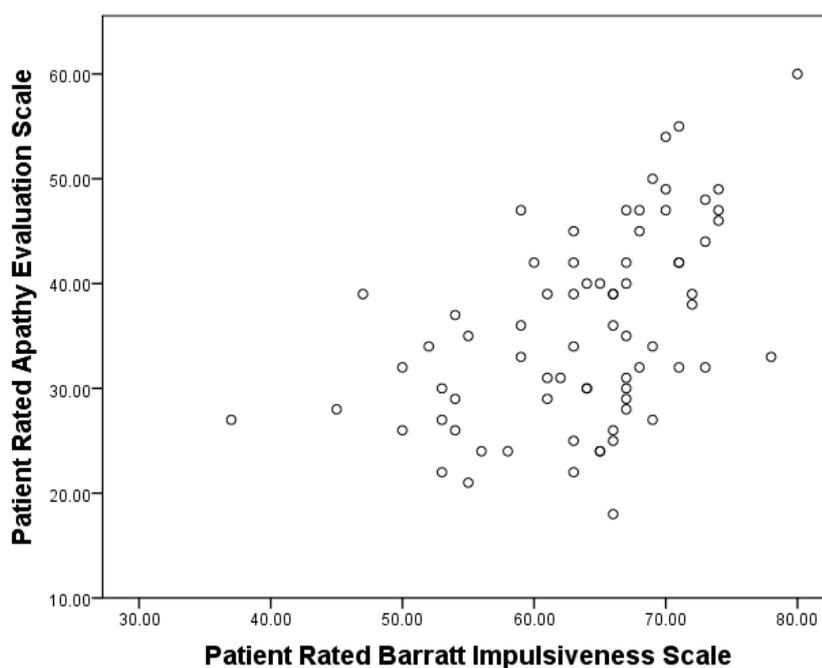


Figure 12: Correlation between the Self-rated Apathy Evaluation Scale and Barrett Impulsiveness Scale

3.1.4.2 Patient and Carer Ratings on Analogous Tests

The discrepancy between raters was explored by employing tests with analogous versions for the clinician, patient and carer. The Apathy Evaluation Scale had three versions, which are compared in a correlation analysis below. Although the CBI was designed for the carer, rather than the patient, the PiPPIN study also collected self-reported change as measured by the first question in each of the subdomains of the questionnaire, to provide an additional measure of rater agreement/disagreement. Note that the below analysis uses patient data only (N=149).

The Apathy Evaluation Scale

Correlation analysis of patient, carer and clinician ratings on the apathy evaluation scale revealed a discrepancy (Figure 13). Clinician ratings correlated with both patient and carer ratings (Pearson's Correlation: carer vs clinician $r=.586$, $p<0.001^{**}$, patient vs clinician $r=.719$, $p<0.001^{**}$), likely reflecting clinician dependency on insights reported by the patient and close relatives in a limited clinical setting. Only ~5% of the variance in carer ratings was accounted for by patient ratings (Pearson's Correlation: carer vs patient $r=.234$ $p<0.05^*$), emphasising a clear discrepancy in their interpretation of apathy as measured by the AES.

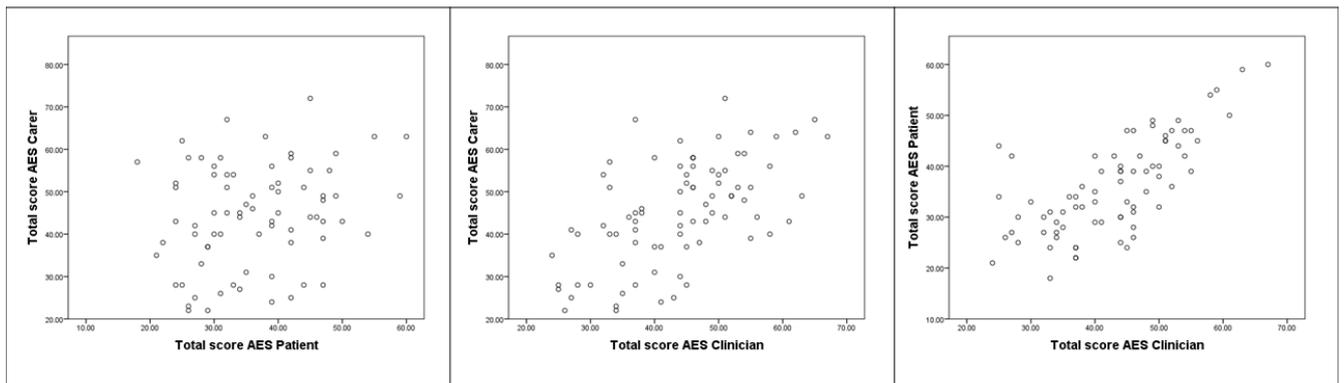


Figure 13: Correlation Analysis between the Carer, Patient and Clinician Apathy Evaluation Scale.

ANOVA revealed significant differences between all raters ($F_{2,270}=27.7$, $p<0.001$: Tukey HSD *post hoc* patient vs carer <0.001 , vs clinician <0.001 , carer vs clinician $p=0.004$), with carers reporting highest scores on average, followed by the clinician and patient (Figure 14). The underlying causes of this discrepancy are unclear. Possible explanations include patient lack of insight into their behavioural change and/or the influence of carer distress.

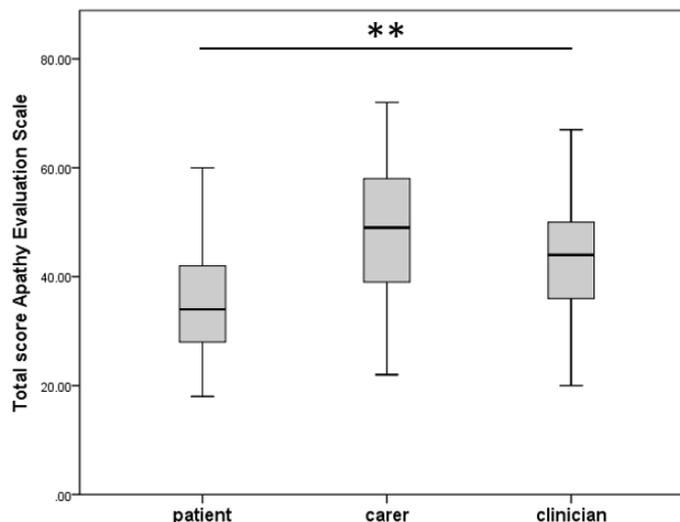


Figure 14: Box Plot Showing AES Scores by Rater

Apathy as rated by the carer and clinician correlated strongly with markers of functional decline, including the FRS and PSP-RS (Table 9). Clinician ratings also correlated weakly with the FAB, while carer ratings correlated weakly with cognitive decline as measured by the MMSE. Patient ratings bore no relationship to cognitive and functional markers.

Higher scores on the AES and PSP-RS reflect increased apathy and functional decline respectively, hence the observed positive correlation. In contrast, lower scores reflect increased cognitive and functional impairment on the FRS, FAB, ACE-R and MMSE, accounting for the negative correlation with apathy ratings.

Table 9: Correlation of the Apathy Evaluation Scale Versions with Cognition and Functional Measures

	FRS	PSP-RS	FAB	ACE-R	MMSE
AES Carer	-0.720**	0.408**	-0.178	-0.196	-0.250*
AES Patient	-0.102	0.195	-0.171	-0.047	-0.084
AES Clinician	-0.483**	0.445**	-0.242*	-0.108	-0.172

Note: Higher scores on the ACER, MMSE, FRS, and FAB indicate better performance while higher scores on the PSP_RS indicate more severe disability.

The Cambridge Behavioural Inventory

The CBI also revealed discrepancies between carer and patient ratings of behavioural change, showing an overall significant difference in total scores (carer mean 14.0, patient mean 10.8, $t=3.4$ $p=0.001$). In line with the discrepancy observed on the AES, carers generally rated higher than patients (6/10 questions, Figure 15), including for all questions which showed significant differences; CBI 1 ‘Has poor day-to-day memory [e.g. About conversations, trips, etc]’ ($t=2.6$, $p<0.05$), CBI 9 ‘Has difficulties with electrical appliances’ [e.g. TV, radio, cooker, washing machine] ($t=6.8$, $p<0.001$), CBI 14 ‘Has difficulties grooming self [e.g. shaving or putting on make-up]’ ($t=3.7$, $p<0.001$) and CBI 41 ‘Shows less enthusiasm for his or her usual interests’ ($t=4.0$, $p<0.001$). Questions reflecting higher average endorsement by patients than carers (for example, visual hallucinations, cries), were infrequent in this population and discrepancies were marginal.

Correlation analysis of the CBI total scores for carers again showed strong correlations with cognitive and functional measures, while patient ratings correlated only with functional measures (Table 10). Once again, higher scores on the CBI and PSP-RS reflect increased behavioural change and functional impairment respectively, with lower scores on all other measures reflecting greater impairment.

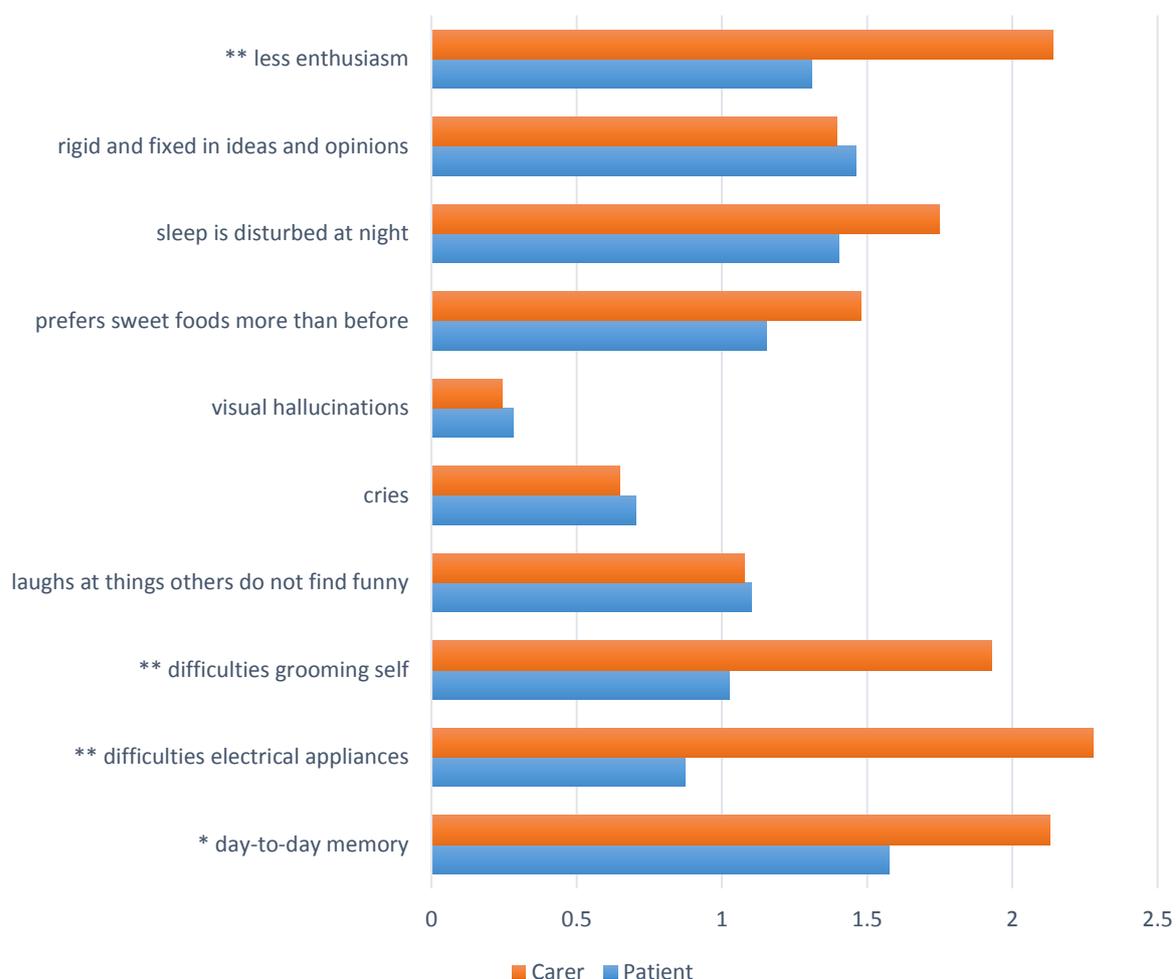


Figure 15: Discrepancy between Carer and Patient Scores on the Cambridge Behavioural Inventory (T-test, * $p < 0.05$, ** $p < 0.001$).

Table 10: Correlation of CBI Versions with Measures of Cognition, Function and Disease Severity

	FRS	PSP-RS	FAB	ACE-R	MMSE
CBI Carer	-0.841**	0.338**	-0.268*	-0.344**	-0.401**
CBI Self	-0.327**	0.436**	-0.148	-0.096	-0.174

Together, these findings highlight important discrepancies between carer, clinician and patient ratings, which have implications for clinical trial design (see discussion).

3.2 Principal Component Analysis Results

3.2.1 Cohort

Principal component analysis was carried out on patient and control data combined (N=199: noting that there were no major differences to the component structure if using only 149 patients' data).

3.2.2 Local Principal Component Analyses (LPCA)

The results of the local principal component analyses are presented in Table 11. Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity were used to determine the adequacy of the sample size for PCA analysis for each test. Varimax rotation was used and the correlation matrix extracted components meeting Kaiser's and/or Cattell's criteria (whichever was more inclusive). An additional threshold of accounting for >10% of the initial variance was included for local PCAs. Scores were generated using the regression method.

3.2.3 Final Principal Component Analysis (FPCA)

The sample size was adequate for analysis (KMO=0.743) and correlations between items were sufficiently large for PCA (Bartlett's test of sphericity₂₃₁=508.013, $p < 0.001$). Eight components were extracted from the final PCA (initial eigenvalues range: 1.039-4.963). The rotated component matrix is provided in Table 12. Note that assessments that are traditionally considered to be associated with apathy and impulsivity load onto the same factors (for example, AES and BIS), reflecting a high positive correlation between components of apathy and components of impulsivity. Inclusion of the CGT task data from 37 participants did not alter the factor structure, but in view of limited numbers this test was removed from the main analyses.

Components were named based on their major contributors. Short summary terms are adopted that encapsulate the main elements of the component in terms of strongly weighted processes or tasks. The weighting of each questionnaire or behavioural test onto the separate components is detailed in Table 12. Component 1 reflected patient ratings on questionnaires of apathy, impulsivity and related changes, termed "Patient-Rated Change". Higher scores reflected increased questionnaire endorsement of apathy (AES), impulsivity (BIS), depression (BDI), anhedonia (SHAPS) and low motivation (demonstrated by the negative MEI loading).

Table 11: Local Principal Component Results

Test Name	Summary of Components Extracted from LPCAs
AES	2 components (Eigenvalues Initial: 5.226, 1.455 respectively; Rotated: 3.478, 3.203 respectively) accounting for 74.2% of the total variance. 1. + AES-Patient (cognition 0.855, emotion 0.811, and behaviour 0.723) & AES-Clinician (cognition 0.669, emotion 0.755, and behaviour 0.645) 2. + AES-Informant (cognition 0.939, emotion 0.865, and behaviour 0.862) & AES-Clinician (cognition 0.547 & behaviour 0.547 subscores)
BIS	2 components (Eigenvalues Initial: 1.982, 1.342 respectively; Rotated: 1.968, 1.342 respectively) accounting for 55.4% of the total variance. 1) + Attention(0.762), self-control(0.759), cognitive complexity(0.674), perseverance(0.594) 2) + Motor (0.695), cognitive instability(0.795)
BIS/BAS	2 components (Eigenvalues 2.107, 1.041 respectively; Rotated: 2.107, 1.041 respectively) accounting for 78.7% of the total variance. 1) + BAS drive(0.851), fun seeking(0.874) and reward responsiveness(0.777) 2) + BIS (0.978)
CBI	2 components (Eigenvalues Initial 5.808 and 1.152 respectively; Rotated 3.957, 3.002 respectively) accounting for 70.0% of the total variance. PC1 was named “behaviour” and PC2 “everyday skills”. 1) + Memory/orientation (0.683), abnormal behaviour (0.838), mood (0.717), beliefs (0.541), eating habits (0.728), stereotypic behaviour (0.882), motivation (0.654). 2) + Everyday skills (0.855), self-care (0.927), sleep (0.693), motivation (0.568).
SST	1 component (Eigenvalue 2.306) extracted, accounting for 76.9% of the total variance. 1) Proportion of successful stops (0.691) 2) SSRT (0.983) 3) Median Correct reaction time on GO Trials (0.929)

Test Name	Summary of Components Extracted from LPCAs
IST	<p>3 components (Initial Eigenvalue 5.137, 2.953, 1.892 respectively; Rotated: 4.317, 2.938, 2.243, 1.598 respectively) extracted, accounting for 71.3% of the total variance. A fourth component also just met Kaiser's criteria for extraction, however it accounted for <10% of the initial variance and so was discarded for FPCA (also supported by examination of the scree plot).</p> <ol style="list-style-type: none"> 1) Probability of being correct decreasing/fixed (loading 0.912/0.947) Mean boxes opened per trial decreasing/fixed (loading 0.646/0.926) Total correct decreasing/fixed (loading 0.833/0.926) 2) Mean Box latency decreasing/fixed (loading 0.779/0.724) Mean Colour latency decreasing/fixed (loading 0.876/0.903) 3) Sampling error decreasing/fixed (0.879/0.720) -Mean boxes opened per trial decreasing/fixed (-0.641/-0.557)
CRRT	<p>2 components (Initial eigenvalues 2.324, 1.001 respectively; Rotated: 2.000, 1.325 respectively) extracted, accounting for 58.1% of the total variance.</p> <ol style="list-style-type: none"> 1) Difference in speeding on the first and second half of trials (0.782) Total Error (0.750) -Speeding on 20% to 80% probability of reward trials, first half of trials (-0.909) 2) Speeding from 20% to 80% probability of reward on the second half of trials (0.965) Difference in speeding on the first and second half of trials (0.591)

Note the MEI, SHAPS and BDI total scores were moved directly to FPCA. These scales are designed to give one outcome measure and were therefore not appropriate for LPCA. The NPI subscores 'apathy' and 'disinhibition', the Kirby difference between K_Small and K_large and the Go/NoGo motor and saccade dprime scores (calculated as $d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$) were also moved directly to FPCA. Scores were z transformed prior to FPCA input.

Chapter 3

Component 2 and 3 were associated with carer ratings of patient change, with higher scores reflecting increased endorsement of abnormal behaviours. Component 2, termed “carer rated change in everyday skills and self care”, had strong loadings from the carer AES, CBI (specifically everyday skills, self care, sleep and motivation subscores) and the NPI apathy subscore. The carer AES also loaded onto component 3 “Carer rated change in Complex Behaviours”, in addition to the remaining subscores of the CBI (abnormal behaviour, eating habits, stereotypic behaviours) and the NPI disinhibition subscore. The final questionnaire based component, component 5, was termed “Impulsivity self report”, to reflect increased ratings on BIS-motor and -cognitive instability and BAS subscores of the BIS/BAS.

Higher scores on component 4 were associated with poor performance the Go/NoGo motor and saccade tasks (lower dprime), information sampling task (more errors, increased box/colour latency) and cued reinforcement reaction time task (no reward-related speeding and increased error) and was termed “Impulsive/Reward-related behaviours”. In contrast, higher scores on component 6, termed “Goal directed decision making”, reflected accurate performance on the information sampling task (increased probability of being correct at the time of decision) and sensitivity to reward on the cued reinforcement reaction time task (reward-related speeding).

Component 7 was named “SST performance”, with high scores reflecting shorter SSRT and Go reaction times (negative loading). Component 8 captured the incentive motivation elements of the Kirby and behavioural avoidance on the BIS/BAS, and was termed “Outcome Sensitivity”. Higher scores reflect reduced difference in temporal discounting from small to large values of K on the Kirby and increased behavioural avoidance.

Table 12: Rotated Component Matrix Extracted from Final Principal Component Analysis

INPUT VARIABLE	COMPONENT STRUCTURE							
	PC1 Patient Rated Change	PC2 Carer Rated Everyday Skills & Self Care	PC3 Carer Rated Challenging Behaviours	PC4 Impulsive/Reward Related Behaviours	PC5 Impulsivity Self Report	PC6 Goal-directed Decision making	PC7 Stop Signal Task	PC8 Outcome Sensitivity
<i>Eigenvalue I/R</i>	4.963/3.438	2.183/2.284	1.664/2.145	1.514/1.819	1.385/1.640	1.186/1.284	1.111/1.245	1.039/1.188
AES 1	0.832	-0.069	-0.121	0.151	-0.078	-0.003	-0.041	-0.069
BIS 1	0.735	0.086	0.083	0.221	0.080	-0.003	-0.095	-0.052
BDI-T	0.756	0.345	0.100	0.073	0.158	0.097	-0.026	-0.030
MEI-T	-0.837	-0.232	-0.061	-0.109	-0.023	0.034	0.142	0.007
SHAPS-T	0.688	0.147	0.281	-0.067	-0.276	-0.136	0.068	0.075
AES 2	0.067	0.714	0.529	0.074	0.035	0.006	-0.110	-0.151
CBI 2	0.233	0.831	-0.084	0.151	-0.113	0.023	-0.155	0.042
NPI-A	0.192	0.705	0.355	0.119	-0.086	0.048	0.029	-0.050
CBI 1	0.035	0.118	0.880	0.078	0.104	-0.135	-0.066	-0.069
NPI-D	0.135	0.083	0.825	-0.008	-0.017	0.039	0.017	0.092
IST 2	0.170	0.030	-0.037	0.683	-0.128	0.365	-0.166	0.006
CRRT 1	0.007	0.014	-0.006	0.658	-0.013	-0.104	0.390	0.109
Go/NoGo	-0.259	-0.135	-0.113	-0.642	0.130	0.042	0.259	0.007
Saccades	-0.162	-0.198	-0.081	-0.530	-0.319	0.221	0.018	0.158
BIS 2	0.022	-0.121	-0.015	-0.100	0.841	-0.023	-0.065	0.077
BISBAS 1	-0.198	-0.005	0.265	0.083	0.631	0.375	-0.209	-0.011
IST 1	-0.188	-0.204	-0.080	-0.177	0.013	0.556	0.311	0.052
CRRT 2	0.084	0.162	-0.037	0.063	0.078	0.725	-0.031	-0.078
SST 1	0.183	0.109	0.021	0.044	0.167	-0.087	-0.793	0.030
BISBAS 2	0.068	0.090	-0.088	0.042	0.242	-0.179	0.141	0.804
Kirby	0.199	0.230	-0.126	0.040	0.220	-0.151	0.215	-0.658
IST 3	0.255	0.382	-0.198	-0.167	0.335	-0.007	0.283	-0.001

Numbers (1, 2, 3) indicate the different components extracted from LPCA for AES, CBI, BIS, BIS/BAS, IST, SST, CRRT. Additional input variables included the total score for BDI, MEI and SHAPS, NPI apathy and disinhibition subscores, Kirby difference value representing the difference in delayed discounting for low versus high rewards and Dprime performance accuracy values for Go/NoGo tasks. High scores on component 1-5 and 8 indicate worse performance, whereas low scores on component 6 and 7 indicate worse performance. Initial (I) and rotated (R) eigenvalues are reported.

