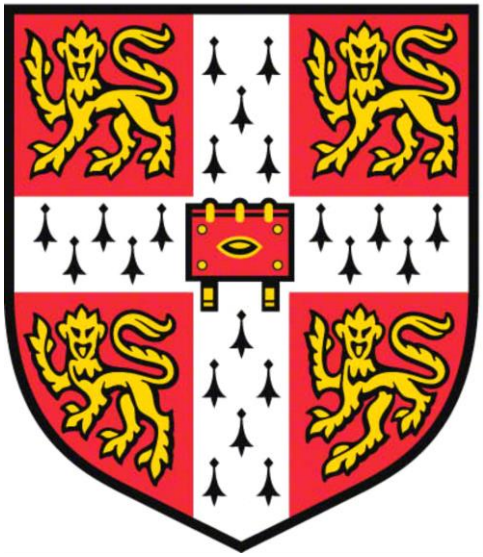
Behavioural disinhibition in the syndromes associated with frontotemporal lobar degeneration



Alexander George Murley

Queens' College

University of Cambridge

This thesis is submitted for the degree of Doctor of Philosophy

February 2020

Declaration

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the preface and specified in the text. It is not substantially the same as any work that has already been submitted before for any degree or other qualification. It does not exceed the prescribed word limit for the Degree Committee for the Faculties of Clinical Medicine and Veterinary Medicine.

Summary

The different clinical syndromes caused by frontotemporal lobar degeneration (FTLD) have highly heterogenous and overlapping features which complicate clinical and research practice. Behavioural impairments are associated with all FTLD syndromes, cause high morbidity and lack proven symptomatic treatments. Treatments for cognitive and behavioural impairment in other neurodegenerative diseases include restoration of neurotransmitter deficits. Deficits in the neurotransmitters glutamate and GABA occur in FTLD syndromes and are associated with behavioural disinhibition in other diseases. I propose that these neurotransmitter deficits contribute to behavioural change in FTLD syndromes. This thesis has two main aims. First, to develop a transdiagnostic approach to FTLD syndromes to facilitate a better understanding of aetiology, pathophysiology and in due course their symptomatic treatment. Second, to use this approach to test the hypothesis that glutamate and GABA deficits are associated with behavioural disinhibition in FTLD syndromes.

In a cross-sectional epidemiological study, I examined 310 of 365 regional patients with a FTLD-associated syndrome, including behavioural variant frontotemporal dementia, the non-fluent and semantic variants of primary progressive aphasia, progressive supranuclear palsy and corticobasal syndrome. Multivariate analyses of clinical features and brain morphometry identified components that showed considerable overlap across the diagnostic groups. The transdiagnostic components of clinical features predicted neuropathology better than the current FTLD diagnostic labels. Behavioural disturbance, including disinhibition, was associated with reduced functionally independent survival, irrespective of diagnosis. Next, I investigated the role of glutamate and GABA in behavioural disinhibition. Ultrahigh-field magnetic resonance spectroscopy was used to measure glutamate and GABA in the frontal cortex of 44 patients with a FTLD syndrome and 20 healthy controls. Bayesian modelling of a response inhibition task was used to quantify behavioural disinhibition. Both neurotransmitters were reduced in the frontal cortex, but not occipital cortex, of patients compared to controls. Glutamate and GABA concentrations in the frontal cortex were inversely associated with behavioural disinhibition.

In summary, the transdiagnostic approach provided new insights into the phenotypic heterogeneity in FTLD syndromes. Behavioural disinhibition, which can occur to a variable degree in all FTLD syndromes, was associated with reduced functionally independent survival. GABA and glutamate deficits in the frontal cortex are associated with behavioural disinhibition and are a potential target for future treatments.

Acknowledgements

I am very grateful to the large number of people who helped with this research. Thank you to Professor James Rowe, for his supervision of this PhD and for his teaching and guidance in academic and clinical neurology. The opportunity to learn from both his detailed, rigorous approach to neuroscience and his holistic and compassionate care of patients with neurodegenerative disease has been invaluable and inspiring. Thank you to all the members of the Cambridge Centre for Frontotemporal Dementia and Related Disorders for making my PhD so enjoyable. I have benefited hugely from many members of the group who very generously shared their diverse range of experience and skills. Thank you to Matthew Rouse, Win Li and Julie Wiggins for their help with patient recruitment and testing. Thank you to Simon Jones and Kamen Tsevetanov for their help with imaging analysis and statistics. Thank you to Claire O'Callaghan, Ron Ye and Frank Hezemans for our combined effort on stop signal task analysis. Thank you to all the staff at the Wolfson Brain Imaging Centre including Hannah Rhatigan, Karen Welch, Vicky Lupson, Guy Williams, Catarina Rua, Chris Rodgers and Adrian Carpenter. Thank you to Sanne Kaalund for her help with the *post-mortem* ELISA. Thank you to my examiners.

I am very grateful for the Holt fellowship which funded this research, with additional support from the Wellcome Trust, Medical Research Council and National Institute for Health Research. Thank you to all the patients and their families and carers. It is inspiring to see the selflessness of people who, faced with devastating, life-limiting, progressive diseases, volunteer to take part in clinical research.

Thank you to my family, especially my wife Emily, without whose limitless support and understanding this thesis would never had been possible.

Dedication

To William Joseph Murley, who kindly waited until I had finished this thesis before arriving on the 14th February 2020.

Table of Contents

Table of Figures

Abbreviations

ACER	Addenbrooke's Cognitive Examination - Revised
AD	Alzheimer's disease
BvFTD	Behavioural variant frontotemporal dementia
CBIR	Cambridge Behavioural Inventory - Revised
CBD	Corticobasal degeneration
CBS	Corticobasal syndrome
CRLB	Cramer Rao Lower Bound
FDR	False discovery rate
FWE	Family wise error
FAB	Frontal Assessment Battery
FTD	Frontotemporal dementia
FRS	Frontotemporal Dementia Rating Scale
FTLD	Frontotemporal lobar degeneration
FUS	Fused in sarcoma
GABA	gamma-Aminobutyric acid
GWAS	Genome wide association study
Glu	Glutamate
HDI	Highest density interval
IFG	Inferior frontal gyrus
ICD	International Classification of Diseases
lvPPA	Logopenic variant primary progressive aphasia
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MAPT	Microtubule associated protein tau
MND	Motor neuron disease
nfvPPA	Non-fluent variant primary progressive aphasia
PD	Parkinson's disease
PiD	Pick's disease
PIPPIN	Pick's disease and Progressive Supranuclear Palsy Prevalence and Incidence study
PPA	Primary progressive aphasia
PCA	Principal Component Analysis
PSP	Progressive supranuclear palsy
PSP-F	PSP Frontal variant
PSP-RS	PSP Richardson's syndrome variant
REM	Rapid eye movement
ROPE	Region of practical equivalence
RIFG	Right inferior frontal gyrus
ROCC	Right occipital
svPPA	Semantic variant primary progressive aphasia
SD	Standard deviation
SSRT	Stop signal reaction time
TDP43	Transactive response DNA-binding protein 43 kDa
TF	Trigger failure

Introduction

Preface

Part of this discussion is included in a review article I wrote with Professor Rowe (Murley and Rowe, 2018).

Neurodegenerative diseases are a major worldwide cause of morbidity and mortality. They are the commonest cause of dementia, a condition of progressive multidomain cognitive impairment that affects an individual's ability to perform everyday activities (McKhann *et al.*, 2011; Erkkinen *et al.*, 2018). The global burden of neurodegenerative diseases is worsening, due to increased life expectancy and more effective treatment of other age-related conditions such as ischaemic heart disease and cancer (Salthouse, 2004; Feigin *et al.*, 2019). The global number of people living with dementia doubled between 1990 to 2016 and it is projected that over 100 million people will be living with dementia by 2050 (Nichols *et al.*, 2019). The financial cost of caring for people with neurodegenerative diseases is estimated at over one trillion dollars (Wimo *et al.*, 2017) and this does not reflect the even greater personal cost of these diseases to the affected individual and their family (Winblad *et al.*, 2016). Currently, there are no effective disease modifying treatments for any neurodegenerative disease, although there are encouraging early stage results of some therapies (Sevigny *et al.*, 2016; Boxer *et al.*, 2019; Panza *et al.*, 2019). These treatments, even if effective in large randomised trials, may only slow disease progression and would then need to be combined with effective symptomatic treatments to reduce overall disease burden (Winblad *et al.*, 2016).

In this thesis, I focus on the syndromes associated with frontotemporal lobar degeneration (FTLD). These diseases can present at any time in adulthood and are the third most common neurodegenerative cause of dementia after Alzheimer's disease and Dementia with Lewy bodies (Harvey *et al.*, 2003; Van Der Flier and Scheltens, 2005; Cairns *et al.*, 2007). The severity and complexity of the rapidly progressive and life limiting cognitive, behavioural and motor symptoms associated with FTLD result in a high disease burden. The overarching aim of my PhD was to help progress towards better symptomatic treatments by improving our understanding of the neurobiology of behavioural impairments in FTLD syndromes.

Introduction to frontotemporal lobar degeneration and associated clinical syndromes

The rapidly evolving field of research into FTLD and its clinical manifestations has resulted in confusing definitions and diagnostic labels. In this thesis, I use the current consensus nosology for the main clinical and pathological diagnoses. Frontotemporal lobar degeneration (FTLD) refers to the neuropathological diagnosis (MacKenzie *et al.*, 2010). The phrase "frontotemporal lobar degeneration syndromes" refers to the clinical diagnoses of syndromes known to be associated with FTLD neuropathology: behavioural variant frontotemporal dementia (bvFTD),

the non-fluent (nfvPPA) and semantic (svPPA) variants of primary progressive aphasia, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). Although logopenic aphasia (lvPPA) is a form of primary progressive aphasia, it is closely associated with Alzheimer pathology (Sajjadi *et al.*, 2012).

Neuropathology and genetics of frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is a pathologically heterogenous neurodegenerative disease that causes a spectrum of cognitive, behaviour and motor features (Figure 1-1). Macroscopically, FTLD results in disproportionate atrophy of the frontal and/or temporal lobes (Cairns *et al.*, 2007). Many cases also have atrophy of the basal ganglia, brainstem and other subcortical structures (Cairns *et al.*, 2007; Garibotto *et al.*, 2011). Microscopically, FTLD is characterised by neuronal loss, microvaculation and accumulation of misfolded protein inclusions in neurons and glial cells (Cairns *et al.*, 2007). There are three major FTLD subtypes, which are classified by either tau (FTLD-tau), TDP-43 (FTLD-TDP43) or FET (FTLD-FET) protein accumulation (Mackenzie and Neumann, 2016; Neumann and Mackenzie, 2019). Rarely, a case of FTLD does not have the typical features of any of these three subtypes and these cases usually contain ubiquitin positive inclusions (FTLD-U) (Roeber *et al.*, 2008). The mechanistic link between protein aggregation and neurodegeneration is still not fully understood, as there is incomplete overlap between the intracellular protein aggregates, neuronal degeneration and cell death (Ross and Poirier, 2005). This suggests that the visible aggregates of insoluble protein fibrils represent the final stage of a molecular cascade, earlier steps of which, possibly soluble oligomers, are pathogenic rather than the insoluble fibrils themselves (Ross and Poirier, 2004; Brunden *et al.*, 2008; Lee *et al.*, 2012).

Most cases of FTLD occur sporadically and have an unclear aetiology that is likely to be a combination of genetic (Chen *et al.*, 2015; Yokoyama *et al.*, 2017; Raffaele *et al.*, 2019) and environmental (Litvan *et al.*, 2016; Park *et al.*, 2018) risk factors. Other are caused by a highly penetrant, autosomal dominant, genetic mutation (Rademakers *et al.*, 2012; Raffaele *et al.*, 2019). The prevalence of these familial cases depends on the population, clinical syndrome and FTLD subtype (Moore *et al.*, 2019). For example, progressive supranuclear palsy is very rarely associated with genetic mutations, which are even an exclusion criteria in the most recent diagnostic criteria (Höglinger *et al.*, 2017). Behavioural variant frontotemporal dementia is associated with an autosomal dominant monogenic mutation in up to 40% of cases (Bang *et al.*, 2015). However, disease age of onset and clinical phenotype varies even within families with a familial FTLD syndrome (Boeve *et al.*, 2005; Tuite *et al.*, 2005; Borroni *et al.*, 2011; Foxe *et*

al., 2018; Moore *et al.*, 2019), suggesting there are other genetic and environmental risk modifiers (Van Blitterswijk *et al.*, 2014; Zhang *et al.*, 2018). Next, I introduce the primary FTLD pathological subtypes, FTLD-tau, FTLD-TDP43 and FTLD-FET and summarise their molecular and genetic characteristics.

FTLD-Tau

In health, the tau protein is present in high concentrations in the axons of neurons and in low concentrations in astrocytes and oligodendrocytes (Yoshiyama *et al.*, 2013; Irwin *et al.*, 2015). Normal tau supports neuron structure and intercellular transport by binding and stabilising microtubules (Lee *et al.*, 2011*c*; Yoshiyama *et al.*, 2013). Tau occurs in six isoforms due to alternative splicing of the tau gene, MAPT (Goedert *et al.*, 1989). Inclusion or exclusion of one tau gene exons during transcription results in either three- (3R) or four-repeat (4R) tau, depending on the number of microtubular binding repeats in the tau protein (Hong *et al.*, 1998). In the healthy brain there is an equal ratio of 3R and 4R tau (Hong *et al.*, 1998).

In neurodegenerative tauopathies there is accumulation of misfolded, hyperphosphorylated tau, which takes the form of insoluble fibrils in neurons and glia (Ballatore *et al.*, 2007, Lee *et al.*, 2011*c*). The classification of different tauopathies is complex, depending on the presence or absence of other abnormal proteins, the morphological appearance and distribution of tau, and imbalance in the 3R:4R tau ratio (Josephs, 2017). For example, Alzheimer's Disease (AD) is classed as a secondary tauopathy, as it is characterised by both intracellular neurofibrillary tangles containing equal ratios of 3R and 4R tau and extracellular deposits of amyloid-β peptides in plaques (Hyman *et al.*, 2012; Irwin, 2016). Frontotemporal lobar degeneration is associated with several primary tauopathies which differ in the ratios of 3R and 4R tau. These primary tauopathies include progressive supranuclear palsy, corticobasal degeneration, globular glial tauopathy and Pick's disease.

Pick's disease is a 3R-tau predominant tauopathy characterised by Pick's bodies, round, tau-positive intranuclear inclusions which are seen in neurons and glial cells in the frontotemporal neocortex, white matter and basal ganglia (Irwin, 2016; Irwin *et al.*, 2016). Brains with Pick's disease have swollen, ballooned neurons, with tau pathology spread through superficial and deep layers of the neocortex (Irwin *et al.*, 2016). Historically, Pick's disease referred to a clinical syndrome of progressive behavioural and language decline that was first described by Arnold Pick in 1892 (Pick, 1892). Alois Alzheimer then reported the associated microscopic features of Pick's bodies and ballooned cells (Alzheimer, 1911). The label of Pick's disease

now refers to this specific tau pathology that is only associated with a small proportion of cases with frontotemporal dementia (FTLD-tau-PiD) (Perry *et al.*, 2017*a*).

Progressive supranuclear palsy is a 4R-tau predominant tauopathy associated with tau inclusions in brainstem, subcortical and cortical neurons. There are also fibrillary tau inclusions in astrocytes and these "tufted astrocytes" are a characteristic feature of FTLD-tau-PSP (Dickson *et al.*, 2007). The term PSP is also used to describe the typical clinical syndrome of a vertical gaze palsy, axial rigidity and falls associated with FTLD-tau-PSP, which was first described by Steele, Richardson and Olszewski in 1964 (Steele *et al.*, 1964). However, FTLD-tau-PSP pathology can present with other behaviour, speech and motor symptoms (Respondek and Hoglinger, 2016) so this "typical" presentation is now labelled PSP-Richardson's syndrome (PSP-RS) (Litvan *et al.*, 1996*c*; Höglinger *et al.*, 2017). The macroscopic appearance of the brain with FTLD-tau-PSP depends on the clinical syndrome, but at *post-mortem* most patients have severe atrophy in the midbrain and pons (Dickson *et al.*, 2007; Sakae *et al.*, 2019). Corticobasal degeneration (CBD) is 4R-tauopathy characterised by tau-positive diffuse astrocytic plaques and swollen, ballooned neurons in neocortical and limbic grey matter (Dickson *et al.*, 2002; Irwin, 2016). The brainstem and basal ganglia contain large numbers of tau-positive inclusions (Dickson *et al.*, 2002). Macroscopically, there is typically marked asymmetrical atrophy of the motor cortex (Dickson *et al.*, 2002). Corticobasal degeneration can be difficult to distinguish from progressive supranuclear palsy pathology (Irwin, 2016) and there is an ongoing debate if these are separate entities (Höglinger, 2018; Ling and Macerollo, 2018). Globular glial tauopathy is a 4R tauopathy associated with widespread tau-positive globular inclusions in oligodendrocytes and other glial cells that is more rarely seen in FTLD syndromes (Ahmed *et al.*, 2013).

FTLD-tau can be caused by an autosomal dominant genetic mutation. Over 50 mutations in the MAPT gene have been identified. (Ghetti *et al.*, 2015). These mutations have autosomal dominant inheritance (Ghetti *et al.*, 2015). Tauopathies due to MAPT mutations were considered a separate entity (FTDP-17), but more recent evidence suggests they are genetic forms of sporadic primary tauopathies (Forrest *et al.*, 2018; Josephs, 2018). MAPT mutations can cause both 3R (Pick's disease) and 4R (progressive supranuclear palsy, corticobasal degeneration and globular glial) tauopathies (Fujioka *et al.*, 2015; Forrest *et al.*, 2018). Interestingly, the neuropathology associated with specific MAPT mutation can vary, suggesting that there are additional modifying factors that are currently unknown (Ghetti *et al.*, 2015; Forrest *et al.*, 2018). Genome wide association studies have found variants in the MAPT gene

are associated with an increased risk of sporadic frontotemporal dementia, progressive supranuclear palsy and corticobasal degeneration (Houlden *et al.*, 2001; Höglinger *et al.*, 2011; Kouri *et al.*, 2015; Chen *et al.*, 2019).

FTLD-TDP43

In health, TDP-43 is a DNA/RNA-binding protein that is highly conserved and ubiquitously expressed in cells (Ratti and Buratti, 2016). Physiological TDP-43 has a wide range of roles, including regulating RNA metabolism and DNA repair (Ratti and Buratti, 2016). It is essential for neuronal survival and TDP43 knockout animal models are not viable (Kraemer *et al.*, 2010). In FTLD-TDP43, normal neuronal TDP43 is depleted and there is abnormal aggregation of TDP43 in the cytoplasm. Microscopically, there are neuronal cytoplasmic and intranuclear inclusions and dystrophic neurites that are immunoreactive for TDP-43 (MacKenzie *et al.*, 2010; Neumann and Mackenzie, 2019). There is a strong association between the density and regional distribution of TDP-43 pathology and neurodegeneration (Drubach, 2009) but it is unclear if TDP43 mediates neurodegeneration through gain of toxic function, loss of normal function or both (Lee *et al.*, 2012; Neumann and Mackenzie, 2019).

Four TDP-43 subtypes are currently recognised (FTLD TDP43A-D), based on the morphological and distribution of the TDP-43 immunoreactive inclusions (Mackenzie *et al.*, 2011). Type A cases are characterised by short, thick dystrophic neurites and compact neuronal cytoplasmic inclusions in layer II of the neocortex of affected regions. Type B cases have diffuse granular cytoplasmic inclusions in all cortical layers, with relatively few neuronal inclusions and dystrophic neurites. Some cases have features of both TDP-43A and B, these tend to be associated with a C9orf72 hexanucleotide expansion, suggesting there may be an additional subtype specific to this mutation (Mackenzie and Neumann, 2017; Neumann and Mackenzie, 2019). TDP43 type C is characterised by abundant, long and thick dystrophic neurites in all cortical layers with few cytoplasmic inclusions. Type D is exclusively seen with *VCP* mutations, with lentiform nuclear inclusions and short dystrophic neurites in the neocortex.

Several autosomal dominant genetic mutations associated with FTLD-TDP43 have been identified. A hexanucleotide GGGCC repeat expansion in the *C9orf72* gene is the most frequent genetic cause of frontotemporal lobar degeneration and motor neuron disease in Europe and North America (DeJesus-Hernandez *et al.*, 2011; Renton *et al.*, 2011; Balendra and Isaacs, 2018; Moore *et al.*, 2019). *C9orf72* expanded repeats are translated into dipeptide repeat

proteins which form neuronal cytoplasmic TDP43 inclusions (Mori *et al.*, 2013, Rohrer *et al.*, 2015*a*). Most healthy individuals have less than eleven hexanucleotide repeats, greater than thirty is considered abnormal and patients with FTLD can have thousands of repeats (Rutherford *et al.*, 2012). There is no correlation between the mutation size in blood and age of onset of disease, no clear evidence of intergenerational anticipation and the number of repeats varies among different somatic tissues (Rohrer *et al.*, 2015*a*; Fournier *et al.*, 2019). The penetrance of C9orf72 is unclear, given the wide variability in age of onset within families (Moore *et al.*, 2019) and the finding of C9orf72 expansions in very elderly individuals without dementia (Galimberti *et al.*, 2014).

Mutations in the progranulin gene (*GRN*) on chromosome 17 also cause FTLD-TDP43 (Baker *et al.*, 2006). Progranulin is a growth factor that regulates cell growth and survival (De Muynck and Van Damme, 2011). *GRN* mutations appear to cause disease by reducing levels of functional progranulin, but how this leads to TDP-43 aggregation is currently unknown (Neumann and Mackenzie, 2019). Mutations in the TARDBP gene, which encodes TDP-43, usually cause isolated motor neuron disease, but have been reported in FTLD (Borroni *et al.*, 2009*a*). *VCP* mutations cause a rare syndrome of frontotemporal dementia, inclusion body myositis and Paget's disease of the bone, which is associated with TDP43 inclusions (Ju and Weihl, 2010). Other rare mutations have been identified in FTLD-TDP43 (Neumann and Mackenzie, 2019).

FTLD-FET

The FET family consists of the fused in sarcoma (FUS), Ewing's sarcoma (EWS) and TAF15 proteins. These proteins, first identified via oncogenes that causes specific cancers, have widespread roles in DNA and RNA transcriptional regulation, processing and repair (Schwartz *et al.*, 2015). The majority of FTLD without tau or TDP43 immunoreactive inclusions (5-10% of cases) have coaggregation of these three proteins (Neumann *et al.*, 2009; Neumann and Mackenzie, 2019). Three FTLD-FET subtypes are currently recognised, again based on the morphological and distribution of the FET immunoreactive inclusions (Neumann and Mackenzie, 2019). The three subtypes are atypical FTLD-U (aFTLD-U), neuronal intermediate filament inclusion disease (NIFID) and basophilic inclusion body disease (BIBD) (Neumann and Mackenzie, 2019). *FUS* gene mutations have been found in patients with FTLD syndromes (Broustal *et al.*, 2010) but no patients with this mutation have yet had neuropathological diagnosis *post mortem* (Neumann and Mackenzie, 2019).

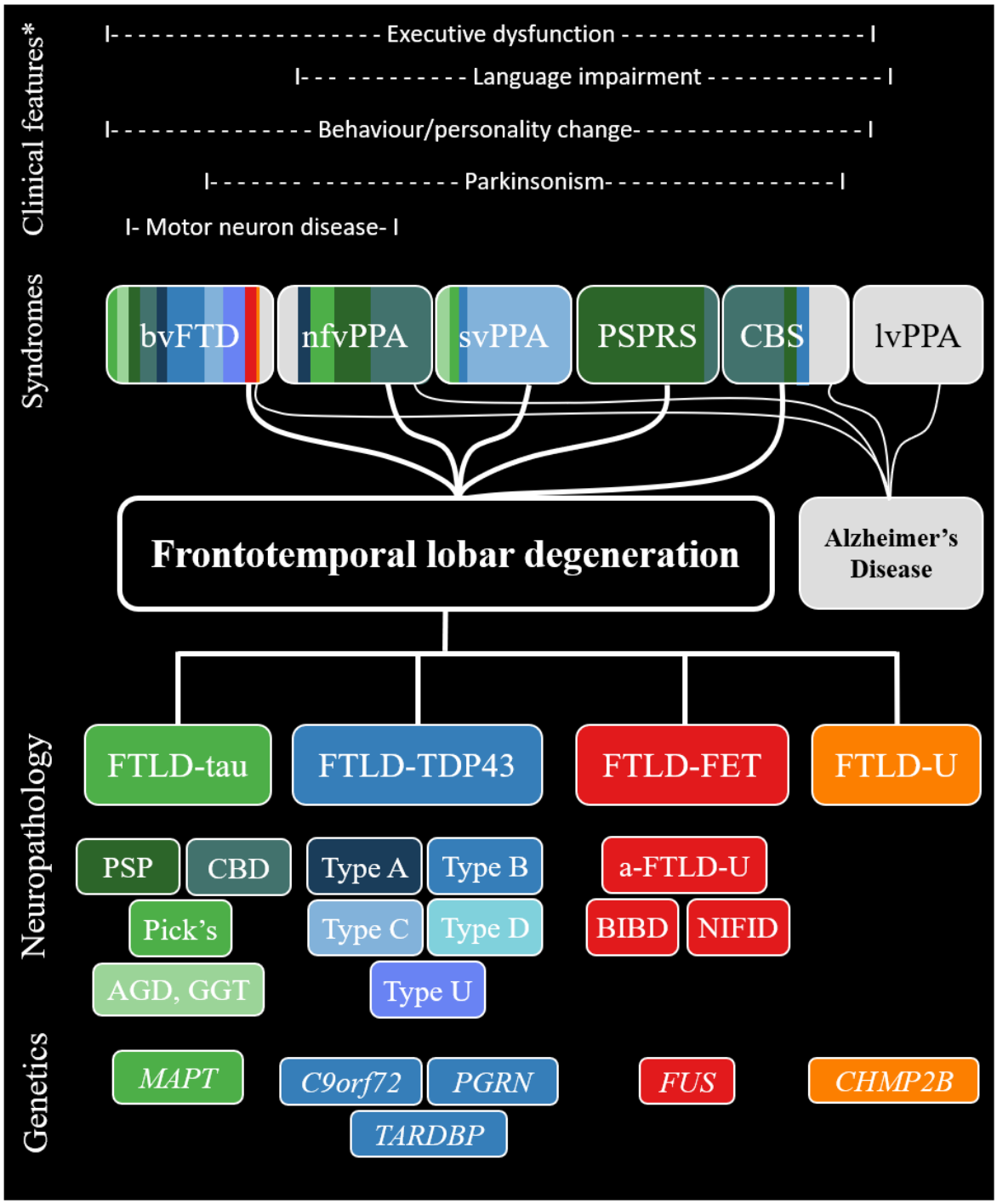


Figure 1-1: The clinicopathological spectrum of frontotemporal lobar degeneration. The top section shows the prevalence of different cognitive and movement features in FTLD. *Not all patients have all the clinical features associated with each syndrome. The next row shows the syndromes associated with FTLD; colour coded by the proportion of cases associated with each FTLD subtype. bvFTD: Behavioural variant frontotemporal dementia. nfvPPA: Non-fluent variant primary progressive aphasia. svPPA: Semantic variant primary progressive aphasia. PSPRS: Progressive supranuclear palsy-Richardson's syndrome. CBS: Corticobasal syndrome. lvPPA: Logopenic variant primary progressive aphasia. Clinicopathological correlation data from (Rascovsky *et al.*, 2011; Alexander *et al.*, 2014, Perry *et al.*, 2017*a*; Spinelli *et al.*, 2017; Gazzina *et al.*, 2019; Sakae *et al.*, 2019). Note that some patients with an FTLD-syndrome have Alzheimer's disease pathology and some patients with FTD (logopenic variant primary progressive aphasia (lvPPA) are not associated with FTLD. Next row shows the neuropathological subtypes of FTLD. PSP: Progressive supranuclear palsy. CBD: Corticobasal degeneration. AGD: Argyrophilic grain disease. GGT: Globular glial tauopathy. BIBD: Basophilic inclusion body disease. NIFID: Neuronal intermediate filament inclusion disease. Idea for figure from Prof W Seeley, UCSF.

Clinical syndromes associated with FTLD

The clinical syndromes associated with FTLD are currently categorised into behavioural variant frontotemporal dementia (bvFTD), the non-fluent (nfvPPA) and semantic (svPPA) subtypes of primary progressive aphasia, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). However, the first case reports of the clinical presentation of FTLD described a combination of behavioural, language and motor features (Pick, 1892; Akelaitis, 1944; Kertesz, 2007). Even at an early stage, FTLD syndromes have overlapping clinical features and patients diagnosed with one syndrome often develop features characteristic of others with disease progression (De Vivo and Johnston, 2003; Kertesz *et al.*, 2005; Perry *et al.*, 2019). This complicates clinical research and makes individual prognostication difficult. In this thesis, I argue for an alternative approach, taking a transdiagnostic approach to clinical features, brain morphometry, clinicopathological correlation, prognosis and neurotransmitter deficits. In the next section, I introduce each of the clinical syndromes associated with FTLD, describing their typical features but also the overlap with other syndromes associated with FTLD.

Behavioural variant frontotemporal dementia

Behavioural variant frontotemporal dementia (bvFTD) is characterised by a gradual onset and progressive decline in personality, behaviour and cognition (Piguet *et al.*, 2011; Rascovsky *et al.*, 2011) (Diagnostic criteria in Appendix 1). The most prevalent symptom in bvFTD is apathy: a loss of goal directed behaviour, emotion, or social interaction (Robert *et al.*, 2009; Rascovsky *et al.*, 2011; Lansdall *et al.*, 2017; Husain and Roiser, 2018). Other common symptoms include disinhibited, socially inappropriate and impulsive behaviour (González Sánchez *et al.*, 2010; Mendez *et al.*, 2014; Lansdall *et al.*, 2017), loss of empathy and social cognition with diminished social interest (Rankin *et al.*, 2006; Bertoux *et al.*, 2012; Mendez *et al.*, 2014; O'Callaghan *et al.*, 2016), perseverative and stereotyped behaviour (Nyatsanza *et al.*, 2003; González Sánchez *et al.*, 2010), and hyperorality. Hyperorality typically manifests with a sweet tooth and increased appetite (Ahmed *et al.*, 2016*a*, *b*) but in some cases is associated with attempts to eat inedible objects (Ikeda *et al.*, 2002). Most patients with bvFTD have limited insight into their illness (Le Ber *et al.*, 2006; O'Keeffe *et al.*, 2007; Rascovsky *et al.*, 2011; Hornberger *et al.*, 2014).

Executive dysfunction is the most affected cognitive domain in bvFTD (Royall, 2001), with impaired planning and decision making (Seeley *et al.*, 2008; Huey *et al.*, 2009, Torralva *et al.*, 2009*a*; Hornberger *et al.*, 2011), cognitive flexibility (Libon *et al.*, 2007; Huey *et al.*, 2009,

Torralva *et al.*, 2009*a*; Stopford *et al.*, 2012, Ranasinghe *et al.*, 2016*a*), inhibition (Hornberger *et al.*, 2008, O'Callaghan *et al.*, 2013*a*; Hughes *et al.*, 2015) and working memory (Hornberger *et al.*, 2008; Libon *et al.*, 2009, Ranasinghe *et al.*, 2016*a*). Patients are commonly proposed to have preserved episodic memory and visuospatial function (Neary *et al.*, 1998; Possin *et al.*, 2011; Rascovsky *et al.*, 2011). This may be true early in the disease (Ranasinghe *et al.*, 2016*a*) but patients with bvFTD usually develop significant episodic memory deficits during the illness (Hornberger and Piguet, 2012, Ranasinghe *et al.*, 2016*a*; Poos *et al.*, 2018). Psychotic symptoms such as hallucinations and delusions are also increasingly recognised, especially when bvFTD is associated with genetic mutations such as the C9orf72 expansion (Shinagawa *et al.*, 2014; Galimberti *et al.*, 2015).

The clinical presentation of bvFTD is highly variable and no one clinical feature is present in all patients (Rascovsky *et al.*, 2011). Apathy is highly prevalent but not specific, as it occurs across many brain illnesses (Van Duijn *et al.*, 2014; den Brok *et al.*, 2015; Zhao *et al.*, 2016; Radakovic and Abrahams, 2018; Worthington and Wood, 2018; Le Heron *et al.*, 2019). Patients with bvFTD may present with either prominent apathetic/dysexecutive or disinhibited/socially inappropriate phenotypes (Le Ber *et al.*, 2006; O'Connor *et al.*, 2017). However, there is considerable overlap (Le Ber *et al.*, 2006; Borroni *et al.*, 2008) and in most patients apathy and impulsivity positively correlate, rather than form ends of a behavioural spectrum (Lansdall *et al.*, 2017). This phenotypic variability in bvFTD extends beyond differences in behaviour; many patients develop language and/or motor impairments (Kertesz *et al.*, 2005). Verbal semantic impairments are common and patients may have a language profile that is indistinguishable from semantic variant primary progressive aphasia (Hughes *et al.*, 2011; Roca *et al.*, 2013; Hardy *et al.*, 2016). In contrast, other patients with bvFTD develop agrammatism and impaired syntactic comprehension, the characteristic features of non-fluent variant primary progressive aphasia (Peelle *et al.*, 2007, 2008).

Patients with bvFTD commonly develop motor impairments including parkinsonism and motor neuron disease. Parkinsonism, defined as rigidity, akinesia and gait disturbance, is the most common movement disorder in bvFTD and occurs in the majority of patients at some stage in their disease (Diehl-Schmid *et al.*, 2007*b*; Padovani *et al.*, 2007; Baizabal-Carvallo and Jankovic, 2016; Irwin *et al.*, 2016; Rowe, 2019). Prominent motor and other clinical features, including a supranuclear gaze palsy, dystonia, apraxia or cortical sensory loss, can develop with disease progression, resulting in a change in diagnosis to PSP or CBS (Kertesz and Munoz, 2004; Hassan *et al.*, 2012; Coyle-Gilchrist *et al.*, 2016; Sakae *et al.*, 2019). Patients without

overt signs of PSP may still have impaired oculomotor function on detailed testing (Garbutt *et al.*, 2008). Parkinsonism is highly prevalent in familial bvFTD (Siuda *et al.*, 2014; Baizabal-Carvallo and Jankovic, 2016), including patients with MAPT (Hutton *et al.*, 1998; Wszolek *et al.*, 2006), C9orf72 (Boeve *et al.*, 2012; Hsiung *et al.*, 2012) and PGRN (Baker *et al.*, 2006; Rademakers *et al.*, 2007) gene mutations. Motor neuron disease (MND) occurs in 15% of bvFTD but up to a third of patients have neurophysiological evidence of anterior horn cell dysfunction (Lomen-Hoerth *et al.*, 2002; Burrell *et al.*, 2011). Conversely, the majority of patients with motor neuron disease have some degree of cognitive impairment, and in approximately 15% this is severe enough to meet the diagnostic criteria of behavioural variant frontotemporal dementia (Ringholz *et al.*, 2005).

A small proportion of patients present with behavioural change suggestive of bvFTD but have minimal or no progression of these symptoms over time and are labelled as "phenocopy" FTD (Davies *et al.*, 2006; Kipps *et al.*, 2008). These patients typically have no frontotemporal lobar atrophy on neuroimaging (Davies *et al.*, 2006; Valente *et al.*, 2019). It is unclear what causes this syndrome. Some patients do have slowly progressive variant FTLD, often associated with the C9orf72 mutation (Khan *et al.*, 2012; Devenney *et al.*, 2014). However, many phenocopy bvFTD patients do not have this mutation and have stable cognition, behaviour and neuroimaging over prolonged follow up (Devenney *et al.*, 2018). The current consensus is that this is not a neurodegenerative disease and is likely to be a group of psychiatric, neurodevelopmental and functional disorders (Kipps *et al.*, 2010; Gossink *et al.*, 2016; McWhirter *et al.*, 2019). Phenocopy cases are excluded from the main work in this thesis.

Primary progressive aphasia

Primary progressive aphasia (PPA) is the umbrella term for several syndromes associated with progressive language impairment with relative sparing of other cognitive domains (Mesulam, 2003; Gorno-Tempini *et al.*, 2011). The most recent diagnostic criteria for PPA defines three subtypes: non fluent variant (nfvPPA), logopenic variant (lvPPA) and semantic variant (svPPA). However, these variants often have more features in common with other FTLD syndromes, including bvFTD, PSP and CBS, than each other.

Non-fluent variant primary progressive aphasia

Non-fluent variant primary progressive aphasia (nfvPPA), formerly known as progressive non fluent aphasia (PNFA), is characterised by effortful, distorted and hesitant speech with signs of speech apraxia and agrammatism (Gorno-Tempini *et al.*, 2011; Grossman, 2012). Speech

apraxia describes speech that is slow and effortful, with pauses between syllables and words and sound errors and distortions due to reduced articulatory agility (Josephs and Duffy, 2008; Josephs *et al.*, 2012). Agrammatism refers to an impairment in the production and understanding of phrases and sentence structure (Thompson and Mack, 2014). The current diagnostic criteria require only one of these language impairments for a diagnosis (Gorno-Tempini *et al.*, 2011) (Appendix 1) and nfvPPA can be subdivided into agrammatic and apraxic variants (Josephs *et al.*, 2012). However, many clinicians group these syndromes together due to their rarity (Coyle-Gilchrist *et al.*, 2016) and because most patients with nfvPPA develop both speech apraxia and agrammatism with disease progression (Josephs *et al.*, 2014). Patients with nfvPPA also have language comprehension deficits. This is often attributed to difficulty understanding syntactically complicated sentences (Thompson *et al.*, 2013, Cope *et al.*, 2017*b*), but may also be due to binary (e.g. yes/no) confusion (Warren *et al.*, 2016) and true hearing impairment (Hardy *et al.*, 2019).

nfvPPA has a heterogenous clinical phenotype. There is variation in language presentation, as evidenced by the apraxic and agrammatic subtypes, but patients can also develop other cognitive, behavioural and motor impairments. The majority of patients have executive dysfunction, apathy and agitation (Knibb *et al.*, 2009; Rohrer and Warren, 2010, Rohrer *et al.*, 2010*c*) and many patients develop loss of empathy, changes in eating habits, disinhibition and stereotyped behaviour (Singh *et al.*, 2015; Van Langenhove *et al.*, 2016; Hazelton *et al.*, 2017). Parkinsonism is common in nfvPPA (Graff-Radford *et al.*, 2012; Coyle-Gilchrist *et al.*, 2016) and in some case series is seen in all patients within three years from symptom onset (Caso *et al.*, 2014). nfvPPA can be the initial clinical phenotype of FTLD-tau-PSP (Mochizuki *et al.*, 2003; Respondek and Hoglinger, 2016; Gazzina *et al.*, 2019) or FTLD-tau-CBD (Lee *et al.*, 2011*b*; Caso *et al.*, 2014) and with disease progression many patients develop the typical clinical phenotype of progressive supranuclear palsy or corticobasal syndrome (Sánchez-Valle *et al.*, 2006; Josephs and Duffy, 2008; Josephs *et al.*, 2014; Santos-Santos *et al.*, 2016). nfvPPA can also be associated with MND (Vinceti *et al.*, 2019), especially when caused by a genetic mutation (Tan *et al.*, 2019).

Semantic variant primary progressive aphasia

Semantic variant primary progressive aphasia (svPPA) is associated with fluent, empty speech and impaired semantic memory, underlying its former name of Semantic Dementia (Hodges and Patterson, 2007). Semantic memory deficits affect knowledge of objects and concepts (Rogers *et al.*, 2004) meaning that patients have poor knowledge of what an object or concept

is, in addition to difficulty naming. This semantic impairment is typically proportional to the familiarity of the item in question. For example, patients with svPPA will lose semantic knowledge of an anteater or buffalo before a dog or cat. Typical findings on language examination include impaired single word comprehension and object recognition (Gorno-Tempini *et al.*, 2011). Repetition and grammar is preserved, although semantic impairment may complicate assessment (Meteyard and Patterson, 2009). Surface dyslexia, a difficulty pronouncing words with an irregular spelling or pronunciation, is common (Wilson *et al.*, 2009).

SvPPA is associated with cognitive deficits beyond aphasia even at early stages, therefore the term "semantic dementia" may better reflect the widespread cognitive deficits and severe impact on activities of daily living associated with this illness (Hodges and Patterson, 2007). Behavioural impairments are common in svPPA and overlap with the typical features of bvFTD (Rosen *et al.*, 2006). These include apathy, impulsivity, loss of social interest and impaired emotional recognition and changes in appetite and food preference (Seeley *et al.*, 2005; Rosen *et al.*, 2006; Hodges and Patterson, 2007; Lansdall *et al.*, 2017). There is some evidence that the behavioural profiles of bvFTD and svPPA are distinct; compulsive behaviour and more restrictive, selective food preferences are more common in svPPA (Snowden *et al.*, 2001). Patients often develop an intense, obsessive interest in word searches, Sudoku and other puzzles (Hodges and Patterson, 2007). SvPPA can occur with motor neuron disease (Tan *et al.*, 2019; Vinceti *et al.*, 2019) but parkinsonism is rare and is usually only seen in patients with dual neuropathology (Snowden *et al.*, 2019).

SvPPA is typically associated with severe bilateral, but asymmetrical left temporal lobe atrophy (Galton *et al.*, 2001). However, some patients have disproportionate right temporal lobe atrophy (Chan *et al.*, 2001). These patients have a different clinical phenotype, with more prominent behavioural disturbance, visuospatial deficits and prosopagnosia, an inability to recognise familiar faces (Chan *et al.*, 2009; Kumfor *et al.*, 2016). They may not have aphasia and the terms "right semantic dementia" or "right temporal variant FTD" are sometimes used rather than svPPA.

Logopenic variant primary progressive aphasia

Spontaneous speech in logopenic variant primary progressive aphasia (lvPPA) is slow and hesitant with frequent pauses (Gorno-Tempini *et al.*, 2008). Unlike nfvPPA, there is no frank agrammatism or speech apraxia (Wilson *et al.*, 2010). Patients with lvPPA have severe word

finding difficulties and impaired repetition (Gorno-Tempini *et al.*, 2008, 2011). Single word repetition is usually preserved but repetition worsens as the length and complexity of the sentence increases (Raisner *et al.*, 2005). Reading aloud is often more fluent than spontaneous speech (Harris *et al.*, 2019). Patients with logopenic aphasia tend to develop global cognitive deficits faster than other PPA subtypes (Leyton *et al.*, 2013) and the majority of patients have Alzheimer's disease at *post mortem* (Spinelli *et al.*, 2017). Logopenic aphasia is best considered as a language variant of Alzheimer's Disease and not a syndrome associated with FTLD.

Progressive supranuclear palsy

The classical features of progressive supranuclear palsy (PSP), first described by Richardson, Steele and Olszweski (Steele *et al.*, 1964), are a vertical supranuclear gaze palsy, early postural instability and falls. This phenotype is now labelled Richardson's syndrome (PSP-RS), as PSP pathology is associated with many other behavioural, cognitive and motor features (Respondek *et al.*, 2014; Respondek and Hoglinger, 2016) (Appendix 1). Visual symptoms are common in PSP. At early disease stages, patients may have slow, irregular and curved, but unrestricted, vertical saccades (Shaikh *et al.*, 2017) which then progresses to a conjugative gaze restriction that can be overcome by the vestibulo-ocular reflex (Anderson, 2015), termed a supranuclear gaze palsy. Square wave jerks are often present (Garbutt *et al.*, 2004). Eyelid abnormalities include reduced blink rate (Bologna *et al.*, 2009), blepharospasm (Grandas *et al.*, 1988; Yoon *et al.*, 2005) and apraxia of eyelid opening and closing (Golbe *et al.*, 1989; Yoon *et al.*, 2005; Phokaewvarangkul and Bhidayasiri, 2019). PSP causes postural instability and falls, typically within three years of symptom onset (Höglinger *et al.*, 2017; Brown *et al.*, 2020). Falls are multifactorial, due to visual impairments (Williams *et al.*, 2006; Bluett *et al.*, 2017) postural instability (Liao *et al.*, 2008; Zwergal *et al.*, 2011), akinesia (Williams *et al.*, 2006; Bluett *et al.*, 2017) and gait disturbance (Lindemann *et al.*, 2010) but also impaired decision making (Kim *et al.*, 2014), impulsivity (Burrell *et al.*, 2014*a*, Rittman *et al.*, 2016*a*) and loss of insight (O'Keeffe *et al.*, 2007). Akinesia and rigidity is common but disproportionately axial, affecting the neck and torso more than limbs (Litvan *et al.*, 1996*a*; Höglinger *et al.*, 2017). Limb rigidity may develop as the disease progresses (Nath *et al.*, 2003). This parkinsonism usually does not improve with levodopa therapy (Stamelou and Höglinger, 2016).

Most patients with PSP have some degree of cognitive and behavioural impairments on detailed assessment (Brown *et al.*, 2010, Burrell *et al.*, 2014*a*; Kobylecki *et al.*, 2015). These include profound slowness of thinking (bradyphrenia) (Dubois *et al.*, 1988; Robbins *et al.*, 1994) and other executive dysfunctions include impaired attention (Brown *et al.*, 2010) set shifting

(Royall, 2001; Brown *et al.*, 2010), decision making and problem solving (Robbins *et al.*, 1994; Millar *et al.*, 2006). The cognitive features of PSP overlap with those seen in bvFTD and tests of frontal lobe dysfunction, such as the frontal assessment battery (Royall, 2001), are not able to differentiate between the two syndromes (Stamelou *et al.*, 2015). Patients have widespread social cognitive deficits, including impaired emotion recognition and theory of mind (Ghosh *et al.*, 2009, 2012) which may partly explain a loss of empathy and interest in social interactions (Millar *et al.*, 2006; Rankin *et al.*, 2006; Gerstenecker *et al.*, 2013). Other PSP-related behavioural changes include apathy and impulsivity (González Sánchez *et al.*, 2010; Gerstenecker *et al.*, 2013; Lansdall *et al.*, 2017), abnormal eating habits (González Sánchez *et al.*, 2010), stereotyped behaviour (Prioni *et al.*, 2018) and loss of insight (O'Keeffe *et al.*, 2007). Sleep disturbances are common and include reduced total and REM sleep time, frequent waking, and restlessness (Aldrich *et al.*, 1989; Gama *et al.*, 2010; González Sánchez *et al.*, 2010; Abbott and Videnovic, 2014; Walsh *et al.*, 2017). However in contrast to Parkinson's Disease, REM sleep behaviour disturbance is uncommon in PSP (Nomura *et al.*, 2012; Abbott and Videnovic, 2014).

PSP is also associated with speech and language impairments (Peterson *et al.*, 2018). Patients have characteristic speech, which is slow and dysarthrophonic, with hypokinetic, spastic and ataxic components (Kluin *et al.*, 2001; Skodda *et al.*, 2011; Rusz *et al.*, 2015; Tykalova *et al.*, 2017). The most prominent language abnormality is reduced fluency (Rosser and Hodges, 1994; Kaat *et al.*, 2007; Peterson *et al.*, 2018) but deficits in comprehension, naming and syntactic comprehension are also seen (Burrell *et al.*, 2017).

The heterogeneous, overlapping presentation of cognitive, behavioural and language features in PSP are reflected in the new diagnostic criteria, which recognises eight PSP subtypes (Höglinger *et al.*, 2017). A retrospective review of 100 autopsy-confirmed cases of PSP found only 24% of cases presented with the classical PSP-RS phenotype and the majority of the cases had overlapping phenotypes across PSP subgroups (Respondek *et al.*, 2014). Many of these PSP syndrome subtypes relate closely to other FTLD syndromes, for example PSP-SL and nfvPPA, PSP-F and bvFTD and PSP-CBS and CBS (Appendix 1)

Corticobasal syndrome

Corticobasal syndrome (CBS) is a clinical diagnosis (Appendix 1), different from the neuropathological diagnosis of corticobasal degeneration (CBD), which is not associated with all cases of CBS (Gibb *et al.*, 1989). The cortical and subcortical (or basal) features of CBS

typically present asymmetrically, often initially in one limb (Wenning *et al.*, 1998). Cortical features include apraxia (Zadikoff and Lang, 2005), alien limb syndrome (Albrecht *et al.*, 2019; Lewis-Smith *et al.*, 2020) and cortical sensory loss. Apraxia can be present in the limbs; with loss of dexterity (limb-kinetic apraxia) or goal directed movement (ideomotor apraxia) (Pearce, 2009), face (orobuccal apraxia) or eyes; affecting eyelids (apraxia of eye opening/closing) or eye movement (oculomotor apraxia). (Jacobs *et al.*, 1999, Graham *et al.*, 2003*a*; Zadikoff and Lang, 2005, Burrell *et al.*, 2014*b*). Orobuccal apraxia is often associated with motor speech impairments, primarily speech apraxia (Buervenich *et al.*, 2000; Josephs and Duffy, 2008). CBS is associated with visuospatial deficits (Graham *et al.*, 2003*b*; Bak *et al.*, 2006; Rittman *et al.*, 2013, Burrell *et al.*, 2014*a*; Di Stefano *et al.*, 2016), including simultagnosia (Mendez, 2000) and visual inattention (Julayanont *et al.*, 2019).

Subcortical features in CBS include dystonia, rigidity and akinesia. Dystonia is most common the upper limbs but can be cervical, lower limb or affect eyelid muscles causing blepharospasm (Grandas *et al.*, 1988; Stamelou *et al.*, 2012). Rigidity and akinesia do not usually respond to levodopa treatment (Armstrong *et al.*, 2013*a*). Some patients may present with symmetrical limb involvement (Hassan *et al.*, 2010), although this is only defined as possible disease under the current criteria (Armstrong *et al.*, 2013*a*). Myoclonus is common in CBS and may be cortical (Thompson *et al.*, 1994; Carella *et al.*, 1997) or subcortical (Grosse *et al.*, 2003) in origin.

CBS and PSP overlap in both their clinical presentation and neuropathology (Höglinger, 2018). Patients with PSP-RS can develop CBS-like features, including limb dystonia (Barclay and Lang, 1997; Oide *et al.*, 2002; Nath *et al.*, 2003), apraxia (Pharr *et al.*, 2001; Soliveri *et al.*, 2005) and alien limb syndrome (Barclay *et al.*, 1999) during the disease course. Over 70% of patients with CBS develop a supranuclear gaze palsy and falls at some point during the illness (Rinne *et al.*, 1994; Wenning *et al.*, 1998). FTLD-tau-PSP pathology can cause corticobasal syndrome (Ling *et al.*, 2014; Respondek and Hoglinger, 2016) and FTLD-tau-CBD can cause a PSP clinical syndrome (Ling *et al.*, 2010).

Other behavioural and language features are also seen in CBS. Changes in behaviour and personality, similar to those seen in bvFTD, are common (Burrell *et al.*, 2014*a*). Patients who develop a corticobasal syndrome phenotype may initially be given a diagnosis of behavioural variant frontotemporal dementia due to prominent behaviour and personality change (Kertesz *et al.*, 2007). Apathy, disinhibition and impulsivity, loss of empathy and stereotyped motor

behaviours are also frequently seen in CBS (Litvan *et al.*, 1998; Kertesz and McMonagle, 2010; Lansdall *et al.*, 2017). There may be an inability to accurately recognise emotional expressions (Kluger and Heilman, 2007). Speech disturbance due to orobuccal apraxia is common but CBS is also associated with language deficits (Peterson *et al.*, 2018). Patients typically have severely impaired fluency (Bak *et al.*, 2005; Rittman *et al.*, 2013), impaired syntactic comprehension and sentence repetition (Cotelli *et al.*, 2007) and make phonological errors (Graham *et al.*, 2003*a*). These language impairments overlap with those seen in nfvPPA, and many patients presenting with nfvPPA will develop a CBS-like clinical phenotype (Graham *et al.*, 2003*a*; Peterson *et al.*, 2018).

Diagnostic criteria for FTLD syndromes

The current consensus diagnostic criteria for syndromes associated with FTLD are shown in Appendix 1 (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011, Armstrong *et al.*, 2013*a*; Höglinger *et al.*, 2017). The criteria attempt the difficult balance between clinicopathological sensitivity and specificity: including only the classical syndromes may improve specificity but will miss the many atypical presentations. Many clinical features are caveated with "important", "prominent" or "early", which the authors acknowledge is subjective and varies depending on if the patient, relative or carer or clinician's opinion is given most weight. This creates diagnostic ambiguity. For example, a patient may report language symptoms but not (due to reduced insight) the behavioural change that families think is more prominent. A patient may also meet several diagnostic criteria. For example, a 60-year-old presenting with a two year history of progressive language and personality change, behavioural disturbance and examination findings of executive dysfunction, asymmetric limb akinesia and rigidity and non-fluent, agrammatic speech could meet the positive diagnostic criteria for bvFTD, nfvPPA, PSP-SL and CBS-NAV. The diagnostic criteria may contain exclusion clauses, if for example a syndrome is better explained by a non-neurodegenerative cause, but usually do not state when one FTLD syndrome should be diagnosed above another.

Clinicopathological correlation in FTLD syndromes

One aim of diagnostic criteria is to maximise the correlation between clinical phenotype and a specific neuropathology. The ideal criteria would group all patients with one neuropathology into a clinical syndrome (high sensitivity) while at the same time excluding patients with a different disease (high specificity). There are currently no biomarkers that can identify different FTLD subtypes (Meeter *et al.*, 2017) so accurate diagnostic criteria are often the only inclusion

criteria for clinical trials (Boxer *et al.*, 2019). An autosomal dominant genetic mutation can, when present, accurately predict neuropathology (Raffaele *et al.*, 2019). However, most patients with a FTLD syndrome do not have a monogenic mutation, these sporadic cases often only have weak clinicopathological correlations (Figure 1-1).

Some syndromes have a much stronger endophenotype than others. Two FTLD syndromes, PSP-RS and svPPA, have good specificity for FTLD-tau-PSP and FTLD-TDP43C respectively. PSP-Richardson's syndrome (PSPRS) has very high specificity (91-100%) but low sensitivity (30-50%) for PSP neuropathology (FTLD-tau-PSP) (Litvan *et al.*, 1996*b*, *a*, 1997; Osaki *et al.*, 2004). FTLD-tau-PSP can present with other cognitive, behavioural and motor features (Respondek *et al.*, 2014) that are phenotypically suggestive of bvFTD (Perry *et al.*, 2017*a*), nfvPPA (Spinelli *et al.*, 2017) or CBS (Tsuboi *et al.*, 2005; Ling *et al.*, 2014). FTLD-tau-PSP can also cause a levodopa-responsive asymmetric parkinsonism that may be indistinguishable from Parkinson's disease (Williams *et al.*, 2005; Williams and Lees, 2010). This was recognised in the MDS PSP diagnostic criteria with the PSP-F, PSP-NAV, PSP-CBS and PSP-P subtypes respectively (Höglinger *et al.*, 2017). SvPPA has good specificity for FTLD-TDP43C (83-100%) (Snowden *et al.*, 2007; Spinelli *et al.*, 2017). However, some cases have other TDP43 subtypes, FTLD-tau or AD pathology (Hodges *et al.*, 2004; Davies *et al.*, 2005; Gefen *et al.*, 2018) and FTLD-TDP43C is also associated with bvFTD (Perry *et al.*, 2017*a*).

BvFTD, nfvPPA and CBS are neuropathologically more heterogenous. bvFTD can be associated with all major subtypes of FTLD-tau (20-50%), FTLD-TDP43 (30-50%), FTLD-FUS (7%), and AD (10-17%) pathology (Kertesz *et al.*, 2005; Forman *et al.*, 2006; Hu *et al.*, 2007; Josephs *et al.*, 2011, Perry *et al.*, 2017*a*). Some clinical features can predict pathology. For example, patients with FTD-MND have FTLD-TDP pathology (Snowden *et al.*, 2007; Josephs *et al.*, 2011), and eye movement abnormalities or parkinsonism are more associated with FTLD-tau (Josephs *et al.*, 2006*b*). However, even sophisticated algorithms trained on clinical phenotype, genetic results and brain imaging are only 60% accurate in predicting neuropathology (Perry *et al.*, 2017*a*). The subset of patients with AD pathology reflects the phenotypic overlap between bvFTD and the behavioural/dysexecutive presentation of Alzheimer's disease (Alladi *et al.*, 2007, Ossenkoppele *et al.*, 2015*b*). NfvPPA is most often associated with FTLD-tau (50-100%), but can be caused by FTLD-TDP or AD (Grossman, 2010). The FTLD-tau can be Pick's disease, PSP or CBD subtypes (Spinelli *et al.*, 2017). Patients with speech apraxia are more likely to have FTLD-tau, but the subtype can still vary (Josephs *et al.*, 2006*a*). It can be difficult to distinguish nfvPPA from the language presentation

of Alzheimer's diseases, and even in expert centres a proportion of nfvPPA patients have AD pathology at *post mortem* (Grossman, 2012).

CBS is neuropathologically heterogenous and only 20-60% of cases of this clinical syndrome have CBD neuropathology (Boeve *et al.*, 1999, Hu *et al.*, 2009*a*; Ling *et al.*, 2010; Kouri *et al.*, 2011, Lee *et al.*, 2011*b*; Alexander *et al.*, 2014). Other neuropathologies associated with CBS are Alzheimer's disease (15-30%), progressive supranuclear palsy (10-30%) and more rarely TDP-43, Pick's disease, alpha synuclein or prion disease (Boeve *et al.*, 1999, Hu *et al.*, 2009*a*; Ling *et al.*, 2010; Kouri *et al.*, 2011, Lee *et al.*, 2011*b*; Alexander *et al.*, 2014). CBD can commonly present in life as nfvPPA, PSP, bvFTD or posterior cortical atrophy (Boeve *et al.*, 1999, Hu *et al.*, 2009*a*; Ling *et al.*, 2010; Kouri *et al.*, 2011, Lee *et al.*, 2011*b*; Alexander *et al.*, 2014).

There are limitations to these reported clinicopathological correlations. First, older cases series do not use the most recent neuropathological criteria, for example TDP43 immunohistochemistry only became available in 2006. Second, results depend on which clinical syndromes and pathological subtypes are included. For example, some clinicopathological series only include tauopathies, or limit clinical syndromes to bvFTD or PPA cases. Third, case series are usually published by specialists in academic centres, who often developed the diagnostic criteria being tested. Clinicopathological accuracy in the average cognitive or movement disorders clinic may be more variable.

Neurotransmitter deficits in frontotemporal lobar degeneration

One target for symptomatic treatments in FTLD syndromes is to reverse neurotransmitter deficits, similar to dopaminergic therapy of Parkinson's disease or cholinergic therapy for Alzheimer's disease. There are many safe, well tolerated and effective drugs that modulate neurotransmitter pathways in the central nervous system. This removes the need for drug development, meaning identifying neurotransmitter deficits associated with clinical symptoms in FTLD could quickly lead to clinical trials. In this section I review the current evidence on alterations in the major neurotransmitter systems, dopamine, noradrenaline, serotonin, acetylcholine, glutamate and gamma amino butyric acid (GABA), and their relationship to clinical phenotype. For a more comprehensive review see Murley et al 2018.

Dopamine

Loss of dopaminergic neurons in the nigrostriatal pathway causes parkinsonism in frontotemporal lobar degeneration. Dopamine transporter levels (a marker of pre-synaptic neuron integrity) and dopamine receptors are reduced in the striatum in bvFTD (Rinne *et al.*, 2002; Sedaghat *et al.*, 2007), PSP (Baron *et al.*, 1986; Kim *et al.*, 2002; Oyanagi, 2002; Im *et al.*, 2006; Oh *et al.*, 2012) and CBS (Sawle *et al.*, 1991; Nagasawa *et al.*, 1996; Laureys *et al.*, 1999; Klaffke *et al.*, 2006; Pirker *et al.*, 2015). The degree of this loss correlates with extra-pyramidal symptom severity (Rinne *et al.*, 2002; Sedaghat *et al.*, 2007). In contrast to Parkinson's disease, parkinsonism in FTLD typically does not respond well to dopaminergic therapy, possible due to loss of both dopaminergic neurons *and receptors* in the basal ganglia and cerebral cortex.

Degeneration of the dopaminergic mesocortical pathway may contribute to behavioural symptoms. D2 dopamine receptors are reduced in the frontal lobes of patients with bvFTD (Frisoni *et al.*, 1994), while dopamine levels in the CSF are reduced and correlate with behavioural disturbance (Engelborghs *et al.*, 2008). In PSP, there is also degeneration of dopaminergic neurons in the ventral tegmental area (Murphy *et al.*, 2008) and loss of dopamine receptors in the frontal cortex (Ruberg *et al.*, 1985).

Noradrenaline

In PSP there is both tau deposition (Dickson, 1999; Arnold *et al.*, 2013), and neuronal loss (Hauw *et al.*, 1994; Mori *et al.*, 2002; Dickson *et al.*, 2010) in the locus coeruleus, the principle site of noradrenaline synthesis. This neuronal loss correlates with disease severity (Kaalund *et al.*, 2020). A single post mortem study also found reduced levels of noradrenaline in the caudate and putamen (Hornykiewicz and Shannak, 1994). There is limited evidence for noradrenergic changes in frontotemporal dementia. Cell density in the locus coeruleus is relatively preserved with normal noradrenaline levels in the frontal lobe (Vermeiren *et al.*, 2016), despite the presence of pathological tau inclusions (Nagaoka *et al.*, 1995; Yang and Schmitt, 2001; Brunnström *et al.*, 2011; Irwin *et al.*, 2016). However, there may be reduced noradrenaline catabolism and turnover (Vermeiren *et al.*, 2016) which has been shown to correlate with disease severity (Engelborghs *et al.*, 2008).

Serotonin

Serotonin dysfunction is a significant contributor to the behavioural and cognitive symptoms seen in bvFTD (Huey *et al.*, 2006; Hughes *et al.*, 2015). 5HT1A and 2A receptors are reduced in the frontal and temporal lobes (Sparks and Markesbery, 1991; Francis *et al.*, 1993; Procter *et al.*, 1999; Franceschi *et al.*, 2005; Lanctôt *et al.*, 2007; Bowen *et al.*, 2008). Pathological tau inclusions are found *post mortem* in the raphe nuclei with progressive supranuclear palsy (Revesz *et al.*, 1996) while pre-synaptic serotonergic neurons are reduced in the caudate nucleus, frontal and temporal cortex (Chinaglia *et al.*, 1993). There is neuronal loss and gliosis in the raphe nucleus in corticobasal degeneration (Gibb *et al.*, 1989). A meta-analysis of selective serotonin reuptake inhibitors in frontotemporal dementia showed an improvement in behavioural disturbance, noting however that the evidence was mainly from small, non-placebo controlled trials (Huey *et al.*, 2006).

Acetylcholine

Cholinergic pathways are affected in frontotemporal lobar degneneration but not to the same extent as in Alzheimer's disease. *Post mortem* levels of choline acetyltransferase, a marker of pre-synaptic cholinergic neuron integrity, are reduced in the nucleus basalis of Meynert and the hypothalamus but are normal in the frontal, temporal and parietal lobes (Wood *et al.*, 1983; Hansen *et al.*, 1988; Sparks and Markesbery, 1991; Procter *et al.*, 1999). There is evidence of a cholinergic deficit in semantic dementia, with loss of muscarinic receptors in the temporal lobe (Odawara *et al.*, 2003). Despite the possible cholinergic deficits in behavioural variant frontotemporal dementia and primary progressive aphasia, cholinesterase inhibitors do not improve cognitive function (Moretti *et al.*, 2004; Mendez *et al.*, 2007; Kertesz *et al.*, 2008). There are marked cholinergic deficits in progressive supranuclear palsy, which may contribute not only to cognitive impairment but also postural instability via the pedunculopontine nucleus (Jellinger, 1988; Warren *et al.*, 2005). Choline acetyltransferase is reduced in the nucleus basalis of Meynert , midbrain and pedunculopontine nucleus (Juncos *et al.*, 1991; Javoy-Agid, 1994; Kasashima and Oda, 2003). However, a randomised, placebo controlled crossover study found no benefit with donepezil (Litvan *et al.*, 2001).

Glutamate

There is pre-clinical and clinical evidence that glutamate is important in the pathogenesis of frontotemporal dementia. Mouse models of FTLD have glutamate receptor dysfunction and behavioural impairment which is reversed with glutamate receptor agonists (Gascon *et al.*,

2014; Warmus *et al.*, 2014; Decker *et al.*, 2016). In patients, glutamatergic pyramidal neurons are reduced in the thalamus, frontal and temporal cortex (Ferrer, 1999). Magnetic resonance spectroscopy of patients with frontotemporal dementia has found glutamate/glutamine levels are reduced in the frontal and temporal lobes (Ernst *et al.*, 1997; Sarac *et al.*, 2008). There is an inverse correlation between CSF glutamate levels and verbal agitation (Vermeiren *et al.*, 2013). Glutamatergic neurons from the thalamostriatal pathway are reduced in the thalamus in PSP (Henderson *et al.*, 2000). However the severity of this neuronal loss does not correlate with disease duration or severity (Henderson *et al.*, 2000).

Both ionotropic (NMDA and AMPA) and metabotropic glutamate receptors are reduced in the frontal and temporal lobes of patients with bvFTD (Francis *et al.*, 1993; Procter *et al.*, 1999; Bowen *et al.*, 2008; Leuzy *et al.*, 2016). Despite this, randomised placebo-controlled trials of memantine showed no benefit in bvFTD (Boxer *et al.*, 2013) or PPA (Johnson *et al.*, 2010). While there may be no true benefit, it remains possible that small treatment effects exist which would be amplified if other neurotransmitter deficits were also normalised, in particular GABA-ergic impairments. The GABA-glutamate interaction is of particular relevance because it supports precisely tuned oscillatory dynamics of neural circuits for cognition (Bastos *et al.*, 2012).

GABA

There is limited evidence on GABA in FTLD. GABAergic neurons are reduced in upper neocortical layers of the frontal and temporal cortex in bvFTD (Ferrer, 1999) and in subcortical regions in PSP (Levy *et al.*, 1995). GABA concentrations are also decreased in the basal ganglia in behavioural variant frontotemporal dementia (Kanazawa *et al.*, 1988). $GABA_A$ receptors are reduced in cortical (Foster *et al.*, 2000) and subcortical regions (Landwehrmeyer and Palacios, 1994; Suzuki *et al.*, 2002) in PSP. There are case reports of GABA receptor agonists improving speech, eye movements, akinesia and rigidity in progressive supranuclear palsy (Daniele *et al.*, 1999; Cotter *et al.*, 2010; Dash, 2013; Chang and Weirich, 2014), but this phenomenon is very uncommon and there are no randomised placebo controlled studies. GABAergic approaches to treatment of FTLD syndromes warrant further investigation, but evidence of their clinical efficacy is currently lacking.

In summary, FTLD causes dysfunction of dopaminergic, serotonergic, noradrenergic and cholinergic pathways. There is some evidence that the relative alterations in these pathways is associated with clinical phenotype, including behaviour and motor impairments. There is some

evidence of both glutamatergic and GABAergic neuron loss but the functional consequence of their deficits is unclear. The importance of these neurotransmitters, which are the principal excitatory and inhibitory neurotransmitters in the brain, suggest restoring any deficit associated with clinical symptoms may be a potential therapeutic target.

Aims and hypotheses of this thesis

There are overlapping clinical features and neuropathology in FTLD syndromes. Widespread cognitive and behavioural impairments occur in all these syndromes and all patients develop dementia at some stage in their illness. Therefore, the overarching aim of my PhD was to contribute to progress towards better symptomatic treatments for cognitive and behavioural impairment. The thesis has two subsidiary aims. First, to develop a transdiagnostic approach to FTLD syndromes in order to facilitate a better understanding of aetiology, pathophysiology and symptomatic treatments. I use term "transdiagnostic" to refer to research that investigates common clinical features (e.g. behavioural disinhibition) across multiple clinical syndromes. Second, to use this transdiagnostic approach to test the hypothesis that glutamate and GABA deficits are associated with behavioural disinhibition in FTLD syndromes. Specifically, the hypotheses of my thesis were:

1. FTLD syndromes have heterogenous cognitive, behavioural and motor symptoms and exist on a clinical spectrum rather than as separate entities (Chapter 2).
2. A transdiagnostic approach accounts for variation and overlap in the clinical features of FTLD syndromes (Chapter 2).
3. The structural brain changes associated with FTLD relate to the spectrum of clinical features (Chapter 3).
4. A transdiagnostic, spectrum-based approach to FTLD is superior to the current diagnostic criteria in predicting underlying FTLD neuropathology (Chapter 4).
5. Prognosis, whether absolute survival or time to institutionalisation, can be predicted by clinical phenotype (Chapter 5).
6. Behavioural disinhibition is seen across multiple FTLD syndromes (Chapter 6).
7. Glutamate and GABA are reduced in the frontal, but not occipital, lobe of FTLD syndromes (Chapter 7).
8. Glutamate and GABA concentrations are inversely associated with behavioural disinhibition in FTLD syndromes (Chapter 7).

Clinical phenotypes of frontotemporal lobar degeneration syndromes

Preface

This chapter forms part of manuscript which is in preparation (Murley *et al.*, 2020*a*). The clinical assessments in this chapter were performed by Dr Ian Coyle-Gilchrist between 2013 and 2015 and by me between 2016 and 2018. A large group of researchers (listed as co-authors on the above paper) at the Cambridge Centre for FTD and Related Disorders assisted with participant identification, recruitment and testing. I performed all the data analysis in this chapter. The text was written by me, with input from co-authors on the manuscript.

Summary

In this chapter I use a transdiagnostic approach to investigate the overlapping clinical phenotypes of frontotemporal lobar degeneration syndromes. These results form part of the PIPPIN study, an epidemiological cohort study of FTLD syndromes that I led during my PhD. Patients in this study underwent a detailed phenotypic assessment, enabling me to use multivariate analyses to show that FTLD syndromes are not discrete entities, but instead exist on a multidimensional spectrum of behavioural, cognitive and motor features. In a subset of patients with longitudinal data I show this phenotypic overlap increases with disease progression. This chapter provides the evidence for a transdiagnostic approach to FTLD, which I then use throughout the thesis.

Introduction

The clinical disorders caused by frontotemporal lobar degeneration pathologies (FTLD) are highly heterogeneous in their pathology and phenotypes. (MacKenzie et al., 2010; Rohrer et al., 2011). Patients are typically diagnosed as having one of several principal syndromes, including behavioural variant frontotemporal dementia (bvFTD)(Rascovsky *et al.*, 2011), primary progressive aphasia (with the non-fluent nfvPPA and semantic svPPA subtypes)(Gorno-Tempini *et al.*, 2011), progressive supranuclear palsy (PSP)(Höglinger *et al.*, 2017) or corticobasal syndrome (CBS)(Armstrong *et al.*, 2013*a*). The clinicopathological correlations of these syndromes are imprecise (Irwin *et al.*, 2015). For example, bvFTD can be associated with Tau, TDP-43, or FUS protein inclusions or mixed neuropathology (Perry *et al.*, 2017*a*). Some clinical syndromes, such as PSP-Richardson's Syndrome, have good correlation with the associated pathology (Gazzina *et al.*, 2019), however the corresponding pathology may have diverse phenotypic expressions (Respondek *et al.*, 2014). Recent revisions of diagnostic criteria recognise this heterogeneity (Höglinger *et al.*, 2017), and there may be future improvements in clinicopathological correlations by imaging or fluid-based biomarkers, aiming to optimise patient selection for disease modifying therapies (Irwin *et al.*, 2015; Meeter *et al.*, 2017).

In this chapter I propose that the effort to refine diagnostic segregation of FTLD syndromes has fundamental limitations. These are not merely due to the limits of a given test or biomarker but are biologically real constraints that can be informative about the nature of the disorders. Examining the phenotypic patterns across the broad spectrum of all FTLD-associated disease may allow a better understanding of aetiology and pathophysiology, and lead to more effective therapies. In particular, symptomatic therapies may benefit from such a transdiagnostic approach, selecting patients based on the presence of relevant symptoms, whichever their diagnostic label or proteinopathy (Husain, 2017; Fusar-Poli *et al.*, 2019).

A transdiagnostic approach is increasingly used in psychiatry, where it is recognised that there is considerable heterogeneity in clinical features and pathophysiology across different diagnostic criteria, as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (del Barrio, 2004; Goldstein-Piekarski *et al.*, 2016). This led to the development of the Research Dimension Criteria, which enables classification of mental disorders by dimensions of observed behaviour and neurobiological measures, irrespective of the underlying psychiatric diagnosis (Cuthbert, 2014; Kozak and Cuthbert, 2016). This approach has been used to identify subtypes of similar cognitive, behavioural and

neurophysiological features in patients with major depressive, panic or post-traumatic stress disorders (Grisanzio *et al.*, 2018). It has also been used to investigate psychiatric treatments, including a universal cognitive behavioural therapy protocol across multiple diagnoses (Barlow *et al.*, 2017; Fusar-Poli *et al.*, 2019).

A similar transdiagnostic approach may reveal common neurobiology in neurodegenerative diseases with overlapping phenotypes (Husain 2017). Neuropsychiatric symptoms including apathy and anhedonia occur across many disorders including Alzheimer's (Zhao *et al.*, 2016), Parkinson's (den Brok *et al.*, 2015) and Huntington's diseases (Van Duijn *et al.*, 2014), frontotemporal lobar degeneration syndromes (Lansdall *et al.*, 2017), traumatic brain injury (Worthington and Wood, 2018) and vascular dementia and stroke (Staekenborg *et al.*, 2010; Caeiro *et al.*, 2013). A transdiagnostic approach may reveal common neurobiological mechanisms underlying one symptom in different neurological diseases (Husain and Roiser, 2018).

There are many overlapping symptoms and indistinct phenotypic boundaries between FTLD syndromes that may be clarified by a combined, transdiagnostic approach (Kertesz *et al.*, 1999, 2005). For example, executive dysfunction is a common cognitive impairment across FTLD syndromes (Burrell *et al.*, 2014*a*, Ranasinghe *et al.*, 2016*a*) and changes in behaviour and personality, while characteristic of bvFTD (Rascovsky *et al.*, 2007), are also seen in PSP (Cordato *et al.*, 2005; Gerstenecker *et al.*, 2013), CBS (Huey *et al.*, 2009) and the primary progressive aphasias (Rosen *et al.*, 2006; Rohrer and Warren, 2010). Neuropsychiatric symptoms, including apathy and impulsivity, occur in multiple FTLD syndromes (Rohrer *et al.*, 2010*d*; Lansdall *et al.*, 2017). The movement disorders typical of PSP and CBS can also develop in patients diagnosed with bvFTD (Park *et al.*, 2017) and nfvPPA (Santos-Santos *et al.*, 2016). Language impairments are seen across all FTLD syndromes, including bvFTD (Hardy *et al.*, 2016), PSP and CBS (Peterson *et al.*, 2018).

Aims and hypotheses

The aim of this chapter was to use a transdiagnostic approach to assess the clinical phenotype of FTLD syndromes. I had two hypotheses. First, that FTLD syndromes are multidimensional clinical spectra, rather than discrete clinical entities. This is illustrated in the colour maps in Figure 2-1. Figure 2-1A symbolises the current most widely accepted approach, in which patients have a distinct clinical phenotype of a singular syndrome, represented by a discrete colour patch. For example, bvFTD (in red) is distinct from PSP (in blue) or svPPA (orange). My alternate hypothesis is that patients lie in a continuous colour-space, shown in in Figure 2-1B. Intermediate phenotypes like PSP-F, CBS-NAV or svPPA with prominent behavioural disturbance, are readily placed within the continuous phenotypic space. I predicted that while classical syndromes of bvFTD, PPA, PSP and CBS exist, a data-driven approach would reveal phenotypic continuity without clear separation between phenotypes.

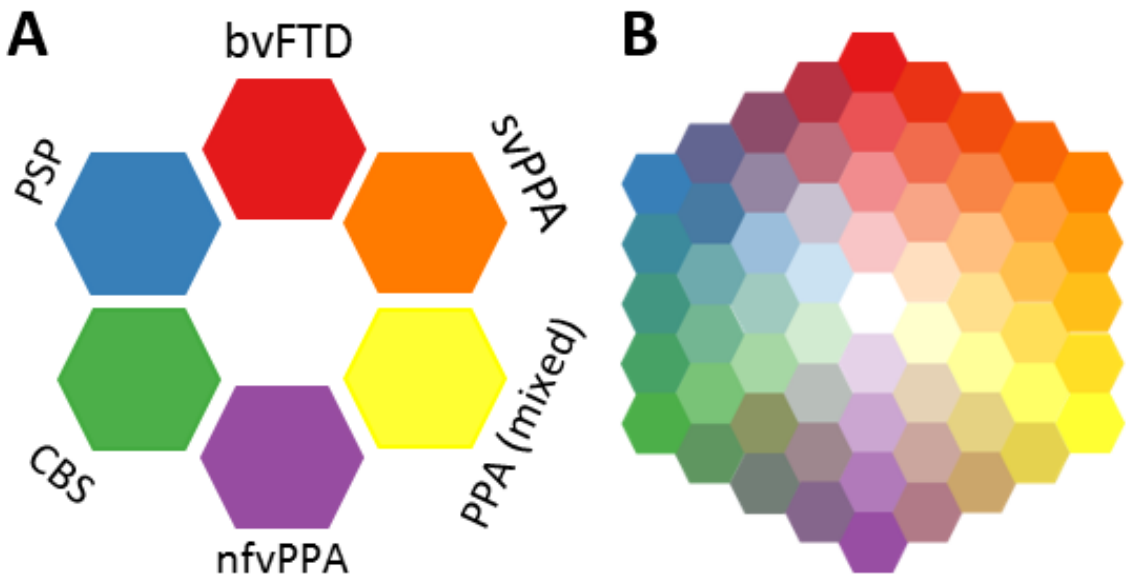


Figure 2-1: Colour map of FTLD syndromes. A: Current consensus, that FTLD syndromes exist as separate entities. B: Colour map that visualises the hypothesis of this chapter, that FTLD syndromes exist as a continuous, multidimensional spectrum, and an individual can lie anywhere on this colour map.

The second hypothesis is that with disease progression, clinical phenotypes merge by the development of new clinical features. The increasing overlap between syndromes is analogous to the move towards the centre of the colour map in Figure 2-1B. I tested these hypotheses using data from the epidemiologically-based PiPPIN study (Coyle-Gilchrist *et al.*, 2016), which undertook a systematic behavioural, cognitive and imaging assessment of patients with syndromes associated with FTLD, in a region of 1.5 million people in the United Kingdom.

Methods

The Pick's Disease and Progressive Supranuclear Palsy Prevalence and Incidence (PIPPIN) study

The Pick's Disease and Progressive Supranuclear Palsy Prevalence and Incidence (PIPPIN) study was an epidemiological, cross sectional study of FTLD syndromes run by the Cambridge Centre for FTD and Related Disorders with Professor Rowe as the Chief Investigator. The PIPPIN study had two broad aims. First, to estimate the incidence and prevalence of all FTLD syndromes in Cambridgeshire and Norfolk. Second, to deeply phenotype the clinical, neuropsychiatric, imaging and genetic features of FTLD syndromes. The study first ran between 2013 and 2015 and the initial epidemiology was reported in 2016 (Coyle-Gilchrist *et al.*, 2016). A secondary analysis investigated apathy and impulsivity, finding these multifaceted neuropsychiatric symptoms are common across FLTD syndromes (Lansdall *et al.*, 2017). Further work investigated the relationship between these neuropsychiatric constructs and grey and white matter abnormalities (Lansdall *et al.*, 2017) and survival (Lansdall *et al.*, 2019). In 2016 I took over the day to day running of the study. I resumed active recruitment into the study, which continued from 1st January 2016 until 31st December 2018.

The study protocol detailed how capacity should be assessed and how patients could give consent to participate in the study. All patients with a FTLD syndrome are likely to have some degree of cognitive impairment, even if it is not to the extent or severity of a dementia. Consent, as defined by the Mental Capacity Act 2005, pertains to a specific decision and requires an ability to understand, retain, weigh and communicate information relevant to the decision in question (Nicholson *et al.*, 2008). Due to executive, language, visuospatial, behavioural or motor impairments many patients with more advanced disease did not have capacity to consent to the study. However, excluding these patients would have reduced the external validity of any results and deprive them of the opportunity to participate in research. A consultee process enabled them to participant in the study. A consultee, usually a spouse or other next of kin, were consulted and signed a consultee form. If a study participant did not want to participate in the study, or a part of it, their views were respected regardless of their capacity. Consent for the transfer of personally identifiable data and diagnosis to the study team was recorded locally by the referring team. The study was ethically approved by the Central Cambridge Research Ethics Committee (REC 12/EE/0475).

Recruitment was encouraged through multiple sources, aiming to recruit all patients with an FTLD syndrome in Cambridgeshire and Norfolk. First, all participants seen by the study team in the cognitive and movement disorders clinics at the research site (Cambridge University Hospitals NHS Foundation Trust) were invited into the study. Referrals from other neurological and psychiatric services in the region (including consultants and specialist nurses) were encouraged with regular visits and presentations by the study team. Self-referral from patients and their relatives was promoted through public engagement events run by the Cambridge Centre for FTD and Related Disorders and advertisements in charity publications, local media or specialist dementia nursing homes. The study also recruited patients via research databases including those run by Parkinson's UK, The PSP Association and Join Dementia Research.

The study had two tiers which are summarised in Figure 2-2. Tier 1 addressed the first aim of the study by recording basic demographic details to measure the incidence and prevalence of FTLD syndromes. All participants in Tier 1 were invited into Tier 2 for more detailed phenotyping. Tier 2 included a detailed clinical review, where a structured clinical assessment systemically recorded the presence or absence of all clinical features associated with FTLD. The structural clinical assessment (Table 2-1) included all clinical features in the diagnostic criteria of any of the FTLD syndromes (Rascovsky *et al.*, 2007; Bensimon *et al.*, 2009; Gorno-Tempini *et al.*, 2011, Armstrong *et al.*, 2013*a*). The PSP diagnostic criteria were updated during the PIPPIN study to increase the number of PSP-related clinical features (Höglinger *et al.*, 2017). Patients' nearest relative or, if no relative was available, carer completed a set of questionnaires; the Cambridge Behavioural Inventory - Revised (CBIR) (Wear *et al.*, 2008), Frontotemporal Dementia Rating Scale (FRS) (Mioshi *et al.*, 2010), Carer-Rated Apathy Evaluation Scale and Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994). An extended neuropsychological test battery included the Addenbrooke's Cognitive Examination – Revised (ACER) (Mioshi *et al.*, 2006), Frontal Assessment Battery (FAB) (Royall, 2001), Self-Rated Apathy Evaluation Scale (Guercio *et al.*, 2015), Barratt Impulsivity Scale (BIS) (Patton *et al.*, 1995) and Beck Depression Inventory (BDI) (Beck *et al.*, 1961). The magnetic resonance imaging is discussed in Chapter 3 of this thesis. A blood sample, including tubes for whole blood, RNA, serum and plasma, were taken and frozen at -80 degrees Celsius pending further analysis. The study was adaptable, participants did not have to commit to completing the full protocol and disease severity was not a contraindication. For example, a patient with severe aphasia or anarthria may be unable to complete the full neuropsychological battery but could participate in the clinical review, MRI scan and blood test. If participants were too impaired to travel to Cambridge the study team visited them at their home or care home for a clinical

assessment, neuropsychology and carer questionnaires. Transport was provided to facilitate patients travelling to Cambridge for an MRI scan.

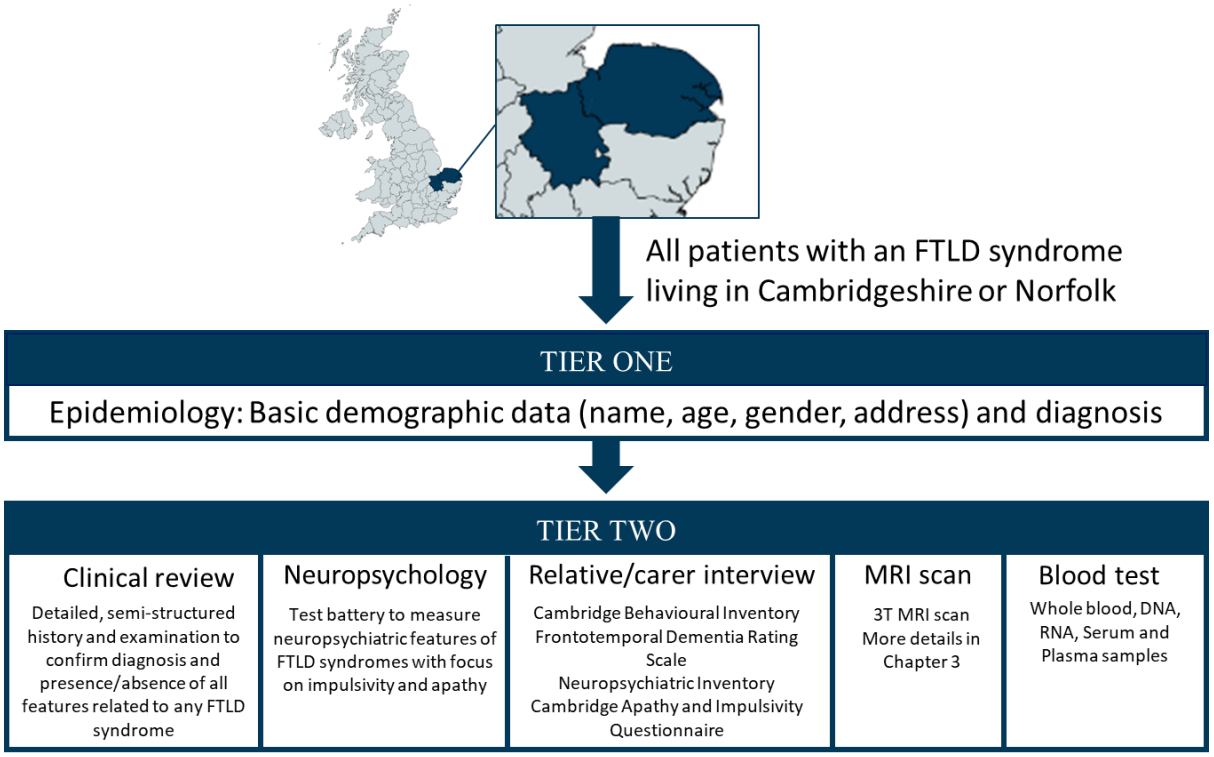


Figure 2-2: Schematic of PIPPIN study protocol. All patients in the region with a known diagnosis of an FTLD syndrome were recruited into Tier 1. Patients were then invited into Tier 2 for a more detailed phenotypic assessment to include clinical review, neuropsychology, carer questionnaires, an MRI scan and phlebotomy.

Patients alive during both study periods (1/1/13-31/12/15 and 1/1/16-31/12/18) were invited to assessment in both periods. Their first visit was used for the cross-sectional analysis reported in this chapter and longitudinal analysis assessed the change in their clinical phenotype between the two assessments. 365 patients were identified in the catchment area (Tier 1), 310 of whom were met in person by the study team for phenotypic assessment (included in Tier 2).

Data analysis

First, I assessed each patient's clinical phenotype against the diagnostic criteria for all FTLD syndromes (Rascovsky *et al.*, 2007; Bensimon *et al.*, 2009; Gorno-Tempini *et al.*, 2011, Armstrong *et al.*, 2013*a*; Höglinger *et al.*, 2017). Each patient's primary diagnosis was made according to these criteria, with reference to the dominant features at the time of presentation and assessment. Patients with a mixed primary progressive aphasia, who met the diagnostic criteria for PPA but not one of the three subtypes (Gorno-Tempini *et al.*, 2011), were grouped with lvPPA, in view of the low numbers and the association of both phenotypes with

Alzheimer's pathology (Sajjadi *et al.*, 2012). For patients who met several sub-diagnostic criteria I grouped probable and possible diagnoses together, and classified by the dominant phenotype and formal Multiple Allocations eXtinction (MAX) rules where available (Grimm *et al.*, 2019). I then re-applied the other diagnostic criteria to each patient to assess if he or she met the diagnostic criteria for any of the other FTLD syndromes (excepting the 'mutual exclusivity' clause included in several criteria). Many diagnostic criteria include imaging-supported diagnoses (e.g. prominent anterior temporal lobe atrophy is supportive of a diagnosis of svPPA (Gorno-Tempini *et al.*, 2011)). The imaging criteria were used to make the initial diagnosis of an FTLD syndrome but not when assessing which of the other FTLD criteria the patient met.

Second, I examined the relationships between individual clinical features using distance measures and multidimensional scaling (Shepard, 1980). Multidimensional scaling is a method to visualise the similarity between individual variables (in this case clinical features) in a dataset. The pairwise Jaccard's distances between clinical features were calculated, resulting in a dissimilarity matrix. Non-classical two-dimensional scaling was performed on this dissimilarity matrix. Non-classical multidimensional scaling produces a plot that reproduces the ranks of distances, rather than the original distances between clinical features which in this case are arbitrary. Pairwise distances and multidimensional scaling were calculated using the *pdist* and *mdscale* functions in MATLAB 2018b (MathWorks, USA).

Third, I looked for patterns of covariation in the presence or absence of clinical features using principal component analysis. Principal component analysis (PCA) uses feature extraction to reduce the dimensionality of a dataset while preserving as much variation as possible (Jolliffe, 2002; Ringnér, 2008). PCA produces latent variables, or principal components, each of which represents the results from a group of covarying features (Jolliffe, 2002). PCA has been used extensively in neuroscience research to identify latent variants from clinical features (Jorm *et al.*, 1993, Perry *et al.*, 2017*a*), neuropsychological tests (Lansdall *et al.*, 2017; Grisanzio *et al.*, 2018; Schumacher *et al.*, 2019) and structural (Yang *et al.*, 2011; Khedher *et al.*, 2015) and functional (Viviani *et al.*, 2005) imaging data. To reduce the dimensionality of the dataset before PCA, I grouped the fifty binary ratings of clinical symptoms and signs into twenty-five groups, by summing the number of present features in each group. Clinical feature groups were defined *a priori* as those that were very closely related or were grouped together in the diagnostic criteria. For example, I grouped apathy and inertia into an "apathy" feature group. A full list of clinical symptoms and signs and their groupings is shown in Table 2-1. The clinical

feature group scores, ACER and CBIR results were standardised into z scores then entered into a principal component analysis. Six principal components were then selected using Cattell's criteria (Cattell, 1966). To help interpret the PCA I performed varimax rotation on the six principal components. Varimax rotation rotates the PCA to try to associate each variable (clinical feature, ACER or CBIR subscore) to only one principal component. Principal component analysis was performed using the *pca* and *rotatefactors* functions in MATLAB 2018b.

Finally, I looked at longitudinal change in clinical feature component scores in the subset of patients (n=46) who were reviewed twice. I converted follow up participant scores into z scores based on the baseline data, by matching each score to the respective z score in the baseline data. This ensured follow up participants were matched to the cross-sectional dataset. I then multiplied these standardised follow-up z scores by the baseline principal component coefficients to get follow-up principal component scores.

All patients had a clinical phenotypic assessment but other measures (Addenbrookes Cognitive Examination - Revised and CBIR) were subject to missing data. Such missing data (6.32% of the total dataset) were imputed using trimmed scored regression as part of a published MATLAB toolbox (Folch-Fortuny *et al.,* 2016) using the partial dataset of that participant as predictors. In this multiple imputation method, a principal component analysis model is created from the dataset, initially with all missing data replaced with zeros. Missing values are then iteratively replaced using a regression model until the model convergences on an optimal solution (Folch-Fortuny *et al.*, 2015). The final principal components are then used to estimate and replace missing data points. The advantage of this method is it uses the relationship of the missing values to all other variables, as part of the latent structure of the dataset. The toolbox provides many different options for multiple imputation, but trimmed scored regression is recommended as the default approach (Folch-Fortuny *et al.*, 2016).

All statistical and imaging analysis was performed in MATLAB 2018b (MathWorks, USA) apart from ANOVA and Chi squared tests which were performed in JASP (version 0.9.2).

Clinical feature group (for PCA)	Symptom/Sign recorded at PIPPIN study assessment
Behavioural disinhibition/impulsivity	Socially inappropriate behaviour Loss of manners or decorum Impulsive rash careless action
Apathy	Apathy Inertia
Loss of sympathy/empathy	Diminished response to other people's needs and feelings Diminished social interest, interrelatedness or personal warmth
Stereotyped/compulsive behaviours	Simple Repetitive movements Complex compulsive or ritualistic behaviour Stereotypy of speech
Hyperorality/dietary change	Altered food preferences Binge eating, increased ETOH or Cigarettes Oral exploration of inedible objects
Executive dysfunction	Deficits in executive tasks Relative sparing of episodic memory Relative sparing of visuospatial skills
Asymmetrical parkinsonism	Asymmetric limb rigidity Asymmetric limb akinesia
Asymmetrical dystonia	Asymmetric limb dystonia
Asymmetrical myoclonus	Asymmetric limb myoclonus
Symmetrical parkinsonism	Symmetric limb rigidity Symmetric limb akinesia
Symmetrical dystonia	Symmetric limb dystonia
Symmetrical myoclonus	Symmetric limb myoclonus
Axial rigidity	Proximal rigidity more than peripheral Axial rigidity or akinesia Abnormal neck posture
Poor response to L-dopa	Poor or absent response to L-dopa
Orobuccal apraxia	Orobuccal apraxia
Limb apraxia	Limb apraxia
Cortical sensory deficit	Cortical sensory deficit
Alien Limb	Alien Limb Syndrome
Visuospatial deficits	Visuospatial deficits
Postural instability	Postural instability with tendency to fall Frequent unprovoked falls within 3 years Tendency to fall on the pull test >2 steps backwards on pull test
Supranuclear gaze palsy	Vertical supranuclear gaze palsy Decreased velocity of vertical saccades
Agrammatic/apraxic speech	Agrammatism in language production Effortful halting speech with inconsistent sound errors (AoS) Impaired comprehension of syntactically complex sentences
Impaired semantics	Impaired confrontation naming Impaired single word comprehension Impaired object knowledge Surface dyslexia or dysgraphia
Logopenic speech	Impaired single word retrieval in spontaneous speech and naming Impaired sentence repetition Phonological errors in spontaneous speech
Motor neuron disease	Clinical signs of motor neuron disease

Table 2-1: Clinical features recorded for each individual in the PIPPIN study (features not included in cluster analysis and PCA not shown here). Prior to PCA, features were grouped according to the first column.

Results

The study team assessed in person 85% (310/365) of the patients identified as living in the study catchment area with a FTLD syndrome. A detailed epidemiological assessment of FTLD in the study area has previously been reported (Coyle-Gilchrist *et al.*, 2016). Further demographic details of the whole PIPPIN study cohort, including the later recruitment period, are shown in Table 2-2.

First, I assessed each patient against all the diagnostic criteria for FTLD syndromes. Sixty-two percent of patients (n=194) met the core diagnostic criteria for more than one syndrome, with patients meeting the inclusion criteria for two (n=112), three (n=69) or four (n=13) diagnoses (Figure 2-3A and B). The most commonly overlapping syndromes were PSP and CBS (n=76), bvFTD and either PSP (n=60) or svPPA (n=38) and nfvPPA with either CBS (n=56) or PSP (n=51).

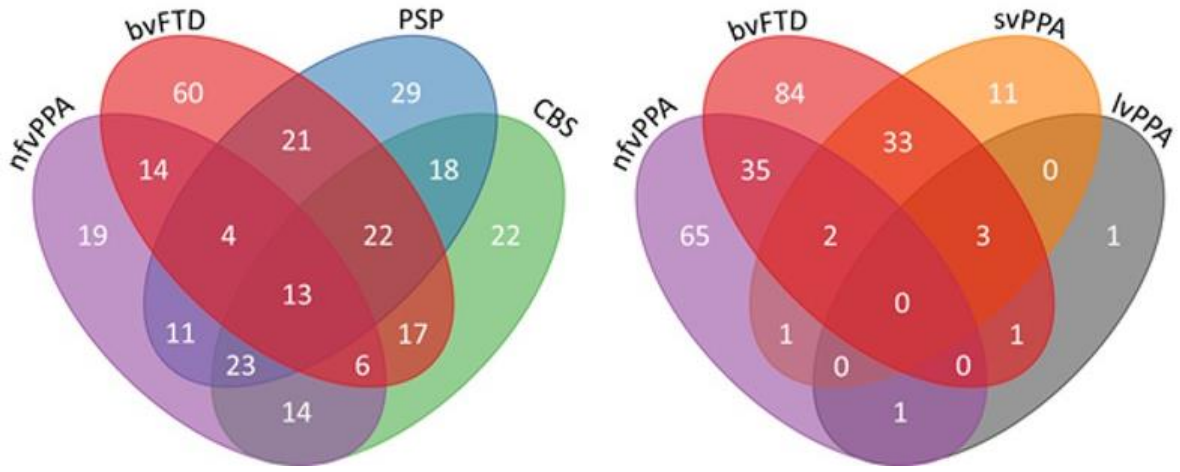


Figure 2-3: Venn Diagrams of diagnostic overlap in FTLD syndromes. The numbers in each oval refer to the number of patients who met the diagnostic criteria for those syndromes.

	All groups	bvFTD	nfvPPA	svPPA	PPA#	PSP	CBS	p*
Total in study area (n)	365	81	40	28	16	123	77	--
Clinical phenotyping, (% of total population)	310 (85)	64 (79)	36 (93)	25 (89)	16 (100)	101 (82)	68 (88)	ns
Age, years (mean and SD)	70.26 (8.57)	64.59 (9.56)	72.09 (8.81)	67.55 (6.43)	70.80 (7.05)	72.56 (7.14)	72.08 (7.69)	<0.001
Male/Female	152/158	33/31	15/21	14/11	7/9	56/45	27/41	ns
Duration of symptoms (years, mean and SD)	4.75 (3.18)	5.70 (4.45)	2.83 (1.93)	4.96 (2.69)	2.76 (1.97)	4.50 (2.94)	4.71 (2.77)	ns
Diagnosis to study (years, mean and SD)	1.44 (2.77)	1.88 (3.88)	1.09 (1.27)	1.65 (2.01)	1.58 (1.67)	1.02 (1.17)	1.73 (2.02)	ns

Table 2-2: Demographics of the study cohort. #lvPPA n=7, mixed PPA n=9. *P values are the result of ANOVA or Chi sqaured test for each row on FTLD subgroups, ns= not significant (p>0.05).

Second, I used cluster analysis to investigate how closely clinical features related to each other. Multidimensional scaling of clinical features (across all patients) broadly recapitulated the phenotypic clustering as represented by the classical phenotypes of each syndrome (Figure 2-4). However, there were also close links between signs conventionally associated with distinct diagnoses. For example, progressive behavioural change, apathy, inertia and impulsivity (typical of bvFTD), were close to symmetrical parkinsonism, falls, axial rigidity and a supranuclear gaze palsy (typical of PSP). Other features suggestive of bvFTD (socially inappropriate and compulsive behaviour and stereotypy of speech), were close to features typical of svPPA features (impaired naming, single word comprehension and object recognition). PSP and CBS features were closely linked, while speech apraxia, agrammatism and impaired syntactic comprehension (indicative of nfvPPA) overlapped with limb apraxia (indicative of CBS).

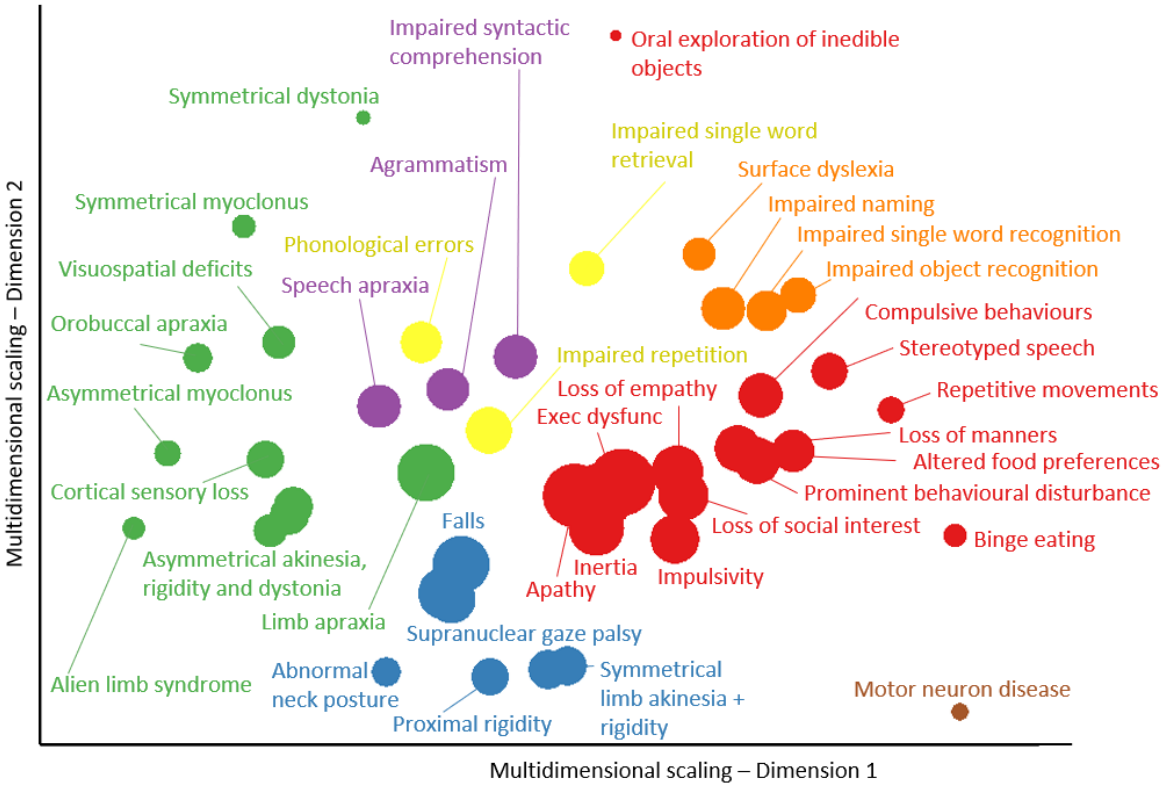


Figure 2-4: Cluster analysis and multidimensional scaling of behavioural, language and motor impairments in FTLD. Each feature is colour coded by FTLD subtype, based on the primary diagnostic criteria which the symptom contributes to: red=bvFTD, blue=PSP-RS, green=CBS, purple=nfvPPA, orange=svPPA, yellow=lvPPA. The size of each point is scaled based on its prevalence in the cohort (larger icons have a higher prevalence). Symptoms from each FTLD syndrome cluster together, but many features are also closely located to those from other syndromes.

Third, I identified latent syndrome dimensions using principal component analysis of the phenotypic data. Six principle components were extracted using Catell's criteria (Figure 2-5), each representing a group of covarying features (encompassing symptoms, signs, ACER and CBI scores, Table 2-3). These six components explained 58.52% of the variance in the dataset (Kaiser-Meyer-Olkin test for sampling accuracy=0.86).

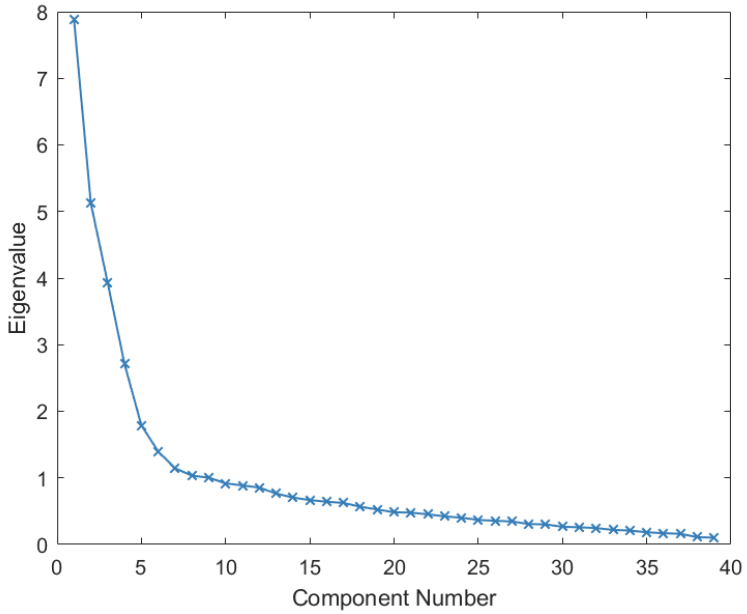


Figure 2-5: Scree plot from principal component analysis. Six principal components were selected according to Cattell's criteria

Syndrome dimension 1 (Figure 2-6A) reflected clinician and carer ratings of behaviour and personality change, with executive dysfunction, impulsivity and disinhibition, loss of empathy, stereotyped behaviours, hyperorality and dietary change, apathy, endorsements of abnormal behaviour, altered eating habits and stereotypic and motor behaviour subscales. This "behaviour" dimension was expressed strongly by patients with bvFTD, but also a high proportion of PSP, CBS and svPPA patients. Some patients in these latter groups had weightings similar to bvFTD. The second syndrome dimension (Figure 2-6B) reflected global cognitive function, with negative loadings from ACER subscores. Carer ratings of everyday function and memory also had positive loading onto this component (higher CBI score, reflecting greater impairment). There was wide variation in this dimension's weighting across all groups, with higher scores reflecting worse cognitive impairment.

The third dimension (Figure 2-6C) reflected axial rigidity, postural instability and a supranuclear gaze palsy (positive loading) in the absence of semantic language impairments (negative loading). Thus, patients with typical PSP and typical svPPA lie at opposite ends of this dimension spectrum, with high and low scores respectively. However other groups had a spread of scores, many patients with corticobasal syndrome had very high scores (PSP-like). Some bvFTD had high scores indicating a PSP-overlap, while others had low scores, implying the presence of semantic impairment.

Positive scores on syndrome dimension four (Figure 2-6D) represented asymmetrical parkinsonism, dystonia and myoclonus with cortical features of apraxia, cortical sensory loss and alien limb syndrome. Patients with corticobasal syndrome and a subset of patients with PSP had high scores in this dimension. Dimension 5 (Figure 2-6E) represented language impairments, agrammatic, apraxic and logopenic speech with motor features (myoclonus and limb apraxia). Patients with CBS, nfvPPA, logopenic variant and mixed PPA had high weighting on this dimension, as did a small subset of those with clinical diagnoses of PSP and bvFTD. Dimension 6 explained less variance than the other components and represented primarily carer ratings of mood and abnormal beliefs (Figure 2-6F).

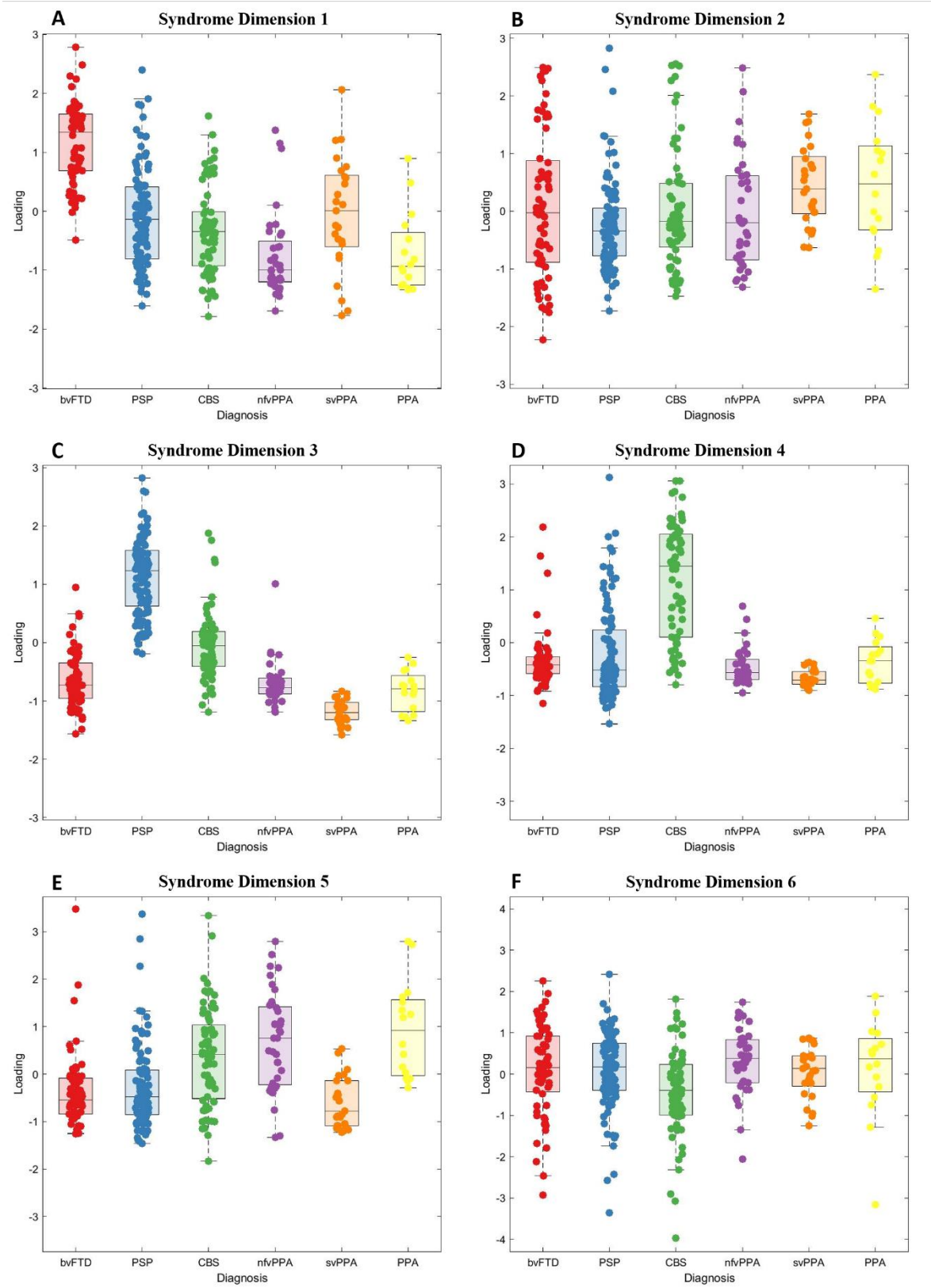


Figure 2-6: Principal component analysis scores of clinical features in FTLD syndromes. Six principal components (4A-F) were selected. 4A: Syndrome dimension 1 - Clinician and carer ratings of behavioural impairment. 4B: Syndrome dimension 2 - Global cognitive impairment (all ACER subscores). 4C: Syndrome dimension 3 - Supranuclear gaze palsy, postural stability and symmetrical rigidity (positive loading) and semantic language impairment (negative loading). 4D: Syndrome dimension 4 - Asymmetrical parkinsonism, dystonia, myoclonus with limb apraxia, cortical sensory loss and alien limb syndrome. 4E: Syndrome dimension 5 - agrammatic, apraxic and logopenic language impairments. 4F: Syndrome dimension 6 - carer ratings of low mood and abnormal beliefs.

	Syndrome Dimension 1	Syndrome Dimension 2	Syndrome Dimension 3	Syndrome Dimension 4	Syndrome Dimension 5	Syndrome Dimension 6
Disinhibition	**0.7399**	0.0774	-0.0790	-0.1423	-0.1576	0.1102
Apathy	**0.5486**	0.0763	**0.4276**	0.1221	-0.1919	0.1450
Loss of empathy	**0.7022**	0.1278	0.0044	-0.0981	-0.1278	0.0205
Stereotypy/compulsion	**0.5789**	0.2890	-0.3103	-0.1798	-0.0536	0.2444
Hyperorality	**0.6234**	0.0459	-0.2198	-0.1270	-0.0932	0.0705
Executive dysfunction	**0.5458**	0.1440	0.1176	-0.0176	-0.0476	0.3155
CBI - Abnormal behav	**0.7497**	0.1251	-0.0348	-0.0545	-0.0898	-0.3164
CBI - Mood	**0.5485**	0.1013	0.0039	0.1709	-0.0077	**-0.5067**
CBI - Eating habits	**0.7647**	0.0394	-0.0486	-0.0500	-0.0074	-0.2188
CBI - Sleep	**0.4569**	-0.0259	0.2813	0.1776	-0.0488	**-0.4043**
CBI - Motor behaviour	**0.7056**	-0.0161	-0.1997	-0.1174	0.0726	-0.2513
CBI - Motivation	**0.7075**	0.2981	0.1511	0.0500	-0.1157	-0.1488
ACER - Attention	-0.1510	**-0.9002**	0.0922	0.0463	-0.0248	0.0724
ACER - Memory	-0.1124	**-0.8258**	0.3410	0.1746	-0.0440	0.0770
ACER - Fluency	-0.1784	**-0.7576**	0.1183	0.1772	-0.0744	-0.1227
ACER - Language	-0.0805	**-0.8460**	0.3405	0.1337	0.0314	0.0238
ACER - Visuospatial	-0.0532	**-0.8299**	-0.1642	-0.1818	-0.0460	0.1518
CBI - Memory	**0.4864**	**0.5544**	-0.2152	-0.0392	0.0199	-0.3158
CBI - Everyday skills	**0.4086**	**0.5214**	0.3309	0.3198	0.0727	-0.1291
Sym parkinsonism	0.0127	-0.0415	**0.7676**	-0.3673	0.0655	-0.0362
Axial rigidity	-0.0156	-0.1158	**0.8077**	0.0425	-0.0231	0.0669
Poor l-dopa response	-0.1307	-0.1057	**0.6757**	0.0873	-0.0629	-0.0536
Postural instability	-0.0504	-0.1069	**0.7719**	0.1690	-0.0640	-0.0241
Supranuclear gaze palsy	-0.0938	-0.1144	**0.8132**	0.1045	-0.0473	0.0526
CBI - Self care	0.3459	0.3996	**0.4524**	0.3626	-0.0628	-0.0775
Impaired semantics	0.1510	0.3067	**-0.5187**	-0.2377	0.0353	0.1970
Asym parkinsonism	-0.0652	-0.0843	0.0700	**0.8343**	-0.0627	0.0202
Asymmetrical dystonia	0.0282	-0.0673	0.0899	**0.8300**	-0.0550	0.1061
Asym myoclonus	-0.0340	-0.0148	-0.0493	**0.6830**	0.1012	0.0621
Limb apraxia	-0.1292	-0.0590	0.1252	**0.5274**	**0.5056**	-0.0233
Cortical sensory loss	-0.1462	-0.0201	0.0584	**0.5635**	0.2569	-0.2505
Alien limb syndrome	-0.0363	-0.0066	0.0504	**0.5423**	0.0749	-0.1367
Sym myoclonus	-0.0658	-0.0350	0.0044	-0.0093	**0.5132**	-0.3228
Agram/apraxic speech	-0.1224	0.1231	-0.0369	0.1137	**0.7667**	0.2703
Logopenic speech	-0.0659	0.0268	-0.1180	-0.0461	**0.7752**	0.0415
CBI - Beliefs	0.1830	0.2358	0.0220	-0.0019	0.0093	**-0.5919**
Symmetrical dystonia	0.1134	0.1176	0.3325	-0.1741	0.2010	0.0008
Orobuccal apraxia	-0.1225	-0.0170	-0.0012	0.2822	0.3727	-0.0267
Visuospatial deficits	-0.1863	0.1862	-0.0106	0.2386	0.3650	-0.2559
Motor neuron disease	0.2615	-0.1304	-0.1584	-0.0617	-0.1683	0.0556

Table 2-3 (previous page): Rotated component matrix from principal component analysis. ACER: Addenbrookes Cognitive Examination – Revised. CBI: Cambridge Behavioural Inventory. Positive loadings indicate worse performance or presence of symptoms, except for ACER where negative loadings indicate worse performance. Factor loadings above 0.4 or below -0.4 shown in bold.

The final analysis considered the longitudinal change in the forty-six patients who were alive and assessed in both 2013-2014 and 2017-2018. The mean time between assessments was 3.6 years (standard deviation 0.87 years). I compared patients with follow-up to those without. At baseline, patients with follow-up were younger (mean 67.0 vs 70.9, t=2.8, p=0.005) but had similar sex ratio and disease duration. Patients with follow-up had lower scores on syndrome dimension three (t=3.55, p<0.001) because fewer had PSP (Chi squared=3.94, p<0.05). The other dimensions scores at baseline were not different between patients with and without follow-up. Between first and second assessments there was progression in all syndrome dimensions across all groups. At the second assessment there was greater overlap between diagnostic groups, across all syndrome dimensions (Figure 2-7). More patients met two or more sets of diagnostic criteria (after removing mutual exclusivity criterion) at follow up (n=42) compared to baseline (n=33) (Chi squared statistic with Yates correction 4.618, p=0.031). An alternative visualisation of the longitudinal results is shown in Figure 2-8. Multidimensional scaling of baseline and follow up data shows individuals with different FTLD syndromes coalesce over time. For example, patients with svPPA (orange) became more like patients with bvFTD (red). Patients with nfvPPA (purple) moved closer to CBS (green) or bvFTD (red). Some bvFTD patients moved closer to PSP (blue) and some PSP patients moved closer to bvFTD.

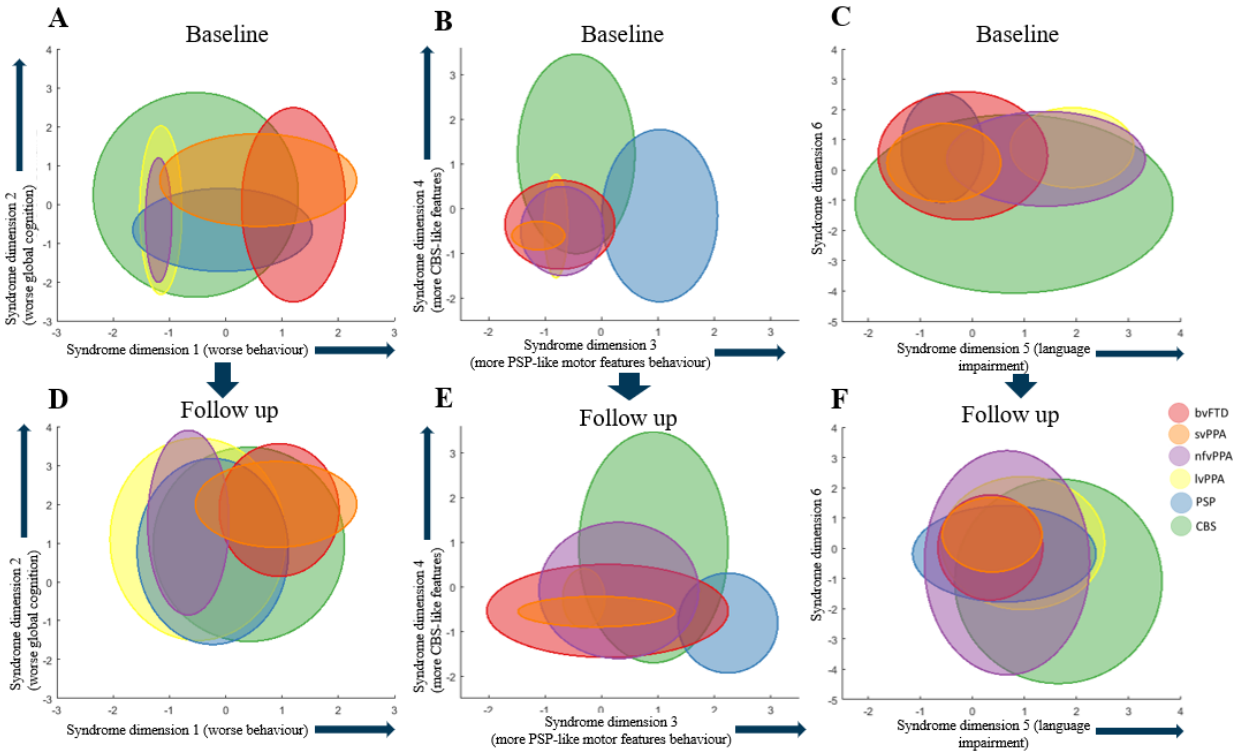


Figure 2-7: Longitudinal phenotype information. A subset of patients were assessed at two timepoints. Each circle shows the 95% confidence intervals of the syndrome dimension scores for each FTLD subgroup at baseline and follow up. At follow up there was greater overlap across all FTLD syndromes in all syndrome dimensions.

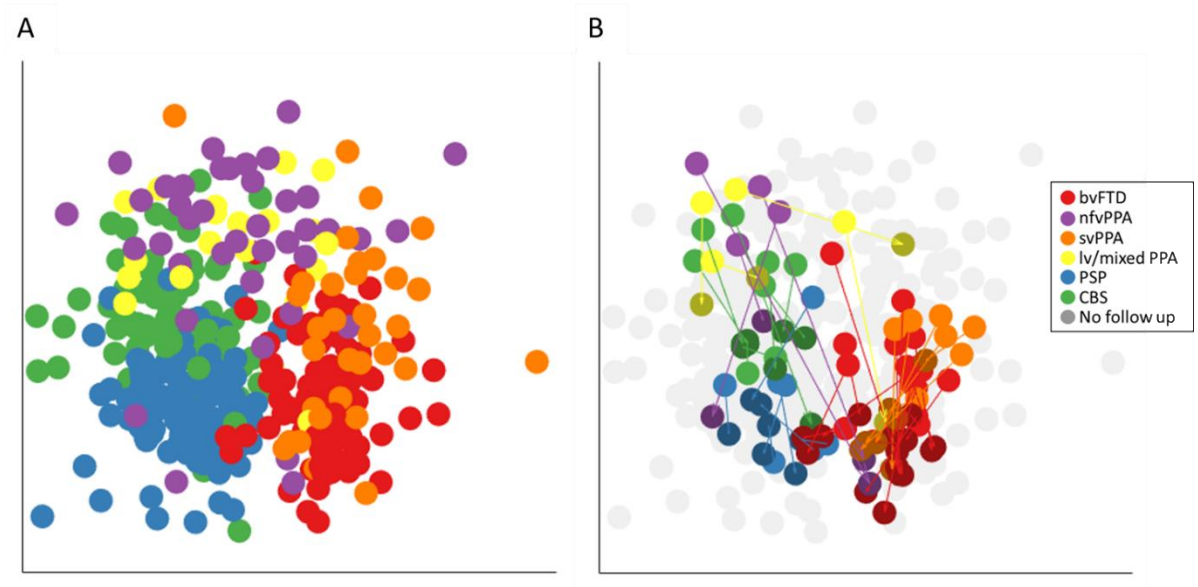


Figure 2-8: Multidimensional scaling of clinical phenotype with disease progression. 7A: Baseline data, individuals colour coded by FTLD syndrome subtype. 7B: Follow up data, lighter points show baseline data and an arrow to darker point showing position of individual, relative to the cross sectional population, at follow up.

Discussion

In this chapter I used a data-driven analysis on results from an epidemiologically based study to show that frontotemporal lobar degeneration syndromes are not discrete in their clinical features (Figure 2-1A), but instead exist as a multidimensional spectrum (Figure 2-1B), with many patients displaying the diagnostic features for multiple diagnoses (Figure 2-3C&D). The dimensions of behaviour, movement and language features occur to varying degrees across all the major diagnostic groups associated with FTLD. Differences between groups were expressed by different weightings along a spectrum rather than by distinctive clinical or imaging features.

Despite the continuity among patient phenotypes, the clinical syndromes are not random associations. This analysis revealed close associations between sets of cognitive, behavioural, language and motor symptoms and signs which are reminiscent of the classical phenotypes (Figure 2-4). For example, syndrome dimension three, which represents a supranuclear gaze palsy, falls, akinesia and preserved semantics, is readily identified as a pattern typical of PSP-Richardson's syndrome. However, forty-four percent of CBS patients expressed this pattern to the same degree as PSP patients. The recognition of such overlap has contributed to the development of intermediate diagnoses like PSP-CBS (Höglinger *et al.*, 2017) and CBS-PSP (Armstrong *et al.*, 2013*a*) but these results indicate that such overlap is common rather than exceptional. However not all potential intermediate phenotypes occur. For example, a supranuclear gaze palsy, axial and symmetrical limb rigidity rarely coexist with semantic impairment, a combination which has only previously been reported in patients with mixed tau and TDP43 pathology (Snowden *et al.*, 2019).

I propose that this spectral approach is critical to understand the biological basis of the complex clinical syndromes and to appropriately target future therapies. Rather than focus on the determinants of disease or its treatment by diagnosis, one can focus on the determinants and treatment of the syndromic dimensions, in whichever disease 'group' these dimensions are expressed. To do otherwise risks the misdirection of a treatment or the dilution of the effects of aetiological factors, whether genetic, environmental, or aggregate of pathogenic proteins. In other words, one could understand and potentially treat the "PSP-like" features whether they occurred in clinically diagnosed PSP-Richardson's syndrome, or CBS or bvFTD groups. I do not suggest that the current diagnostic criteria are invalid. Instead, these results highlight the limitations of a categorical approach to diagnosis when the disorders are inherently multivariate spectra in their clinical features. Indeed, the symptom-based data-driven cluster analysis

broadly reproduced the diagnostic criteria. But, the relative weightings on such clusters were graded, which highlights the difficulties when applying diagnostic criteria to some patients.

I did not differentiate features that are salient to a clinician (e.g. supranuclear gaze palsy) from those that are salient to a relative or carer (e.g. behavioural disturbance, non-fluent aphasia or falls). This difference in perspective is relevant to diagnostic labelling. For example, a patient with apraxia, akinesia, dystonia and non-fluent agrammatic speech might be diagnosed as CBS or nfvPPA according to the dominant clinical features, but whose opinion on dominance matters most, the patient, carer or clinician? This is complicated further by the change in insight associated with many FTLD syndromes (O'Keeffe *et al.*, 2007). A further complication for the categorical approach to diagnosis is the evolution of behavioural, motor or language features over time which raises the question of whether the diagnostic label should be changed or complimented by a secondary, parallel diagnosis. My approach resolves this issue by taking a transdiagnostic approach, which I consider in the next section.

This data-driven approach identified close clustering of the clinical features and six latent syndrome dimensions that demonstrated the high degree of overlap across FTLD syndromes. Behavioural features were closely clustered and loaded onto one syndrome dimension. However, they also clustered near cognitive and motor symptoms/signs. Apathy and impulsivity had a close link, reflecting the fact that they often coexist, rather than representing opposite ends of a hyper-hypo-kinetic spectrum (Lansdall *et al.*, 2017). Most patients had apathy, which lay near the centre of the multidimensional scaling plot (Figure 2-4), suggesting that it is related similarly to other features across FTLD syndromes. The behavioural syndrome dimension was expressed across multiple groups and was not restricted to the subset of the cohort with bvFTD (Figure 2-6A). Interestingly, not all patients with bvFTD had very high scores on this behavioural syndrome dimension. Those with lower behaviour scores, but a clinical diagnosis of bvFTD, may represent bvFTD with prominent apathetic/dysexecutive symptoms (O'Connor *et al.*, 2017), or reflect more advanced disease, when many of the more florid behavioural changes are less pronounced (O'Connor *et al.*, 2016). A proportion of patients with PSP and CBS had high scores on this syndrome dimension. Behavioural changes in PSP and CBS are well recognised (Burrell *et al.*, 2014*a*), but are often thought to be mild. My findings suggest that behavioural impairments in PSP and CBS can very prominent, in fact some patients with PSP and CBS had higher scores on syndrome dimension one than some with bvFTD. Importantly, no other clinical feature had negative loading coefficients on syndrome dimension one, suggesting that behavioural features can coexist with all other FTLD-related

features. Global cognitive impairment was represented by syndrome dimension two. All the Addenbrookes Cognitive Examination subscores and carer ratings of everyday skills and memory loaded onto this dimension. However, the reasons for low ACER scores may vary depending on which other symptom profiles are expressed: a low score on the ACER could be due to progressive dementia or caused by severe behavioural (syndrome dimension one) or language (dimension five) or motor (dimension three and four) impairment, all of which would interfere with the test session. There was agreement between clinicians and patients' relative or carer in ratings of behavioural and cognitive impairments (syndrome dimensions one and two).

My results are also relevant to the current nosology of primary progressive aphasias. Semantic impairments loaded onto a different syndrome dimension and clustered separately from the language impairments associated with non-fluent and logopenic primary progressive aphasia. This provides partial support for the current distinction between svPPA and other forms of PPA. However, nfvPPA and lvPPA were not readily distinguished by the data-driven analysis – as has been noted in a previous independent cohort (Sajjadi *et al.*, 2012). In contrast, patients with svPPA were similar to bvFTD in many respects (Figure 2-4), compulsive behaviours, stereotyped speech and simple repetitive habits were closely linked to semantic language impairments, including object recognition and single word comprehension (Harris *et al.*, 2016). Other language features, such as impaired syntactic comprehension, agrammatism and speech apraxia, were closely related to CBS-like motor features (syndrome dimension 3), in CBS, PSP, and nfvPPA groups - in keeping with the well characterised overlap of non-fluent (Rohrer *et al.*, 2010*d*, *a*) and apraxic (Josephs *et al.*, 2006*a*, 2012) speech with PSP and CBS (Armstrong *et al.*, 2013*a*; Respondek and Hoglinger, 2016; Peterson *et al.*, 2018). The PPA diagnostic criteria require that language impairments are the most prominent clinical feature and the principle cause of difficulty with ADLs. This may not be the case in some patients with svPPA; although clinicians may note prominent semantic impairments, co-existent behavioural impairment may be more conspicuous to relatives or carers and have a greater impact on independence and daily living. In addition, I report the practical difficulties applying the current PPA diagnostic criteria. In this epidemiological-based cohort nineteen patients met criteria for primary progressive aphasia (Gorno-Tempini *et al.*, 2011) but not one of the PPA subtypes. The current diagnostic criteria are stringent and require the presence and absence of multiple language features. Patients with language symptoms may have very isolated deficits (Josephs *et al.*, 2012) or at the other extreme multiple impairments which span more than one PPA subtype, even at diagnosis (Utianski *et al.*, 2019).

Longitudinal analysis in a subset of patients revealed that overlap between FTLD phenotypes increases with disease progression. A greater number of patients met the criteria for several FTLD subtypes compared to the first assessment and there was greater overlap between all syndrome dimensions (Figure 2-7). A transdiagnostic approach allows disease progression, manifesting as worsening clinical features, to be more accurately measured. Assessing FTLD syndromes in isolation, without reference to the whole FTLD syndrome spectrum, risks missing evolving signs of other FTLD syndromes and therefore underestimating disease severity. The time between the two phenotypic assessments was relatively long (mean 3.6 years) given the mean survival in FTLD syndromes (Coyle-Gilchrist *et al.*, 2016); therefore these results may be biased towards patients with more slowly progressive disease.

A strength of these results is that they are embedded within an epidemiological cohort study which improves their external validity. Previous studies of these disorders may have been influenced by low sample sizes and selection bias, by focussing only on patients at earlier disease stages who are well enough to attend subspecialist research centres for detailed phenotypic assessment. The representativeness in the PIPPIN study may partly explain why many patients lay across diagnostic criteria.

These results have several limitations. Applying multiple diagnostic criteria across all patients raises challenges. For example, the criteria can include an exclusion clause, that the illness is not better explained by another diagnosis. I lifted this criterion and applied the clinical features to the other positive and negative criteria. Patients may have symptoms or signs that do not quite reach the threshold needed to meet a diagnostic criterion. The PIPPIN study approach was to try to apply the same threshold in all groups, in asserting the presence of a symptom or sign. The assessment of clinical features was also cross sectional, rather than a retrospective estimate of presenting features. Some of the diagnostic criteria (e.g. for PPA (Gorno-Tempini *et al.*, 2011)) refer to the dominance of a symptom cluster (eg language disorder) at presentation. This sounds straightforward, but the time of presentation varies widely, is often late (Coyle-Gilchrist *et al.*, 2016), and is partially dependent on variations in healthcare services, referral pathways and public awareness of symptoms' significance (Bradford *et al.*, 2009). These factors interfere with the ability of symptomatology to inform the diagnosis and likely pathology, especially in overlap syndromes such as CBS-NAV, or PSP-F. Genetic information could further inform the multivariate analysis of phenotype, mindful that while bvFTD has a strong genetic component, svPPA and PSP do not (Rohrer *et al.*, 2009). This transdiagnostic approach to FTLD may not be appropriate in all situations, for example trials of treatments targeting at a specific

proteinopathy. Currently there are no robust biomarkers that can differentiate between, for example FTLD-tau and FTLD-TDP43 (Meeter *et al.*, 2017; Bevan-Jones *et al.*, 2018), and current trials focus recruitment on subsets of patients with strong clinicopathological correlation like PSP-RS (Boxer *et al.*, 2019). However, this limits patient access to drug trials, given the poor clinicopathological correlation in the majority of FTLD syndromes. Emergence of more accurate biomarkers, whether PET, CSF or blood based (Meeter *et al.*, 2017; Leuzy *et al.*, 2019), may allow a more transdiagnostic approach. This would facilitate accurate drug targeting while maximising power and generalisability of results.

Another limitation is the missing data in my results. Some patients were missing an ACER or CBI, although this represented only a small percentage of the overall dataset (6.32%). The problem of missing data is common in large, observational cohorts like the PIPPIN study and no statistical solution is without limitations and risk of bias (Sterne *et al.*, 2009). Missing data can be missing completely at random (no systemic difference between missing and observed data), missing at random (systematic differences between can be explained by other observed variables) or missing not at random (systematic differences unexplained by observed data) (Sterne *et al.*, 2009). I used imputation, which estimates and replaces missing data based on the relationship between variables in participants with a complete dataset. This approach risks bias if data is not missing at random. For example, if patients had missing data due to more severe cognitive impairment, then imputation will inaccurately overestimate their true result. The PIPPIN study team attempted to visit all patients irrespective of disease severity (including in care homes) to mitigate the risk of missing data occurring not at random.

Research related to disease nosology often raises the issue of whether to 'lump' disorders together or to 'split' them into subtypes (Darwin *et al.*, 1877; Scaravilli *et al.*, 2005). There may be occasions where the decision to lump or split aids insight into the neurobiology of disease. But, lumping and splitting can also obscure insights. I propose an alternative approach, with data-driven spectral analyses, that neither lump nor split arbitrarily, but allow phenotypic and imaging variance to elucidate the pathogenesis of cognitive syndromes. Genetic information could further inform the multivariate analysis of phenotype, mindful that while bvFTD has a strong genetic component, svPPA and PSP do not (Rohrer *et al.*, 2009). A final limitation is the potential for multiple pathologies, in which several pathogenic protein inclusions may co-exist and be synergistic in neurodegeneration (Robinson *et al.*, 2018).

Patient categorisation and selection should depend on the study or question of interest (Husain, 2017; Coulthard and Love, 2018), but for symptomatic treatment and the assessment of diagnostic biomarkers data-driven axes of disease may be more relevant outcomes. Whilst phenotypic variance is ‘noise’ in category-based analysis of disease and treatment effects and undermines the observation of effects, the same variance can be informative through multivariate analyses like PCA. The adoption of such a data-driven approach provides a comprehensive framework with which to understand disease progression and heterogeneity, analogous to the Research Dimension Criteria used in psychiatric diseases.

In this chapter I have presented evidence from a transdiagnostic, data-driven approach to the clinical phenotypes in syndromes associated with FTLD. I show that the syndromes associated with frontotemporal lobar degeneration (FTLD) are not discrete in their clinical features but instead exist as a multidimensional spectrum. Patients often present diagnostic features of multiple disorders, while the dimensions of behaviour, movement and language features are not confined to specific diagnostic groups.

Brain morphometry of frontotemporal lobar degeneration syndromes

Preface

This chapter forms part of manuscript which is in preparation (Murley *et al.*, 2020*a*). The clinical assessments in this chapter were performed by Dr Ian Coyle-Gilchrist between 2013 and 2015 and by me between 2016 and 2018. A large group of researchers (listed as co-authors on the above paper) at the Cambridge Centre for FTD and Related Disorders assisted with participant identification, recruitment and testing. I performed all the data analysis in this chapter, with help from Dr Kamen Tsvetanov and Simon Jones. The text was written by me, with input from co-authors on the manuscript.

Summary

In this chapter, I use *in viv*o MRI imaging results from the PIPPIN study to investigate the brain morphometry of the frontotemporal lobar degeneration (FTLD) syndromes. Using source-based morphometry I identify patterns of co-varying brain atrophy that are represented across groups. Canonical correlation analysis of syndrome dimensions and imaging components show three key brain-behaviour relationships that reveal a continuous spectrum across the cohort, rather than discrete diagnostic entities. These results support a transdiagnostic, multidimensional approach to the FTLD syndrome spectrum by showing atrophy patterns are associated with the clinical syndrome dimensions reported in Chapter 2.

Introduction

Frontotemporal lobar degeneration pathology is associated with varying patterns of brain volume loss. Typically, FTLD causes grey and white matter atrophy in the frontal and temporal lobe but can also affect the parietal lobe and subcortical structures including the basal ganglia, thalamus and brainstem. Even within FTLD syndrome subtypes, the pattern and severity of brain atrophy varies. In this chapter, I investigate how this heterogeneity in brain morphometry relates to the heterogeneity in clinical phenotypes I reported in the previous chapter.

Progressive brain volume loss from neuronal loss due to misfolded protein accumulation is a feature of all neurodegenerative disease, including frontotemporal lobar degeneration (O'Brien *et al.*, 2001; Ridha *et al.*, 2008). This atrophy, which can be measured *in vivo* with magnetic resonance imaging (MRI), correlates well with neuropathology disease severity and distribution, and can be considered a surrogate *in vivo* measure of neuropathology (Whitwell *et al.*, 2005, 2008). MRI can therefore be used to understand the disease mechanisms underlying clinical phenotypes, as structural brain images can be correlated with a participant's cognitive, behavioural and motor deficits at the time of the scan. MRI measures of brain volume are also well validated biomarkers of disease progression (Gordon *et al.*, 2010, Whitwell *et al.*, 2017*a*, 2019; Staffaroni *et al.*, 2019), and often used as secondary endpoints in clinical trials (Höglinger *et al.*, 2014; Desmarais *et al.*, 2019).

There is significant variation, as with clinical phenotype, in brain morphometry within FTLD syndromes which reduces the accuracy of MRI as a diagnostic and prognostic biomarker. Within an FTLD syndrome subtype, the severity of atrophy varies widely across participants at the same temporal disease stage, which may explain differences in clinical phenotype (Ranasinghe *et al.*, 2016*b*; Staffaroni *et al.*, 2019). Recent studies have used volumetric MRI to explain mechanisms underlying phenotypic differences within FTLD syndrome subtypes (Whitwell *et al.*, 2009*b*, Ranasinghe *et al.*, 2016*b*; Jabbari *et al.*, 2019) but there is limited evidence on how changes in brain volume across the FTLD syndrome spectrum relate to clinical phenotype. For example, midbrain atrophy is a useful biomarker for diagnosis and progression of PSP-RS. However, this may not be true for other clinical phenotypes associated with FTLD-tau-PSP pathology (Jabbari *et al.*, 2019). Using a transdiagnostic approach to the FTLD syndrome spectrum, as I suggested in the previous chapter, would be supported by understanding how brain morphometry varies across the FTLD syndrome spectrum.

Better understanding of the brain changes of FTLD, and how they relate to clinical phenotype, could help stratify patients and support development of therapeutic trials.