3.2.4 Component Scores across Diagnostic Groups

The components were not specific to individual disease groups, but reflected the transdiagnostic nature of apathy and impulsivity. Figure 16 shows the distribution of component scores (1-8) in each of the six patient groups and controls. ANOVAs confirmed a significant effect of group (and *post hoc* t-tests comparing each patient group to controls) with respect to component 1 ($F_{6,192}=6.35$, $p<0.001$: post hoc control vs PSP $p<0.001$, vs CBS $p<0.05$); Figure 16A) component 2 ($F_{6,192}=17.1$, $p<0.001$: post hoc control vs PSP $p<0.001$, CBS $p<0.001$, vs bvFTD $p<0.001$, vs svPPA $p<0.05$); Figure 16B) component 3 ($F_{6,192}=19.9$, $p<0.001$: post hoc control vs bvFTD $p<0.001$, vs svPPA $p<0.001$); Figure 16C) component 4 ($F_{6,192}=15.9$, $p<0.001$: post hoc control vs PSP $p<0.001$, vs CBS $p<0.001$, vs PPA $p<0.001$, vs bvFTD $p<0.05$, vs nvPPA $p<0.001$; Figure 16D). Component 5 ($F_{6,192}<1$), 6 ($F_{6,192}<1$), 7 ($F_{6,192}=1.7$, ns), and 8 ($F_{6,192}=2.0$, $p=0.07$) (Figure 16 E-H) revealed no significant differences.

Figure 16 bars indicate post hoc Tukey tests for each group versus controls (thick = $p<0.001$, dotted $p<0.05$, Stars represent extreme outliers (3*interquartile range [IQR]), circles represent mild outlier (1.5*IQR)).

3.2.5 Relationship of Components to Measures of Cognition and Function

Parametric Pearson's correlation analyses (see Table 13) revealed that the patient rated change component (PC1) was related to disease severity (FRS) and frontal dysfunction (FAB). Higher scores on components 2-4 correlated with more severe disease (FRS), greater cognitive decline (ACE-R, MMSE) and frontal dysfunction (FAB). Component 2 was positively correlated with the PSP-RS, reflecting greater PSP-like cognitive and motor impairment. Performance on behavioural impulsivity tasks (component 4) was negatively correlated with PSP-RS. Executive function, measured by ACE-R fluency, correlated with components 1-4 and 7.

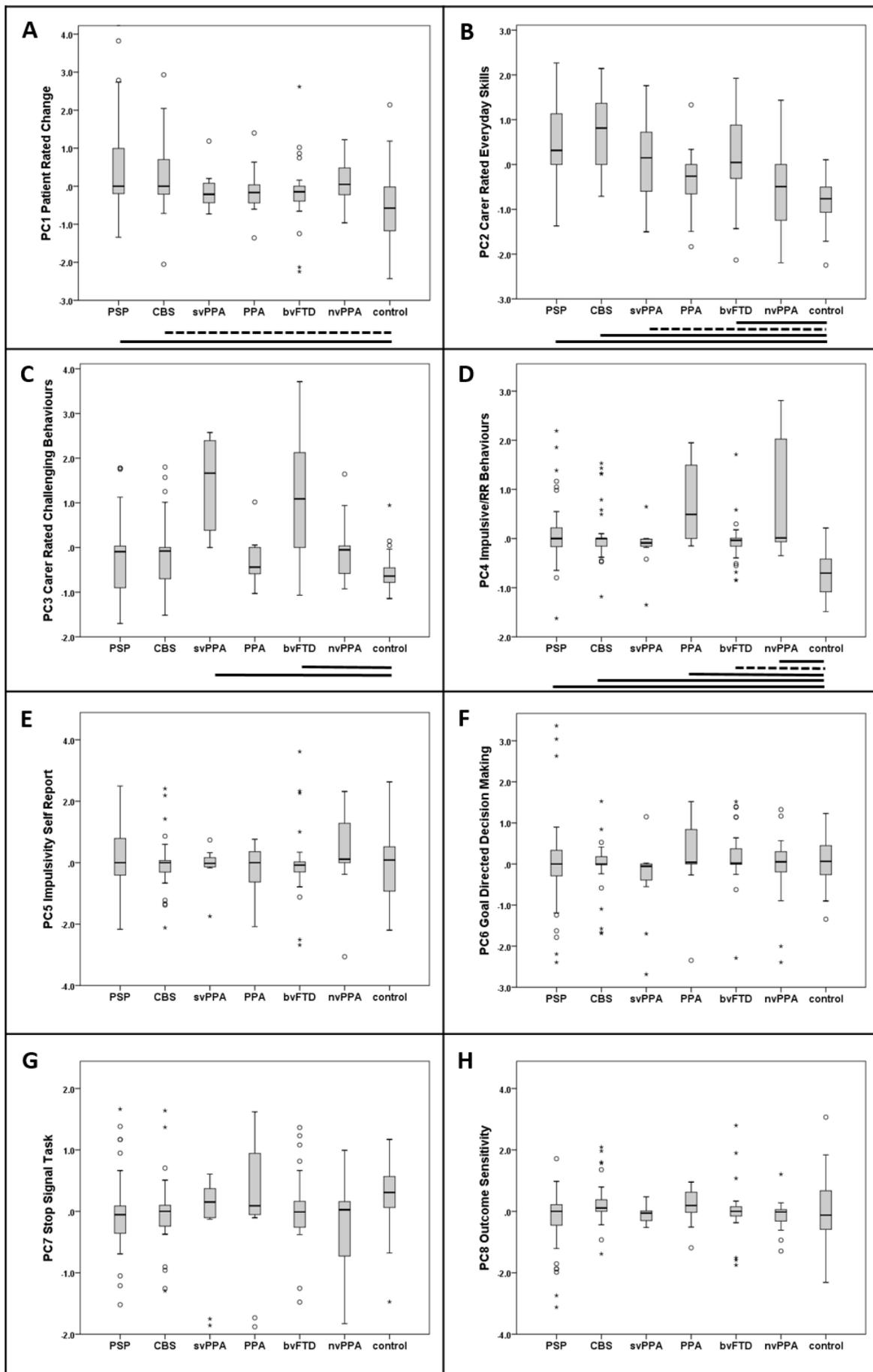


Figure 16: Box Plots of Component Scores by Diagnosis (PC1-8)

Table 13: Pearson's correlations between the eight orthogonal components identified by principal components analysis and demographic, cognitive and severity ratings

Component	Age	FRS %	ACE-R	ACE-R Fluency	MMSE	PSP-RS	FAB
1) Patient Rated Change	0.050	-0.271**	-0.125	-0.277**	-0.085	0.134	-0.258*
2) Carer Rated Change: Everyday Skills & Self Care	-0.047	-0.658**	-0.343**	-0.335**	-0.346**	0.550**	-0.342**
3) Carer Rated Change: Challenging Behaviours	-0.172*	-0.524**	-0.357**	-0.388**	-0.335**	-0.224	-0.308**
4) Impulsive/Reward-related Behaviours	-0.006	-0.213*	-0.354**	-0.428**	-0.293**	-0.281*	-0.397**
5) Impulsivity Self Report	-0.106	0.041	0.087	-0.030	0.109	0.078	-0.001
6) Goal-directed decision-making	0.055	0.017	0.104	0.037	0.077	0.074	0.023
7) Stop Signal Task	-0.037	0.080	0.172*	0.190*	0.170*	-0.170	0.228*
8) Outcome Sensitivity	0.032	0.066	-0.029	0.035	-0.057	-0.130	-0.036

*p<0.05; **p<0.001 (uncorrected, approximating p<0.05 corrected for multiple comparison).

3.3 Discussion

The data described above provide three critical insights into apathy and impulsivity in FTLD disorders, in addition to confirming their multifactorial nature. First, apathy and impulsivity are common in all syndromes associated with frontotemporal lobar degeneration, not only those which include apathy and impulsivity as diagnostic criteria. Second, they are *positively correlated*, such that apathetic individuals are also more impulsive. Third, the components that reflect patients' own ratings of apathy and impulsivity are distinct from those based on carer observations and objective behavioural measures.

In this cross-sectional study, disease progression may have blunted the phenotypic boundaries between syndromes in comparison to their initial presentation^{75,291}. This emphasizes the advantages of transitioning from a traditional 'nominal' diagnostic classification (for example, ICD or DSM) to dimensional approaches such as the Research Domain Criteria (RDoc) with data-driven methods as described here. The recognition of apathy and impulsivity across syndromes highlights the limitations of diagnostic criteria, which overlook these symptom commonalities, and means that symptomatic therapies in one illness may help patients and carers affected by another^{131,205,268}. Current criteria do not fully recognise the extent of behavioural changes in syndromes for which the behavioural disorder is not part of the diagnostic criteria (for example, nvPPA⁶, PSP¹⁴), or the emergence of behavioural disorders with disease progression (for example, svPPA⁶). A clinical trial for such symptoms would be most powerful if stratifying patients into 'apathetic' and/or 'impulsive' groups across the FTLD spectrum, rather than diagnostic groups which include patients with and without the relevant symptoms. For example, both semantic and behavioural variants of frontotemporal dementia were strongly weighted to component 3 (Figure 16). Although svPPA is primarily diagnosed as a language disorder with predominant temporal lobe atrophy the spread of pathology to orbitofrontal systems and increasing behavioural change indicate partial convergence of svPPA and bvFTD phenotypes³⁰.

The data revealed that apathy and impulsivity were positively correlated in FTLD syndromes. Measures of apathy and impulsivity showed a strong positive relationship, both through simple Pearson's correlation analysis (Figure 12) and PCA, where measures loaded onto the same components (Table 12). Component 1 reflected increased patient rated apathy (AES) and impulsivity (BIS), while Component 3 had strong loadings from the Carer rated AES and NPI Disinhibition subscore, in addition to behavioural changes captured by the CBI. Objective measures also supported this finding; Component 4 had strong loadings from measures of

response inhibition (Go/NoGo), information sampling (IST) and incentive motivation (CRRT). This contradicts theoretical models in which impulsivity and apathy represent opposite extremes of a single spectrum. Some authors have proposed that impulsivity represents a dopamine-dependent spectrum of motivational or goal-directed control^{86,100,224} while apathy reflects an independent noradrenaline-dependent spectrum of arousal and uncertainty^{78,189}. However, noradrenaline is also implicated in impulsivity²⁰⁵ and dopamine in apathy^{86,180}, indicating overlapping pharmacology. Although this study did not directly measure or manipulate such neurotransmitters, the results are relevant to the pharmacological analysis of apathy and impulsivity. Specifically, the positive correlation suggests either that there is a common neurobiological basis for apathy and impulsivity, or that the widespread pathology in FTLN syndromes leads to simultaneous deficits in anatomically and/or pharmacologically different networks (see subsequent Chapters 4 and 5).

The cognitive components of apathy and impulsivity differed according to the assessor: patient, carer or experimentalist. This was also observed through comparisons of analogous test versions of the AES and CBI, which highlighted discrepancies between carer and patient ratings of apathy and behavioural changes respectively. The separation of patients' (component 1, 5 and 8) and carers' (components 2 and 3) ratings may reflect patients' lack of insight into disease-related changes or their difficulty with semantics and grammar in questionnaires. It is unlikely that patients lack insight into all aspects of their disease, but clearly they differ from carers in terms of their awareness of certain symptoms. Carer ratings may be biased by personal distress¹⁰⁴ or education about the illness. Indeed, carer ratings of apathy on the AES were higher than both patient and clinician ratings (Figure 14). Eliciting and quantifying behavioural disorders through an interview with carers and/or questionnaires is a feature of both clinical practice and research but may not quantify the differences between a patient's own symptoms (the usual target of treatment in medicine) and the behavioural signs reported by carers (a major contributor to burden and patient risk). These findings suggest that clinical trials in syndromes associated with frontotemporal lobar degeneration must distinguish whether treatments are for patients' or carers' wellbeing and chose outcome measures accordingly.

Critical for translational studies, the subjective questionnaires did not load onto the same components as objective behavioural measures (components 4, 6 and 7). The identification of homologous tasks in preclinical models and clinical populations can successfully facilitate translational therapeutics^{130,131,205}, but may not readily apply to FTLN.

The data confirmed that impulsivity is multifaceted. For example, response inhibition (Go/NoGo) was associated with component 4, whereas action cancellation performance (SST) loaded onto component 7, consistent with prior evidence of separate neural pathways and pharmacology^{130,205,208,268}. However, motor and saccade Go/NoGo performances were highly correlated, both loading negatively onto component 4 (reflecting lower d' and therefore poor performance), supporting the use of saccadometry to evaluate cognitive-behavioural systems in patients with severe limb-motor deficits²²⁰.

In other neuropsychiatric studies of impulsivity such as addiction, the BIS and BIS/BAS questionnaires have been used to quantify individual differences^{228,229}. Similar questions partly explain their presence on Component 5 “Impulsivity Self-Report” (e.g. BIS/BAS: ‘I often act on impulse’ versus BIS: ‘I act on impulse’). But, the transdiagnostic plots (Figure 16) suggest that such responses do not readily distinguish patients affected by FTLT.

Similarly, the last and weakest component, termed “Outcome Sensitivity” due to strong loadings from the Kirby and BIS/BAS’s BIS subscore, did not reflect group differences, consistent with this component being a trait in the general population rather than a disease-specific deficit. The BIS subscore reflects a system for relaying cues of punishment, non-reward and novelty, to regulate behaviour²⁹². Studies of addiction have also reported no significant differences between controls and substance abusers on the BIS subscore²²⁸. In the Kirby paradigm, steeper discounting has been reported in drug addiction, schizophrenia and PD²⁸⁹.

The PiPPIN study and the described statistical analyses have a number of methodological and interpretative limitations. Although the PiPPIN study aimed to assess the multifaceted constructs of apathy and impulsivity, some patients could not perform on certain tasks, and the Cambridge Gambling Task proved especially difficult despite its successful application in milder neuropsychiatric populations. The task was withdrawn after 37 participants (note including the CGT in a subsidiary PCA did not alter the factor structure). Alternative tasks (including the CRRT) and questionnaires remained in the full battery to assess abnormalities in incentive motivation and reward. Pathological gambling is uncommon even in bvFTD, and the impairment may arise partly from executive deficits.

Some of the assessment tools were disease-specific, or developed for a particular cohort, limiting their generalisation. For example, the FRS measure of disease severity in FTD may not be directly applicable to PSP and CBS. It could therefore be argued that one should assess the

neural correlates of performance separately within each diagnosis. However, reducing the analysis to a multiplicity of tests of individual symptoms within syndromes would have significant drawbacks, not just in terms of the severe loss of power to detect correlations in small sub-cohorts. It would also belie the evidence of clinical overlap and convergent symptomatology across the separate diagnostic groups. Moreover, the use of factor loadings for each component for each patient provides a more principled means to accommodate syndromic variance, without bias or diagnostic circularity.

The PiPPIN study sought to obtain the maximum information about potential aspects of apathy and impulsivity, whilst bearing in mind the tolerance and frailty of patients with FTLD associated disorders. However, a neuropsychological test battery is necessarily selective and conclusions can only relate to the patients studied and the domains of cognition and behaviour assessed. There were representative test types (questionnaires, objective and observer characteristics) and tests that were widely used in the literature to capture different aspects of reward motivation, effort mood, movement, inhibition and impulsivity. Questionnaires are clearly limited in their ability to determine the underlying cause of behavioural change. For example, “he/she shows less enthusiasm for his or her usual interests” or “he/she shows little interest in doing new things” on the CBI-R attempts to assess changes in motivation, but might be confounded by learned restrictions arising from physical motor impairments. In addition, performance on questionnaires and behavioural tasks may be influenced by semantics and executive function. By employing many tasks across a number of populations, I suggest that the extracted dimensions of apathy and impulsivity more accurately capture the essence of these behavioural changes than the use of single questions or tasks in isolation.

The variables used and the testing methodology were specifically designed to overcome limitations in this patient group. For example, I used d-prime as the major outcome measure for the Go/NoGo tasks, to provide an indication of performance based on the ratio between correct responses and false alarms, rather than the number of commission and omission errors or reaction times. For the Kirby, I proposed that apathy/impulsivity may exhibit as more change in the rate of temporal discounting (k) or insensitivity to perceived value of reward (no difference in k high - k low [Kirby difference]). However, the Kirby difference variable and the component weighted towards the Kirby (component 8) failed to show differences between groups. A subsidiary PCA using the original outcome measures (discounting rate at high, medium and low rewards) did not impact the structure of extracted components, suggesting that the Kirby measure may not be especially useful in the context of this patient population.

Additional tasks that quantify apathy in the healthy population are especially challenging in FTLN disorders (and were therefore not employed), because of sequential decisions, physical effort and strong executive demands. For example, grip-force effort^{115,116,133} might be confounded by the movement disorders in several FTLN syndromes. Akinesia, depression and executive deficits in particular may confound the assessment of apathy.

Akinesia may readily be confused with apathy by observers. However, it is unlikely that the apathy identified across diagnostic groups is driven solely by akinesia, as it does not mirror the severity of apathy across groups (see Table 6, Figure 16). Motor features were indirectly measured, in terms of physical signs (including akinesia in the PSPRS) and as reaction times in objective behavioural tests. The correlations between the principal components and PSPRS were very limited (Table 13). Depression can also confound the assessment of apathy. Indeed, patient rated apathy, depression and anhedonia scores were positively correlated (component 1), despite distinctions between the proposed underlying neurobiology of these complications¹⁴¹. However, self-rated depression symptom scores as measured the BDI-II, are distinct to the clinical disorder of depression that is primarily a mood disorder. Apathy and depression may have common symptoms, and both contribute to high scores on a questionnaire such as the BDI-II, even as distinct pathological entities. The role of executive function in task performance must also be considered. Executive deficits are part of the diagnostic criteria for bvFTD, and supportive criteria for PSP, and yet they are common in other disorders associated with frontotemporal lobar degeneration⁵⁰ However, a deficit in executive function cannot account for the fractionation of apathy and impulsivity as revealed by the PCA. Rather, the separate impairments in behavioural control, inhibition, goal-directed behaviour and appropriate planning of responses can be construed as a part of the complex dysexecutive status resulting from frontotemporal lobar degeneration. Indeed, verbal fluency, a marker of executive function²⁹³, correlated with components 1-4 and 7, in keeping with the association between executive functions and frontal lobe function²⁹⁴. In summary, the executive dysfunction in the PiPPIN cohort is best seen as encompassing – but not causing – the observed components of apathy and impulsivity.

Years from symptom onset was estimated based on recall of initial relevant symptoms. However, this is clearly not equivalent to disease duration, as the underlying pathological processes associated with FTLN syndromes often occurs years before the onset of symptoms (at least in context of genetic FTLN⁸¹). Even the estimate of symptom duration is not straightforward, as for many of the FTLN syndromes, the initial relevant symptoms may not be

recognised and may have an insidious onset, especially symptoms and signs related to social behaviours. Events such as falls in progressive supranuclear palsy are usually more clear-cut, but may not be the presenting feature, even in PSP. Nevertheless, the estimate of symptom duration provides additional interesting information regarding the PiPPIN cohort tested throughout this thesis.

It is possible that the PiPPIN cohort is biased or unrepresentative of the full spectrum of disorders associated with FTLD. However, the PiPPIN study used multiple sources of referral in community as well as specialist services, to reach all regional patients, and the attrition from case identification (n=204) to neuropsychological assessment (n=149) and MRI (n=70) included all disorders.

Finally, this work relies on clinicopathological correlations and the current consensus criteria, acknowledging that for some disorders (nvPPA, CBS and bvFTD) the clinicopathological correlations are weaker than others (svPPA, PSP).

3.4 Conclusion

In conclusion, apathy and impulsivity are common and overlapping consequences of FTLD. Carer and patient ratings reflect distinct insights into problematic disease features, while the lack of correlation between subjective questionnaires and objective tasks in FTLD syndromes highlight the need for improved, disease-specific assessment tools to facilitate clinical trials. A dimensional, transdiagnostic approach to investigate and treat complex behavioural changes is advantageous and provides new insights into the components of apathy and impulsivity across FTLD syndromes.

Chapter 4 | The Neurobiology of Apathy and Impulsivity in Frontotemporal Lobar Degeneration Syndromes as Measured by Voxel Based Morphometry.

In this chapter, I examine the neural correlates of the eight extracted components from Chapter 3 in terms of grey and white matter structural change. Voxel based morphometry has been used to examine the neural changes associated with the FTLN syndromes, although previous studies often focus on a specific variant. Identifying the neurobiology associated with the components of apathy and impulsivity transdiagnostically will reveal the underlying systems associated with ratings from multiple perspectives and may provide targets for novel treatment development.

4.1 Introduction

4.1.1 Voxel Based Morphometry

Magnetic Resonance Imaging (MRI) has been widely used for differential diagnosis of disease, tracking disease progression and identifying the neural correlates associated with specific disease features. The characteristic loss of neurons, or brain atrophy, that occurs in neurodegenerative conditions can be detected as structural changes on MRI. Analysis of MRI by experienced radiologists and/or manual selection of regions of interest have largely been replaced by automated techniques in the research setting, which facilitate comparisons across large groups. Voxel based morphometry (VBM) is an unbiased, quantitative, automated technique^{295,296} used frequently to statistically identify differences in brain anatomy between groups, most commonly in terms of tissue loss in diseased patients. Studies comparing VBM to manual and visual measurements of brain regions have reported similar results, providing some biological validity for the technique^{297,298}.

Voxel based morphometry studies have provided insights into the neurobiology of the FTLN syndromes and their associated behavioural changes. Most studies have focussed on FTD, PSP or CBS/D in isolation, although comparative studies have also been conducted, aiming to identify regions of atrophy that can effectively dissociate the FTLN syndromes or distinguish them from other neurodegenerative conditions. The substantial overlap in clinical phenotypes, particularly within the spectrum of FTLN disorders, complicates accurate diagnosis. As new therapies are developed to treat specific pathologies, imaging methods to improve accurate *ante mortem* diagnosis are warranted to stratify patients more effectively for targeted treatment.

4.1.2 Structural Neural Correlates of the FTLN syndromes

Specific patterns of atrophy have been associated with the behavioural and language variants of frontotemporal dementia. Semantic variant primary progressive aphasia (svPPA) reflects atrophy largely in the anterior temporal region, whereas bvFTD affects the dorsolateral and frontal lobes. SvPPA is associated predominantly with progressive atrophy in the left anterior temporal and inferior temporal regions^{299–301}, orbitofrontal lobe, and insula caudate^{302–304}. Behavioural variant frontotemporal dementia is also associated with frontal, temporal and insula degeneration^{144,151,299,300}. A recent voxel based morphometry study revealed selective atrophy of the anterior cingulate and frontal insula cortices early in the course of bvFTD, while additional white matter and posterior grey matter structures densely connected to these sites degenerated with advancing disease¹⁶.