Many structural MRI studies have already identified classical patterns of brain morphometry associated with FTLD syndromes. Most have investigated FTLD subgroups in isolation, or further fractionated them into smaller subsets based on different atrophy patterns. Combined studies of several FTLD syndromes have tended to focus on brain regions that separate FTLD syndromes, rather than looking for shared atrophy patterns. Behavioural variant frontotemporal dementia (bvFTD) is associated at early stages with bilateral frontal paralimbic and insula atrophy (Seeley *et al.*, 2008, Whitwell *et al.*, 2009*a*, Rohrer *et al.*, 2015*b*) which over time progresses to involve bilateral frontal and temporal lobes (Pan *et al.*, 2012; Canu *et al.*, 2017; Meyer *et al.*, 2017), the anterior cingulate cortex (Rosen *et al.*, 2002; Schroeter *et al.*, 2007) and subcortical structures including basal ganglia (Schroeter *et al.*, 2007), thalamus (Bocchetta *et al.*, 2018), habenula (Bocchetta *et al.*, 2016) and cerebellum (Meeter *et al.*, 2017, Chen *et al.*, 2018*b*). However, patterns of atrophy in bvFTD vary between individuals. Analysis of large cohorts of patients with bvFTD have identified several anatomical subtypes (Whitwell *et al.*, 2009*b*, Ranasinghe *et al.*, 2016*b*) and different genetic mutations are also associated with distinct atrophy patterns (Whitwell and Josephs, 2012; Whitwell *et al.*, 2012; Cash *et al.*, 2018) For example, patients with MAPT mutations often have severe bilateral anterior temporal lobe atrophy (Whitwell *et al.*, 2012; Ghetti *et al.*, 2015), GRN mutations may cause asymmetrical cortical atrophy (Le Ber *et al.*, 2008, Rohrer *et al.*, 2010*b*) and C9orf72 is associated with symmetrical and global cortical, subcortical and cerebellar atrophy (Cash *et al.*, 2018), which initially may be relatively mild (Devenney *et al.*, 2014). Semantic variant primary progressive aphasia (svPPA) classically causes severe left anterior temporal lobe atrophy (Mummery *et al.*, 2000; Galton *et al.*, 2001) but there is also atrophy in the orbitofrontal, insula and anterior cingulate cortices (Rosen *et al.*, 2002). svPPA can be associated with severe asymmetric right temporal lobe atrophy which has a different clinical phenotype, with greater behavioural impairments, prosopagnosia and social cognitive deficits (Chan *et al.*, 2009; Kumfor *et al.*, 2016). Patients with non-fluent variant primary progressive aphasia (nfvPPA) have relatively minimal atrophy at early disease stages, with atrophy confined to the left inferior frontal gyrus and insula (Raisner *et al.*, 2005, Cope *et al.*, 2017*a*). The typical structural MRI finding in progressive supranuclear palsy is midbrain atrophy, which correlates with disease progression (Dutt *et al.*, 2016, Whitwell *et al.*, 2017*a*, 2019) and results in the "hummingbird" sign due to atrophy of the dorsal midbrain (Mueller *et al.*, 2018). Other subcortical structures affected by

PSP include the thalamus, basal ganglia and cerebellum (Cordato *et al.*, 2002, Josephs *et al.*, 2008*a*; Stezin *et al.*, 2017). However, PSP is also associated with cortical atrophy, especially the frontal lobes, including the premotor and prefrontal cortices (Cordato *et al.*, 2002; Brenneis *et al.*, 2004). The different PSP syndrome subtypes (eg PSP-RS, PSP-F, PSP-CBS) have different patterns of brain atrophy (Jabbari *et al.*, 2019). Atrophy in corticobasal syndrome is typically asymmetrical and affects both cortical and subcortical structures, including the frontal, temporal, parietal and occipital lobes, basal ganglia, thalamus and brain stem (Gröschel *et al.*, 2004; Arai, 2006; Boxer *et al.*, 2006, Josephs *et al.*, 2008*a*, 2010; Whitwell *et al.*, 2010, Lee *et al.*, 2011*b*; Dutt *et al.*, 2016; McMillan *et al.*, 2016; Upadhyay *et al.*, 2016; Di Stasio *et al.*, 2019). The clinical phenotype heterogeneity, varying neuropathology and asymmetric atrophy in CBS can make it difficult to identify common regions of atrophy.

Aims and hypotheses

The aim of this chapter was to use a transdiagnostic approach to assess the brain morphometry of FTLD syndromes. I tested the hypothesis that the multivariate clinical spectrum of FTLD associated disorders, which I discussed in the previous chapter, can be mapped to multivariate regional structural brain change. Moreover, I predicted that clusters of symptoms would be associated with a specific pattern of brain atrophy, and the extent to which a patient has this atrophy pattern determines the severity of the associated symptoms. I hypothesised that the patterns of phenotype-atrophy associations would be spread across FTLD syndrome subtypes, instead of each FTLD syndrome forming discrete clusters.

Methods

Data acquisition

One hundred and thirty-nine patients (bvFTD n=28, nfvPPA n=15, svPPA n=5 PPA n=10, PSP n=53, CBS n=22) from the PIPPIN study were scanned at the Wolfson Brain Imaging Centre, University of Cambridge on a Siemens 3T system. Structural magnetic resonance imaging was performed using a T_1-weighted magnetisation-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR=2000ms,TE=2.93ms, TI=850ms, FA=8°, 208 slices, 1.1mm isotropic voxels). Images were pre-processed using SPM12. First, images were segmented into grey and white matter except the "old segment" function, because during initial analysis I found the "new segment" function did not accurately segment the MPRAGE images. Grey and white matter segments were combined to make whole brain images for further analysis. The DARTEL pipeline was used to create a study specific template using all images. Images were then transformed to MNI space with modulation and 8mm isotropic full width at half maximum Gaussian smoothing. An explicit mask was created from unmodulated images using the Masking toolbox with 50% consensus from 0.15 threshold (Ridgway *et al.*, 2009). Age, sex and total intracranial volume (TIV) were included in a multiple regression and regressed out of the data. Source based morphometry was used on the residual images to identify covarying networks of grey and white matter atrophy, further details of this step are given in the statistics paragraph.

Data analysis

There are many methods that enable morphometric analysis of structural MRI images. The most widely used is voxel-based morphometry (VBM). VBM was first developed at the Institute of Neurology at University College London with the Statistical Parametric Mapping (SPM) software (Ashburner and Friston, 2000). In brief, VBM spatially normalises all brains in a study to the same space, segments and smooths grey and white matter images and then performs statistical analysis to localise between-group differences (Ashburner and Friston, 2000). VBM is a mass-univariate statistical technique, meaning the statistical test, a general linear model, is repeated for every brain voxel. The results are then corrected for multiple comparisons and a map of statistical results is superimposed on an average brain image (Ashburner and Friston, 2000). A commonly used alternative approach is to measure cortical thickness with the FreeSurfer software, which again uses a mass univariate technique to compare groups. VBM is well validated but does have several limitations. It does not reveal any information on

relationships between voxels and will only reveal voxels for which there is a specified statistical result.

An alternative approach, which I used in this study, is source based morphometry (SBM) (Xu *et al.*, 2009). SBM is a multivariate, data-driven approach that uses independent component analysis (ICA) to identify covarying regions of atrophy (Xu *et al.*, 2009; Tharwat, 2018). These patterns of brain atrophy can be used to look for group differences in brain structure or reveal brain mechanisms associated with different clinical phenotypes. SBM has been used to report the brain morphometry of neurodevelopment (O'Muircheartaigh *et al.*, 2014), evolution (Hecht *et al.*, 2019), ageing (Hafkemeijer *et al.*, 2014), autistic spectrum disorders (Itahashi *et al.*, 2015), schizophrenia (Palaniyappan *et al.*, 2015), multiple sclerosis (Steenwijk *et al.*, 2016) and Parkinson's (Rektorova *et al.*, 2014), Huntington's (Coppen *et al.*, 2016) and Alzheimer's (Willette *et al.*, 2014) disease.

I used the GIFT software package to perform source based morphometry (Xu *et al.*, 2009). Source based morphometry was performed on the residual values from the pre-processed images (see data acquisition section for details). I extracted 15 independent components of covarying brain atrophy. ICASSO (Himberg and Hyvärinen, 2003) was performed 100 times to test the reliability of these components. Next, I looked at the relationship between clinical phenotype and brain atrophy. I used canonical correlation analysis (CCA) to identify canonical variates between the six principal components from the clinical feature data and the fifteen components from the imaging analysis (Tsvetanov *et al.*, 2018). All inputs were standardised into z scores before CCA. Pearson's correlations were corrected for multiple comparisons by estimating the false discovery rate using the *mafdr* function in MATLAB 2018b.

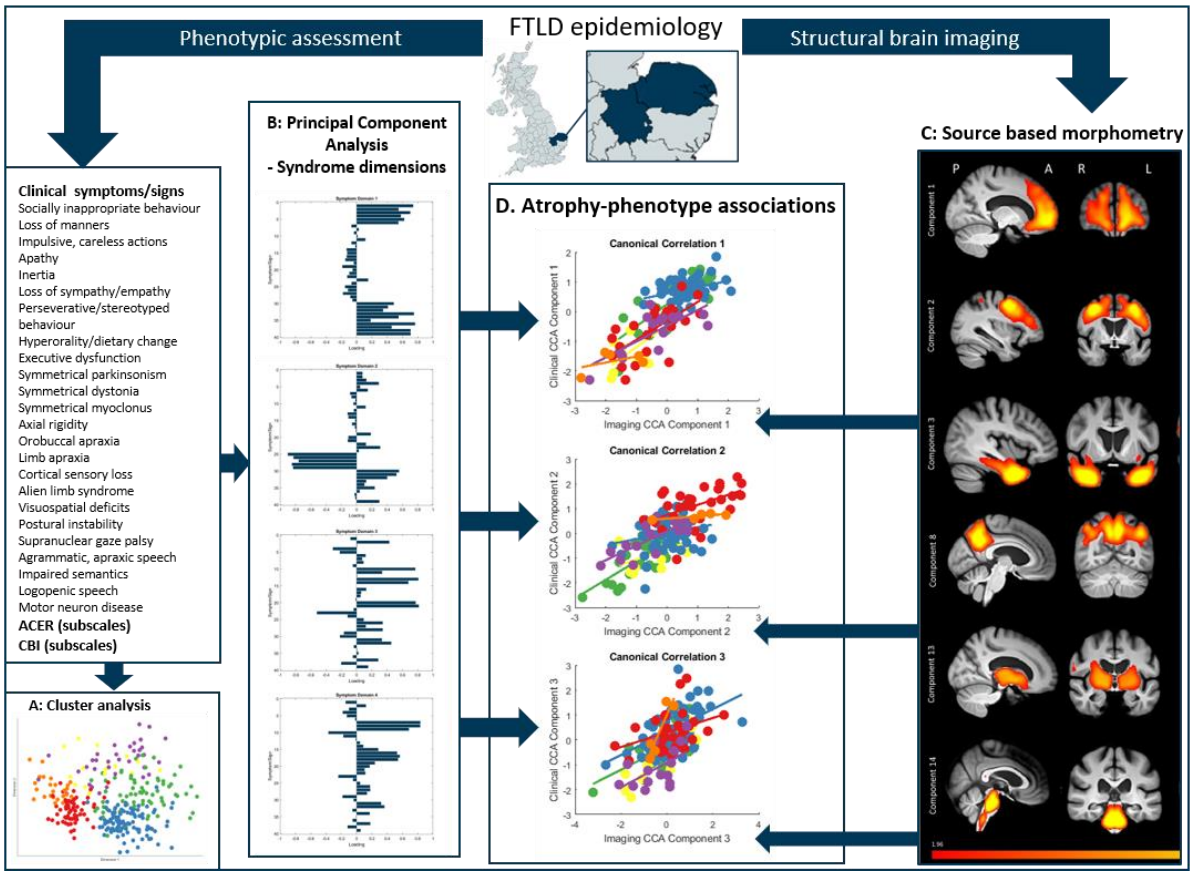


Figure 3-1: Schematic of data processing. First, patients were recruited from the study catchment area for phenotypic assessment and structural brain imaging. Second, a cluster analysis was performed on clinical features. Third, I performed a principal component analysis on all clinical features to find latent syndrome dimensions across FTLD. Fourth, I used source-based morphometry (independent component analysis on grey and white matter) created atrophy components. Finally, I then explored the relationship between phenotype (syndrome dimensions from the principal component analysis) and brain structure (source-based morphometry imaging components) using canonical correlation analysis.

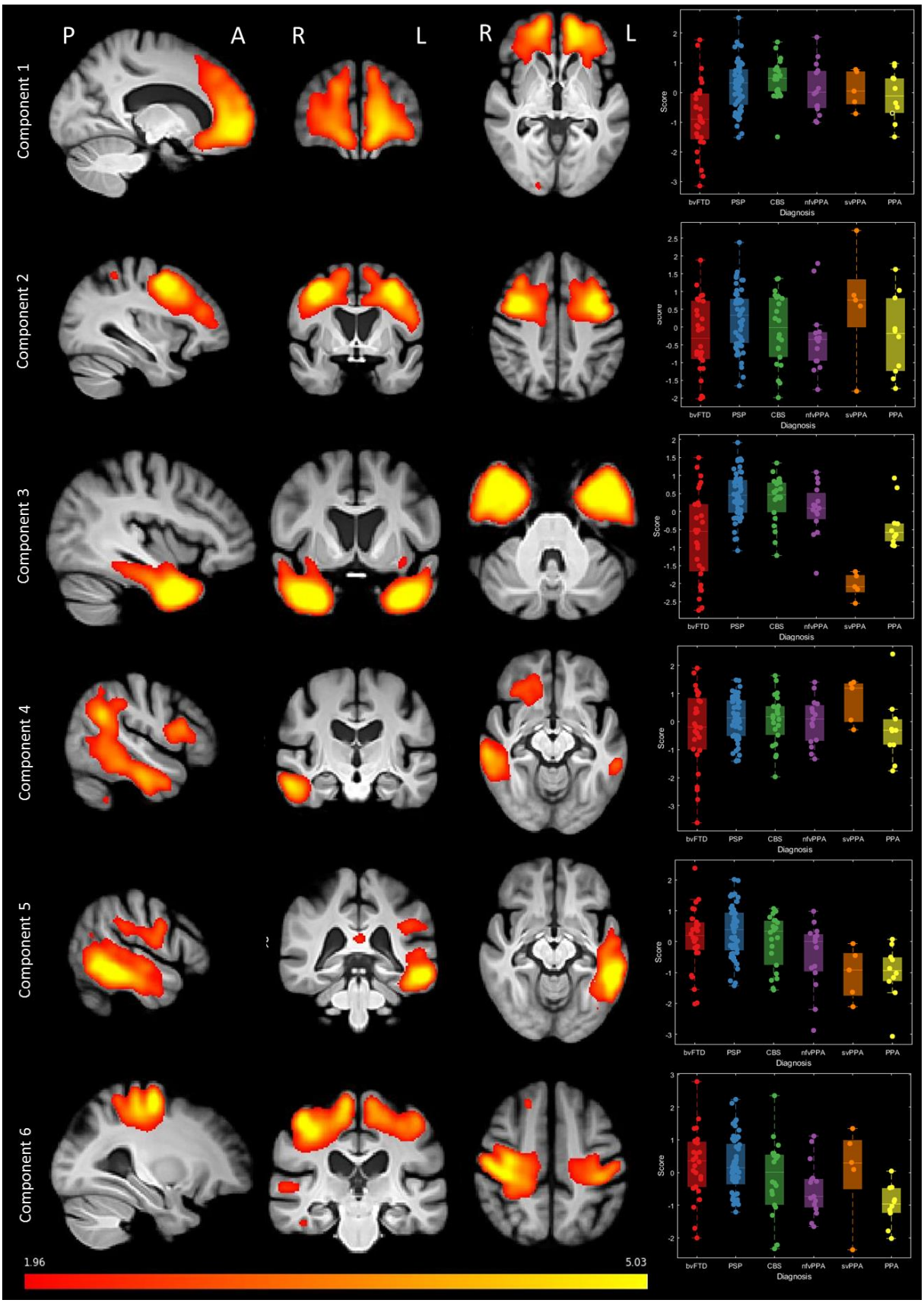
Results

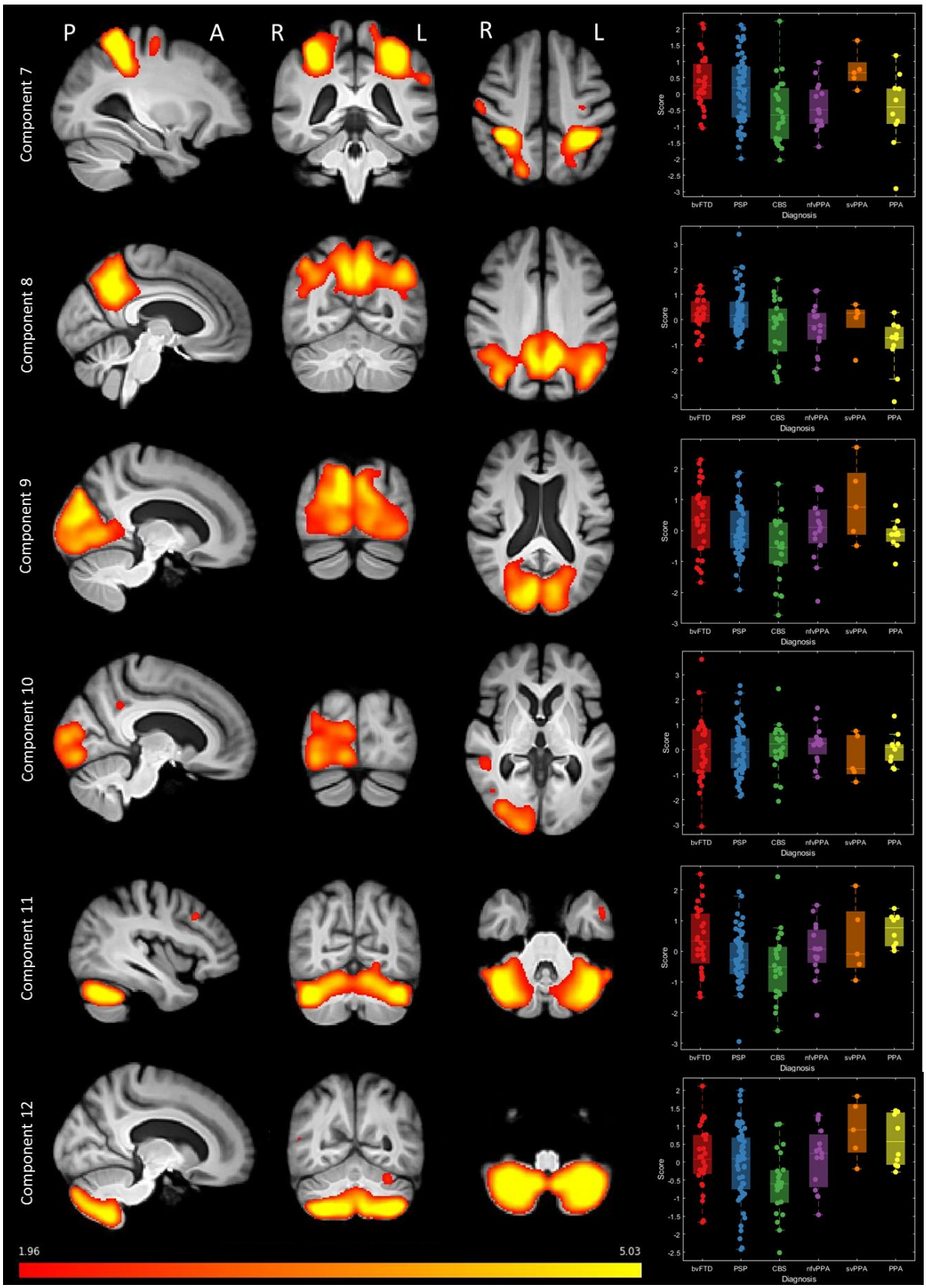
A subset of one hundred and thirty-nine patients (bvFTD n=28, nfvPPA n=15, svPPA n=5 PPA n=10, PSP n=53, CBS n=22) in the PIPPIN study had an MRI scan. The scanned subset of participants was similar to the population without a scan, with no statistically significant differences in age (t=0.65, p=0.52), sex (X^2=2.8, p=0.1), disease duration (t=0.69, p=0.49) or scores on syndrome dimensions 1,2,3,5, and 6 (all p>0.05 uncorrected). The differences in syndrome dimension 4 (t=2.41, p=0.016) indicated less severe global cognitive impairment in those who were scanned. Source based morphometry revealed fifteen significant structural components, each representing a pattern of covaried atrophy (Figure 3-2). The components had high stability across 100 ICASSO runs (mean=0.981, standard deviation=0.004).

	All groups	**bvFTD**	**nfvPPA**	**svPPA**	**PPA#**	**PSP**	**CBS**	**p***
Clinical phenotyping (n)	310	64	36	25	16	101	68	ns
MRI scan (n, % of phenotyped)	133 (43)	28 (44)	15 (41)	5 (20)	10 (62)	53 (52)	22 (32)	ns
Age (years, mean and SD)	69.98 (7.52)	66.11 (7.89)	71.95 (7.20)	69.75 (3.86)	58.58 (7.50)	72.16 (6.7)	69.29 (8.17)	0.019
Male/Female	60/70	14/14	5/9	0/5	6/4	22/29	13/9	ns
Duration of symptoms (years, mean and SD)	4.53 (2.87)	4.11 (2.79)	4.63 (2.56)	5.48 (2.90)	3.82 (1.61)	4.82 (3.45)	4.46 (2.18)	0.031
Diagnosis to study (years, mean and SD)	1.16 (1.23)	0.59 (0.62)	1.73 (1.36)	2.05 (1.22)	1.51 (1.41)	1.10 (1.17)	1.33 (1.52)	ns

Table 3-1: Demographics of the sub-set of the study cohort who underwent MRI. #lvPPA n=7, mixed PPA n=9. *P values are the result of ANOVA or Chi sqaured test for each row on FTLD subgroups, ns= not significant (p>0.05).

The loadings on these imaging components were not confined to single diagnostic groups (Figure 3-2). Imaging components one and two related to the frontal and prefrontal cortex; patients with bvFTD tended to have low scores on these components (i.e. atrophy), but many patients with nfvPPA, PSP and CBS also had low scores indicating a frontal cortical atrophy. Component three, with bitemporal atrophy, had very strong negative scores in all svPPA patients, but also many bvFTD patients. Component six represented atrophy in the motor cortex, with low scores in a subset of patients from all groups. Some participants with CBS, nfvPPA and PPA had negative scores on imaging component eight, which reflected biparietal atrophy. Only a few patients had significant atrophy in the occipital lobe, reflected by components nine and ten. Cerebellar atrophy, reflected by components eleven and twelve, was seen in some patients with bvFTD, PSP and CBS. Imaging component thirteen represented the volumes of corticospinal tracts and basal ganglia. Many patients with PSP, but also some patients with bvFTD, CBS and nfvPPA had low scores on this component. Component fourteen represented brainstem atrophy, with large negative scores in PSP and CBS but also some nfvPPA patients.


P
A
R
L
R
L
Component 1
Component 2
Component 3
Component 4
Component 5
Component 6
Score
bvFTD
PSP
CBS
nfvPPA
svPPA
PPA
Diagnosis
1.96
5.03


P
A
R
L
R
L
Component 7
Component 8
Component 9
Component 10
Component 11
Component 12
1.96
5.03
Score
bvFTD
PSP
CBS
nfvPPA
svPPA
PPA
Diagnosis

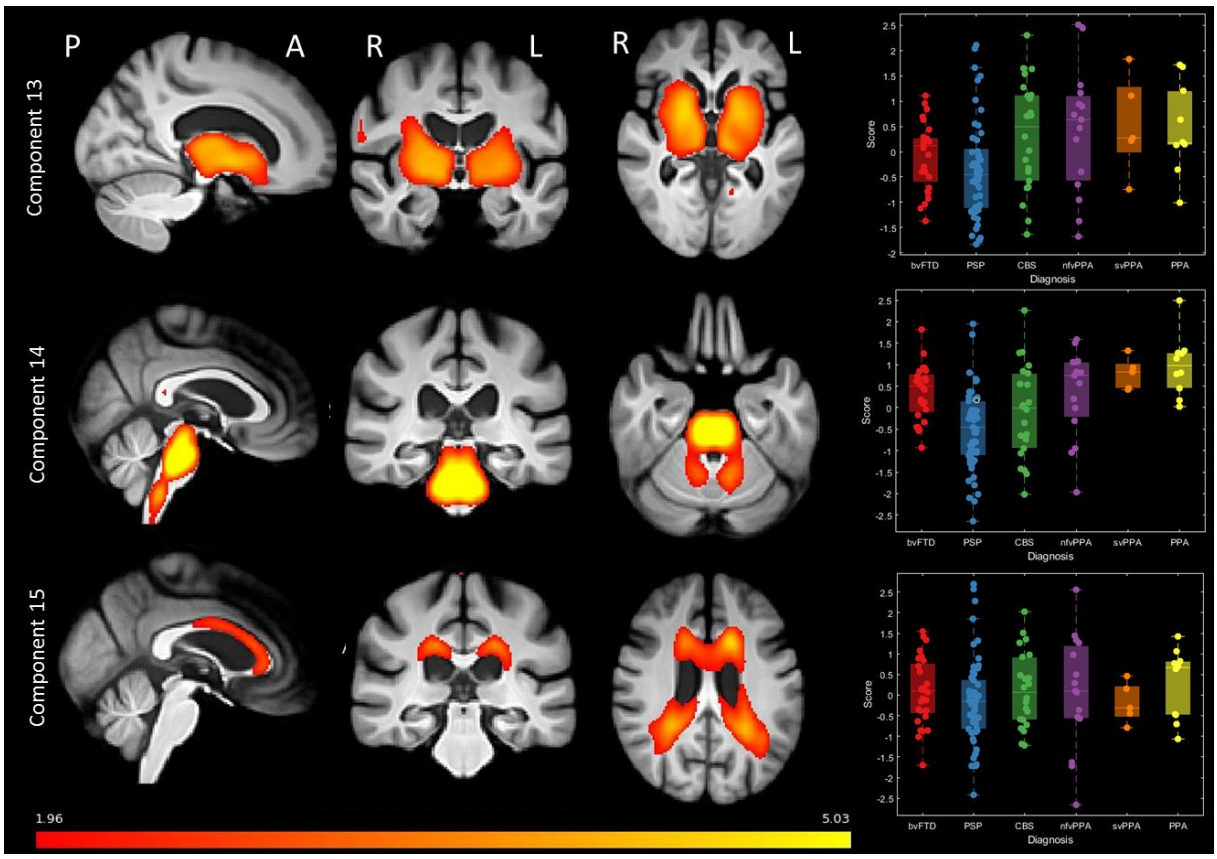


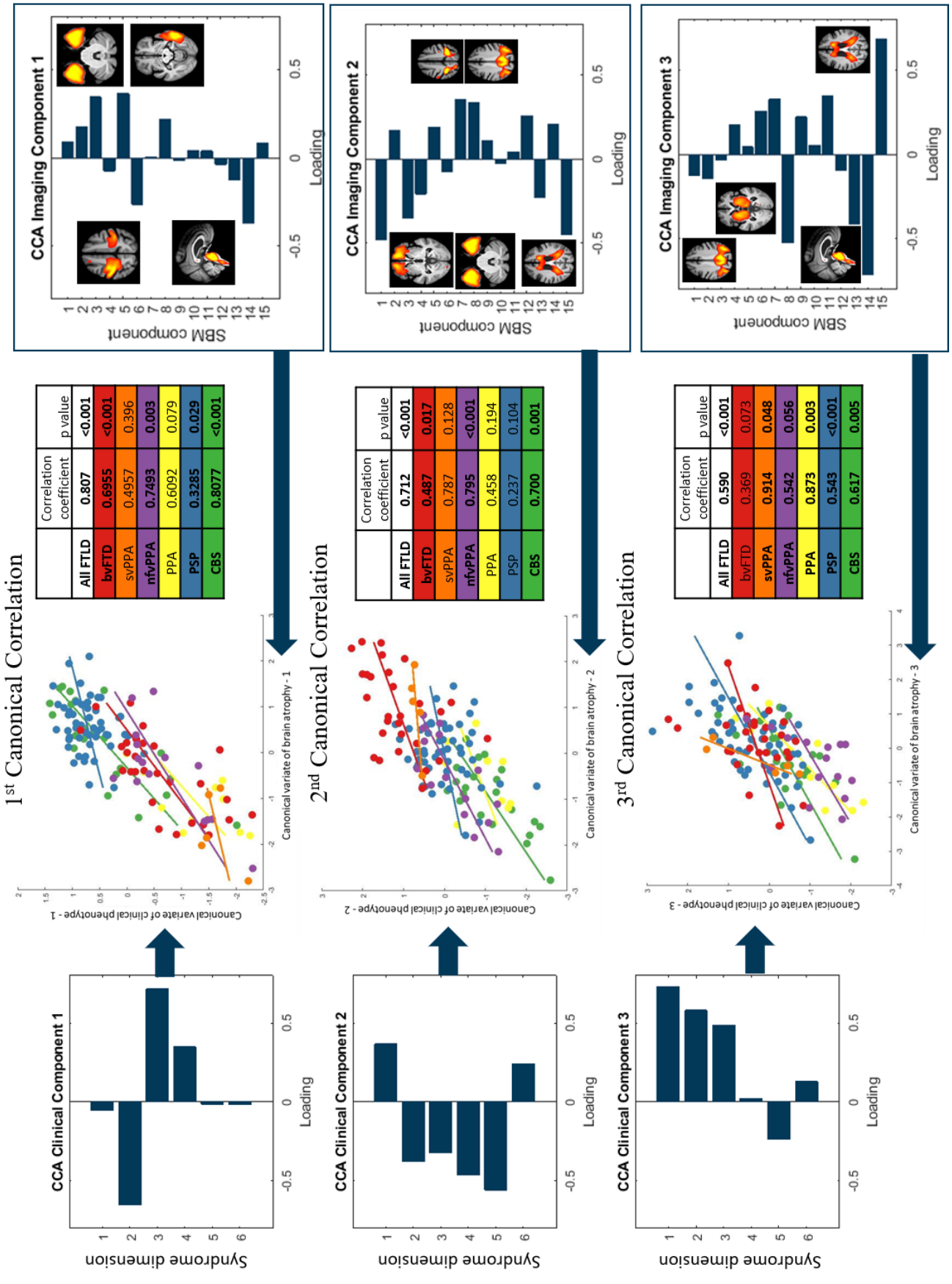
Figure 3-2: Source based morphometry of structural MRI images. Fifteen components were selected using the GIFT toolbox. Loadings for each voxel onto each component were standardised into z scores, thresholded at 1.96 and plotted onto an average brain from all participants. Sagittal, coronal and axial sections are shown for each component. A scatterboxplot for each component shows the score for each participant, grouped by FTLD subtype. Negative scores represent low brain volumes for that participant in the region represented by that component.

Next, I looked for structure-function correlations between the clinical and imaging components (Figure 3-3). Since both cognition and atrophy are intrinsically multivariate, I used canonical correlation analysis between the six cognitive dimension and fifteen atrophy components. Three canonical correlations were selected for further analysis (each $p<0.05$, rejecting the null hypothesis that the canonical correlation is zero). The first canonical correlation ($R=0.81$, $p<0.001$) represented the association between motor impairments (syndrome dimensions three and four) and relatively preserved cognition (syndrome dimension two) with motor cortex and brain stem atrophy (atrophy components six and fourteen). Patients with PSP, CBS and some patients with bvFTD had positive loadings, while patients with primary progressive aphasia (notably the svPPA subtype) and some with bvFTD had negative loadings (Figure 3-3). Four of the six FTLD subgroups had significant correlations in this canonical correlation: PSP (Pearson's R:0.33, p:0.03), CBS (R:0.81 p:<0.001), bvFTD R:0.70 p:<0.001) and nfvPPA (R:0.74 p:0.03) .

The second canonical correlation (R=0.71, p<0.001) represented another spectrum of cognitive and motor phenotypes correlating with different patterns of brain atrophy (B). Positive loadings, most common in bvFTD, svPPA and a subset of PSP, were associated with behavioural impairment (syndrome dimension 1) correlating with atrophy in the frontal and temporal lobes (atrophy components 1 and 3). Negative loadings, predominantly seen in CBS and a few patients with nfvPPA and mixed PPA, were associated with global cognitive impairment, apraxia, cortical sensory loss and language impairments correlating with atrophy in the parietal cortex (atrophy components 7 and 8).bvFTD (R=0.49, p=0.02), nfvPPA (R=0.79 p=0.001) and CBS (R=0.7, p=0.001) most contributed to this canonical variate.

The third canonical correlation (R=0.58 p<0.001) represented a combination of behavioural, cognitive and motor symptoms in association with atrophy in motor and parietal cortices, basal ganglia and brainstem (Figure 3-3). This canonical correlation had positive loadings across a wide range of diagnoses, with no clear group separation. This canonical variate was driven by CBS (R=0.62 p=0.005), PSP (R=0.54 p<0.001) and PPA (R=0.87 p=0.002) subgroups with a weaker contribution from svPPA (R=0.91, p=0.048). The three residual, unselected canonical covariates did not correlate in any FTLD subgroup.

Figure 3-3 (on next page): Canonical correlation analysis of clinical (syndrome dimensions from PCA) and imaging (atrophy components from SBM) components. The left column shows the loading plots from each syndrome domain onto the first, second and third clinical canonical components respectively. The right column shows the atrophy component loadings onto the imaging canonical components. The middle plots show the correlations between the clinical and imaging components. The table shows the correlations for each subgroup. P values are false discovery rate corrected for multiple comparisons and p<0.05 highlighted in blue.


1st Canonical Correlation
2nd Canonical Correlation
3rd Canonical Correlation
CCA Imaging Component 1
CCA Imaging Component 2
CCA Imaging Component 3
SBM component
Loading
CCA Clinical Component 1
CCA Clinical Component 2
CCA Clinical Component 3
Syndrome dimension
Canonical variate of clinical phenotype - 1
Canonical variate of clinical phenotype - 2
Canonical variate of clinical phenotype - 3
Canonical variate of brain atrophy - 1
Canonical variate of brain atrophy - 2
Canonical variate of brain atrophy - 3
All FTLD 0.807 <0.001
bvFTD 0.6955 <0.001
svPPA 0.4957 0.396
nfvPPA 0.7493 0.003
PPA 0.6092 0.079
PSP 0.3285 0.029
CBS 0.8077 <0.001
All FTLD 0.712 <0.001
bvFTD 0.487 0.017
svPPA 0.787 0.128
nfvPPA 0.795 <0.001
PPA 0.458 0.194
PSP 0.237 0.104
CBS 0.700 0.001
All FTLD 0.590 <0.001
bvFTD 0.369 0.073
svPPA 0.914 0.048
nfvPPA 0.542 0.056
PPA 0.873 0.003
PSP 0.543 <0.001
CBS 0.617 0.005

Discussion

In this chapter, I used a data-driven analysis of frontotemporal lobar degeneration syndromes to confirm the hypothesis that individual atrophy patterns are not confined to specific diagnostic groups, but instead exist as a multidimensional spectrum that matches the spectrum of clinical phenotypes reported in the previous chapter.

The imaging cohort was generally representative of the whole FTLD population, with similar weightings across five out of six dimensions and demographics. Participants who underwent MRI were less affected in the global cognitive impairment syndrome dimension, likely due to the practical difficulties of scanning participants with advanced dementia. Frontal lobe atrophy patterns were seen in participants from all groups, especially bvFTD and PSP. Subcortical atrophy was more prevalent in PSP and CBS but was also seen in bvFTD and PPA, and a majority of bvFTD patients had negative scores on the basal ganglia imaging component. This has been noted previously in symptomatic bvFTD and PPA (Schroeter *et al.*, 2007; Bocchetta *et al.*, 2018), and those at genetic risk of FTD (Rohrer *et al.*, 2015*b*). Brainstem atrophy, while characteristic of PSP (Whitwell *et al.*, 2017*a*), was also seen in some patients with CBS and nfvPPA, but this has previously been shown not to predict PSP pathology (Whitwell *et al.*, 2013). The source based morphometry approach also revealed a group of patients who are not well accommodated in the current diagnostic criteria. Five patients with a nominal diagnosis of bvFTD had very low scores on the right temporal lobe imaging component, and these might better be called the right variant of semantic dementia, which causes a combination of behavioural and semantic impairments with prosopagnosia (Chan *et al.*, 2009; Kumfor *et al.*, 2016). A subset of patients with CBS and mixed PPA had negative scores on component 8, indicating posterior cortical atrophy. These patients may speculatively be more likely to have Alzheimer's Disease pathology (Lee *et al.*, 2011*b*).

Many studies have correlated clinical syndromes with structural change, using computational morphometry on volume, thickness, curvature or cortical diffusivity. Typically, these compare patient groups to each other or to controls, to reveal group-based patterns of atrophy in bvFTD (Schroeter *et al.*, 2007; Whitwell *et al.*, 2012, Ranasinghe *et al.*, 2016*b*; Meeter *et al.*, 2017, Perry *et al.*, 2017*a*, Chen *et al.*, 2018*b*; Illán-Gala *et al.*, 2019), svPPA (Raisner *et al.*, 2005; Schroeter *et al.*, 2007; Kumfor *et al.*, 2016), nfvPPA (Raisner *et al.*, 2005; Schroeter *et al.*, 2007; Santos-Santos *et al.*, 2016), PSP (Brenneis *et al.*, 2004; Lagarde *et al.*, 2013; Piattella *et al.*, 2015; Dutt *et al.*, 2016, Whitwell *et al.*, 2017*a*, 2019) and CBS (Josephs *et al.*, 2010; Whitwell *et al.*, 2010; Dutt *et al.*, 2016). However, these previous methods are limited by the

categorical approach to diagnosis. In order to reveal the associations between phenotypic features and structural change, across diagnostic groups, I used source based morphometry to identify regions of covarying atrophy patterns (Xu *et al.*, 2009).

I identified three significant canonical "structure-function" correlations in the cohort (Figure 3-3). These represent the spectrums of anatomical change underlying behavioural, motor and language impairments. These structure-function correlations did not replicate classical nosological distinctions. Instead they provide an alternative data-driven approach with which to understand and target treatments for syndromes associated with FTLD. The first canonical correlation found an association between motor cortex and brainstem atrophy with PSP or CBS-like motor impairments. Unsurprisingly, PSP and CBS had significant correlations between these canonical covariates but so did bvFTD and nfvPPA, reflecting the motor impairments that are seen in a subgroup of these patients. The second canonical correlation represented the spectrum between frontotemporal (positive scores) and posterior cortical atrophy (negative scores). This canonical covariate may differentiate FTLD from Alzheimer's disease pathology, as negative scores on this imaging covariate resemble an AD-like atrophy pattern. The third canonical covariate was associated with significant correlations in all FTLD subgroups apart from bvFTD, and encompassed a range of cognitive, behaviour and motor clinical features associated with cortical and subcortical atrophy.

There are several limitations with these results. First, the brain metrics I used are only crude measures of atrophy. Other brain measures, of brain elasticity , white matter tracts (Mahoney *et al.*, 2015; Staffaroni *et al.*, 2019), tau burden (Passamonti *et al.*, 2017, Whitwell *et al.*, 2017*b*; Bevan-Jones *et al.*, 2020), synaptic density (Chen *et al.*, 2018*a*), physiology (Hughes *et al.*, 2018*a*; Sami *et al.*, 2018) and functional connectivity (Seeley *et al.*, 2009; Rittman *et al.*, 2019; Tsvetanov *et al.*, 2019) may enrich the source based morphometric approach, integrating PET markers of pathology (Passamonti *et al.*, 2019) or spectroscopic measures of the neurotransmitter deficits in FTLD (Kantarci *et al.*, 2010; Murley and Rowe, 2018). Second, the syndrome dimensions used in the analysis are broad, for example syndrome dimension 1 relates to global behavioural disturbance and syndrome dimension 2 to global cognitive impairment. The syndrome-atrophy correlations in this chapter are similarly broad. Including more detailed neuropsychology would give greater information on the neurobiology of specific behavioural and cognitive deficits which may have greater relevance for targeted symptomatic treatments.

Another limitation is the potential for heterogeneous and/or multiple pathologies, in which several pathogenic protein inclusions may co-exist and be synergistic in neurodegeneration (Robinson *et al.*, 2018). The results in this and the previous chapter would be strengthened by neuropathological results, to test the phenotype-pathology and atrophy-pathology correlations of FTLD.

Neuropathology of the frontotemporal lobar degeneration syndrome spectrum

Preface

The brain donation, tissue preparation and neuropathological assessment was performed by members of the Cambridge Brain Bank, including the lead neuropathologist Dr Kieran Allison. I performed all the data analysis and wrote all the text in this chapter. Some of the results shown here are included in supplementary materials of this manuscript in preparation (Murley *et al.*, 2020*a*)

Summary

In this chapter, I report the interim neuropathological results from the PIPPIN study, which replicate the clinicopathological correlations in other FTLD cohorts. I go on to show the neuropathological correlations of the syndrome dimensions, atrophy components and phenotype-atrophy correlations reported in the previous two chapters. I then look at the accuracy of classifiers (linear discriminant analysis and decision trees with leave-one-out cross validation) to predict the major neuropathology subtypes (FTLD-tau vs. FTLD-TDP43 vs. AD). The syndrome dimensions are marginally more accurate than current syndrome labels (overall accuracy 77% vs 67%).

Introduction

The neuropathology of FTLD is heterogeneous and clinicopathological correlations are inconsistent. Some syndromes associated with FTLD have good specificity, for example PSP-Richardson's Syndrome (PSPRS) for FTLD-tau or svPPA for TDP43. However, syndromes with high specificity may have poor sensitivity if the same neuropathology causes other clinical phenotypes (Respondek *et al.*, 2014; Gazzina *et al.*, 2019). Trials of potential disease modifying therapies in FTLD typically require a syndrome with high specificity, to avoid including patients with a different pathology who are unlikely to benefit. This excludes patients with the same pathology but a different clinical phenotype (eg bvFTD or CBS due to PSP pathology) which reduces study power and external validity. The absence of effective biomarkers for FTLD pathology (Meeter *et al.*, 2017) means that many FTLD syndromes are therefore unsuitable candidates for clinical trials. There is an urgent need to improve clinicopathological correlations in FTLD syndromes.

In this chapter, I will test the predictive accuracy of the transdiagnostic, spectrum-based approach to FTLD syndromes that I used in the previous chapters. There have been previous attempts to refine clinical phenotyping to improve clinicopathological correlation, over and above FTLD subtype. For example, motor neuron disease, when seen in patients with FTLD syndromes, is predictive of FTLD-TDP43 (Mackenzie, 2007; Josephs *et al.*, 2011). However, no other clinical features can accurately distinguish FTLD-TDP43 from FTLD-tau in bvFTD (Perry *et al.*, 2017*a*). Both semantic impairment and extrapyramidal features are seen in bvFTD with either pathology (Perry *et al.*, 2017*a*). Corticobasal syndrome is most commonly associated with FTLD-tau or Alzheimer's disease pathology (Alexander *et al.*, 2014) and visual neglect, when seen in CBS, is more predictive of Alzheimer's disease pathology (Lee *et al.*, 2011*b*). However, this is not a common feature of CBS and in most patients it is not possible to differentiate CBS-AD from CBS-CBD using clinical phenotype (Hu *et al.*, 2009*a*, Lee *et al.*, 2011*b*). In summary, there is limited evidence that phenotypic variation within FTLD subtypes can predict pathology.

Aims and hypotheses

The aim of this chapter was to investigate the clinicopathological correlations in syndromes associated with FTLD, using the neuropathology results from the PIPPIN study. Specially, I hypothesised that a transdiagnostic, spectrum approach to FTLD clinical phenotype would better predict neuropathology than diagnostic subgroup.

Methods

Brain donation and post-mortem assessment

All patient participants in PIPPIN study were approached to consider brain donation. Participants consented to brain donation via a declaration of intent, with further assent from their next of kin after their death. All brain donation and neuropathological examination took place at the Cambridge Brain Bank at Cambridge University Hospitals NHS Foundation Trust. Brain removal took place as quickly as possible after death for processing. After removal, the brain was divided into two hemispheres along the sagittal midline. The left cerebral hemisphere, hemi-brainstem and cerebellum was fixed in 10% formalin for 2-3 weeks and the right side of the brain was frozen. Neuropathological diagnosis, and the results in this chapter, are from the left side of the brain. Dr Kieran Allison, lead neuropathologist at the Cambridge Brain Bank, assessed all brains from patients in the PIPPIN study while blinded to the patient's clinical diagnosis.

Neuropathological assessment followed a defined protocol. The whole brain was weighed and the left hemisphere was then assessed macroscopically. Macroscopic examination started with inspection of the leptomeninges and cerebral cortex for haemorrhage, exudate and/or volume loss. Coronal slices were then examined for ischaemic lesions and to assess ventricle size. Next, axial slices were used for macroscopic examination of subcortical structures such as the substantia nigra and locus coeruleus, assessing for atrophy and loss of pigmentation. Microscopic examination was performed on samples from the anterior prefrontal, inferior frontal, primary motor and premotor, primary somatosensory, parietal, fusiform, angular, middle and superior temporal gyri, entorhinal cortex, hippocampus, basal ganglia (putamen and globus pallidus), hypothalamus, thalamus, internal capsule, midbrain, pons and cerebellum. Silver and Nissl stains were used to assess neuronal density and morphology. Immunohistochemistry was used to identify the pathological protein aggregates tau (antibody to tau11/57 from 2010 to mid-2016 and AT8 from mid-2016 to date, MN1020, Thermo Scientific, USA), TDP43 (TIP-PTD-P02, Cosmo Bio Co Ltd, Japan), alpha-synuclein (SA3400, Enzo Life Sciences, USA) and beta-amyloid (Clone 6F/3D, M0872, Dako, Denmark). The hippocampus and entorhinal cortex were assessed first then other brain regions were stained as required, to make a diagnosis and to enable disease staging. The final neuropathological diagnosis, based on macro and microscopic neuropathological findings, was used for the analyses reported in this chapter. Mixed or combined neuropathology is increasingly recognised

in neurodegenerative diseases, but all patients in this study had a single predominant neuropathology to allow a single final diagnosis.

Data analysis

The demographic characteristics of patients in the brain bank were compared with the whole PIPPIN cohort with two tailed independent t tests for continuous variables and Chi squared test for categorical variables. Multivariate supervised pattern recognition was used to test the classification accuracy of either FTLD subtype (bvFTD, nfvPPA, svPPA, lv/mixed PPA, PSP and CBS) or FTLD syndrome dimensions (the six components from the clinical phenotype principal component analysis from Chapter 2) for FTLD neuropathology. I grouped neuropathological diagnoses into four groups: FTLD-tau (which included Pick's disease, PSP and CBD), FTLD-TDP43 (all subtypes), Alzheimer's Disease and Other.

Different classification models were used for FTLD subtype, which is one categorical variable, and syndrome dimension, which has six continuous variables. A binary decision tree was trained for FTLD subtype. In decision tree analysis, a set of decisions rules is found that best explain the relationship between the predictor (FTLD syndrome subtype) and outcome (FTLD neuropathology) variables. This results in a "tree" of binary decisions that can intuitively be used for new participants (Myles *et al.*, 2004). Decision tree models are appropriate for categorical data and are easily interpretable. However, they are less suitable for continuous and multivariate datasets because they force binary splits in the data and can only consider one variable at a time. Linear discriminant analysis was used for the syndrome dimension classification. This model finds a linear combination of features that separates groups (Balakrishnama and Ganapathiraju, 1998). Linear discriminant analysis is appropriate when class sizes are unequal and there are multiple continuous predictor variables. Both models were weighted by the relative prevalence of each disease group in the population, syndromes that were more prevalent in the brain bank than the population were down weighted and *vice-versa* (

Table 4-1).

FTLD syndrome	bvFTD	nfvPPA	svPPA	PPA (lv/mixed)	PSP (all)	CBS
Number in brain bank	7	4	4	1	14	9
Relative brain bank prevalence	0.1429	0.0816	0.0816	0.0204	0.2857	0.3878
Population prevalence	38	25	21	11	48	38
Relative population prevalence	0.2099	0.1381	0.1160	0.0608	0.2652	0.2099
Classifier weight	1.4696	1.6920	1.4213	2.9779	0.9282	0.5414

Table 4-1: Weighting to match brain bank to population prevalence for each FTLD syndrome in the PIPPIN catchment area. Population prevalence data taken from Coyle-Gilchrist et al, 2016, which first reported epidemiological results from the PIPPIN study.

Classification techniques, including decision tree and linear discriminant analysis, are vulnerable to overfitting (Hawkins, 2004). Overfitting occurs when a classifier fits the data it is trained on too closely. An overfitted model is neither generalisable nor accurate when predicting new, unseen data. To prevent this, I used leave-one-out cross validation for both classifiers. Before training the classifier one participant is removed, the model is then trained on the residual dataset and then tested on the left-out participant. This is repeated so that every participant is tested. The model accuracy is determined from the mean accuracy of the predictions of all test cases.

Finally, I looked at the neuropathological correlates of the brain morphology components from Chapter 3. Only a small number of patients had a complete dataset (clinical review, MRI and neuropathology) which prevented statistical analyses. All analysis was performed in MATLAB 2018b (MathWorks, USA) with the standard functions.

Results

Forty-nine patients reviewed in PIPPIN study had a *post-mortem* pathological diagnosis by 1st November 2019. Demographic details of the patients in the brain bank are in Table 4-2. Patients in the brain bank had a similar age and gender distribution compared to the whole study population ($p>0.05$) but on average were assessed later in their illness ($t=2.67$, $p=0.008$). A breakdown of neuropathology results by FTLD syndrome subtype are shown in Table 4-3 and Figure 4-1. All patients with a clinical diagnosis of PSP had PSP pathology (n=14). Most patients with svPPA had FTLD-TDP-43 Type C (n=3) but one had Pick's disease. bvFTD was associated with FTLD-tau (Picks' n=1, PSP n=1) or TDP43 (n=5). Three patients with bvFTD had motor neuron disease, all with TDP43 pathology. Most patients with CBS had either CBD (n=6) or Alzheimer's disease (8). Two CBS patients had Multiple System Atrophy pathology and one had micro metastatic renal cell carcinoma and paraneoplastic cerebellar degeneration. Of the four patients with nfvPPA three had FTLD-tau and one had Alzheimer's disease. The one patient with lvPPA had Alzheimer's Disease pathology.

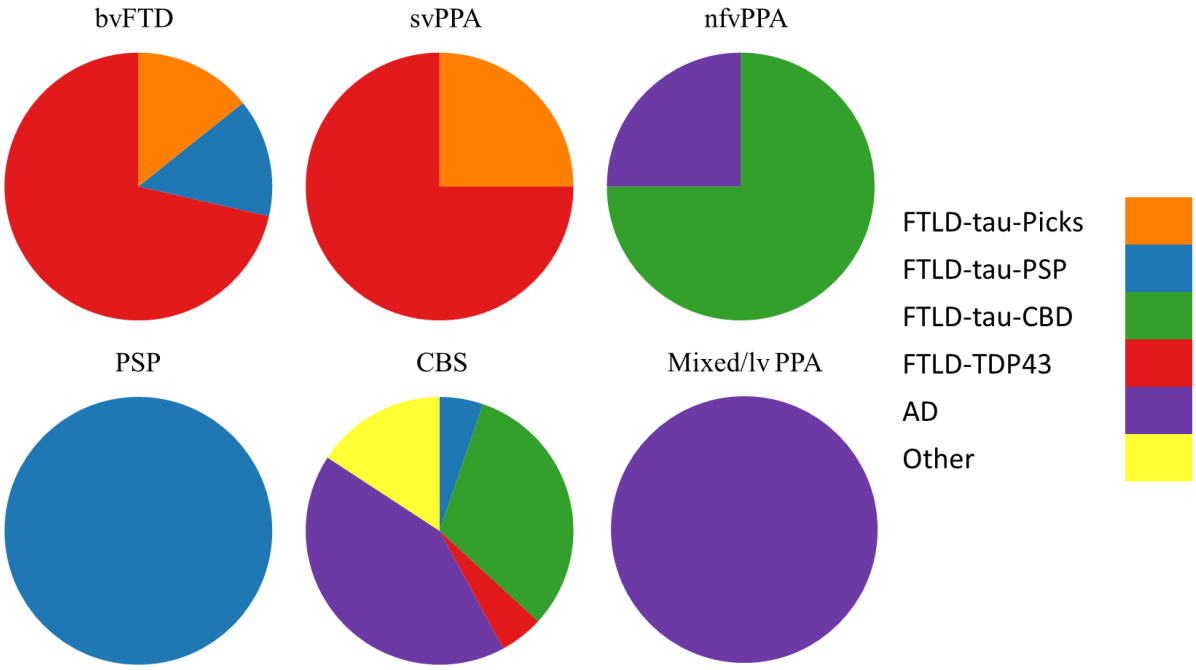


Figure 4-1: Pie charts of clinicopathological correlations for each FTLD syndrome. This is a visual representation of the data shown in Table 4-3

	All FTLD	bvFTD	nfvPPA	svPPA	PPA	PSP	CBS
Number in brain bank	49	7	4	4	1	14	18
Age, years (mean and SD)	71.10 (7.54)	69.22 (8.38)	78.76 (3.76)	69.24 (2.20)	74.98 (NA)	70.74 (7.81)	70.61 (7.70)
Male/Female	27/22	5/2	3/1	3/1	0/1	9/5	7/12
Time from diagnosis to study review (mean and SD)	2.23 (2.17)	1.28 (1.46)	2.03 (2.04)	3.33 (2.42)	4.28 (NA)	1.22 (1.13)	2.86 (2.50)
Time from study review to death (mean and SD)	2.30 (1.88)	1.74 (1.34)	2.66 (41)	5.15 (3.34)	0.84 (NA)	1.94 (1.19)	2.17 (1.60)

Table 4-2: Demographics of the subset of the study cohort in the brain bank

	FTLD-tau-Picks	FTLD-tau-PSP	FTLD-tau-CBS	FTLD TDP-43	AD	Other	Total
bvFTD	**1**	**1**	0	**5**	0	0	**7**
nfvPPA	0	0	**3**	0	**1**	0	**4**
svPPA	**1**	0	0	3	0	0	**4**
lvPPA	0	0	0	0	**1**	0	**1**
PSP	0	14	0	0	0	0	**14**
CBS	0	**1**	**6**	**1**	**8**	**3**	**19**
Total	**2**	**16**	**9**	**9**	**10**	**3**	**49**

Table 4-3: Neuropathology results: each cell contains total number of patients with the respective clinical syndrome and neuropathological diagnosis.

In four patients a second neuropathology was included in the final neuropathological diagnosis. One brain with PSP pathology had alpha-synuclein deposition suggestive of Parkinson's disease. This patient had an atypical clinical phenotype, with a 15-year history of symptoms, initially with a slowly progressive Parkinson's disease-like phenotype that responded well to levodopa. Two years before death they developed a more rapidly progressive syndrome with cognitive impairment, falls, a supranuclear gaze palsy and asymmetrical apraxia and dystonia. Two patients, one with lvPPA and one with nfvPPA, had primary Alzheimer's disease pathology (both Braak stage VI) with a secondary pathology of TDP43 confined to the medial temporal lobe. The final patient had a clinical diagnosis of corticobasal syndrome but at *post-mortem* had Alzheimer's disease (Braak stage VI), Lewy body disease (Braak stage III), temporal lobe TDP43 deposition and cerebrovascular disease. One patient with CBS had a *post-mortem* diagnosis of paraneoplastic cerebellar degeneration and micro metastatic renal cell carcinoma throughout the cerebral and cerebellar white matter. He was diagnosed with renal cell carcinoma in life but had no evidence of metastatic disease for over 3 years until a lung metastasis was diagnosed shortly before he died. He had no detectable serum autoimmune or paraneoplastic antibodies during the workup of his corticobasal syndrome.

First, I looked at the neuropathological diagnoses across the FTLD clinical syndrome dimensions, reported in detail in Chapter 2. Figure 4-2 shows the neuropathology results for each syndrome dimension, broken down by subgroup. Behavioural (syndrome dimension 1) and global cognitive impairment (dimension 2) did not help differentiate neuropathological subtypes. Two syndrome dimensions did help separate neuropathology. Syndrome dimension 3, reflecting the opposing features of a supranuclear gaze palsy and symmetrical and axial parkinsonism (positive loading) with semantic impairment (negative loading) appeared to separate FTLD-tau (high scores) from FTLD-TDP43 (low scores). The one patient with bvFTD and PSP pathology had a high score on this domain and all patients with TDP-43 had low scores. One patient with corticobasal syndrome and PSP pathology had a low score, in contrast to most cases of PSP pathology. All patients with Alzheimer's disease pathology, which manifested as CBS, nfvPPA or lvPPA syndromes, had positive scores on syndrome dimension 5. This dimension had high loadings from agrammatic, apraxic and logopenic speech, limb apraxia and myoclonus.

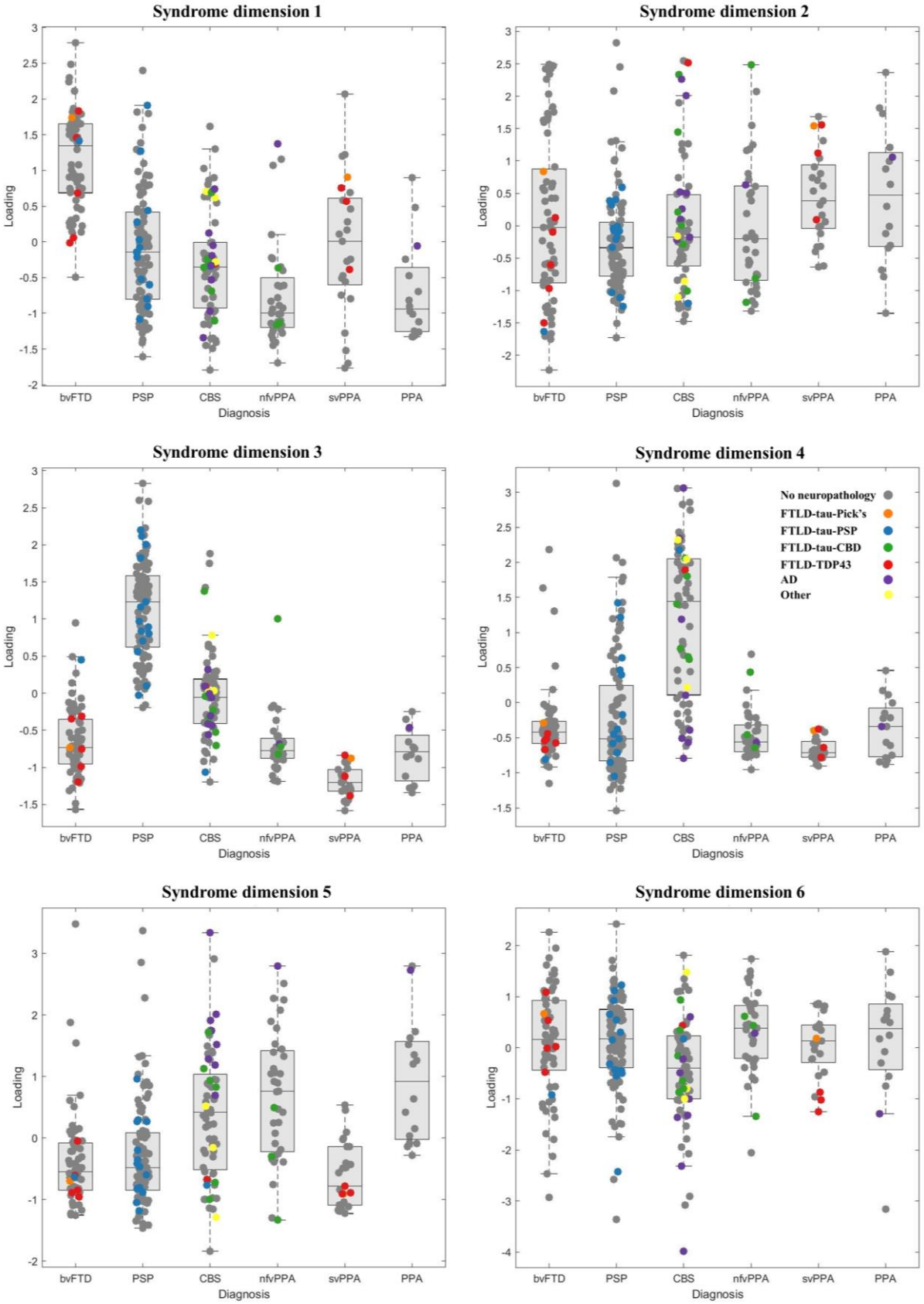


Figure 4-2: Boxplots of the participant scores on each syndrome dimensions reported in detail in Chapter 2. Scatter plots are colour coded by neuropathological diagnosis. Participants coloured grey were either still alive at the time of analysis or did not have a neuropathological diagnosis.

I then tested the clinicopathological accuracy of the FTLD syndrome dimensions and FTLD syndrome subtype. FTLD pathology subtypes were grouped into FTLD-tau, FTLD-TDP43, Alzheimer's Disease and other neuropathology, due to low numbers in some groups. A decision tree model was used to test the accuracy of FTLD syndrome subtype in predicting neuropathology. This model had a leave-one-out cross validated accuracy of 67%. It used the diagnostic labels bvFTD and svPPA to predict FTLD-TDP43, CBS and mixed/lvPPA for Alzheimer's disease pathology and PSP and nfvPPA to predict FTLD-tau (Figure 4-3). The confusion matrix, positive predictive values and true positive rates are shown in Figure 4-4. FTLD syndrome subtype had high positive predictive value for FTLD-tau (89.5%) but the true positive rate was low (63%). The positive predictive value and true positive rates were high for FTLD-TDP43 but low for Alzheimer's disease pathology.

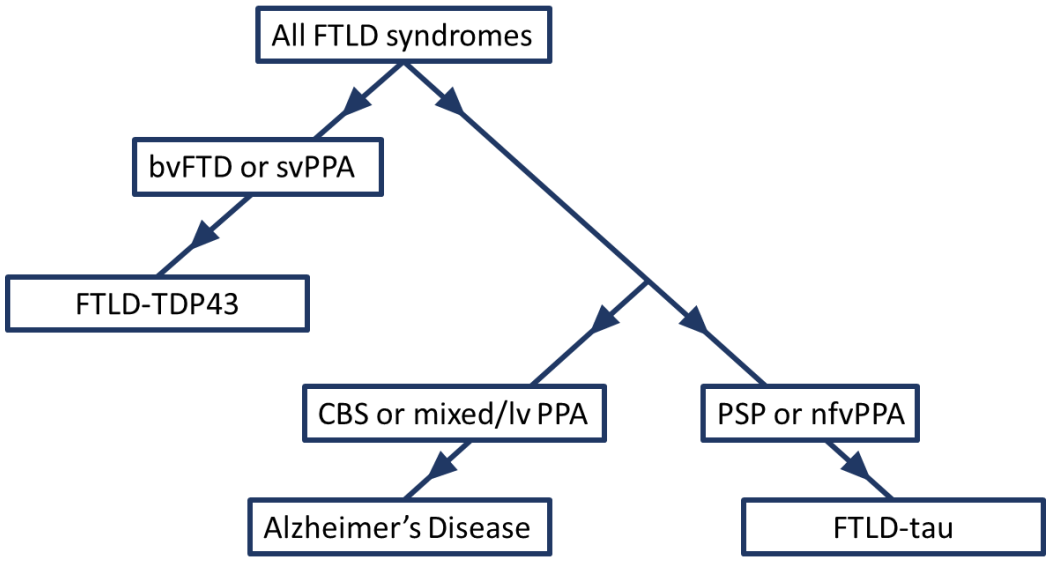


Figure 4-3: Decision tree using FTLD syndrome subtype to predict pathology.

A linear discriminant analysis was used to test the accuracy of the FTLD syndrome dimensions in predicting neuropathology. The overall leave-one-out cross validated accuracy of the FTLD syndrome dimensions in predicting neuropathology was slightly higher than FTLD subtype (77% vs 67%). Adding FTLD subgroup, in the form of dummy binary variables, to the FTLD dimension data did not improve classification accuracy. The confusion matrix, positive predictive values and true positive rates are shown in Figure 4-5. Compared to the decision tree model, the positive predictive value and true positive rates were high for FTLD-tau and Alzheimer's disease, but lower for FTLD-TDP43.

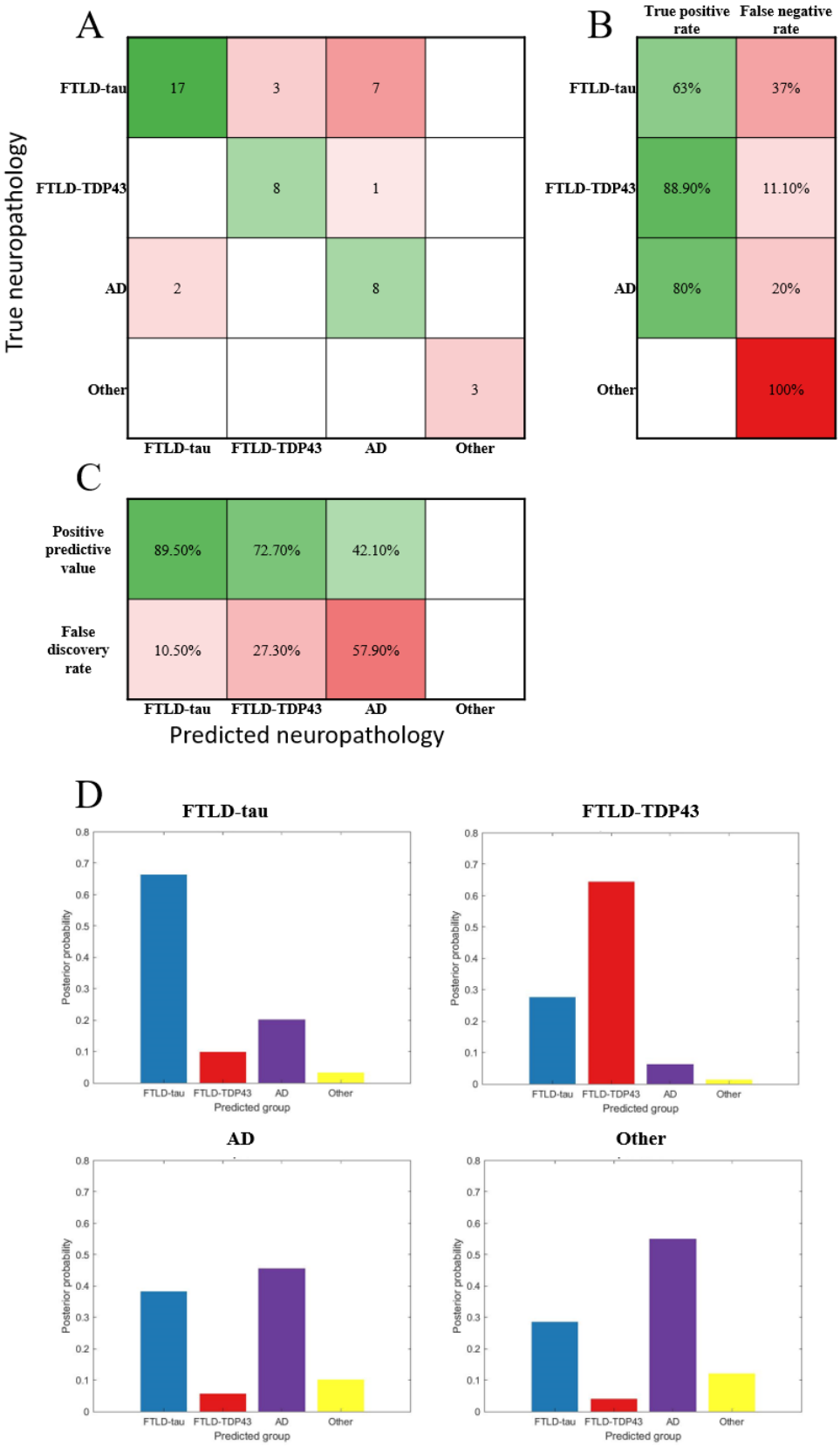


Figure 4-4: Accuracy of decision tree model predicting FTLD pathology from syndrome subtype. A: Confusion matrix of accurate (green) and inaccurate (red) predictions from the decision tree. Numbers in each cell are the total number with the corresponding predicted (x axis) and true (y axis) neuropathology. B: True and false positive rates for each pathology. C: Positive predictive value and false discovery rate for each pathology. D: Posterior probabilities for each pathology. Each bar chart shows a true neuropathology, and the height of each bar shows the probability that the true neuropathology was given that pathological label.

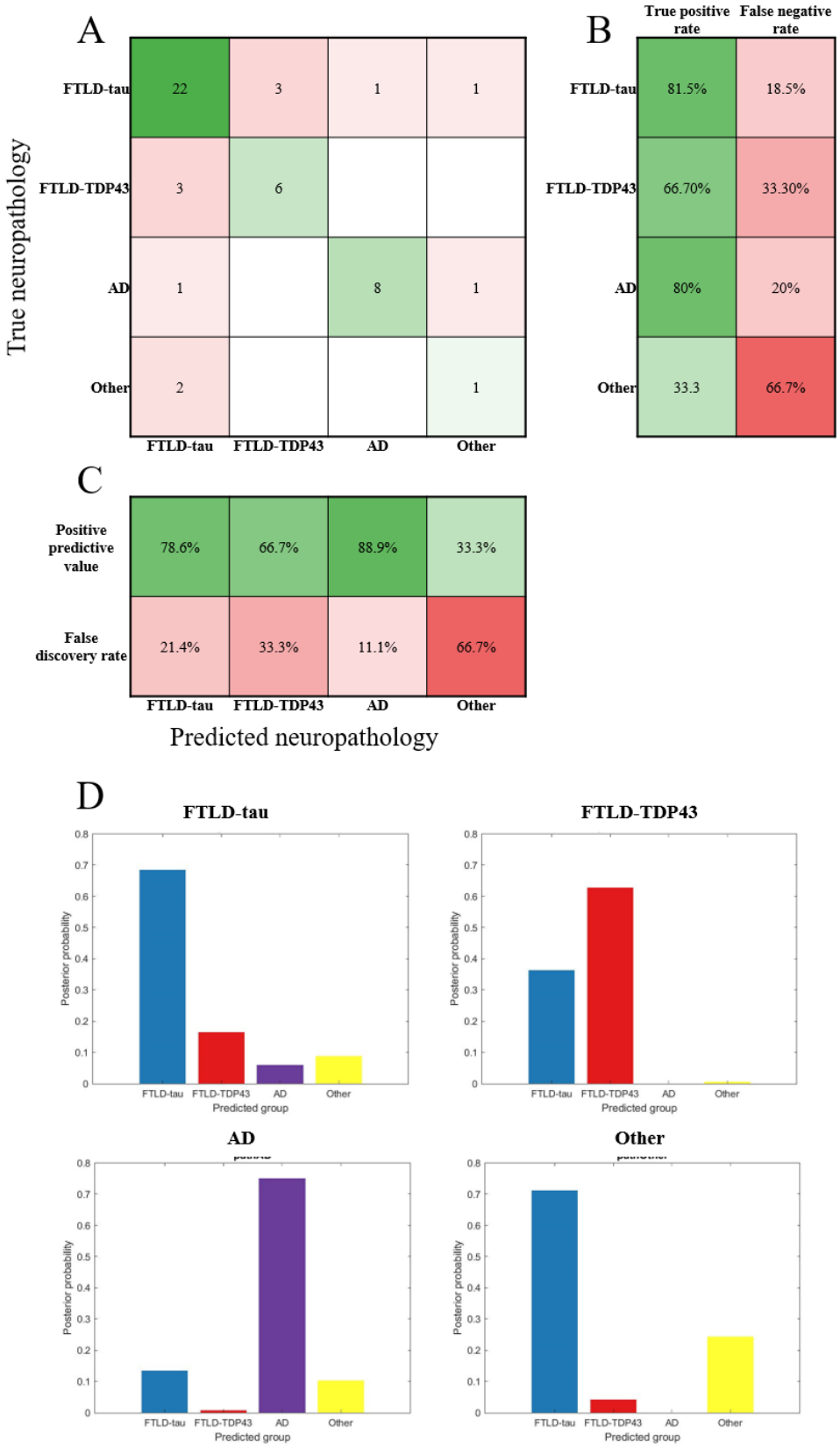


Figure 4-5: Accuracy of linear discriminant analysis predicting FTLD pathology from syndrome dimension. A: Confusion matrix of accurate (green) and inaccurate (red) predictions from the model. B: True and false positive rates for each pathology. C: Positive predictive value and false discovery rate for each pathology. D: Posterior probabilities for each pathology.

The cross validation of each model creates a posterior probability for each tested participant (the "left out" participant in the leave-one-out cross validation). This is analogous to the confidence of the model in that prediction so gives further detail on the model accuracy. The mean posterior probabilities for each correct FTLD pathology in both the FTLD subtype and dimension models are shown in Figure 4-6.

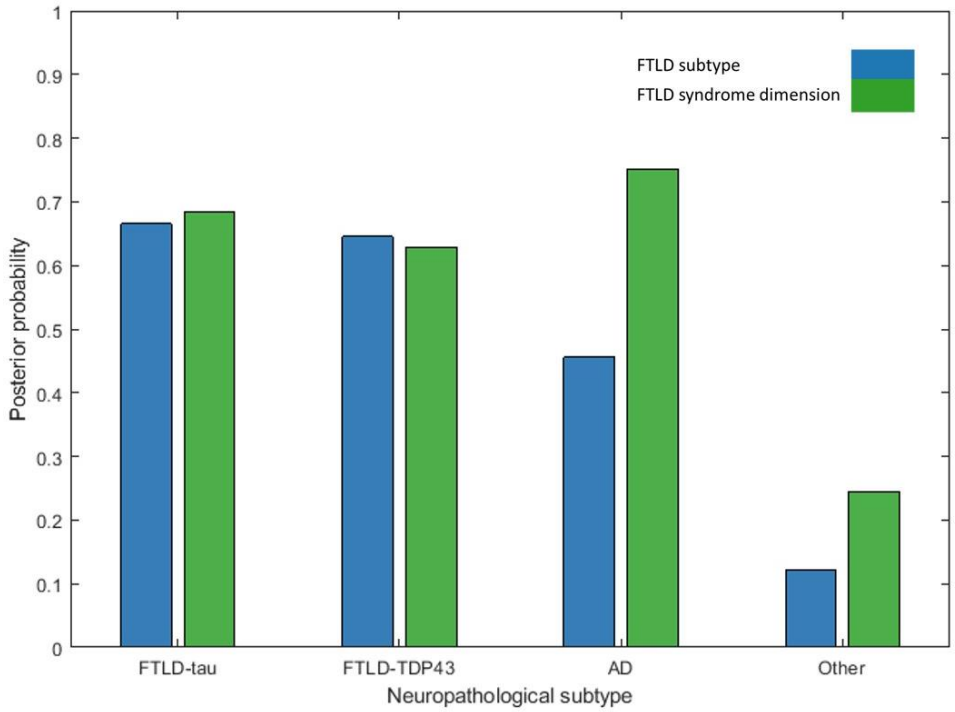


Figure 4-6: Bar plot of mean posterior probabilities. FTLD neuropathological subtype was predicted using either FTLD subtype (in blue) or FTLD syndrome dimension (in green). The posterior probabilities for the correct FTLD subtype are shown. More detailed plot showing the posterior probabilities for all FTLD subtypes is in supplementary materials. The posterior probability for FTLD-tau and TDP43 was similar between classifiers, but FTLD dimension had higher posterior probability for correctly identifying Alzheimer's disease pathology.

Only twenty-one patients had clinical phenotyping, imaging and neuropathology. This was too few to enable valid statistical analysis, so the following results are only descriptive. Volume loss in the brainstem was most associated with FTLD-tau-PSP pathology. Basal ganglia atrophy (imaging component 13) was associated with FTLD-TDP43 and FTLD-tau but not AD. No other imaging components were associated with specific neuropathology (sample in Figure 4-7, all components in Appendix 2). For example, all FTLD pathological subtypes were associated with volume loss in the frontal lobe (components one and two). Parietal atrophy, reflected by low scores on imaging component 8, is typically associated with Alzheimer's disease pathology. Both cases of Alzheimer's disease had low scores, but so did cases with FTLD-tau and FTLD-TDP43.

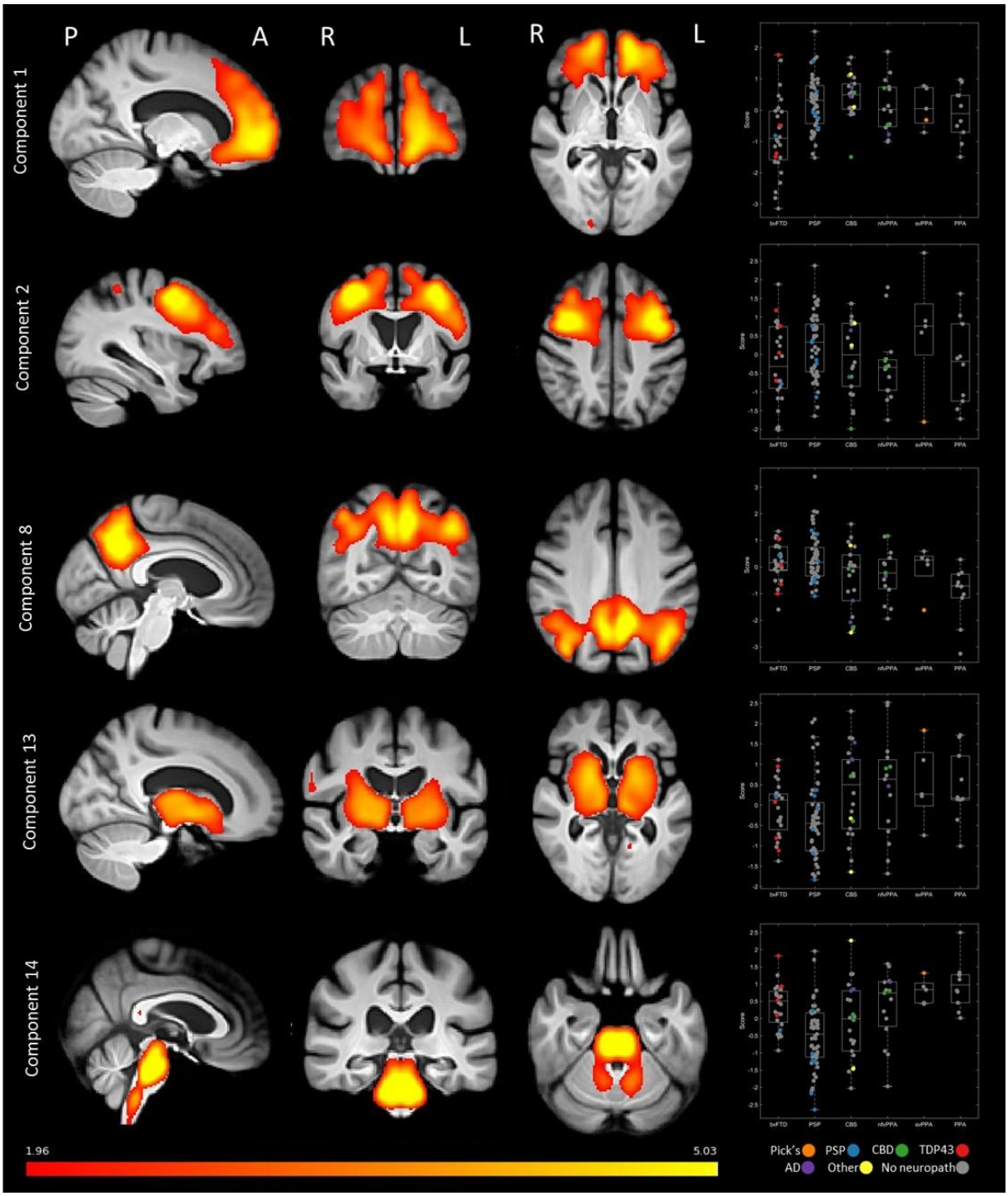


Figure 4-7: Neuropathology of the imaging components from Chapter 3. Five representative components are shown here, all components in Appendix 3.

Finally, I looked at the distribution of neuropathology within the three canonical correlation component, which showed the multivariate relationships between clinical and imaging dimensions (Figure 4-8). In the first canonical correlation positive scores were associated with FTLD-tau-PSP and negative scores with FTLD-TDP43 and Alzheimer's disease. Positive scores on the second canonical correlation were associated with FTLD-TDP43, and the three cases with AD pathology all had negative scores. The third canonical correlation did not separate FTLD pathological subtypes.

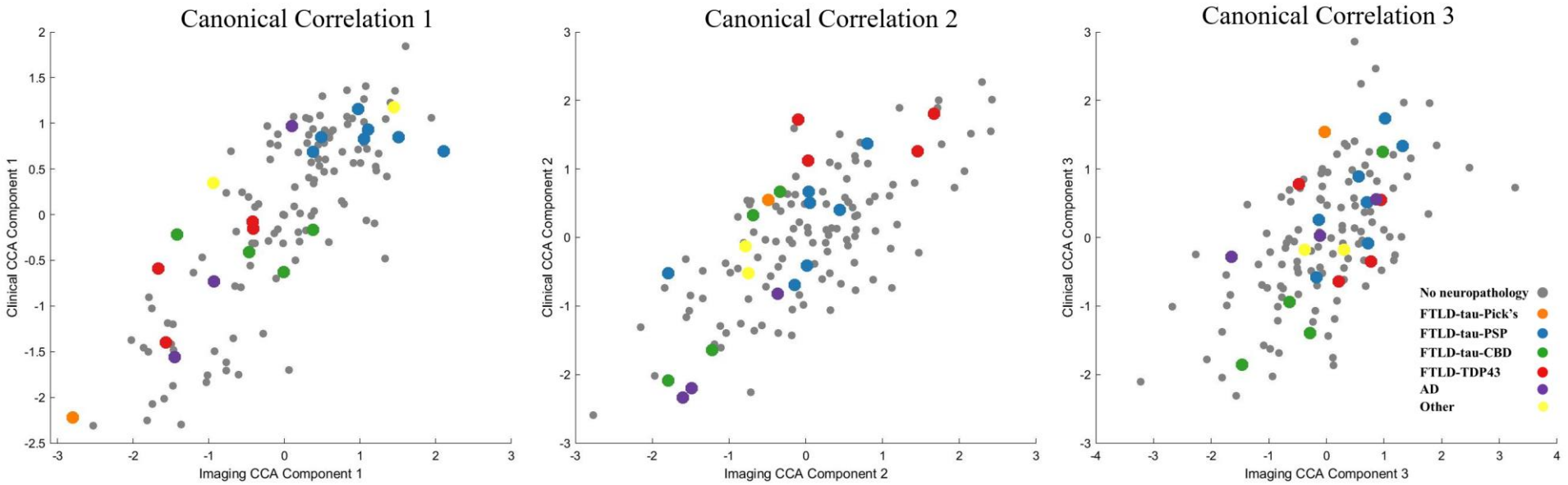


Figure 4-8: Scatter plots of the canonical correlation analysis of clinical and imaging components. Points are colour coded by neuropathological diagnosis (FTLD-tau-Pick's disease=orange, PSP=blue, CBD=green, TDP43=red, Alzheimer's disease (AD)=purple). Participants coloured grey were either still alive at the time of analysis or did not have a neuropathological diagnosis.

Discussion

These results show that a transdiagnostic, multidimensional approach to clinical phenotype marginally increases the overall accuracy of clinicopathological correlation in FTLD syndromes. The numbers of patients with imaging and neuropathology results was too low to enable statistical analysis, but there was no clear association between neuropathology subtypes and patterns of brain atrophy.

The clinicopathological correlations of the FTLD syndromes in my thesis are consistent with other studies. All clinical diagnoses of PSP were associated with PSP pathology (Osaki *et al.*, 2004; Gazzina *et al.*, 2019). CBS was predominantly due to CBD or AD pathology (Kouri *et al.*, 2011, Lee *et al.*, 2011*b*; Alexander *et al.*, 2014). All cases of bvFTD were associated with either Tau (3R or 4R) or TDP43 pathology (Josephs *et al.*, 2011; Rascovsky *et al.*, 2011, Perry *et al.*, 2017*a*). Most patients with svPPA had TDP43 pathology (Grossman, 2010; Spinelli *et al.*, 2017). The one patient with logopenic variant PPA had Alzheimer's disease pathology (Spinelli *et al.*, 2017). The incidence of bvFTD associated with TDP43 was higher in this study than in other studies (Rascovsky *et al.*, 2011, Perry *et al.*, 2017*a*). Three of these cases had bvFTD-MND had motor neuron disease, which confers a poorer prognosis and is strongly associated with TDP43 pathology (Lillo and Hodges, 2009; Coon *et al.*, 2011). My results may be biased toward these rapidly progressive cases due to the short follow up time. Two patients with AD pathology had secondary TDP43 deposition in the medial temporal lobes. This pattern of TDP43 deposition, now called limbic-predominant age-related TDP43 encephalopathy (Nelson *et al.*, 2019) is often associated with AD pathology in older individuals and is not an FTLD subtype (Josephs *et al.*, 2019). One patient had coexistent PD and PSP pathology, and clinical features that were initially consistent with Parkinson's disease then many years later changed to a PSP-RS phenotype. This is rare, but has previously been reported (Rigby *et al.*, 2015).

These neuropathology results support the transdiagnostic multidimensional approach to FTLD proposed in this thesis. Many patients had clinical phenotypic, brain morphology and neuropathological results that spread across diagnostic boundaries. For example, one patient had prominent early semantic impairment and temporal lobe atrophy, resulting in a clinical diagnosis of svPPA but atypically *post-mortem* had Pick's disease pathology. The transdiagnostic approach helps explain this, they had high loadings on syndrome dimension 1 (behavioural impairment) and frontal lobe atrophy. Another patient was diagnosed in life with

bvFTD but also had a high score on syndrome domain 3 and brainstem atrophy, with a low score on imaging component 14. At *post-mortem* this patient had PSP pathology. These patients' clinical diagnoses were not incorrect, they met the diagnostic criteria and their respective neuropathologies have been associated with these clinical syndromes (svPPA and Pick's disease and bvFTD and PSP pathology) in other cohorts (Grossman, 2010, Perry *et al.*, 2017*a*; Spinelli *et al.*, 2017). Instead, they are examples of limitations with the current diagnostic criteria, which force patients into discrete categories when instead they exist on a multidimensional spectrum. The transdiagnostic approach allows patients to span diagnostic labels, which in these cases helped predict their underlying neuropathology.

The overall accuracy of linear discriminant analysis using FTLD syndrome dimensions was marginally higher than the decision tree using FTLD subtype. This is primarily due to higher positive predictive value for Alzheimer's disease (AD) pathology. In the decision tree, any diagnosis of CBS or lv/mixed PPA was classified as AD and any cases of nfvPPA were classed as FTLD-tau. In reality, a significant proportion of CBS was associated with CBD, and a minority of nfvPPA was due to AD, which were all misclassified by the decision tree. In contrast, using a multidimensional transdiagnostic approach all cases of AD were associated with high scores on syndrome dimension 5 and most had low scores on syndrome dimension 4. This profile reflects cortical features of agrammatic, apraxic and logopenic language deficits with limb apraxia and symmetrical myoclonus and the relative absence of subcortical features, including asymmetrical parkinsonism and dystonia. Previous attempts to find isolated clinical features that predict AD pathology in CBS have mostly been unsuccessful (Lee *et al.*, 2011*b*; Alexander *et al.*, 2014) but this multivariate approach, which uses patterns of covarying clinical features, appears more accurate. However, the linear discriminant analysis could not differentiate cases of bvFTD due to FTLD-tau or FTLD-TDP43. This has not been possible in any clinicopathological study of bvFTD (Hodges *et al.*, 2004, Perry *et al.*, 2017*a*), and the relatively high positive predictive value for FTLD-TDP43 in the decision tree is due to the disproportionate number of TDP43 cases in my bvFTD cohort.

The number of participants with clinical phenotyping, *in-vivo* imaging and *post-mortem* neuropathology was too low to enable statistical analysis but can still inform the relationship between FTLD pathological subtype and focal brain atrophy. Some FTLD pathological subtypes were associated with specific atrophy patterns, for example FTLD-TDP43 was associated with bitemporal atrophy and FTLD-tau-PSP with brainstem atrophy. However, overall there was limited relationship between a specific neuropathology and atrophy pattern.

The three phenotype-atrophy associations identified in chapter three did not separate neuropathological subtypes and cases with the same FTLD pathology had high or low scores within the same component. Most imaging components reflecting focal cortical atrophy in the frontal, parietal and occipital lobes did not isolate an individual neuropathology. For example, frontal lobe atrophy was seen in cases of Pick's disease, PSP, CBD and TDP43 and parietooccipital atrophy was seen with PSP, CBD, TDP43 and Alzheimer's disease. Selective vulnerability, both for cell type and brain region, is characteristic of all neurodegenerative diseases (Seeley, 2008; Fu *et al.*, 2018). However, in FTLD this appears to be independent of pathology subtype in most brain regions. Von Economo neurons in the anterior cingulate cortex may be selectively vulnerably to FTLD, but this is seen with both FTLD-tau and FTLD-TDP43 and across different genetic mutations (Seeley *et al.*, 2006; Santillo *et al.*, 2013; Santillo and Englund, 2014; Yang *et al.*, 2017; Gami-Patel *et al.*, 2019; Lin *et al.*, 2019). In summary, different FTLD pathologies can be associated with similar selective vulnerability, brain atrophy and clinical phenotype. In addition, the same FTLD pathology can be associated with different clinical phenotypes, even in family members with the same genetic mutation (Boeve *et al.*, 2005; Benussi *et al.*, 2015; Foxe *et al.*, 2018). This pleiotropy suggests additional individual variables, environmental or genetic, may have a greater effect on selective vulnerability than a specific neuropathology.

There are other limitations to the results reported in this chapter. First, I grouped neuropathology diagnosis by the major subtypes, FTLD-tau, FTLD-TDP43 and Alzheimer's Disease. It is possible that treatments targeting a given molecular substrate of FTLD will be effective for all the subtypes within that molecule – whether Tau, TDP43 or other. For example, the same anti-tau treatment is being tested in primary 3R and 4R and secondary tauopathies (Boxer *et al.*, 2019). However, this proposition is not yet proven and my method disadvantages syndrome labels with high clinicopathological correlations for specific FTLD subtypes (e.g. PSP-RS for FTLD-tau-PSP and svPPA for FTLD-TDP43-C). Even within the primary tauopathies, the ultrastructure and epitopes of tau vary (Falcon *et al.*, 2018; Goedert, 2018; Arakhamia *et al.*, 2020; Zhang *et al.*, 2020), which may affect susceptibility to treatment. Second, the neuropathological results are limited to one diagnosis, with no information on stage or distribution. The location and severity of neuropathology is likely to influence clinical phenotype. For example, PSP with executive and behavioural impairment (PSP-F) or apraxia, cortical sensory loss or alien limb syndrome (PSP-CBS) is associated with greater cortical tau deposition in the frontal and parietal lobes respectively (Dickson *et al.*, 2010; Ling *et al.*, 2014; Sakae *et al.*, 2019). The "subcortical" variants of PSP, with predominant gait freezing or

parkinsonism (PSP-PGF and PSP-P) have more pathological tau deposition in the basal ganglia and brain stem (Williams *et al.*, 2005, 2007*a*, *b*). This variability in the distribution of neuropathology may explain more variation in clinical phenotype than proteinopathy (i.e. tau or TDP43). Third, I did not report comorbid pathology. This is increasingly recognised in neurodegenerative disease and may partly explain clinical phenotype (Robinson *et al.*, 2018; Cornblath *et al.*, 2019). Two patients in the PIPPIN cohort had primary Alzheimer's disease pathology with secondary TDP43 disease confined to the temporal lobe. The co-occurrence of AD and TDP43 is well recognised, and has recently been relabelled as limbic-predominant age-related TDP43 encephalopathy (Nelson *et al.*, 2019). However, many other patients had early stage amyloid-beta and very limited age-associated TDP43 deposition. This may contribute to clinical phenotype in FTLD syndromes and requires further research. Another limitation is that the subset of patients in the brain bank had more advanced disease, as they were assessed at a later timepoint in their illness when compared to the whole PIPPIN cohort. This is unsurprising, given the relatively short follow up time between the data collection and preparing this thesis. In Chapter 1 I showed that over time the clinical phenotypes of FTLD syndromes merge and patients with more advanced disease often have features of several FTLD syndromes. Patients at an early disease stage may have a phenotype which could have better clinicopathological accuracy.

My results add to the evidence that even very detailed phenotyping cannot select all cases associated with one FTLD pathology with high accuracy. Therefore, imaging or fluid-based biomarkers are required for an accurate, *in vivo* diagnosis of a specific neuropathology. There has been great progress in Alzheimer's Disease and CSF and PET biomarkers for β-amyloid are increasingly used in clinical practice and to confirm eligibility for research trials (Ossenkoppele *et al.*, 2015*a*; Olsson *et al.*, 2016; Blennow and Zetterberg, 2018). Plasma-based assays for β-amyloid (Nakamura *et al.*, 2018), tau (Foiani *et al.*, 2018) and TDP43 (Suárez-Calvet *et al.*, 2014) are also in development and may soon be available for clinical research. First generation tau-PET ligands have strong affinity for the paired helical filament tau associated with Alzheimer's Disease (Leuzy *et al.*, 2019). However, the same ligands have less specificity in FTLD syndromes, with off target binding in syndromes such as svPPA that are only very rarely associated with tau pathology (Bevan-Jones *et al.*, 2018). Second-generation ligands are in development, but at present there are no biomarkers that can different FTLD-tau and FTLD-TDP43 *in vivo* (Bevan Jones *et al.*, 2016; Meeter *et al.*, 2017; Bevan-Jones *et al.*, 2018). Fluid biomarkers are also in development, but are not yet available (Zetterberg *et al.*, 2019). In summary, clinical phenotyping is currently the most accurate and accessible method

of differentiating FTLD neuropathology, and a transdiagnostic, spectrum-based approach is more accurate than grouping patients into discrete entities.

Prognosis of frontotemporal lobar degeneration syndromes

Preface

This chapter is largely the same as a manuscript which is in preparation (Murley *et al.*, 2020*b*). I performed all the data analysis in this chapter. The text was written by me, with input from co-authors on the manuscript.

Summary

In this chapter I test the prognostic value of a transdiagnostic, spectrum-based approach to FTLD syndromes. I show that behavioural disturbance is associated with reduced functionally independent survival even if patients with bvFTD are removed from the analysis. I then show that motor impairments were associated with reduced absolute mortality, even if patients with PSP and CBS are removed from the analysis. These results may help individualised prognostication and support a transdiagnostic approach to symptomatic treatments trials.

Introduction

Prognosis in syndromes associated with frontotemporal lobar degeneration (FTLD) is highly variable and difficult to predict. Disease duration is not fully explained by the diagnostic categorisation to behavioural variant frontotemporal dementia (bvFTD), non-fluent (nfvPPA) or semantic (svPPA) variants of primary progressive aphasia, progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS) (Hodges *et al.*, 2003, 2010; Coyle-Gilchrist *et al.*, 2016; Kansal *et al.*, 2016; Agarwal *et al.*, 2019). Better prognostic models would aid both trial design and clinical management.

In the previous chapters, I showed that the syndromes caused by frontotemporal lobar degeneration (FTLD) have highly heterogenous and overlapping clinical features. In this chapter, I explore how these clinical features, represented across the spectrum of disorders, explain variation in functional independence and survival (Kertesz *et al.*, 2005, Murley *et al.*, 2020*a*). I used the syndrome dimensions from chapter two to identify prognostic clinical features across the FTLD syndrome spectrum (Borroni *et al.*, 2009*b*; Lansdall *et al.*, 2019). Previous work has identified that features of motor neuron disease reduce life expectancy in bvFTD (Hodges *et al.*, 2003, Hu *et al.*, 2009*b*; Kansal *et al.*, 2016), while dysphagia and cognitive impairment worsen prognosis in PSP-Richardson's syndrome (Glasmacher *et al.*, 2017). Here I focus on all the cognitive, behavioural and motor features of the disease.

Mortality is a definite endpoint in FTD, PSP and CBS. However, these disorders also increase dependency and caregiver burden (Riedijk *et al.*, 2006; Cordner *et al.*, 2010; Pekmezović *et al.*, 2015; Schmotz *et al.*, 2017; Agarwal *et al.*, 2019). Community-based studies suggest increased dependency, whether due to cognitive or physical disability, predicts care home admission (Tun *et al.*, 2007; Rockwood *et al.*, 2014). Many patients with FTLD syndromes are admitted to care homes as their illness progresses (Diehl-Schmid *et al.*, 2017), so this could be used as an indirect outcome of loss of functional independence (Riedijk *et al.*, 2006; Agarwal *et al.*, 2019).

Aims and hypotheses

The aim of this chapter was to identify how the clinical phenotypes associated with FTLD are associated with prognosis. I had two hypotheses. First, behavioural impairments, represented by syndrome dimension one, increase risk of care home admission, over and above the FTLD syndrome diagnostic label. Second, motor impairments, represented by syndrome dimensions three and four, are associated with increased mortality.

Methods

Survival data were collected for all participants in the PIPPIN study (Pick's disease and Progressive Supranuclear Palsy Prevalence and Incidence), a cross-sectional epidemiological study, detailed methods of which are in Chapter 2 (Coyle-Gilchrist *et al.*, 2016, Murley *et al.*, 2020*a*). I recorded dates of care home admission and death from each participant's NHS Summary Care Record. This database includes information on the address and date of death of every UK resident, minimising loss to follow up. I defined a care home as an institution registered with the UK government to provide residential and/or nursing care.

I used a Cox proportional hazards regression analysis to test the association between the six clinical syndrome dimensions reported in Chapter 2 and the time from clinical assessment to death (covariates of age, gender and disease group). This allows all participants to be included in the survival analysis, censoring participants who failed to reach the end point (death). The predictor variables (subject-weightings on each syndrome component) were z scored to aid interpretation. If a syndrome dimension closely resembled typical features of a specific diagnostic group, I repeated the Cox proportional hazards regression analysis without that group.

Next, I tested the association between the syndrome dimensions and time to care home admission using logistic regression, with the binary outcome of care home admission by 2 years from study assessment. Patients in a care home at study assessment or those with incomplete follow up were excluded from this analysis. I used logistic rather than Cox proportional hazards regression for two reasons. First, to allow assessment of care home admission risk independent of mortality and second, because it could be argued that the risk of care admission does not remain constant over time (an assumption of Cox hazards regression). All analyses were performed in MATLAB 2018b (MathWorks, USA). Kaplan Meir curves were plotted using the *MatSurv* function (https://github.com/aebergl/MatSurv).

Results

At the censor date (1st August 2019), 169 FTLD patients (54.5%) had been admitted to a care home and 200 patients (64.5%) had died. Most patients were admitted to a care home before they died (131/200, 62.3%). Summary demographic and survival results are shown in Table 5-1.

	All FTLD	bvFTD	nfvPPA	svPPA	PPA (lv/mixed)	PSP	CBS
Clinical phenotyping (n)	310	64#	36##	25	16	101	68
Age (mean years) (SD)	70.26 (8.57)	64.59 (9.56)	72.09 (8.81)	67.55 (6.43)	70.80 (7.05)	72.56 (7.14)	72.08 (7.69)
Gender (male/female)	152/158	33/31	15/21	14/11	7/9	56/45	27/41
Symptom onset to study assessment (years, mean and SD)	4.75 (3.18)	5.70 (4.45)	2.83 (1.93)	4.96 (2.69)	2.76 (1.97)	4.50 (2.94)	4.71 (2.77)
Diagnosis to study assessment (years, mean and SD)	1.44 (2.77)	1.88 (3.88)	1.09 (1.27)	1.65 (2.01)	1.58 (1.67)	1.02 (1.17)	1.73 (2.02)
Symptom onset to death (years, mean and SD)*	7.71 (4.37)	9.08 (7.00)	7.93 (3.47)	11.03 (3.39)	9.29 (3.14)	6.39 (3.67)	7.30 (3.12)
Diagnosis to care home (years, mean and SD)*	2.94 (2.43)	2.26 (2.90)	4.43 (1.75)	5.31 (1.86)	4.44 (2.48)	1.69 (1.20)	3.13 (2.28)
Diagnosis to death (years, mean and SD)*	4.40 (3.25)	5.49 (5.06)	5.50 (2.62)	7.95 (2.61)	5.74 (2.19)	2.78 (2.7)	4.12 (2.35)

Table 5-1: Demographics of the study cohort. *Subgroup of cohort with complete follow up. 6 patients were living in a care home at diagnosis. #12 patients with bvFTD had motor neuron disease. ##1 patient with nfvPPA had motor neuron disease.

There was high variability in the time from diagnosis to care home admission or death in all groups (Figure 5-1). Life expectancy differed between groups (ANOVA, $F_{1,5}$ =10.41, p<0.001). This was primarily due to longer life expectancy in svPPA compared to PSP (mean difference 5.24 years, p<0.001), CBS (3.83 years, p<0.001) and bvFTD (2.69 years, p=0.047). PSP patients also had a worse prognosis compared to bvFTD (mean difference 2.55 years, p<0.001) and nfvPPA (2.54 years, p<0.001). Thirteen patients with FTD-MND had a lower mean time between diagnosis and death than the whole bvFTD cohort (2.67 vs 5.49 years).

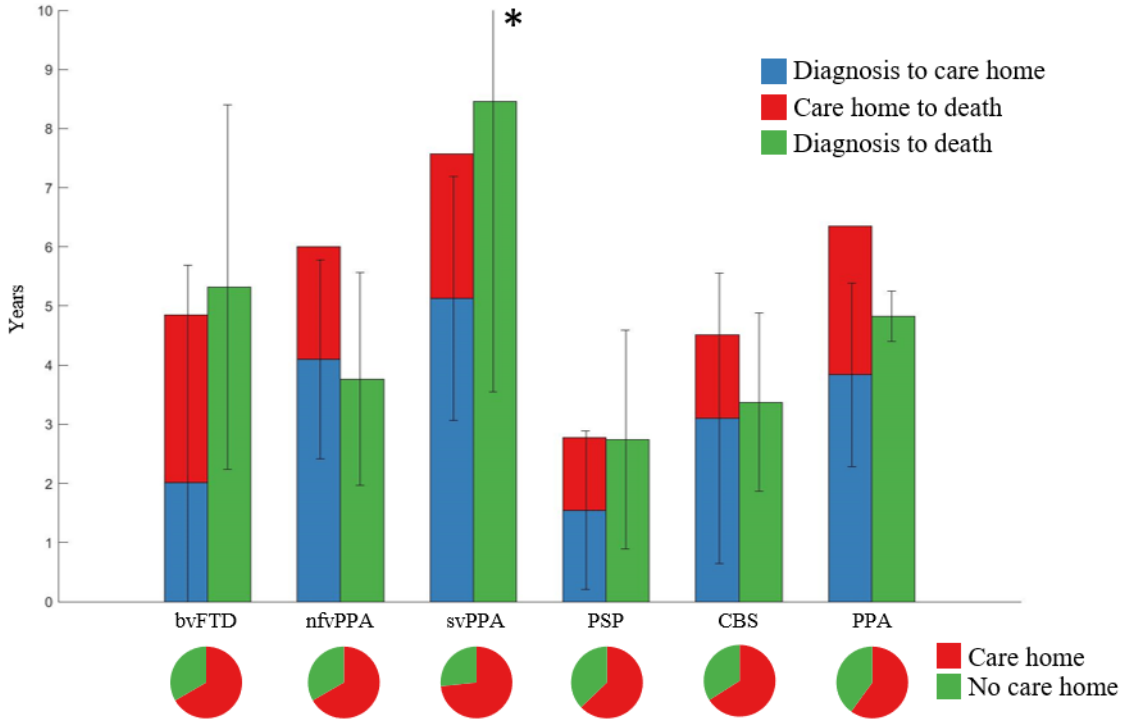


Figure 5-1: Survival in frontotemporal lobar degeneration syndromes. The bar plot shows disease duration in FTLD syndromes in patients with complete follow up from disease onset to death. Survival in each FTLD subgroup is shown grouped by care home vs no care home admission. The error bars are the standard deviation. The pie charts show proportion of each FTLD subgroup admitted to a care home during the disease course.

Next, I tested the association between the FTLD syndrome dimensions (detailed in chapter two) and survival. An individual's score on each dimension showed the extent to which they expressed that clinical phenotype. In summary, syndrome dimension 1 reflected clinician and carer rating of behavioural impairment. Syndrome dimension 2 reflected cognitive impairment, with contribution from all ACER subscales and carer ratings of memory and everyday skills. Syndrome dimension 3 mirrored a PSP-RS-like motor phenotype, with positive loadings reflecting symmetrical parkinsonism, falls and supranuclear gaze palsy. Negative loadings on this dimension reflected semantic language impairment. The fourth syndrome dimension represented asymmetrical parkinsonism, myoclonus and dystonia with cortical features of alien limb syndrome, apraxia and cortical sensory loss. Syndrome dimension five was driven by language impairments including speech apraxia, loss of syntactic comprehension and impaired repetition. Syndrome dimension six reflected carer ratings of low mood and abnormal beliefs. There was a spread of scores across FTLD subgroups onto these symptom domains.

Cox proportional hazards regression indicated that syndrome dimensions 3 and 4 and age at clinical assessment, were associated with time to death (Table 5-2). Syndrome dimension 3 remained a significant predictor of death after PSP was removed (HR 2.30, CI 1.50-3.52,

p<0.001). Absolute survival (time from assessment to death) differed between participants in high, medium and low severity tertiles for syndrome dimensions 3 (Figure 5-2B) and 4 (Figure 5-2E) severity score. This result persisted after removing the highest scoring FTLD subgroups, PSP for syndrome dimension 3 (log rank p<0.001) and CBS for syndrome dimension 4 (log rank p<0.001).

	Hazard ratio	Hazard ratio (CI)	Coefficient	SE	P value
Age	1.04	(1.02-1.06)	0.04	0.01	<0.01
Gender	1.18	(0.87-1.59)	0.16	0.16	0.29
Diagnosis 1	0.64	(0.23-1.80)	-0.45	0.53	0.40
Diagnosis 2	0.87	(0.48-1.57)	-0.14	0.3	0.64
Diagnosis 3	1.16	(0.53-2.54)	0.15	0.4	0.71
Diagnosis 4	0.99	(0.5-1.97)	-0.01	0.35	0.97
Diagnosis 5	0.65	(0.25-1.64)	-0.44	0.48	0.36
Syndrome dimension 1	1.23	(0.98-1.55)	0.21	0.12	0.07
Syndrome dimension 2	1.15	(0.99-1.35)	0.14	0.08	0.07
Syndrome dimension 3	1.97	(1.41-2.75)	0.68	0.17	<0.01
Syndrome dimension 4	1.31	(1.07-1.61)	0.27	0.1	<0.01
Syndrome dimension 5	0.87	(0.73-1.03)	-0.14	0.09	0.12
Syndrome dimension 6	0.88	(0.75-1.03)	-0.13	0.08	0.12

Table 5-2: Cox proportional hazards model of time from study assessment to death.

Next, I tested which syndrome dimensions predicted care home admission at two years with age, gender and disease group as covariates. Eighty-nine patients with a follow up of less than two years were excluded from this analysis. Syndrome dimension one, reflecting behavioural impairment, was associated with care home admission (OR 2.46, p<0.001) (Table 5-3). This remained a significant predictor of care home admission even after bvFTD, the subgroup with highest scores, was removed (OR 3.20 p=0.03). Independent survival (time from clinical assessment to care home admission or death) differed between participants in high, medium and low severity tertiles for syndrome dimension 1 severity score (log rank p=0.007) (Figure 5-3C). This result persisted after removing the bvFTD group (log rank p<0.001).

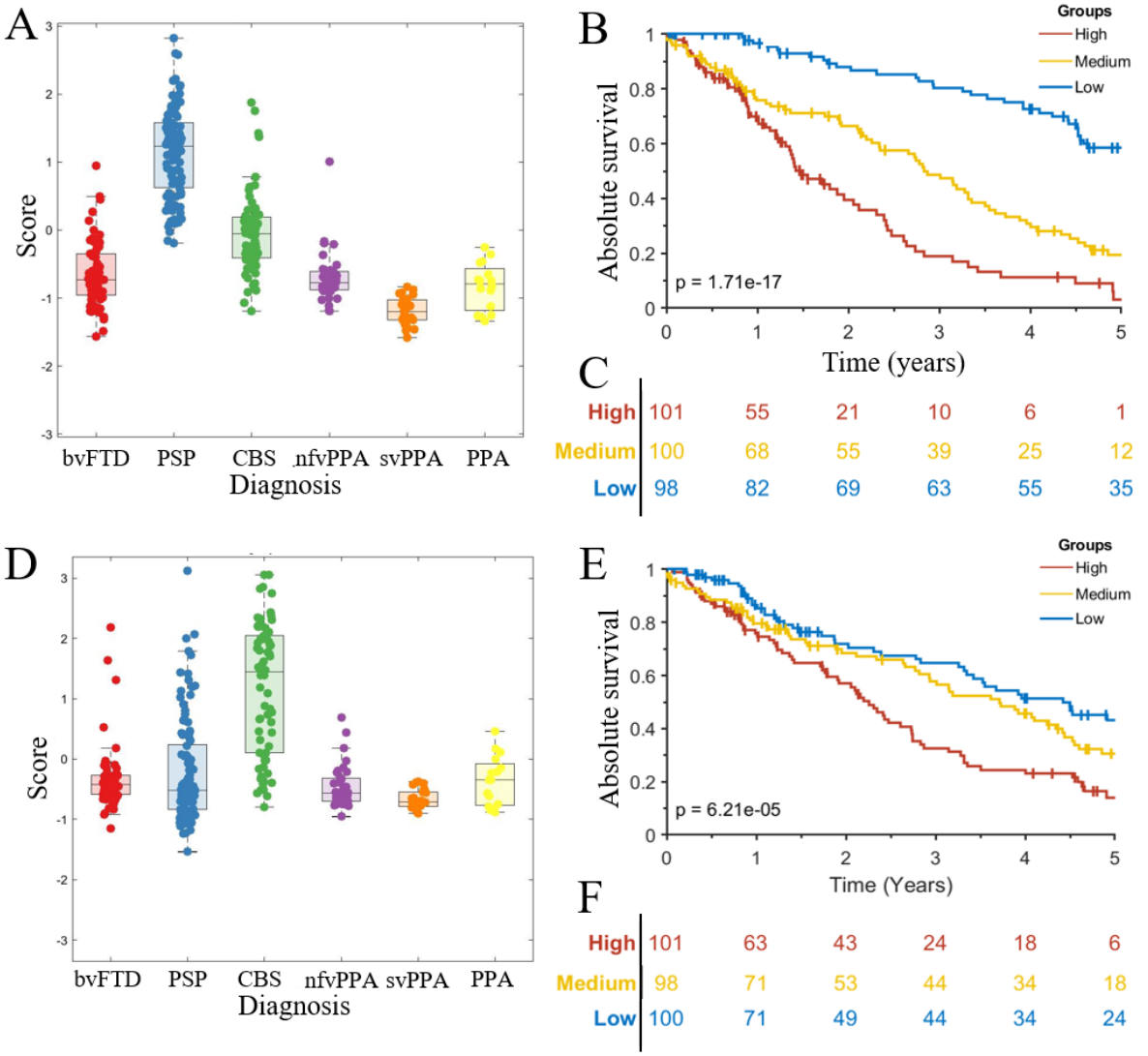


Figure 5-2: Absolute survival (time to death) in frontotemporal lobar degeneration syndrome. 2A: Scatterboxplot of individual's scores on syndrome dimension three, grouped by FTLD syndrome subtype. 2B: Kaplan Meier survival curve for high, medium and low scoring tertiles for syndrome dimension three. The p value is from a log rank test of the null hypothesis of no difference in survival between all groups. Vertical lines show censored data. 2C: At risk table for the data shown in 2B. 2D: Scatterboxplot of individual's scores on syndrome dimension four 2E: Kaplan Meier survival curve for high, medium and low scoring tertiles for syndrome dimension four. 2F: At risk table for the data shown in 2E.

	Odds ratio	Coefficient	*t* value	p value
Constant	0.10	-2.26	-1.17	0.24
Age	1.02	0.02	0.79	0.43
Gender	0.78	-0.25	-0.60	0.55
Diagnosis 1	0.79	-0.23	-0.20	0.84
Diagnosis 2	2.89	1.06	1.40	0.16
Diagnosis 3	0.50	-0.70	-0.72	0.47
Diagnosis 4	0.13	-2.02	-1.54	0.12
Diagnosis 5	0.28	-1.28	-1.07	0.28
Syndrome dimension 1	2.46	0.90	3.11	<0.01
Syndrome dimension 2	1.42	0.35	1.60	0.11
Syndrome dimension 3	1.13	0.12	0.28	0.78
Syndrome dimension 4	0.99	-0.01	-0.03	0.98
Syndrome dimension 5	1.08	0.08	0.36	0.72
Syndrome dimension 6	0.77	-0.26	-1.20	0.23

Table 5-3: Logistic regression of predictors of care admission by 2 years from clinical assessment.

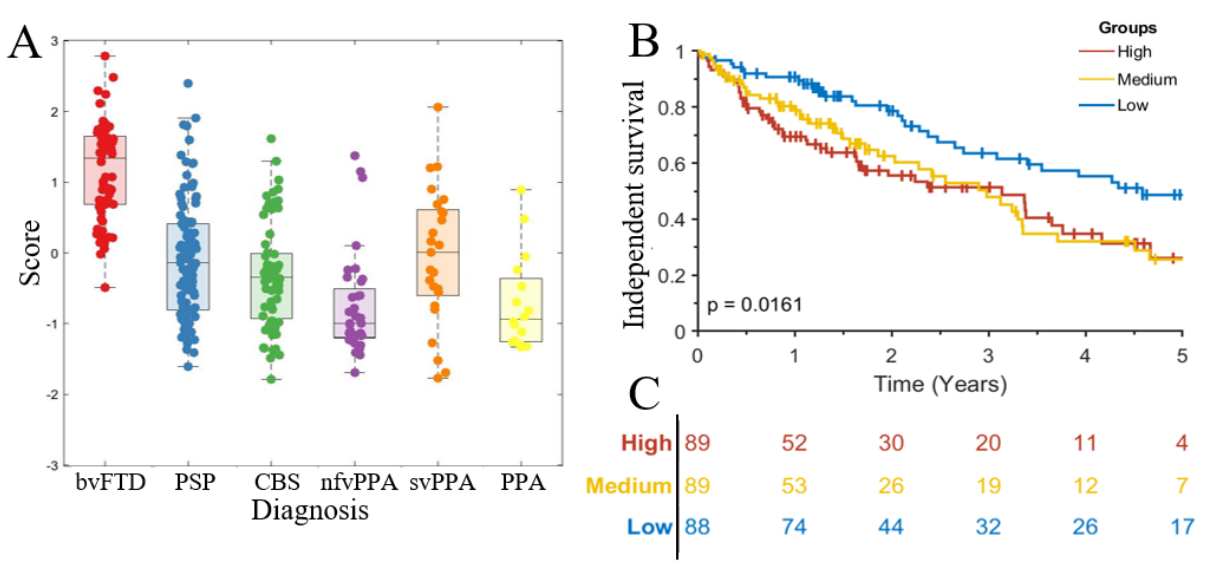


Figure 5-3: Independent survival (time to care home admission) in frontotemporal lobar degeneration syndromes. 3A: Scatterboxplot of each participant's score on syndrome dimension one. 3B: Kaplan Meier survival curve for high, medium and low scoring tertiles for syndrome dimension one. The p value is from a log rank test of the null hypothesis of no difference in survival between all groups. Vertical lines show censored data. 3C: At risk table for the data shown in 3B.

Discussion

Clinician- and carer-rated behavioural disturbance is associated with shorter functionally independent survival and the presence of motor features (including parkinsonism, postural instability, supranuclear gaze palsy, dystonia and apraxia), is associated with reduced absolute survival. These associations are found across the spectrum of common syndromes associated with FTLD, even when groups classically associated with these clinical features (bvFTD, PSP and CBS respectively) are excluded. A transdiagnostic approach, that captures the clinical overlap and mixed phenotype, adds clinically relevant information for prognostication to that available from the diagnostic group label.

Behavioural impairment, represented here by syndrome dimension one, was associated with a greater risk of care home admission. This complements previous findings in bvFTD (Agarwal *et al.*, 2019), Parkinson's and Alzheimer's disease (Aarsland *et al.*, 2000; Knapp *et al.*, 2016). Syndrome dimension one reflects many behavioural impairments including apathy, impulsivity, socially inappropriate behaviour and hyperorality. More detailed neuropsychological tests and measures of carer burden could fractionate behavioural impairment to more closely determine which behavioural impairments have the greater effect on prognosis (Boutoleau-Bretonnière *et al.*, 2008; Kaizik *et al.*, 2017; Lansdall *et al.*, 2019). The results of this chapter show correlation and not causation, and I lack data on the reasons given for care home admission. However, behavioural impairments in frontotemporal dementia and PSP are known to increase carer burden (Mioshi *et al.*, 2009, Armstrong *et al.*, 2013*b*) and there are no proven effective pharmacological treatments (Huey *et al.*, 2006, Rittman *et al.*, 2016*a*). Patients with more severe behavioural impairments may require continuous supervision which becomes difficult for spouses or families to sustain at home. Treating behavioural disturbance may delay the need for care home admission, with benefits to individual health and health-economics. Pharmacological strategies could include restoration of neurotransmitter deficits associated with behavioural change (Lebert *et al.*, 2004; Hughes *et al.*, 2015; Murley and Rowe, 2018; Desmarais *et al.*, 2019).

The relationship between cognitive impairment and prognosis is complex. Some studies show a clear association (Borroni *et al.*, 2009*b*), but others do not (Garcin *et al.*, 2009; Lansdall *et al.*, 2019). This discrepancy may be due to the indirect contribution of behavioural and motor impairments to performance on 'cognitive' tests. For example, speech or constructional deficits in nfvPPA or CBS respectively may impair performance tasks that require spoken, written or

drawn response. However, the separation of cognitive and motor deficits across the six dimensions argues against such a simple interference effect.

The clinical phenotype reflected by syndrome dimensions 3 and 4 are classically associated with PSP Richardson's syndrome and CBS respectively, but in this cohort was also expressed to a degree by many other patients except for those with svPPA (Figure 5-2A&D). PSP-RS typically has a worse prognosis than bvFTD (unless there is coexistent MND) and PPA (Chiu *et al.*, 2010; Kansal *et al.*, 2016) while FTLD-tau has a worse prognosis than FTLD-TDP43 if clinical MND cases are excluded (Xie *et al.*, 2008). With disease progression many patients with nfvPPA develop the phenotype of progressive supranuclear palsy or corticobasal syndrome, which is an adverse prognostic sign (Sánchez-Valle *et al.*, 2006; Josephs and Duffy, 2008; Josephs *et al.*, 2014; Santos-Santos *et al.*, 2016). In keeping with these observations, previous survival analyses of frontotemporal dementia (bvFTD and PPA) have shown reduced letter fluency, motor cortex atrophy and brainstem hypoperfusion were associated with reduced survival (Roberson *et al.*, 2005; Le Ber *et al.*, 2006; Agarwal *et al.*, 2019). My results go beyond these findings, suggesting that development of motor impairments, irrespective of diagnostic group, is an adverse prognostic sign. However, the correlation between syndrome dimensions 3 and 4 and mortality does not prove causation. It is unclear if that these syndrome dimensions are indicative of a more aggressive disease or increased risk of complications, such as aspiration pneumonia due to dysphagia, sarcopenia and other aspects of frailty (Brunnström and Englund, 2009; Landi *et al.*, 2013). These complications could in turn increase mortality.

These results have several limitations. The survival analysis only contained a limited number of covariates (age, gender and main diagnostic group). Medical and psychiatric comorbidities, marital status, social class, ethnicity and financial status are also known to influence rates of care home admission and death (Knapp *et al.*, 2016; Harrison *et al.*, 2017) and may explain some of the variance in prognosis. I attempted to recruit all patients with a designated syndrome associated with FTLD in the catchment area (Cambridgeshire and Norfolk). Most referrals came from secondary care, so survival rates could be overestimated if patients with rapidly progressively disease died before they could enter the study. However, average survival in this FTLD cohort was similar to those published previously (Kansal *et al.*, 2016). I did not distinguish between residential or nursing care from basic demographic information. This was not differentiated in the demographic data because many institutions provide both levels of care at the same site. It is important to note that admission to a residential or nursing home is not a sign of inadequate home care and not inevitably associated with reduced quality of life. Patients

with FTLD often benefit from the skilled holistic care provided in these institutions (Patterson, 2014). However, I argue that at a group level care home admission is a measure of reduced independence, and a potential study end point in trials.

In summary, functionally independent and absolute survival in syndromes associated with frontotemporal lobar degeneration are predicted by a subset of clinical features, over and above the diagnostic label. Given these findings, and the overlapping clinical (Kertesz and Munoz, 2004), structural (Whitwell and Josephs, 2012; Lagarde *et al.*, 2013, Murley *et al.*, 2020*a*), functional (Hughes *et al.*, 2013; Sami *et al.*, 2018), neuropathological (Seelaar *et al.*, 2011; Irwin *et al.*, 2015) and neurochemical (Murley and Rowe, 2018) features in these syndromes, I suggest a transdiagnostic approach to develop better treatment strategies. Effective treatments for behavioural and motor features could improve functionally independent survival and might ameliorate absolute mortality.

Behavioural disinhibition in frontotemporal lobar degeneration syndromes

Preface

I recruited and tested all the participants in this study with help from Matthew Rouse. The Bayesian analysis of the stop no-go task was a collaborative effort between me, Frank Hezemans, Claire O'Callaghan and Ron Ye. I performed the remaining analysis and interpretation and wrote the text.

Summary

In this chapter, I report the neuropsychological results from the second study of my PhD, which used a transdiagnostic approach to test if behavioural disinhibition was associated with glutamate and GABA neurotransmitter deficits in the frontal lobe of FTLD syndromes. I used a recently developed Bayesian modelling program to calculate the stop signal reaction time and trigger failure rate from a stop no-go task. I show that different neuropsychological tests of frontal lobe function and different carer questionnaires both have good inter-test reliability. However, the correlations and inter-test reliability between carer questionnaires and neuropsychology are weaker. I show that the stop signal reaction time is prolonged in both bvFTD and PSP and correlates with carer ratings of global behavioural impairment. I then show that attentional failures alone do not explain stopping impulsivity in FTLD, as the stop signal reaction time correlates better than the stop trigger failure with other measures of impulsivity. This chapter confirms that the stop signal reaction time is a useful quantitative measure of behavioural disinhibition and could be used to investigate the neurobiology of one aspect of disinhibited behaviour in FTLD.

Introduction

In the previous chapters, I showed that behavioural disturbance is seen with all FTLD syndromes and associated with greater risk of care home admission. Better treatment of behavioural symptoms is likely to improve functionally independent survival and quality of life for patients and their families. Improved understanding of the aetiology of behavioural disturbance in FTLD, including structural (Lansdall *et al.*, 2017, 2018), neurophysiological (Cotelli *et al.*, 2018, Hughes *et al.*, 2018*a*; Sami *et al.*, 2018) and neurochemical (Huey *et al.*, 2006; Passamonti *et al.*, 2018) alterations, may reveal targets for symptomatic treatments. However, it is important to carefully define what behavioural feature is of interest. Behavioural impairment in FTLD is multifactorial and includes disinhibition, apathy, loss of empathy, compulsions and hyperorality (Rascovsky *et al.*, 2007). These features overlap and correlate, as evidenced by them all loading onto the same principal component in chapter one, but this does not mean they have a common neural correlate (Rosen *et al.*, 2005). In this chapter, I chose to focus on the neuropsychology of behavioural disinhibition, a common and disabling behavioural impairment in FTLD syndromes (Lansdall *et al.*, 2017).

Disinhibited behaviour encompasses a range of socially inappropriate and impulsive actions. Socially inappropriate behaviours include violations of social norms, for example kissing strangers, public urination or shoplifting, telling inappropriate or offensive jokes, poor table manners or queue jumping (Panchal *et al.*, 2016). Impulsive behaviour describes decisions or actions that are premature and without foresight, poorly conceived and risky or inappropriate, for example reckless driving, spending excessive amounts of money or the motor recklessness which causes many falls in PSP (Franken *et al.*, 2008; Dalley *et al.*, 2011; Dalley and Robbins, 2017). It may not always be clear which of these factors contribute to a manifestly disinhibited behaviour. Consider for example a patient who eats food off a stranger's plate (Aiello *et al.*, 2016): is this caused by a loss of awareness of social norms (Lough *et al.*, 2006; Mendez *et al.*, 2014; O'Callaghan *et al.*, 2016), a change in the relative reward value of food (Perry *et al.*, 2014; Bertoux *et al.*, 2015), hyperorality due to hypothalamic dysfunction (Ahmed *et al.*, 2015, 2016*a*) insensitivity to negative consequences (Perry *et al.*, 2017*b*), a failure to inhibit an environmentally-dependent action (Lansdall *et al.*, 2017), or a combination of factors? Impulsive behaviours can be further fractionated into the waiting and stopping forms of impulsivity (Dalley and Robbins, 2017). Waiting impulsivity refers to an inability to wait before making an appropriate decision, either until enough information has been gathered or a signal is given. Stopping impulsivity refers to an inability to inhibit an action after it has been initiated, but before it is fully executed. Response inhibition enables suppression of inappropriate or

unwanted actions and is critical for many everyday tasks (Mostofsky and Simmonds, 2008). These impulsivity subtypes may occur together. However, in studies of both health and disease they are only partially correlated and are regulated by distinct brain regions, neurotransmitters and networks (Dalley *et al.*, 2011; Green and Myerson, 2013; MacKillop *et al.*, 2016; Dalley and Robbins, 2017). This fractionation of behaviour implies a differential response to symptomatic treatments.

Impulsive behaviours are regulated by parallel neural networks between cortical and subcortical structures and modulated by several neurotransmitter systems. Waiting impulsivity is regulated by interactions between prefrontal regions, including the anterior cingulate, prelimbic and infralimbic cortices, and the hippocampus, amygdala and the nucleus accumbens core and shell in the ventral striatum (Basar *et al.*, 2010; Dalley *et al.*, 2011; Dalley and Robbins, 2017). Stopping impulsivity, or response inhibition, is closely associated with a network between motor and premotor cortex and inferior frontal gyrus with the dorsal striatum and subthalamic nucleus (Aron *et al.*, 2003, 2004; Chambers *et al.*, 2009; Dalley *et al.*, 2011; Dalley and Robbins, 2017). The right inferior frontal gyrus is strongly associated with response inhibition (Aron *et al.*, 2014). Loss of awareness for social norms is also associated with atrophy or loss of connectivity between orbitofrontal cortex, anterior cingulate, insula and right inferior frontal gyrus (Healey *et al.*, 2015; Baez *et al.*, 2016; O'Callaghan *et al.*, 2016). Impaired response inhibition (Hughes *et al.*, 2018*a*) and socially inappropriate behaviour (Melloni *et al.*, 2016) are both associated with abnormal frontotemporal beta oscillation connectivity, which may be a common mechanism underlying these impaired behaviours in FTLD (Hughes *et al.*, 2018*b*; Ibáñez, 2018).

Frontotemporal lobar degeneration syndromes are associated with all forms of impulsive behaviour (González Sánchez *et al.*, 2010, O'Callaghan *et al.*, 2013*a*; Passamonti *et al.*, 2018). The PIPPIN study included both patient and carer impulsivity questionnaires and neuropsychological tests of risk taking, waiting and stopping impulsivity. All impulsivity subtypes were more severe in one or more of the FTLD syndromes compared to healthy controls (Lansdall *et al.*, 2017). However, the correlations between them were limited and different modes of impulsivity were associated with distinct patterns of brain atrophy (Lansdall *et al.*, 2017). This occurs in other neurodegenerative conditions, for example Parkinson's disease (O'Callaghan *et al.*, 2013*b*; Mosley *et al.*, 2019; O'Callaghan, 2019).

There is evidence for the multifaceted nature of impulsivity in FTLD syndromes. Carer questionnaires report impulsive behaviours in bvFTD (Bozeat *et al.*, 2000; Zamboni *et al.*, 2008, O'Callaghan *et al.*, 2013*a*) and PSP (Aarsland *et al.*, 2001; González Sánchez *et al.*, 2010; Gerstenecker *et al.*, 2013), with evidence of waiting impulsivity (Bertoux *et al.*, 2015; Beagle *et al.*, 2020) and risk-taking (Rahman *et al.*, 1999) and impulse control disorders in bvFTD (Manes *et al.*, 2010) and PSP (O'Sullivan *et al.*, 2010). Response inhibition is impaired in both bvFTD (O'Callaghan *et al.*, 2013*b*; Hughes *et al.*, 2015) and PSP (Dubois *et al.*, 2005, Zhang *et al.*, 2016*a*). Some deficits in cognitive and inhibitory control, including the Stroop and Hayling tests, occur in bvFTD, PSP and also Alzheimer's disease (Collette *et al.*, 2007; Mariano *et al.*, 2019). The new PSP diagnostic criteria reflects this behavioural overlap between bvFTD and PSP, with the PSP-F subtype, which describes patients who have behavioural and executive dysfunction and slow vertical saccades (Höglinger *et al.*, 2017).

Impulsivity can be measured via questionnaires to participants or their relatives, which tend to measure global behavioural impairment, or neuropsychological tests designed to elicit specific impulsivity subtypes, e.g. the stop-signal task. Self-ratings of impulsivity, using questionnaires such as the Barratt Impulsivity Scale (Patton *et al.*, 1995), are often used. These have less utility in FTLD syndromes, which is associated with reduced insight into behaviour and personality change (O'Keeffe *et al.*, 2007). Self-assessment questionnaires are often intended for healthy, working-age adults and include questions which are not readily applicable to patients with neurodegenerative diseases (eg "How often do you change job?" or "How often do you move house?"). Questionnaires for relatives or carers may be more appropriate and several scales, including the Cambridge Behavioural Inventory (Wear *et al.*, 2008) and Neuropsychiatric Inventory (Cummings *et al.*, 1994), have been validated in neurodegenerative disease. However, these questionnaires are not measuring impulsive behaviour in isolation and may be influenced by the carer's own insight, personality and carer burden (Austin *et al.*, 1998; Mioshi *et al.*, 2013).

Specific neuropsychology tests can be useful biomarkers in human studies of impulsivity. Although they lack the direct clinical relevance of clinician- or carer-ratings of symptoms, they can be designed for specific cognitive and motor processes. This enables targeted studies to determine the neurobiology underlying behaviour impairments, for example neurotransmitter deficits. Stop-signal and no-go tasks (Verbruggen *et al.*, 2019) have been used to measure response inhibition associated with impulsivity in health (Bartholdy *et al.*, 2016; Tsvetanov *et al.*, 2018) and diseases such as attention deficit hyperactivity disorder (Lipszyc and Schachar,

2010; Senderecka *et al.*, 2012), obsessive compulsive disorder (Penadés *et al.*, 2007; McLaughlin *et al.*, 2016), addiction (Smith *et al.*, 2014), schizophrenia (Hughes *et al.*, 2012, Matzke *et al.*, 2017*a*), Parkinson's disease (Ye *et al.*, 2015; Rae *et al.*, 2016) and FTLD syndromes (O'Callaghan *et al.*, 2013*a*; Hughes *et al.*, 2015; Lansdall *et al.*, 2017). I therefore chose the stop signal task to measure response inhibition in FTLD syndromes.

Successful response inhibition requires sustained attention to stop in response to countermanding cues, in addition to inhibitory control (Badcock *et al.*, 2002). Stop-signal task performance can be analysed to identify attentional (e.g. trigger failure rate) and inhibitory deficits (e.g. stop-signal reaction time). They show that trigger failures are frequent in health and disease (Badcock *et al.*, 2002, Matzke *et al.*, 2017*b*, Skippen *et al.*, 2019*b*). Methods that fail to model trigger failures are liable to overestimate stop-signal reaction time, which then confounds the attentional and inhibitory impairments (Matzke *et al.*, 2017*a*). This may account for the poor correlation between SSRT and other measures of impulsivity in some studies (Enticott *et al.*, 2008; Shen *et al.*, 2014; McLaughlin *et al.*, 2016). In this study, I use a task that combines the stop-signal and no-go trials, to measure stopping impulsivity. I apply a recently developed Bayesian analysis to estimate both stop-signal reaction time and trigger failures.

Aims and hypotheses

I aimed to investigate the neurotransmitter changes associated with disinhibition (or stopping impulsivity) in FTLD syndromes. In this chapter, I report the basic demographics and neuropsychology of the study cohort. In the next chapter, I show the structural imaging and neurotransmitter results. I used the transdiagnostic approach to FTLD syndromes which I introduced in previous chapters. However, I limited recruitment to PSP and bvFTD as they showed the greatest behavioural impairment in the PIPPIN study and in particular targeted PSP patients with prominent behavioural impairments (PSP-F).

The aim of this chapter was to use the stop no-go task to quantify behavioural disinhibition in FTLD syndromes, and to compare this with carer ratings of global behavioural impairment. Specifically, I tested four hypotheses:

1. FTLD syndromes (bvFTD and PSP) are associated with behavioural disinhbition.
2. Carer questionnaires and neuropsychological tests measure different facets of impulsivity and poorly correlate.
3. Relative/carer questionnaires have high inter-test reliability and report multifacted disinhibition in FTLD syndromes.

4. The combined stop/no-go task identifies both disinhibited behaviour (stop signal reaction time) and attentional deficits (stop trigger failure) in FTLD syndromes.

Methods

Participant recruitment

Forty-four patients with bvFTD or PSP were recruited from the PIPPIN cohort, specialist cognitive and movement disorder clinics at the Cambridge Centre for FTD and Related Disorders and the "Join Dementia Research" patient database. All patients had a clinical assessment, including history, examination and carer interview, to confirm they met the diagnostic criteria for bvFTD (Rascovsky *et al.*, 2011) and/or PSP-RS and/or PSP-F (Höglinger *et al.*, 2017). Disease severity was assessed with the Clinical Dementia Rating scale modified for FTLD (Knopman *et al.*, 2008, 2011) and Progressive Supranuclear Palsy Rating Scale (Golbe and Ohman-Strickland, 2007). Twenty age and sex matched controls with no history of a neurological or psychiatric illness were recruited from the Join Dementia Research database. All participants gave written informed consent. The study had ethical approval from the Cambridge Central Research Ethics Committee (REC 16/EE/0351 and 16/EE/0084).

Cognitive and behavioural assessment

Participants underwent a cognitive and neuropsychological assessment. This included an assessment of global cognitive function, the Addenbrooke's Cognitive Examination-Revised (ACER) (Mioshi *et al.*, 2006), and tests of executive function including the Frontal Assessment Battery (FAB) (Royall, 2001), Hayling Sentence Completion test (Burgess and Shallice, 1997) and INECO Frontal Screening test (Torralva *et al.*, 2009*b*). Each participant's closest relative completed questionnaires including the Cambridge Behavioural Inventory-Revised (CBI-R) (Wear *et al.*, 2008), Frontotemporal Dementia Rating Scale (FRS) (Mioshi *et al.*, 2010) and Cambridge Questionnaire of Apathy and Impulsivity. I report the Hayling A+B score instead of total, as this is a better measure of response inhibition than the total scaled score (O'Callaghan *et al.*, 2013*b*; Martyr *et al.*, 2019). A "CBI-Impulsivity" score was calculated using the abnormal behaviour, euphoria mood, eating habits and stereotyped and motor behaviour subscores of the CBI (Borroni *et al.*, 2012; Hughes *et al.*, 2015).

Many carer questionnaires are not specific to the impulsive behaviours in FTLD syndromes, instead capturing global cognitive and behavioural impairments. Moreover, in PIPPIN, some carers found them hard to complete. Questionnaires are often long and susceptible to carer fatigue, which can result in repetitive box ticking without taking time to consider the questions individually (Edwards, 2010). I therefore designed, with input from Dr Luca Passamonti and Dr Claire O'Callaghan, a very short pragmatic questionnaire. It asked four questions on the

frequency of different manifestations of disinhibited behaviour typically reported in FTLD syndromes (Figure 6-1). The questionnaire total was the sum of all the questions (never=0, monthly=1, weekly=2, daily=3, greater than daily=4).

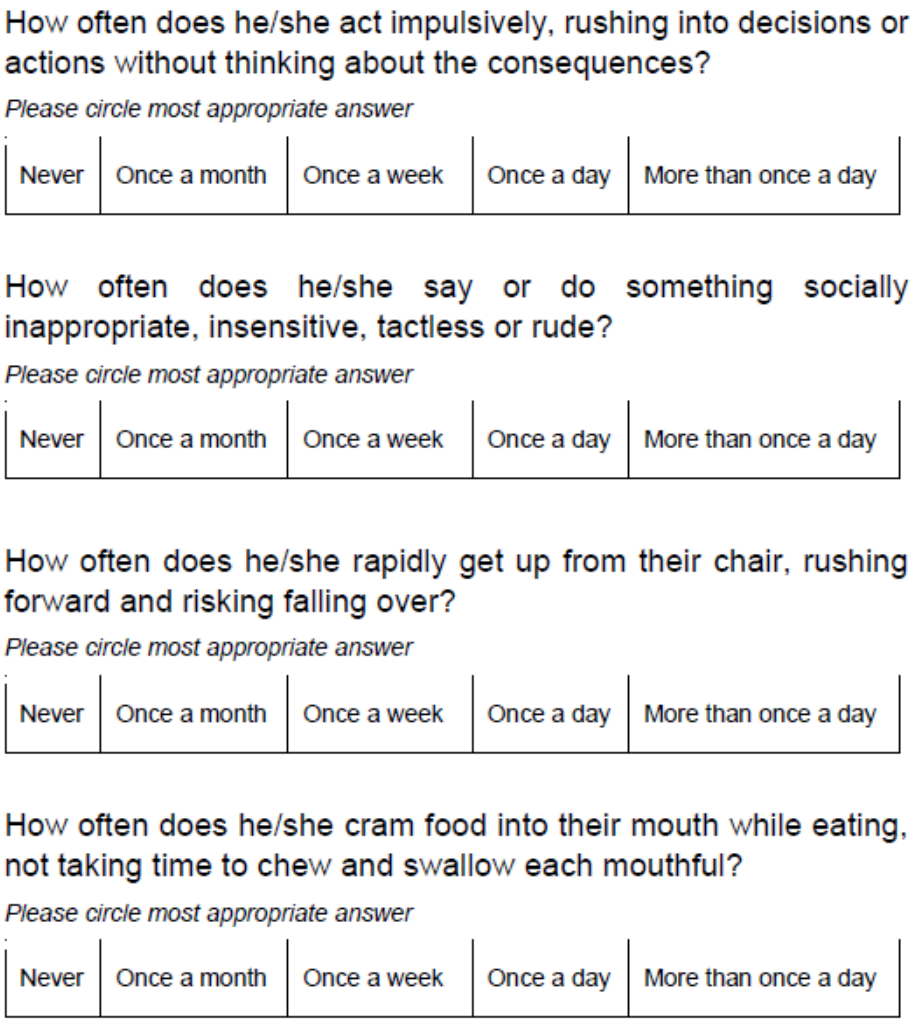


Figure 6-1: Proposed FTLD Impulsivity questionnaire.

Missing data (2.94% of the total dataset) was replaced with trimmed scored regression (Folch-Fortuny *et al.*, 2016). A standardised Cronbach's alpha was calculated to measure the internal consistency between tests of impulsive behaviour. Independent, two-sample t-tests were used to compare neuropsychology results between FTLD and controls, p values were Bonferroni-corrected for multiple comparisons (Dunn, 1961).

Stop No Go task data collection and analysis

A combined stop-signal and no-go task was used to measure behavioural disinhibition. I used the same version of the "SNG" task used by the Cambridge Centre for Ageing and Neuroscience

population-based study (CAMCAN) (Tsvetanov *et al.*, 2018). Participants were presented with a series of trials consisting of either Go, No-go or Stop tasks and responded using a two-button box (Figure 6-2). On Go trials, participants pressed the left button when shown a left-pointing black arrow and pressed the right button when shown a right-pointing black arrow. On Stop trials, a black arrow was displayed and after a delay (the Stop Signal Delay, SDD), the arrow turned red and a beep sounded: participants were required to not make the response. On No-go trials, a red arrow was displayed from the start of the trial (SSD=0) and participants were required to make no response. Participants were asked to respond as quickly and accurately as possible and told neither to slow down on Go trials nor wait for a possible Stop signal. I ran this task with all participants to avoid any inter-operator variability.

The task consisted of 5 blocks of 120 trials. The Go task comprised 75% of all trials (n=450), the No-Go task 8.5% (n=51) and the Stop task 16.5% (n=99). On stop trials the delay between go and stop signals, the stop signal delay (SSD), was changed using a staircase algorithm to reach a cumulative stop accuracy of 50%. The starting SSD was calculated from twenty go trials at the start of each block (average Go RT minus 250ms, equivalent to a starting estimated SSRT of 250ms). Participants had a practice session of twenty trials prior to the first block.