VBM studies of PSP have reported predominant atrophy in brainstem structures, including the midbrain, pons, thalamus, striatum and caudate nucleus^{166,183,305–307}. Similar patterns of atrophy have been confirmed by pathological studies^{14,190,308} and are highly consistent with the anatomical distribution of tau protein deposits³⁰⁸. The classical PSP supranuclear gaze palsy has been linked to neuronal loss in the nucleus raphe interpositus of the midbrain³⁰⁹, while motor deficits correlate with atrophy of the caudate and motor cingulate. Behavioural disturbances and executive dysfunction in PSP were initially considered to result largely from neurodegeneration in subcortical structures which disrupt cortical-subcortical circuitry^{14,310}. However, frontal atrophy, specifically in the orbitofrontal and medial cortices, are increasingly recognised^{183,257,311}. A correlation of frontal neuropsychological deficits with frontal hypometabolism and total frontal atrophy has also been documented^{257,312}.

VBM studies of CBD have reported a largely asymmetric (left>right) pattern of brain atrophy involving the bilateral premotor cortex, superior parietal lobes, posterior cingulate cortex, occipital cortex and striatum (caudate, putamen)³⁰⁵. Both grey and white matter loss occurs in the posterior frontal and parietal cortex and basal ganglia^{36,305,306,311}. Changes are also observed in the premotor cortex and frontal subcortical white matter, most significantly affecting the junction of the superior frontal sulci and the precentral sulci bilaterally³⁰⁵, a region thought to contain the frontal eye fields³¹³.

Despite the substantial overlap in clinical features of PSP and CBS/D, structural imaging studies have identified several brain regions that are differentially atrophied, facilitating accurate dissociation of the two syndromes. Overall, atrophy in CBD is markedly more severe

than PSP at autopsy for any given disease severity³¹⁴. Greater brainstem atrophy is observed in PSP compared to CBS/D and greater cortical atrophy in CBS/D than PSP. Indeed, Boxer et al., (2006) reported that the degree of atrophy in the midbrain, pontine tegmentum and left frontal eye field could differentiate PSP and CBS/D groups with 93% accuracy. Soliveri et al., (1999) also reported midbrain atrophy in 89.3% of PSP patients compared to only 6.3% in CBD³⁶. Increased atrophy of the brainstem in PSP has been linked to significantly more microglial burden in this brain region than in CBD³¹⁵. In a study of autopsy proven PSP and CBD, Josephs (2006) concluded that midbrain and superior cerebellar peduncle atrophy was indicative of PSP while frontoparietal lobe and pallidum atrophy in the absence of brainstem atrophy reflected CBD pathology. Premotor cortices and supplementary motor area appear affected in both pathologically confirmed PSP and CBD, and are therefore not appropriate for differentiating between the two clinical syndromes³⁰⁶.

4.1.3 Neural correlates of FTLN-associated Apathy and Impulsivity.

Voxel based morphometry analysis has provided important insights into the neuroanatomical correlates of cognitive and behavioural deficits associated with FTLN syndromes. Studies have focussed on behavioural variant FTD, as neuropsychiatric changes are widely recognised and form part of the diagnostic criteria.

Studies of bvFTD have consistently linked behavioural changes to atrophy of the frontotemporal lobes^{138,316}, with specific regions linked to different behavioural features. Disinhibition has been linked to the orbitofrontal cortex^{102,144,217,317}, temporal lobe^{100,144}, right nucleus accumbens (ventral striatum)¹⁰⁰, and the ventromedial prefrontal cortex¹³⁸. Hornberger et al., (2011) reported a correlation between atrophy of the orbitofrontal cortex/temporal pole and disinhibition as measured by both the subjective Neuropsychiatric Inventory disinhibition frequency score and objective Hayling Test¹⁴⁴. In addition to VBM, PET studies have reported significant changes in glucose metabolism bilaterally in the orbitofrontal cortex, anterior cingulate cortex, hippocampus/amygdala and nucleus accumbens in disinhibited FTD patients¹⁶⁸.

Studies assessing the neural correlates of apathy have been less conclusive, implicating the medial prefrontal cortex¹³⁸, dorsolateral prefrontal cortex^{100,102}, orbitofrontal cortex¹⁰⁰, anterior cingulate¹⁰², temporal lobe and caudate¹⁰¹, reflecting the anatomic organisation of fronto-subcortical circuits. Hypometabolism in the frontal medial and dorsolateral cortices bilaterally

have also been reported¹⁶⁸, in addition to the ventral polar frontal cortex, which is also implicated in impulsivity^{168,169}.

Increased awareness of the neuropsychiatric, cognitive and behavioural features of PSP has prompted research into their associated neurobiological underpinnings. Apathy and impulsivity are particularly common^{53,54,68}, but have largely been overlooked previously due to prominent motor features. Limited imaging studies suggest frontal atrophy in mesio-frontal targets of striatal projections likely account for the associated behavioural deficits in PSP^{166,183}.

It has become increasingly clear that there are similarities in the neurobiological changes implicated in apathetic and impulsive behaviours in FTLD disorders. This likely reflects the disruption of overlapping fronto-subcortical pathways, specifically those involving the orbitofrontal cortex which has been implicated in personality, social conduct and inhibition and the anterior cingulate, which are highly involve in cognitive control and motivational states^{112,310}.

4.1.4 Examining the Neural Correlates of Apathy and Impulsivity Components across the FTLD Spectrum

An important caveat to consider when interpreting the results of previous studies assessing the correlation between brain changes and behaviour, is the lack of accurate, disease-specific assessment tools available to quantify behavioural change in FTLD syndromes, particularly in the context of apathy. Development of numerous assessment tools for impulsivity likely accounts for the variability in the reported neural correlates^{100,144}. Furthermore, the available subjective and objective measures may bear little relationship to each other in FTLD syndromes (loading onto distinct components; Chapter 3). This may lead to inconsistent findings when examining the underlying neurobiological changes associated with apathy and impulsivity. Given these limitations, I suggest it may be more appropriate to assess the neural correlates of the psychological constructs underlying apathy and impulsivity and employ these as covariates in an imaging design matrix.

Differences in patient populations may also account for the variability in imaging findings. Previous studies have often focused on behavioural changes within each of the FTLD variants in isolation, with a particular focus on bvFTD patients, despite their presence across disorders. This risks overlooking other variants in which behavioural changes are also prominent. Understanding the complex relationship between brain changes and clinical features across

groups may provide insights into the neural systems underlying symptom commonalities. One of the advantages of using dimensional weighting rather than individual diagnostic classification in an imaging analysis, is that it enables better characterization of the neural systems underlying given behaviours. This approach is especially important when a set of behaviours are manifest across multiple conditions such as component 2 and 4, which were particularly abnormal in multiple disorders (see Chapter 3, Figure 16). To reduce the analysis to a myriad of “symptoms within syndromes” would greatly reduce both statistical power and insight into the commonality of disordered behaviour in FTLD syndromes.

Here, I employ voxel based morphometry to determine the grey and white matter neural correlates of the eight extracted components of apathy and impulsivity.

4.2 Methods

4.2.1 Cohort

Of the 149 participants included in the PCA analysis, a subset of 70 patients (PSP 22, CBS 13, bvFTD 14, nvPPA 12, svPPA 4, other PPA 5) and 27 controls underwent MRI. The imaging subset were representative of the cohort, with no significant differences between the imaging subset (n=70) and the non-imaged patients (n=79) in terms of demographics, disease characteristics and the major outcome variables included in the analysis (Table 14). Most patients underwent MRI on the same day as cognitive assessment (median and mode=0 days).

4.2.2 Imaging Acquisition

Magnetic resonance imaging (MRI) was performed at the Wolfson Brain Imaging Centre, using a TIM-Trio 3T scanner (Siemens, Germany <http://www.medical.siemens.com/>). T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) images were acquired with a TR=2300 ms, TE=2.86 ms, matrix=192×192, in-plane resolution of 1.25x1.25mm, 144 slices of 1.25mm thickness, inversion time=900 ms and flip angle =9°.

Preprocessing used diffeomorphic anatomical registration using exponentiated Lie algebra (DARTEL) in SPM12 following brain extraction. The T1 images were segmented using default settings to output the DARTEL import images for grey and white matter. Then a study-specific template was created using 5 age-matched participants from each of the diagnostic groups (to reduce group bias). The remaining subjects' data were warped to the template. Next, the grey and white matter template segments were affine-transformed to MNI space. The affine template transformation was applied to the maps of the individual participants together with smoothing

by an 8mm isotropic full width at half maximum Gaussian kernel. The total intracranial volume was calculated using Tissue Volumes function in SPM12, and study-specific masks created from voxels with a value of > 0.1 in $>80\%$ ³¹⁸ of the images.

4.2.3 Voxel-Based Morphometry

Due to orthogonality of PCA components, their neural correlates were identified by a general linear model, using the smoothed normalised grey and white matter segments. The design matrix included the eight mean centered Principal Component Factor scores, age, gender and total intracranial volume and an intercept. Both positive and negative contrasts were examined from the General Linear Model for all eight principal components. Significant effects were identified using cluster-level statistics (FWE_c $p < 0.05$, corrected for multiple comparisons) above a height threshold of $p < 0.005$ (unc). The non-stationary cluster extent correction was applied in view of the non-uniformity of the data.

4.3 Results

The components of apathy and impulsivity were correlated with distinct grey and white matter abnormalities, in corticospinal, frontotemporal, frontostriatal and subcortical systems. Figures 17 and 18 illustrate the distributions of significant clusters.

Significant grey matter correlates were identified for components 2, 3, 4 and 7 (Figure 17, Appendix A) and white matter correlates for components 1, 2, 3 and 7 (Figure 18, Appendix B). Note that patients' (component 1) and carers' (components 2 & 3) ratings were associated with distinct white matter correlates. The patient ratings of component 1 were related to impairments in the corticospinal tracts, from the mid centrum semiovale, through corona radiata to the upper brainstem. In contrast, the carer ratings correlated with frontostriatal and brainstem systems. Specifically, carer rated change in everyday skills and self care (component 2) reflected localised brainstem white matter changes (medulla, pons, and lower midbrain largely sparing the thalamus, and white matter deep to the middle frontal gyrus) (Figure 18), with grey matter changes extending from the caudate, putamen and thalamus into multiple cortical regions including medial and lateral premotor and sensorimotor cortex, and scattered foci in prefrontal, parietal and occipital cortex (see Figure 17). Carer rated behavioural change (component 3) was associated with widespread but complementary changes in both grey and white matter of the temporal pole, frontal pole, orbitofrontal and medial frontal cortex and their connecting tracts (Figure 17 & 18).

Performance on the motor/saccade response inhibition, cued reinforcement and information sampling tasks (component 4) reflected grey matter change in multiple regions including thalamus, lateral temporal cortex, posterior and dorsal-anterior cingulate cortex, and parieto-occipital cortex (Figure 17). Performance on the Stop-Signal task (component 7) reflected localised grey matter change in the right inferior frontal region, anterior cingulate and white matter change in the left frontal lobe (Figures 18 and 19).

Component 5 “Impulsivity Self-Report”, Component 6 “Goal-Directed Decision Making” and Component 8 “Outcome Sensitivity” did not reveal any significant anatomical correlates.

4.4 Discussion

These imaging results build on the major findings of the previous chapter, briefly that a) apathy and impulsivity are present across the frontotemporal lobar degeneration spectrum, b) apathy and impulsivity are positively correlated and c) the components that reflect patients’ own ratings of apathy and impulsivity are distinct from those based on carer observations and objective behavioural measures.

Here, I show that the anatomical networks associated with apathy and impulsivity in this cohort correspond with established networks for goal-directed behaviour, social cognition, motor control and vegetative functions. Specifically, carer ratings (AES, NPI, CBI) reflect widespread disruption in frontostriatal and brainstem systems required for motivation and arousal, while patient ratings (AES, BIS, SHAPS, BDI, MEI) correlated with changes in cortico-spinal tracts which I suggest reflects patients’ awareness of their motor deficits despite lack of insight into cognitive decline. Objective measures reflected localised changes in previously identified task-specific brain regions (e.g. SST and right inferior frontal gyrus).

Although patients with frontotemporal dementia are said to lack insight, component 1 correlated with well-defined and largely symmetric neural systems including the corticospinal tracts. PSP and CBS cases scored highly on Component 1, but the neural correlates differ from atrophy patterns identified by voxel based morphometry studies of PSP and CBD versus controls^{183,306,319–322}, which highlight deficits in the medial frontal cortex, parietal lobe and brainstem. The observed neural correlates may reflect patients’ awareness of motor deficits, while their insight into cognitive decline and behavioural change remains limited; the latter changes being identified by carers.

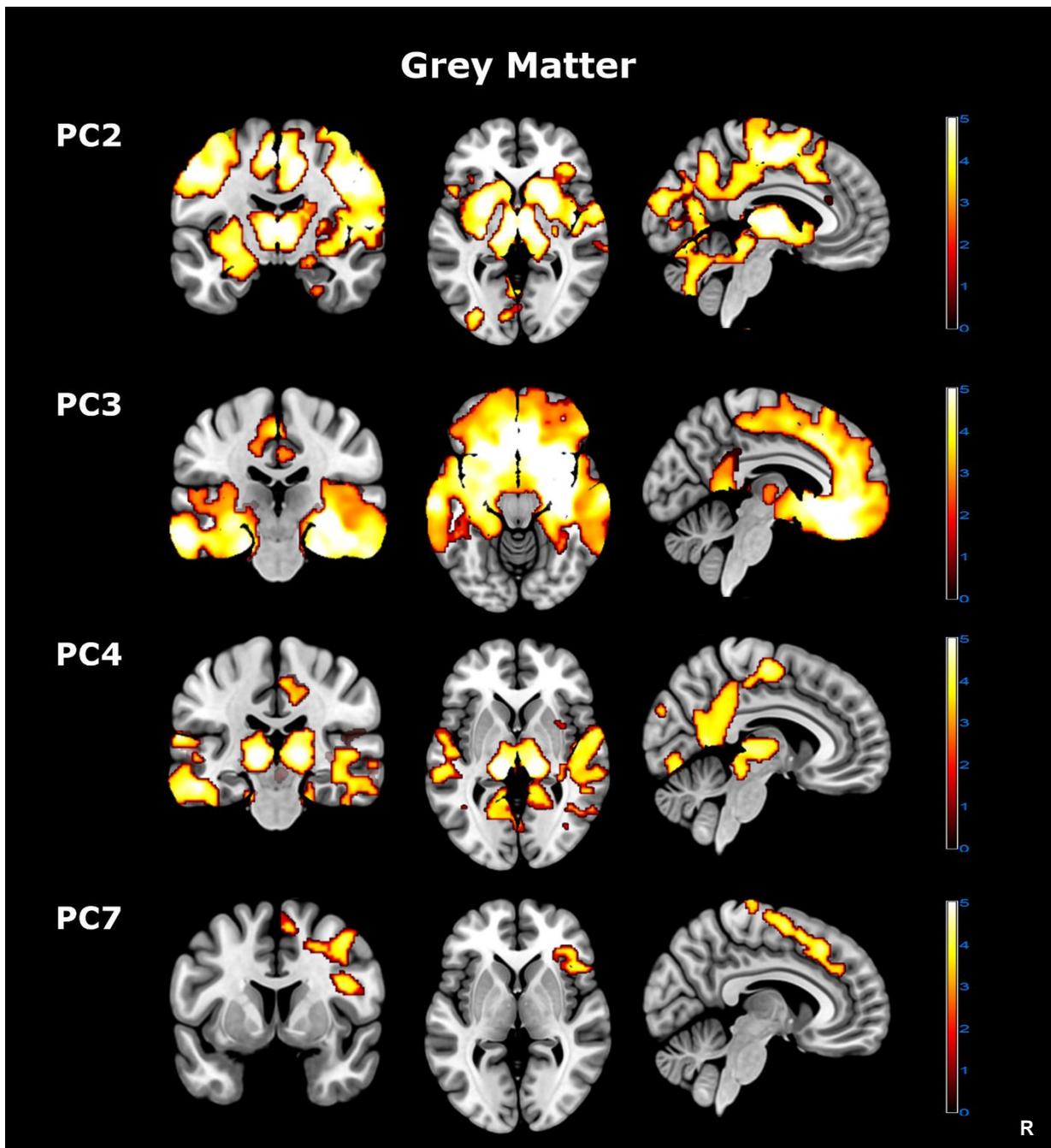


Figure 17: Grey Matter VBM Neural Correlates of Apathy and Impulsivity in FTLD Syndromes.

VBM analysis revealed distinct neural grey matter correlates for principal components 2-4 and 7. Components 2-4 represent negative correlations, with higher component scores reflecting a loss of grey matter in the relevant brain regions. Component 7 was positively correlated with the highlighted brain regions, with higher component scores representing increased grey matter in these areas.

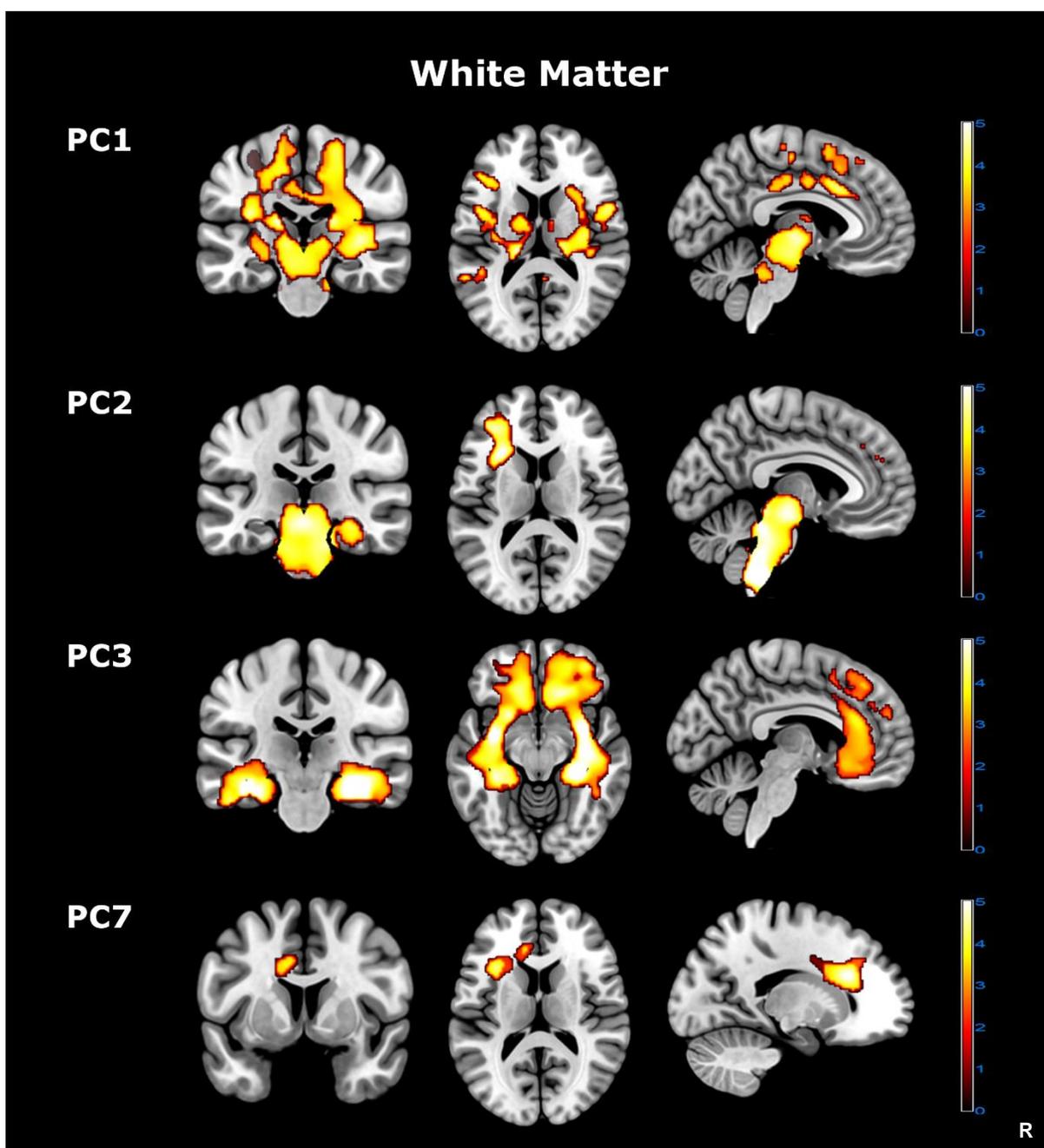


Figure 18: White Matter VBM Neural Correlates of Apathy and Impulsivity in FTLD Syndrome.

VBM analysis revealed distinct neural white matter correlates for principal components 1-3 and 7. PC 1-3 represent negative correlations, with higher component scores reflecting a loss of white matter in the relevant brain regions. PC7 was positively correlated with the associated brain regions, with higher component scores reflecting increased white matter in the highlighted areas.

Table 14: Comparison of Imaging Subset (N=70) and Non-Imaging Subset (N=79) of the PCA Sample (N=149)

	Variable	Imaged (N=70)	Non Imaged (N=79)	T Stat	P value (unc)
Demographics & Cognition	Age	68.2±8.2	70.4±8.6	1.6	0.12
	Gender M:F	39:31	37:42	($\chi^2=1.2$)	0.33
	ACE-R Total (max 100)	67.3±22.2	58.9±23.0	-1.7	0.10
	MMSE Total (max 30)	23.0±6.8	20.7±6.7	-1.6	0.12
	FRS % Score (max 100)	41.4±27.9	32.5±23.6	-1.8	0.08
Questionnaires	Apathy Evaluation Scale (AES, max 72):				
	- <i>carer</i>	46.5±12.6	50.8±11.7	1.8	0.08
	- <i>patient</i>	36.6±9.2	34.5±10.2	-0.8	0.44
	- <i>clinician</i>	43.1±9.6	45.1±11.3	0.76	0.45
	Barratt Impulsiveness Scale (BIS, max 120)	64.1±7.9	61.5±8.8	-1.1	0.29
	Behavioural Inhibition System/Behavioural Activation System (BIS/BAS):				
	- <i>BIS subscore</i>	11.0±3.3	10.8±2.9	-0.2	0.83
	- <i>BAS drive</i>	11.2±2.9	11.7±3.8	0.5	0.60
	- <i>BAS funseeking</i>	16.4±2.7	17.4±2.8	1.2	0.25
	- <i>BAS Reward Responsivness</i>				
	Motivation and energy inventory (MEI, max 144)	80.5±27.2	83.8±22.6	0.4	0.69
	Beck depression inventory (BDI, max 63)	13.1±10.7	12.7±7.6	-0.2	0.88
	Snaith Hamilton pleasure scale (SHAPS, max 56)	22.3±5.1	23.1±3.8	0.6	0.58
	Neuropsychiatric inventory (NPI, fraction with positive response):				
	-Apathy subscore	.59±.50	.66±.48	0.7	0.46
	-Disinhibition subscore	.35±.50	.31±.47	-0.5	0.65
	Cambridge behavioural inventory (CBI-R, max 180)	62.0±35.7	73.8±33.7	1.8	0.08
Kirby (difference)	0.01±0.05	0.04±0.07	1.5	0.13	
Behavioural Tasks	Information Sampling Task (IST)				
	-Probability of being correct Fixed	0.75±0.15	0.71±0.11	-0.8	0.41
	-Probability of being correct Decreasing	0.67±0.17	0.66±0.08	-0.1	0.89
	Cued reinforcement reaction time (CRRT)				
	-reward related speeding	62.1±331.8	128.0±853.7	0.57	0.57
	-Total Errors	4.1±5.0	4.5±8.3	0.2	0.82
	Stop Signal Task (SST)				
	-Stop signal reaction time (SSRT)	401.8±213.1	430.6±242.3	0.4	0.81
	Motor Go/NoGo Dprime	3.2±1.3	3.0±1.2	-0.7	0.48
	Saccade Dprime	0.79±1.1	0.62±1.1	-0.4	0.68

Comparison of imaged versus non-imaged sample using Student's Independent T-Test and Chi-squared for gender comparison between groups. All variables were non-significant.