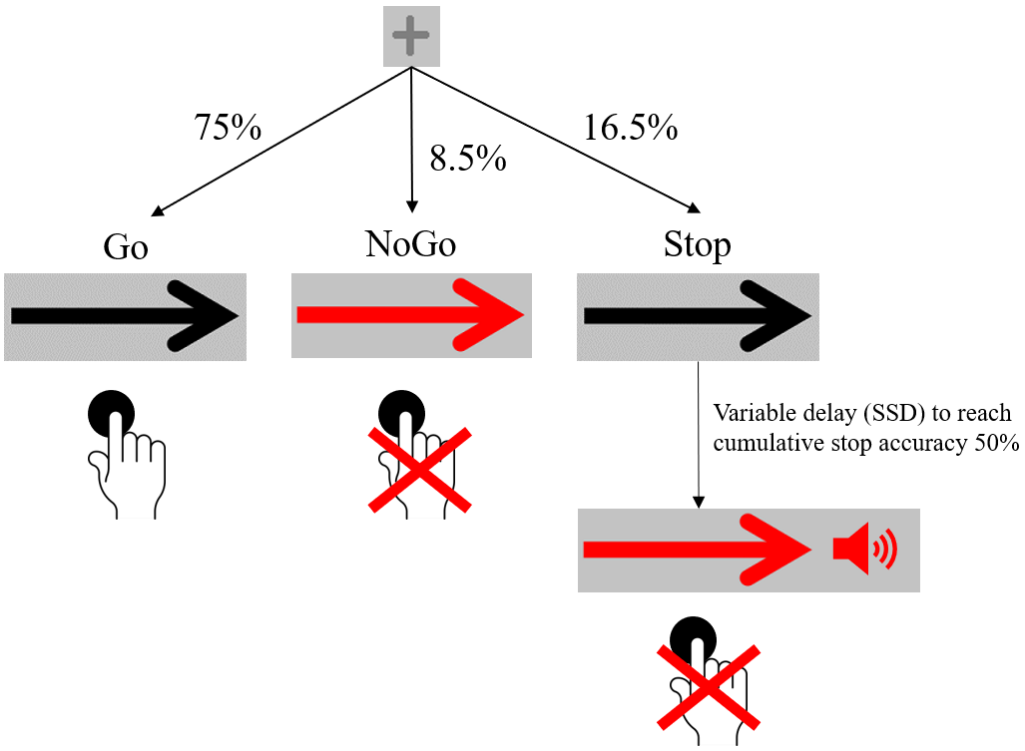


Figure 6-2: Description of the Stop No-Go task. Each trial started with a fixation cross, then either a go (black arrow) or no-go (red arrow) or stop (black arrow followed by red arrow and beep) stimulus presented. The delay between the go and stop arrow on stop trials (the stop signal delay) varied in a staircase algorithm to target a cumulative stop accuracy of 50%

The primary outcome of the task is the time required to successfully inhibit responses, called the stop-signal reaction time, SSRT. The task is conceived as a "race" between a go process, which is triggered by the go stimulus, and a stop process, which is triggered by the stop signal (Logan *et al.*, 2014). If the stop process is faster than the go process, response inhibition is successful; and no response made (successful stop trial). If the go process is faster than the stop process, inhibition is unsuccessful and a commission error response is made (unsuccessful stop trial). The latency of successful stop trials is the primary end point but this cannot be measured directly, as successful response inhibition does not result in an observable response. Therefore, analysis requires calculation of the SSRT. The SSRT is an estimation of the speed of the unobserved stop process.

There are several methods of calculating the SSRT (Verbruggen *et al.*, 2019). I used the recently developed Dynamic Models of Choice (DMC), which uses parametric Bayesian hierarchical analysis of the stop-signal tasks (Matzke *et al.*, 2013; Heathcote *et al.*, 2019). This model has several advantages over other methods. First, it provides a probabilistic distribution, rather than a single mean, SSRT which may more accurately reflect disease-related disinhibition (Matzke *et al.*, 2013). Second, the model quantifies attentional failures, which occur when a participant fails to react. These "trigger failures" are common in health (Matzke *et al.*, 2017*b*) and diseases

such as schizophrenia (Matzke *et al.*, 2017*a*), and if not modelled may cause overestimation of the SSRT (Matzke *et al.*, 2019, Skippen *et al.*, 2019*b*) . Third, the model can accommodate choice errors by including two Go processes, separately for left and right responses (Heathcote *et al.*, 2019). Finally, hierarchical Bayesian methods regularise participant-level estimates according to group statistics, which enables reliable group-level inference and produces, on average, more accurate participant-level estimates (Millsap *et al.*, 2012).

I pre-processed the task results before the Dynamic Models of Choice analysis. Implausibly short (<250ms) or long (>4500ms) reaction time trials were excluded, as were any go reaction times that were greater than 2.5 standard deviations from the participant's mean. The pre-processing pipeline also created a figure for each participant that enabled quality assurance prior to modelling (example in Appendix 4).

The model assumes a race between three independent processes: one corresponding to the stop process, and two corresponding to go process that match or mismatch the choice stimulus. A correct go response occurs when the matching go process finishes before the mismatching go process. Successful stop trials occur when the stop process finishes before either of the go processes. The model assumes that the finishing times of these processes follow an ex-Gaussian distribution, which is typical for reaction time data (Dawson, 1988; Heathcote *et al.*, 1991; Whelan, 2008). The model estimates the mean μ, standard deviation σ and exponential decay τ of the ex-Gaussian distribution separately for each process. It also includes two attentional failure parameters that represent the probability that the go and stop processes fail to start ("trigger failure").

In Bayesian parameter estimation, the priors are updated with the observed study data, or likelihood, so as to give a posterior probability distribution. This posterior distribution cannot be derived analytically and is approximated with a differential-evolution Markov chain Monte-Carlo (MCMC) algorithm (Turner *et al.*, 2013). The prior probabilities were based on the reference priors provided by the model developers (Heathcote *et al.*, 2019). The priors for mean Go and Stop RT were increased to 1000 and 1500ms respectively, because slow reaction times are a feature of both bvFTD and PSP (Dubois *et al.*, 1988, Torralva *et al.*, 2009*a*). MCMC sampling draws sequences of samples of the posterior distribution, which continues until equilibrium is reached between the multiple iterations of each chain. Initially I ran the model using 33 chains (i.e., three times the number of parameters), with thinning of every 10^{th} sample and a 5% probability of migration for both the group and participant levels (Matzke *et al.*,

2019). I then assessed convergence of the MCMC chains with visual inspection of the trace plots and the Gelman-Rubin statistic (Gelman and Rubin, 1992). After this, I obtained an additional 500 iterations for each chain to create a final posterior distribution of each parameter, to be used for further analyses.

Separate models were run for patient and control participants. The hierarchical modelling uses information from the entire group to estimate population-level parameter estimates which are then used to improve individual-level parameter estimates. This assumes parameters from individuals in a group come from the same population distribution. Hierarchical estimates tend to be more precise and accurate than individual estimates, especially where there are a limited number of trials for each participant. In the current task, each participant completes a relatively small number of stop trials (16.5% of all trials, half of which are successful). The hierarchical modelling improves parameter estimates of the stop process (Matzke *et al.*, 2017*b*).

The Dynamic Models of Choice software was run using R (Version 3.6.1) on the High-Performance Hub for Informatics computing cluster at the University of Cambridge.

Statistical analysis

I compared neuropsychology results between FTLD and healthy control participants with independent two-tailed t-tests. Inferred p-values were false discovery rate adjusted to correct for multiple comparisons (Benjiamini *et al.*, 1995). For the results of the Dynamic Models of Choice analysis, a credible interval was defined as the 95% high-density interval (HDI) from each parameter posterior distributions. A between-group difference was reported if there was no overlap between the FTLD and control group-level 95% HDIs (Kruschke, 2018) .

Results

Forty-four patients with an FTLD syndrome participated in the study. The primary diagnoses were evenly split between bvFTD (n=22) and PSP (n-22) but there was considerable overlap in patients meeting the diagnostic criteria for bvFTD, PSP-F and PSP-RS (Figure 6-3). Thirty-six patients met the diagnostic criteria for probable bvFTD, nineteen patients met criteria for PSP-F and twenty-three patients met criteria for PSP-RS. Fifteen patients met the diagnostic criteria for all three of these FTLD syndromes. Two patients with bvFTD had parkinsonism but did not meet the diagnostic criteria for PSP. I therefore use a transdiagnostic approach when reporting these results and refer to all patient with bvFTD or PSP as "FTLD". Twenty age and sex-matched healthy volunteers were recruited as controls (Table 6-1).

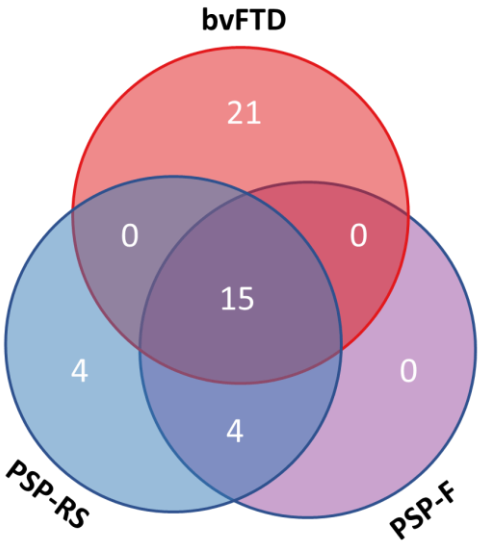


Figure 6-3: Venn diagram of overlapping FTLD syndrome subtypes. Each number is the number of participants meeting the respective diagnostic criteria

	Control	FTLD	t value	p value
Number	20	44		
Age mean (SD)	67.12 (5.61)	66.72 (8.20)	-0.044	0.965
Sex (%male)	65.00	71.43	0.263 *	0.608
Years of education	14.95 (2.95)	12.30 (3.14)	3.19	0.002
Onset to study	NA	5.84 (11.3)	NA	NA
Diagnosis to study	NA	1.08 (1.48)	NA	NA

Table 6-1: Demographics of the study cohort.

The neuropsychology results are shown in Table 6-2. Patients had impairments in multiple cognitive domains, with reduced scores in the memory, fluency, language and visuospatial domains of the Addenbrooke's Cognitive Examination compared to healthy controls (Table 6-2). In particular, FTLD patients had impaired executive function, with lower scores on the Frontal Assessment Battery (FAB), INECO Frontal Screening and Hayling Sentence Repetition test (Table 6-2). A carer questionnaire, the Cambridge Behavioural Inventory Revised (CBIR), confirmed profound behavioural impairments across a range of domains, including self-care, mood, abnormal eating, stereotyped motor behaviours, motivation and everyday skills (Table 6-2). Patients with FTLD also had high scores on the Cambridge Questionnaire of Apathy and

Impulsivity (CAMQUAIT), the CBI Impulsivity composite score (Borroni *et al.*, 2012) and the FTLD impulsivity questionnaire designed for this study. Statistical comparison of the FTLD subgroups is in Appendix 3. There were differences between bvFTD and PSP on several measures, but not on a carer rating of impulsive behaviour (CBI Impulsivity composite).

Test	Control mean (SD)	FTLD mean (SD)	t value	Mean difference (95% CI)	p value
CDR-FTLD SOB	0 (0)	9.81 (5.19)	-8.42	(-12.1:-7.48)	**9.39E-12**
PSPRS Total	0.1 (0.31)	23.1 (17.81)	-5.75	(-31:-14.99)	**3.21E-07**
ACER Attention	17.95 (0.22)	14.24 (5.16)	3.2	(1.4:6.03)	2.17E-03
ACER Memory	21.3 (1.38)	15.93 (7.04)	3.37	(2.18:8.56)	**1.34E-03**
ACER Fluency	12.85 (1.04)	4.33 (3.27)	11.32	(7.01:10.02)	**1.57E-16**
ACER Language	25.5 (0.83)	20.1 (6.83)	3.51	(2.33:8.48)	**8.50E-04**
ACER Visuospatial	15.8 (0.52)	12.14 (4.55)	3.57	(1.61:5.71)	**7.16E-04**
ACER Total	96.2 (2.71)	68 (24.11)	5.19	(17.3:39.06)	**2.61E-06**
FAB	17.45 (0.83)	11.14 (5.14)	5.43	(3.98:8.63)	**1.09E-06**
Hayling (A+B score)	4.3 (7.12)	24.31 (19.58)	-4.42	(-29.1:-10.9)	**4.24E-05**
Hayling Total	18.45 (2.28)	11.26 (4.83)	6.31	(4.91:9.47)	**3.72E-08**
INECO	25.78 (2.83)	14.2 (7.53)	6.63	(8.08:15.06)	**1.06E-08**
FTLD Impulsivity	0.52 (0.85)	5.55 (4.13)	-5.36	(-6.9:-3.15)	**1.39E-06**
CBIR Memory	2.06 (2.01)	12.12 (8.43)	-5.24	(-13.9:-6.22)	**2.14E-06**
CBIR Everyday skills	0.15 (0.5)	9.33 (7.24)	-5.64	(-12.4:-5.92)	**4.87E-07**
CBIR Selfcare	0.02 (0.09)	5.12 (5.36)	-4.24	(-7.5:-2.69)	**7.90E-05**
CBIR Behaviour	0.72 (0.93)	6.38 (6.11)	-4.1	(-8.42:-2.9)	**1.25E-04**
CBIR Mood	0.86 (1.35)	3.4 (2.7)	-3.97	(-3.82:-1.26)	**1.93E-04**
CBIR Abnormal beliefs	0 (0)	1.21 (1.83)	-2.96	(-2.04:-0.39)	4.42E-03
CBIR Eating	0.3 (0.57)	6.07 (4.93)	-5.2	(-7.99:-3.55)	**2.55E-06**
CBIR Sleep	0.89 (1.28)	3.38 (2.53)	-4.15	(-3.69:-1.29)	**1.06E-04**
CBIR Motor behaviour	0.77 (1.21)	6.79 (5.8)	-4.57	(-8.65:-3.39)	**2.46E-05**
CBIR Motivation/apathy	0.58 (0.94)	10.81 (6.39)	-7.09	(-13.1:-7.34)	**1.77E-09**
CBIR Impulsivity	2.32 (2.73)	21.5 (16.57)	-5.12	(-26.7:-11.7)	**3.39E-06**
CBIR Total	6.35 (6.13)	64.62 (36.52)	-7.06	(-74.8:-41.8)	**1.98E-09**
FRS Total (Logit)	0.86 (0.3)	0.37 (0.28)	6.31	(0.33:0.64)	**3.66E-08**
CAMQUAIT	34.25 (8.95)	56.83 (10.3)	-8.41	(-28:-17.21)	**9.91E-12**

Table 6-2: Neuropsychology of FTLD syndromes (bvFTD and PSP). CDR-FTLD SOB: Clinical Dementia Rating scaling sum of boxes modified for FTLD. PSPRS: Progressive Supranuclear Palsy rating scale. ACER: Addenbrooke's Cognitive Examination-Revised. FAB: Frontal Assessment Battery. CBIR: Cambridge Behavioural Inventory Revised. FRS: Frontotemporal Dementia Rating Scale. CAMQAUIT: Cambridge Questionnaire for Apathy and Impulsivity. T and p values are from independent two-tailed t test for each test. P values in bold remain significant ($p<0.05$) after Bonferroni correction (1.85E-03).

First, I investigated the correlations between the tests of executive function and impulsivity (Figure 6-4). Neuropsychological measures of executive function, the Frontal Assessment Battery (FAB), Hayling Inhibition Score and INECO frontal screening test, correlated. The FAB and the INECO, which have many questions in common, correlated strongly (R 0.87, $p<0.001$). The Hayling verbal inhibition test weakly correlated with the FAB (R-0.35, $p<0.05$)

and INECO (R -0.49, p<0.01). Overall, the inter-test reliability between the three tests was very low (standardised Cronbach's alpha 0.026). There were stronger correlations between the carer measures of behavioural impairment, particularly the CBI Impulsivity composite score and the four impulsivity questions I created for the study (R 0.76, p<0.001). Overall, there was good inter-test reliability between the FTLD Impulsivity, CBI Impulsivity and CAMQUAIT questionnaires (standardised Cronbach's alpha 0.866). Correlations between tests of executive function and impulsivity were generally weak, apart from between the CBI Impulsivity score and Hayling (R0.44, p<0.01).

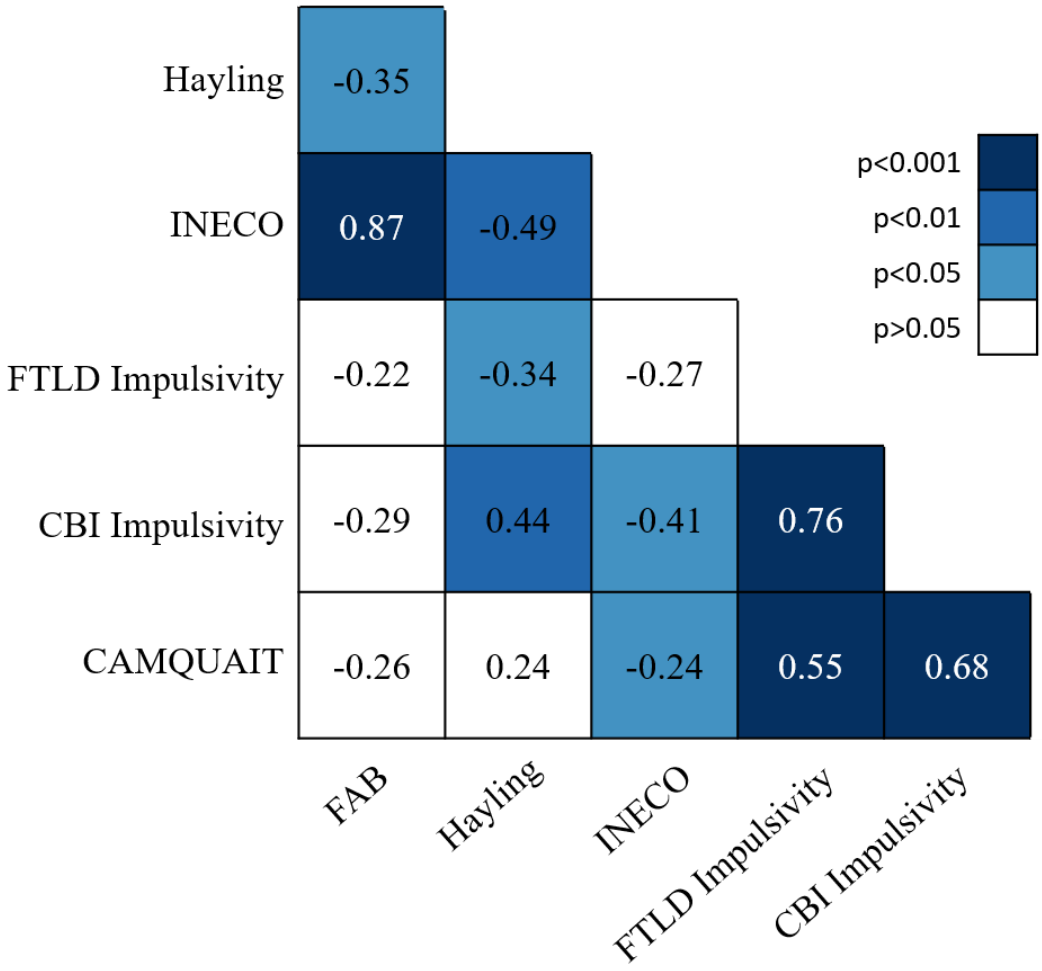


Figure 6-4: Correlation matrix of neuropsychology and carer questionnaires of behaviour. Values in each cell are Pearson's R for each pairwise correlation. Cells are colour-coded by FDR-corrected p values, pairwise correlations with FDR-p>0.05 are coloured white. FAB: Frontal Assessment Battery. Hayling: Hayling inhibition score (A+B errors). FTLD Impulsivity is the score from the questionnaire devised for this study (Figure 6-1).

Second, I used Bayesian hierarchical modelling of a stop no-go task to estimate the stop signal reaction time, a measure of response inhibition, and trigger failures, a measure of inattention, in FTLD. Data from eight FTLD participants was excluded, due to low number of completed trials (<50 stop trials). Remaining FTLD (bvFTD n=17, PSP n=18) and control participants completed a similar total number of trials (mean 663 vs 670 trials, Mann Whitney=300,

p=0.228) but FTLD participants made more go errors (Mann Whitney=185.5, p=0.003) and omissions (Mann Whitney=231.5, p=0.005). Results are summarised in Appendix 4.

Markov chain Monte-Carlo (MCMC) sampling adequately estimated the posterior distribution of each parameter. Visual inspection of the trace plots showed good convergence of MCMC chains (Posterior likelihood for FTLD and Control in Figure 6-5, trace plots for all parameters in Appendix 5). The Gelman-Rubin convergence statistics, which test MCMC overlap, were less than 1.1 for all parameters (FTLD: mean=1.00 SD=0.00 Control: mean=1.00 SD=0.01).

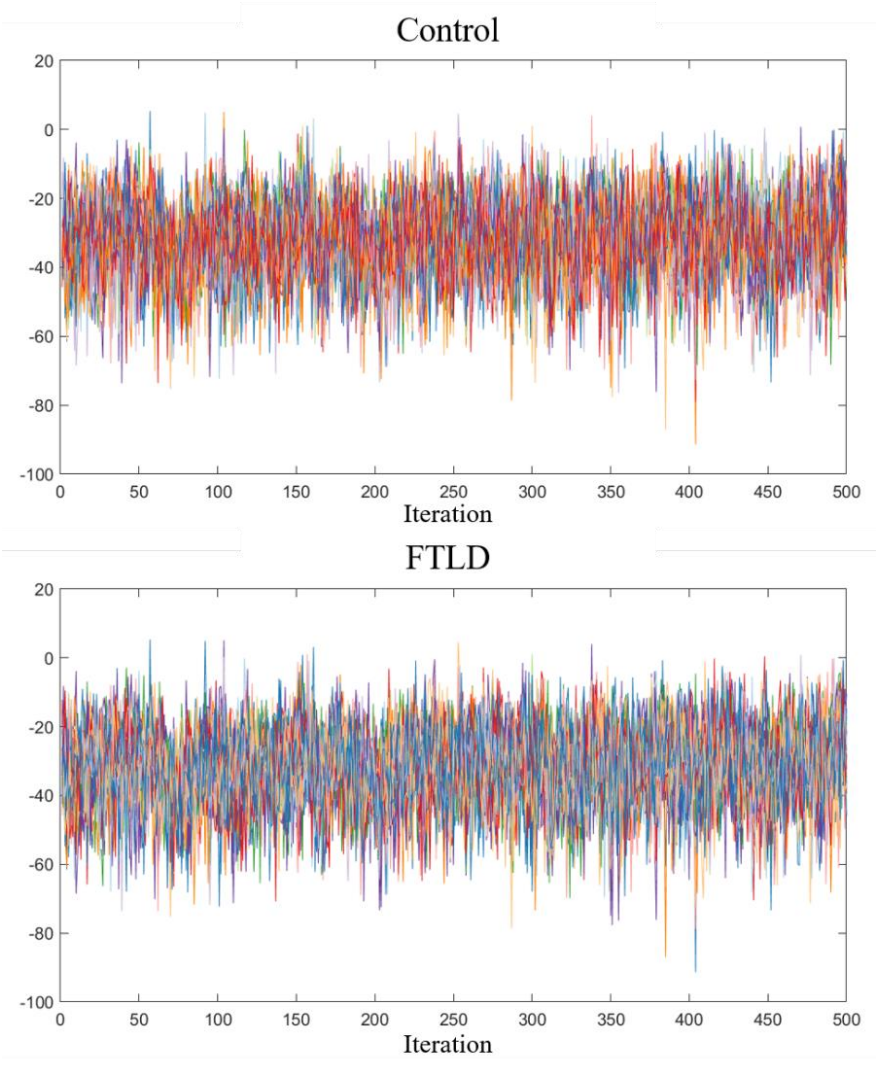


Figure 6-5: Trace plots of posterior likelihoods of DMC models for control and FTLD participants. Each line corresponds to one MCMC chain sampled from the model's joint posterior distribution. These plots (together with those in Appendix 5) enable visual inspection of the MCMC chains to ensure common problems (e.g. too few samples, serial correlations between samples, diverging sample chains) have not occurred. The ideal plot (like those above) should look like hairy caterpillars, where all the lines overlap, explore a sufficiently broad sample space and are flat (i.e. not trending up or down towards a final value that has not yet been reached).

The posterior estimates for the group and individual level go and stop reaction time distributions for FTLD syndromes and controls are shown in Figure 6-6. All control individual-level reaction

times were similar to the group-level distribution, with no evidence of strategic slowing. In FTLD, individual go reaction time distributions varied widely, some overlapped with the control distributions, but many were markedly longer (Figure 6-6A). There was similar variability in FTLD stop reaction time distributions (Figure 6-6C). There was a group-level difference in stop reaction time between FTLD and controls, with clear separation of the ex-Gaussian distributions and no overlap in the 95% highest density intervals of the mean reaction time (Figure 6-6D). Go reaction time did not differ significantly between groups, as evidenced by the overlapping HDI boundaries (Figure 6-6B).

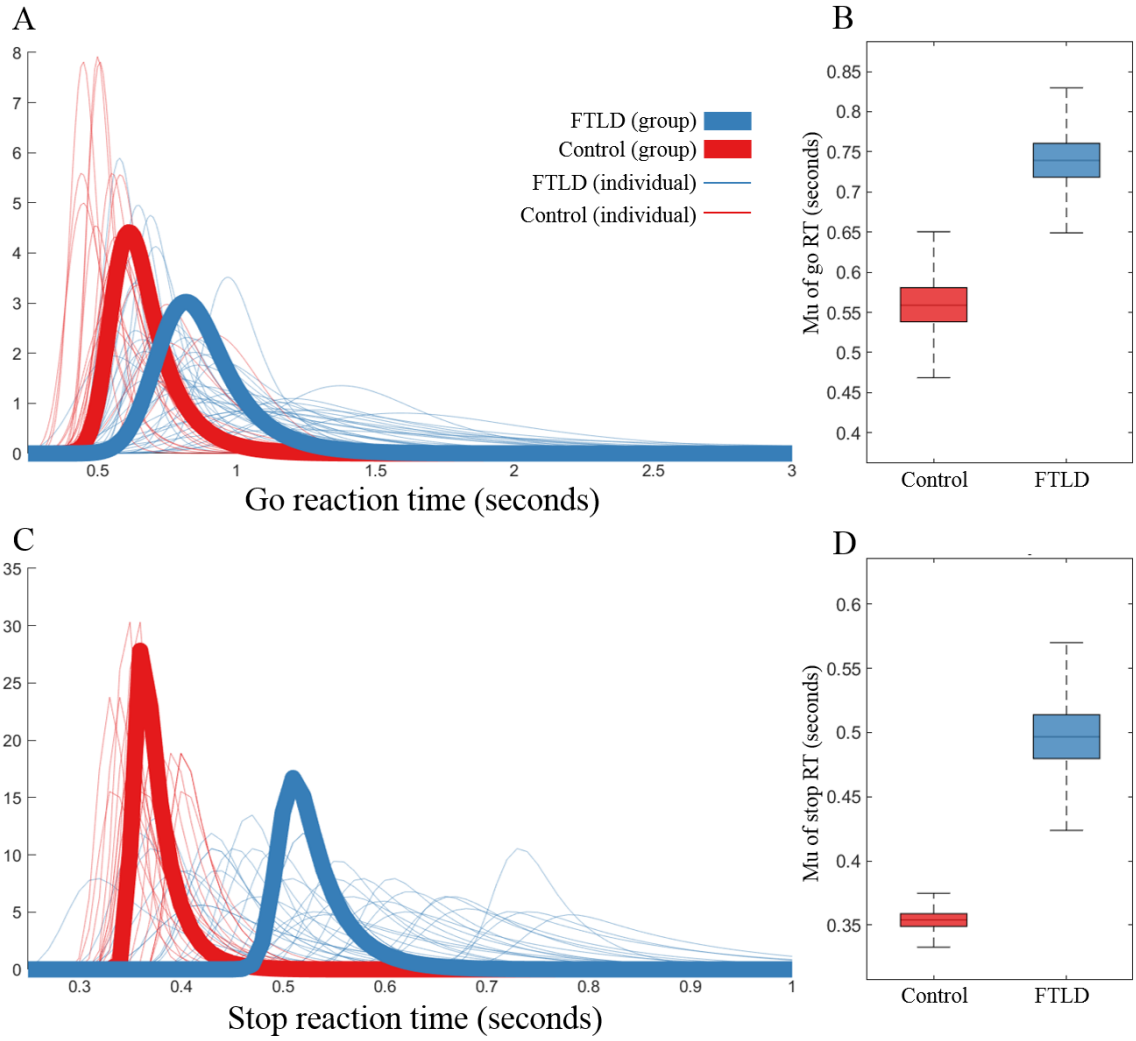


Figure 6-6: Reaction time distributions for FTLD syndromes (blue) and healthy controls (red). Group-level result is the thick line, individual-level results are the thinner lines. A: Go reaction time distributions. B: Boxplot of highest density interval for the μ of the go reaction time. The boxes represent the 25th to 75th highest density interval, the whiskers the 5th to 95th highest density interval.

The SSRT was longer in FTLD, indicating poor response inhibition (95% HDI 0.48-0.59 seconds) compared to controls (95% HDI 0.35-0.39 seconds) (Figure 6-7A). The probability of stop trigger failures was also higher in FTLD compared to healthy controls (FTLD 95% HDI

0.03-0.12, Control 95% HDI $3.72x10^{-4}$-0.008) (Figure 6-7B). There was no association between stop signal reaction time and stop trigger failure in FTLD participants (Spearman's rank correlation, R=0.17, p=0.33) (Figure 6-7C). The probability of go trigger failures was higher in FTLD, but the absolute trigger failure rate was very low in both groups (FTLD 95% HDI $1.79x10^{-4}$-0.002, Control 95% HDI $4.92x10^{-6}$-$7.79x10^{-5}$)

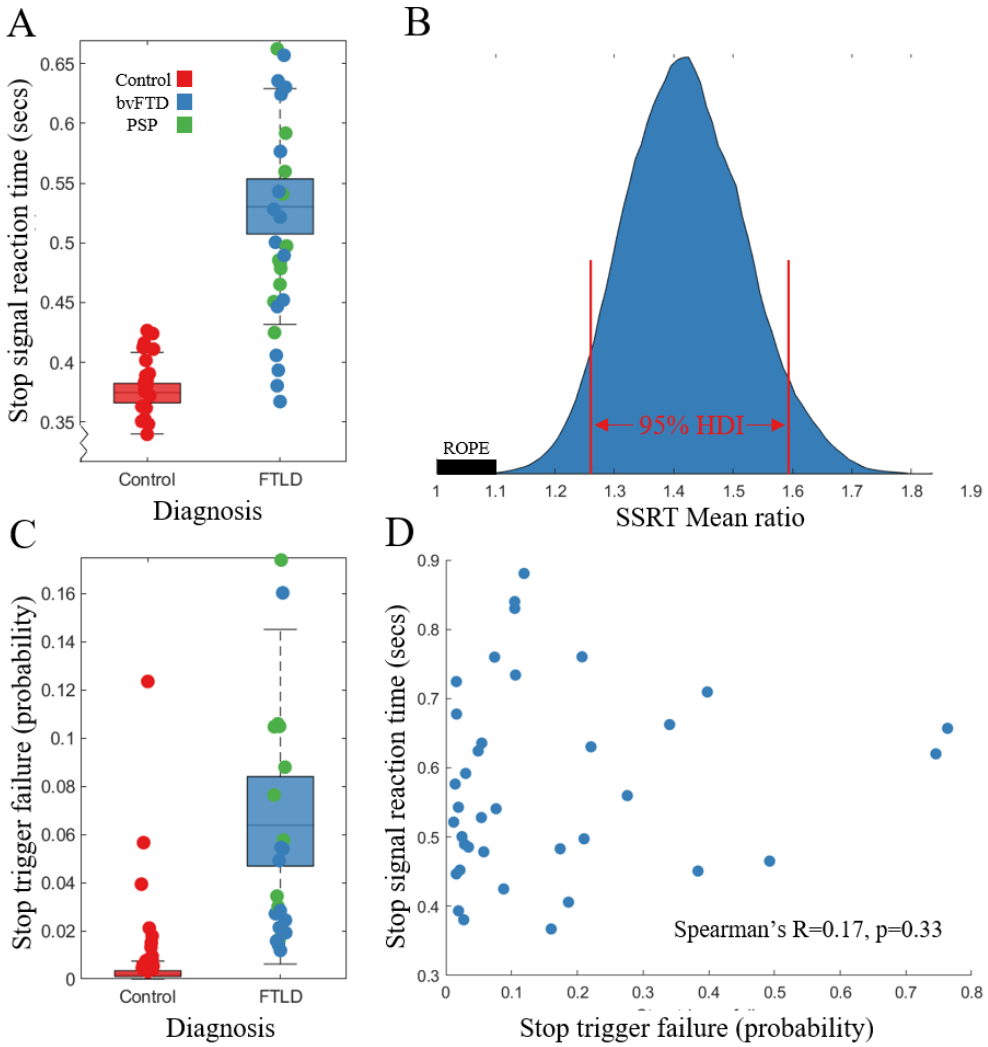


Figure 6-7: Primary outcomes of the Bayesian hierarchical modelling of the stop no-go task. A: Boxplot of highest density interval of stop signal reaction time (SSRT) by group. The scatterplot shows results from the individual analysis, colour coded by FTLD syndrome subgroup. B: Histogram of SSRT mean ratio (FTLD/Control) distribution. The 95% highest density interval (HDI) did not overlap with the pre-specified region of practical equivalence (ROPE) of -0.9 to 1.1. C: Boxplot of 95% highest density intervals for stop trigger failure probability. There was no overlap between the group 95% HDI trigger failure probability, suggesting there is a group difference. The scatterplot shows results from the individual analysis, colour coded by FTLD syndrome subgroup. For all boxplots the box shows the 50% highest density interval and the whiskers show the 95% highest density interval. D: Scatterplot comparing stop trigger failure and stop signal reaction time across all individuals.

Finally, I tested the correlation between stop no-go task performance (SSRT and stop trigger failure rate) and the other cognitive tests, neuropsychology and questionnaires (Figure 6-8). The SSRT correlated with the fluency (R=-0.57) and visuospatial (R=-0.45) subscore of the

Addenbrooke's Cognitive Examination, the Frontal Assessment Battery (R=-0.50) and INECO (R=-0.46). SSRT was also associated with higher scores on the total Cambridge Behavioural Inventory (CBI) (R=0.39) but not more specific questionnaires targeting impulsive behaviour (FTLD Impulsivity R=0.31, CBI Impulsivity R=0.18).

Stop trigger failures correlated with severity of global cognitive impairment (ACER total R=-0.41), including in attention (R=-0.44), memory (R=0.36) and visuospatial (R=-0.35) domains. There were weak correlations with executive function (FAB R=-0.39, INECO R=-0.35). There was no association between stop trigger failure and any carer ratings of behavioural impairment.

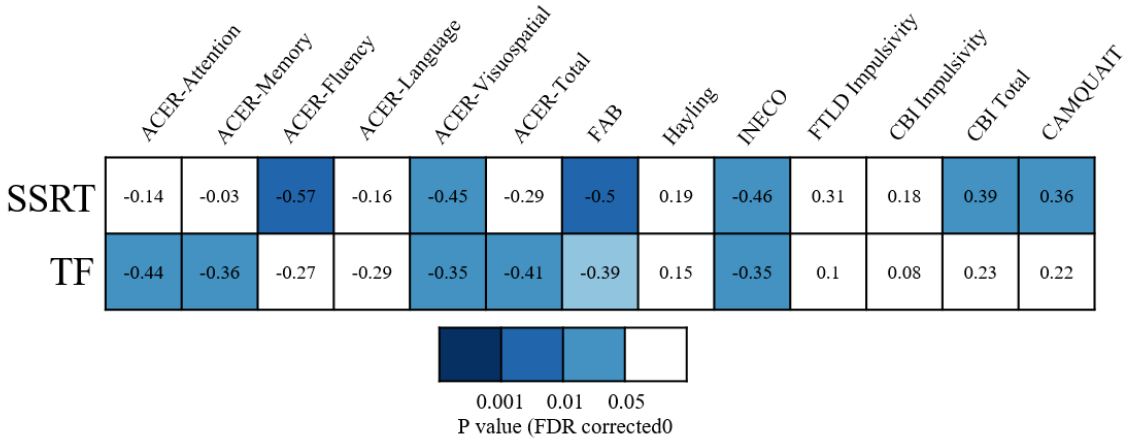


Figure 6-8: Correlation matrix between SSRT (stop signal reaction time) and TF (stop trigger failure probability) and the other neuropsychological tests and carer questionnaires of impulsivity. Results are from only the FTLD participants. The numbers in each cell are the R value from a Pearson's correlation between groups. Each cell is colour coded by the FDR (false discovery rate)-corrected p values. Cells with FDR-p <0.05 are white.

Discussion

This transdiagnostic study of behaviour in FTLD syndromes has four main findings. First, it confirmed multifaceted disinhibited behaviours are prevalent in FTLD syndromes. Second, the tests of different facets of executive dysfunction and behavioural impairment do not correlate but carer ratings of global behavioural impairment have good intra-rater reliability. Third, response inhibition is worse in FTLD syndromes and correlates with carer ratings of global behavioural impairment. Fourth, attentional failures alone do not explain stopping impulsivity in FTLD, as the stop signal reaction time rather than the stop trigger failure correlates with other measures of impulsivity. This chapter confirms that the stop signal reaction time is a potentially useful quantitative measure of stopping impulsivity and could be used to investigate the neurobiological basis of this facet of disinhibited behaviour in FTLD.

Carer ratings of global behavioural impairment were consistent. In contrast, there was limited association between neuropsychological tests of behaviour and executive function. The FAB, Hayling and INECO, all tests of executive function, correlated but had poor internal consistency. The strength of the correlation was associated with the number of questions in common between tests. The FAB and INECO, which share some questions (Royall, 2001, Torralva *et al.*, 2009*b*), strongly correlated. The Hayling and FAB, which do not overlap, only weakly correlated. Stop signal reaction time and stop trigger failure rates, despite being both proposed as measures of stopping impulsivity (Skippen *et al.*, 2019*b*; Verbruggen *et al.*, 2019), do not correlate. This heterogeneous behavioural phenotype is seen in other studies, even in the way patients with FTLD answer a single question. The ability to make conceptual links when answering a question like "in what way are a banana and an orange alike?" is tested by the FAB. Patients with a FTLD syndrome typically make either linking or abstraction errors, but these do not correlate and are associated with atrophy in distinct regions (Lagarde *et al.*, 2015; Garcin *et al.*, 2018). The different cognitive processes associated with executive function and behaviour have distinct anatomical (Turken and Swick, 1999; Alvarez and Emory, 2006; Clark *et al.*, 2008), neurophysiological (Neal and Gable, 2016; Mirza *et al.*, 2018; Parr *et al.*, 2019) and neuropharmacological correlates (Dalley and Roiser, 2012; Le Heron *et al.*, 2018; Passamonti *et al.*, 2018). This suggests that FTLD pathology simultaneously affects multiple brain networks, but to a variable extent across individuals

Neuropsychology and carer ratings of similar cognitive processes typically correlated, albeit weakly. For example, the CBI, a carer questionnaire of behavioural impairment, correlated with neuropsychological tests of response inhibition such as the Hayling inhibition score and SSRT.

However, the shared variance is small. This confirms the results from the PIPPIN study (Lansdall *et al.*, 2017). Importantly, it suggests that positive neuropsychology outcomes in pre-clinical (Bari *et al.*, 2009; Eagle *et al.*, 2009) and human studies (Hughes *et al.*, 2015; Rae *et al.*, 2016) may not translate into trials with clinical endpoints, such as a carer rating of behaviour. In a clinical trial, it may be important to use targeted assessments of behavioural subtypes, in addition to carer-ratings of global behavioural impairment.

Both SSRT and stop trigger failures were increased in FTLD syndromes but they did not correlate. The SSRT correlated with carer measures of behavioural impairment and stop trigger failure correlated with global, including attentional, cognitive impairment. In contrast, similar analyses in healthy volunteers (Skippen *et al.*, 2019*b*, *a*) and attention deficit hyperactivity disorder (ADHD) (Weigard *et al.*, 2019) found that impulsivity was associated with trigger failure, (i.e. attentional impairment) rather than SSRT (a measure of response inhibition). This may reflect a difference between trait impulsivity in healthy adults and ADHD (Chamberlain *et al.*, 2018), and pathological impulsivity due to neurodegeneration (O'Callaghan *et al.*, 2013*a*; O'Callaghan, 2019).

The SSRT correlated with carer ratings of global behavioural impairment (CBI-total) and impulsivity (CAMQUAIT). Response inhibition has been proposed to reflect a "brake" on the expression of multiple motor and cognitive states (Hughes *et al.*, 2018*b*). This can be considered in relation to disinhibited behaviour in FTLD syndromes. Consider again the example of eating food off other people's plates (Aiello *et al.*, 2016). The relative contribution of different behaviours outlined in the introduction may vary between patients but inhibitory control could be a final common pathway which, if impaired, fails to prevent the motor manifestations of disinhibition (Bari and Robbins, 2013, O'Callaghan *et al.*, 2013*a*). If this hypothesis was correct, partially restoring response inhibition could be an effective treatment for many behavioural impairments in FTLD syndromes.

This study used a transdiagnostic approach to impulsivity in FTLD syndromes, grouping bvFTD and PSP together. There were differences in many cognitive and behavioural measures between these FTLD syndrome subtypes. Patients with bvFTD tended to have greater cognitive impairment, executive dysfunction and behavioural impairment compared to the PSP group. This is because a proportion of PSP patients did not have severe cognitive and behavioural impairment, as evidenced by not meeting the criteria for PSP-F or bvFTD. However, fifteen patients with PSP met the diagnostic criteria for bvFTD, which is reflected in the overlap in

results between bvFTD and PSP. Interestingly, the CBI-behaviour and impulsivity composite score and the individual-level stop signal reaction time did not differ between bvFTD and PSP after correction for multiple comparisons. This, together with their shared structural (Lagarde *et al.*, 2013), neurophysiological (Sami *et al.*, 2018), neuropathological (Mackenzie and Neumann, 2016) and neurotransmitter (Murley and Rowe, 2018) deficits, justifies the transdiagnostic approach used in this study.

This study has several limitations. Patients with very severe behavioural disturbance were either unable to take part in the study or found the neuropsychology too difficult. Six patients were unable to complete the stop no-go task which requires sustained attention over 20 minutes. Any neuropsychological assessment of behaviour in FTLD syndromes may underestimate symptom severity at a population level. However, carer questionnaires are not limited by disease severity, and the CBI-R scores in this study were not different to the population-based PIPPIN study (bvFTD and PSP subgroups, $t(43)=-0.08$, $p=0.93$). SSRT only weakly correlated with carer ratings of behaviour, so any treatments that successfully shorten SSRT (i.e. improve response inhibition) may not have the same effect on carer ratings of behaviour. In this study, reaction times in the stop no-go task were recorded from button release rather that button press. That is likely to result in longer go and inaccurate stop reaction times and may disproportionately increase reaction time in individuals with akinesia. However, the critical SSRT estimation is unaffected. The hierarchical model used to estimate SSRT has many advantages, including the ability to account for trigger failures, produce a distribution of SSRT values and use group-level results to inform individual-level results to reduce the effect of outliers. However, this modelling is more complex and computationally demanding that the mean subtraction or integration methods (Verbruggen *et al.*, 2019).

Clinical trials of treatments for behavioural impairment in dementia tend to use carer questionnaires as the primary endpoint (Cummings *et al.*, 2014; Ballard *et al.*, 2018) but these have limitations. Answers may be influenced by many carer factors that change their perception of behavioural impairments. These include carer empathy (Hsieh *et al.*, 2013), resiliency (Jones *et al.*, 2019), stress (Mioshi *et al.*, 2009) and burden (Boutoleau-Bretonnière *et al.*, 2008, Armstrong *et al.*, 2013*b*). For example, an anxious, stressed, sleep-deprived spouse providing continuous care without respite is likely to have a different perspective on behavioural impairments to an adult child who lives separately and only sees their relative once a day. Using carer questionnaires as a study endpoint also raises ethical questions of who is being treated – the carer or the patient? This may be justified if, as the case with behavioural impairment in

FTD, carer ratings are associated with adverse patient outcomes such as increased care home admission.

In summary, carer questionnaires can be useful measures of widespread and heterogenous behavioural impairments in FTLD syndromes. The stop signal reaction time correlates, albeit weakly, with carer questionnaires of global behavioural impairment, and offers a specific measure of stopping impulsivity and behavioural disinhibition. The response inhibition task was taken forward to relate to the neurotransmitter deficits associated with behavioural disinhibition, in the next chapter.

The role of GABA and glutamate in behavioural disinhibition in frontotemporal lobar degeneration syndromes

Preface

I recruited all the participants, performed the magnetic spectroscopy scans, analysed the data and wrote the text of this chapter. I had help from Matthew Rouse with participant recruitment, the radiographers at the Wolfson Brain Imaging Centre with the 7T MRI scanning and Simon Jones and Dinesh Deelchand with data analysis. Part of the discussion is included in a review article I co-authored (Murley and Rowe, 2018).

Summary

Neurotransmitter deficits associated with disease are a promising target for symptomatic treatments. In this chapter I use ultra-high-field magnetic resonance spectroscopy to measure glutamate and GABA *in vivo* in FTLD syndromes. I show that frontal lobe GABA and glutamate concentrations are reduced *in vivo* in FTLD, but there is a disproportionate GABAergic deficit that persists after partial volume correction. This neurotransmitter deficit is associated with disinhibition, as measured by the stop signal reaction time.

Introduction

Impulsivity is a prominent symptom in FTLD syndromes but has few effective pharmacological treatments (Huey *et al.*, 2006; Manoochehri and Huey, 2012). Improving our understanding of the neurobiology of impulsivity in FTLD may reveal new targets for symptomatic treatments. One strategy is to reverse any neurotransmitter deficits, which has been effective in other neurodegenerative diseases. For example, reversing the dopaminergic deficit in Parkinson's disease improves motor symptoms (Cotzias *et al.*, 1967; Bernheimer *et al.*, 1973; Marsden and Parkes, 1977; Hornykiewicz, 2002) and partially restoring the cholinergic deficit in Alzheimer's disease (Francis *et al.*, 1999) slows cognitive decline and reduce rates of nursing home admission (Lopez *et al.*, 2002; Birks, 2006). These positive results suggest that neurotransmitter deficits could be a tractable target for symptomatic treatments in FTLD syndromes (Huey *et al.*, 2006; Murley and Rowe, 2018).

Neurotransmitter deficits contribute to many symptoms and the phenotypic overlap in FTLD syndromes. For example, dopaminergic deficits in bvFTD are associated with a PSP-like parkinsonism (Rinne *et al.*, 2002; Sedaghat *et al.*, 2007) and cholinergic deficits in PSP contribute to cognitive impairment (Warren *et al.*, 2005). The neurotransmitters glutamate and gamma-Aminobutyric acid (GABA) are associated with behavioural impairment in health and other neurological and psychiatric diseases but there is limited evidence on their role in FTLD.

In this chapter I aimed to measure glutamate and GABA concentrations in FTLD syndromes and test their association with disinhibition. Glutamate and GABA are the primary excitatory and inhibitory neurotransmitters in the brain (DeFelipe, 1993; Markram *et al.*, 2004). Neocortical micro networks consist of excitatory glutamate-producing (glutamatergic) neurons and inhibitory GABA-producing (GABAergic) interneurons (Tremblay *et al.*, 2016; Schmidt-Wilcke *et al.*, 2018). Synchronised interaction between and within these neural networks generates oscillations which are thought to underlie complex brain functions such as consciousness, cognition and behaviour (Ward, 2003; Buzsaki *et al.*, 2004; Bastos *et al.*, 2012). Glutamate and GABA neurotransmission is critical to regulate and coordinate activity within these neural networks and disrupting the balance between glutamate and GABA levels has adverse effects on cognition and behaviour (Tremblay *et al.*, 2016). For example, glutamate receptor (NMDA) antagonists impair attention, reaction time, processing speed and working memory (Malhotra *et al.*, 1996; Newcomer *et al.*, 2000) and exacerbate psychotic symptoms (Morgan *et al.*, 2010; Gilmour *et al.*, 2012) in healthy adults. Drugs that act on GABA receptors,

including alcohol (Krystal *et al.*, 2006), barbiturates (Ito *et al.*, 1996) and benzodiazepines (Tan *et al.*, 2011), have widespread and well recognised effects on cognition and behaviour.

Research into the neurobiology of impulsivity in health and disease has primarily focussed on monoamine neurotransmitters such as dopamine, serotonin and noradrenaline (Dalley *et al.*, 2011; Dalley and Robbins, 2017). However, there is evidence that GABA and glutamate have an important role (Hayes *et al.*, 2014). In health, cerebrospinal fluid (Lee *et al.*, 2009) and prefrontal cortex (Boy *et al.*, 2011; Silveri *et al.*, 2013; Hermans *et al.*, 2018) GABA concentrations inversely correlate with disinhibition and risky decision making (Fujihara *et al.*, 2015). Magnetic resonance spectroscopy (MRS) has enabled *in vivo* measurement of glutamate and GABA in the human brain and has identified deficits in many diseases associated with impulsivity (Ende, 2015; Yasen *et al.*, 2017). GABA deficits are seen in addiction to cocaine (Ke *et al.*, 2004), opiates (Li *et al.*, 2020), alcohol (Behar *et al.*, 1999; Prisciandaro *et al.*, 2017) and gambling (Mick *et al.*, 2017), neurofibromatosis type 1 (Ribeiro *et al.*, 2015), autism (Puts *et al.*, 2017), attention deficit hyperactivity disorder (ADHD) (Edden *et al.*, 2012; Ende *et al.*, 2016) and obsessive compulsive disorder (Zhang *et al.*, 2016*b*). There is also an association between glutamate, measured in vivo with MRS, and self-reported impulsivity in healthy volunteers (Schmaal *et al.*, 2012*a*; Coccaro *et al.*, 2013), personality disorders (Hoerst *et al.*, 2010), ADHD (Naaijen *et al.*, 2015; Ende *et al.*, 2016) and addiction (Schmaal *et al.*, 2012*b*). The direction of the relationship between glutamate, GABA and impulsive behaviour is complex and may depend on disease (Ende, 2015), brain region (Dharmadhikari *et al.*, 2015; Naaijen *et al.*, 2015) and receptor subtype (Lee *et al.*, 2011*a*; Hermans *et al.*, 2018).

There is pre-clinical and clinical evidence of GABA and glutamate deficits in FTLD. In mouse models with pathological tau aggregates there is impairment of both glutamatergic (Gascon *et al.*, 2014; Warmus *et al.*, 2014; Decker *et al.*, 2016) and GABAergic (Levenga *et al.*, 2014; Li *et al.*, 2017; Jiang *et al.*, 2018) neuron function. In *post mortem* human studies, glutamatergic pyramidal neurons (Ferrer, 1999; Henderson *et al.*, 2000) and receptors (Francis *et al.*, 1993; Procter *et al.*, 1999; Bowen *et al.*, 2008; Gascon *et al.*, 2014) are reduced in FTLD. GABAergic neurons are reduced in frontotemporal dementia (Ferrer, 1999) and progressive supranuclear palsy (Levy *et al.*, 1995) with loss of $GABA_A$ receptors in some brain regions (Landwehrmeyer and Palacios, 1994; Suzuki *et al.*, 2002). *Post mortem* GABA concentrations are decreased in the basal ganglia in bvFTD (Kanazawa *et al.*, 1988). There is also emerging evidence of *in vivo* glutamate deficits (Benussi *et al.*, 2019). Magnetic resonance spectroscopy in FTD shows reduced glutamate/glutamine levels in the frontal and temporal lobes (Ernst *et al.*, 1997; Sarac

et al., 2008) and there is an inverse correlation between CSF glutamate levels and verbal agitation (Vermeiren *et al.*, 2013). PET studies have shown loss of glutamate and GABA receptors (Foster *et al.*, 2000; Leuzy *et al.*, 2016).

Aims and hypotheses

I aimed to measure *in vivo* glutamate and GABA concentrations in FTLD syndromes, using magnetic resonance spectroscopy (MRS), and to look for any association with behavioural disinhibition. Current MRS sequences measure glutamate and GABA in single brain regions, so regions of interest must be selected *a priori*. I chose the right inferior frontal gyrus as my experimental region of interest. The right inferior frontal gyrus has a critical role in response inhibition (Aron *et al.*, 2004, 2014), as shown with structural (Aron *et al.*, 2003) and functional studies (Swann *et al.*, 2009; Levy and Wagner, 2011; Rae *et al.*, 2015). Right inferior frontal gyrus GABA concentrations are also associated with impulsivity in healthy ageing (Hermans *et al.*, 2018). In FTLD, loss of functional connectivity in the inferior frontal gyrus is associated with impulsivity (Hughes *et al.*, 2015, 2018*a*). I measured neurotransmitters in a control region, the right occipital lobe, which is minimally affected by FTLD pathology (Riedl *et al.*, 2014).

The specific hypotheses for this chapter were: (1) GABA and glutamate levels are reduced in the frontal but not occipital cortex in FTLD compared to controls; (2) the *in-vivo* neurotransmitter deficits in the frontal lobe are associated with impulsivity, as measured by carer rating of impulsivity and the stop signal task, a neuropsychological measure of disinhibition. To test how neurotransmitter deficits relate to behaviour, one must account for atrophy. I hypothesised that frontal lobe grey and white matter volumes are reduced in FTLD and the severity of this atrophy is associated with disinhibition. I aimed to correct GABA and glutamate concentrations for the grey matter volume in the MRS region of interest.

Methods

Participant recruitment

The methods section in chapter 6 described the participant recruitment and neuropsychology test battery for this study. All participants who consented to the study and underwent neuropsychology were scanned on a Siemens MAGNETOM Terra 7T MRI scanner at the Wolfson Brain Imaging Centre, University of Cambridge. Participants were screened for contraindications before each scan. During piloting, I excluded participants with any metal implants or tattoos. With increasing awareness of the specific risks of 7T, published recommendations (Noureddine *et al.*, 2015; Hoff *et al.*, 2019) and communication with specialists at the Universities of Leiden and Minnesota this was relaxed. At the time of this study, the only contraindications, above 3T MRI, were dental implants, tattoos on the face or neck and any cardiac or neurological implanted devices. Participants were asked to abstain from alcohol, or *ad hoc* benzodiazepines and sleeping tablets for 24 hours prior to the scan. No changes were made to participants' regular prescribed medication. All participants provided written informed consent. The study had ethical approval from the Cambridge Central Research Ethics Committee (REC 16/EE/0351 and 16/EE/0084).

Structural imaging and analysis

A MP2RAGE image was acquired on all participants (TR=4300ms, TE=1.99ms, TI_1/TI_2=840/2370ms, FA_1/FA_2=5/6°, 224 slices, 0.75mm isotropic voxels). This sequence is an adaptation of the Magnetisation Prepared – Rapid Gradient Echo (MPRAGE) sequence that is the predominant 3D T1-weighted sequence on Siemens 3T MRI scanners. The MP2RAGE sequence differs in that two images are acquired, only with a short inversion time (840ms) and another with a longer inversion time (2370ms). These two images are combined, to cancel out T2* and B1 inhomogeneities and create a strongly T1-weighted imaging with improved grey to white matter contrast compared to conventional MPRAGE images (Marques *et al.*, 2010).

Voxel-based morphometry was performed with the standard settings in SPM12 as follows (Ashburner and Friston, 2000; Ashburner and Reg, 2010). First, MP2RAGE images were aligned to an average image in MNI space, cropped to a standard bounding box then segmented into six tissue probability maps: grey matter, white matter, CSF, bone, soft tissue and air. A study-specific template was created using diffeomorphic anatomical registration using exponentiated Lie algebra (DARTEL) on images from all participants. The tissue probability maps for each participant were then warped to this template. Next, the grey and white matter

templates were affine transformed to MNI space. This transformation was then applied to each participant's tissue probability images. Smoothing was performed with an 8mm isotropic full width at half maximum Gaussian kernel. The total intracranial volume for each participant was calculated using the Tissue Volumes function in SPM12. Study-specific grey and white matter masks were created from voxels with a value of >0.15 in more than half of the images (Ridgway *et al.*, 2009). An average of the all participants' structural images was created to visualise thresholded cluster maps and spectroscopy voxels. After skull stripping, all images were normalised using the study specific DARTEL template, but with no smoothing or modulation. An averaged image was created using the *AverageImages* function in ANTS (Avants *et al.*, 2009).

Grey and white matter volumes for each diagnostic group were compared with independent two-sample t-tests with age, sex and total intracranial volume as covariates of no interest (Barnes *et al.*, 2010). The conjunction between bvFTD and PSP was tested on the combined pairwise contrasts (bvFTD vs control and PSP vs control) on an ANCOVA across all groups with the same covariates of no interest (Nichols *et al.*, 2005). The association between impulsivity measures (CBI-Impulsivity composite score and stop signal reaction time (SSRT)) and brain volumes were compared with ANCOVA, with either CBI-Impulsivity or SSRT as the covariate of interest and FTLD subgroup, age, gender and total intracranial volume as covariates of no interest. Significant effects were identified using cluster-level statistics ($p<0.05$, family-wise error corrected for multiple comparisons) above a height threshold of $p<0.001$ (uncorrected).

Magnetic resonance spectroscopic imaging and analysis

Principles of Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a molecular imaging technique that enables the detection and quantification of molecules in the brain (Wilson *et al.*, 2019). MRS is enabled by the principle of chemical shift. In any given molecule, the magnetic field experienced by protons is influenced by their surrounding electrons. The resonant frequency of nuclei (Lamour frequency) may be "shifted" if they are partially shielded from the magnetic field by their surrounding electrons. Different molecules have different "chemical shifts", as the degree of shifting depends on the density of the electrons in the molecule (Govindaraju *et al.*, 2000; Hajek and Dezortova, 2008). An MRS sequence output is a frequency spectrum from multiple nuclei, each peak of the spectrum comes from a different molecule. More complex molecules may have several peaks if their constituent protons resonant at different frequencies. The area beneath

each peak represents each metabolite's concentration in the region of interest. Not all molecules are visible in the MRS spectrum, including those with very complex structures, high molecular weight, low concentrations or when bound to other large compounds (Hajek and Dezortova, 2008; Tognarelli *et al.*, 2015).

Different spectroscopy sequences have been developed, each with advantages and disadvantages. MRS of GABA is difficult, as the GABA molecule is represented by three low amplitude peaks in the MRS spectrum, each of which overlaps with the peaks of other metabolites with much greater concentrations. Specific GABA MRS sequences, for example MEGA-PRESS, have been developed which use editing pulses to select the GABA signal from the whole frequency spectrum (Mullins *et al.*, 2014). These sequences have limitations: participant movement can prevent accurate editing and macromolecular contamination may form a large proportion of the final "GABA" signal (Mullins *et al.*, 2014). Ultra-high field MRS at 7T enables more accurate GABA measurement without these limitations, due to higher signal to noise and greater separation of individual metabolites in the MRS spectrum (Ladd *et al.*, 2018).

Spectroscopy data acquisition

Magnetic resonance spectroscopy was performed with single voxel short-echo semi-LASER sequence (TR/TE=5000/26ms,64 averages) (Öz and Tkáč, 2011; Deelchand *et al.*, 2015). This sequence was developed by Gülin Öz and Dinesh Deelchand and was provided by the University of Minnesota. A 2x2x2cm voxel was placed over the region of interest. The voxel was aligned to the plane of the magnetic field and rotated in at most one dimension to avoid non-brain structures. My primary experimental region was the right inferior frontal gyrus (IFG) and control region was the right primary visual cortex. I attended all scans and placed all the voxels to avoid inter-operator variability in voxel placement. The order of the first two voxels was randomised between the right IFG and occipital cortex. A third MRS measurement, depending on time and patient tolerability, was acquired from the right superior temporal gyrus. Dielectric pads (Snaar *et al.*, 2011) were not used, due to patient tolerability, multiple regions of interest and limited improvement in signal to noise ratio during piloting.

I defined the inferior frontal gyrus as superior to the Sylvian fissure and anterior to the inferior aspect of the precentral sulcus. Within these limits, the voxel was placed over the gyri anterior and posterior to the diagonal branch of the Sylvian fissure. I defined the medial aspect of the control region as the longitudinal fissure. Within this limit, I placed the voxel over the calcarine

fissure and as posteriorly as possible, without including the skull or superior sagittal sinus. I defined the superior temporal gyrus as limited superiorly by the Sylvian fissure and posteriorly by an imaginary line connecting the Sylvian fissure with the preoccipital notch.

Automated shimming was performed with first and second-order shim coils using the FASTESTMAP software (Gruetter, 1993; Gruetter and Tkáč, 2000). VAPOR water suppression and outer volume suppression pulses were used to remove the water signal and contaminating signals from outside the region of interest. A flip angle calibration sequence was included, but all flip angle calculations reached as ceiling of 300V, which was used as the transmitter voltage for all participants. A water calibration sequence was used to determine the optimal water suppression flip angle. The spectroscopy sequences then ran, which include two acquisitions for eddy current correction, two for water scaling and 64 water suppressed metabolite acquisitions.

Spectroscopy data analysis

The 64 individual spectra from each region of interest were eddy-current, phase, and frequency corrected then summed together using the MRspa software package (courtesy of Dr Dinesh Deelchand: www.cmrr.umn.edu/downloads/mrspa).

All spectra were visually inspected and any very low-quality scans, where the model fit failed or signal to noise was very low (<10), were removed. Using these criteria, I excluded all voxels' data from one participant and the temporal lobe voxel data from five other participants. GABA and glutamate levels were quantified, along with 17 other metabolites, using LCModel Version 6.2-3 (Provencher, 1993). The basis set included simulated model spectra for 19 neurochemicals and a experimentally obtained macromolecule spectra from four healthy subjects (Deelchand *et al.*, 2015). Metabolite results were water scaled after correction for tissue water content, assuming the CSF contribution to the voxel to be zero. Absolute Cramer-Rao Lower Bounds were calculated by multiplying each metabolite value with its relative Cramer-Rao Lower Bound (Kreis, 2016).

Spectroscopy region of interest maps and atlas results (Figure 7-4A+C) were created by extracting the voxel coordinates from the spectroscopy header files, then transforming all images to MNI space. These images were overlaid on segmented tissue probability maps and the Hammer's atlas of brain regions to get tissue composition and brain regions covered by each voxel. All analysis was performed using SPM12.

GABA and glutamate results were corrected for age, gender and tissue volume using a generalised linear model. The residuals from the generalised linear model ($metabolite = \beta(intercept) + \beta(age) + \beta(gender) + \beta(grey\ matter)$) were used as the corrected results. A fourth covariate ($\beta(white\ matter)$) was added to the glutamate correction, as glutamate is present in both grey and white matter (Kukley *et al.*, 2007; Bakiri *et al.*, 2009). The absolute Cramer-Rao lower bound, a measure of LCModel fit accuracy, was used to weight the linear model (Miller *et al.*, 2017). Analysis of variance, with region of interest and neurotransmitter as within subject factors and diagnosis as a between subject factor, was used to compare neurotransmitter levels. All p values were corrected for multiple comparisons using the Tukey multiple comparison test. Analysis was performed in MATLAB 2018b (MathWorks, USA) apart from ANOVA which was performed in JASP (Version 0.11).

Comparison between neurotransmitter concentrations and behavioural measures

I tested the association in FTLD participants between the right inferior frontal gyrus GABA and glutamate concentrations and the stop signal reaction time. A Spearman's correlation coefficient was calculated for each value in the individual-level posterior distribution of stop signal reaction times. The region of practical equivalence was defined as a Spearman's R between -0.1 and 0.1, corresponding to a negligible effect size (Cohen, 1992; Kruschke, 2018). The null hypotheses was rejected if the 95% highest density interval of R values did not overlap with the region of practical equivalence (Kruschke, 2018).

Results

Forty-four participants with an FTLD syndrome (bvFTD n=22, PSP n=22) and twenty age and sex matched healthy controls had ultra-high-resolution magnetic resonance structural and spectroscopic imaging. The demographic, clinical and neuropsychological characteristics of the study participants were reported in the previous chapter.

First, I compared grey and white matter volumes between FTLD and healthy controls using voxel-based morphometry. FTLD participants had reduced grey matter volume in the frontal and temporal lobes, basal ganglia, thalamus and cerebellum bilaterally (Figure 7-1A). There was corresponding white matter volume loss in frontostriatal and corticospinal tracts and brainstem (Figure 7-1B). Both bvFTD and PSP had reduced grey matter in the right orbitofrontal and anterior cingulate cortex, bilateral inferior frontal gyri, insula and motor cortices, as shown by a conjunction analysis (Nichols *et al.*, 2005) (Figure 7-2A). This also revealed volume loss in subcortical structures including the caudate, putamen and globus pallidus and superior cerebellum. There was white matter volume loss in frontostriatal pathways (Figure 7-2B).

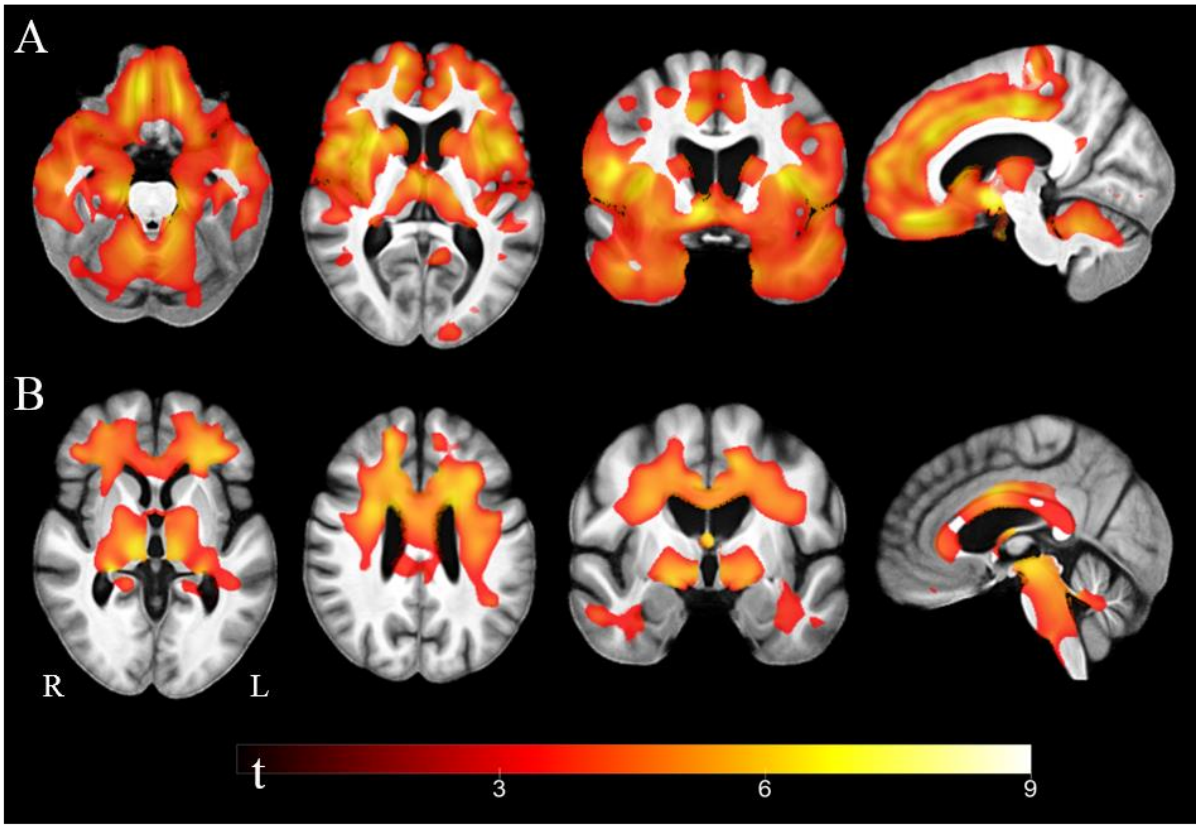


Figure 7-1: Voxel based brain morphometry of FTLD (bvFTD and PSP combined). A: Grey matter B: White matter. Representative axial, coronal and sagittal slices are shown. More brain slices are in Appendix 6.

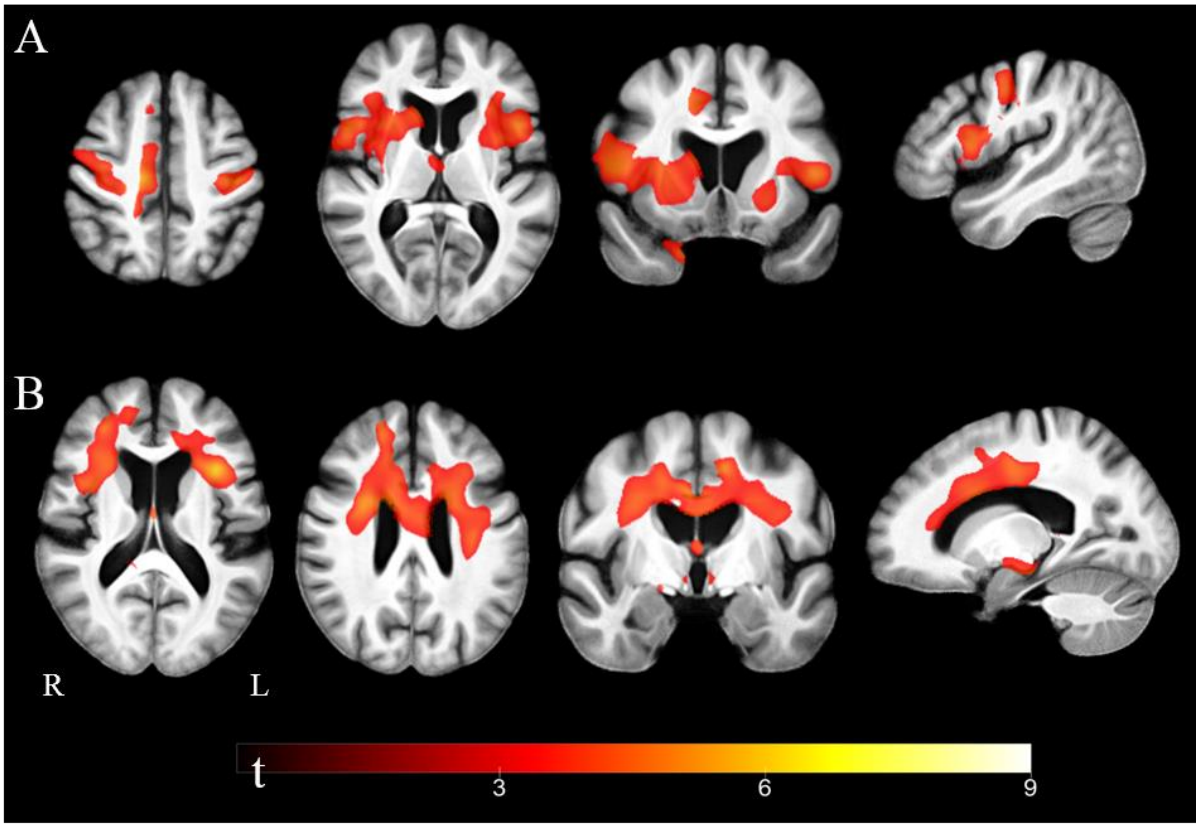


Figure 7-2: Conjunction analysis of bvFTD vs Control and PSP vs Control. The colourmap shows voxels that are significant in both groups, at a cluster-level of FWE p<0.05 above a height threshold of p<0.001. A: Grey matter. B: White matter. Representative axial, coronal and sagittal slices are shown. More brain slices are in Appendix 6.