In contrast to patient ratings, carer ratings of challenging behaviours (component 3) and vegetative features (component 2) correlated with frontostriatal and frontotemporal networks for motivational and arousal systems^{145,323,324} and brainstem integrity. Component 3 represents a coherent “behaviour” score based on the abnormal behaviour, mood, beliefs, eating habits, stereotypical behaviour, memory and motivation sections of the CBI-R, in contrast to everyday skills and vegetative functions associated with Component 2. Components 2 and 3 correlated with functional/disease severity (FRS) and cognitive decline (ACE-R, MMSE, FAB), supporting the hypothesised association between apathy, cognition and functional decline⁸⁴.

Both semantic and behavioural variants of frontotemporal dementia were strongly weighted to component 3 (Figure 16). Although svPPA is primarily diagnosed as a language disorder with temporal lobe atrophy, the spread of pathology to orbitofrontal systems and increasing behavioural change indicate partial convergence of svPPA and bvFTD phenotypes³⁰. The neural correlates of component 3 (Figures 18 & 19) suggest disrupted motivation and reward processing circuitry with both apathy and impulsivity, consistent with the regulation of reward, motivation and reinforcement by projections from the orbitomedial prefrontal cortex and anterior cingulate to ventral striatum^{101,208,224}. Carer ratings closely reflect changes in these brain circuits previously implicated in apathetic and impulsive behaviours^{86,100,111}. Analogous changes have been observed in many neurological and psychiatric impulsivity disorders^{86,111,208,228}.

The white matter correlates of component 2 (everyday skills and vegetative functions) were concentrated in the brainstem (Figure 18), with grey matter correlates extending from the thalamus to posterior regions of cingulate and parietal cortex (Figure 17). These changes were most strongly associated with PSP and CBS, consistent with previous reports⁵⁰. Degeneration of the brainstem is proposed to affect the reticular activating system that regulates wakefulness, attention and alertness. Furthermore, sustained attention and oculomotor control require functional integration of the brainstem, thalamus and neocortical areas associated with this component, and are particularly affected by PSP and CBS.

The stop-signal task was weighted to component 7 and revealed localized changes in focal brain regions within the right frontal lobe. Previous studies of health, Parkinson’s disease, ADHD and ageing have consistently associated this task with the integrity, activity and connectivity of the right inferior frontal gyrus^{208,211}, pre-supplementary area and subthalamic nucleus²⁵⁵, as well as noradrenergic^{130,205} and serotonergic²⁶⁸ function. Higher scores on component 7

(better performance) correlated with increased grey matter volumes in the right inferior frontal gyrus and its connections to the striatum, providing further construct validation of this dimensional approach.

This imaging study incorporates the methodological and interpretative limitations discussed in Chapter 3, in addition to some imaging specific limitations. Despite the substantial literature using white matter VBM, there are recognised limitations. Voxel-based methods have used either the white matter volume estimates, analogous to grey matter VBM, or voxel based comparisons of diffusion metrics like FA and MD. I used the former method in SPM, similar to several other studies^{183,305,307,325}. The use of SPM-style VBM (using white matter estimates from the T1 image) is of course different from voxel-based analyses of diffusion metrics. There are several limitations, including normalisation and mislocalisation errors, as discussed for example by³²⁶, and while these may motivate DTI based analyses, they qualify but do not invalidate VBM of white matter. Agosta for example, has suggested that DTI metrics may serve as an early marker of white matter integrity loss that later becomes detectable by VBM³²⁷.

VBM changes in white matter should therefore be interpreted with caution³²⁶, especially where white matter correlates are observed in the absence of grey matter correlates (for example, component 1). They may reflect true white matter influences on complex behavioural repertoires, but false positive correlations may arise from normalisation and mislocalisation errors and the partial-volume effects of smoothing. In contrast, the complementarity of white and grey matter correlates of component 2 and 3 strengthens their interpretation. VBM has been used extensively in the literature to examine white matter volumes in PSP^{166,183,305–307,322}, CBS/D^{305–307,320} and frontotemporal dementia¹⁰. However, alternative methods are increasingly common to study white matter changes in FTLN syndromes, including diffusion-weighted imaging with voxel-wise, regions-of-interest or tract-based statistics^{328–330} (Chapter 5).

In disorders of extreme atrophy like svPPA, the risk of mislocalisation in the VBM is acute and something which has motivated alternative methods such as TBSS³²⁶. However, in head to head trials between voxel based and tract based white matter analysis²⁵⁶, the inferences on group-wise disease-related changes in white matter are remarkably similar. Similar results are seen across separate studies by different groups using white matter VBM and DTI based measures^{10,320,329,330}. Therefore, despite differences in assumptions, confounds and sensitivity, there is generally consensus across methods in the regional effects of FTLN syndromes on white matter.

4.5 Conclusion

This dimensional approach provides new insights into the neural basis of apathy and impulsivity in FTLD. Structural brain imaging revealed corticospinal tract impairments in relation to patient ratings, while carer ratings correlated with frontostriatal, frontotemporal and brainstem systems. Objective tests correlated with changes in localised, task-specific brain regions. Recognition and quantification of separate neurocognitive systems for behaviour will facilitate the development of new symptomatic therapies. The neuroimaging correlates of the different “modes” of apathy and impulsivity provide a principled way to clinically assess the benefits of symptomatic and disease-modifying drugs on the neural systems that regulate different behaviours.

Chapter 5 | White Matter Tract Changes Associated with Apathy and Impulsivity in Frontotemporal Lobar Degeneration Syndromes: A Diffusion Weighted Imaging Analysis.

In the previous chapter, I presented the structural grey and white matter changes associated with the components of apathy and impulsivity across frontotemporal lobar degeneration syndromes, as measured by voxel based morphometry. In view of the limitations associated with white matter analysis using this technique (discussed in Chapter 4), here I employ diffusion weighted imaging, specifically tract based spatial statistics, to examine the white matter tract changes associated with the components of apathy and impulsivity.

5.1 Introduction

5.1.1 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is an application of diffusion weighted magnetic resonance imaging (DWI) that is sensitive to changes in white matter microstructure and macroscopic connectivity in health and disease³³¹, including syndromes associated with FTLD^{256,322,330,332–335}. DTI measures the diffusion rate (mean diffusivity) and directionality (fractional anisotropy, radial and axial diffusivity) of water molecules within a tissue. The tissue type, integrity, and architecture all influence molecular diffusion. White matter is considered directionally dependent or anisotropic, with preference for diffusion along tracts, while grey matter is less anisotropic and cerebral spinal fluid is unrestricted or isotropic^{331,336}. Potential barriers to diffusion across white matter tracts include the axon membrane, myelin sheath, microtubules and neurofilaments³³⁷.

5.1.2 White Matter Change in FTLD Syndromes

Diffuse structural change in white matter tracts is recognised as a pathological characteristic of FTLD syndromes^{322,332,338}. Consistent patterns of grey and white matter pathology are reported^{2,339–342}, but white matter disruption often extends beyond regions of grey matter atrophy^{327,332}. White matter damage is therefore unlikely to occur simply as a consequence of grey matter atrophy, but instead represents a core hallmark of FTLD pathophysiology, consistent with autopsy evidence of tau deposition in both grey and white matter³⁴³. Changes in white matter may even provide greater accuracy for FTLD classification than brain atrophy^{344,345}.

Across multiple FTLD phenotypes, grey matter atrophy is reported in the dorsolateral and medial frontal cortex with white matter abnormalities involving the genu and body of the corpus callosum and ventral frontotemporal and dorsal frontoparietal pathways³⁴⁶. However, syndrome specific patterns are also observed. Diffusion weighted magnetic resonance imaging has revealed widespread reductions of fractional anisotropy (FA) and increased mean diffusivity (MD) in frontal, temporal and parietal white matter in bvFTD^{144,338,347,348}. Affected tracts include the superior/inferior longitudinal fasciculus, anterior cingulum, genu and body of the corpus callosum, anterior commissure, corona radiata, corticospinal tracts, uncinate fasciculus and forceps minor^{327,338,345,348,349}. These regions have also been implicated in previous studies reporting combined grey and white matter change involving the ventromedial prefrontal cortex, insula, temporal and striatal regions and their underlying white matter tracts^{16,350}. Most severe changes are reported in the anterior portions of the superior longitudinal fasciculus and inferior longitudinal fasciculus, corresponding to high atrophy rates in the anterior frontal and temporal lobes³⁴¹. Despite predominant involvement of the fronto-temporal regions in bvFTD, the lateral and medial parietal lobe become increasingly involved with disease progression, reflecting associated changes in posterior white matter tracts, including the posterior cingulate and posterior aspects of the superior longitudinal fasciculus³⁴¹.

Language variants also demonstrate structural abnormalities in frontotemporal pathways (svPPA) and fronto-parieto-temporal pathways (nvPPA)³³⁰, including the anterior corpus callosum, uncinate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and corona radiata¹⁶⁴. Consistent distributions of grey and white matter change have been reported; svPPA show abnormalities (predominantly left-sided) in ventrostriatal temporal white matter, in line with previous structural and functional imaging of grey matter atrophy in these regions³³⁹.

Degeneration of the brainstem and the associational and commissural fibres are hallmarks of PSP, with significant white matter change in the superior cerebellar peduncles, body of the corpus callosum, inferior longitudinal fasciculus, and superior longitudinal fasciculus³³⁴. In CBS, changes in frontoparietal connecting fibres, intraparietal associative fibres, sensorimotor fibres of the hand cortical representation, and body and splenium of the corpus callosum have been reported³³⁵.

5.1.3 White Matter Changes Associated with Apathy and Impulsivity in FTLD Syndromes

Commonalities in the distribution of grey and white matter change across syndromes likely account for the observed overlap in clinical phenotypes^{342,346}, and the development of complex, multifaceted behavioural changes including apathy and impulsivity. Disease specificity may reflect the pattern and staging of large-scale network breakdown, providing further support for a dimensional approach to FTLD research. Studies assessing the white matter correlates of apathy and impulsivity in FTLD syndromes are limited and have largely focused on bvFTD, for which apathy and impulsivity are clinical criteria. This limits their relevance to other syndromes, for which these behaviours are also present. Increased behavioural deficits have been associated with atrophy of the frontotemporal lobes and their associated white matter connections^{138,316}, with disinhibition linked specifically to FA changes in the uncinate, forceps minor, and genu of the corpus callosum¹⁴⁴.

The reported white matter neural correlates of apathy are more varied³⁴¹. Cortico-subcortical white matter tracts have been associated with psychological processes linked to apathy, including emotion regulation, reward sensitivity and goal-directed behaviour¹¹². Damage to the uncinate fasciculus, a large white matter tract which connects the frontal and limbic regions, is linked to apathy in AD¹⁶⁵, small vessel disease⁹⁷, PSP³²⁷ and normal ageing³⁵¹.

The neural mechanisms underlying the clinical coexistence of apathy and impulsivity in frontotemporal lobar degeneration syndromes are unclear, but likely reflect disruption to white matter tracts connecting frontal-subcortical regions required for selection and initiation of goal directed behaviour and motivation³⁵².

In view of this literature reporting white matter changes across the FTLD spectrum, I tested the hypothesis that there are distinctive white matter correlates of the major components of apathy and impulsivity, using diffusion tensor imaging with tract based spatial statistics^{316,322,332,338}. Based on the volumetric changes discussed in Chapter 4, I predicted that regionally specific pathology of white matter tracts leads to different apathetic and impulsive behaviours in FTLD^{50,220}. I further hypothesized that separate dimensions of apathy and impulsivity, identified from the patients' perspective, carers' observation and neuropsychological measures, reflect degeneration of distinct white matter tract in the neural systems supporting motivational and cognitive control.

5.2 Methods

5.2.1 Cohort

A subset of 100 participants underwent diffusion weighted magnetic resonance imaging, mostly on the same day as cognitive assessment (median and mode=0). After quality control the imaging group comprised of 69 patients: 22 PSP, 14 bvFTD, 14 CBS, 11 nvPPA, 4 svPPA, 4 PPA other and 28 controls from the original 149 PCA subset. The imaged subset did not differ significantly from the non-imaged group in terms of demographics, disease features and the major outcome variables included in the analysis (Table 15). For the purposes of this analysis, the language variants are classified into a single PPA group, providing near equal sample sizes for further analysis (22 PSP, 14 bvFTD, 14 CBS, 19 PPA).

5.2.2 Group Comparisons

Statistical analysis of group differences and correlations used SPSS v23.0. Student's T-Tests comparing the imaged vs non-imaged sample were corrected for multiple comparisons.

5.2.3 Imaging Acquisition

MRI used a Siemens Magnetom Tim Trio at 3T ([Siemens, Erlangen](#)). Diffusion-weighted images (DWI) were acquired using a 63-direction gradient sequence with the following parameters: b value 1000s/mm²; TR 7800ms; TE 90ms; axial in-plane acquisition matrix 96×96; field of view 192×192mm; slice thickness 2mm and a total of 63 contiguous slices with in-plane resolution 2 mm isotropic. A single b value of 0 s/mm² image was acquired.

5.2.4 Diffusion Tensor Imaging

Diffusion-weighted images were processed using FMRIB Software Library (FSLv5.0; www.fmrib.ox.ac.uk/fsl), correcting for eddy currents and subject motion by affine registration to the first b_0 image using FSL *eddy_correct*. The $bvecs$ were rotated using *fdt_rotate_bvecs*. The b_0 image was extracted and a brain mask created using Brain Extraction Tool (*BET*). Diffusion tensors were fitted using *dtifit* to create maps of fractional anisotropy (FA) and mean diffusivity (MD). FA maps from five representative subjects from each group were non-linearly registered to the FMRIB58_FA_1mm target using the *tbss_2_reg* script, to avoid bias towards groups with a larger sample size. The resulting warped FA images were averaged to produce a study-specific FA template³⁵³. The *tbss_2_reg* script was then repeated for all subjects using the study-specific FA template as target, thereby bringing all subjects into the same anatomical space. From this study-specific template, a mean FA skeleton was produced and individual FA

skeletons mapped to this using a threshold of 0.2. Finally, the transformations putting the individual FA maps into the skeletonised standard space were applied to the L1, RD and MD maps.

5.2.5 Tract Based Spatial Statistics

Tract-based spatial statistics were used to examine the relationships between changes in diffusion metrics and behaviour³²⁶. Correlations between the skeleton DTI-tracts and principal components of apathy and impulsivity were assessed by non-parametric permutation analysis using FSL randomise with Threshold-Free Cluster Enhancement (TFCE), 2D optimisation and 5000 permutations. The design matrix contained a constant-term to model the intercept and each of the eight orthogonal principal components of behaviour. Cluster significance was tested at $p < 0.01$ and $p < 0.05$, corrected for multiple comparisons.

5.3 Results

5.3.1 Neuropsychological and Behavioural Results

Demographic, cognitive, neuropsychological and behavioural results of patients and controls who underwent DTI imaging (N=97) are displayed in Table 16. Groups were matched for age and sex, while patients were impaired on measures of cognition (ACE-R, MMSE, FAB) and disease severity (FRS, PSP-RS), and most measures of apathy and impulsivity.

5.3.2 Diffusion Tensor Imaging

Tract-based spatial statistics identified significant changes in white matter integrity in relation to Component 2 (yellow-red) and Component 3 (green-blue; TFCE corrected $p < 0.01$; see Figure 19). Changes in MD and FA were complementary and highlighted concordant patterns of white matter change in relation to carer-rated change in everyday skills and self care (Component 2) and carer rated change in complex behaviours (Component 3). Component 2 correlated with global FA (negative) and MD (positive) changes affecting the majority of white matter tracts extending from anterior to posterior regions, including the centrum semiovale and corticospinal tracts. In contrast, Component 3 reflected disruption in anterior brain regions, correlating with FA (negative) and MD (positive) changes in frontotemporal connections between the orbital- and ventrolateral-prefrontal cortex, anterior cingulate and temporal pole. The anterior-posterior dissociation between component 3 and 2 is most apparent for MD (see Figure 19A). Decreased FA and increased MD in the highlighted regions relate to impairments in performance (higher scores on components 2 and 3).

At the more liberal threshold of $p < 0.05$ corrected, Component 4 correlated with MD changes in regions connecting the pre-supplementary motor area to the right dorsolateral prefrontal cortex, as well as the occipital lobe (Figure 19B).

Table 15: Comparison of Diffusion Tensor Imaged versus Non Imaged Patients

	Variable	Imaged (N=69)	Non Imaged (N=80)	T Stat (χ^2)	P value (unc)
Demographics & Cognition	Age	68.7±8.0	71.1±8.4	1.5	0.14
	Gender M:F	38:31	38:42	($\chi^2=0.85$)	0.40
	ACE-R Total (max 100)	67.3±22.3	59.3±22.7	-1.6	0.12
	MMSE Total (max 30)	23.0±6.8	20.8±6.7	-1.6	0.14
	FRS % Score (max 100)	40.6±27.3	40.6±27.3	-1.3	0.19
Questionnaires	Apathy Evaluation Scale (AES, max 72):				
	- <i>carer</i>	46.9±12.4	50.2±12.3	1.4	0.17
	- <i>patient</i>	36.7±9.2	34.0±10.0	-1.0	0.29
	- <i>clinician</i>	43.4±9.6	44.5±11.3	0.5	0.61
	Barratt Impulsiveness Scale (BIS, max 120)	64.2±7.8	61.0±8.7	-1.4	0.17
	Behavioural Inhibition System/Behavioural Activation System (BIS/BAS):				
	- <i>BIS subscore</i>	20.8±4.7	19.7±3.4	-1.0	0.41
	- <i>BAS drive</i>	11.0±3.3	10.6±2.8	-0.4	0.70
	- <i>BAS funseeking</i>	11.2±2.9	11.6±3.7	0.4	0.70
	- <i>BAS Reward Responsivness</i>	16.4±2.7	17.3±2.7	1.1	0.29
	Motivation and energy inventory (MEI, max 144)	80.3±27.4	84.6±21.8	0.5	0.59
	Beck depression inventory (BDI, max 63)	13.3±10.7	12.2±7.6	-0.4	0.70
	Snaith Hamilton pleasure scale (SHAPS, max 56)	22.4±5.1	22.9±3.7	0.4	0.70
	Neuropsychiatric inventory (NPI, fraction with positive response):				
	-Apathy subscore	0.60±0.49	0.64±0.48	0.5	0.62
	-Disinhibition subscore	0.36±0.48	0.30±0.47	-0.6	0.60
	Cambridge behavioural inventory (CBI-R, max 180)	62.8±35.2	72.3±34.9	1.4	0.16
Kirby (difference)	0.01±0.05	0.03±0.06	1.4	0.17	
Behavioural Tasks	Information Sampling Task (IST)				
	-Probability of being correct Fixed	0.75±0.15	0.74±0.13	-0.3	0.80
	-Probability of being correct Decreasing	0.67±0.17	0.67±0.10	0.1	0.91
	Cued reinforcement reaction time (CRRT)				
	-Total Errors	4.2±5.0	1.9±2.0	-1.5	0.15
	Stop Signal Task (SST)				
	-Stop signal reaction time (SSRT)	447.0±244.3	548.5±176.7	1.3	0.20
Motor Go/NoGo Dprime	3.2±1.3	2.9±1.1	-0.8	0.41	
Saccade Dprime	0.79±1.1	0.62±1.1	-0.4	0.68	

Comparison of imaged versus non-imaged sample using Student's Independent T-Test and Chi-squared for gender comparison between groups. All variables were non-significant.