Second, I looked for atrophy associated with measures of behavioural impairment. In FTLD, no grey or white matter regions were significantly associated with the CBI-Impulsivity composite score or SSRT. There was a trend to an association between bilateral inferior frontal gyrus volume and SSRT (p<0.001 uncorrected) but this finding did not survive cluster correction (Figure 7-3).

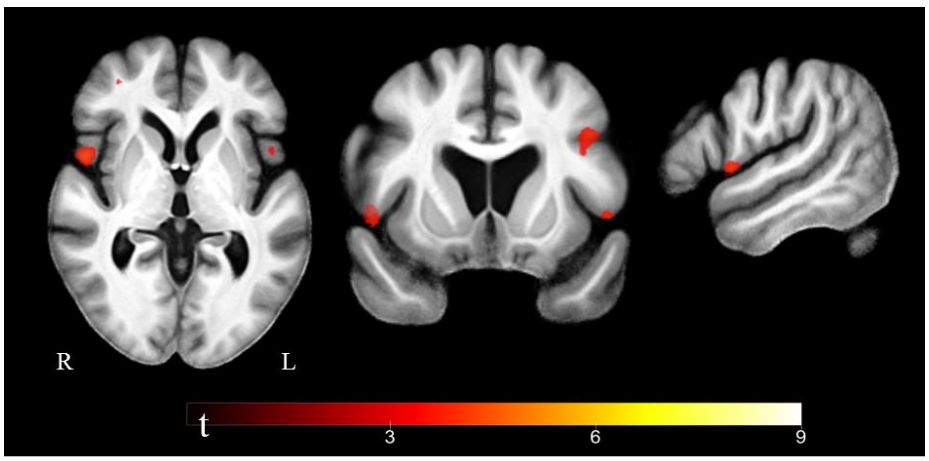


Figure 7-3: Voxel based morphometry of grey matter volume association with stop signal reaction time in FTLD. Colourmap shows voxels with p<0.001 uncorrected. More brain slices are in Appendix 6.

Third, I used magnetic resonance spectroscopy to measure glutamate and GABA concentrations in the right frontal, temporal and occipital lobes. All healthy volunteers and 42/44 FTLD participants underwent both the frontal and occipital sequences. Two FTLD participants had inadequate data for further analysis due to movement artefact and were excluded. Only 29/44 patients completed the temporal lobe sequence and data was inadequate for analysis in an additional 25 participants (Controls n=9, FTLD n=16) due to inadequate model fitting. Therefore, the temporal voxel was excluded from further analysis and only results from the frontal and occipital voxels are reported.

Spectroscopy voxel placement was consistent across participants in all brain regions (Figure 7-4A+C). The frontal lobe voxel was primarily located in the inferior frontal gyrus, with a smaller proportion in the middle frontal gyrus and insular cortex. In the frontal voxel there was proportionately less grey and white matter in both bvFTD and PSP (Figure 7-4B). The control voxel, in the occipital lobe, was centred over the calcarine sulcus and included parts of the lateral occipital lobe, cuneus and lingual gyrus. There was no difference in grey or white matter volume between groups (Figure 7-4D). Spectral quality was good in the inferior frontal gyrus and occipital lobe (Figure 7-5). The Cramer-Rao Lower Bound, a general measure of fit accuracy, was less than thirty in most participants in both glutamate and GABA. The water linewidth, a surrogate measure of shim quality, was similar between groups however the signal to noise was lower in FTLD in the frontal and occipital regions. The mean correlation coefficients between all metabolites and both GABA and glutamate were greater than -0.3, suggesting both neurotransmitters were accurately distinguished from other metabolites (Provencher, 1993).

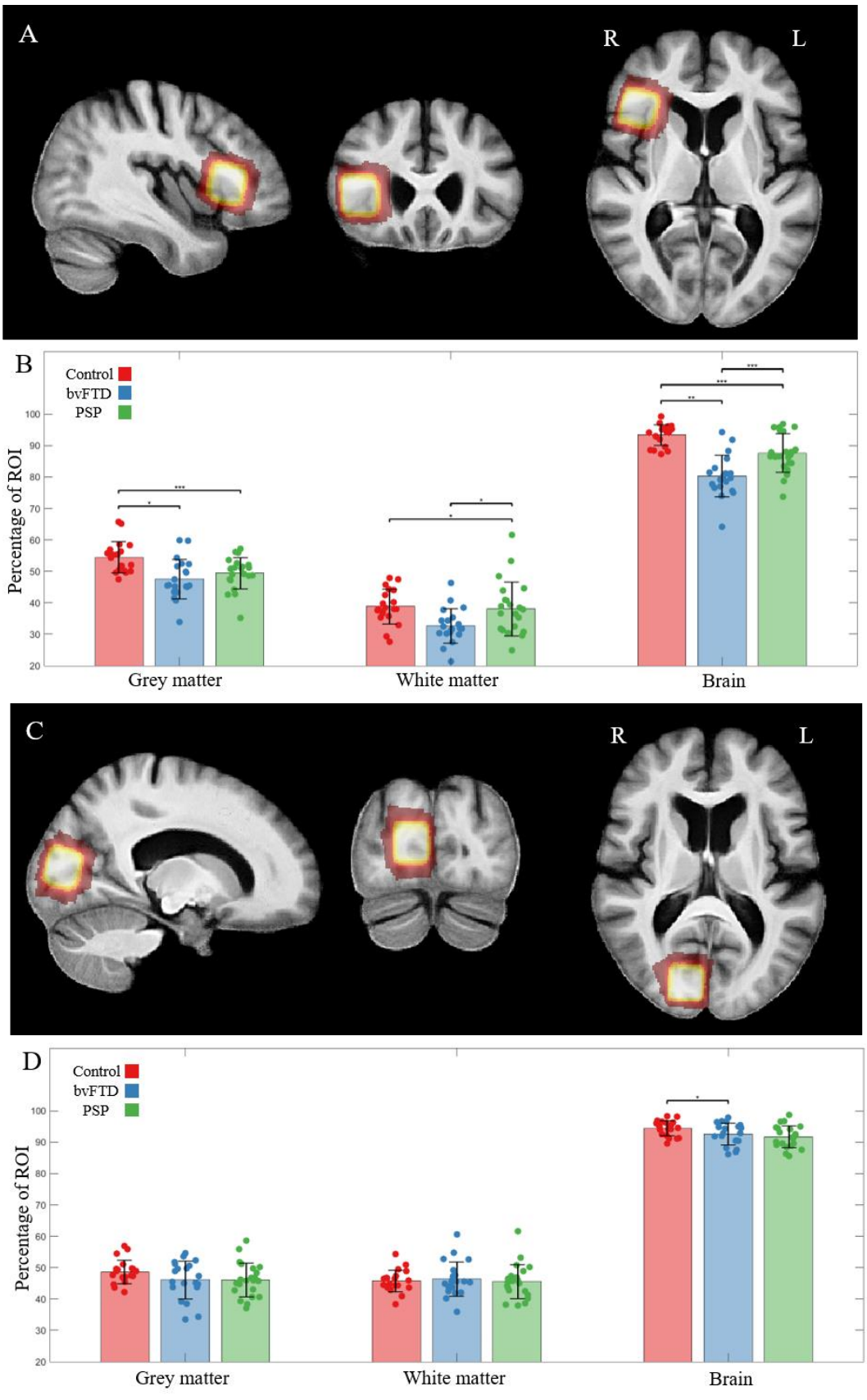


Figure 7-4: Spectroscopy voxel location and composition. A: Frontal voxel (sum of all participants) superimposed on a mean structural image of all participants. B: Grey, white and whole brain composition of the voxel by group. There was less grey and white matter, as a proportion of the voxel, in bvFTD and PSP compared to controls. C: Occipital voxel location. There was consistent voxel placement in all participants. D: Grey, white and whole brain composition of the occipital voxel. There was no difference in grey and white matter across the three groups.

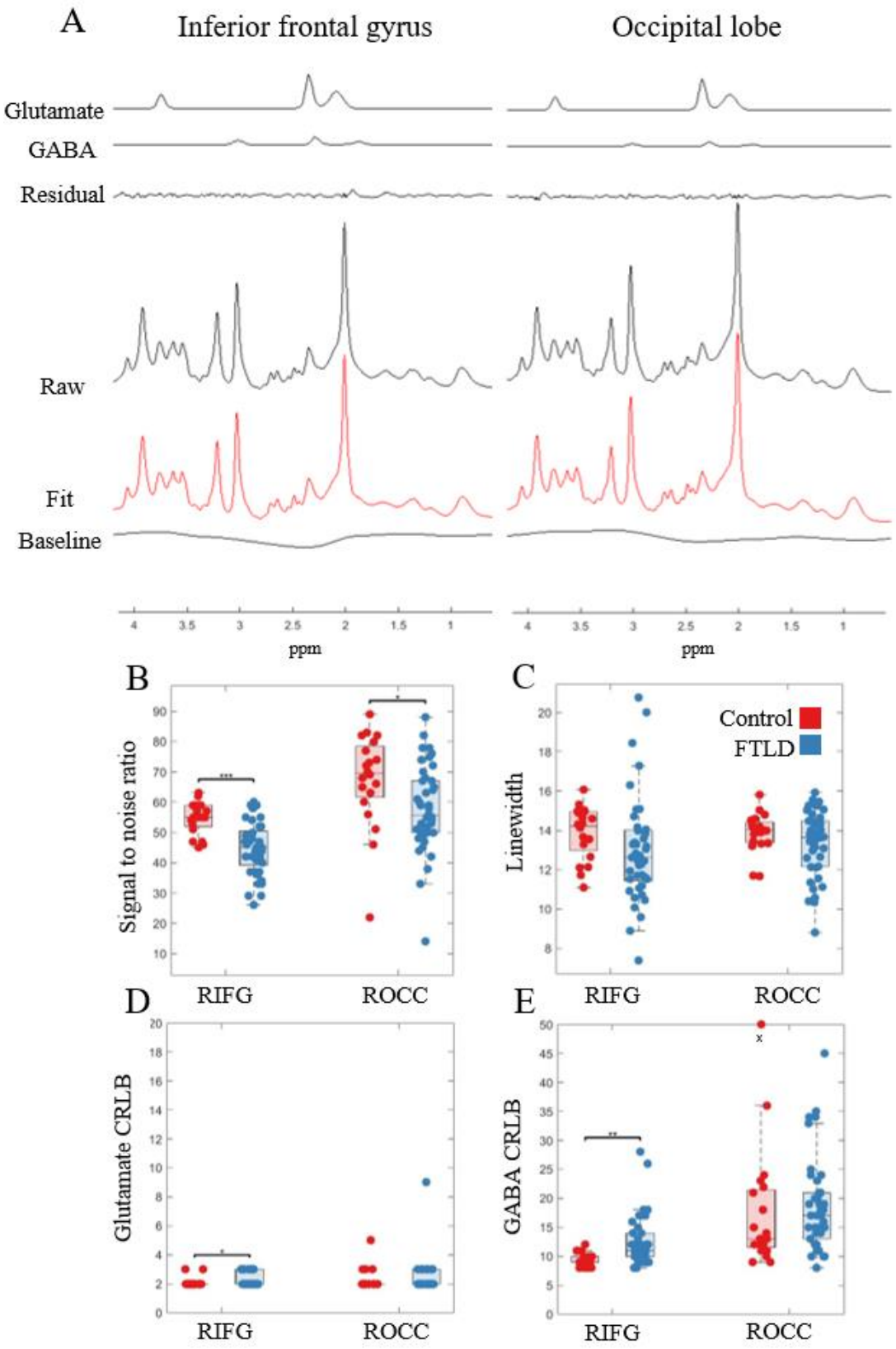


Figure 7-5: Magnetic resonance spectroscopy data quality. A: Mean spectra from all participants showing the raw data, LCModel fit, baseline, residual (fit-raw data), glutamate and GABA fits. Classically the GABA fit has a triplet for each peak, this was present for individuals scans but was removed during spectral averaging. Spectrum for each individual are shown in Appendix 7. B: Signal to noise ratio for all participants by group. RIFG: right inferior frontal gyrus, ROCC: right occipital cortex. There was lower signal to noise in the FTLD group in the right inferior frontal gyrus and right occipital cortex. C: Water linewidth for all participants by group. There was no difference between groups for any region. D: Glutamate Cramer-Rao Lower Bound (CRLB). X: outlier of one Control ROCC CRLB 87. Boxplots show median and 25th and 75th quartiles, whiskers include all data not considered an outlier.

Neurotransmitter results are water scaled, then reported both with and without correction for partial volume, age and sex. Glutamate was reduced in right inferior frontal gyrus in FTLD compared to controls (F20.63, p<0.001) but there was no difference after regression of age, sex and grey and white matter effects (Figure 7-6). GABA was also reduced in the right inferior frontal gyrus in FTLD compared to controls (F23.37 p<0.001) and this difference remained significant after regression of age, sex and grey matter effects (F8.67, p=0.005) (Figure 7-7). Including white matter volume in the regression analysis did not change the result. The GABA deficit in the right inferior frontal gyrus was present in both FTLD subgroups (bvFTD t=2.52, p=0.036, PSP t=2.56, p=0.034). Glutamate and GABA concentrations did not correlate after partial volume correction (Spearman's R=0.06, p=0.70). There was no difference in either neurotransmitter between groups in the right occipital lobe.

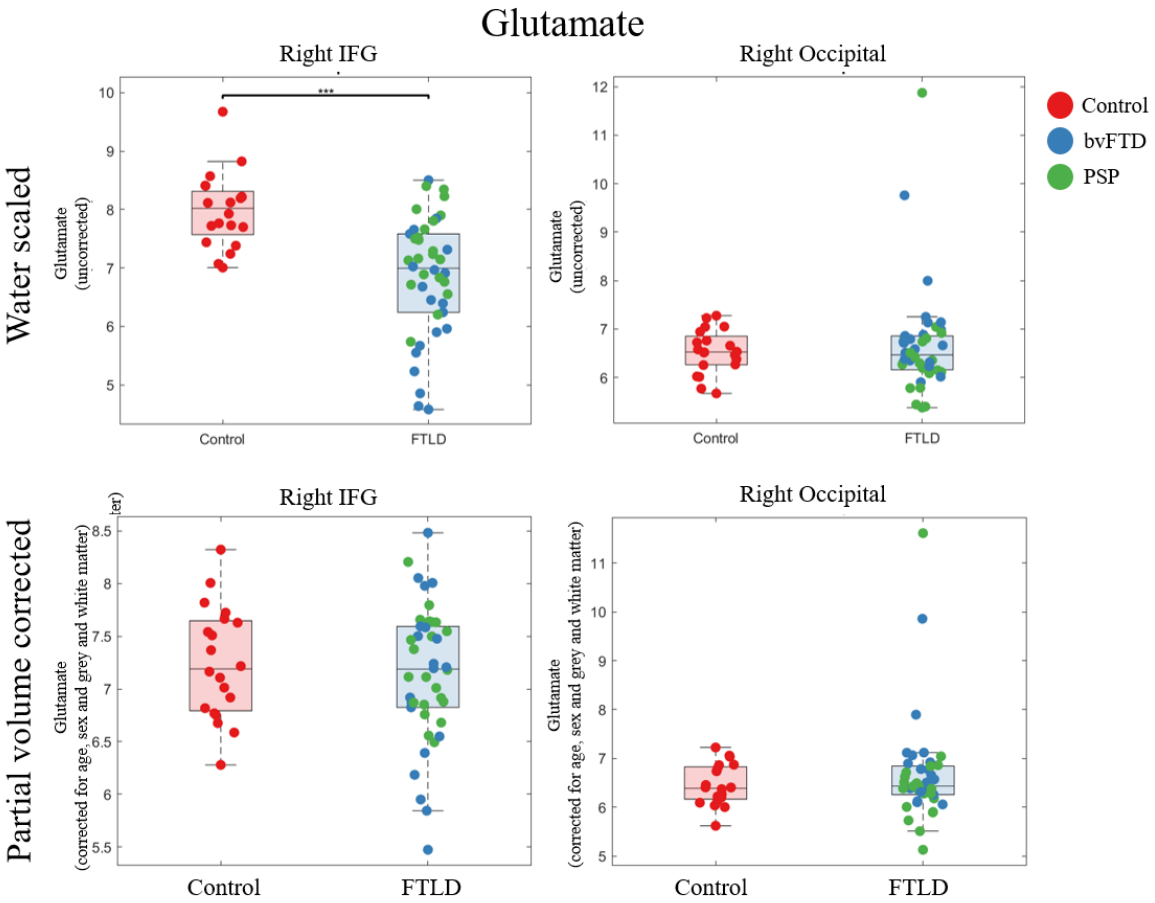


Figure 7-6: MRS measurement of glutamate in FTLD. Top row: water scaled values with no partial volume correction for the right inferior frontal gyrus (IFG) and primary visual cortex (occipital) voxels. Bottom row: The same data after age, sex and partial volume (grey and white matter) correction. On each boxplot, the middle line is the median and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Whiskers include any data not considered an outlier (within 2.7 standard deviations of the mean). Each dot represents the value from an individual participant, colour coded by group. ***=p<0.001 (after Bonferroni correction).

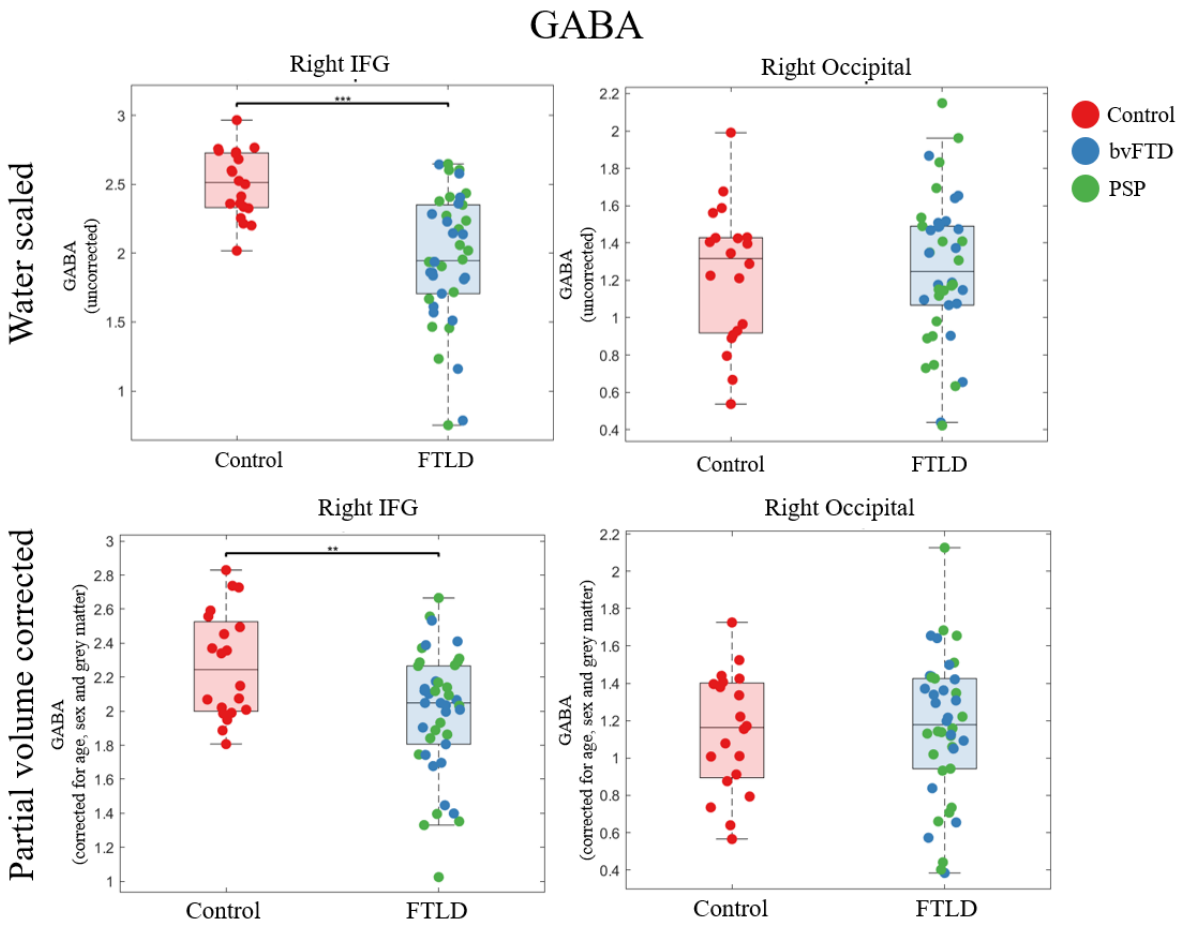


Figure 7-7: MRS measurement of GABA in FTLD. Top row: water scaled values with no partial volume correction for the right inferior frontal gyrus (IFG) and primary visual cortex (occipital) voxels. Bottom row: The same data after age, sex and partial volume (grey matter) correction. On each boxplot, the middle line is the median and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Whiskers include any data not considered an outlier (within 2.7 standard deviations of the mean). Each dot represents the value from an individual participant, colour coded by group. **=p<0.01, ***=p<0.001 (after Bonferroni correction).

Finally, I tested the hypothesis that GABA and glutamate deficits in the right inferior frontal gyrus were associated with impulsivity. Both GABA and glutamate concentration in the right inferior frontal gyrus, after correction for partial volume, age and sex, inversely correlated with the stop signal reaction time. This association with impaired response inhibition was stronger for glutamate (95% highest density interval -0.38:-0.56) than GABA (95% highest density interval -0.13:-0.35) but both these credible intervals were outside the pre-specified region of practical equivalence (R 0.1:-0.1). Stop trigger failure probability was not associated with either GABA (95% HDI -0.13:0.18) or glutamate (95% HDI -0.01:0.31) concentration. There was no association between neurotransmitter concentrations in the right inferior frontal gyrus and carer ratings of impulsivity (glutamate R=-0.01 p=0.97, GABA R=-0.12 p=0.46).

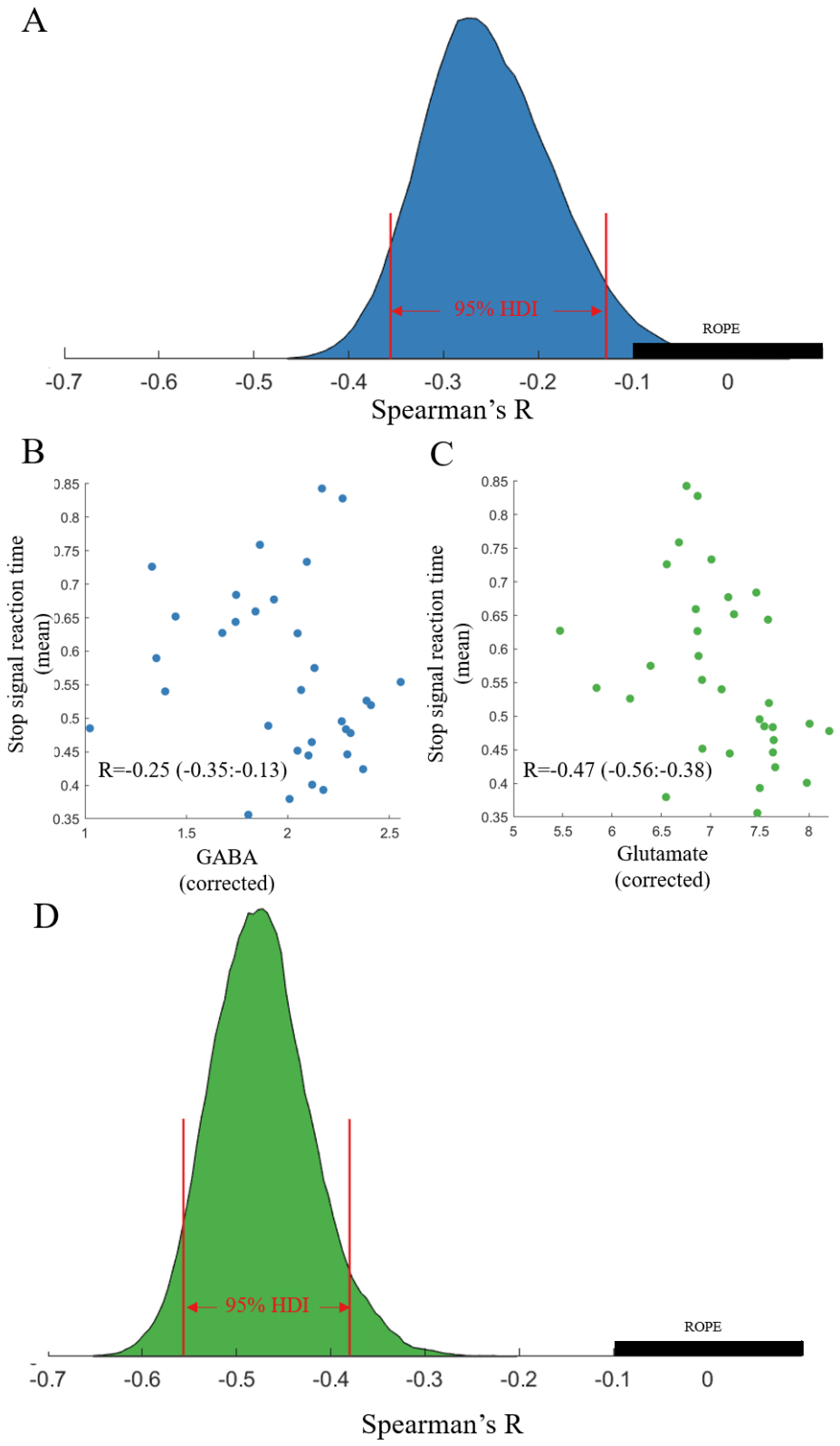


Figure 7-8: Correlation between neurotransmitters (GABA and glutamate) and stop signal reaction time (SSRT) result from Chapter 6. A: Histogram of R values for the Spearman's correlation between glutamate, after corrected for grey matter, age and sex, and the posterior distribution of SSRT. Red lines show 95% highest density interval (HDI). Black bar shows region of practical equivalence (R -0.1:0.1). B: Scatter plot of mean SSRT and corrected GABA, values in brackets are 95% HDI. C: Scatter plot of mean SSRT and corrected glutamate. D: Histogram of R values for the Spearman's correlation between glutamate and the posterior distribution of SSRT.

Discussion

This chapter has two main findings. First, GABA and glutamate levels are reduced in the right inferior frontal gyrus in FTLD, but only the GABA deficit remains significant after correction for age, gender and partial volume. Second, glutamate and GABA concentrations in the inferior frontal gyrus correlate with disinhibition, as measured by the SSRT, but not a carer rating of behavioural impairment.

The finding of a frontal lobe GABA deficit, as measured by magnetic resonance spectroscopy (MRS), is supported by other *in vivo* and *post mortem* evidence of GABAergic neuron loss in FTLD (Ferrer, 1999; Levenga *et al.*, 2014). This GABAergic deficit may contribute to the abnormal functional connectivity associated with cognitive impairment in FTLD syndromes. GABAergic interneurons have widespread functions, beyond inhibition of excitatory neurons. They have a key role in the regulation of oscillatory dynamics, including their generation and regulation of magnitude and frequency (Owens and Kriegstein, 2002; Mann and Paulsen, 2007; Buzsáki and Wang, 2012). In health, increasing synaptic GABA levels increases gamma power during cognitive control tasks (Frankle *et al.*, 2009) whereas inhibiting GABA receptors reduces gamma oscillatory power and impairs inhibition and working memory (Hines *et al.*, 2013). Gamma and beta oscillation frequency correlates with GABA concentration, as measured by MR spectroscopy, in the visual (Muthukumaraswamy *et al.*, 2009), motor (Gaetz *et al.*, 2011; Baumgarten *et al.*, 2016) and dorsolateral prefrontal cortex (Kujala *et al.*, 2015) while $GABA_A$ receptor density (measured by Flumazenil-PET) correlates with gamma frequency and magnitude (Kujala *et al.*, 2015). Brain network connectivity is altered in the inferior frontal gyrus in FTLD during response inhibition paradigms (Hughes *et al.*, 2015, 2018*a*) and at rest (Seeley *et al.*, 2009; Sami *et al.*, 2018). This altered beta and gamma oscillation power and their associated cognitive deficits in FTD may be caused, at least partially, by GABAergic deficits and raises the possibility that correcting GABAergic deficits may restore functional connectivity and improve cognition and behaviour.

Glutamate levels were low in the right inferior frontal gyrus, which replicates previous findings in other frontal lobe regions in FTLD syndromes (Ernst *et al.*, 1997; Sarac *et al.*, 2008). Interestingly, the non-competitive NMDA-inhibitor memantine has no beneficial effect in FTLD syndromes and worsened cognition in some patients. This would be explained by my results, which suggest a glutamatergic deficit in FTLD, rather than overactivation or excess

(Vercelletto *et al.*, 2011; Boxer *et al.*, 2013). There was no difference in glutamate concentration between FTLD and controls after correction for grey and white matter volume loss. However, it would be misleading to conclude there is no glutamatergic deficit in FTLD. Given the high density of glutamatergic neurons in the neocortex, grey matter atrophy typically correlates with the number of glutamatergic neurons in the remaining brain tissue (Harding, 1998; Zarow *et al.*, 2005). Correcting MRS measures of glutamate for atrophy may remove any disease effect and any glutamatergic difference between FTLD and controls.

It is unclear how closely MRS measurements correlate with synaptic concentrations of glutamate and GABA (Stagg *et al.*, 2011*a*). Both neurotransmitters are found at different concentrations within neurons, glia, the extra-cellular space and synapses (Martin and Rimvall, 1993; Zhou and Danbolt, 2014). MRS cannot distinguish between these different pools, only measuring the total concentration of neurotransmitter within a large region of interest (8cm^3 in my study). Some GABA and glutamate may be invisible to MRS, for example if bound to proteins or other macromolecules (Tognarelli *et al.*, 2015). However, it is unlikely that MRS is just an indirect measure of neural density. Several research modalities have shown that MRS can detect within-subject neurotransmitter changes, suggesting that MRS is not just an indirect measure of neuronal populations (Stagg, 2014). Changes in MRS-measured GABA concentrations occur after drug administration (Sanacora *et al.*, 2002; Milak *et al.*, 2016), during visual (Frangou *et al.*, 2018, 2019) and motor (Floyer-Lea *et al.*, 2006) tasks and after transcranial magnetic simulation (Stagg *et al.*, 2009, 2011*b*). There is less evidence of similar within-participant changes in MRS-measured glutamate. Unlike GABA, glutamate has many functions in the central nervous system beyond neurotransmission, including neuron and glia metabolism and protein synthesis (Hertz, 2013; Zhou and Danbolt, 2014). Only a small proportion of total glutamate acts as a neurotransmitter and only 0.05% of total glutamate is present in the extracellular space (Danbolt, 2001). Therefore, it is possible that MRS of glutamate is a measure of glutamatergic neuron density.

There was no association between glutamate and GABA concentrations after partial volume correction. This is surprising, as glutamate and GABA are linked functionally and biochemically. Both are amino acids and form part of the Glutamine-Glutamate/GABA cycle (Walls *et al.*, 2014). Glutamate, after release from excitatory glutamatergic neurons and binding to post-synaptic receptors, is removed from the synapse into astrocytes (Walls *et al.*, 2014). Glutamate is then converted to glutamine by glutamine synthetase then transferred back to either excitatory neurons (where it is recycled back to glutamate) or inhibitory neurons where

it forms the precursor for GABA (Walls *et al.*, 2014). The lack of a correlation between the two neurotransmitters in my study is further evidence that MRS-visible glutamate has a wide range of cellular functions, beyond neurotransmission.

Both GABA and glutamate concentration in the right inferior frontal gyrus inversely correlated with response inhibition, as measured by the stop signal reaction time (SSRT). This complements results with other functional imaging modalities, including fMRI and electrophysiology, that show activation of the IFG during the stop signal task in healthy volunteers (Chambers *et al.*, 2006, 2009; Levy and Wagner, 2011; Aron *et al.*, 2014; Rae *et al.*, 2015). The IFG forms part of a cognitive control network which is activated during response inhibition and also includes the pre-supplementary motor area (preSMA) and subthalamic nucleus (Rae *et al.*, 2015). GABA levels in this network, specifically the preSMA, inversely correlate with SSRT in healthy older adults (Hermans *et al.*, 2018). This study, performed at 3T with an edited MRS sequence, did not measure glutamate levels. One strength of my 7T MRS study is that both glutamate and GABA can be measured at the same time in the same brain region to show that both contribute to response inhibition in FTLD syndromes.

There was no association between GABA and glutamate concentration in the IFG and carer ratings of global behavioural impairment. This may be because I only measured these neurotransmitters in one region and so only see a relationship between glutamate and GABA and a cognitive process associated with that region. Due to the heterogeneity in FTLD, it cannot be assumed that GABA and glutamate concentrations in the IFG are representative of the whole frontal lobe. Global behavioural impairment results from pathology in multiple brain regions and impairment in many disparate cognitive processes. New sequences that can measure glutamate and GABA across the whole brain may show correlation with other behavioural impairments in FTLD syndromes and are a promising area for future research (Moser *et al.*, 2019). In addition, deficits in other neurotransmitter pathways, including serotonin, dopamine, noradrenaline and acetylcholine also contribute to behavioural impairment in FTLD syndromes (Huey *et al.*, 2006; Murley and Rowe, 2018). Ultimately, an effective treatment for behaviour symptoms in FTLD is likely to target multiple neurotransmitter pathways, including glutamate and GABA.

It has been suggested that different symptoms in FTLD relate to specific neurotransmitter deficits. For example, apathy is due to reduced excitatory glutamatergic neurotransmission and impulsivity is due to reduced inhibitory GABAergic neurotransmission (Benussi *et al.*, 2019).

This would be analogous to the extra-pyramidal motor symptoms' association with dopaminergic neuron loss (Oyanagi, 2002; Murley and Rowe, 2018). This is likely to be too simplistic for several reasons. First, as the results from this chapter show, both neurotransmitters are associated with impaired response inhibition. Second, apathy and impulsivity positively correlate and are associated with atrophy in similar brain regions (Peters *et al.*, 2006; Lansdall *et al.*, 2017). Third, both glutamate and GABA are required to generate and regulate the neural oscillations that underlie many cognitive processes including apathy and impulsivity (Buzsáki and Wang, 2012, Hughes *et al.*, 2018*a*; Zhu *et al.*, 2019).

Voxel based morphometry of the 7T structural images revealed grey matter atrophy in the frontal and temporal lobes, basal ganglia, thalamus and cerebellum with white matter atrophy of frontostriatal pathways and the brainstem in FTLD syndromes compared to healthy controls. Frontotemporal lobar atrophy is classically associated with bvFTD (Rosen *et al.*, 2002), but also PSP (Brenneis *et al.*, 2004; Lagarde *et al.*, 2013), particularly in the PSP-F subtype (Cordato *et al.*, 2002; Jabbari *et al.*, 2019) which formed a large proportion of cases in this study. This volume loss in the regions is unlikely to be seen equally in all participants. For example, patients with PSP with limited cognitive impairment have less cortical grey matter atrophy (Jabbari *et al.*, 2019). A conjunction analysis of the two t-tests of FTLD subtypes (bvFTD and PSP) compared to controls showed volume loss in the anterior cingulate cortex, bilateral inferior frontal gyri, insula and motor cortices and basal ganglia. Interestingly, many of these regions are activated as part of a cognitive control network during executive function tasks in fMRI studies (Aron *et al.*, 2007; Cole and Schneider, 2007; Niendam *et al.*, 2012). This is further evidence that impaired cognitive, and specifically inhibitory, control is a feature of both bvFTD and PSP.

There was a trend to an association between bilateral IFG volume loss and increased SSRT, but this did not survive correction for multiple comparisons at a cluster-level. There was no trend to any association with brain volume and stop trigger failure or carer ratings of behavioural impairment. This may reflect the heterogenous patient population (bvFTD and PSP) with relatively low numbers in each group. Other studies, with greater sample sizes and less stringent statistical thresholds, do show an association between carer ratings of behavioural impairment and frontal, striatal and temporal regions (Hornberger *et al.*, 2011; Lansdall *et al.*, 2017; Passamonti *et al.*, 2018). It is surprising that there was no association between the severe behavioural impairments and frontal lobe atrophy in the current study. This may reflect the phenotypical and morphological heterogeneity in FTLD syndromes. Alternatively, it is possible

that functional changes are more important cause of behaviour and cognitive impairment than volume loss (Rittman *et al.*, 2019; Tsvetanov *et al.*, 2019). If true, this would suggest that cognitive deficits could be ameliorated even in the presence of brain atrophy.

There are many technical challenges to MRS which can reduce scan quality and limit metabolite measurement accuracy (Wilson *et al.*, 2019). Metabolite concentrations are estimated from modelling of the MRS spectra. If the modelling fit of the experimental data is imprecise, which is more likely with low quality scans, then the resulting concentrations will be inaccurate. There are many measures of scan accuracy, with no consensus on how to determine acceptable scan quality, although recommendations have been recently published (Wilson *et al.*, 2019). Magnetic field inhomogeneities, which are greater at 7T, change the resonant frequencies of molecules at different locations with the MRS voxel, broadening the MRS spectrum and making resolution of different metabolites more difficult (Tkac, 2010; Juchem and de Graaf, 2017). I used automated FASTESTMAP shimming to reduce magnetic inhomogeneity (Gruetter, 1993; Tkac, 2010). Water linewidth is a surrogate measure of the quality of magnetic field shimming (Juchem and de Graaf, 2017) and my results were similar to other 7T studies (Marjańska *et al.*, 2019; Wijtenburg *et al.*, 2019), did not differ between groups and were below the recommended cut-off (Öz *et al.*, 2020). Absolute Cramer Rao Lower-Bound values, a measure of model fit accuracy (Kreis, 2016), also did not differ between groups and were below the recommended threshold (Bonny and Pagès, 2019; Wilson *et al.*, 2019). Signal to noise ratios were lower in the FTLD, likely due to brain atrophy, but adequate for accurate model fitting. Ineffective water suppression pulses can also prevent accurate measurement of low concentration metabolites, including GABA (Mitchell *et al.*, 1945; Tkáč and Gruetter, 2005; Mcmaster *et al.*, 2010; Wilson *et al.*, 2019), so I ran two water suppression calibration sequences and a VAPOR water suppression pulse was included in the spectroscopy sequence (Tkac *et al.*, 1999). I used a modified semi-LASER MRS sequence with proven test-retest and multisite reproducibility (Deelchand *et al.*, 2015; van de Bank *et al.*, 2015; Terpstra *et al.*, 2016). Finally, each participant had an internal control region, the occipital lobe, where I expected to see no neurotransmitter deficit due to limited atrophy and FTLD pathology (Cairns *et al.*, 2007). The absence of a group difference in the control region suggests the results in the inferior frontal gyrus reflect a true neurotransmitter deficit, and not an artefact of movement or another patient-related bias.

This study has several other limitations. First, the spectroscopy regions of interest are may have varied between individuals, both in their anatomical location and proportion of brain included. Participants had different total brain volumes, but their MRS voxels remained the same size.

This was necessary to avoid a confound of varying signal to noise but means that the region of interest covers a different proportion of the brain between participants. In addition, MRS voxels were placed manually, using anatomical landmarks which vary between individuals. For example, the diagonal branch of the Sylvian fissure, a landmark of the inferior frontal gyrus, is not present in over half of healthy volunteers (Idowu, 2014). Voxel placement appeared consistent (Figure 7-4A+C) but there are likely to small between-participant differences in voxel placement. Second, brain volume within the MRS voxel was lower in the FTLD group. CSF GABA and glutamate concentrations are not high enough to be MRS-visible, therefore this partial volume effect must be considered when reporting MRS-results (Quadrelli *et al.*, 2016; Porges *et al.*, 2017). One option is to report the relative concentration of the metabolite of interest to an internal standard, usually another metabolite such as creatine. This approach is common in MRS of healthy brains (Kolasinski *et al.*, 2017; Frangou *et al.*, 2019) but creatine is likely to also be abnormal in FTLD, which is associated with energy pathway impairments (Foster *et al.*, 1988, Diehl-Schmid *et al.*, 2007*a*; Pathak *et al.*, 2013), so is an inappropriate reference for my results. Absolute metabolite concentration uses tissue water concentration to "water scale" metabolite results and some studies enter the voxel fraction of CSF at this stage of analysis. This does not account for voxel differences in grey and white matter volume, which have different GABA and glutamate concentrations (Choi *et al.*, 2006; Gasparovic *et al.*, 2009; Bhattacharyya *et al.*, 2011). Therefore, I used a generalised linear model, weighted for CRLB, to independently model the effects of age, sex, grey and white matter and remove their effects from the results. This approach may still bias results if tissue volume closely correlates with metabolite concentration, which is likely with glutamate. Third, using a longer scan time, prospective motion correction and dielectric pads to reduce B_1 inhomogeneity would improve MRS accuracy (Keating *et al.*, 2010; Huang *et al.*, 2018; Deelchand *et al.*, 2019), but at the cost of reduced patient tolerability. All participants completed the frontal and occipital sequences but drop-out before or during the final temporal sequence was high (35%). Extending the sequence time or causing patient discomfort with mouthpieces or dielectric pads may have resulted in an even higher drop-out rate, causing missing data in the frontal and occipital results.

Further research would strengthen and validate the results in this chapter. First, *post mortem* investigation of the glutamate and GABA concentrations, using high performance liquid chromatography (Buck *et al.*, 2009), would validate the MRS-measured neurotransmitter deficits of my study. Many of the participants in this study have made a declaration of intent to donate their brain after death. In the Cambridge Brain Bank protocol, the right hemisphere is typically frozen, enabling neurotransmitter quantification in the same regions assessed with

MRS. Second, placebo-controlled, double-blinded studies testing the effect of altered GABA or glutamate levels on stop signal reaction time would strengthen my findings of an association between these neurotransmitter levels and behavioural disinhibition. Similar studies with serotonin and noradrenaline have shown an effect on SSRT in other neurodegenerative diseases (Kehagia *et al.*, 2014; Hughes *et al.*, 2015; Ye *et al.*, 2016).

The results in this chapter have two clinical applications. First, MRS has potential as an imaging biomarker of early cell loss in FTLD. In early FTD, there is selective vulnerability of glutamatergic Von Economo neurons in the anterior cingulate and frontoinsular cortex (Seeley *et al.*, 2006; Kim *et al.*, 2012). MRS, which could enable *in vivo* quantification of this glutamatergic deficit, would be an interesting adjunct to ongoing studies of presymptomatic carriers of FTLD-causative mutations (Rohrer *et al.*, 2015*b*). Second, the association with neurotransmitter deficits and impaired response inhibition leads to the hypothesis that correcting these deficits can increase inhibitory control and behavioural disinhibition in FTLD syndromes.

Discussion

Preface

Part of this discussion is included in a review article I wrote with Professor Rowe (Murley and Rowe, 2018).

Discussion

In this thesis, I have shown that the syndromes associated with frontotemporal lobar degeneration have heterogeneous and overlapping clinical features, brain morphometry, neuropathology and prognosis. I suggested that categorising patients by their predominant clinical features, as opposed to the current disease labels, will improve our understanding of the origin of symptoms, assessment of diagnostic biomarkers and development of symptomatic treatments. I then used this transdiagnostic approach to investigate the neurobiology of impulsivity in FTLD syndromes, showing that GABA and glutamate deficits are associated with behavioural disinhibition. Each chapter contained a discussion of its results, so here I discuss three general themes arising from the thesis, each of which has potential for future research. First, the phenotypic heterogeneity in FTLD, and the role of nosology in neurodegenerative disease. Second, the characteristics and aetiology of the selective vulnerability of different brain regions and networks in FTLD. Third, neurotransmitters deficits in FTLD, their relationship to clinical phenotypes and their potential as targets for symptomatic treatments.

Phenotypic heterogeneity in FTLD syndromes

This thesis raises several questions; what is the fundamental purpose of a disease label and what is the most appropriate way to describe the presentation of patients with neurodegenerative disease? Diagnostic labels have several purposes including 1) optimising clinicopathological correlations, 2) concisely summarising disease phenotypes to aid communication between healthcare professionals, 3) guiding treatments and support for patients and their families and 4) prognostication. I suggest that a transdiagnostic, combined approach to FTLD syndromes better addresses these aims compared to the current disease labels. Next, I discuss the nosology of FTLD syndromes, comparing a transdiagnostic approach to FTLD syndromes to the current diagnostic subtypes.

In chapter four, I showed the clinicopathological correlations of the current syndrome labels are complex and inconsistent. I replicated previous results showing that some syndrome labels have high specificity but overall clinicopathology accuracy is low (Rascovsky *et al.*, 2011; Alexander *et al.*, 2014, Perry *et al.*, 2017*a*; Spinelli *et al.*, 2017; Gazzina *et al.*, 2019; Sakae *et al.*, 2019). The high specificity of some disease labels, for example PSP-RS for FTLD-tau-PSP, enable their use as inclusion criteria for trials of disease modifying therapies (Boxer *et al.*, 2019). However, their low overall accuracy would prevent their use clinically. If an effective

disease modifying therapy for FTLD-tau-PSP became available, restricting its use to patients with a PSP-RS phenotype will mean that up to half of patients with FTLD-tau-PSP would be ineligible. Including all patients with a syndrome possibly associated with FTLD-tau-PSP would mean a large majority of patients would be exposed to a potentially toxic and probably expensive treatment with no benefit. It has been argued that clinicopathological correlations could be improved by further refining the current diagnostic criteria, subdividing clinical syndromes by certain features most associated with a certain neuropathology (Josephs *et al.*, 2012). However, clinical phenotype is likely determined by the distribution of neuropathology, rather than molecular subtype (Dickson *et al.*, 2010; Jabbari *et al.*, 2019; Sakae *et al.*, 2019). My thesis supports this theory. In chapter two I identified several core phenotype-atrophy correlations in FTLD that were not associated with different pathological subtypes, as shown in chapter four. This result is limited by the low sample size and requires replication after more participants have donated to the brain bank. If true, it suggests that FTLD syndrome classifications will never provide highly accurate clinicopathological correlations. Other biomarkers, whether imaging (Ossenkoppele *et al.*, 2018; Leuzy *et al.*, 2019) or fluid (Meeter *et al.*, 2017; Lleó *et al.*, 2018; Zetterberg *et al.*, 2019)-based, will be needed to stratify patients. This approach would mirror those in other medical specialities. For example in oncology, patients are given a broad organ-specific diagnosis then extensively stratified based on the molecular and genetic characteristics of their tumour (Weigelt *et al.*, 2008; Reis-Filho and Pusztai, 2011). This subclassification can continuously evolve to include advances in research and new treatments, while the overall disease label is unchanged.

Given these limitations in clinicopathological accuracy, FTLD nosology must meet the other aims of a diagnostic label. There is extensive evidence of overlapping clinical features in FTLD syndromes, but this often results from pairwise comparisons between syndromes (Snowden *et al.*, 2001; Boeve *et al.*, 2003; Sánchez-Valle *et al.*, 2006; González Sánchez *et al.*, 2010, Rohrer *et al.*, 2010*a*; Lagarde *et al.*, 2013; Hardy *et al.*, 2016; Harris *et al.*, 2016). In chapter two, I compared all syndromes together to demonstrate the benefits of a transdiagnostic approach in capturing the clinical heterogeneity in FTLD. This has practical implications for both clinical and research practice, which I shall discuss next. Importantly, I am not suggesting all these diseases should be renamed, instead I suggest that increased emphasis is placed on their heterogeneity and overlap by considering them as a spectrum, rather than discrete entities.

For clinical care, a transdiagnostic approach to FTLD syndromes has several advantages over the current diagnostic labels and in many specialist centres is already established practice. First,

it resolves the diagnostic confusion that occurs when a patient has features of several FTLD syndromes, either at first or subsequent clinic visits. In one large USA cohort, the initial diagnosis of some FTLD syndromes changed in over a third of patients during their disease (Perry *et al.*, 2019). In some patients, the diagnosis was changed to another neurodegenerative or psychiatric illness disease, but in many the new diagnosis was another FTLD syndrome. This causes confusion for patients and their families; Was the first diagnosis incorrect? Has a new disease progress started? This confusion (for patients, families and healthcare professionals) can divert time and attention from focusing on treating symptoms. Second, it would simplify education of non-specialist doctors and healthcare professionals. In the UK, most patients with neurodegenerative diseases receive the majority of their healthcare in primary care (Greaves and Jolley, 2010; Meeuwsen *et al.*, 2012). Resource limitations often mean that, outside of specialist centres with research funding, patients may not see a specialist after their initial appointment. The change in FTLD phenotype with disease progression may mean that treatments that are beneficial at early stages are harmful at later stages. For example, severe behavioural disturbance may be improved with an atypical antipsychotic, but the same drug will worsen parkinsonism and gait disturbance that may develop with disease progression. Doctors need to be aware of FTLD syndrome overlap and monitor patients closely for emergence of any new features that may change symptomatic management. Third, a combined approach to FTLD syndromes may improve support for patients and their families. In the UK, there is no patient charity for bvFTD, nfvPPA or svPPA. The charity for PSP, the PSP Association, also helps patients with CBS, who anecdotally often feel subordinate to patients with PSP (given the title and primary focus of the charity). One charity for all FTLD syndromes could improve patient support, fundraising and disease awareness. It might be argued that the breadth of different phenotypes across FTLD would be confusing – why does the person sitting next to me, with nominally the same illness, have different problems? I suggest that this is already the case, as the new diagnostic criteria for PSP already include presentations with predominant behavioural, language or motor features (Höglinger *et al.*, 2017). Instead, a transdiagnostic approach would help patients and their families understand and manage changes in the nature and burden of symptoms with disease progression.

A combined approach to FTLD syndromes would also benefit clinical research. I suggest trials of symptomatic treatments need careful stratification, selecting participants for their relevant symptoms rather than the diagnosis alone. For example, in a trial to demonstrate a clinical effect of serotonergic treatment on impulsivity in bvFTD, based on experimental medicines evidence (Hughes *et al.*, 2015), participants should not merely have bvFTD by consensus criteria, but

also have impulsivity; noting that disinhibition is one of six criteria, only three of which are required for the diagnosis. Including patients with bvFTD who are not disinhibited is likely to reduce the power of a symptomatic treatment trial. Moreover, it may be better to include all patients with disinhibition arising from syndromes associated with FTLD in which disinhibition is common but not a diagnostic criterion (Lansdall et al., 2017). This would increase the power and relevance of the trial to a wider patient group (Figure 8-1). A transdiagnostic approach can also be helpful in trials of disease modifying therapies (Figure 8-1). Basket studies are clinical trials that recruit patients with a common molecular pathology, irrespective of their clinical phenotype (Tao *et al.*, 2018). They are increasingly used in oncology trials that enrol patients with specific genetic mutations, irrespective of their tumour location (Hyman *et al.*, 2015, 2018). In neurodegenerative disease, they have been used to test anti-tau therapies in several tauopathies including Alzheimer's disease, PSP, CBS, chronic traumatic encephalopathy, and FTD due to *MAPT* mutations (Panza *et al.*, 2019; Tsai *et al.*, 2019).

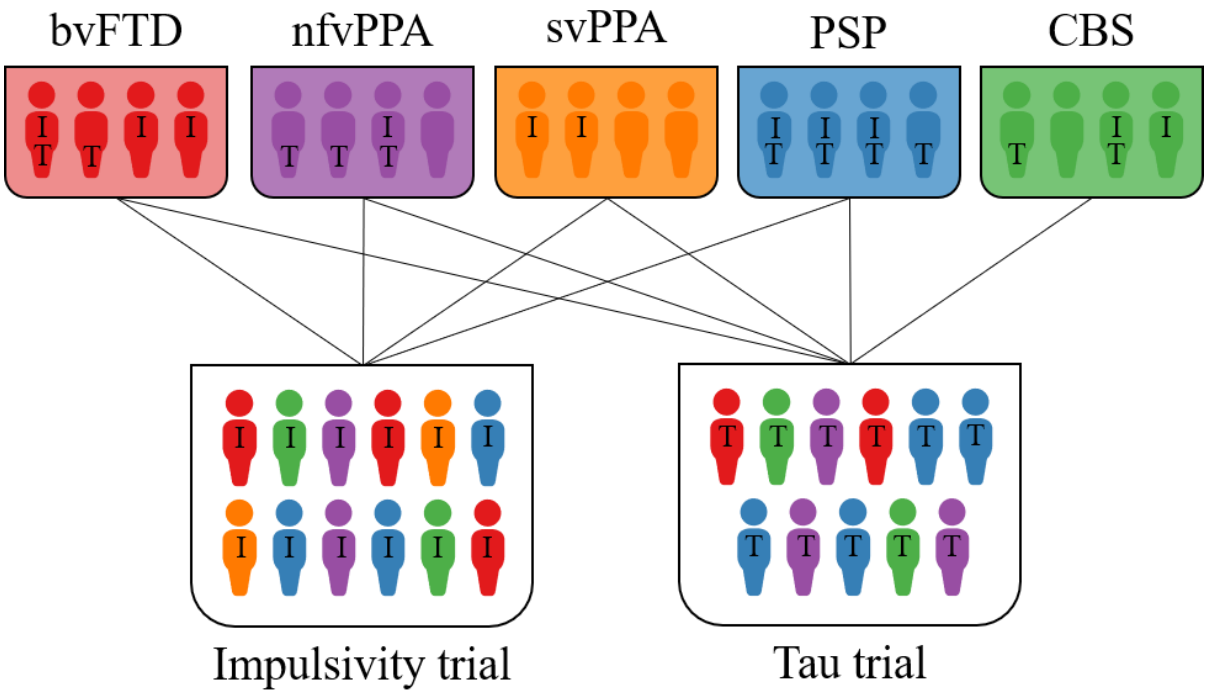


Figure 8-1: Examples of potential basket trials in FTLD syndromes. Instead of selecting patients based on their disease label (top row), they are selected based on a symptom (I=impulsivity) or molecular (T=tauopathy) characteristic for the relevant trial (bottom row). Idea for figure from (Tao *et al.*, 2018).

The transdiagnostic, "basket trial" approach to research trials has limitations. First, it is important that the selected feature is the same across syndromes, otherwise an effective treatment for one may not work for another. For example, a basket trial for impulsivity in FTLD assumes that the neurobiology of impulsivity is the same across FTLD syndromes. This cannot

be assumed, impulsivity in PSP could be related to motor disinhibition, whereas in svPPA it may be caused by loss of knowledge of social norms. In this thesis, I showed glutamate and GABA deficits in the frontal lobes of both bvFTD and PSP and have similar impairments on a disinhibition task, which would support a basket trial approach to behavioural disinhibition. Similarly, a basket trial of an anti-tau therapy would be weakened if the molecular biology of FTLD-tau-PSP, CBD and Picks tauopathies were fundamentally different (Falcon *et al.*, 2018; Goedert, 2018; Zhang *et al.*, 2020). Interestingly, a recent transdiagnostic study that measured six key proteinopathies across multiple neurodegenerative diseases identified four data-driven clusters, each of which had different genetic and clinical profiles (Cornblath *et al.*, 2019). FTLD cases clustered into one of two clusters, that corresponded broadly to tau and TDP43, supporting a combined approach to these pathology superfamilies. Further research on FTLD molecular biology and symptom aetiology is required, but this could be helped by secondary analysis of basket study results. Second, basket studies would need different disease outcome measures to those used for individual FTLD syndromes. Currently, disease outcome measures tend to be validated for one FTLD syndrome, for example the PSP-RS for PSP (Golbe and Ohman-Strickland, 2007) or FRS for bvFTD (Mioshi *et al.*, 2010). These scales tend to be heavily weighted on either behavioural, cognitive, language or motor features and may be insensitive to significant changes in symptoms or disease progression in the FTLD syndrome spectrum (Desmarais *et al.*, 2019). Third, basket trials require alternative biostatistical designs to conventional clinical trials. Currently, many basket trials are designed as a series of independent studies for each subgroup (e.g. PSP, CBS, nfvPPA, FTD) run in parallel. This limits the benefits of a combined, transdiagnostic approach and risks type I error due to multiple hypothesis testing (Tao *et al.*, 2018).

Prognostication was also more accurate with a transdiagnostic approach. In chapter five, I showed that the presence of certain clinical features better predicts prognosis than the current disease labels. Irrespective of FTLD syndrome subtype, parkinsonism and other PSP-like motor features are associated with increased mortality and behavioural impairments are associated with greater risk of care home admission. This is relevant for two reasons. First, it helps counsel patients and their families. Individual prognosis can vary widely from the average patient with the same disease label. This variability is partly due other patient-specific factors such as age and comorbidities, but it also reflects the heterogeneity within disease labels. Second, it helps prioritise clinical and research care. Care in residential and nursing homes is very expensive and any intervention proven to reduce the impact of behavioural disturbance in FTLD, whether

increased community care, counselling for families and carers or more effective medication, is likely to be cost effective.

I suggest that the overlap between FTLD syndromes is recognised in diagnostic criteria and disease classifications. Worldwide, the gold standard for disease classification is the International Classification Diseases (ICD). This provides the framework for public health planning, including allocation of healthcare and research funding, and the current (10^{th}) revision was introduced in 1994 (Bramer, 1988). The syndromes associated with frontotemporal lobar degeneration are not well categorised in the ICD-10. For example, the label for bvFTD is "Dementia in Pick's disease" which has not been used as a clinical diagnosis since the late 1980s (Gustafson, 1987). This has practical implications for clinical and research practice. During the recruitment stages of the PIPPIN study, I tried to record the total number of patients with an FTLD syndrome known to our local tertiary hospital to determine the proportion recruited to the epidemiological arm of PIPPIN study. This proved challenging, as NHS hospital records use the ICD-10 classification system. The next version of the ICD (ICD-11) is due to be introduced in 2022. Pick's disease has been corrected to frontotemporal dementia, but other syndromes associated with FTLD remain scattered across many different categories. For example, progressive supranuclear palsy is classed as a subtype of "atypical parkinsonism" and corticobasal syndrome is not mentioned at all. Interestingly, frontotemporal lobar degeneration is included in ICD-11, as subtype of "disorders with neurocognitive impairment as a major feature". Using this term as a common code for all syndromes associated with FTLD, with appropriate syndrome subtypes, would help accurate diagnostic coding and improve clinical and research practice by supporting referral to specialist clinics and recruitment into research studies.

Selective vulnerability in FTLD

This thesis has replicated the widespread evidence that frontotemporal lobar degeneration causes selective, focal brain atrophy. In chapter three, I used source-based morphometry to identify regions of covarying grey and white matter volume loss. Each participant had varying weights on these atrophy components, or put another way each patient had focal atrophy but the topography of the atrophy varied between individuals. I replicated the classical patterns of atrophy associated with each FTLD syndrome, for example, between the PSP syndrome and brainstem atrophy and bvFTD and frontal lobe atrophy. However, the patterns of focal atrophy overlapped across FTLD syndromes. Individual participants from all disease groups had a

spread of scores across different components, reflecting the overlapping syndrome dimensions I reported in chapter 2. There was additional evidence of a close relationship between atrophy and phenotype, with three key phenotype-atrophy correlations identified by canonical correlation analysis. In chapter four I showed these atrophy patterns, which represent the topography of neurodegeneration, did not match closely with specific pathological proteins, suggesting poor correlations between specific proteinopathies and atrophy patterns.

It is well recognised that one FTLD neuropathology can cause different clinical phenotypes. For example, FTLD-tau-PSP is associated with at least seven clinical phenotypes (Respondek *et al.*, 2017). Clinical phenotype and age of onset varies widely even within families with the same genetic mutation (Boeve *et al.*, 2005; Snowden *et al.*, 2006; Rademakers *et al.*, 2007; Benussi *et al.*, 2015; Murphy *et al.*, 2017; Foxe *et al.*, 2018) and some gene carriers of putatively fully penetrant, autosomal dominant mutations remain asymptomatic even in old age (Munoz *et al.*, 2007). Understanding what causes this selective vulnerability in some regions and selective resistance in others may open opportunities for novel disease modifying treatments.

There is evidence that some neuronal subtypes are selectively vulnerable to FTLD pathology. Von Economo neurons (VEN) have a unique morphology and are restricted to the anterior cingulate and frontoinsular cortices. They are present in high numbers in humans (Nimchinsky *et al.*, 1999) and to a lesser extent in other higher order mammals including great apes (Allman *et al.*, 2010), old world monkeys (Evrard *et al.*, 2012), elephants (Hakeem *et al.*, 2009) and cetaceans (Butti *et al.*, 2009) and may have a role in social and emotional cognition (Seeley *et al.*, 2006). VENs are affected early in bvFTD, when caused by either FTLD-tau (Lin *et al.*, 2019) and FTLD-TDP43 (Yang *et al.*, 2017; Gami-Patel *et al.*, 2019) pathology (Seeley *et al.*, 2006; Santillo *et al.*, 2013; Santillo and Englund, 2014). This selective vulnerability of VEN and anterior cingulate at the early stages of bvFTD has been confirmed by neuropathological studies of patients who died from MND with very mild bvFTD (Kim *et al.*, 2012) and the incidental finding of presymptomatic, early Pick's disease in the brain of a patient who died of other causes (Miki *et al.*, 2014). VEN loss has been found in PSP and nfvPPA associated with MAPT mutations, but there is limited evidence on if they are reduced in sporadic PSP or other FTLD syndromes. It would be interesting to look if VENs were disproportionately reduced in all FTLD syndromes with behavioural impairment.

Genetic factors predispose certain individuals to FTLD, either due to autosomal dominant monogenetic mutations or genetic polymorphisms identified by genome wide association

studies (GWAS) (Raffaele *et al.*, 2019). Could genetic differences between individuals explain differences in selective vulnerability? A polymorphism in the TRIM11 gene, which is expressed in the basal ganglia and cerebellum and codes proteins in the ubiquitin proteasome system, may partially determine if patients develop the more rapidly progressive PSP-Richardson's syndrome or other PSP syndrome subtypes (Jabbari *et al.*, 2018). Regional differences in gene mutation and expression across the brain could also contribute to selective vulnerability of different neuronal populations. Somatic mutations occur postzygotically, either during the intensive cell division associated with brain development or due to the increasing cell vulnerability associated with ageing (Leija-Salazar *et al.*, 2018). This genetic mosaicism is increasingly recognised in both healthy and diseased human brains (Baillie *et al.*, 2011; Keogh *et al.*, 2018; Wei *et al.*, 2019). There are higher rates of somatic mutations in Alzheimer's disease compared to control brains (Helgadottir *et al.*, 2019; Park *et al.*, 2019). Variability in gene expression is also associated with both focal atrophy (Altmann *et al.*, 2019) and functional connectivity (Rittman *et al.*, 2016*b*) in FTLD. Somatic mosaicism in the brain may explain both the diversity in phenotype and age of onset of genetic FTLD and the phenotypic heterogeneity across individuals with sporadic disease. Further research is required, and the PIPPIN study would be a useful resource to use, given many patients with detailed clinical phenotyping will donate their brains for research over the next few years.

Other individual premorbid differences could contribute to syndrome heterogeneity. Some patients with FTLD-tau-PSP and CBD present with a nfvPPA phenotype. Developmental dyslexia or previous injury to the language network may predispose individuals who develop FTLD pathology to present with language symptoms (Rogalski *et al.*, 2013). There is a higher prevalence of dyslexia in patients with PPA compared to bvFTD and controls (Rogalski *et al.*, 2008, 2013; Miller *et al.*, 2013). PPA in later life has been reported in patients with mild left hemicranial hypoplasia due to childhood injury (Alberca *et al.*, 2004). In the PIPPIN cohort there was one patient with a gradual onset, progressive nfvPPA phenotype who had an incidental finding of a left Broca's area infarct on his MRI. There is a higher incidence of left-handedness in svPPA, though the significance of this is unclear (Miller *et al.*, 2013). Could the premorbid personality of patients with bvFTD influence which behavioural symptoms they develop? Anecdotally, some families report their relative's bvFTD-related symptoms represent an exaggeration of premorbid personality traits, however this could reflect recall bias. There is limited and conflicting research on the influence of premorbid personality of clinical phenotype in neurodegenerative diseases (Lebert *et al.*, 1995; Sevinçer *et al.*, 2017; Rouch *et al.*, 2019). Age at onset may influence FTLD syndrome phenotype (Baborie *et al.*, 2012), though this is

likely to be due to differences in FTLD pathology subtype and comorbid neuropathology (Seo *et al.*, 2018).

The presence of multiple proteinopathies in the same brain is increasingly recognised and is likely to affect selective vulnerability, the topography of neurodegeneration and clinical phenotype. In chapter four, I reported comorbid neuropathology when the neuropathologist thought this was clinically significant. This was rare, but when present was associated with an atypical phenotype (chapter four). However, other patients may have had low levels of comorbid proteinopathies, including AD, tau, TDP43 and alpha-synuclein, and cerebrovascular disease. Recent reports suggest that "pure" FTLD is atypical, in one study a majority of both FTLD-tau-PSP and FTLD-TDP43 had comorbid proteinopathies (Robinson *et al.*, 2018). Proteinopathies can act synergistically (Giasson *et al.*, 2003; Clinton *et al.*, 2010; Fang *et al.*, 2014) so a second protein may change the topography and spread of neurodegeneration, even when present at low levels. There is already evidence that comorbid pathology in other neurodegenerative diseases influences clinical phenotype. Alzheimer's disease can be associated with TDP-43 deposition in the hippocampus and amygdala, now termed limbic-predominant age-related TDP-43 encephalopathy (LATE) (Josephs *et al.*, 2019; Nelson *et al.*, 2019). The combination of both AD and LATE is associated with greater medial temporal lobe volume loss and worse cognitive impairment (Josephs *et al.*, 2008*b*; Chang *et al.*, 2016). Similarly, the co-occurrence of tau and/or amyloid-beta is associated with more severe and rapidly progressive cognitive decline in Dementia with Lewy Bodies (Abdelnour *et al.*, 2016; Gomperts *et al.*, 2016; Coughlin *et al.*, 2019). In contrast, there is limited evidence on the role of comorbid pathology in FTLD and how this contributes to disease severity and clinical phenotype. This is also a limitation of my thesis and requires further research.

Finally, neuroinflammation may contribute to selective vulnerability of different brain regions and the distribution and spread of neurodegeneration. It is unclear if the neuroinflammation associated with frontotemporal lobar degeneration (Cagnin *et al.*, 2004; Bevan-Jones *et al.*, 2020) and Alzheimer's disease (Malpetti *et al.*, 2019; Passamonti *et al.*, 2019) is primary or secondary to protein aggregation nor if it is beneficial or harmful (Bright *et al.*, 2019). Neuroinflammation can be imaged *in vivo* with PET ligands of activated microglia (Zhang, 2015) which shows neuroinflammation precedes protein aggregation in a pre-symptomatic MAPT carrier (Bevan-Jones *et al.*, 2019). Together, these results suggest neuroinflammation may influence protein aggregation, neurodegeneration and clinical phenotype in FTLD syndromes, but further research is required.

Neurotransmitter deficits as potential targets for symptomatic treatment in FTLD syndromes

Impulsivity is an early feature in many FTLD syndromes, not just bvFTD (Rascovsky *et al.*, 2011; Gerstenecker *et al.*, 2013, Rittman *et al.*, 2016*a*; Lansdall *et al.*, 2017) but in longitudinal studies, carer ratings of disinhibited behaviour improve with disease progression (Chow *et al.*, 2012; O'Connor *et al.*, 2016). This may be because worsening apathy, global cognitive impairment, parkinsonism and/or gait disturbance masks impulsive behaviours. This non-linear change in behavioural impairments has important implications. Disease modifying therapies, when/if developed, are likely to be given early in the disease course and slow rather than reverse or halt disease progression, extending the duration of "early" stage disease and so increasing the overall prevalence of impulsivity. Symptomatic treatments therefore must be developed in conjunction with slowing progression of the underlying neurodegeneration to prevent a paradoxical increase in disease burden.

Currently, all symptomatic drug treatments for FTLD syndromes aim to partially correct neurotransmitter deficits (Buoli *et al.*, 2017). Serotonin dysfunction is a significant contributor to the behavioural and cognitive symptoms seen in FTLD syndromes (Huey *et al.*, 2006; Murley and Rowe, 2018). There is loss of serotonergic neurons in bvFTD (Yang and Schmitt, 2001) and PSP (Chinaglia *et al.*, 1993; Revesz *et al.*, 1996) and serotonin levels are associated with behavioural impairment in some studies (Engelborghs *et al.*, 2004). Several open label studies without placebo-control have shown improvement in behavioural symptoms with serotonergic drugs (Moretti *et al.*, 2003; Anneser *et al.*, 2007; Herrmann *et al.*, 2012) but this has not been replicated in a placebo-controlled blinded study (Deakin *et al.*, 2004). Antipsychotic medications with dopaminergic receptor affinity are often used to treat severe behavioural disturbance in FTLD but patients can be extremely sensitive to extra-pyramidal side effects due to nigrostriatal deficits (Oyanagi, 2002; Pijnenburg *et al.*, 2003; Huey *et al.*, 2006; Murley and Rowe, 2018). A meta-analysis of antidepressants in bvFTD showed a reduction in carer-ratings of behavioural impairment, noting, however, that the evidence was mainly from small, non-placebo controlled trials (Huey *et al.*, 2006). Trazodone does improve behavioural symptoms in bvFTD, based on a randomized control cross-over study (Lebert *et al.*, 2004). Interestingly, trazodone is a multifunctional drug that acts on serotonergic, noradrenergic, dopaminergic and histamine pathways (Stahl, 2009).