Table 16: Demographics, Neuropsychiatric and Behavioural Results for Imaged Patients and Controls

Variable		Imaged Controls	Imaged Patients	T-Test P value	PSP	CBS	PPA	bvFTD
Demographics and Cognition/Function	N	28	69	NA	22	14	19	14
	Age	68.4±6.0	68.7±8.0	NS	71.4±7.4	66.9±8.0	71.2±7.5	63.9±7.4
	Gender M:F	15:13	38:31	NS	12:10	7:7	11:8	8:6
	ACE-R Total (/100)	96.8±3.2	67.3±22.3	**	78.6±11.8	66.1±25.3	53.4±21.9	67.2±25.1
	MMSE Total (/30)	29.5±1.0	23.0±6.8	**	25.9±4.3	21.7±8.2	19.8±7.3	23.5±6.7
	FRS % Score (/100)	95.0±6.8	40.6±27.3	**	44.4±29.2	34.5±25.7	51.5±29.7	26.0±12.3
	PSP-RS	NA	29.9±18.6	**	40.0±11.4	37.3±19.0	7.3±5.4	16.0±10.5
	FAB	17.2±0.9	10.5±4.2	**	11.4±3.4	10.8±4.8	8.9±3.8	10.9±5.1
	Apathy Evaluation Scale (AES /72):							
- <i>carer</i>	24.3±5.4	46.9±12.4	**	47.2±11.1	47.4±10.7	41.2±14.9	53.6±9.4	
- <i>patient</i>	24.5±5.2	36.7±9.2	**	39.7±10.9	35.2±5.7	37.6±6.3	32.6±10.2	
- <i>clinician</i>	25.4±7.6	43.4±9.6	**	46.6±10.8	42.4±8.4	38.8±10.0	43.4±6.7	
Barratt Impulsiveness Scale (BIS /120)								
	57.1±7.8	64.2±7.8	**	65.4±7.7	61.1±10.5	65.4±7.0	63.7±6.3	
Behavioural Inhibition System Behavioural Activation System (BIS/BAS):								
- <i>BIS subscore</i>	20.3±3.0	20.8±4.7	NS	19.9±3.3	21.9±3.0	22.4±7.6	19.7±3.3	
- <i>BAS drive</i>	10.5±1.6	11.0±3.3	NS	11.1±3.1	9.5±3.2	10.6±3.2	12.7±3.4	
- <i>BAS funseeking</i>	10.9±2.1	11.2±2.9	NS	10.7±2.8	9.5±3.1	11.8±2.3	13.0±2.6	
- <i>BAS Reward Responsivness</i>	15.7±2.8	16.4±2.7	NS	16.1±2.9	16.6±2.2	16.4±2.3	16.9±3.2	
Motivation and energy inventory (MEI /144)								
	112.8±15.8	80.3±27.4	**	67.5±30.4	76.9±25.6	86.7±14.6	97.3±24.9	
Beck depression inventory (BDI /63)								
	3.6±4.1	13.3±10.7	**	19.0±12.5	12.6±8.2	9.0±10.0	9.2±6.0	
Snaith Hamilton pleasure scale (SHAPS /56)								
	18.7±4.8	22.4±5.1	*	22.4±4.7	23.1±5.7	20.6±3.8	23.5±6.3	
Neuropsychiatric inventory (NPI, fraction with positive response):								
-Apathy subscore	0.00±0.00	0.60±0.49	**	0.60±0.50	0.71±0.47	0.42±0.51	0.71±0.47	
-Disinhibition subscore	0.04±0.19	0.36±0.48	**	0.29±0.46	0.14±0.36	0.32±0.51	0.77±0.44	
Cambridge behavioural inventory (CBI-R /180)								
	4.5±4.2	62.8±35.2	**	50.9±33.9	69.8±36.1	53.3±37.8	85.2±20.4	
Kirby (difference)								
	0.01±0.02	0.01±0.05	NS	0.03±0.04	0.02±0.05	0.01±0.03	-0.01±0.08	

	Variable	Imaged Controls	Imaged Patients	T-Test P value	PSP	CBS	PPA	bvFTD
Behavioural Tasks	Information Sampling Task (IST)							
	-Probability of being correct Fixed	0.78±0.10	0.75±0.15	*	0.68±0.15	0.59±0.24	0.64±0.11	0.73±0.19
	-Probability of being correct Decreasing	0.85±0.12	0.67±0.17	*	0.75±0.15	0.72±0.14	0.68±0.12	0.83±0.14
	Cued reinforcement reaction time (CRRT)							
	-Total errors	3.1±2.9	4.2±5.0	NS	3.7±3.3	5.2±5.0	7.0±9.4	2.6±2.1
	Stop Signal Task (SST)							
	-Stop signal reaction time (SSRT)	175.8±42.8	447.0±244.3	**	449.4±189.0	544.3±430.7	471.8±242.5	353.0±152.2
	Motor Go/NoGo Dprime	4.5±0.3	3.2±1.3	**	3.4±1.0	2.9±1.6	3.0±1.4	3.6±1.5
Saccade Dprime	2.6±0.9	0.8±1.1	**	0.7±0.9	1.0±0.8	0.5±1.2	1.1±1.4	

Stats indicate Student's T-test results comparing imaged controls (N=28) and patients (N=67) *p<0.05, **p<0.001, **survives Bonferroni correction for multiple comparison.

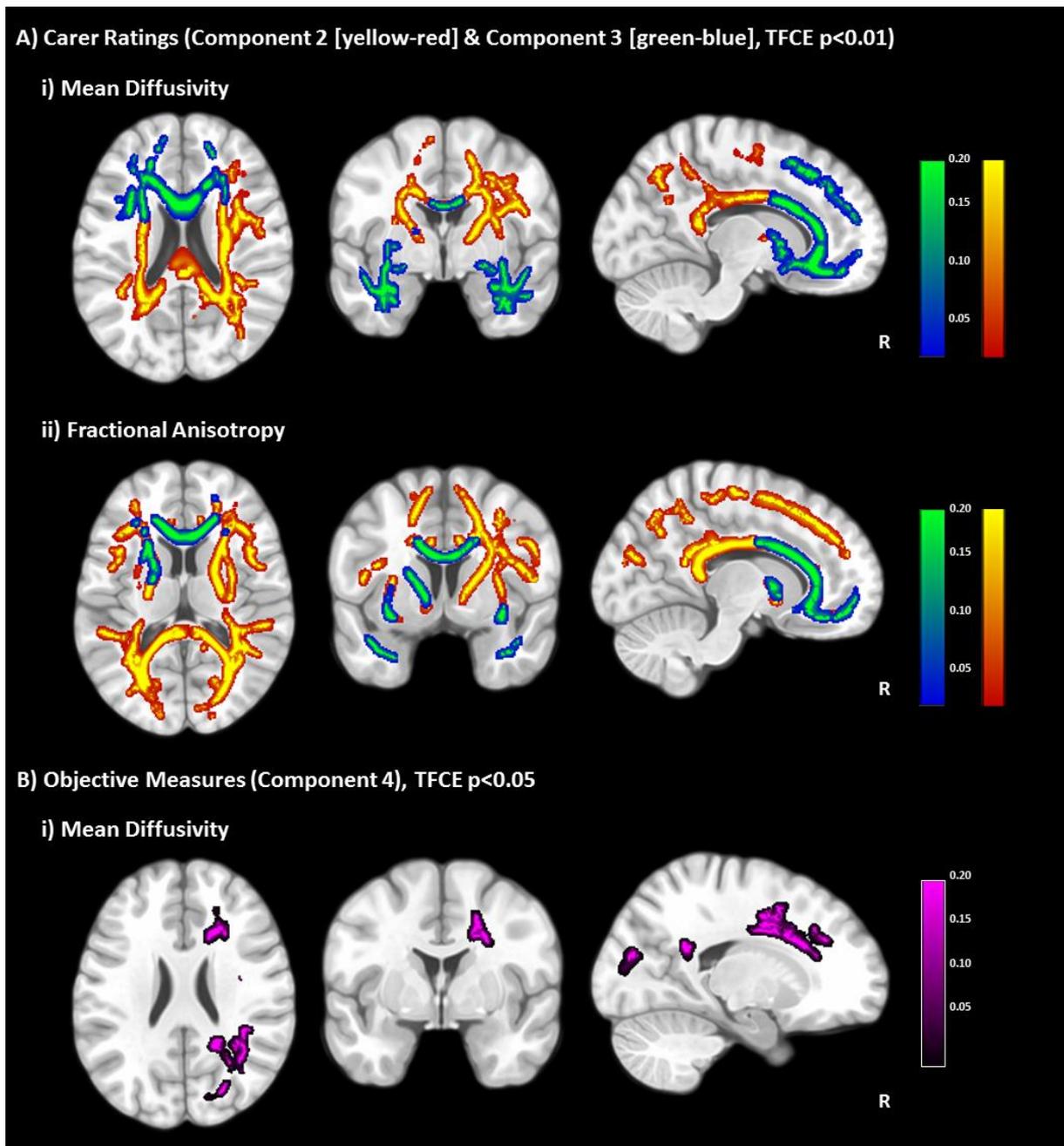


Figure 19: White Matter Diffusion Tensor Imaging Correlates of Components 2-4.

A) Correlates of carer rated change in everyday skills and self care (component 2: yellow-red) and carer rated change in complex behaviours (component 3: green-blue) in terms of (i) mean diffusivity and (ii) fractional anisotropy. Higher scores correlated with increased mean diffusivity and decreased fractional anisotropy. B) Mean diffusivity correlates of patient performance on objective measures, including the motor and saccadic Go/NoGo, IST and CRRT (Component 4). Higher scores correlated with increased mean diffusivity. Correlations between the skeletonised DTI-based tracts and the components were assessed by non-parametric permutation analysis using FSL randomise with Threshold-Free Cluster Enhancement (TFCE) correction, 2D optimisation and 5000 permutations. Cluster significance was tested at A) $p < 0.01$ and B) $p < 0.05$.

5.4 Discussion

Diffusion tensor imaging confirmed that distinct spatial distributions of white matter tract pathology are related to the separate dimensions of apathy and impulsivity, across multiple FTLN syndromes. Carers' ratings of both apathy and impulsivity (Component 3, Figure 19) were associated with changes in the white matter tracts connecting ventro-lateral and orbitofrontal cortex and temporal poles. In contrast, carers' ratings of everyday skills, self care and apathy (Component 2, Figure 19) correlated with changes in widespread frontal, parietal and corticospinal tracts. The objective behavioural tasks of cognitive control (component 4) were associated with abnormal white matter connecting the pre-supplementary motor area (pre-SMA) and lateral prefrontal cortex. The use of tract-based statistics overcomes the limitations of voxel-based morphometry used previously to study white matter changes in FTLN^{326,354}, especially in populations in which regional atrophy can be severe. There were no significant DTI correlates for patient ratings (component 1), in contrast to VBM of white matter which revealed correlations with the corticospinal tracts. Potential explanations for these findings are discussed below.

The abnormalities of white matter tracts associated with challenging behaviours related to apathy and impulsivity (Component 3: AES, NPI disinhibition subscore, and CBI abnormal/stereotypic behaviours, eating habits, and motivation subscores), are consistent with previous studies of individual disorders relating disinhibition and apathy separately to white matter tracts and metabolic activity in these frontotemporal regions^{100,102,144,164,317}^{100,102}. Apathy is also reported after anterior cingulate cortex damage due to focal lesions^{113,355}, small vessel disease⁹⁷, neurodegeneration¹⁴⁴ and ageing¹⁶⁷, while change in the uncinate fasciculus is associated with apathy in Alzheimer's¹⁶⁵, small vessel disease⁹⁷, PSP³²⁷, bvFTD¹⁶⁴ and normal ageing³⁵¹.

The tract-based statistics were broadly consistent with voxel based volumetry of FTLN³⁵⁴ suggesting parallel breakdown of frontotemporal circuits for motivation and goal directed behaviour^{13,144,166,342,356}. One difference to note is the absence of a tract-based deficit in relation to patients' observations of their own symptomatology, in contrast to the earlier VBM analysis of white matter (Chapter 4 and ³⁵⁴). There are a number of possible explanations for this discordance. First, patient ratings may reflect heterogeneous, multifocal changes in white matter, which prevent the identification of any consistently localized tract correlate. Second, VBM and DTI assess fundamentally distinct neural changes (tissue volumetric loss versus the diffusional integrity of white matter connections respectively), and may therefore give rise to

different results. For example, patient ratings may reflect changes in deep white matter structures which are not captured by DTI but are apparent volumetrically. Third, this difference may reflect the limitations of white-matter VBM³²⁶, including normalisation errors, mislocalisation errors and the partial-volume effects of smoothing, which can give rise to false positives. The current tract-based method is less vulnerable to these issues, although there are potential limitations to tract-based methods and the interpretation of DTI, discussed below.

With the current imaging and statistical modelling methods, the significant white matter changes appear to extend beyond significant grey matter atrophy. For example, component 4 revealed white matter changes extending to the right frontal cortex, while grey matter changes were localized to posterior cortical and subcortical regions (Chapter 4)³⁵⁴. This difference may be due to differential signal-to-noise of the methods, but may also indicate that white matter dysfunction represents a core pathophysiology in FTLD³³². I suggest that disruption to neural circuits for selection and initiation of goal directed behaviour and motivation, give rise to apathy and disinhibition^{245,352} and account for their clinical coexistence in FTLD syndromes.

Carer rated change in everyday skills, self-care, motivation and apathy (Component 2: CBI, AES and NPI apathy), correlated with widespread white matter changes including the centrum semiovale and corticospinal tracts, forceps major, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and corpus callosum. In contrast to component 3, there was less in terms of significant frontotemporal involvement (see MD images, Figure 19A). This supports previous DTI studies showing (i) degeneration of the brainstem and association and commissural fibres in PSP, with significant white matter change in the superior cerebellar peduncles, body of the corpus callosum, inferior longitudinal fasciculus, and superior longitudinal fasciculus³³⁴; (ii) CBS changes in frontoparietal connecting fibres, intraparietal associative fibres, sensorimotor fibres of the hand cortical representation, and body and splenium of the corpus callosum³³⁵ and (iii) widespread changes in FTD^{345,346}.

The widespread white matter correlates support the concept of network based disruption in FTLD^{16,245,271,357}, as opposed to focal areas of damage. However, widespread changes associated with carer reports may also reflect their inability to discriminate between syndromes of goal directed behaviour using these questionnaires.

Although Component 4 showed weaker correlations with FA and MD, its correlates are of particular interest. First, all patient groups scored higher on average than controls (see Figure

16), confirming the objective neuropsychological deficits as a transdiagnostic deficit, not driven by single diagnostic groups. Second, the poor performance on decision making, cued reinforcement and response inhibition reflected unilateral FA changes in connections of the right pre-SMA, dorsolateral prefrontal cortex and inferior frontal gyrus. These regions are strongly associated with cognitive control and goal-directed behaviour in preclinical models and human studies³⁵⁸. Effective inhibitory control is mediated by cortical and subcortical connections between the pre-SMA, prefrontal cortex, inferior frontal gyrus and subthalamic nucleus^{129,211,255,272,359} and reduced connectivity among these regions impairs response inhibition³⁶⁰ and choices between alternate actions^{145,361}. Component 4 also correlated with changes in the occipital lobe, which may reflect shared dependency of the behavioural tasks on rapid visual processing.

Components 2-4 correlated with cognitive and functional decline (Table 13). Previous studies have reported a link between apathy and poor outcome^{83,84,95,97}, with rapid cognitive and functional deterioration in apathetic patients compared to non-aphathetic and depressed individuals⁸². Further investigations assessing the prognostic implications of apathy and impulsivity in FTLD syndromes are warranted (see Chapter 6). Apathy may represent a marker of rapid cognitive decline and a potential target for disease-modifying treatment intervention (Chapter 6 and 7).

There are several limitations to this study, including caveats to the imaging and behavioural methods. DTI is an indirect measure of the physical properties of white matter connections, such as axon density, calibre, and myelination^{336,362}. Despite this limitation, DTI provides *in vivo*, semi quantitative measures that provide important anatomical insights into the human brain which can be cross-validated in animal models. For example, preclinical studies link fractional anisotropy to myelination, membrane permeability and fibre density in white matter^{337,363,364}. However, comparative studies of anatomy across species and in FTLD post mortem are required to determine the pathological mechanisms of the observed imaging changes. Although different DTI metrics may reflect distinct processes (for example demyelination, neurodegeneration, gliosis, calcification, and axonal degeneration), linking them to specific leucopathologies remains challenging. One must also consider artefacts from motion and registration errors, as multiple directional measurements are obtained at each voxel, introducing false-positive differences especially if movement differs by group³⁶⁵. Registration also poses significant challenges for analysing disease groups with highly atrophic brains, obscuring some tracts. Registration errors may affect the absolute diffusivities or eigenvalues,

mimicking the effects of pathology³⁴⁴. White matter change in areas with substantial grey matter may lead to changes in estimated FA that reflect differences in the relative amounts of tissue types rather than change in white matter³²⁶.

5.5 Conclusion

In conclusion, white matter is markedly abnormal in FTLD syndromes. Diffusion tensor imaging is highly sensitive to the white matter changes underlying FTLD-associated behaviours, and revealed distinct spatial profiles of FA and MD relating to different components of apathy and impulsivity. White matter abnormalities extended beyond grey matter change, adding to the growing literature reporting white matter dysfunction as a core pathophysiology in FTLD.

Chapter 6 | Prognostic Implications of Apathy and Impulsivity in Frontotemporal Lobar Degeneration Syndromes.

In this chapter, I employ logistic regression analysis to examine the impact of the apathy and impulsivity components (Chapter 3) on prognosis and survival in the PiPPIN cohort.

6.1 Introduction

Dementia causes functional decline and ultimately leads to early mortality. In FTLD disorders, some studies report striking similarities in survival rates across behavioural and language variants of frontotemporal dementia³⁶⁶, while others report longer survival rates for svPPA (10-12 years) than bvFTD (5-8 years)^{19,200,367}. Shorter survival is typical in PSP (typically 5-7 years)^{19,368} and CBS (typically 6-8 years)³⁶⁷, while FTD with motor neurone disease (FTD-MND) is associated with the shortest survival rates (2-5 years)^{200,366,367}.

Overall, FTLD syndromes are associated with reduced median survival and faster rate of cognitive and functional decline compared to Alzheimer's disease (AD)^{366,367,369}, which is more striking in view of the younger median age of onset. This suggests that degeneration of frontal-subcortical circuits in FTLD may have greater influence on mortality than AD related atrophy of parieto-temporal circuits³⁶⁷. Indeed, predominant frontal atrophy has been linked to fast-progressing FTLD cases, while patients with predominant temporal lobe atrophy progress at a similar rate to those with AD³⁷⁰.

Variations in the estimated survival rates in part reflect the use of clinical versus neuropathological cohorts. Clinical cohorts of FTD report 7-13 years median survival from diagnosis^{367,371} while neuropathological series report 6-8 years^{366,372}. Poor clinicopathological correlations leading to diagnostic inaccuracy, and the inclusion of non-progressive "phenocopy" patients⁵⁸, who present clinically with superficial bvFTD-like behaviour but have normal structural and metabolic imaging, may account for varied and higher survival rates among some clinical cohorts. Indeed, the removal of 24 "phenocopy" cases from a cohort of 91 clinical bvFTD cases caused the median survival to drop from 9.0 years from onset and 5.4 years from diagnosis to 7.6 and 4.2 years respectively³⁷¹. Broad convergence of syndromes with disease progression further hinders accurate estimation of survival in clinical cohorts. Instead, survival should be considered across the unitary continuum of FTLD.

Despite improved knowledge of the clinical features and neuropathological hallmarks of FTLN syndromes, their influence on survival is unclear. Predicting disease progression and patient trajectories therefore remains challenging and the mechanisms underlying variations in survival rates remain elusive. Previous studies have reported minor or null-associations between survival and patient demographics, a positive family history and dementia severity at the time of diagnosis^{57,366,367,373}.

Neuropathological studies have led to increased fractionation of FTLN syndromes, but the influence of distinct pathologies on survival remain unclear, with both tau-positive and tau-negative cases correlating with reduced survival^{366,367,372,374,375}. Although variations in the survival rates across clinical phenotypes have been reported, diagnosis alone is not strongly predictive of survival in some series³⁷³, except for FTD-MND.

Apathy has been associated with worse outcomes across a range of neurological, psychiatric and medical conditions including Alzheimer's Disease^{91,92}, stroke^{87,94-97}, Huntington's Disease⁹³, Parkinson's Disease^{83,88,91} FTLN syndromes^{92,99-103}, head injury⁹⁸ and pre-dementia states⁸²⁻⁸⁴. Apathy is linked to decreased functioning^{84,94}, caregiver distress¹⁰⁴, cognitive decline^{83,105,106}, increased dementia conversion rates^{82,84}, poor response to treatment/rehabilitation^{94,107}, reduced quality of life⁹⁷ and poor prognosis¹⁰⁸. The direct influence of apathy and related behaviours on survival rates has received less attention^{373,376,377}.

The link between apathy and increased morbidity and mortality suggests that apathy may represent a clinical biomarker of disease severity and a predictor of poor prognosis. The ability to predict survival rates among the FTLN syndromes and subsequently stratify patients into rapid and slow progressors would be important for defining disease outcomes, informing sample size calculations for future clinical trials and monitoring disease modifying therapeutics³⁷⁸. Predicting survival trajectories for newly diagnosed patients will guide clinical management, including patient care and caregiver counselling. Furthermore, in view of the negative influence of apathy on survival, effective intervention may prove to be "disease modifying".

Here, I use the PiPPIN cohort to test the hypothesis that neurobehavioural components of apathy and impulsivity are significant predictors of survival. I employ logistic regression to estimate the probability of death occurring within 2.5 years (30 months, 913 days) from PiPPIN assessment. Logistic regression estimates the probability of an event occurring; if the modelled

probability is greater than or equal to 0.5, then the model classifies the event as occurring while probabilities lower than 0.5 are classified as not occurring. By comparing modelled classification to real-world data, one can determine whether the model can correctly classify patients based on the chosen independent/predictor variables.

For this analysis, predictor variables included age at assessment, gender, cognitive status (ACE-R), collapsed diagnosis (PSP, CBS, PPA, bvFTD) and the eight principal neuropsychological components identified in chapter 3. In view of previous studies highlighting the importance of apathy and related behavioural change over demographics, diagnosis and cognitive status, I hypothesised that the neurobehavioural components would be most influential on survival. Specially, I hypothesised that the major carer-rated components [two and three], which reflected widespread neural changes on VBM and DTI would significantly predict death.

6.2 Methods

6.2.1 Cohort

Of the 149 PiPPIN patients included in the PCA, 129 patients (PSP 38, CBS 31, PPA 33, bvFTD 27) were included in a logistic regression analysis to determine survival at 2.5 years post PiPPIN assessment. The occurrence and date of death were obtained using the NHS SPINE, an electronic register of all NHS patients. Exclusion was due to insufficient complete data for logistic regression (eg. limited cognitive/functional, self-rated, carer rated or behavioural assessment). Cohort numbers differed slightly depending on the chosen survival cut off and are reported in the results. Logistic regression removes cases with missing data “list-wise” by default. Therefore, the inclusion of multiple predictor variables (each of which may have a small but finite percentage of missing data) results in the additional exclusion of patients.

Kaplan-Meier Survival curves were used to illustrate survival, by diagnostic group. Survival rates at 24 and 36 months are also presented, but the principal outcome assessment refers to 30 months’ survival due to near equal sample sizes across groups (deceased=53 and alive=63). Death rates by group were compared by chi-squared test. Logistic regression was used to identify predictors of survival.

6.2.2 Logistic Regression

Logistic regression was carried out using the “Enter” method in SPSS v22. Predictor variables included age at assessment, gender, cognitive status (ACE-R), collapsed diagnosis (PSP, CBS, PPA, bvFTD) and the eight principal components. In order to predict survival at 30 months,

patients were classified as “dead (1)” or “alive (0)” using a cut off of 913 days. Patients who were alive but had not yet lived 2.5 years from their PiPPIN assessment were classified as “insufficient follow up time (13)” and were excluded from the analysis.

Overall fit of the model was determined by the -2log-likelihood statistic and its associated chi-square statistic, using a threshold of $p < 0.05$ (indicating significant fit of the data). Cox and Snell’s R^2 values provided an additional indication of model effect size. The influence of the independent variables on predicting outcome (death within 2.5 years) were determined by the significance of the Wald statistic ($p < 0.05$). Additional information regarding the directionality of effect was provided by the odds ratio [$Exp(B)$]; values > 1 indicate increasing odds of outcome occurrence (death) with increased values of the predictor variable while values < 1 indicate decreasing odds of outcome occurrence with increased values of the predictor variable. Confidence intervals of the $Exp(B)$ values were used to confirm the direction of the relationship in the population.

Classification accuracy of the final model was compared to the baseline model (baseline model [constant only] % – new model [all predictor variables] %) to determine whether inclusion of the independent variables resulted in significant model improvement.

Sensitivity (the percentage of cases that have the observed characteristic and were correctly predicted by the model (true positives)) and specificity (the percentage of cases that did not have the observed characteristics and were correctly predicted as not having it (true negatives)) of the model were also calculated (Positive predictive value = $\text{Number of true positives} / [\text{number of true positives} + \text{number of false positives}]$, Negative predictive value = $\text{Number of true negatives} / [\text{Number of true negatives} + \text{number of false negatives}]$).