In chapter six, I used a novel analysis of the stop no go task to measure behavioural disinhibition in bvFTD and PSP. In chapter seven, I showed both glutamate and GABA concentrations were reduced in the frontal lobe of both syndromes and this deficit was associated with behaviour disinhibition. Testing if GABA and glutamate replacement reduces behavioural disinhibition requires a randomised, double-blinded, placebo-controlled clinical trial. There are already approved medications that modulate synaptic GABA and glutamate, so pre-clinical and safety and tolerability studies would not be required. However, there are a several limitations of my results that mean further research is required before a large clinical trial can be justified. First, neurotransmitters only correlated with a neuropsychological stop no-go task and not carer ratings of behavioural impairment and daily function. Carer ratings reflect widespread behavioural and cognitive deficits and are confounded by motor and language impairments. Right inferior frontal gyrus neurotransmitter levels are unlikely to be associated with all these behavioural, cognitive, language and motor impairments. Also, the inferior frontal gyrus cannot be assumed to be representative of the whole frontal lobe, due to heterogeneity in FTLD brain morphometry (chapter three). Second, it is not known if MRS measures an extra-neuronal neurotransmitter deficit or is indirectly measuring glutamatergic and GABAergic neuronal loss. In healthy volunteers, a GABA reuptake inhibitor has no effect on 3T MRS of GABA (Myers *et al.,* 2014) but this may be due to macromolecule contamination of the GABA spectra, a recognised complication of 3T edited spectroscopy (Harris *et al.,* 2015). Ultra-high-field (9-11 Tesla) MRS is sensitive to the effects of GABA and glutamate reuptake inhibitors in animal models (Waschkies *et al.,* 2014; Rizzo *et al.,* 2017) but this has not yet been replicated in humans. The loss of post-synaptic receptors in FTLD (Foster *et al.,* 2000; Jiang *et al.,* 2018; Murley and Rowe, 2018) may mean increasing synaptic GABA and glutamate concentrations is futile. This already hampers the efficacy of other neurotransmitter treatments in FTLD, for example levodopa does not typically improve parkinsonism, possibly due to loss of D2 receptors in the basal ganglia (Oyanagi, 2002; Murley and Rowe, 2018). Third, drugs that modulate neurotransmitter levels tend to have non-linear, inverted U-shaped responses. GABA and glutamate deficits were only seen in the frontal, not occipital lobes so drugs that increase neurotransmitter levels across the whole brain may restore a deficit in affected but "overdose" unaffected brain regions. This problem is well established in Parkinson's disease, in the sometimes difficult balance between motor disability and impulse control disorders and cognitive impairment with dopaminergic treatments (Napier *et al.,* 2015; Voon *et al.,* 2017). The application of focal treatments to restore biochemical function, such as dopaminergic stem cell transplants or gene therapy to induce dopamine synthesis in striatal cells, can overcome some of the adverse consequences of systemic drug treatment in Parkinson's disease. However,

such localized treatments seem even more challenging in a diffuse lobar cortical disorder and for the time being, systemic drug delivery is likely to be the mainstay of clinical therapeutics. These limitations mean that additional research is required to clarify the relationship between GABA, glutamate and clinical features of FTLD syndromes before a clinical trial can be justified.

GABA may be a more tractable treatment target than glutamate as GABA reuptake inhibitors, such as tiagabine, have been approved for clinical use whereas glutamate reuptake inhibitors have only been used in animal models (Adkins and Noble, 1998; Dunlop, 2006). One advantage of magnetic resonance spectroscopy is that it could enable a personalised approach to a clinical trial, with drug-doses titrated to an individual's neurochemical deficit. My results show that GABA levels vary widely between participants with FTLD, some patients have near normal levels whereas others have less than half the concentrations of healthy controls. The same dose of a GABA reuptake inhibitor is likely to have varying effects in different patients, even before accounting for pharmacokinetic differences. MRS could allow for titration of drug dose, with higher doses given to patients with greater GABAergic deficits. Interestingly, there are case reports of transient but significant symptomatic improvement with $GABA_A$ agonists in PSP (Daniele *et al.*, 1999; Cotter *et al.*, 2010; Dash, 2013; Chang and Weirich, 2014) but this has never been investigated systemically in a clinical trial and has not been replicated in most PSP patients. Selective serotonin reuptake inhibitors increase cortical GABA concentrations (Sanacora *et al.*, 2002) which may partly explain the behavioural improvements associated with SSRI use in FTLD syndromes (Huey *et al.*, 2006; Hughes *et al.*, 2015). Together, these results suggest GABA is a promising target for symptomatic treatment in FTLD syndromes.

Replacing neurotransmitter deficits will not slow FTLD progression but could act indirectly to delay symptom onset or improve life expectancy. Preserved functional connectivity despite progressive atrophy and neurodegeneration enables carriers of FTLD-related genetic mutations to maintain cognitive performance (Rittman *et al.*, 2019; Tsvetanov *et al.*, 2019). Brain network connectivity depends on glutamate and GABA neurotransmission (Fries, 2009; Buzsáki and Wang, 2012) so restoring these neurotransmitter deficits, if present in pre-symptomatic gene carriers, could delay disease age of onset. One cause of death in early and moderate stage FTLD is choking, causes of which include impulsive food cramming (Lewis *et al.*, 2019). Treating impulsivity may prevent or reduce choking. This may not have an overall effect on survival at a group-level (Papapetropoulos *et al.*, 2005), although the introduction of dopamine replacement improved life expectancy in Parkinson's disease (Uitti *et al.*, 1993).

Conclusion

I have shown that a combined, transdiagnostic approach to the syndromes associated with frontotemporal lobar degeneration provides new insights into the clinical phenotypes, brain morphometry, neuropathology and prognosis of these diseases. The clinical phenotypes and brain morphometry in FTLD are heterogeneous and overlapping. But, the pattern of clinical features found across FTLD syndromes is a better predictor of neuropathology and prognosis than the current diagnostic labels. Frontal lobe GABA and glutamate deficits were associated with behavioural disinhibition in FTLD syndromes. Together, these results inform the development of symptomatic treatment strategies and design of future clinical trials. Such progress towards better treatments is urgently required to reduce the devastating burden of these diseases to patients and their families.

References

Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. J Am Geriatr Soc 2000; 48: 938–942.

Aarsland D, Litvan I, Larsen JP. With Progressive Supranuclear Palsy and Parkinson ' s Disease. J Neuropsychiatry Clin Neurosci 2001; 13: 42–49.

Abbott SM, Videnovic A. Sleep Disorders in Atypical Parkinsonism. Mov Disord Clin Pract 2014; 1: 89–96.

Abdelnour C, van Steenoven I, Londos E, Blanc F, Auestad B, Kramberger MG, et al. Alzheimer's disease cerebrospinal fluid biomarkers predict cognitive decline in lewy body dementia. Mov Disord 2016; 31: 1203–1208.

Adkins JC, Noble S. Tiagabine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. Drugs 1998; 55: 437–460.

Agarwal S, Ahmed RM, D'Mello M, Foxe D, Kaizik C, Kiernan MC, et al. Predictors of survival and progression in behavioural variant frontotemporal dementia. Eur J Neurol 2019; 26: 774–779.

Ahmed RM, Irish M, Henning E, Dermody N, Bartley L, Kiernan MC, et al. Assessment of eating behavior disturbance and associated neural networks in frontotemporal dementia. JAMA Neurol 2016; 73: 282–290.

Ahmed RM, Irish M, Piguet O, Halliday GM, Ittner LM, Farooqi S, et al. Amyotrophic lateral sclerosis and frontotemporal dementia: distinct and overlapping changes in eating behaviour and metabolism. Lancet Neurol 2016; 15: 332–342.

Ahmed RM, Latheef S, Bartley L, Irish M, Halliday GM, Kiernan MC, et al. Eating behavior in frontotemporal dementia. Neurology 2015; 85: 1310–1317.

Ahmed Z, Bigio EH, Budka H, Dickson DW, Ferrer I, Ghetti B, et al. Globular glial tauopathies (GGT): Consensus recommendations. Acta Neuropathol 2013; 126: 537–544.

Aiello M, Silani V, Rumiati RI. You stole my food! Eating alterations in frontotemporal dementia. Neurocase 2016; 22: 400–409.

Akelaitis AJ. Atrophy of basal ganglia in pick's disease: A clinicopathologic study. Arch Neurol Psychiatry 1944; 51: 27–34.

Alberca R, Montes E, Russell E, Gil-Néciga E, Mesulam M. Left Hemicranial Hypoplasia in 2 Patients with Primary Progressive Aphasia. Arch Neurol 2004; 61: 265–268.

Albrecht F, Mueller K, Ballarini T, Lampe L, Diehl-Schmid J, Fassbender K, et al. Unraveling corticobasal syndrome and alien limb syndrome with structural brain imaging. Cortex 2019; 117: 33–40.

Aldrich MS, Foster NL, White RF, Bluemlein L, Ba GP. Sleep abnormalities in progressive

supranuclear palsy. Ann Neurol 1989; 25: 577–581.

Alexander SK, Rittman T, Xuereb JH, Bak TH, Hodges JR, Rowe JB. Validation of the new consensus criteria for the diagnosis of corticobasal degeneration. J Neurol Neurosurg Psychiatry 2014; 85: 923–927.

Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, et al. Focal cortical presentations of Alzheimer's disease. Brain 2007; 130: 2636–2645.

Allman JM, Tetreault NA, Hakeem AY, Manaye KF, Semendeferi K, Erwin JM, et al. The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. Brain Struct Funct 2010; 214: 495–517.

Altmann A, Cash DM, Bocchetta M, Heller C, Reynolds R, Moore K, et al. Analysis of brain atrophy and local gene expression implicates astrocytes in Frontotemporal dementia. bioRxiv 2019: 2019.12.11.872143.

Alvarez JA, Emory E. Executive Function and the Frontal Lobes: A Meta-Analytic Review. Neuropsychol Rev 2006; 16: 17–42.

Alzheimer A. Ueber eigenartige Krankheitsfaelle des spaeteren Alters. Z ges Neurol Psychiat 1911; 4: 356–385.

Anderson T. How Do I Examine for a Supranuclear Gaze Palsy? Mov Disord Clin Pract 2015; 2: 106–106.

Anneser JMH, Jox RJ, Borasio GD. Inappropriate sexual behaviour in a case of ALS and FTD: Successful treatment with sertraline. Amyotroph Lateral Scler 2007; 8: 189–190.

Arai K. MRI of progressive supranuclear palsy, corticobasal degeneration and multiple system atrophy. J Neurol 2006; 253: iii25–iii29.

Arakhamia T, Lee CE, Carlomagno Y, Duong DM, Kundinger SR, Wang K, et al. Posttranslational Modifications Mediate the Structural Diversity of Tauopathy Strains. Cell 2020; 180: 633-644.e12.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013; 80: 496–503.

Armstrong N, Schupf N, Grafman J, Huey ED. Caregiver burden in frontotemporal degeneration and corticobasal syndrome. Dement Geriatr Cogn Disord 2013; 36: 310–318.

Arnold SE, Toledo JB, Appleby DH, Xie SX, Wang LS, Baek Y, et al. Comparative survey of the topographical distribution of signature molecular lesions in major neurodegenerative diseases. J Comp Neurol 2013; 521: 4339–4355.

Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a cognitive control network using diffusion-weighted Magnetic Resonance Imaging (MRI) and functional MRI. J Neurosci 2007; 27: 3743–3752.

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 2003; 6: 115–116.

Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends

Cogn Sci 2004; 8: 170–177.

Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: One decade on. Trends Cogn Sci 2014; 18: 177–185.

Ashburner J, Friston KJ. Voxel-based morphometry - The methods. Neuroimage 2000; 11: 805–821.

Ashburner J, Reg C. VBM tutorial_ja. Options 2010: 1–18.

Austin EJ, Deary IJ, Gibson GJ, McGregor MJ, Dent JB. Individual response spread in self-report scales: Personality correlations and consequences. Pers Individ Dif 1998; 24: 421–438.

Avants BB, Tustison N, Song G. Advanced normalization tools (ANTS). Insight j 2009; 2: 1–35.

Baborie A, Griffiths TD, Jaros E, Momeni P, McKeith IG, Burn DJ, et al. Frontotemporal dementia in elderly individuals. Arch Neurol 2012; 69: 1052–1060.

Badcock J, Michie P, Johnson L, Combrinck J. Acts of control in schizophrenia: dissociating the components of inhibition. Psychol Med 2002; 32: 287–297.

Baez S, Morales JP, Slachevsky A, Torralva T, Matus C, Manes F, et al. Orbitofrontal and limbic signatures of empathic concern and intentional harm in the behavioral variant frontotemporal dementia. Cortex 2016; 75: 20–32.

Baillie JK, Barnett MW, Upton KR, Gerhardt DJ, Richmond TA, De Sapio F, et al. Somatic retrotransposition alters the genetic landscape of the human brain. Nature 2011; 479: 534–537.

Baizabal-Carvallo JF, Jankovic J. Parkinsonism, movement disorders and genetics in frontotemporal dementia. Nat Rev Neurol 2016; 12: 175–185.

Bak TH, Caine D, Hearn VC, Hodges JR. Visuospatial functions in atypical parkinsonian syndromes. J Neurol Neurosurg Psychiatry 2006; 77: 454–456.

Bak TH, Crawford LM, Hearn VC, Mathuranath PS, Hodges JR. Subcortical dementia revisited: Similarities and differences in cognitive function between progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). Neurocase 2005; 11: 268–273.

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

Bakiri Y, Burzomato V, Frugier G, Hamilton NB, Káradóttir R, Attwell D. Glutamatergic signaling in the brain's white matter. Neuroscience 2009; 158: 266–274.

Balakrishnama S, Ganapathiraju A. Linear discriminant analysis-a brief tutorial. Inst Signal Inf Process 1998; 18: 1–8.

Balendra R, Isaacs AM. C9orf72-mediated ALS and FTD: multiple pathways to disease. Nat Rev Neurol 2018; 14: 544–558.

Ballard C, Banister C, Khan Z, Cummings J, Demos G, Coate B, et al. Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease

psychosis: a phase 2, randomised, placebo-controlled, double-blind study. Lancet Neurol 2018; 17: 213–222.

Ballatore C, Lee VMY, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat Rev Neurosci 2007; 8: 663–672.

Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet 2015; 386: 1672–1682.

van de Bank BL, Emir UE, Boer VO, van Asten JJA, Maas MC, Wijnen JP, et al. Multi-center reproducibility of neurochemical profiles in the human brain at 7T. NMR Biomed 2015; 28: 306–316.

Barclay CL, Bergeron C, Lang AE. Arm levitation in progressive supranuclear palsy. Neurology 1999; 52: 879–882.

Barclay CL, Lang AE. Dystonia in progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 1997; 62: 352–356.

Bari A, Eagle DM, Mar AC, Robinson ESJ, Robbins TW. Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. Psychopharmacology (Berl) 2009; 205: 273–283.

Bari A, Robbins TW. Inhibition and impulsivity: Behavioral and neural basis of response control. Prog Neurobiol 2013; 108: 44–79.

Barlow DH, Farchione TJ, Bullis JR, Gallagher MW, Murray-Latin H, Sauer-Zavala S, et al. The unified protocol for transdiagnostic treatment of Emotional Disorders compared with diagnosis-specific protocols for anxiety disorders: A randomized clinical trial. JAMA Psychiatry 2017; 74: 875–884.

Barnes J, Ridgway GR, Bartlett J, Henley SMD, Lehmann M, Hobbs N, et al. Head size, age and gender adjustment in MRI studies: A necessary nuisance? Neuroimage 2010; 53: 1244–1255.

Baron JC, Maziere B, Loc'h C. Loss of striatal [76Br]bromospiperone binding sites demonstrated by positron tomography in progressive supranuclear palsy. J Cereb Blood Flow Metab 1986; 6: 131–136.

del Barrio V. Diagnostic and Statistical Manual of Mental Disorders. Encycl Appl Psychol Three-Volume Set 2004; 17: 607–614.

Bartholdy S, Dalton B, O'Daly OG, Campbell IC, Schmidt U. A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. Neurosci Biobehav Rev 2016; 64: 35–62.

Basar K, Sesia T, Groenewegen H, Steinbusch HWM, Visser-Vandewalle V, Temel Y. Nucleus accumbens and impulsivity. Prog Neurobiol 2010; 92: 533–557.

Bastos AM, Usrey WM, Adams RA, Mangun GR, Fries P, Friston KJ. Canonical Microcircuits for Predictive Coding. Neuron 2012; 76: 695–711.

Baumgarten TJ, Oeltzschner G, Hoogenboom N, Wittsack HJ, Schnitzler A, Lange J. Beta peak frequencies at rest correlate with endogenous GABA+/Cr concentrations in sensorimotor cortex areas. PLoS One 2016; 11: 1–15.

Beagle AJ, Zahir A, Borzello M, Kayser AS, Hsu M, Miller BL, et al. Amount and delay insensitivity during intertemporal choice in three neurodegenerative diseases reflects dorsomedial prefrontal atrophy. Cortex 2020; 124: 54–65.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An Inventory for Measuring Depression. Arch Gen Psychiatry 1961; 4: 561–571.

Behar KL, Rothman DL, Petersen KF, Hooten M, Delaney R, Petroff OAC, et al. Preliminary evidence of low cortical GABA levels in localized 1H-MR spectra of alcohol-dependent and hepatic encephalopathy patients. Am J Psychiatry 1999; 156: 952–954.

Benjiamini Y, Hochberg Y, Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 1995; 57: 289–300.

Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN, et al. Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: The NNIPPS Study. Brain 2009; 132: 156–171.

Benussi A, Alberici A, Buratti E, Ghidoni R, Gardoni F, Luca M Di, et al. Toward a glutamate hypothesis of frontotemporal dementia. Front Neurosci 2019; 13: 1–9.

Benussi A, Padovani A, Borroni B. Phenotypic heterogeneity of monogenic frontotemporal dementia. Front Aging Neurosci 2015; 7: 1–19.

Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, et al. Phenotype variability in progranulin mutation carriers: A clinical, neuropsychological, imaging and genetic study. Brain 2008; 131: 732–746.

Le Ber I, Guedj E, Gabelle A, Verpillat P, Volteau M, Thomas-Anterion C, et al. Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. Brain 2006; 129: 3051–3065.

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington Clinical, morphological and neurochemical correlations. J Neurol Sci 1973; 20: 415–455.

Bertoux M, Delavest M, De Souza LC, Funkiewiez A, Lépine JP, Fossati P, et al. Social cognition and emotional assessment differentiates frontotemporal dementia from depression. J Neurol Neurosurg Psychiatry 2012; 83: 411–416.

Bertoux M, de Souza LC, Zamith P, Dubois B, Bourgeois-Gironde S. Discounting of future rewards in behavioural variant frontotemporal Dementia and Alzheimer'S disease. Neuropsychology 2015; 29: 933–939.

Bevan-Jones WR, Cope TE, Jones PS, Kaalund SS, Passamonti L, Allinson K, et al. Neuroinflammation and protein aggregation co-localize across the frontotemporal dementia spectrum. Brain 2020; 143: 1010–1026.

Bevan-Jones WR, Cope TE, Jones PS, Passamonti L, Hong YT, Fryer T, et al. In vivo evidence for pre-symptomatic neuroinflammation in a MAPT mutation carrier. Ann Clin Transl Neurol 2019; 6: 373–378.

Bevan-Jones WR, Cope TE, Simon Jones P, Passamonti L, Hong YT, Fryer TD, et al. AV-1451 binding in vivo mirrors the expected distribution of TDP-43 pathology in the semantic variant

of primary progressive aphasia. J Neurol Neurosurg Psychiatry 2018; 89: 1032–1037.

Bevan Jones WR, Cope TE, Passamonti L, Fryer TD, Hong YT, Aigbirhio F, et al. [18F]AV-1451 PET in behavioral variant frontotemporal dementia due to MAPT mutation. Ann Clin Transl Neurol 2016; 3: 940–947.

Bhattacharyya PK, Phillips MD, Stone LA, Lowe MJ. In vivo magnetic resonance spectroscopy measurement of gray-matter and white-matter gamma-aminobutyric acid concentration in sensorimotor cortex using a motion-controlled MEGA point-resolved spectroscopy sequence. Magn Reson Imaging 2011; 29: 374–379.

Birks JS. Cholinesterase inhibitors for Alzheimer's disease. In: Birks JS, editor(s). Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006. p. 1–3

Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med 2018; 284: 643–663.

Van Blitterswijk M, Mullen B, Nicholson AM, Bieniek KF, Heckman MG, Baker MC, et al. TMEM106B protects C9ORF72 expansion carriers against frontotemporal dementia. Acta Neuropathol 2014; 127: 397–406.

Bluett B, Litvan I, Cheng S, Juncos J, Riley DE, Standaert DG, et al. Understanding falls in progressive supranuclear palsy. Park Relat Disord 2017; 35: 75–81.

Bocchetta M, Gordon E, Cardoso MJ, Modat M, Ourselin S, Warren JD, et al. Thalamic atrophy in frontotemporal dementia — Not just a C9orf72 problem. NeuroImage Clin 2018; 18: 675–681.

Bocchetta M, Gordon E, Marshall CR, Slattery CF, Cardoso MJ, Cash DM, et al. The habenula: An under-recognised area of importance in frontotemporal dementia? J Neurol Neurosurg Psychiatry 2016; 87: 910–912.

Boeve BF, Boylan KB, Graff-Radford NR, Dejesus-Hernandez M, Knopman DS, Pedraza O, et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain 2012; 135: 765–783.

Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol 2003; 54: 15–19.

Boeve BF, Maraganore DM, Parisi JE, Ahlskog JE, Graff-Radford N, Caselli RJ, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. Neurology 1999; 53: 795–800.

Boeve BF, Tremont-Lukats IW, Waclawik AJ, Murrell JR, Hermann B, Jack CR, et al. Longitudinal characterization of two siblings with frontotemporal dementia and parkinsonism linked to chromosome 17 associated with the S305N tau mutation. Brain 2005; 128: 752–772.

Bologna M, Agostino R, Gregori B, Belvisi D, Ottaviani D, Colosimo C, et al. Voluntary, spontaneous and reflex blinking in patients with clinically probable progressive supranuclear palsy. Brain 2009; 132: 502–510.

Bonny JM, Pagès G. Uncertainties of calculated Cramér-Rao lower bounds: implications for quantitative MRS. Magn Reson Med 2019; 81: 759–764.

Borroni B, Agosti C, Bellelli G, Padovani A. Is early-onset clinically different from late-onset frontotemporal dementia? Eur J Neurol 2008; 15: 1412–1415.

Borroni B, Bonvicini C, Alberici A, Buratti E, Agosti C, Archetti S, et al. Mutation within TARDBP leads to frontotemporal dementia without motor neuron disease. Hum Mutat 2009; 30

Borroni B, Bonvicini C, Galimberti D, Tremolizzo L, Papetti A, Archetti S, et al. Founder effect and estimation of the age of the Progranulin Thr272fs mutation in 14 Italian pedigrees with frontotemporal lobar degeneration. Neurobiol Aging 2011; 32: 555.e1-555.e8.

Borroni B, Grassi M, Agosti C, Premi E, Alberici A, Paghera B, et al. Survival in frontotemporal lobar degeneration and related disorders: Latent class predictors and brain functional correlates. Rejuvenation Res 2009; 12: 33–43.

Borroni B, Grassi M, Premi E, Gazzina S, Alberici A, Cosseddu M, et al. Neuroanatomical correlates of behavioural phenotypes in behavioural variant of frontotemporal dementia. Behav Brain Res 2012; 235: 124–129.

Boutoleau-Bretonnière C, Vercelletto M, Volteau C, Renou P, Lamy E. Zarit burden inventory and activities of daily living in the behavioral variant of frontotemporal dementia. Dement Geriatr Cogn Disord 2008; 25: 272–277.

Bowen DM, Procter AW, Mann DMA, Snowden JS, Esiri MM, Neary D, et al. Imbalance of a serotonergic system in frontotemporal dementia: Implication for pharmacotherapy. Psychopharmacology (Berl) 2008; 196: 603–610.

Boxer AL, Geschwind MD, Belfor N, Gorno-Tempini ML, Schauer GF, Miller BL, et al. Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. Arch Neurol 2006; 63: 81–86.

Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, et al. Memantine in patients with frontotemporal lobar degeneration: A multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2013; 12: 149–156.

Boxer AL, Qureshi I, Ahlijanian M, Grundman M, Golbe LI, Litvan I, et al. Safety of the tau-directed monoclonal antibody BIIB092 in progressive supranuclear palsy: a randomised, placebo-controlled, multiple ascending dose phase 1b trial. Lancet Neurol 2019; 18: 549–558.

Boy F, Evans CJ, Edden RAE, Lawrence AD, Singh KD, Husain M, et al. Dorsolateral prefrontal γ-aminobutyric acid in men predicts individual differences in rash impulsivity. Biol Psychiatry 2011; 70: 866–872.

Bozeat S, Gregory CA, Lambon Ralph MA, Hodges JR. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? J Neurol Neurosurg Psychiatry 2000; 69: 178–186.

Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: Prevalence and contributing factors. Alzheimer Dis Assoc Disord 2009; 23: 306–314.

Bramer GR. International statistical classification of diseases and related health problems - Tenth revision. World Health Organisation; 1988

Brenneis C, Seppi K, Schocke M, Benke T, Wenning GK, Poewe W. Voxel based morphometry reveals a distinct pattern of frontal atrophy in progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 2004; 75: 246–249.

Bright F, Werry EL, Dobson-Stone C, Piguet O, Ittner LM, Halliday GM, et al. Neuroinflammation in frontotemporal dementia. Nat Rev Neurol 2019; 15: 540–555.

den Brok MGHE, van Dalen JW, van Gool WA, Moll van Charante EP, de Bie RMA, Richard E. Apathy in Parkinson's disease: A systematic review and meta-analysis. Mov Disord 2015; 30: 759–769.

Broustal O, Camuzat A, Guillot-Noël L, Guy N, Millecamps S, Deffond D, et al. FUS mutations in frontotemporal lobar degeneration with amyotrophic lateral sclerosis. J Alzheimer's Dis 2010; 22: 765–769.

Brown FS, Rowe JB, Passamonti L, Rittman T. Falls in Progressive Supranuclear Palsy. Mov Disord Clin Pract 2020; 7: 16–24.

Brown RG, Lacomblez L, Landwehrmeyer BG, Bak T, Uttner I, Dubois B, et al. Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy. Brain 2010; 133: 2382–2393.

Brunden KR, Trojanowski JQ, Lee VMY. Evidence that non-fibrillar tau causes pathology linked to neurodegeneration and behavioral impairments. J Alzheimer's Dis 2008; 14: 393–399.

Brunnström H, Friberg N, Lindberg E, Englund E. Differential degeneration of the locus coeruleus in dementia subtypes. Clin Neuropathol 2011; 30: 104–110.

Brunnström HR, Englund EM. Cause of death in patients with dementia disorders. Eur J Neurol 2009; 16: 488–492.

Buck K, Voehringer P, Ferger B. Rapid analysis of GABA and glutamate in microdialysis samples using high performance liquid chromatography and tandem mass spectrometry. J Neurosci Methods 2009; 182: 78–84.

Buervenich S, Sydow O, Carmine A, Zhang Z, Anvret M, Olson L. Dysarthria and orofacial apraxia in corticobal degeneration. Mov Disord 2000; 15: 905–910.

Buoli M, Serati M, Caldiroli A, Galimberti D, Scarpini E, Altamura AC. Pharmacological management of psychiatric symptoms in frontotemporal dementia: A systematic review. J Geriatr Psychiatry Neurol 2017; 30: 162–169.

Burgess PW, Shallice T. The Hayling and Brixton Tests: Thames Valley Test Company Bury St. Edmonds, Engl 1997

Burrell JR, Ballard KJ, Halliday GM, Hodges JR. Aphasia in Progressive Supranuclear Palsy: As Severe as Progressive Non-Fluent Aphasia. J Alzheimer's Dis 2017; 61: 705–715.

Burrell JR, Hodges JR, Rowe JB. Cognition in corticobasal syndrome and progressive supranuclear palsy: A review. Mov Disord 2014; 29: 684–693.

Burrell JR, Hornberger M, Vucic S, Kiernan MC, Hodges JR. Apraxia and motor dysfunction in corticobasal syndrome. PLoS One 2014; 9

Burrell JR, Kiernan MC, Vucic S, Hodges JR. Motor Neuron dysfunction in frontotemporal dementia. Brain 2011; 134: 2582–2594.

Butti C, Sherwood CC, Hakeem AY, Allman JM, Hof PR. Total number and volume of Von Economo neurons in the cerebral cortex of cetaceans. J Comp Neurol 2009; 515: 243–259.

Buzsaki G, Draughn A, Buzsáki G, Draguhn A, Buzsaki G, Draughn A. Neuronal Oscillations in Cortical Networks. Science (80-) 2004; 304: 1926–1930.

Buzsáki G, Wang X-J. Mechanisms of Gamma Oscillations. Annu Rev Neurosci 2012; 35: 203–225.

Caeiro L, Ferro JM, Costa J. Apathy secondary to stroke: A systematic review and meta-analysis. Cerebrovasc Dis 2013; 35: 23–39.

Cagnin A, Rossor M, Sampson EL, MacKinnon T, Banati RB. In vivo detection of microglial activation in frontotemporal dementia. Ann Neurol 2004; 56: 894–897.

Cairns NJ, Bigio EH, Mackenzie IRA, Neumann M, Lee VMY, Hatanpaa KJ, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: Consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol 2007; 114: 5–22.

Canu E, Agosta F, Mandic-Stojmenovic G, Stojković T, Stefanova E, Inuggi A, et al. Multiparametric MRI to distinguish early onset Alzheimer's disease and behavioural variant of frontotemporal dementia. NeuroImage Clin 2017; 15: 428–438.

Carella F, Ciano C, Panzica F, Scaioli V. Myoclonus in corticobasal degeneration. Mov Disord 1997; 12: 598–603.

Cash DM, Bocchetta M, Thomas DL, Dick KM, van Swieten JC, Borroni B, et al. Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. Neurobiol Aging 2018; 62: 191–196.

Caso F, Mandelli ML, Henry M, Gesierich B, Bettcher BM, Ogar J, et al. In vivo signatures of nonfluent/agrammatic primary progressive aphasia caused by FTLD pathology. Neurology 2014; 82: 239–247.

Cattell RB. The scree test for the number of factors. Multivariate Behav Res 1966; 1: 245–276.

Chamberlain SR, Stochl J, Redden SA, Grant JE. Latent traits of impulsivity and compulsivity: Toward dimensional psychiatry. Psychol Med 2018; 48: 810–821.

Chambers CD, Bellgrove MA, Stokes MG, Henderson TR, Garavan H, Robertson IH, et al. Executive 'brake failure' following deactivation of human frontal lobe. J Cogn Neurosci 2006; 18: 444–455.

Chambers CD, Garavan H, Bellgrove MA. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 2009; 33: 631–646.

Chan D, Anderson V, Pijnenburg Y, Whitwell J, Barnes J, Scahill R, et al. The clinical profile of right temporal lobe atrophy. Brain 2009; 132: 1287–1298.

Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, et al. Patterns of temporal

lobe atrophy in semantic dementia and Alzheimer's disease. Ann Neurol 2001; 49: 433–442.

Chang AY, Weirich E. Trial of zolpidem, eszopiclone, and other gaba agonists in a patient with progressive supranuclear palsy. Case Rep Med 2014; 2014: 107064.

Chang XL, Tan MS, Tan L, Yu JT. The Role of TDP-43 in Alzheimer's Disease. Mol Neurobiol 2016; 53: 3349–3359.

Chen JA, Wang Q, Davis-Turak J, Li Y, Karydas AM, Hsu SC, et al. A multiancestral genome-wide exome array study of Alzheimer Disease, frontotemporal dementia, and progressive supranuclear palsy. JAMA Neurol 2015; 72: 414–422.

Chen MK, Mecca AP, Naganawa M, Finnema SJ, Toyonaga T, Lin SF, et al. Assessing Synaptic Density in Alzheimer Disease with Synaptic Vesicle Glycoprotein 2A Positron Emission Tomographic Imaging. JAMA Neurol 2018; 75: 1215–1224.

Chen Y, Kumfor F, Landin-Romero R, Irish M, Hodges JR, Piguet O. Cerebellar atrophy and its contribution to cognition in frontotemporal dementias. Ann Neurol 2018; 84: 98–109.

Chen Z, Chen JA, Shatunov A, Jones AR, Kravitz SN, Huang AY, et al. Genome-wide survey of copy number variants finds MAPT duplications in progressive supranuclear palsy. Mov Disord 2019; 34: 1049–1059.

Chinaglia G, Landwehrmeyer B, Probst A, Palacios JM. Serotoninergic terminal transporters are differentially affected in Parkinson's disease and progressive supranuclear palsy: An autoradiographic study with [3H]citalopram. Neuroscience 1993; 54: 691–699.

Chiu WZ, Kaat LD, Seelaar H, Rosso SM, Boon AJW, Kamphorst W, et al. Survival in progressive supranuclear palsy and frontotemporal dementia. J Neurol Neurosurg Psychiatry 2010; 81: 441–445.

Choi IY, Lee SP, Merkle H, Shen J. In vivo detection of gray and white matter differences in GABA concentration in the human brain. Neuroimage 2006; 33: 85–93.

Chow TW, Fridhandler JD, Binns MA, Lee A, Merrilees J, Rosen HJ, et al. Trajectories of behavioral disturbance in dementia. J Alzheimer's Dis 2012; 31: 143–149.

Clark L, Bechara A, Damasio H, Aitken MRF, Sahakian BJ, Robbins TW. Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. Brain 2008; 131: 1311–1322.

Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM. Synergistic interactions between Aβ, tau, and α-synuclein: Acceleration of neuropathology and cognitive decline. J Neurosci 2010; 30: 7281–7289.

Coccaro EF, Lee R, Vezina P. Cerebrospinal fluid glutamate concentration correlates with impulsive aggression in human subjects. J Psychiatr Res 2013; 47: 1247–1253.

Cohen J. A power primer. Psychol Bull 1992; 112: 155–159.

Cole MW, Schneider W. The cognitive control network: Integrated cortical regions with dissociable functions. Neuroimage 2007; 37: 343–360.

Collette F, Amieva H, Adam S, Hogge M, Van der Linden M, Fabrigoule C, et al. Comparison

of inhibitory functioning in mild Alzheimer's disease and frontotemporal dementia. Cortex 2007; 43: 866–874.

Coon EA, Sorenson EJ, Whitwell JL, Knopman DS, Josephs KA. Predicting survival in frontotemporal dementia with motor neuron disease. Neurology 2011; 76: 1886–1892.

Cope TE, Sohoglu E, Sedley W, Patterson K, Jones PS, Wiggins J, et al. Evidence for causal top-down frontal contributions to predictive processes in speech perception. Nat Commun 2017; 8

Cope TE, Wilson B, Robson H, Drinkall R, Dean L, Grube M, et al. Artificial grammar learning in vascular and progressive non-fluent aphasias. Neuropsychologia 2017; 104: 201–213.

Coppen EM, van der Grond J, Hafkemeijer A, Rombouts SARB, Roos RAC. Early grey matter changes in structural covariance networks in Huntington's disease. NeuroImage Clin 2016; 12: 806–814.

Cordato NJ, Duggins AJ, Halliday GM, Morris JGL, Pantelis C, Melbourne R, et al. Clinical deficits correlate with regional cerebral atrophy in progressive supranuclear palsy. Brain 2005; 128: 1259–1266.

Cordato NJ, Pantelis C, Halliday GM, Velakoulis D, Wood SJ, Stuart GW, et al. Frontal atrophy correlates with behavioural changes in progressive supranuclear palsy. Brain 2002; 125: 789–800.

Cordner Z, Blass DM, Rabins P V., Black BS. Quality of life in nursing home residents with advanced dementia. J Am Geriatr Soc 2010; 58: 2394–2400.

Cornblath EJ, Robinson JL, Lee VM-Y, Trojanowski JQ, Bassett DS. Defining and predicting transdiagnostic categories of neurodegenerative disease. bioRxiv 2019; 25: 664250.

Cotelli M, Adenzato M, Cantoni V, Manenti R, Alberici A, Enrici I, et al. Enhancing theory of mind in behavioural variant frontotemporal dementia with transcranial direct current stimulation. Cogn Affect Behav Neurosci 2018; 18: 1065–1075.

Cotelli M, Borroni B, Manenti R, Ginex V, Calabria M, Moro A, et al. Universal grammar in the frontotemporal dementia spectrum. Evidence of a selective disorder in the corticobasal degeneration syndrome. Neuropsychologia 2007; 45: 3015–3023.

Cotter C, Armytage T, Crimmins D. The use of zolpidem in the treatment of progressive supranuclear palsy. J Clin Neurosci 2010; 17: 385–386.

Cotzias GC, Van Woert MH, Schiffer LM. Aromatic Amino Acids and Modification of Parkinsonism. N Engl J Med 1967; 276: 374–379.

Coughlin D, Xie SX, Liang M, Williams A, Peterson C, Weintraub D, et al. Cognitive and Pathological Influences of Tau Pathology in Lewy Body Disorders. Ann Neurol 2019; 85: 259–271.

Coulthard EJ, Love S. A broader view of dementia: Multiple co-pathologies are the norm. Brain 2018; 141: 1894–1897.

Coyle-Gilchrist ITS, Dick KM, Patterson K, Rodríquez PV, Wehmann E, Wilcox A, et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes.

Neurology 2016; 86: 1736–1743.

Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson's disease psychosis: A randomised, placebo-controlled phase 3 trial. Lancet 2014; 383: 533–540.

Cummings J, Mega M, Gray K, Rosenberg-Thompson S, Carusi D, Gornbein J. The Neuropsychiatric Inventory : Comprehensive assessment of psychopathology in dementia. Neurology 1994; 44: 2308–2314.

Cuthbert BN. Research domain criteria: Toward future psychiatric nosology. Asian J Psychiatr 2014; 7: 4–5.

Dalley JW, Everitt BJ, Robbins TW. Impulsivity, Compulsivity, and Top-Down Cognitive Control. Neuron 2011; 69: 680–694.

Dalley JW, Robbins TW. Fractionating impulsivity: Neuropsychiatric implications. Nat Rev Neurosci 2017; 18: 158–171.

Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. Neuroscience 2012; 215: 42–58.

Danbolt NC. Glutamate uptake. Prog Neurobiol 2001; 65: 1–105.

Daniele A, Moro E, Bentivoglio AR. Zolpidem in progressive supranuclear palsy [8]. N Engl J Med 1999; 341: 543–544.

Darwin C, Burkhardt F, Secord JA. The correspondence of Charles Darwin [Internet]. 1877Available from: https://www.darwinproject.ac.uk/letter/DCP-LETT-2130.xml

Dash SK. Zolpidem in Progressive Supranuclear Palsy. Case Rep Neurol Med 2013; 2013: 1–2.

Davies RR, Hodges JR, Kril JJ, Patterson K, Halliday GM, Xuereb JH. The pathological basis of semantic dementia. Brain 2005; 128: 1984–1995.

Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Progression in frontotemporal dementia: Identifying a benign behavioral variant by magnetic resonance imaging. Arch Neurol 2006; 63: 1627–1631.

Dawson MRW. Fitting the ex-Gaussian equation to reaction time distributions. Behav Res Methods, Instruments, Comput 1988; 20: 54–57.

Deakin JB, Rahman S, Nestor PJ, Hodges JR, Sahakian BJ. Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: A double-blind randomized controlled trial. Psychopharmacology (Berl) 2004; 172: 400–408.

Decker JM, Krüger L, Sydow A, Dennissen FJ, Siskova Z, Mandelkow E, et al. The Tau/A152T mutation, a risk factor for frontotemporal-spectrum disorders, leads to NR 2B receptor-mediated excitotoxicity . EMBO Rep 2016; 17: 552–569.

Deelchand DK, Adanyeguh IM, Emir UE, Nguyen TM, Valabregue R, Henry PG, et al. Two-site reproducibility of cerebellar and brainstem neurochemical profiles with short-echo, single-voxel MRS at 3T. Magn Reson Med 2015; 73: 1718–1725.

Deelchand DK, Joers JM, Auerbach EJ, Henry PG. Prospective motion and B0 shim correction

for MR spectroscopy in human brain at 7T. Magn Reson Med 2019; 82: 1984–1992.

DeFelipe J. Neocortical neuronal diversity: chemical heterogeneity revealed by colocalization studies of classic neurotransmitters, neuropeptides, calcium-binding proteins, and cell surface molecules. Cereb Cortex 1993; 3: 273–289.

DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. Neuron 2011; 72: 245–256.

Desmarais P, Rohrer JD, Nguyen QD, Herrmann N, Stuss DT, Lang AE, et al. Therapeutic trial design for frontotemporal dementia and related disorders. J Neurol Neurosurg Psychiatry 2019; 90: 412–423.

Devenney E, Hornberger M, Irish M, Mioshi E, Burrell J, Tan R, et al. Frontotemporal dementia associated with the C9ORF72 mutation: A unique clinical profile. JAMA Neurol 2014; 71: 331–339.

Devenney E, Swinn T, Mioshi E, Hornberger M, Dawson KE, Mead S, et al. The behavioural variant frontotemporal dementia phenocopy syndrome is a distinct entity - evidence from a longitudinal study. BMC Neurol 2018; 18: 1–6.

Dharmadhikari S, Ma R, Yeh CL, Stock AK, Snyder S, Zauber SE, et al. Striatal and thalamic GABA level concentrations play differential roles for the modulation of response selection processes by proprioceptive information. Neuroimage 2015; 120: 36–42.

Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. J Neurol Suppl 1999; 246: II6-I15.

Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA. Neuropathology of variants of progressive supranuclear palsy. Curr Opin Neurol 2010; 23: 394–400.

Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K, et al. Office of rare diseases neuropathologic criteria for corticobasal degeneration. J Neuropathol Exp Neurol 2002; 61: 935–946.

Dickson DW, Rademakers R, Hutton ML. Progressive supranuclear palsy: Pathology and genetics. Brain Pathol 2007; 17: 74–82.

Diehl-Schmid J, Grimmer T, Drzezga A, Bornschein S, Riemenschneider M, Förstl H, et al. Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study. Neurobiol Aging 2007; 28: 42–50.

Diehl-Schmid J, Richard-Devantoy S, Grimmer T, Förstl H, Jox R. Behavioral variant frontotemporal dementia: advanced disease stages and death. A step to palliative care. Int J Geriatr Psychiatry 2017; 32: 876–881.

Diehl-Schmid J, Schulte-Overberg J, Hartmann J, Förstl H, Kurz A, Häussermann P. Extrapyramidal signs, primitive reflexes and incontinence in fronto-temporal dementia. Eur J Neurol 2007; 14: 860–864.

Drubach DA. Clinical and Pathological Continuum of Multisystem TDP-43 Proteinopathies. Yearb Neurol Neurosurg 2009; 2009: 6–7.

Dubois B, Pillon B, Legault F, Agid Y, Lhermitte F. Slowing of Cognitive Processing in Progressive Supranuclear Palsy: A Comparison With Parkinson's Disease. Arch Neurol 1988; 45: 1194–1199.

Dubois B, Slachevsky A, Pillon B, Beato R, Villalponda JM, Litvan I. 'Applause sign' helps to discriminate PSP from FTD and PD. Neurology 2005; 64: 2132–2133.

Van Duijn E, Craufurd D, Hubers AAM, Giltay EJ, Bonelli R, Rickards H, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). J Neurol Neurosurg Psychiatry 2014; 85: 1411–1418.

Dunlop J. Glutamate-based therapeutic approaches: Targeting the glutamate transport system. Curr Opin Pharmacol 2006; 6: 103–107.

Dunn OJ. Multiple Comparisons Among Means. J Am Stat Assoc 1961; 56: 52.

Dutt S, Binney RJ, Heuer HW, Luong P, Attygalle S, Bhatt P, et al. Progression of brain atrophy in PSP and CBS over 6 months and 1 year. Neurology 2016; 87: 2016–2025.

Eagle DM, Lehmann O, Theobald DEH, Pena Y, Zakaria R, Ghosh R, et al. Serotonin depletion impairs waiting but not stop-signal reaction time in rats: Implications for theories of the role of 5-HT in behavioral inhibition. Neuropsychopharmacology 2009; 34: 1311–1321.

Edden RAE, Crocetti D, Zhu H, Gilbert DL, Mostofsky SH. Reduced GABA concentration in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2012; 69: 750–753.

Edwards P. Questionnaires in clinical trials: Guidelines for optimal design and administration. Trials 2010; 11: 1–8.

Ende G. Proton Magnetic Resonance Spectroscopy: Relevance of Glutamate and GABA to Neuropsychology. Neuropsychol Rev 2015; 25: 315–325.

Ende G, Cackowski S, Van Eijk J, Sack M, Demirakca T, Kleindienst N, et al. Impulsivity and Aggression in Female BPD and ADHD Patients: Association with ACC Glutamate and GABA Concentrations. Neuropsychopharmacology 2016; 41: 410–418.

Engelborghs S, Vloeberghs E, Le Bastard N, Van Buggenhout M, Mariën P, Somers N, et al. The dopaminergic neurotransmitter system is associated with aggression and agitation in frontotemporal dementia. Neurochem Int 2008; 52: 1052–1060.

Engelborghs S, Vloeberghs E, Maertens K, Marescau B, De Deyn PP. Evidence for an association between the CSF HVA:5-HIAA ratio and aggressiveness in frontotemporal dementia but not in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004; 75: 1080.

Enticott PG, Ogloff JRP, Bradshaw JL. Response inhibition and impulsivity in schizophrenia. Psychiatry Res 2008; 157: 251–254.

Erkkinen MG, Kim MO, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. Cold Spring Harb Perspect Biol 2018; 10: a033118.

Ernst T, Chang L, Melchor R, Mark Mehringer C. Frontotemporal dementia and early Alzheimer disease: Differentiation with frontal lobe H-1 MR spectroscopy. Radiology 1997; 203: 829–836.

Evrard HC, Forro T, Logothetis NK. Von Economo Neurons in the Anterior Insula of the Macaque Monkey. Neuron 2012; 74: 482–489.

Falcon B, Zhang W, Murzin AG, Murshudov G, Garringer HJ, Vidal R, et al. Structures of filaments from Pick's disease reveal a novel tau protein fold. Nature 2018; 561: 137–140.

Fang YS, Tsai KJ, Chang YJ, Kao P, Woods R, Kuo PH, et al. Full-length TDP-43 forms toxic amyloid oligomers that are present in frontotemporal lobar dementia-TDP patients. Nat Commun 2014; 5

Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019; 18: 459–480.

Ferrer I. Neurons and their dendrites in frontotemporal dementia. Dement Geriatr Cogn Disord 1999; 10: 55–60.

Van Der Flier WM, Scheltens P. Epidemiology and risk factors of dementia. Neurol Pract 2005; 76: 2–7.

Floyer-Lea A, Wylezinska M, Kincses T, Matthews PM. Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. J Neurophysiol 2006; 95: 1639–1644.

Foiani MS, Woollacott IOC, Heller C, Bocchetta M, Heslegrave A, Dick KM, et al. Plasma tau is increased in frontotemporal dementia. J Neurol Neurosurg Psychiatry 2018; 89: 804–807.

Folch-Fortuny A, Arteaga F, Ferrer A. PCA model building with missing data: New proposals and a comparative study. Chemom Intell Lab Syst 2015; 146: 77–88.

Folch-Fortuny A, Arteaga F, Ferrer A. Missing Data Imputation Toolbox for MATLAB. Chemom Intell Lab Syst 2016; 154: 93–100.

Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, et al. Frontotemporal dementia: Clinicopathological correlations. Ann Neurol 2006; 59: 952–962.

Forrest SL, Kril JJ, Stevens CH, Kwok JB, Hallupp M, Kim WS, et al. Retiring the term FTDP-17 as MAPT mutations are genetic forms of sporadic frontotemporal tauopathies. Brain 2018; 141: 521–534.

Foster NL, Gilman S, Berent S, Morin EM, Brown MB, Koeppe RA. Cerebral hypometabolism in progressive supranuclear palsy studied with positron emission tomography. Ann Neurol 1988; 24: 399–406.

Foster NL, Minoshima S, Johanns J, Little R, Heumann ML, Kuhl DE, et al. PET measures of benzodiazepine receptors in progressive supranuclear palsy. Neurology 2000; 54: 1768–1773.

Fournier C, Barbier M, Camuzat A, Anquetil V, Lattante S, Clot F, et al. Relations between C9orf72 expansion size in blood, age at onset, age at collection and transmission across generations in patients and presymptomatic carriers. Neurobiol Aging 2019; 74: 234.e1-234.e8.

Foxe D, Elan E, Burrell JR, Felicity F V., Devenney E, Kwok JB, et al. Intrafamilial phenotypic variability in the C9orf72 gene expansion: 2 case studies. Front Psychol 2018; 9: 1–7.

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

Francis PT, Holmes C, Webster MT, Stratmann GC, Procter AW, Bowen DM. Preliminary neurochemical findings in non-Alzheimer dementia due to lobar atrophy. Dementia 1993; 4: 172–177.

Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease : a review of progress. J Neurol Neurosurg Psychiatry 1999: 137–147.

Frangou P, Correia M, Kourtzi Z. GABA, not BOLD, reveals dissociable learning-dependent plasticity mechanisms in the human brain. Elife 2018; 7: 1–22.

Frangou P, Emir UE, Karlaftis VM, Nettekoven C, Hinson EL, Larcombe S, et al. Learning to optimize perceptual decisions through suppressive interactions in the human brain. Nat Commun 2019; 10: 1–12.

Franken IHA, van Strien JW, Nijs I, Muris P. Impulsivity is associated with behavioral decision-making deficits. Psychiatry Res 2008; 158: 155–163.

Frankle WG, Cho RY, Narendran R, Mason NS, Vora S, Litschge M, et al. Tiagabine increases [11C]flumazenil binding in cortical brain regions in healthy control subjects. Neuropsychopharmacology 2009; 34: 624–633.

Fries P. Neuronal Gamma-Band Synchronization as a Fundamental Process in Cortical Computation. Annu Rev Neurosci 2009; 32: 209–224.

Frisoni GB, Pizzolato G, Bianchetti A, Chierichetti F, Ferlin G, Battistin L, et al. Single photon emission computed tomography with [99Tc]-HM-PAO and [123I]-IBZM in Alzheimer's disease and dementia of frontal type: preliminary results. Acta Neurol Scand 1994; 89: 199–203.

Fu H, Hardy J, Duff KE. Selective vulnerability in neurodegenerative diseases. Nat Neurosci 2018; 21: 1350–1358.

Fujihara K, Narita K, Suzuki Y, Takei Y, Suda M, Tagawa M, et al. Relationship of γ-aminobutyric acid and glutamate+glutamine concentrations in the perigenual anterior cingulate cortex with performance of Cambridge Gambling Task. Neuroimage 2015; 109: 102–108.

Fujioka S, Sanchez Contreras MY, Strongosky AJ, Ogaki K, Whaley NR, Tacik PM, et al. Three sib-pairs of autopsy-confirmed progressive supranuclear palsy. Park Relat Disord 2015; 21: 101–105.

Fusar-Poli P, Solmi M, Brondino N, Davies C, Chae C, Politi P, et al. Transdiagnostic psychiatry: a systematic review. World Psychiatry 2019; 18: 192–207.

Gaetz W, Edgar JC, Wang DJ, Roberts TPL. Relating MEG measured motor cortical oscillations to resting γ-Aminobutyric acid (GABA) concentration. Neuroimage 2011; 55: 616–621.

Galimberti D, Arosio B, Fenoglio C, Serpente M, Cioffi SMG, Bonsi R, et al. Incomplete penetrance of the C9ORF72 hexanucleotide repeat expansions: Frequency in a cohort of geriatric non-demented subjects. J Alzheimer's Dis 2014; 39: 19–22.

Galimberti D, Dell'Osso B, Altamura AC, Scarpini E. Psychiatric Symptoms in Frontotemporal Dementia: Epidemiology, Phenotypes, and Differential Diagnosis. Biol Psychiatry 2015; 78: 684–692.

Galton CJ, Patterson K, Graham K, Lambon-Ralph MA, Williams G, Antoun N, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. Neurology 2001; 57: 216–225.

Gama RL, Távora DG, Bomfim RC, Silva CE, de Bruin VM, de Bruin PFC. Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy - a comparative study. Park Relat Disord 2010; 16: 275–279.

Gami-Patel P, van Dijken I, van Swieten JC, Pijnenburg YAL, Rozemuller AJM, Hoozemans JJM, et al. Von Economo neurons are part of a larger neuronal population that are selectively vulnerable in C9orf72 frontotemporal dementia. Neuropathol Appl Neurobiol 2019; 45: 671–680.

Garbutt S, Matlin A, Hellmuth J, Schenk AK, Johnson JK, Rosen H, et al. Oculomotor function in frontotemporal lobar degeneration, related disorders and Alzheimer's disease. Brain 2008; 131: 1268–1281.

Garbutt S, Riley DE, Kumar AN, Han Y, Norwood MB, Leigh RJ. Abnormalities of optokinetic nystagmus in progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 2004; 75: 1386–1394.

Garcin B, Lillo P, Hornberger M, Piguet O, Dawson K, Nestor PJ, et al. Determinants of survival in behavioral variant frontotemporal dementia. Neurology 2009; 73: 1656–1661.

Garcin B, Volle E, Funkiewiez A, Miller BL, Dubois B, Levy R. A mosquito bites and a butterfly flies: A specific response type of frontal patients in a similarity task. Neuropsychologia 2018; 117: 371–378.

Garibotto V, Borroni B, Agosti C, Premi E, Alberici A, Eickhoff SB, et al. Subcortical and deep cortical atrophy in Frontotemporal Lobar Degeneration. Neurobiol Aging 2011; 32: 875–884.

Gascon E, Lynch K, Ruan H, Almeida S, Verheyden JM, Seeley WW, et al. Alterations in microRNA-124 and AMPA receptors contribute to social behavioral deficits in frontotemporal dementia. Nat Med 2014; 20: 1444–1451.

Gasparovic C, Yeo R, Mannell M, Ling J, Elgie R, Phillips J, et al. Neurometabolite concentrations in gray and white matter in mild traumatic brain injury: An 1H-magnetic resonance spectroscopy study. J Neurotrauma 2009; 26: 1635–1643.

Gazzina S, Respondek G, Compta Y, Allinson KS, Spillantini MG, Molina-Porcel L, et al. Neuropathological validation of the MDS-PSP criteria with PSP and other frontotemporal lobar degeneration. bioRxiv 2019: 520510.

Gefen T, Ahmadian SS, Mao Q, Kim G, Seckin M, Bonakdarpour B, et al. Combined pathologies in FTLD-TDP types A and C. J Neuropathol Exp Neurol 2018; 77: 405–412.

Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Stat Sci 1992; 7: 457–472.

Gerstenecker A, Duff K, Mast B, Litvan I. Behavioral abnormalities in progressive supranuclear

palsy. Psychiatry Res 2013; 210: 1205–1210.

Ghetti B, Oblak AL, Boeve BF, Johnson KA, Dickerson BC, Goedert M. Invited review: Frontotemporal dementia caused by microtubule-associated protein tau gene (MAPT) mutations: A chameleon for neuropathology and neuroimaging. Neuropathol Appl Neurobiol 2015; 41: 24–46.

Ghosh BCP, Calder AJ, Peers P V., Lawrence AD, Acosta-Cabronero J, Pereira JM, et al. Social cognitive deficits and their neural correlates in progressive supranuclear palsy. Brain 2012; 135: 2089–2102.

Ghosh BCP, Rowe JB, Calder AJ, Hodges JR, Bak TH. Emotion recognition in progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 2009; 80: 1143–1145.

Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, et al. Initiation and synergistic fibrillization of tau and alpha-synuctein. Science (80-) 2003; 300: 636–640.

Gibb WRG, Luthert PJ, Marsden CD. Corticobasal degeneration. Brain 1989; 112: 1171–1192.

Gilmour G, Dix S, Fellini L, Gastambide F, Plath N, Steckler T, et al. NMDA receptors, cognition and schizophrenia - Testing the validity of the NMDA receptor hypofunction hypothesis. Neuropharmacology 2012; 62: 1401–1412.

Glasmacher SA, Leigh PN, Saha RA. Predictors of survival in progressive supranuclear palsy and multiple system atrophy: A systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2017; 88: 402–411.

Goedert M. Tau filaments in neurodegenerative diseases. FEBS Lett 2018; 592: 2383–2391.

Goedert M, Spillantini MG, Jakes R, Rutherford D, Crowther RA. Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. Neuron 1989; 3: 519–526.

Golbe LI, Davis PH, Lepore FE. Eyelid movement abnormalities in progressive supranuclear palsy. Mov Disord 1989; 4: 297–302.

Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain 2007; 130: 1552–1565.

Goldstein-Piekarski AN, Williams LM, Humphreys K. A trans-diagnostic review of anxiety disorder comorbidity and the impact of multiple exclusion criteria on studying clinical outcomes in anxiety disorders. Transl Psychiatry 2016; 6

Gomperts SN, Locascio JJ, Makaretz SJ, Schultz A, Caso C, Vasdev N, et al. Tau positron emission tomographic imaging in the lewy body diseases. JAMA Neurol 2016; 73: 1334–1341.

González Sánchez JJ, Nora JE, De Notaris M, Arboix JR, García CA, Rodríguez EF. A case of malignant monophasic multiple sclerosis (Marburg's disease type) successfully treated with decompressive hemicraniectomy. J Neurol Neurosurg Psychiatry 2010; 81: 1056–1057.

Gordon E, Rohrer JD, Kim LG, Omar R, Rossor MN, Fox NC, et al. Measuring disease progression in frontotemporal lobar degeneration: A clinical and MRI study. Neurology 2010; 74: 666–673.

Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcone A, et al. The logopenic/phonological variant of primary progressive aphasia. Neurology 2008; 71: 1227–1234.

Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology 2011; 76: 1006–1014.

Gossink FT, Dols A, Kerssens CJ, Krudop WA, Kerklaan BJ, Scheltens P, et al. Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia. J Neurol Neurosurg Psychiatry 2016; 87: 64–68.

Govindaraju V, Young K, Maudsley AA. Proton NMR chemical shifts and coupling constants for brain metabolites. NMR Biomed 2000; 13: 129–153.

Graff-Radford J, Duffy JR, Strand EA, Josephs KA. Parkinsonian motor features distinguish the agrammatic from logopenic variant of primary progressive aphasia. Park Relat Disord 2012; 18: 890–892.

Graham NL, Bak T, Patterson K, Hodges JR. Language function and dysfunction in corticobasal degeneration. Neurology 2003; 61: 493–499.

Graham NL, Bak TH, Hodges JR. Corticobasal degeneration as a cognitive disorder. Mov Disord 2003; 18: 1224–1232.

Grandas F, Elston J, Quinn N, Marsden CD. Blepharospasm: a review of 264 patients. J Neurol Neurosurg Psychiatry 1988; 51: 767–772.

Greaves I, Jolley D. National Dementia Strategy: Well intentioned - But how well founded and how well directed? Br J Gen Pract 2010; 60: 193–198.

Green L, Myerson J. How many impulsivities? A discounting perspective. J Exp Anal Behav 2013; 99: 3–13.

Grimm MJ, Respondek G, Stamelou M, Arzberger T, Ferguson L, Gelpi E, et al. How to apply the movement disorder society criteria for diagnosis of progressive supranuclear palsy. Mov Disord 2019; 34: 1228–1232.

Grisanzio KA, Goldstein-Piekarski AN, Wang MY, Ahmed APR, Samara Z, Williams LM. Transdiagnostic symptom clusters and associations with brain, behavior, and daily function in mood, anxiety, and trauma disorders. JAMA Psychiatry 2018; 75: 201–209.

Gröschel K, Hauser TK, Luft A, Patronas N, Dichgans J, Litvan I, et al. Magnetic resonance imaging-based volumetry differentiates progressive supranuclear palsy from corticobasal degeneration. Neuroimage 2004; 21: 714–724.

Grosse P, Kühn A, Cordivari C, Brown P. Coherence analysis in the myoclonus of corticobasal degeneration. Mov Disord 2003; 18: 1345–1350.

Grossman M. Primary progressive aphasia: Clinicopathological correlations. Nat Rev Neurol 2010; 6: 88–97.

Grossman M. The non-fluent/agrammatic variant of primary progressive aphasia. Lancet Neurol 2012; 11: 545–555.

Gruetter R. Automatic, localized in Vivo adjustment of all first-and second-order shim coils. Magn Reson Med 1993; 29: 804–811.

Gruetter R, Tkáč I. Field mapping without reference scan using asymmetric echo-planar techniques. Magn Reson Med 2000; 43: 319–323.

Guercio BJ, Donovan NJ, Munro CE, Aghjayan SL, Wigman SE, Locascio JJ, et al. The Apathy Evaluation Scale: A Comparison of Subject, Informant, and Clinician Report in Cognitively Normal Elderly and Mild Cognitive Impairment. J Alzheimer's Dis 2015; 47: 421–432.

Gustafson L. Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. Arch Gerontol Geriatr 1987; 6: 209–223.

Hafkemeijer A, Altmann-Schneider I, de Craen AJM, Slagboom PE, van der Grond J, Rombouts SARB. Associations between age and gray matter volume in anatomical brain networks in middle-aged to older adults. Aging Cell 2014; 13: 1068–1074.

Hajek M, Dezortova M. Introduction to clinical in vivo MR spectroscopy. Eur J Radiol 2008; 67: 185–193.

Hakeem AY, Sherwood CC, Bonar CJ, Butti C, Hof PR, Allman JM. Von Economo neurons in the elephant brain. Anat Rec 2009; 292: 242–248.

Hansen LA, Deteresa R, Tobias H, Alford M, Terry RD. Neocortical morphometry and cholinergic neurochemistry in Pick's disease. Am J Pathol 1988; 131: 507–18.

Harding A. Variation in hippocampal neuron number with age and brain volume. Cereb Cortex 1998; 8: 710–718.

Hardy CJD, Buckley AH, Downey LE, Lehmann M, Zimmerer VC, Varley RA, et al. The language profile of behavioral variant frontotemporal dementia. J Alzheimer's Dis 2016; 50: 359–371.

Hardy CJD, Frost C, Sivasathiaseelan H, Johnson JCS, Agustus JL, Bond RL, et al. Findings of Impaired Hearing in Patients with Nonfluent/Agrammatic Variant Primary Progressive Aphasia. JAMA Neurol 2019; 76: 607–611.

Harris AD, Puts NAJ, Barker PB, Edden RAE. Spectral-editing measurements of GABA in the human brain with and without macromolecule suppression. Magn Reson Med 2015; 74: 1523–1529.

Harris JM, Jones M, Gall C, Richardson AMT, Neary D, Du Plessis D, et al. Co-Occurrence of Language and Behavioural Change in Frontotemporal Lobar Degeneration. Dement Geriatr Cogn Dis Extra 2016; 6: 205–213.

Harris JM, Saxon JA, Jones M, Snowden JS, Thompson JC. Neuropsychological differentiation of progressive aphasic disorders. J Neuropsychol 2019; 13: 214–239.

Harrison JK, Walesby KE, Hamilton L, Armstrong C, Starr JM, Reynish EL, et al. Predicting discharge to institutional long-term care following acute hospitalisation: A systematic review and meta-analysis. Age Ageing 2017; 46: 547–558.

Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry 2003; 74: 1206–1209.

Hassan A, Parisi JE, Josephs KA. Autopsy-proven progressive supranuclear palsy presenting as behavioral variant frontotemporal dementia. Neurocase 2012; 18: 478–488.

Hassan A, Whitwell JL, Boeve BF, Jack CR, Parisi JE, Dickson DW, et al. Symmetric corticobasal degeneration (S-CBD). Park Relat Disord 2010; 16: 208–214.

Hauw J, Daniel SE, Dickson D, Horoupian DS. Preliminary NINDS neuropathologic criteria for Steele- Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 1994; 44: 2015–2019.

Hawkins DM. The Problem of Overfitting. J Chem Inf Comput Sci 2004; 44: 1–12.

Hayes DJ, Jupp B, Sawiak SJ, Merlo E, Caprioli D, Dalley JW. Brain γ-aminobutyric acid: A neglected role in impulsivity. Eur J Neurosci 2014; 39: 1921–1932.

Hazelton JL, Irish M, Hodges JR, Piguet O, Kumfor F. Cognitive and Affective Empathy Disruption in Non-Fluent Primary Progressive Aphasia Syndromes. Brain Impair 2017; 18: 117–129.

Healey ML, McMillan CT, Golob S, Spotorno N, Rascovsky K, Irwin DJ, et al. Getting on the same page: The neural basis for social coordination deficits in behavioral variant frontotemporal degeneration. Neuropsychologia 2015; 69: 56–66.

Heathcote A, Lin YS, Reynolds A, Strickland L, Gretton M, Matzke D. Dynamic models of choice. Behav Res Methods 2019; 51: 961–985.

Heathcote A, Popiel SJ, Mewhort DJK. Analysis of response time distributions: an example using the stroop task. Psychol Bull 1991; 109: 340–347.

Hecht EE, Smaers JB, Dunn WJ, Kent M, Preuss TM, Gutman DA. Significant neuroanatomical variation among domestic dog breeds Significant neuroanatomical variation among domestic dog breeds Abbreviated title: Neuroanatomical variation in dogs Multimedia: 0. Cite as J Neurosci 2019

Helgadottir HT, Lundin P, Wallén Arzt E, Lindström AK, Graff C, Eriksson M. Somatic mutation that affects transcription factor binding upstream of CD55 in the temporal cortex of a late-onset Alzheimer disease patient. Hum Mol Genet 2019; 28: 2675–2685.

Henderson JM, Carpenter K, Cartwright H, Halliday GM. Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and therapeutic implications. Brain 2000; 123 (Pt 7: 1410–1421.

Hermans L, Leunissen I, Pauwels L, Cuypers K, Peeters R, Puts NAJ, et al. Brain GABA levels are associated with inhibitory control deficits in older adults. J Neurosci 2018; 38: 7844–7851.

Le Heron C, Holroyd CB, Salamone J, Husain M. Brain mechanisms underlying apathy. J Neurol Neurosurg Psychiatry 2019; 90: 302–312.

Le Heron C, Plant O, Manohar S, Ang YS, Jackson M, Lennox G, et al. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. Brain 2018; 141: 1455–1469.

Herrmann N, Black SE, Chow T, Cappell J, Tang-Wai DF, Lanctôt KL. Serotonergic function and treatment of behavioral and psychological symptoms of frontotemporal dementia. Am J

Geriatr Psychiatry 2012; 20: 789–797.

Hertz L. The glutamate-glutamine (GABA) cycle: Importance of late postnatal development and potential reciprocal interactions between biosynthesis and degradation. Front Endocrinol (Lausanne) 2013; 4: 1–16.

Himberg J, Hyvärinen A. ICASSO: Software for investigating the reliability of ICA estimates by clustering and visualization. Neural Networks Signal Process - Proc IEEE Work 2003; 2003-Janua: 259–268.

Hines RM, Hines DJ, Houston CM, Mukherjee J, Haydon PG, Tretter V, et al. Disrupting the clustering of GABAA receptor ?2 subunits in the frontal cortex leads to reduced ?-power and cognitive deficits. Proc Natl Acad Sci U S A 2013; 110: 16628–16633.

Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. Neurology 2003; 61: 349–354.

Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol 2004; 56: 399–406.

Hodges JR, Mitchell J, Dawson K, Spillantini MG, Xuereb JH, McMonagle P, et al. Semantic dementia: Demography, familial factors and survival in a consecutive series of 100 cases. Brain 2010; 133: 300–306.

Hodges JR, Patterson K. Semantic dementia: a unique clinicopathological syndrome. Lancet Neurol 2007; 6: 1004–1014.

Hoerst M, Weber-Fahr W, Tunc-Skarka N, Ruf M, Bohus M, Schmahl C, et al. Correlation of glutamate levels in the anterior cingulate cortex with self-reported impulsivity in patients with borderline personality disorder and healthy controls. Arch Gen Psychiatry 2010; 67: 946–954.

Hoff MN, McKinney A, Shellock FG, Rassner U, Gilk T, Watson RE, et al. Safety Considerations of 7-T MRI in Clinical Practice. Radiology 2019; 292: 509–518.

Höglinger GU. Is it Useful to Classify Progressive Supranuclear Palsy and Corticobasal Degeneration as Different Disorders? No. Mov Disord Clin Pract 2018; 5: 141–144.

Höglinger GU, Huppertz HJ, Wagenpfeil S, Andrés M V., Belloch V, León T, et al. Tideglusib reduces progression of brain atrophy in progressive supranuclear palsy in a randomized trial. Mov Disord 2014; 29: 479–487.

Höglinger GU, Melhem NM, Dickson DW, Sleiman PMA, Wang LS, Klei L, et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet 2011; 43: 699–705.

Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord 2017; 32: 853–864.

Hong M, Zhukareva V, Vogelsberg-Ragaglia V, Wszolek Z, Reed L, Miller BI, et al. Mutation-specific functional impairments in distinct tau isoforms of hereditary FTDP-17. Science (80-) 1998; 282: 1914–1917.

Hornberger M, Piguet O. Episodic memory in frontotemporal dementia: A critical review. Brain

2012; 135: 678–692.

Hornberger M, Piguet O, Kipps C, Hodges JR. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. Neurology 2008; 71: 1481–1488.

Hornberger M, Savage S, Hsieh S, Mioshi E, Piguet O, Hodges JR. Orbitofrontal dysfunction discriminates behavioral variant frontotemporal dementia from Alzheimer's disease. Dement Geriatr Cogn Disord 2011; 30: 547–552.