Residuals were examined to confirm model fit. Statistics included: standardized residuals to measure the model fit to the sample data ($< 1\%$ of observations ± 2.58); Cook’s distance to measure the overall influence of an individual case on the model (values < 1); and DFBeta statistics to measure the influence of a case on the values of b (values < 1)³⁷⁹.

6.3 Results

6.3.1 Cohort

Of the 129 patients included in the survival analysis, 53 had died at 30 months post assessment, including 23 PSP, 16 CBS, 5 PPA and 9 bvFTD. Sixty three patients were classified as “alive”

at 30 months after assessment, while thirteen patients were excluded from the analysis due to “insufficient follow up time” between assessment date and the current analysis date to determine survival within this time frame, leaving 116 patients total for analysis. A further 28 cases were removed list-wise during the logistic regression due to missing data of interest leaving 88 to be included in the logistic regression. The survival subset (N=88) were representative of the PCA patient subset (N=149), with no significant differences in terms of age, gender, diagnosis and cognitive status (see Table 17).

Table 17: Comparison between Patients Included in the Logistic Regression Cohort and those Excluded

	Excluded (N=61)	Included (N=88)	T-stat or χ^2 *	P Value
Age	70.4±8.6	69.7±8.0	0.46	0.65
Gender	Male:37 Female:26	Male:39 Female:47	2.61*	0.11
Diagnosis	PSP:15 CBS:16 PPA: 16 bvFTD 16	PSP: 26 CBS: 21 PPA: 23 bvFTD: 16	1.36*	0.71
Cognitive Status (ACE_R)	72.1±23.2	63.8±22.6	0.54	0.59

The number of deaths were also calculated at 24 and 36 months (Figure 20). Of the 129 patients included in the survival analysis, 45 had died at 24 months, including 22 PSP, 12 CBS, 3 PPA and 8 bvFTD and 1 with insufficient follow up time. At 36 months, 58 patients had died including 24 PSP, 19 CBS, 6 PPA and 9 bvFTD and 32 with insufficient follow up time. Of those who were alive at 24 months, 16 had subsequently died and of those alive at 36 months, 3 had since died.

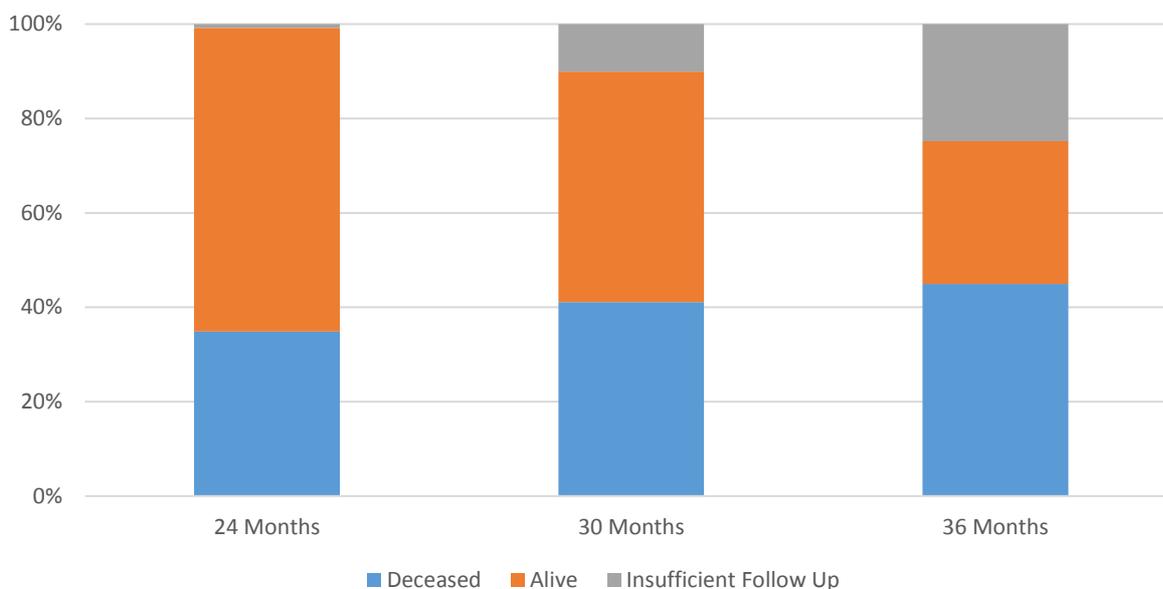


Figure 20: Percentage of PiPPIN Patients Deceased at 24, 30 and 36 Months Post Assessment.

Death rates were highest at all time points for PSP patients, followed by CBS, bvFTD and PPA (Figure 21). At 30 months (the time point used in the logistic regression analysis), 23 PSP patients, 16 CBS, 9 bvFTD and 5 PPA patients had died.

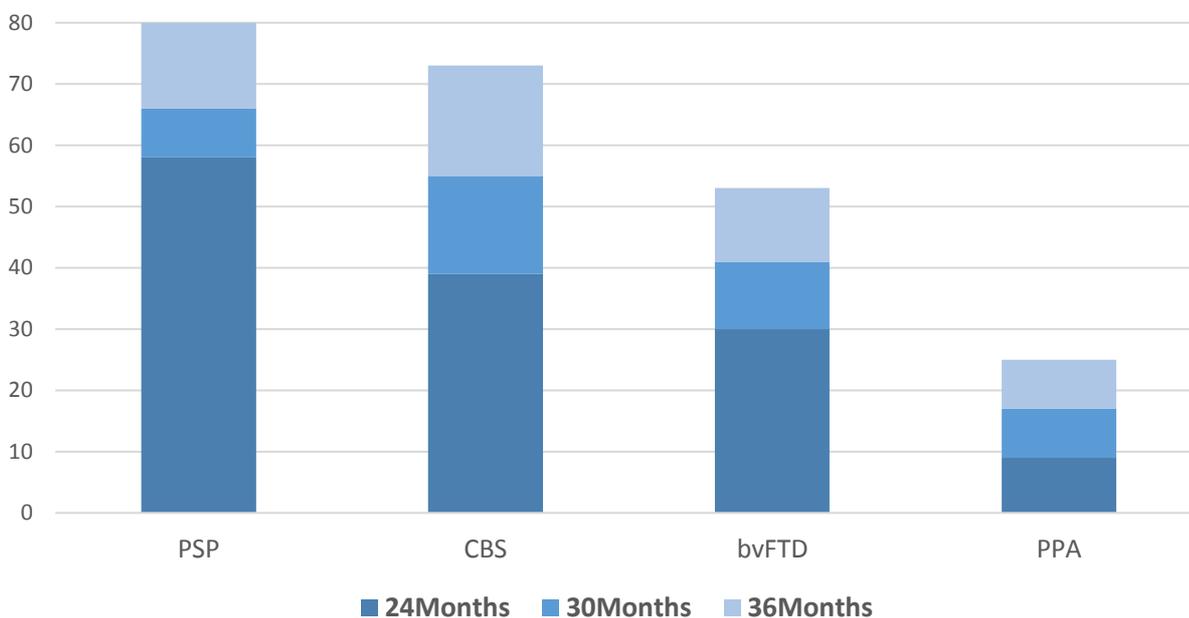


Figure 21: Mortality by Diagnostic Group

Death rates by diagnostic group at 24, 30 and 36 months: PSP (58%, 66%, 80%), CBS (39%, 55%, 73%), bvFTD (30%, 41%, 53%), and PPA (9%, 17%, 25%). Note that cases with insufficient follow up time are excluded from each time point.

Survival rates from PiPPIN assessment and from symptom onset were significantly different depending on the diagnostic group (see Figures 22 and 23). Kaplan-Meier survival curves showed significant differences in survival from PiPPIN assessment (Log Rank [Mantel-Cox] $\chi^2=22.960$, $df=3$, $p<0.001$, pairwise comparisons revealed significant differences for PSP vs PPA ($\chi^2=19.0$, $p<0.001$), PSP vs bvFTD ($\chi^2=7.5$, $p<0.01$), CBS vs PPA ($\chi^2=13.8$, $p<0.001$), and CBS vs bvFTD ($\chi^2=4.7$, $p<0.05$)). Kaplan-Meier survival curves also showed significant differences in survival patterns across diagnostic groups from symptom onset (estimate based recall of initial relevant symptoms) (Log Rank [Mantel-Cox] $\chi^2=18.8$, $df=3$, $p<0.001$, pairwise comparisons revealed significant differences for PSP vs PPA ($\chi^2=11.7$, $p=0.001$), PSP vs bvFTD ($\chi^2=5.1$, $p<0.05$), CBS vs PPA ($\chi^2=14.0$, $p<0.001$), CBS vs bvFTD ($\chi^2=5.9$, $p<0.05$)).

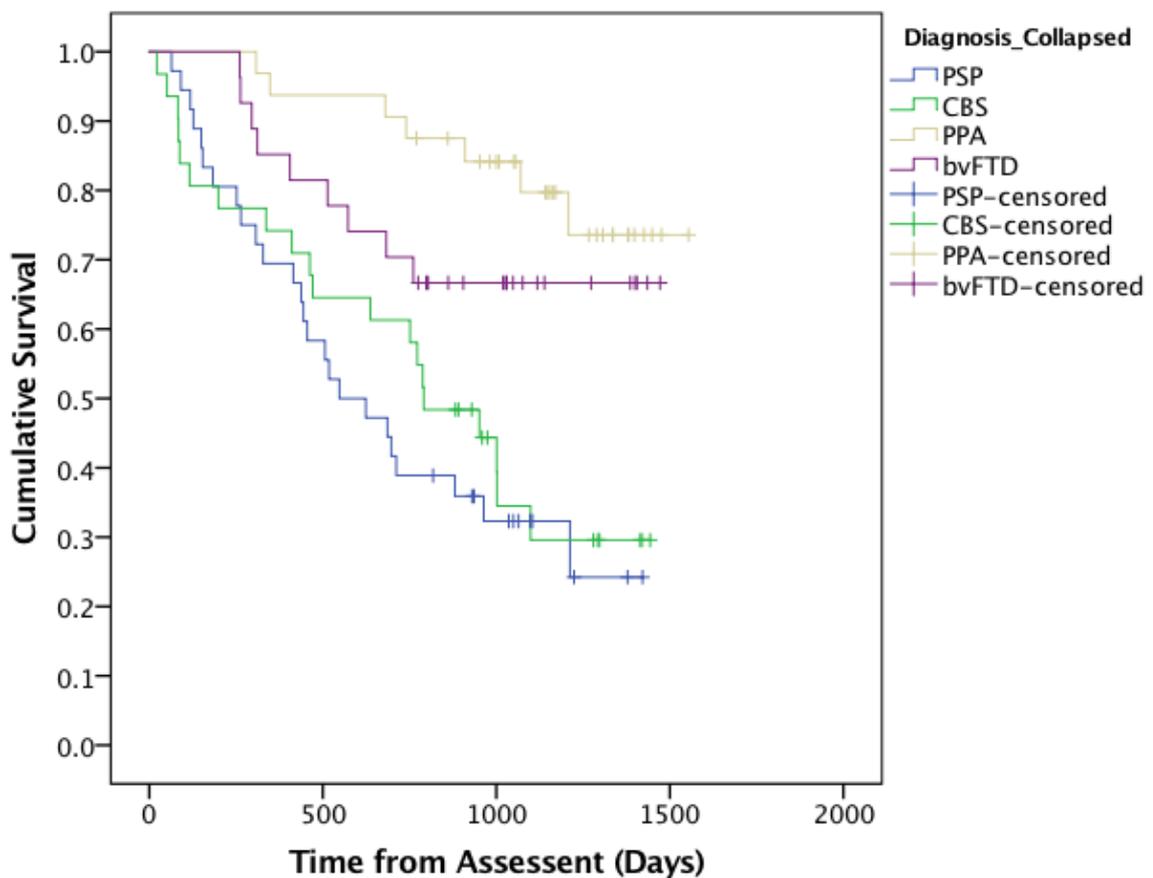


Figure 22: Kaplan-Meier Survival Curves from PiPPIN Assessment.

Log Rank [Mantel-Cox] $\chi^2=22.960$, $df=3$, $p<0.001$, pairwise comparisons revealed significant differences for PSP vs PPA ($\chi^2=19.0$, $p<0.001$), PSP vs bvFTD ($\chi^2=7.5$, $p<0.01$), CBS vs PPA ($\chi^2=13.8$, $p<0.001$), and CBS vs bvFTD ($\chi^2=4.7$, $p<0.05$).

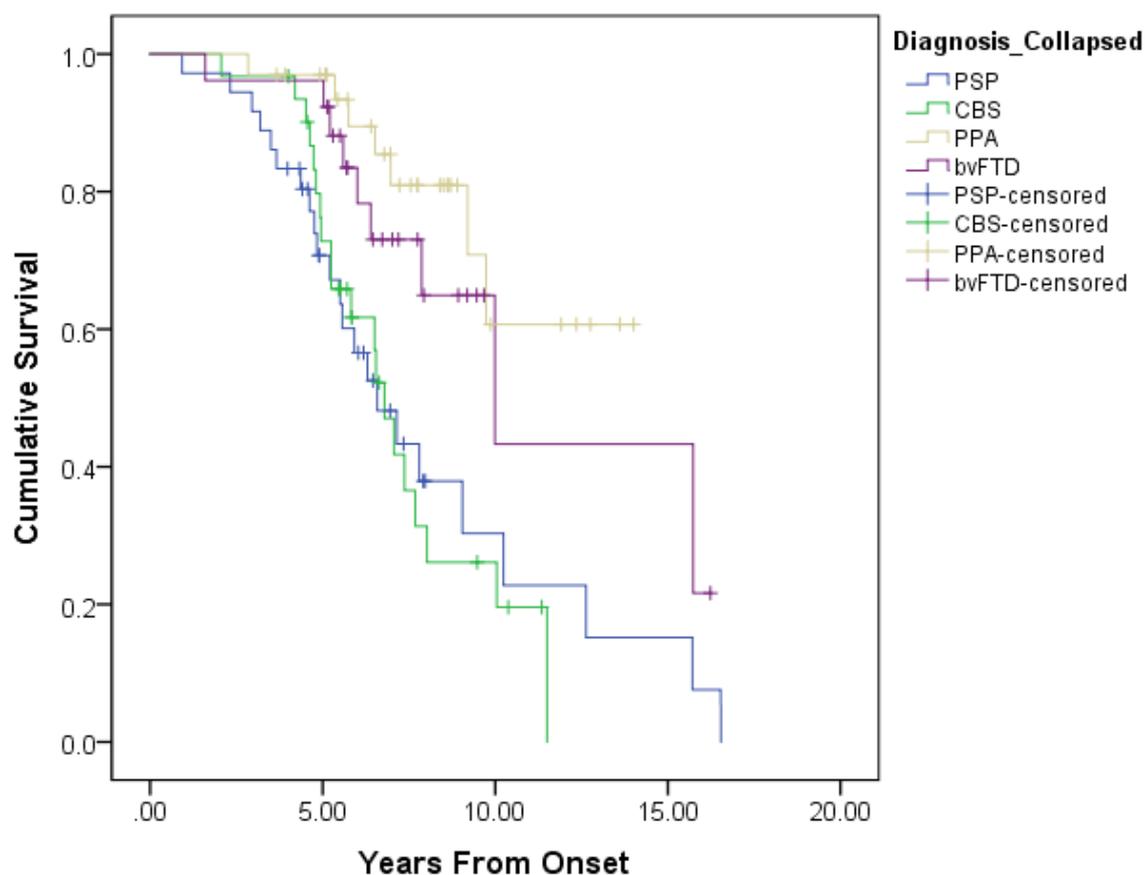


Figure 23: Kaplan-Meier Survival Curves from Onset.

Log Rank [Mantel-Cox] $\chi^2=18.8$, $df=3$, $p<0.001$, pairwise comparisons revealed significant differences for PSP vs PPA ($\chi^2=11.7$, $p=0.001$), PSP vs bvFTD ($\chi^2=5.1$, $p<0.05$), CBS vs PPA ($\chi^2=14.0$, $p<0.001$), CBS vs bvFTD ($\chi^2=5.9$, $p<0.05$).

6.3.2 Logistic Regression

Including all predictors in the model resulted in a significant fit to the model (-2 log likelihood=88.401, $\chi^2=29.9$, $df=14$, $p=0.008$, Cox & Snell $R^2=0.288$, Nagelkerke $R^2=0.390$). Model classification accuracy improved from 60.2% at baseline (including only a constant) to 73.9% following inclusion of the predictor variables. The model correctly classified 43 as alive while incorrectly classifying 13, and correctly classified 22 as dead while incorrectly classifying an additional 10, resulting in a positive predictive value of 81% and negative predictive value of 63% ($PPV = 43 / 43+10 = .811$, $NPV = 22 / 22+13 = .629$).

Of the predictor variables, Component 2 was the most significant predictor of death within 2.5 years from PiPPIN assessment (Wald Statistic=8.119, $p=0.004$, $Exp(B)=2.912$, C.I.=>1 [1.396-6.075]; Table 18). An $Exp(B)$ value>1 (and confidence intervals both>1) indicated that increases in Component 2 (weighted towards carer rated AES, NPI-apathy and CBI everyday

skills, self care, sleep and motivation) significantly increased the odds of death within the 2.5-year time period. Note that Component 2 was the most significant predictor of death across all three time points (subsidiary analyses). Component 8 was also significant at the $p < 0.05$ level. Age at assessment had only a trend towards significance. Examination of the residuals confirmed model fit: standardised residuals were all within ± 2.58 , Cook's distance and DFBeta values were < 1 .

6.4 Discussion

This study confirms the deleterious effect of apathy on patient survival in the major syndromes associated with FTLD. Component 2, representing carer ratings of apathy (as weighted towards the Apathy Evaluation Scale and Neuropsychiatric Inventory Apathy subscores) and functional decline in everyday skills, self-care, sleep, and motivation (as measured by the respective CBI subscores), was the most significant predictor of death within 30 months from PiPPIN assessment (Wald stat=8.119, $p=0.004$, see Table 18), even after adjusting for diagnostic group differences in the model. Demographics (age, sex) and cognitive performance (ACE-R) did not significantly predict survival, in keeping with previous studies^{367,373}. Over two and a half years, 53 (41%) of FTLD patients died, with survival ranging from 22 to 910 days post assessment (PSP 64-881 days, CBS 22-791 days, PPA 308-910 days, bvFTD 261-761 days). Kaplan-Meier curves revealed significant differences in survival across groups (Log Rank [Mantel-Cox] $\chi^2=22.960$, $df=3$, $p < 0.001$), with pairwise comparisons highlighting differences between CBS versus bvFTD and PPA and PSP versus bvFTD and PPA groups (See Figure 22 and 23). Death rates were highest for PSP patients (N=23), followed by CBS (N=16), bvFTD (N=9) and PPA (N=5), consistent with the full PiPPIN cohort¹⁹.

These findings add to the growing literature emphasizing the prognostic importance of behavioural change in FTLD syndromes, over and above demographics, cognitive status and diagnostic classification^{373,377,380}. Borroni et al (2007) classified FTLD patients into specific phenotypes using latent profile analysis; “pseudomaniac behaviour”, “cognitive”, and “pseudodepressed” on the basis of neuropsychological, functional and behavioural data³⁸¹. They subsequently showed that prognosis and survival was significantly worse in the “pseudomaniac” group, who exhibited greater behavioural disturbances, disinhibition and abnormal social conduct³⁷³. In line with previous studies, “pseudodepressed” patients had the best prognosis over time³⁷³. Although apathy and depression often co-occur and may even be confused by observers, it is apathy, but not depression, that is most associated with poor outcomes and increased cognitive and functional decline towards dementia^{82,382}. This likely

reflects the distinct underlying neurobiology and neurocircuitry of apathy and depression^{97,141}. Clearly the neural correlates of apathy, including disruption to numerous cortico-subcortical networks connecting the prefrontal cortex to the basal ganglia (Chapter 4 and 5)¹¹¹, are more closely related to sustained survival.

The influence of dysexecutive syndrome on survival is further emphasised by the observation that comorbid FTD-ALS patients survive up to a year less than patients with ‘motor only’ symptoms³⁸³. Apathy is common in ALS, affecting 40-80% of patients¹⁰⁸, and may often precede motor symptoms³⁸⁴. Recent studies suggest apathy is an independent, negative prognostic factor in ALS, significantly predicting survival even after controlling for clinical factors and symptom duration at study entry. Median survival of patients with moderate to severe apathy is significantly shorter than those with both mild apathy and no apathy (21.7 vs 49.9 months vs 51.9 months respectively, $p=0.0001$)¹⁰⁸.

Voxel based morphometry of component 2 (chapter 4) revealed marked white matter atrophy of the brainstem, also extending to frontal regions, while widespread grey matter changes were observed both subcortically and throughout the middle to posterior cortical areas. Similar neural correlates were observed using diffusion tensor imaging, including extensive white matter tract abnormalities extending from subcortical to cortical areas, with a predominant middle-posterior focus (chapter 5). Patients with PSP and CBS scored highly on component 2, in line with previous studies suggesting patients with Pick’s disease survive longer than those with PSP and CBD pathology due to differences in the rate of brainstem degeneration^{12,305,306}. Predominant bulbar symptoms, reflective of brainstem pathology, are recognised to increase the likelihood of death by choking and aspiration¹². However, frontal atrophy has also been linked to poor outcomes in CBS³⁷⁷, PSP¹⁶⁶ and FTD³⁶⁷. Across FTLD, the “pseudomaniac” phenotype classified by the Borroni cohort and linked to reduced survival, demonstrated greater hypoperfusion of the orbitomesial frontal cortex. Greater frontal subcortical dysfunction, which often gives rise to behavioural changes such as apathy, may be an important predictor of increased mortality. Indeed, frontal lobe symptoms, including apathy, disinhibition or irritability, reduced survival in a sample of confirmed CBD cases³⁷⁷. Whether specific pathologies underlying dysfunction and atrophy in these brain regions influence survival is unclear, with available studies reporting inconsistent results^{367,372,374}.

Table 18: Logistic Regression Assessing the Influence of Predictor Variables on Survival 2.5 Years Post PiPPIN Assessment

Variables	Wald Statistic	Degrees of freedom	Exp (B)	Significance	95% C.I. for Exp(B)	
					Lower	Upper
ACE-R total score	0.095	1	0.995	0.758	0.967	1.025
Age at assessment	3.601	1	1.077	0.058	0.998	1.162
Sex	0.027	1	1.096	0.871	0.365	3.293
Diagnosis Collapsed	1.855	3	-	0.603	-	-
Diagnosis 1	1.080	1	1.710	0.299	0.622	4.705
Diagnosis 2	0.012	1	0.940	0.912	0.312	2.828
Diagnosis 3	1.274	1	0.518	0.259	0.165	1.625
PC1	2.913	1	1.646	0.088	0.929	2.919
PC2	8.119	1	2.912	0.004**	1.396	6.075
PC3	1.849	1	1.474	0.174	0.843	2.580
PC4	0.093	1	0.880	0.760	0.386	2.006
PC5	1.188	1	1.290	0.276	0.816	2.038
PC6	1.572	1	1.377	0.210	0.835	2.272
PC7	2.653	1	.672	0.103	0.416	1.084
PC8	4.354	1	.509	0.037*	0.270	0.960
Constant	4.321	1	.002	.038	-	-

Bold figures highlight significant predictors of death 2.5 years (30 months) post PiPPIN assessment (p<0.01, *p<0.05). Key: C.I. confidence intervals, PC principal component. Degrees of freedom is equal to the number of parameters in the model.**

The non-significant influence of cognitive status on survival is of interest, and complements previous studies emphasizing the importance of behavioural features rather than cognitive decline as a marker of disease progression and prognosis^{373,380}. The relationship between apathy and cognition is complex: does apathy cause cognitive worsening or is apathy a marker of cognitive worsening? In pre-dementia states, apathetic patients consistently show rapid cognitive and functional decline and increased dementia conversion rates compared to non-apathetic groups with no neuropsychiatric features⁸²⁻⁸⁴. In a small PD sample, eight of twenty apathetic patients converted to dementia, compared to one of twenty non-apathetic patients, after a median of eighteen months follow up⁸³. Even in those who did not develop dementia, apathetic groups showed significantly greater cognitive decline, specifically in terms of executive function deficits in response inhibition and action initiation, emphasising the link between cognition and apathy. In an MCI/AD sample, patients with apathy, specifically of the type causing lack of interest as measured by interview or the Apathy Inventory lack of interest dimension, had a greater risk of conversion to dementia over three years, even after controlling for potential confounds including age, gender, education and episodic memory performance³⁸⁵. Vicini Chilovi et al., (2009) reported dementia conversion rates as high as 60% in apathetic MCI patients, compared to 7.9% for depressed MCI and 24% for MCI normal over two years. In a study of 131 memory-clinic outpatients with amnesic MCI, patients with apathy had close to a seven fold risk of AD progression compared to those without apathy, even following adjustment for age, gender, education, baseline global cognitive and functional status and depression³⁸². The consistently reported link between apathy and dementia conversion suggests successful intervention may alter patient trajectories and delay onset of full blown dementia, consequently influencing survival. Addressing this will require development of more effective symptomatic treatments targeting the underlying causes of apathy.

In line with previous studies of FTD^{367,373}, diagnostic classification was also not a significant predictor of survival, suggesting that the use of predefined clinical criteria for FTLD syndromes are unhelpful for prognostic purposes in clinical practice³⁷³. Instead, the presence and severity of apathy across the spectrum of FTLD disorders largely determines survival, which suggests that the remaining features that underlie diagnosis (but are not captured by the components) do not influence prognosis. Therefore, I suggest that significant differences in prognosis and survival across syndromes (Figure 22 and 23) are driven by the phenotypic features measured by component 2, or their neurobiological correlates. Whether the relationship between apathy and mortality is causal or correlational is yet to be clarified. Apathy may cause rapid decline to death or may represent a marker of other underlying factors that correlate with both apathy and

survival, such as brainstem degeneration (neural correlate of component 2). Here, I do not present proof of causality, but the relationship between apathy and survival raises the hypothesis that treating apathy would improve outcome. To address this, studies are warranted to treat apathy either at the behavioural level (symptomatic) or by targeting the underlying correlates of apathy, in terms of neural changes (disease modifying).

The observation that diagnosis is not predictive of survival provides additional support for the transdiagnostic approach adopted by this study and has direct implications for the design of future clinical studies. I propose that emphasis should be placed on recruiting patients who present with apathy, or in this case patients who score highly on measures captured by component two, rather than focusing on diagnostic labels that require the presence of behavioural changes as part of the clinical criteria. Component two was abnormal across diagnostic groups, with particularly high scores in PSP and CBS groups, reflecting high endorsement of apathetic behaviours and ultimately reduced survival in these patients. Profound apathy and associated behavioural changes are increasingly recognised in PSP and CBS^{5,14,201,322}, despite being largely overlooked due to predominant motor impairments. In a pathological cohort of fourteen CBD patients, frontal lobe symptoms were the initial manifestation in 20% of cases³⁷⁷, highlighting the importance of early behavioural changes. Apathy has also been associated with executive dysfunction and worse outcomes in PSP^{319,386}.

A number of limitations should be acknowledged. Inherent to all clinical studies estimating survival in FTLD syndromes is the variable clinic-pathological correlations, resulting in potential misdiagnosis and thereby inaccurate within-syndrome estimates. A recent study reported correct clinical diagnosis of PSP in 25% of pathologically proven cases at first visit, and 63% at last visit, highlighting that PSP is underdiagnosed^{15,49}, even though PSP-RS has very high predictive value for PSP pathology. Reports of syndrome-specific survival rates are therefore likely pathologically heterogeneous. Here, I included collapsed diagnostic groups of PSP, CBS, bvFTD and PPA in the logistic regression and acknowledge that the clinical diagnosis does not confirm the underlying cause of disease.

Logistic regression removes cases list-wise, reducing the power of the analysis. Due to the nature of neurodegenerative diseases, some patients are too severely impaired to be assessed cognitively. Missing variables resulted in the removal of the 28 patients from the analysis, despite recorded behavioural changes, demographics and diagnosis. Although methods such as multiple imputation can be employed to estimate scores based on other available measures, they

are not without limitations and are uncommon in logistic regression. Importantly, missing data are often not missing at random, as those who do not complete an ACE-R are often too impaired to do so. Missing data can therefore often be informative in itself.

6.5 Conclusion

In conclusion, apathy and related behavioural change (component 2) in FTLD syndromes significantly predict death within 2.5 years from assessment, while demographics, diagnosis, and cognitive status do not. The prognostic importance of high scores on component 2 suggests these neurobehavioural components may provide a means to effectively predict survival and stratify patients for clinical trials, for example into apathetic (rapid progressor) and non-apathetic (slow progressor) groups. The irrelevance of diagnosis for predicting survival suggests that currently available diagnostic criteria are unhelpful in clinical practice for this purpose³⁸⁷. Identification and enrolment of subjects at greater risk of disease progression, such as in those with high scores of component 2, or belonging to the “pseudomaniac” group identified by Borroni et al (2007, 2009), would maximise power to detect a therapeutic effect and dramatically decrease the number of patients needed for power calculation. Finally, the prognostic importance of apathy highlights the need to develop more effective and targeted measurement tools to improve recognition and provide outcome measures for clinical studies. Clearly the neural correlates of apathy bear some relationship to prognosis, suggesting the implicated neural systems are essential for sustained survival. This raises the possibility that effective symptomatic interventions targeting the neurobiology of apathy may also be disease modifying, and improve prognosis.

Chapter 7 | Thesis Discussion

This thesis provides support for maintaining the clinical and pathological variants of FTD, PSP and CBS under a unitary umbrella term based on the pathology within the FTLD spectrum. Despite progress in the clinical, pathological, and genetic fractionation of the disorders, the PiPPIN data confirm extensive overlap and convergence of syndromes. Their heterogeneity and overlap is also recognised for example in the recently developed International Movement Disorder Society diagnostic criteria for PSP¹⁵, which define multiple clinical syndromes associated with a PSP pathology, moving away from a predominantly motor disorder to a complex disorder of cognitive, behavioural and motor changes^{49,59}. Critical for this study is the recognition of a frontal variant of PSP, which presents with predominant behavioural changes such as apathy and impulsivity.

Clinicopathological correlations vary across FTLD syndromes and misdiagnosis is also common. This is one reason why several of the newly developed criteria incorporate different levels of diagnostic certainty including “possible”, “probable” and “definite”. Advances in neuroimaging techniques may facilitate improvements in diagnostic accuracy, but for now pathological studies are required for diagnostic confirmation.

Although there are clear differences between the FTLD syndromes in their classical forms, there are also similarities, particularly with regard to behavioural changes. This thesis does not attempt to undermine the significant advances within each of the conditions, including the development of syndrome-specific diagnostic criteria, identification of neuroimaging signatures and classification of pathological distinctions. However, the categorical approach to diagnosis may be inappropriate for advancing our understanding of symptom commonalities and their treatment, which may benefit from the transdiagnostic approaches adopted throughout this thesis.

Specifically, this thesis reports the characteristics, components and neural correlates of apathy and impulsivity in FTD, CBS and PSP. The data presented are largely concordant with the literature and add to the growing body of research highlighting the multifactorial nature of apathy and impulsivity.

This thesis reports four critical findings specific to FTLD syndromes, in relation to the initial hypotheses:

- 1) apathy and impulsivity are multifaceted constructs, positively correlated, and observed across the spectrum of FTLD syndromes.
- 2) patient ratings, carer ratings and objective measures do not correlate, reflecting distinct aspects of apathy and impulsivity and dissociable neural systems.
- 3) apathy and impulsivity reflect changes in both cerebral grey and white matter.
- 4) apathy is a significant predictor of survival.

7.1 Apathy and Impulsivity are Positively Correlated and Observed across FTLD Syndromes

Apathy and impulsivity were positively correlated in the PiPPIN cohort, supporting a growing literature recognising their frequent coexistence^{100,102,224}. This contradicts earlier proposals that apathy and impulsivity lie at opposite ends of a dopamine-dependent spectrum of motivation⁸⁶ and suggests additional non-dopaminergic mechanisms (discussed below in relation to treatments).

Apathy and impulsivity were also prevalent across FTD, PSP and CBS, not only in syndromes for which they are diagnostic criteria. This has been reported previously. For example, svPPA often develop behavioural changes consistent with bvFTD^{19,30}. Furthermore, newly developed criteria for PSP¹⁵ and CBS⁵ recognise a “frontal” variant with prominent behavioural change. The observation that apathy and impulsivity are present across the spectrum of FTLD syndromes has clinical and research implications. First, neurologists should not be overly bound by diagnostic criteria, but be aware of behavioural changes that may be masked by predominant motor changes in some disorders. Although diagnostic criteria are useful, they attempt to classify patients into distinct, clear cut categories which is not always appropriate in the context of FTLD. Indeed, some patients may meet criteria for multiple variants. With this in mind, clinical studies attempting to treat problematic behavioural changes may benefit from stratifying patients based on the presence and severity of symptoms, rather than diagnostic labels. By assessing behavioural change only in groups for which apathy and impulsivity are diagnostic criteria, for example, bvFTD and PSP, similar changes in language variants and CBS may be overlooked.

7.2 Patient ratings, Carer ratings and Objective measures do not Correlate, Reflecting Distinct Aspects of Apathy and Impulsivity and Dissociable Neural Correlates

Measuring the multifaceted constructs of apathy and impulsivity poses a significant challenge and development of numerous assessment tools have led to variations in their reported prevalence across disease groups^{89,98,231,388}. Subjective and objective measures may be unrelated^{196,241,252}, consistent with the lack of correlation between questionnaires and behavioural tasks in the PiPPIN study (chapter 3). Although there are some studies reporting correlations between subjective questionnaires and behavioural tasks³⁸⁹, they likely reflect differences between healthy controls and disease groups (for example, self-report measures and behavioural tasks may correlate in the healthy population but characteristics such as cognitive decline and lack of insight may alter this relationship in disease groups). The observed lack of correlation between measures has implications for translation from preclinical to clinical populations. Clinical studies (particularly large scale clinical trials) often employ questionnaires which are cheap, quick and easy to use, while pre-clinical studies adopt behavioural tasks, for which homologous human tasks have been developed (for example, SST)²³³. The PiPPIN data suggests the components of apathy and impulsivity measured by the objective tasks may not readily relate to subjectively reported apathy and impulsivity in FTLD. Choice of appropriate and sensitive outcome measures are critical for clinical trials and more effective, disease-specific assessment tools for FTLD are therefore warranted.

Cross-species translation rests on the concept of homologous tasks in preclinical models and clinical populations. This can successfully facilitate translational therapeutics, for example atomoxetine improves response inhibition (stop-signal task performance) in rodent, marmoset and human studies^{130,131,205,222,272}. Methylphenidate and modafinil also have similar effects in humans and animal models²³³. Although standard research practice relies on animal models to provide key insights into the biological basis of various diseases, they may be inappropriate for diseases affecting social cognition and other high order cognitive processes, such as FTLD. Extrapolating such high order cortical functions across species from rodents to humans is difficult and remains controversial²⁰⁸, either because of lack of evidence of the function in animals, or major differences in regional cortical functions. For example, action cancellation on the SST is associated with the right inferior frontal gyrus in humans, whereas the orbitofrontal cortex, but not the infralimbic and prelimbic cortex, is implicated in animal studies²³³. In contrast to the frontal cortex, the subcortical (for example basal ganglia) structures appear largely conserved in evolutionary terms, allowing more direct comparisons across species²³³.

In this thesis, objective behavioural tasks loaded onto distinct, orthogonal components (Chapter 3), providing evidence for the multifactorial nature of impulsivity^{208,216,219,232} and the differing sensitivity of the behavioural tasks to distinct components of impulsivity. For example, the SST and Go/NoGo are widely recognised to measure distinct aspects of response inhibition and reflect dissociable neuropharmacology; action cancellation (SST) is modulated by noradrenaline, while action inhibition (Go/NoGo) is influenced by serotonin. Accordingly, the SST and Go/NoGo loaded onto different components (Chapter 3) and reflected distinct underlying neural correlates (Chapter 4). Concordant with previous studies, the SST reflected changes in the right inferior frontal gyrus^{129,211,255,272}, while the Go/NoGo related to other measures of disinhibition including reflection impulsivity (information sampling) and reward sensitivity (cued reinforcement) and correlated with multiple regions including the thalamus, lateral temporal cortex, posterior and dorsal-anterior cingulate cortex and parieto-occipital cortex (Chapter 4).

The PiPPIN study data also revealed a discrepancy between patient and carer ratings of behavioural change, which has also been observed in PD³⁹⁰ and AD³⁹¹. Discrepancies may reflect loss of patient insight; PD and AD patients demonstrate impaired self-awareness in multiple domains, based on discrepancy between patients and their caregivers³⁹². Loss of insight is also reported across FTLD syndromes¹⁸. Caregiver distress may also contribute to the observed discrepancy. Merrilees et al., (2013) reported a correlation between apathy and caregiver emotional distress in bvFTD and svPPA¹⁰³. Carer burden is reported to increase with disease progression in FTD, which may also account for higher ratings of apathy/impulsivity with increased cognitive decline¹²⁸, although the exact relationship between apathy and cognition remains unclear⁹⁰.

In contrast, high correlations between patient and carer ratings have been reported for apathy in HD³⁹³ and ALS³⁹⁴, which may reflect retained patient insight in the early stages of disease (while motor features are predominant) or reduced caregiver burden in these groups. Indeed, severity of caregiver burden varies across groups and may account for the contrasting discrepancy results across dementia types¹²⁸. While this thesis does not clarify the cause of discrepancy between carers and patients, it emphasizes the importance of outcome measure selection for clinical trials.

The discrepancy between carer and patient insights raises an important issue; are we to treat the patient or the carer? Routine clinical practice and clinical trials largely focus on treating the

patient. Where trials aim to reduce carer burden and distress, they may do so by engaging the carer directly in the intervention, for example in program of “carer-training”, rather than intervening in the patient. Although patient and carer ratings are both important and valid, they are distinct. Critically, they can reflect differences in terms of the disease-related features which cause the most distress. The observation that patient and carer ratings also reflect distinct neural correlates (Chapter 3 and 4) suggests that a treatment for apathy may improve distressing behaviours reported by one, while having no influence on behaviours that are of concern to the other. For example, by treating features of the disease that are most distressing to the carer, one may miss features that are more problematic to the patient – effectively treating the carer and not the patient.

7.3 Apathy and Impulsivity reflect Changes in Grey and White Matter

The components of apathy and impulsivity reflect changes in widespread grey and white matter, which have been discussed in the relevant chapters. The neural correlates were broadly consistent with the wider literature reporting the neurobiology of apathy and impulsivity (also discussed in Chapter 4 and 5), which emphasise the importance of corticostriatal loops, including their grey matter targets and white matter connections. Carer ratings reflected widespread grey and white matter changes in frontotemporal, frontostriatal and brainstem systems, which have been implicated previously in arousal, goal-directed behaviour and motivation. Patient ratings reflected changes in the corticospinal tracts, as measured by VBM, which I suggest may reflect patients’ retained awareness of their physical impairment while their cognitive/behavioural insight is limited. The lack of DTI white matter correlates for patient ratings suggests either that the VBM white matter correlates are unreliable due to methodological issues (see Chapter 4), or that the multifocal white matter pathology associated with FTLD syndromes prevents identification of a single unitary correlate on DTI (see Chapter 5). The objective tasks correlated with more focal, task-specific brain regions on both VBM and DTI. A key validation for the methods adopted by this study was the observation that the Stop Signal Task (component 7) correlated with the right inferior frontal gyrus (despite accounting for a small proportion of the variance), which is consistently implicated with performance on this task in the broader literature^{209,211,255,272}.

7.4 Apathy is a Significant Predictor of Survival

The link between apathy and rapid cognitive and functional decline is widely recognised, particularly in mild cognitive impairment and Alzheimer’s Dementia^{82–84}, but also in FTLD

syndromes^{100,102,103,139}. Beyond this, there is accumulating evidence that apathy may be linked to reduced survival (Chapter 6 and ^{367,372–374,377,395}).

In PiPPIN, apathy (as measured by Component 2 loadings from the carer rated Apathy Evaluation Scale, Neuropsychiatric Inventory Apathy subscore, and Cambridge Behavioural Inventory subscores of everyday skills, self-care, sleep and motivation), was a significant predictor of death within 2.5 years from assessment. This raises the question of causality; does apathy *cause* a more rapid decline towards death, or is it a *biomarker* of a more aggressive disease? The relationship between the neural changes associated with dementia (including pathology (TDP-43, Tau), neurotransmitter systems and neurodegeneration/atrophy), the severity of apathy and survival is unclear. This thesis does not attempt to claim causality, but discusses the potential mechanisms accounting for the strong correlation between apathy and reduced survival in the PiPPIN cohort. Figure 24 suggests four alternate causal relationships of the interplay between apathy, neural changes and death, which are explained in more detail below.

Clarifying the link between apathy, disease progression and survival is critical for clinical trials of novel therapies. The relevance of the four alternative causal relationships (Figure 24) to clinical studies are discussed below.

Under model 1, apathy represents a potential biomarker of disease that may identify and stratify patients with severe or rapidly progressive disease, but without mediating the effect of neurodegeneration on survival. If apathy occurs early in disease, it may also represent a marker of *early* disease changes, or a “pre-diagnosis decline” towards mild cognitive impairment and dementia. However, it remains unclear when apathy is first apparent. Advances in our genetic understanding of FTLD has enabled studies of presymptomatic mutation carriers, who show neural changes 5-10 years prior to the onset of full-blown dementia⁸¹. These patients exhibit a long prodrome of subtle cognitive, behavioural and neurological changes, occurring years before the functional decline that triggers a clinical diagnosis of dementia. Whether increased apathy is observed in these genetically predisposed individuals warrants investigation in large cohorts targeting the relevant patients (based on the presence and severity of apathy) and using the appropriate assessment tools (depending on the *type* of apathy in question and the target population). Previous studies have been hindered by lack of sensitive measurement tools. However, recent interest in the biological basis of apathy in the healthy population has led to

behavioural paradigms and questionnaires that may capture very subtle changes in apathetic states^{114,117}, which may be applicable to presymptomatic groups.

Treatment of apathy under model 1 would be entirely symptomatic, improving quality of life but having no influence on survival, while disease modifying treatments must target the underlying neurodegenerative process.

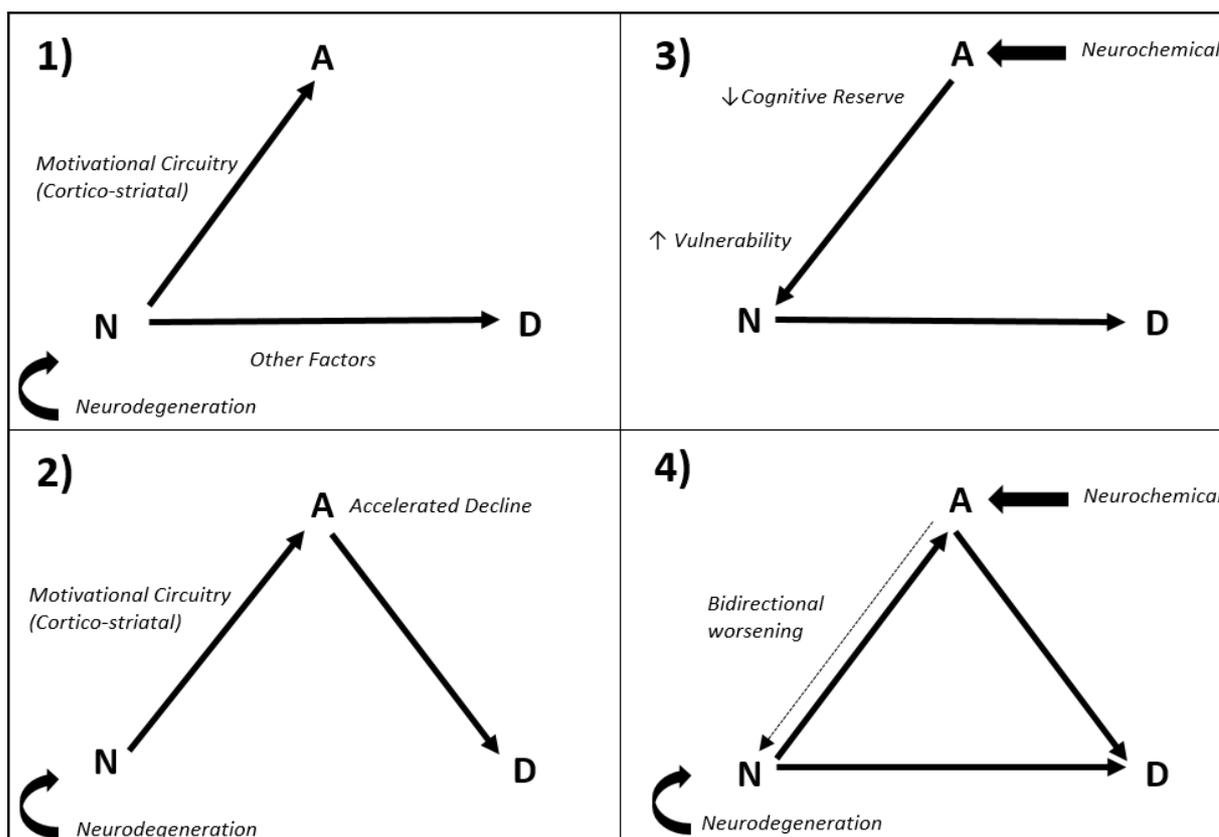


Figure 24: Causal models for the Impact of Apathy on Survival.

Four causal models explaining the relationship between apathy (A), neurodegeneration (N) and death (D). In brief, 1) apathy and death are incidental but unrelated effects of neurodegeneration, 2) neurodegenerative processes affect motivational circuitry underlying apathy, which in turn accelerates decline to death, 3) apathy, caused by factors such as chemical brain changes in motivational circuitry, mediates death by reducing “cognitive reserve” and subsequently increasing vulnerability to neurodegeneration 4) apathy and neurodegeneration each cause death, while also exacerbating each other; increased neurodegeneration worsens apathy, and reduced motivation accelerates neurodegeneration.

Alternatively, under model 2, apathy mediates a more rapid cognitive and functional decline. Neurodegenerative processes targeting the neural systems underlying motivation cause apathy, which in turn accelerates decline to death. The reverse model 3 is also plausible. Here, apathy (caused by non-neurodegenerative factors including chemical/neurotransmitter changes) leads

to decreased “cognitive reserve”, increasing vulnerability to neurodegeneration and therefore accelerating decline to death. The influence of “cognitive reserve” on dementia risk is widely recognised in the literature. This theoretical concept suggests that environmental factors, such as education, intelligence and ‘cognitive training’, can influence the brain’s capacity to sustain insult and modulate disease onset^{396,397}. Those with greater cognitive reserve are therefore thought to have increased neural network flexibility, increasing their ability to sustain greater levels of pathology before presenting clinically, and effectively counteracting the disease process (for example, those showing substantial AD pathology despite being cognitively ‘normal’³⁹⁸). I suggest the opposite may be true for apathy, consistent with previous studies reporting reduced cognitive reserve in individuals with smaller social networks and increased social isolation³⁹⁹

In model 4, apathy and neurodegeneration both cause death via a series of other (physical) factors, while also influencing each other; apathy accelerates neurodegeneration and neurodegeneration worsens apathy. From the literature (and Chapters 4/5), it seems most likely that neurodegenerative processes predominantly drive apathy ($N \rightarrow A$), although it is possible that increased apathy may in turn accelerate the underlying neurodegenerative processes ($A \rightarrow N$) perhaps through reduced “cognitive reserve” (discussed above). Neurodegeneration ultimately causes death via a number of physical factors, such as dysphagia in PSP, and secondary medical complications, for example pneumonia, while apathy may also reduce survival through poor self-care, inactivity and reduced food intake.

In models 2-4, apathy represents a target for both symptomatic and disease-modifying treatments; treatments targeting apathy would directly influence survival. Randomised controls trials targeting apathy as the primary outcome measure are warranted to clarify causality. Potential treatment options are discussed below.

7.5 Treatment of Apathy and Impulsivity

This thesis has focused largely on understanding the components and neural correlates of apathy with the view to informing future treatment studies. However, should one treat apathy? Although apathy causes substantial carer distress^{104,240}, apathetic patients may be inherently content with their apathetic state (for example, they are happy to sit in front of the TV and do nothing all day). This speaks to the question raised earlier: Does one treat the patient or the carer? In the event that apathy is *correlative* (Model 1) rather than *causative* (Model 2-4) of rapid cognitive and functional decline to death, one could argue against the treatment of apathy.

Although symptomatic treatment in this context may improve carer burden and distress, reducing apathy may improve patient insight and awareness which may have negative consequences in the context of a fatal condition. Furthermore, some treatments for apathy may have negative side effects; dopaminergic treatment for apathy can cause impulsivity and impulse control disorders, which are particularly dangerous and distressing^{225,262,263}.

The widely reported link between apathy, poor outcomes⁹⁰ and reduced survival^{373,380}(this thesis), provides a strong argument in favour of treatment. If apathy is indeed a *cause* of rapid decline, symptomatic intervention to reduce apathy may prove disease-modifying, warranting further investigations into potential neural targets. Current treatment options are limited; previous studies have been hindered by problems with accurate quantification of apathy. Furthermore, the exact underlying causal mechanisms of apathy remain unknown, with multiple neural systems implicated¹⁹⁹, complicating target identification for neuropharmacological treatment trials. The multifaceted nature of apathy and impulsivity and their neurobiological dissociations suggests the need for combinational therapy; the cortico-striatal loops implicated in the proposed framework for apathy and impulsivity^{111,310,356}, and also identified in this thesis (Chapters 4 & 5), receive inputs from a number of neurotransmitter systems including dopamine, noradrenaline and serotonin. Previous studies have therefore focused on manipulating these systems through available dopaminergic, noradrenergic and serotonergic drugs.

The dopaminergic system is widely implicated in incentive motivation and reward-related behaviours, in both animal and humans studies^{176–178,400,401}. Parkinson's patients ON dopamine medication show greater physical effort expenditure for reward¹¹⁶ and have greater pupillary response to rewards relative to OFF patients⁴⁰², reflecting greater reward sensitivity. Apathy and impulsivity are often considered to represent opposite ends of a dopamine-dependent spectrum of motivation, with apathy representing a hypodopaminergic state and impulsivity a hyperdopaminergic state. Indeed, dopaminergic treatment may improve apathy, while dopaminergic overdose of the ventral striatum leads to impulse control disorders^{86,225,250,262}. However, apathy and impulsivity are positively correlated and often coexist, suggesting involvement of other neurotransmitter systems. Furthermore, dopamine-resistant aspects of apathy and impulsivity are increasingly apparent, supporting the proposed pharmacological distinction between their components. For example, there is no clear evidence to support role for dopamine in action cancellation²³³. Instead, SST performance appears to be modulated by the noradrenergic system, while Go/NoGo is influenced by the serotonergic system^{131,258,268}.

The noradrenergic system, which projects from the locus coeruleus (LC) to many regions in the cortex, may play a key role in both apathetic and impulsive behaviours and may modulate dopaminergic transmission¹⁸⁵. The neural pathways mediating pupillary response to reward may be regulated by both dopamine and noradrenaline, which have common connections and may interact to mediate reward sensitivity and motivation⁴⁰². There is now substantial evidence that noradrenaline improves impulsivity, specifically response inhibition, in PSP, PD, ADHD and healthy controls^{129,245,271,272}. Currently, there are few studies providing evidence of the LC-NA system in apathy due to the difficulty of imaging small brainstem regions. However, the ventral striatum, which is often implicated in apathy, receives noradrenergic projections from the LC, in addition to its dopaminergic projections^{78,403}. High resolution imaging at 7 Tesla will provide the opportunity to investigate the LC and other deep brain structures in more detail, which may play a crucial role in apathetic and impulsive behaviours but have not been accessible previously through 3T imaging.

There are a number of limitations to previous studies assessing treatments for apathy and impulsivity. First, they often focused on a single diagnostic group, despite the prevalence of apathy and impulsivity across a number of disorders. This has hindered our understanding of the similarities and differences across syndromes. For example, apathy is widely recognised across a number of neuropsychiatric illness, but direct comparisons between apathy in psychiatric populations and neurological disease groups are lacking. It therefore remains unclear whether treatments that improve apathy/impulsivity in one group will do so in another. There have been initial reports of improved response inhibition following atomoxetine administration in a number of groups including ADHD, PSP, PD and healthy controls^{214,272}, providing support for modulating noradrenergic pathways to improve impulsivity across syndromes.

Second, cross-species translation may be limited for many available tools, particularly for those which measure apathy. Correlations between objective and subjective measures of apathy are limited. Most previous studies rely on questionnaire based assessments, which may be inappropriate for dementia populations due to cognitive decline and lack of insight. Better objective, translational measures that can measure motivation in a preclinical and clinical setting, are essential for quantitative assessment of targeted, novel therapeutics. There have been promising reports in schizophrenia^{404,405} and HD (Heath et al., *not published*) that progressive-ratio tasks⁴⁰⁶, designed to measure the “breakpoint” of effort based behaviour

(defined as the point at which an individual is no longer willing to exert the required effort to obtain a reward) may facilitate translation of pre-clinical findings into patient populations. Consistent findings in clinical cohorts and animal models suggest this task may facilitate assessment of the underlying neurobiological mechanisms of apathy and evaluate future treatments. Progressive ratio tasks are also reported to correlate with clinical subjective measures of apathy such as the AES (Professor Barbara Sahakian, personal communication from unpublished data), suggesting they may support the transition from preclinical and small detailed clinical studies, to large clinical trials (which often employ questionnaire-based measures).

Future studies aiming to understand the components and neural correlates of apathy and impulsivity should stratify patients based on the presence and severity of apathy and impulsivity, irrespective of their diagnosis, in order to establish similarities and differences across groups. Furthermore, choice of assessment tool is dependent on the component of apathy/impulsivity in question. Better translational tools are desperately required. Progressive ratio tasks demonstrate good face validity, and may provide a better platform for translation across species in the context of apathy research. Carefully designed clinical studies targeting the relevant patients and using the appropriate outcome measures will clarify whether effective intervention is purely symptomatic or also disease modifying. In turn, this may provide some clarification regarding causality.

7.6 Study Limitations

Specific limitations are discussed in each chapter, but in this section, a few general limitations to the study are highlighted, and possible alternative methods are considered.

7.6.1 Cohort

The limitations of the PiPPIN cohort have been discussed in detail in Chapter 3. Briefly, the PiPPIN study attempted to reach all patients throughout Cambridgeshire and Norfolk with a FTLD diagnosis, although it is possible that the cohort is biased and under representative of the population. Inherent to studies of apathy, it is likely that individuals taking part in the study were more motivated (less apathetic) than those who never present to clinic. However, multiple sources of identification were used for patient recruitment and the study team made regular home visits in order to reach patients who would otherwise be unable to take part in the study for medical or practical reasons.

The inclusive approach to this study, considering all FTLD variants together, provides key insights into the commonalities observed across the spectrum, but may consequently neglect important and well recognised differences between diagnostic groups. By examining the component scores by diagnostic group (Chapter 3), distinctions were observed and acknowledged. However, the data confirmed the presence of apathy, impulsivity and related behaviours (captured by the components) across diagnostic groups, providing support for the transdiagnostic approach employed throughout this thesis.

7.6.2 Methods: Limitations and alternative approaches

The PiPPIN assessment battery attempted to capture all aspects of apathy and impulsivity while considering the ability and frailty of FTD, PSP and CBS patients. The battery was necessarily selective, attempting to assess the recognised components of apathy and impulsivity through available questionnaires and subjective tasks, and results are therefore only applicable to measured aspects of motivation. Studies using additional measures may identify distinct or additional components.

The selective nature of the assessment battery means that aspects of apathy and impulsivity may have been missed. For example, risky decisions and impulsive choice on the Cambridge Gambling Task was not assessed, due to difficulty with task engagement in patient groups. However, reward sensitivity was quantified using other assessments including the CRRT and Kirby.

It is possible that the presence of apathy in severely impaired patients was missed, due to their inability to perform on certain questionnaires/tasks. Self-rated questionnaires rely on introspection, insight and semantics, while behavioural tasks are heavily dependent on motor function, all of which may be limited in FTLD patients. These confounds are inherent to studies of dementia populations. By adopting carer reports, some insight was gained regarding behavioural changes in these patients, although these are potentially confounded by personal distress. Furthermore, the discrepancy between patient and carer ratings suggests they differ in their opinion of distressing disease features. Use of large datasets, and examination of components rather than individual tests, minimizes the impact of these confounds.

Since the PiPPIN study, there have been a number of new objective measures targeting apathy in the healthy population¹¹⁷ and in disease groups^{116,404,406} which provide useful insights into the sub processes underlying motivation. Of particular interest are progressive ratio tasks,

which assess the motivational “breakpoint” of an individual or the point at which an individual is no longer willing to work for a reward due to effort⁴⁰⁶. Studies in HD report lower “breakpoints” for patients compared to controls, reflecting reduced motivation. Critically, progressive ratio tasks show strong translation across species and correlate with subjective measures of clinical apathy (AES) (Sahakian et al., unpublished). Whether FTLN patients also show lower breakpoints has yet to be investigated.

Pupillometry may also be useful in the assessment of reward sensitivity; reduced pupil dilation in response to reward is proposed to reflect insensitivity to reward⁴⁰², although the associated underlying neuropharmacological mechanisms (dopaminergic versus noradrenergic) require clarification^{270,407}. Employing eye-related tasks can overcome confounds such as motor impairments, which are characteristic of some FTLN groups. In the PiPPIN study, saccade and motor Go/NoGo performance loaded onto the same component (Chapter 3, Table 12), suggesting the saccadic task is a useful alternative to motor tasks assessing response inhibition and cognitive control.

7.6.3 Imaging

Limitations specific to the imaging methods, including voxel based morphometry (Chapter 4) and diffusion weighted imaging (Chapter 5), have been discussed in the relevant chapters. Here, I focus on alternative imaging methods which may be useful in the context of the PiPPIN study.

White matter changes were assessed using tract based spatial statistics of diffusion weighted imaging, a widely adopted technique developed by Smith et al., (2006). There are of course alternative quantitative analysis techniques that could be used, including region of interest (ROI) analysis. However, ROI requires manual delineation of *a priori* specific regions of the brain or automated parcellations, which would be inappropriate for the current study, which looked at *components* of behaviours which therefore limited the ability to make *a priori* assumptions.

Resting state MRI is increasingly adopted to measure the brain at rest (‘task-free’), minimizing task-related performance confounds which are common to neurodegenerative diseases. This imaging method is useful to examine network-related differences between groups (for example controls versus patients), providing an ideal platform for future studies assessing the impact of candidate treatments on the brain networks that underlie apathy and impulsivity. Borchert et al

(2016), reported increased connectivity from the right inferior frontal gyrus to dorsal anterior cingulate in PD patients following atomoxetine²⁷¹, a drug which improves response inhibition in multiple disease groups^{129,214,272}, and may represent a potential therapeutic for impulsivity (and apathy) in FTLD⁷⁸.

Positron Emission Tomography (PET) is a useful tool to assess changes in glucose metabolism (FDG-PET). Previous studies have reported correlations between brain metabolism and behavioural changes in FTLD syndromes; hypometabolism in the dorsolateral and frontal medial cortex bilaterally is associated with apathy, while hypometabolism in the orbitofrontal cortex, anterior cingulate cortex, hippocampus/amygdala and nucleus accumbens is reported in disinhibited FTD patients¹⁶⁸. PET imaging is also increasingly used to target the underlying neuropathology of neurodegenerative diseases, using radiotracers (for example for amyloid and tau). Neuropathological burden in certain brain regions may cause specific behavioural changes; post mortem studies have reported a correlation between NPI apathy and neurofibrillary tangles in the anterior cingulate in AD¹⁷⁰. There are a number of ongoing PET imaging studies in Cambridge assessing the neuropathological changes underlying FTLD syndromes⁴⁰⁸, including their associated behavioural changes. However, these methods are not without limitations. Although amyloid imaging has been relatively successful in Alzheimer's research, the reported off-target binding of tau tracers may limit their applicability to FTLD.

Magnetic Resonance Spectroscopy may also have been useful to assess the biochemical changes underlying apathy and impulsivity in FTLD syndromes. This is currently being investigated in an ongoing study at Cambridge.

7.6.4 Future Directions

Replication of findings is critical to scientific research. A follow up PiPPIN 2 study is currently ongoing, obtaining longitudinal data from PiPPIN 1 participants (who are still alive) while also accumulating additional cross-sectional data in a new sample of FTD, PSP and CBS patients. The assessment battery is broadly consistent with PiPPIN 1, and will allow replication studies for the findings presented throughout this thesis. Additional tests include novel objective behavioural tasks such as the progressive-ratio task⁴⁰⁶.

The PiPPIN 2 study also includes a novel questionnaire called the CamQUAIT (Cambridge Questionnaire for Apathy and Impulsivity Traits), which I developed using Rasch Analysis⁴⁰⁹. The scale has yet to be fully validated in a new cohort, and it would therefore be premature to

include it in this thesis. The PiPPIN 2 study will provide the ideal platform to validate the CamQUAIT, gathering sufficient data in the intended target population (FTLD) to re-analyse the questionnaire's properties through Rasch analysis and determine its face, construct and predictive validity.

At the Cambridge Centre for Frontotemporal Dementia and Related Disorders, we are interested in pathological validation of these behaviours and their underlying neural systems, including neurotransmitter involvement. For example, post-mortem studies are ongoing to clarify the noradrenergic hypothesis of apathy and impulsivity, by assessing whether PSP pathology in the locus coeruleus, the major source of noradrenaline in the brain, correlates retrospectively with impulsivity. Additional noradrenergic studies include 1) 7T imaging of the LC and 2) treatment studies of atomoxetine (noradrenaline reuptake inhibitor) in PSP, to determine whether it has a similar beneficial effect on network connectivity and clinical impulsivity as reported previously in PD^{205,245,271}.

Although genetics analysis was beyond the scope of this thesis, there is some evidence to suggest genetic variation influences impulsive behaviours⁴¹⁰. Allelic variation in the SLC6A2 gene, which encodes the noradrenaline transporter, is related to activity in the right inferior frontal gyrus and influences response inhibition²⁰⁹. Polymorphisms in the DRD2 gene may also influence behavioural inhibition and impulsivity through variations in dopamine neurotransmission^{411,412}. Dysregulation of noradrenergic and dopaminergic systems give rise to various manifestations of apathy, and may have underlying genetic influences^{410,413}. The extent to which genetics can determine clinical expression of FTLD, including the presence and severity of apathy and impulsivity, warrants further investigation.

7.7 Conclusion

This thesis has demonstrated the advantages of *transdiagnostic* approaches to assess complex neurodegenerative disorders and their associated symptom commonalities, including apathy and impulsivity. Components of apathy and impulsivity are positively correlated, and observed across the FTLD spectrum, not only in syndromes for which they are diagnostic criteria. Novel, disease-specific, translational assessment tools are warranted to capture the dissociable components or neurocognitive endophenotypes²¹⁹ of these behaviours. Clinical studies should consider the *type* and *severity* of apathy and/or impulsivity exhibited, moving away from classification based on clinical diagnosis to consider dimensional behavioural constructs.

The prognostic importance of apathy suggests it may represent both a symptomatic and disease-modifying treatment target. Future studies should clarify the onset of apathy and its associated genetic, neurobiological and neuropharmacological influences. Continued advances in our understanding of the biological basis of apathy and impulsivity in the healthy population will inform studies in disease populations. Recent studies targeting neurotransmitter systems underlying apathy and/or impulsivity have reported improvements on clinical and neuroimaging measures, although their long term impact on prognosis requires investigation.

Advances in our understanding of these particularly distressing but potentially treatable conditions are moving us closer towards effective therapeutic strategies for neurodegenerative conditions. The importance of quality, as well as quantity, of life highlights the need to develop improved symptomatic therapies in parallel with ongoing studies into disease modifying treatments. Studies targeting the disease early, before widespread neuropathology and neuronal loss, may provide a breakthrough. The complex multifaceted nature of neurodegenerative diseases suggests the need for combinational therapy, targeting both the underlying neuropathology and neuropharmacology of disease and its associated disabling symptoms.

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Appendix A: Grey Matter Voxel-based Morphometry Coordinates

Component	Brain Regions	Cluster Extent	Peak (x, y, z)			Peak Z score
2	Precentral/postcentral gyrus and putamen	44087	54	-4	42	6.00
			2	-22	54	4.79
			26	8	4	4.59
			-26	4	8	4.58
			40	-60	-26	4.20
			-12	-88	18	4.14
			8	-78	-14	4.09
			58	-12	10	4.02
			0	-30	-12	3.97
			-12	-60	44	3.96
			-38	-62	-30	3.93
			-25	18	64	3.88
			0	20	38	3.84
			20	-52	-54	3.69
			36	32	44	3.64
			30	-22	70	3.56
			-30	46	26	3.50
			-16	-40	-48	3.49
			60	-44	48	3.26
			16	-56	16	3.20
-6	-72	-44	3.19			
24	-16	-32	3.04			
66	-46	12	2.90			
		3739	-38	-14	52	4.86
		1080	-42	-46	46	4.04
			-42	-62	12	3.59
3	Temporal pole, orbitofrontal cortex and anterior insula	68792	-32	16	-28	6.24
			26	10	-32	6.24
			36	-20	-10	5.74
			-2	26	-8	5.69
			-56	-18	-24	5.34
			60	-12	-32	5.33
			8	40	24	5.06
			-22	-26	-26	4.92
			-8	20	44	4.50
			52	38	-14	4.32
			-38	-8	8	4.31

Component	Brain Regions	Cluster Extent	Peak (x, y, z)			Peak Z score	
3 (continued)	Temporal pole, orbitofrontal cortex and anterior insula	68792	-2	-26	52	4.12	
			-12	-46	8	4.09	
			-24	48	-18	3.88	
			-4	62	4	3.79	
			-28	46	28	3.75	
			64	-54	-8	3.73	
			60	-10	10	3.49	
			-44	-4	54	3.49	
			50	26	20	2.96	
			0	-16	4	2.89	
			-68	-40	4	2.86	
4	Thalamus	16149	-12	-30	0	4.40	
			-38	-58	54	4.03	
			-54	-36	22	4.03	
			-52	-26	-20	3.95	
			10	-14	58	3.95	
			-36	-56	-10	3.86	
			18	-22	18	3.45	
			18	-80	28	3.44	
			36	-60	-4	3.43	
			-10	-84	44	3.42	
			-50	-70	22	3.41	
			20	-24	-32	3.39	
			6	-76	-10	3.18	
			-4	-42	38	3.13	
			6213	18	4	-14	4.05
			58	-12	38	3.65	
			56	-8	6	3.47	
			58	-40	12	3.44	
			58	8	-22	3.25	
36	12	54	2.86				
46	-22	-30	2.83				
7	Middle frontal gyrus, supplementary motor cortex	3618	44	12	48	4.52	
			4	24	46	3.56	
			32	42	30	3.31	
			50	20	4	3.21	
			4	-6	66	3.16	

Cluster FWE $p < 0.05$ corrected, peak-level $p < 0.001$ uncorrected. Brain regions identified using Neuromorphometrics atlas in SPM12.

Appendix B: White Matter Voxel-based Morphometry Coordinates

Component	Brain Regions	Cluster Extent	Peak (x, y, z)			Peak Z score
1	Middle frontal gyrus, cerebral white matter	20478	-38	10	50	4.72
			36	-14	2	4.32
			-16	-26	14	4.13
			-8	18	34	3.86
			10	-44	58	3.71
			24	16	54	3.66
			22	18	-18	3.59
			-46	-36	22	3.45
			-16	-18	54	3.32
			-44	2	8	3.18
			62	-14	26	3.01
			20	-32	-26	3.01
			-20	-32	-28	3.01
20	-38	28	2.60			
2	Brain stem	7360	-6	-38	-58	5.02
			8	-36	-26	4.18
			-16	-14	-16	3.40
			32	-56	-12	2.85
			2064	-28	20	14
-12	10	48	3.35			
-18	60	18	2.85			
3	Right cerebral white matter (including amygdala, hippocampus), temporal pole	23273	32	-2	-28	6.64
			-36	0	-18	5.71
			34	-30	-12	5.44
			18	30	-14	4.69
			38	26	18	4.56
			-32	-38	-10	4.56
			-16	46	18	4.40
			-10	14	44	4.29
-40	8	18	3.50			
7	Left Cerebral white matter (including anterior cingulate, frontal gyrus and supplementary motor cortex)	1818	-14	24	26	3.93
			-48	16	4	2.93

Cluster FWE $p < 0.05$ corrected, peak-level $p < 0.001$ uncorrected. Brain regions identified using Neuromorphometrics atlas in SPM12.