Hornberger M, Yew B, Gilardoni S, Mioshi E, Gleichgerrcht E, Manes F, et al. Ventromedial-frontopolar prefrontal cortex atrophy correlates with insight loss in frontotemporal dementia and Alzheimer's disease. Hum Brain Mapp 2014; 35: 616–626.

Hornykiewicz O. Dopamine miracle: From brain homogenate to dopamine replacement. Mov Disord 2002; 17: 501–508.

Hornykiewicz O, Shannak K. Brain monoamines in progressive supranuclear palsy--comparison with idiopathic Parkinson's disease. J Neural Transm Suppl 1994; 42: 219–227.

Houlden H, Baker M, Morris HR, MacDonald N, Pickering-Brown S, Adamson J, et al. Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. Neurology 2001; 56: 1702–1706.

Hsieh S, Irish M, Daveson N, Hodges JR, Piguet O. When one loses empathy: Its effect on carers of patients with dementia. J Geriatr Psychiatry Neurol 2013; 26: 174–184.

Hsiung GYR, Dejesus-Hernandez M, Feldman HH, Sengdy P, Bouchard-Kerr P, Dwosh E, et al. Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. Brain 2012; 135: 709–722.

Hu WT, Mandrekar JN, Parisi JE, Knopman DS, Boeve BF, Petersen RC, et al. Clinical features of pathologic subtypes of behavioral-variant frontotemporal dementia. Arch Neurol 2007; 64: 1611–1616.

Hu WT, Rippon GW, Boeve BF, Knopman DS, Petersen RC, Parisi JE, et al. Alzheimer's disease and corticobasal degeneration presenting as corticobasal syndrome. Mov Disord 2009; 24: 1375–1379.

Hu WT, Seelaar H, Josephs KA, Knopman DS, Boeve BF, Sorenson EJ, et al. Survival profiles of patients with frontotemporal dementia and motor neuron disease. Arch Neurol 2009; 66: 1359–1364.

Huang P, Carlin JD, Alink A, Kriegeskorte N, Henson RN, Correia MM. Prospective motion correction improves the sensitivity of fMRI pattern decoding. Hum Brain Mapp 2018; 39: 4018–4031.

Huey ED, Goveia EN, Paviol S, Pardini M, Krueger F, Zamboni G, et al. Executive dysfunction in frontotemporal dementia and corticobasal syndrome. Neurology 2009; 72: 453–459.

Huey ED, Putnam KT, Grafman J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. Neurology 2006; 66: 17–22.

Hughes LE, Ghosh BCP, Rowe JB. Reorganisation of brain networks in frontotemporal dementia and progressive supranuclear palsy. NeuroImage Clin 2013; 2: 459–468.

Hughes LE, Nestor PJ, Hodges JR, Rowe JB. Magnetoencephalography of frontotemporal dementia: Spatiotemporally localized changes during semantic decisions. Brain 2011; 134: 2513–2522.

Hughes LE, Rittman T, Regenthal R, Robbins TW, Rowe JB. Improving response inhibition systems in frontotemporal dementia with citalopram. Brain 2015; 138: 1961–1975.

Hughes LE, Rittman T, Robbins TW, Rowe JB. Reorganization of cortical oscillatory dynamics underlying disinhibition in frontotemporal dementia. Brain 2018; 141: 2486–2499.

Hughes LE, Rittman T, Robbins TW, Rowe JB. Reply: Brain oscillations, inhibition and social inappropriateness in frontotemporal degeneration. Brain 2018; 141: 2018.

Hughes ME, Fulham WR, Johnston PJ, Michie PT. Stop-signal response inhibition in schizophrenia: Behavioural, event-related potential and functional neuroimaging data. Biol Psychol 2012; 89: 220–231.

Husain M. Transdiagnostic neurology: Neuropsychiatric symptoms in neurodegenerative diseases. Brain 2017; 140: 1535–1536.

Husain M, Roiser JP. Neuroscience of apathy and anhedonia: A transdiagnostic approach. Nat Rev Neurosci 2018; 19: 470–484.

Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden HH, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998; 393: 702–704.

Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimer's Dement 2012; 8: 1–13.

Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, Shapiro GI, et al. HER kinase inhibition in patients with HER2-and HER3-mutant cancers. Nature 2018; 554: 189–194.

Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 2015; 373: 726–736.

Ibáñez A. Brain oscillations, inhibition and social inappropriateness in frontotemporal degeneration. Brain 2018; 141: e73–e73.

Idowu OE. Morphometry, Asymmetry and Variations of the Sylvian Fissure and Sulci Bordering and Within the Pars Triangularis and Pars Operculum: An Autopsy Study. J Clin Diagnostic Res 2014: 11–14.

Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002; 73: 371–376.

Illán-Gala I, Montal V, Borrego-Écija S, Vilaplana E, Pegueroles J, Alcolea D, et al. Cortical microstructure in the behavioural variant of frontotemporal dementia: Looking beyond atrophy. Brain 2019; 142: 1121–1133.

Im JH, Chung SJ, Kim JS, Lee MC. Differential patterns of dopamine transporter loss in the basal ganglia of progressive supranuclear palsy and Parkinson's disease: Analysis with

[123I]IPT single photon emission computed tomography. J Neurol Sci 2006; 244: 103–109.

Irwin DJ. Tauopathies as clinicopathological entities. Park Relat Disord 2016; 22: S29–S33.

Irwin DJ, Brettschneider J, McMillan CT, Cooper F, Olm C, Arnold SE, et al. Deep clinical and neuropathological phenotyping of Pick disease. Ann Neurol 2016; 79: 272–287.

Irwin DJ, Cairns NJ, Grossman M, McMillan CT, Lee EB, Van Deerlin VM, et al. Frontotemporal lobar degeneration: defining phenotypic diversity through personalized medicine. Acta Neuropathol 2015; 129: 469–491.

Itahashi T, Yamada T, Nakamura M, Watanabe H, Yamagata B, Jimbo D, et al. Linked alterations in gray and white matter morphology in adults with high-functioning autism spectrum disorder: A multimodal brain imaging study. NeuroImage Clin 2015; 7: 155–169.

Ito T, Suzuki T, Wellman SE, Ho IK. Pharmacology of barbiturate tolerance/dependence: GABAA receptors and molecular aspects. Life Sci 1996; 59: 169–195.

Jabbari E, Holland N, Chelban V, Jones PS, Lamb R, Rawlinson C, et al. Diagnosis Across the Spectrum of Progressive Supranuclear Palsy and Corticobasal Syndrome [Internet]. JAMA Neurol 2019Available from: https://jamanetwork.com/journals/jamaneurology/fullarticle/2757604

Jabbari E, Woodside J, Tan MMX, Shoai M, Pittman A, Ferrari R, et al. Variation at the TRIM11 locus modifies progressive supranuclear palsy phenotype. Ann Neurol 2018; 84: 485–496.

Jacobs DH, Adair JC, Macauley B, Gold M, Gonzalez Rothi LJ, Heilman KM. Apraxia in corticobasal degeneration. Brain Cogn 1999; 40: 336–354.

Javoy-Agid F. Cholinergic and peptidergic systems in PSP. J Neural Transm Suppl 1994; 42: 205–218.

Jellinger K. The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 1988; 51: 540–543.

Jiang S, Wen N, Li Z, Dube U, Del Aguila J, Budde J, et al. Integrative system biology analyses of CRISPR-edited iPSC-derived neurons and human brains reveal deficiencies of presynaptic signaling in FTLD and PSP. Transl Psychiatry 2018; 8: 1–16.

Johnson NA, Rademaker A, Weintraub S, Gitelman D, Wienecke C, Mesulam M. Pilot trial of memantine in primary progressive aphasia. Alzheimer Dis Assoc Disord 2010; 24: 308.

Jolliffe I. Principal Component Analysis, Second Edition. 2002

Jones SM, Killett A, Mioshi E. The role of resilient coping in dementia carers' wellbeing. Br J Neurosci Nurs 2019; 15: 6–12.

Jorm AF, Fratiglioni L, Winblad B. Differential Diagnosis in Dementia: Principal Components Analysis of Clinical Data From a Population Survey. JAMA Neurol 1993; 50: 72–77.

Josephs KA. Current Understanding of Neurodegenerative Diseases Associated With the Protein Tau. Mayo Clin Proc 2017; 92: 1291–1303.

Josephs KA. Rest in peace FTDP-17. Brain 2018; 141: 324–326.

Josephs KA, Duffy JR. Apraxia of speech and nonfluent aphasia: A new clinical marker for corticobasal degeneration and progressive supranuclear palsy. Curr Opin Neurol 2008; 21: 688–692.

Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Gunter JL, et al. The evolution of primary progressive apraxia of speech. Brain 2014; 137: 2783–2795.

Josephs KA, Duffy JR, Strand EA, MacHulda MM, Senjem ML, Master A V., et al. Characterizing a neurodegenerative syndrome: Primary progressive apraxia of speech. Brain 2012; 135: 1522–1536.

Josephs KA, Duffy JR, Strand EA, Whitwell JL, Layton KF, Parisi JE, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain 2006; 129: 1385–1398.

Josephs KA, Hodges JR, Snowden JS, MacKenzie IR, Neumann M, Mann DM, et al. Neuropathological background of phenotypical variability in frontotemporal dementia. Acta Neuropathol 2011; 122: 137–153.

Josephs KA, Mackenzie I, Frosch MP, Bigio EH, Neumann M, Arai T, et al. Late to the part-y. Brain 2019; 142: 1–5.

Josephs KA, Petersen RC, Knopman DS, Boeve BF, Whitwell JL, Duffy JR, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology 2006; 66: 41–48.

Josephs KA, Whitwell JL, Boeve BF, Knopman DS, Petersen RC, Hu WT, et al. Anatomical differences between CBS-corticobasal degeneration and CBS-Alzheimer's disease. Mov Disord 2010; 25: 1246–1252.

Josephs KA, Whitwell JL, Dickson DW, Boeve BF, Knopman DS, Petersen RC, et al. Voxel-based morphometry in autopsy proven PSP and CBD. Neurobiol Aging 2008; 29: 280–289.

Josephs KA, Whitwell JL, Knopman DS, Hu WT, Stroh DA, Baker M, et al. Abnormal TDP-43 immunoreactivity in AD modifies clinicopathologic and radiologic phenotype. Neurology 2008; 70: 1850–1857.

Ju JS, Weihl CC. Inclusion body myopathy, Paget's disease of the bone and fronto-temporal dementia: A disorder of autophagy. Hum Mol Genet 2010; 19: 38–45.

Juchem C, de Graaf RA. B0 magnetic field homogeneity and shimming for in vivo magnetic resonance spectroscopy. Anal Biochem 2017; 529: 17–29.

Julayanont P, Burks DW, Heilman KM. Vertical and Radial Attentional Neglect in Corticobasal Syndrome. Cogn Behav Neurol 2019; 32: 208–213.

Juncos JL, Hirsch EC, Malessa S, Duyckaerts C, Hersh LB, Agid Y. Mesencephalic cholinergic nuclei in progressive supranuclear palsy. Neurology 1991; 289: 25.

Kaalund SS, Passamonti L, Allinson KSJ, Murley AG, Robbins TW, Spillantini MG, et al. Locus coeruleus pathology in progressive supranuclear palsy, and its relation to disease severity. Acta Neuropathol Commun 2020; 8: 11.

Kaat LD, Boon AJW, Kamphorst W, Ravid R, Duivenvoorden HJ, Van Swieten JC. Frontal

presentation in progressive supranuclear palsy. Neurology 2007; 69: 723–729.

Kaizik C, Caga J, Camino J, O'Connor CM, McKinnon C, Oyebode JR, et al. Factors Underpinning Caregiver Burden in Frontotemporal Dementia Differ in Spouses and their Children. J Alzheimer's Dis 2017; 56: 1109–1117.

Kanazawa I, Kwak S, Sasaki H, Muramoto O, Mizutani T, Hori A, et al. Studies on neurotransmitter markers of the basal ganglia in Pick's disease, with special reference to dopamine reduction. J Neurol Sci 1988; 83: 63–74.

Kansal K, Mareddy M, Sloane KL, Minc AA, Rabins P V., McGready JB, et al. Survival in Frontotemporal Dementia Phenotypes: A Meta-Analysis. Dement Geriatr Cogn Disord 2016; 41: 109–122.

Kantarci K, Boeve BF, Wszolek ZK, Rademakers R, Whitwell JL, Baker MC, et al. MRS in presymptomatic MAPT mutation carriers: A potential biomarker for tau-mediated pathology. Neurology 2010; 75: 771–778.

Kasashima S, Oda Y. Cholinergic neuronal loss in the basal forebrain and mesopontine tegmentum of progressive supranuclear palsy and corticobasal degeneration. Acta Neuropathol 2003; 105: 117–124.

Ke Y, Streeter CC, Nassar LE, Sarid-Segal O, Hennen J, Yurgelun-Todd DA, et al. Frontal lobe GABA levels in cocaine dependence: A two-dimensional, J-resolved magnetic resonance spectroscopy study. Psychiatry Res - Neuroimaging 2004; 130: 283–293.

Keating B, Deng W, Roddey JC, White N, Dale A, Stenger VA, et al. Prospective motion correction for single-voxel1H MR spectroscopy. Magn Reson Med 2010; 64: 672–679.

Kehagia AA, Housden CR, Regenthal R, Barker RA, Müller U, Rowe J, et al. Targeting impulsivity in Parkinson's disease using atomoxetine. Brain 2014; 137: 1986–1997.

Keogh MJ, Wei W, Aryaman J, Walker L, van den Ameele J, Coxhead J, et al. High prevalence of focal and multi-focal somatic genetic variants in the human brain. Nat Commun 2018; 9: 4257.

Kertesz A. Pick complex - Historical introduction. Alzheimer Dis Assoc Disord 2007; 21: S5–S7.

Kertesz A, Davidson W, Munoz DG. Clinical and pathological overlap between frontotemporal dementia, primary progressive aphasia and corticobasal degeneration: the Pick complex. Dement Geriatr Cogn Disord 1999; 10 Suppl 1: 46–49.

Kertesz A, Davidson W, Munoz DG. The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. Neurology 2007; 55: 1368–75.

Kertesz A, McMonagle P. Behavior and cognition in corticobasal degeneration and progressive supranuclear palsy. J Neurol Sci 2010; 289: 138–143.

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain 2005; 128: 1996–2005.

Kertesz A, Morlog D, Light M, Blair M, Davidson W, Jesso S, et al. Galantamine in frontotemporal dementia and primary progressive aphasia. Dement Geriatr Cogn Disord 2008;

25: 178–185.

Kertesz A, Munoz D. Relationship between frontotemporal dementia and corticobasal degeneration/progressive supranuclear palsy. Dement Geriatr Cogn Disord 2004; 17: 282–286.

Khan BK, Yokoyama JS, Takada LT, Sha SJ, Rutherford NJ, Fong JC, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. J Neurol Neurosurg Psychiatry 2012; 83: 358–364.

Khedher L, Ramírez J, Górriz JM, Brahim A, Segovia F. Early diagnosis of Alzheimer's disease based on partial least squares, principal component analysis and support vector machine using segmented MRI images. Neurocomputing 2015; 151: 139–150.

Kim EJ, Sidhu M, Gaus SE, Huang EJ, Hof PR, Miller BL, et al. Selective frontoinsular von economo neuron and fork cell loss in early behavioral variant frontotemporal dementia. Cereb Cortex 2012; 22: 251–259.

Kim SL, Lee MJ, Lee MS. Cognitive dysfunction associated with falls in progressive supranuclear palsy. Gait Posture 2014; 40: 605–609.

Kim YJ, Ichise M, Ballinger JR, Vines D, Erami SS, Tatschida T, et al. Combination of dopamine transporter and D2 receptor SPECT in the diagnostic evaluation of PD, MSA, and PSP. Mov Disord 2002; 17: 303–312.

Kipps CM, Hodges JR, Hornberger M. Nonprogressive behavioural frontotemporal dementia: Recent developments and clinical implications of the 'bvFTD phenocopy syndrome'. Curr Opin Neurol 2010; 23: 628–632.

Kipps CM, Nestor PJ, Dawson CE, Mitchell J, Hodges JR. Measuring progression in frontotemporal dementia Implications for therapeutic interventions. Neurology 2008; 70: 2046–2051.

Klaffke S, Kuhn AA, Plotkin M, Amthauer H, Harnack D, Felix R, et al. Dopamine transporters, D2 receptors, and glucose metabolism in corticobasal degeneration. Mov Disord 2006; 21: 1724–1727.

Kluger BM, Heilman KM. Dysfunctional facial emotional expression and comprehension in a patient with corticobasal degeneration. Neurocase 2007; 13: 165–168.

Kluin KJ, Gilman S, Foster NL, Sima AAF, D'Amato CJ, Bruch LA, et al. Neuropathological correlates of dysarthria in progressive supranuclear palsy. Arch Neurol 2001; 58: 265–269.

Knapp M, Chua KC, Broadbent M, Chang CK, Fernandez JL, Milea D, et al. Predictors of care home and hospital admissions and their costs for older people with Alzheimer's disease: Findings from a large London case register. BMJ Open 2016; 6: 1–15.

Knibb JA, Woollams AM, Hodges JR, Patterson K. Making sense of progressive non-fluent aphasia: An analysis of conversational speech. Brain 2009; 132: 2734–2746.

Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain 2008; 131: 2957–2968.

Knopman DS, Weintraub S, Pankratz VS. Language and behavior domains enhance the value

of the clinical dementia rating scale. Alzheimer's Dement 2011; 7: 293–299.

Kobylecki C, Jones M, Thompson JC, Richardson AM, Neary D, Mann DMA, et al. Cognitive–behavioural features of progressive supranuclear palsy syndrome overlap with frontotemporal dementia. J Neurol 2015; 262: 916–922.

Kolasinski J, Logan JP, Hinson EL, Manners D, Divanbeighi Zand AP, Makin TR, et al. A Mechanistic Link from GABA to Cortical Architecture and Perception. Curr Biol 2017; 27: 1685-1691.e3.

Kouri N, Ross OA, Dombroski B, Younkin CS, Serie DJ, Soto-Ortolaza A, et al. Genome-wide association study of corticobasal degeneration identifies risk variants shared with progressive supranuclear palsy. Nat Commun 2015; 6: 7247.

Kouri N, Whitwell JL, Josephs KA, Rademakers R, Dickson DW. Corticobasal degeneration: A pathologically distinct 4R tauopathy. Nat Rev Neurol 2011; 7: 263–272.

Kozak MJ, Cuthbert BN. The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics. Psychophysiology 2016; 53: 286–297.

Kraemer BC, Schuck T, Wheeler JM, Robinson LC, Trojanowski JQ, Lee VMY, et al. Loss of Murine TDP-43 disrupts motor function and plays an essential role in embryogenesis. Acta Neuropathol 2010; 119: 409–419.

Kreis R. The trouble with quality filtering based on relative Cramér-Rao lower bounds. Magn Reson Med 2016; 75: 15–18.

Kruschke JK. Rejecting or Accepting Parameter Values in Bayesian Estimation. Adv Methods Pract Psychol Sci 2018; 1: 270–280.

Krystal JH, Staley J, Mason G, Petrakis IL, Kaufman J, Harris RA, et al. γ-Aminobutyric acid type A receptors and alcoholism: Intoxication, dependence, vulnerability, and treatment. Arch Gen Psychiatry 2006; 63: 957–968.

Kujala J, Jung J, Bouvard S, Lecaignard F, Lothe A, Bouet R, et al. Gamma oscillations in V1 are correlated with GABAA receptor density: A multi-modal MEG and Flumazenil-PET study. Sci Rep 2015; 5: 16347.

Kukley M, Capetillo-Zarate E, Dietrich D. Vesicular glutamate release from axons in white matter. Nat Neurosci 2007; 10: 311–320.

Kumfor F, Landin-Romero R, Devenney E, Hutchings R, Grasso R, Hodges JR, et al. On the right side? A longitudinal study of left-versus right-lateralized semantic dementia. Brain 2016; 139: 986–998.

Ladd ME, Bachert P, Meyerspeer M, Moser E, Nagel AM, Norris DG, et al. Pros and cons of ultra-high-field MRI/MRS for human application. Prog Nucl Magn Reson Spectrosc 2018; 109: 1–50.

Lagarde J, Valabrégue R, Corvol JC, Garcin B, Volle E, Le Ber I, et al. Why do patients with neurodegenerative frontal syndrome fail to answer: 'In what way are an orange and a banana alike?' Brain 2015; 138: 456–471.

Lagarde J, Valabrègue R, Corvol JC, Pineau F, Le Ber I, Vidailhet M, et al. Are frontal cognitive

and atrophy patterns different in PSP and bvFTD? A comparative neuropsychological and VBM study. PLoS One 2013; 8: e80353.

Lanctôt KL, Herrmann N, Ganjavi H, Black SE, Rusjan PM, Houle S, et al. Serotonin-1A receptors in frontotemporal dementia compared with controls. Psychiatry Res - Neuroimaging 2007; 156: 247–250.

Landi F, Cruz-Jentoft AJ, Liperoti R, Russo A, Giovannini S, Tosato M, et al. Sarcopenia and mortality risk in frail olderpersons aged 80 years and older: Results from iLSIRENTE study. Age Ageing 2013; 42: 203–209.

Landwehrmeyer B, Palacios JM. Alterations of neurotransmitter receptors and neurotransmitter transporters in progressive supranuclear palsy. J Neural Transm Suppl 1994; 42: 229–246.

Van Langenhove T, Leyton CE, Piguet O, Hodges JR. Comparing Longitudinal Behavior Changes in the Primary Progressive Aphasias. J Alzheimer's Dis 2016; 53: 1033–1042.

Lansdall CJ, Coyle-Gilchrist ITS, Jones PS, Rodríguez PV, Wilcox A, Wehmann E, et al. Apathy and impulsivity in frontotemporal lobar degeneration syndromes. Brain 2017; 140: 1792–1807.

Lansdall CJ, Coyle-Gilchrist ITS, Simon Jones P, Rodríguez PV, Wilcox A, Wehmann E, et al. White matter change with apathy and impulsivity in frontotemporal lobar degeneration syndromes. Neurology 2018; 90: e1066–e1076.

Lansdall CJ, Coyle-Gilchrist ITS, Vázquez Rodríguez P, Wilcox A, Wehmann E, Robbins TW, et al. Prognostic importance of apathy in syndromes associated with frontotemporal lobar degeneration. Neurology 2019; 92: E1547–E1557.

Laureys S, Salmon E, Garraux G, Peigneux P, Lemaire C, Degueldre C, et al. Fluorodopa uptake and glucose metabolism in early stages of corticobasal degeneration. J Neurol 1999; 246: 1151–1158.

Lebert F, Pasquier F, Petit H. Personality traits and frontal lobe dementia. Int J Geriatr Psychiatry 1995; 10: 1047–1049.

Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: A randomised, controlled trial with trazodone. Dement Geriatr Cogn Disord 2004; 17: 355–359.

Lee EB, Lee VMY, Trojanowski JQ. Gains or losses: Molecular mechanisms of TDP43-mediated neurodegeneration. Nat Rev Neurosci 2012; 13: 38–50.

Lee R, Chong B, Coccaro E. Growth hormone responses to GABAB receptor challenge with baclofen and impulsivity in healthy control and personality disorder subjects. Psychopharmacology (Berl) 2011; 215: 41–48.

Lee R, Petty F, Coccaro EF. Cerebrospinal fluid GABA concentration: Relationship with impulsivity and history of suicidal behavior, but not aggression, in human subjects. J Psychiatr Res 2009; 43: 353–359.

Lee SE, Rabinovici GD, Mayo MC, Wilson SM, Seeley WW, Dearmond SJ, et al. Clinicopathological correlations in corticobasal degeneration. Ann Neurol 2011; 70: 327–340.

Lee VMY, Brunden KR, Hutton M, Trojanowski JQ. Developing therapeutic approaches to tau,

selected kinases, and related neuronal protein targets. Cold Spring Harb Perspect Med 2011; 1: a006437–a006437.

Leija-Salazar M, Piette C, Proukakis C. Review: Somatic mutations in neurodegeneration. Neuropathol Appl Neurobiol 2018; 44: 267–285.

Leuzy A, Chiotis K, Lemoine L, Gillberg PG, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies—still a challenge. Mol Psychiatry 2019; 24: 1112–1134.

Leuzy A, Zimmer ER, Dubois J, Pruessner J, Cooperman C, Soucy JP, et al. In vivo characterization of metabotropic glutamate receptor type 5 abnormalities in behavioral variant FTD. Brain Struct Funct 2016; 221: 1387–1402.

Levenga J, Krishnamurthy P, Rajamohamedsait H, Wong H, Franke TF, Cain P, et al. Tau pathology induces loss of GABAergic interneurons leading to altered synaptic plasticity and behavioral impairments. Acta Neuropathol Commun 2014; 2: 34.

Levy BJ, Wagner AD. Cognitive control and right ventrolateral prefrontal cortex: Reflexive reorienting, motor inhibition, and action updating. Ann N Y Acad Sci 2011; 1224: 40–62.

Levy R, Ruberg M, Herrero MT, Villares J, Javoy-Agid F, Agid Y, et al. Alterations of GABAergic neurons in the basal ganglia of patients with progressive supranuclear palsy: an in situ hybridization study of GAD67 messenger RNA. Neurology 1995; 45: 127–134.

Lewis-Smith DJ, Wolpe N, Ghosh BCP, Rowe JB. Alien limb in the corticobasal syndrome: phenomenological characteristics and relationship to apraxia [Internet]. J Neurol 2020Available from: https://doi.org/10.1007/s00415-019-09672-8

Lewis C, Walterfang M, Velakoulis D, Vogel AP. A review: Mealtime difficulties following frontotemporal lobar degeneration. Dement Geriatr Cogn Disord 2019; 46: 285–297.

Leyton CE, Hsieh S, Mioshi E, Hodges JR. Cognitive decline in logopenic aphasia: More than losing words. Neurology 2013; 80: 897–903.

Li JN, Liu XL, Li L. Prefrontal GABA and glutamate levels correlate with impulsivity and cognitive function of prescription opioid addicts: A 1H-magnetic resonance spectroscopy study. Psychiatry Clin Neurosci 2020; 74: 77–83.

Li X, Wang Z, Tan L, Wang Y, Lu C, Chen R, et al. Correcting miR92a-vGAT-Mediated GABAergic Dysfunctions Rescues Human Tau-Induced Anxiety in Mice. Mol Ther 2017; 25: 140–152.

Liao K, Wagner J, Joshi A, Estrovich I, Walker MF, Strupp M, et al. Why do patients with psp fall?: Evidence for abnormal otolith responsessymbol. Neurology 2008; 70: 802–809.

Libon DJ, Xie SX, Moore P, Farmer J, Antani S, McCawley G, et al. Patterns of neuropsychological impairment in frontotemporal dementia. Neurology 2007; 68: 369–375.

Libon DJ, Xie SX, Wang X, Massimo L, Moore P, Vesely L, et al. Neuropsychological Decline in Frontotemporal Lobar Degeneration: A Longitudinal Analysis. Neuropsychology 2009; 23: 337–346.

Lillo P, Hodges JR. Frontotemporal dementia and motor neurone disease: Overlapping clinic-

pathological disorders. J Neurosci 2009; 16: 1131–1135.

Lin LC, Nana AL, Hepker M, Hwang JHL, Gaus SE, Spina S, et al. Preferential tau aggregation in von Economo neurons and fork cells in frontotemporal lobar degeneration with specific MAPT variants. Acta Neuropathol Commun 2019; 7: 159.

Lindemann U, Nicolai S, Beische D, Becker C, Srulijes K, Dietzel E, et al. Clinical and dual-tasking aspects in frequent and infrequent fallers with progressive supranuclear palsy. Mov Disord 2010; 25: 1040–1046.

Ling H, Macerollo A. Is it Useful to Classify PSP and CBD as Different Disorders? Yes. Mov Disord Clin Pract 2018; 5: 145–148.

Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR, et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain 2010; 133: 2045–2057.

Ling H, de Silva R, Massey LA, Courtney R, Hondhamuni G, Bajaj N, et al. Characteristics of progressive supranuclear palsy presenting with corticobasal syndrome: A cortical variant. Neuropathol Appl Neurobiol 2014; 40: 149–163.

Lipszyc J, Schachar R. Inhibitory control and psychopathology: A meta-analysis of studies using the stop signal task. J Int Neuropsychol Soc 2010; 16: 1064–1076.

Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996; 47: 1–9.

Litvan I, Agid Y, Jankovic J, Goetz C, Brandel JP, Lai EG, et al. Accuracy of clinical criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). Neurology 1996; 46: 922–930.

Litvan I, Campbell G, Mangone CA, Verny M, McKee A, Chaudhuri KR, et al. Which clinical features differentiate progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) from related disorders? A clinicopathological study. Brain 1997; 120: 65–74.

Litvan I, Cummings JJLJJL, Mega M. Neuropsychiatric features of corticobasal degeneration. J Neurol Neurosurg Psychiatry 1998; 65: 717–721.

Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol 1996; 55: 97–105.

Litvan I, Lees PSJ, Cunningham CR, Rai SN, Cambon AC, Standaert DG, et al. Environmental and occupational risk factors for progressive supranuclear palsy: Case-control study. Mov Disord 2016; 31: 644–652.

Litvan I, Phipps M, Pharr VL, Hallett M, Grafman J, Salazar A. Randomized placebo-controlled trial of donepezil in patients with progressive supranuclear palsy. Neurology 2001; 57: 467–473.

Lleó A, Irwin DJ, Illán-Gala I, McMillan CT, Wolk DA, Lee EB, et al. A 2-step cerebrospinal algorithm for the selection of frontotemporal lobar degeneration subtypes. JAMA Neurol 2018; 75: 738–745.

Logan GD, Van Zandt T, Verbruggen F, Wagenmakers EJ. On the ability to inhibit thought and action: General and special theories of an act of control. Psychol Rev 2014; 121: 66–95.

Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. Neurology 2002; 59: 1077–1079.

Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002; 72: 310–314.

Lough S, Kipps CM, Treise C, Watson P, Blair JR, Hodges JR. Social reasoning, emotion and empathy in frontotemporal dementia. Neuropsychologia 2006; 44: 950–958.

Mackenzie IR, Neumann M. Reappraisal of TDP-43 pathology in FTLD-U subtypes. Acta Neuropathol 2017; 134: 79–96.

Mackenzie IRA. The neuropathology of FTD associated with ALS. Alzheimer Dis Assoc Disord 2007; 21: S44–S49.

Mackenzie IRA, Neumann M. Molecular neuropathology of frontotemporal dementia: insights into disease mechanisms from postmortem studies. J Neurochem 2016; 138: 54–70.

Mackenzie IRA, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, et al. A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol 2011; 122: 111–113.

MacKenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: An update. Acta Neuropathol 2010; 119: 1–4.

MacKillop J, Weafer J, C. Gray J, Oshri A, Palmer A, de Wit H. The latent structure of impulsivity: impulsive choice, impulsive action, and impulsive personality traits. Psychopharmacology (Berl) 2016; 233: 3361–3370.

Mahoney CJ, Simpson IJA, Nicholas JM, Fletcher PD, Downey LE, Golden HL, et al. Longitudinal diffusion tensor imaging in rontotemporal dementia. Ann Neurol 2015; 77: 33–46.

Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, et al. NMDA receptor function and human cognition: The effects of ketamine in healthy volunteers. Neuropsychopharmacology 1996; 14: 301–307.

Malpetti M, Passamonti L, Kievit RA, Jones PS, Tsvetanov KA, Rittman T, et al. Microglial Activation and Tau Burden Predict Cognitive Decline in Alzheimer'S Disease. Alzheimer's Dement 2019; 15: P78–P79.

Manes FF, Torralva T, Roca M, Gleichgerrcht E, Bekinschtein TA, Hodges JR. Frontotemporal dementia presenting as pathological gambling. Nat Rev Neurol 2010; 6: 347–352.

Mann EO, Paulsen O. Role of GABAergic inhibition in hippocampal network oscillations. Trends Neurosci 2007; 30: 343–349.

Manoochehri M, Huey ED. Diagnosis and management of behavioral issues in frontotemporal dementia. Curr Neurol Neurosci Rep 2012; 12: 528–536.

Mariano LI, O'callaghan C, Guimarães HC, Gambogi LB, Da Silva TBL, Yassuda MS, et al. Disinhibition in Frontotemporal Dementia and Alzheimer's Disease: A Neuropsychological and Behavioural Investigation. J Int Neuropsychol Soc 2019: 1–9.

Marjańska M, Riley McCarten J, Hodges JS, Hemmy LS, Terpstra M. Distinctive Neurochemistry in Alzheimer's Disease via 7 T in Vivo Magnetic Resonance Spectroscopy. J Alzheimer's Dis 2019; 68: 559–569.

Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C. Interneurons of the neocortical inhibitory system. Nat Rev Neurosci 2004; 5: 793–807.

Marques JP, Kober T, Krueger G, van der Zwaag W, Van de Moortele PF, Gruetter R. MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. Neuroimage 2010; 49: 1271–1281.

Marsden CD, Parkes JD. Success and Problems of Long-Term Levodopa Therapy in Parkinson'S Disease. Lancet 1977; 309: 345–349.

Martin DL, Rimvall K. Regulation of gamma-aminobutyric acid synthesis in the brain. J Neurochem 1993; 60: 395–407.

Martyr A, Boycheva E, Kudlicka A. Assessing inhibitory control in early-stage Alzheimer's and Parkinson's disease using the Hayling Sentence Completion Test. J Neuropsychol 2019; 13: 67–81.

Matzke D, Curley S, Gong CQ, Heathcote A. Inhibiting responses to difficult choices. J Exp Psychol Gen 2019; 148: 124–142.

Matzke D, Dolan C V., Logan GD, Brown SD, Wagenmakers EJ. Bayesian parametric estimation of stop-signal reaction time distributions. J Exp Psychol Gen 2013; 142: 1047–1073.

Matzke D, Hughes M, Badcock JC, Michie P, Heathcote A. Failures of cognitive control or attention? The case of stop-signal deficits in schizophrenia. Attention, Perception, Psychophys 2017; 79: 1078–1086.

Matzke D, Love J, Heathcote A. A Bayesian approach for estimating the probability of trigger failures in the stop-signal paradigm. Behav Res Methods 2017; 49: 267–281.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011; 7: 263–269.

McLaughlin NCR, Kirschner J, Foster H, O'Connell C, Rasmussen SA, Greenberg BD. Stop Signal Reaction Time Deficits in a Lifetime Obsessive-Compulsive Disorder Sample. J Int Neuropsychol Soc 2016; 22: 785–789.

Mcmaster ML, Kristinsson SY, Turesson I, Bjorkholm M, Landgren O. Structure of the HIV-1 gp41 Membrane-Proximal Ectodomain Region in a Putative Prefusion Conformation. Biochemistry 2010; 9: 19–22.

McMillan CT, Boyd C, Gross RG, Weinstein J, Firn K, Toledo JB, et al. Multimodal imaging evidence of pathology-mediated disease distribution in corticobasal syndrome. Neurology 2016; 87: 1227–1234.

McWhirter L, Ritchie C, Stone J, Carson A. Functional cognitive disorders: a systematic review. The Lancet Psychiatry 2019; 0366: 1–17.

Meeter LH, Kaat LD, Rohrer JD, Van Swieten JC. Imaging and fluid biomarkers in frontotemporal dementia. Nat Rev Neurol 2017; 13: 406–419.

Meeuwsen EJ, Melis RJF, Van Der Aa GCHM, Golüke-Willemse GAM, De Leest BJM, Van Raak FHJM, et al. Effectiveness of dementia follow-up care by memory clinics or general practitioners: Randomised controlled trial. BMJ 2012; 344: e3086–e3086.

Melloni M, Billeke P, Baez S, Hesse E, De La Fuente L, Forno G, et al. Your perspective and my benefit: multiple lesion models of self-other integration strategies during social bargaining. Brain 2016; 139: 3022–3040.

Mendez MF. Corticobasal Ganglionic Degeneration With Balint's Syndrome. Clin Neurosci 2000: 1999–2001.

Mendez MF, Fong SS, Shapira JS, Jimenez EE, Kaiser NC, Kremen SA, et al. Observation of social behavior in frontotemporal dementia. Am J Alzheimers Dis Other Demen 2014; 29: 215–221.

Mendez MF, Shapira JS, McMurtray A, Licht E. Preliminary findings? Behavioral worsening on donepezil in patients with frontotemporal dementia. Am J Geriatr Psychiatry 2007; 15: 84–87.

Mesulam M-M. Primary Progressive Aphasia — A Language-Based Dementia. N Engl J Med 2003; 349: 1535–1542.

Meteyard L, Patterson K. The relation between content and structure in language production: An analysis of speech errors in semantic dementia. Brain Lang 2009; 110: 121–134.

Meyer S, Mueller K, Stuke K, Bisenius S, Diehl-Schmid J, Jessen F, et al. Predicting behavioral variant frontotemporal dementia with pattern classification in multi-center structural MRI data. NeuroImage Clin 2017; 14: 656–662.

Mick I, Ramos AC, Myers J, Stokes PR, Chandrasekera S, Erritzoe D, et al. Evidence for GABA-A receptor dysregulation in gambling disorder: correlation with impulsivity. Addict Biol 2017; 22: 1601–1609.

Miki Y, Mori F, Tanji K, Kurotaki H, Kakita A, Takahashi H, et al. An autopsy case of incipient Pick's disease: Immunohistochemical profile of early-stage Pick body formation. Neuropathology 2014; 34: 386–391.

Milak MS, Proper CJ, Mulhern ST, Parter AL, Kegeles LS, Ogden RT, et al. A pilot in vivo proton magnetic resonance spectroscopy study of amino acid neurotransmitter response to ketamine treatment of major depressive disorder. Mol Psychiatry 2016; 21: 320–327.

Millar D, Griffiths P, Zermansky AJ, Burn DJ. Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. Mov Disord 2006; 21: 199–207.

Miller JJ, Cochlin L, Clarke K, Tyler DJ. Weighted averaging in spectroscopic studies improves statistical power. Magn Reson Med 2017; 78: 2082–2094.

Miller ZA, Mandelli ML, Rankin KP, Henry ML, Babiak MC, Frazier DT, et al. Handedness

and language learning disability differentially distribute in progressive aphasia variants. Brain 2013; 136: 3461–3473.

Millsap R, Maydeu-Olivares A, Hoijtink H. Bayesian Data Analysis. Chapman and Hall/CRC; 2012

Mioshi E, Bristow M, Cook R, Hodges JR. Factors underlying caregiver stress in frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord 2009; 27: 76–81.

Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry 2006; 21: 1078–1085.

Mioshi E, Foxe D, Leslie F, Savage S, Hsieh S, Miller L, et al. The impact of dementia severity on caregiver burden in frontotemporal dementia and alzheimer disease. Alzheimer Dis Assoc Disord 2013; 27: 68–73.

Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR. Clinical staging and disease progression in frontotemporal dementia Acknowledgements: The authors thank Lindy Clemson (Occupational Therapy. Neurology 2010; 0776229: 1591–1597.

Mirza MB, Adams RA, Parr T, Friston K. Impulsivity and active inference. J Cogn Neurosci 2018; 31: 202–220.

Mitchell HS, Hamilton TS, Steggerda R, Bean HW. The chemical composition of the adult human body and its bearing on the biochemistry of growth. J Biol Chem 1945; 158: 625–637.

Mochizuki A, Ueda Y, Komatsuzaki Y, Tsuchiya K, Arai T, Shoji S. Progressive supranuclear palsy presenting with primary progressive aphasia - Clinicopathological report of an autopsy case. Acta Neuropathol 2003; 105: 610–614.

Moore KM, Nicholas J, Grossman M, McMillan CT, Irwin DJ, Massimo L, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. Lancet Neurol 2019; 4422: 1–13.

Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Rivastigmine in frontotemporal dementia: An open-label study. Drugs and Aging 2004; 21: 931–937.

Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Frontotemporal dementia: Paroxetine as a possible treatment of behavior symptoms: A randomized, controlled, open 14-month study. Eur Neurol 2003; 49: 13–19.

Morgan CJA, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: A 1-year longitudinal study. Addiction 2010; 105: 121–133.

Mori H, Oda M, Komori T, Arai N, Takanashi M, Mizutani T, et al. Lewy bodies in progressive supranuclear palsy. Acta Neuropathol 2002; 104: 273–278.

Mori K, Arzberger T, Grässer FA, Gijselinck I, May S, Rentzsch K, et al. Bidirectional transcripts of the expanded C9orf72 hexanucleotide repeat are translated into aggregating dipeptide repeat proteins. Acta Neuropathol 2013; 126: 881–893.

Moser P, Hingerl L, Strasser B, Považan M, Hangel G, Andronesi OC, et al. Whole-slice mapping of GABA and GABA + at 7T via adiabatic MEGA-editing, real-time instability correction, and concentric circle readout. Neuroimage 2019; 184: 475–489.

Mosley PE, Paliwal S, Robinson K, Coyne T, Silburn P, Tittgemeyer M, et al. The structural connectivity of discrete networks underlies impulsivity and gambling in Parkinson's disease. Brain 2019; 142: 3917–3935.

Mostofsky SH, Simmonds DJ. Response Inhibition and Response Selection: Two Sides of the Same Coin. J Cogn Neurosci 2008; 20: 751–761.

Mueller C, Hussl A, Krismer F, Heim B, Mahlknecht P, Nocker M, et al. The diagnostic accuracy of the hummingbird and morning glory sign in patients with neurodegenerative parkinsonism. Park Relat Disord 2018; 54: 90–94.

Mullins PG, McGonigle DJ, O'Gorman RL, Puts NAJ, Vidyasagar R, Evans CJ, et al. Current practice in the use of MEGA-PRESS spectroscopy for the detection of GABA. Neuroimage 2014; 86: 43–52.

Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RSJ, Hodges JR. A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. Ann Neurol 2000; 47: 36–45.

Munoz DG, Ros R, Fatas M, Bermejo F, De Yebenes JG. Progressive nonfluent aphasia associated with a new mutation V363I in tau gene. Am J Alzheimers Dis Other Demen 2007; 22: 294–299.

Murley AG, Coyle-Gilchrist I, Rouse MA, Jones PS, Li W, Wiggins J, et al. Redefining the multidimensional clinical phenotypes of frontotemporal lobar degeneration syndromes. Brain 2020; 143: 1555–1571.

Murley AG, Rouse MA, Coyle-Gilchrist I, Simon P, Li W, Wiggins J, et al. Predicting loss of independence and mortality in frontotemporal lobar degeneration syndromes. 2020

Murley AG, Rowe JB. Neurotransmitter deficits from frontotemporal lobar degeneration. Brain 2018; 141: 1263–1285.

Murphy KE, Karaconji T, Hardman CD, Halliday GM. Excessive dopamine neuron loss in progressive supranuclear palsy. Mov Disord 2008; 23: 607–610.

Murphy NA, Arthur KC, Tienari PJ, Houlden H, Chiò A, Traynor BJ. Age-related penetrance of the C9orf72 repeat expansion. Sci Rep 2017; 7: 1–7.

Muthukumaraswamy SD, Edden R a E, Jones DK, Swettenham JB, Singh KD. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. Proc Natl Acad Sci U S A 2009; 106: 8356–8361.

De Muynck L, Van Damme P. Cellular effects of progranulin in health and disease. J Mol Neurosci 2011; 45: 549–560.

Myers JFM, Evans CJ, Kalk NJ, Edden RAE, Lingford-Hughes AR. Measurement of GABA using J-difference edited 1H-MRS following modulation of synaptic GABA concentration with tiagabine. Synapse 2014; 68: 355–362.

Myles AJ, Feudale RN, Liu Y, Woody NA, Brown SD. An introduction to decision tree modeling. J Chemom 2004; 18: 275–285.

Naaijen J, Lythgoe DJ, Amiri H, Buitelaar JK, Glennon JC. Fronto-striatal glutamatergic compounds in compulsive and impulsive syndromes: A review of magnetic resonance spectroscopy studies. Neurosci Biobehav Rev 2015; 52: 74–88.

Nagaoka S, Arai H, Iwamoto N, Ohwada J, Ichimiya Y, Nakamura M, et al. A juvenile case of frontotemporal dementia: Neurochemical and neuropathological investigations. Prog Neuropsychopharmacol Biol Psychiatry 1995; 19: 1251–1261.

Nagasawa H, Tanji H, Nomura H, Saito H, Itoyama Y, Kimura I, et al. PET study of cerebral glucose metabolism and fluorodopa uptake in patients with corticobasal degeneration. J Neurol Sci 1996; 139: 210–7.

Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature 2018; 554: 249–254.

Napier TC, Corvol JC, Grace AA, Roitman JD, Rowe J, Voon V, et al. Linking neuroscience with modern concepts of impulse control disorders in Parkinson's disease. Mov Disord 2015; 30: 141–149.

Nath U, Ben-Shlomo Y, Thomson RG, Lees AJ, Burn DJ. Clinical features and natural history of progressive supranuclear palsy: A clinical cohort study. Neurology 2003; 60: 910–916.

Neal LB, Gable PA. Neurophysiological markers of multiple facets of impulsivity. Biol Psychol 2016; 115: 64–68.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546–1554.

Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. Brain 2019; 142: 1503–1527.

Neumann M, Mackenzie IRA. Review: Neuropathology of non-tau frontotemporal lobar degeneration. Neuropathol Appl Neurobiol 2019; 45: 19–40.

Neumann M, Rademakers R, Roeber S, Baker M, Kretzschmar HA, MacKenzie IRA. A new subtype of frontotemporal lobar degeneration with FUS pathology. Brain 2009; 132: 2922–2931.

Newcomer JW, Farber NB, Olney JW. NMDA receptor function, memory, and brain aging. Dialogues Clin Neurosci 2000; 2: 219–32.

Nichols E, Szoeke CEI, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019; 18: 88–106.

Nichols T, Brett M, Andersson J, Wager T, Poline JB. Valid conjunction inference with the minimum statistic. Neuroimage 2005; 25: 653–660.

Nicholson TRJ, Cutter W, Hotopf M. Assessing mental capacity: the Mental Capacity Act. BMJ 2008; 336: 322–325.

Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cogn Affect Behav Neurosci 2012; 12: 241–268.

Nimchinsky EA, Gilissen E, Allman JM, Perl DP, Erwin JM, Hof PR. A neuronal morphologic type unique to humans and great apes. Proc Natl Acad Sci U S A 1999; 96: 5268–5273.

Nomura T, Inoue Y, Takigawa H, Nakashima K. Comparison of REM sleep behaviour disorder variables between patients with progressive supranuclear palsy and those with Parkinson's disease. Park Relat Disord 2012; 18: 394–396.

Noureddine Y, Bitz AK, Ladd ME, Thürling M, Ladd SC, Schaefers G, et al. Experience with magnetic resonance imaging of human subjects with passive implants and tattoos at 7 T: a retrospective study. Magn Reson Mater Physics, Biol Med 2015; 28: 577–590.

Nyatsanza S, Shetty T, Gregory C, Lough S, Dawson K, Hodges JR. A study of stereotypic behaviours in Alzheimer's disease and frontal and temporal variant frontotemporal dementia. J Neurol Neurosurg Psychiatry 2003; 74: 1398–1402.

O'Brien JT, Paling S, Barber R, Williams ED, Ballard C, McKeith IG, et al. Progressive brain atrophy on serial MRI in dementia with Lewy bodies, AD, and vascular dementia. Neurology 2001; 56: 1386 LP – 1388.

O'Callaghan C. The multifaceted nature of impulsivity in Parkinson's disease. Brain 2019; 142: 3666–3669.

O'Callaghan C, Bertoux M, Irish M, Shine JM, Wong S, Spiliopoulos L, et al. Fair play: Social norm compliance failures in behavioural variant frontotemporal dementia. Brain 2016; 139: 204–216.

O'Callaghan C, Hodges JR, Hornberger M. Inhibitory dysfunction in frontotemporal dementia: A review. Alzheimer Dis Assoc Disord 2013; 27: 102–108.

O'Callaghan C, Naismith SL, Hodges JR, Lewis SJG, Hornberger M. Fronto-striatal atrophy correlates of inhibitory dysfunction in parkinson's disease versus behavioural variant frontotemporal dementia. Cortex 2013; 49: 1833–1843.

O'Connor C, Landin-Romero R, Clemson L, Kaizik C, Daveson N, Hodges J, et al. Behavioral-variant frontotemporal dementia: Distinct phenotypes with unique functional profiles. Neurology 2017; 0

O'Connor CM, Clemson L, Hornberger M, Leyton CE, Hodges JR, Piguet O, et al. Longitudinal change in everyday function and behavioral symptoms in frontotemporal dementia. Neurol Clin Pract 2016; 6: 419–428.

O'Keeffe FM, Murray B, Coen RF, Dockree PM, Bellgrove MA, Garavan H, et al. Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy. Brain 2007; 130: 753–764.

O'Muircheartaigh J, Dean DC, Ginestet CE, Walker L, Waskiewicz N, Lehman K, et al. White matter development and early cognition in babies and toddlers. Hum Brain Mapp 2014; 35: 4475–4487.

O'Sullivan SS, Djamshidian A, Ahmed Z, Evans AH, Lawrence AD, Holton JL, et al.

Impulsive-compulsive spectrum behaviors in pathologically confirmed progressive supranuclear palsy. Mov Disord 2010; 25: 638–642.

Odawara T, Shiozaki K, Iseki E, Hino H, Kosaka K. Alterations of muscarinic acetylcholine receptors in atypical Pick's disease without Pick bodies. J Neurol Neurosurg Psychiatry 2003; 74: 965–7.

Oh M, Kim JS, Kim JY, Shin KH, Park SH, Kim HO, et al. Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. J Nucl Med 2012; 53: 399–406.

Oide T, Ohara S, Yazawa M, Itoh N, Tokuda T, Ikeda SI. Progressive supranuclear palsy with asymmetric tau pathology presenting with unilateral limb dystonia. Acta Neuropathol 2002; 104: 209–214.

Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016; 15: 673–684.

Osaki Y, Ben-Shlomo Y, Lees AJ, Daniel SE, Colosimo C, Wenning GK, et al. Accuracy of clinical diagnosis of progressive supranuclear palsy. Mov Disord 2004; 19: 181–189.

Ossenkoppele R, Jansen WJ, Rabinovici GD, Knol DL, van der Flier WM, van Berckel BNM, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. Jama 2015; 313: 1939–1949.

Ossenkoppele R, Pijnenburg YAL, Perry DC, Cohn-Sheehy BI, Scheltens NME, Vogel JW, et al. The behavioural/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. Brain 2015; 138: 2732–2749.

Ossenkoppele R, Rabinovici GD, Smith R, Cho H, Scholl M, Strandberg O, et al. Discriminative accuracy of [18F]flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. JAMA - J Am Med Assoc 2018; 320: 1151–1162.

Owens DF, Kriegstein AR. Is there more to GABA than synaptic inhibition? Nat Rev Neurosci 2002; 3: 715–727.

Oyanagi C. Comparison of Striatal Dopamine D2 Receptors in Parkinson ' s Disease and Progressive Supranuclear Palsy Patients Using [I] Iodobenzofuran Single-Photon Emission Computed Tomography. J Neuroimaging 2002; 12: 316–324.

Öz G, Deelchand DK, Wijnen JP, Mlynárik V, Xin L, Mekle R, et al. Advanced single voxel 1 H magnetic resonance spectroscopy techniques in humans: Experts' consensus recommendations . NMR Biomed 2020: 1–18.

Öz G, Tkáč I. Short-echo, single-shot, full-intensity proton magnetic resonance spectroscopy for neurochemical profiling at 4 T: Validation in the cerebellum and brainstem. Magn Reson Med 2011; 65: 901–910.

Padovani A, Agosti C, Premi E, Bellelli G, Borroni B. Extrapyramidal symptoms in Frontotemporal Dementia: Prevalence and clinical correlations. Neurosci Lett 2007; 422: 39–42.

Palaniyappan L, Mahmood J, Balain V, Mougin O, Gowland PA, Liddle PF. Structural

correlates of formal thought disorder in schizophrenia: An ultra-high field multivariate morphometry study. Schizophr Res 2015; 168: 305–312.

Pan PL, Song W, Yang J, Huang R, Chen K, Gong QY, et al. Gray matter atrophy in behavioral variant frontotemporal dementia: A meta-analysis of voxel-based morphometry studies. Dement Geriatr Cogn Disord 2012; 33: 141–148.

Panchal H, Paholpak P, Lee G, Carr A, Barsuglia JP, Mather M, et al. Neuropsychological and Neuroanatomical Correlates of the Social Norms Questionnaire in Frontotemporal Dementia Versus Alzheimer's Disease. Am J Alzheimers Dis Other Demen 2016; 31: 326–332.

Panza F, Imbimbo BP, Lozupone M, Greco A, Seripa D, Logroscino G, et al. Disease-modifying therapies for tauopathies: agents in the pipeline. Expert Rev Neurother 2019; 19: 397–408.

Papapetropoulos S, Singer C, McCorquodale D, Gonzalez J, Mash DC. Cause, seasonality of death and co-morbidities in progressive supranuclear palsy (PSP). Park Relat Disord 2005; 11: 459–463.

Park HK, Ilango S, Charriez CM, Checkoway H, Riley D, Standaert DG, et al. Lifetime exposure to estrogen and progressive supranuclear palsy: Environmental and Genetic PSP study. Mov Disord 2018; 33: 468–472.

Park HK, Park KH, Yoon B, Lee JH, Choi SH, Joung JH, et al. Clinical characteristics of parkinsonism in frontotemporal dementia according to subtypes. J Neurol Sci 2017; 372: 51–56.

Park JS, Lee J, Jung ES, Kim MH, Kim I Bin, Son H, et al. Brain somatic mutations observed in Alzheimer's disease associated with aging and dysregulation of tau phosphorylation. Nat Commun 2019; 10: 3090.

Parr T, Rikhye RV, Halassa MM, Friston KJ. Prefrontal Computation as Active Inference. Cereb Cortex 2019: 1–14.

Passamonti L, Lansdall CJ, Rowe JB. The neuroanatomical and neurochemical basis of apathy and impulsivity in frontotemporal lobar degeneration. Curr Opin Behav Sci 2018; 22: 14–20.

Passamonti L, Rodríguez PV, Hong YT, Allinson KSJ, Williamson D, Borchert RJ, et al. 18F-AV-1451 positron emission tomography in Alzheimer's disease and progressive supranuclear palsy. Brain 2017; 140: 781–791.

Passamonti L, Tsvetanov KA, Jones PS, Bevan-Jones WR, Arnold R, Borchert RJ, et al. Neuroinflammation and Functional Connectivity in Alzheimer's Disease: Interactive Influences on Cognitive Performance. J Neurosci 2019; 39: 7218–7226.

Pathak D, Berthet A, Nakamura K. Energy failure: Does it contribute to neurodegeneration? Ann Neurol 2013; 74: 506–516.

Patterson L. Making our health and care systems fit for an ageing population: David Oliver, Catherine Foot, Richard Humphries. King's Fund March 2014. Age Ageing 2014; 43: 731.

Patton JH, Stanford M, Barratt E. Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol 1995; 51: 768–774.

Pearce JM. Hugo Karl Liepmann and apraxia. Clin Med (Northfield Il) 2009; 9: 466–470.

Peelle JE, Cooke A, Moore P, Vesely L, Grossman M. Syntactic and thematic components of sentence processing in progressive nonfluent aphasia and nonaphasic frontotemporal dementia. J Neurolinguistics 2007; 20: 482–494.

Peelle JE, Troiani V, Gee J, Moore P, McMillan C, Vesely L, et al. Sentence comprehension and voxel-based morphometry in progressive nonfluent aphasia, semantic dementia, and nonaphasic frontotemporal dementia. J Neurolinguistics 2008; 21: 418–432.

Pekmezović T, Ječmenica-Lukić M, Petrović I, Špica V, Tomić A, Kostić VS. Quality of life in patients with progressive supranuclear palsy: one-year follow-up. J Neurol 2015; 262: 2042–2048.

Penadés R, Catalán R, Rubia K, Andrés S, Salamero M, Gastó C. Impaired response inhibition in obsessive compulsive disorder. Eur Psychiatry 2007; 22: 404–410.

Perry DC, Brown JA, Possin KL, Datta S, Trujillo A, Radke A, et al. Clinicopathological correlations in behavioural variant frontotemporal dementia. Brain 2017; 140: 3329–3345.

Perry DC, Datta S, Miller ZA, Rankin KP, Gorno-Tempini ML, Kramer JH, et al. Factors that predict diagnostic stability in neurodegenerative dementia. J Neurol 2019; 266: 1998–2009.

Perry DC, Datta S, Sturm VE, Wood KA, Zakrzewski J, Seeley WW, et al. Reward deficits in behavioural variant frontotemporal dementia include insensitivity to negative stimuli. Brain 2017; 140: 3346–3356.

Perry DC, Sturm VE, Seeley WW, Miller BL, Kramer JH, Rosen HJ. Anatomical correlates of reward-seeking behaviours in behavioural variant frontotemporal dementia. Brain 2014; 137: 1621–1626.

Peters F, Perani D, Herholz K, Holthoff V, Beuthien-Baumann B, Sorbi S, et al. Orbitofrontal Dysfunction Related to Both Apathy and Disinhibition in Frontotemporal Dementia. Dement Geriatr Cogn Disord 2006; 21: 373–379.

Peterson KA, Patel N, Barrick TR, Cappa SF, Patterson K, Rowe JB, et al. Language Impairment in Progressive Supranuclear Palsy and Corticobasal Syndrome. Alzheimer's Dement 2018; 14: P1301.

Pharr V, Uttl B, Stark M, Litvan I, Fantie B, Grafman J. Comparison of apraxia in corticobasal degeneration and progressive supranuclear palsy. Neurology 2001; 56: 957–963.

Phokaewvarangkul O, Bhidayasiri R. How to spot ocular abnormalities in progressive supranuclear palsy? A practical review. Transl Neurodegener 2019; 8: 20.

Piattella MC, Upadhyay N, Bologna M, Sbardella E, Tona F, Formica A, et al. Neuroimaging evidence of gray and white matter damage and clinical correlates in progressive supranuclear palsy. J Neurol 2015; 262: 1850–1858.

Pick A. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. Prager Med Wochenschrift 1892; 17: 165–167.

Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: Diagnosis, clinical staging, and management. Lancet Neurol 2011; 10: 162–172.

Pijnenburg YAL, Sampson EL, Harvey RJ, Fox NC, Rossor MN. Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration. Int J Geriatr Psychiatry 2003; 18: 67–72.

Pirker S, Perju-Dumbrava L, Kovacs GG, Traub-Weidinger T, Pirker W. Progressive dopamine transporter binding loss in autopsy-confirmed Corticobasal Degeneration. J Parkinsons Dis 2015; 5: 907–912.

Poos JM, Jiskoot LC, Papma JM, Van Swieten JC, Van Den Berg E. Meta-analytic review of memory impairment in behavioral variant frontotemporal dementia. J Int Neuropsychol Soc 2018; 24: 593–605.

Porges EC, Woods AJ, Lamb DG, Williamson JB, Cohen RA, Edden RAE, et al. Impact of tissue correction strategy on GABA-edited MRS findings. Neuroimage 2017; 162: 249–256.

Possin KL, Laluz VR, Alcantar OZ, Miller BL, Kramer JH. Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. Neuropsychologia 2011; 49: 43–48.

Prioni S, Redaelli V, Soliveri P, Fetoni V, Barocco F, Caffarra P, et al. Stereotypic behaviours in frontotemporal dementia and progressive supranuclear palsy. Cortex 2018; 109: 272–278.

Prisciandaro JJ, Tolliver BK, Prescot AP, Brenner HM, Renshaw PF, Brown TR, et al. Unique prefrontal GABA and glutamate disturbances in co-occurring bipolar disorder and alcohol dependence. Transl Psychiatry 2017; 7: 1–8.

Procter AW, Qurne M, Francis PT. Neurochemical features of frontotemporal dementia. Dement Geriatr Cogn Disord 1999; 10: 80–84.

Provencher SW. Estimation of metabolite concentrations from localizedin vivo proton NMR spectra. Magn Reson Med 1993; 30: 672–679.

Puts NAJ, Wodka EL, Harris AD, Crocetti D, Tommerdahl M, Mostofsky SH, et al. Reduced GABA and altered somatosensory function in children with autism spectrum disorder. Autism Res 2017; 10: 608–619.

Quadrelli S, Mountford C, Ramadan S. Hitchhiker'S Guide to Voxel Segmentation for Partial Volume Correction of in Vivo Magnetic Resonance Spectroscopy. Magn Reson Insights 2016; 9: MRI.S32903.

Radakovic R, Abrahams S. Multidimensional apathy: evidence from neurodegenerative disease. Curr Opin Behav Sci 2018; 22: 42–49.

Rademakers R, Baker M, Gass J, Adamson J, Huey ED, Momeni P, et al. Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C→T (Arg493X) mutation: an international initiative. Lancet Neurol 2007; 6: 857–868.

Rademakers R, Neumann M, MacKenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. Nat Rev Neurol 2012; 8: 423–434.

Rae CL, Hughes LE, Anderson MC, Rowe JB. The prefrontal cortex achieves inhibitory control by facilitating subcortical motor pathway connectivity. J Neurosci 2015; 35: 786–794.

Rae CL, Nombela C, Rodríguez PV, Ye Z, Hughes LE, Jones PS, et al. Atomoxetine restores the response inhibition network in Parkinson's disease. Brain 2016; 139: 2235–2248.

Raffaele F, Claudia M, John H. Genetics and molecular mechanisms of frontotemporal lobar degeneration: an update and future avenues. Neurobiol Aging 2019; 78: 98–110.

Rahman S, Sahakian BJ, Hodges JR, Rogers RD, Robbins TW. Specific cognitive deficits in mild frontal variant frontotemporal dementia. Brain 1999; 122: 1469–1493.

Raisner RM, Hartley PD, Meneghini MD, Bao MZ, Liu CL, Schreiber SL, et al. Histone variant H2A.Z Marks the 5′ ends of both active and inactive genes in euchromatin. Cell 2005; 123: 233–248.

Ranasinghe KG, Rankin KP, Lobach I V., Kramer JH, Sturm VE, Bettcher BM, et al. Cognition and neuropsychiatry in behavioral variant frontotemporal dementia by disease stage. Neurology 2016; 86: 600–610.

Ranasinghe KG, Rankin KP, Pressman PS, Perry DC, Lobach I V., Seeley WW, et al. Distinct subtypes of behavioral variant frontotemporal dementia based on patterns of network degeneration. JAMA Neurol 2016; 73: 1078–1088.

Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, et al. Structural anatomy of empathy in neurodegenerative disease. Brain 2006; 129: 2945–2956.

Rascovsky K, Hodges JR, Kipps CM, Johnson JK, Seeley WW, Mendez MF, et al. Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): Current limitations and future directions. Alzheimer Dis Assoc Disord 2007; 21: S14-8.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011; 134: 2456–2477.

Ratti A, Buratti E. Physiological functions and pathobiology of TDP-43 and FUS/TLS proteins. J Neurochem 2016; 138: 95–111.

Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: Classification, prognostication, and prediction. Lancet 2011; 378: 1812–1823.

Rektorova I, Biundo R, Marecek R, Weis L, Aarsland D, Antonini A. Grey matter changes in cognitively impaired Parkinson's disease patients. PLoS One 2014; 9

Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 2011; 72: 257–268.

Respondek G, Hoglinger GU. The phenotypic spectrum of progressive supranuclear palsy. Park Relat Disord 2016; 22: S34–S36.

Respondek G, Kurz C, Arzberger T, et al. Which ante-mortem clinical features predict PSP pathology? Mov Disord 2017; in press

Respondek G, Stamelou M, Kurz C, Ferguson LW, Rajput A, Chiu WZ, et al. The phenotypic spectrum of progressive supranuclear palsy: A retrospective multicenter study of 100 definite cases. Mov Disord 2014; 29: 1758–1766.

Revesz T, Sangha H, Daniel SE. The nucleus raphe interpositus in the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Brain 1996; 119 (Pt 4: 1137–1143.

Ribeiro MJ, Violante IR, Bernardino I, Edden RAE, Castelo-Branco M. Abnormal relationship between GABA, neurophysiology and impulsive behavior in neurofibromatosis type 1. Cortex 2015; 64: 194–208.

Ridgway GR, Omar R, Ourselin S, Hill DLG, Warren JD, Fox NC. Issues with threshold masking in voxel-based morphometry of atrophied brains. Neuroimage 2009; 44: 99–111.

Ridha BH, Anderson VM, Barnes J, Boyes RG, Price SL, Rossor MN, et al. Volumetric MRI and cognitive measures in Alzheimer disease: Comparison of markers of progression. J Neurol 2008; 255: 567–574.

Riedijk SR, De Vugt ME, Duivenvoorden HJ, Niermeijer MF, Van Swieten JC, Verhey FRJ, et al. Caregiver burden, health-related quality of life and coping in dementia caregivers: A comparison of frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord 2006; 22: 405–412.

Riedl L, Mackenzie IR, Förstl H, Kurz A, Diehl-Schmid J. Frontotemporal lobar degeneration: Current perspectives. Neuropsychiatr Dis Treat 2014; 10: 297–310.

Rigby HB, Dugger BN, Hentz JG, Adler CH, Beach TG, Shill HA, et al. Clinical Features of Patients with Concomitant Parkinson's Disease and Progressive Supranuclear Palsy Pathology. Mov Disord Clin Pract 2015; 2: 33–38.

Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology 2005; 65: 586–590.

Ringnér M. What is principal component analysis? Nat Biotechnol 2008; 26: 303–304.

Rinne JO, Laine M, Kaasinen V, Norvasuo-Heila MK, Nagren K, Helenius H. Striatal dopamine transporter and extrapyramidal symptoms in frontotemporal dementia. Neurology 2002; 58: 1489–1493.

Rinne JO, Lee MS, Thompson PD, Marsden CD. Corticobasal degeneration: A clinical study of 36 cases. Brain 1994; 117: 1183–1196.

Rittman T, Borchert R, Jones S, van Swieten J, Borroni B, Galimberti D, et al. Functional network resilience to pathology in presymptomatic genetic frontotemporal dementia. Neurobiol Aging 2019; 77: 169–177.

Rittman T, Coyle-Gilchrist IT, Rowe JB. Managing cognition in progressive supranuclear palsy. Neurodegener Dis Manag 2016; 6: 499–508.

Rittman T, Ghosh BC, McColgan P, Breen DP, Evans J, Williams-Gray CH, et al. The Addenbrooke's Cognitive Examination for the differential diagnosis and longitudinal assessment of patients with parkinsonian disorders. J Neurol Neurosurg Psychiatry 2013; 84: 544–551.

Rittman T, Rubinov M, Vértes PE, Patel AX, Ginestet CE, Ghosh BCP, et al. Regional expression of the MAPT gene is associated with loss of hubs in brain networks and cognitive impairment in Parkinson disease and progressive supranuclear palsy. Neurobiol Aging 2016; 48: 153–160.

Rizzo F, Abaei A, Nespoli E, Fegert JM, Hengerer B, Rasche V, et al. Aripiprazole and Riluzole treatment alters behavior and neurometabolites in young ADHD rats: A longitudinal 1 H-NMR

spectroscopy study at 11.7T [Internet]. Transl Psychiatry 2017; 7Available from: http://dx.doi.org/10.1038/tp.2017.167

Robbins TW, James M, Owen AM, Lange KW, Lees AJ, Leigh PN, et al. Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. J Neurol Neurosurg Psychiatry 1994; 57: 79–88.

Roberson ED, Hesse JH, Rose KD, Slama H, Johnson JK, Yaffe K, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. Neurology 2005; 65: 719–725.

Robert P, Onyike CU, Leentjens AFG, Dujardin K, Aalten P, Starkstein S, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry 2009; 24: 98–104.

Robinson JL, Lee EB, Xie SX, Rennert L, Suh E, Bredenberg C, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain 2018; 141: 2181–2193.

Roca M, Manes F, Gleichgerrcht E, Watson P, Ibáñez A, Thompson R, et al. Intelligence and executive functions in frontotemporal dementia. Neuropsychologia 2013; 51: 725–730.

Rockwood JKH, Richard M, Garden K, Hominick K, Mitnitski A, Rockwood K. Precipitating and predisposing events and symptoms for admission to assisted living or nursing home care. Can Geriatr J 2014; 17: 16–21.

Roeber S, Mackenzie IRA, Kretzschmar HA, Neumann M. TDP-43-negative FTLD-U is a significant new clinico-pathological subtype of FTLD. Acta Neuropathol 2008; 116: 147–157.

Rogalski E, Johnson N, Weintraub S, Mesulam M. Increased frequency of learning disability in patients with primary progressive aphasia and their first-degree relatives. Arch Neurol 2008; 65: 244–248.

Rogalski E, Weintraub S, Mesulam MM. Are there susceptibility factors for primary progressive aphasia? Brain Lang 2013; 127: 135–138.

Rogers TT, Lambon Ralph MA, Garrard P, Bozeat S, McClelland JL, Hodges JR, et al. Structure and Deterioration of Semantic Memory: A Neuropsychological and Computational Investigation. Psychol Rev 2004; 111: 205–235.

Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology 2009; 73: 1451–1456.

Rohrer JD, Isaacs AM, Mizlienska S, Mead S, Lashley T, Wray S, et al. C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis. Lancet Neurol 2015; 14: 291–301.

Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, et al. Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain 2011; 134: 2565–2581.

Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: A cross-sectional analysis. Lancet Neurol 2015; 14: 253–262.

Rohrer JD, Paviour D, Bronstein AM, O'Sullivan SS, Lees A, Warren JD. Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: A neuropsychological and neuroimaging analysis. Mov Disord 2010; 25: 179–188.

Rohrer JD, Ridgway GR, Modat M, Ourselin S, Mead S, Fox NC, et al. Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations. Neuroimage 2010; 53: 1070–1076.

Rohrer JD, Rossor MN, Warren JD. Syndromes of nonfluent primary progressive aphasia: A clinical and neurolinguistic analysis. Neurology 2010; 75: 603–610.

Rohrer JD, Rossor MN, Warren JD. Apraxia in progressive nonfluent aphasia. J Neurol 2010; 257: 569–574.

Rohrer JD, Warren JD. Phenomenology and anatomy of abnormal behaviours in primary progressive aphasia. J Neurol Sci 2010; 293: 35–38.

Rosen HJ, Allison SC, Ogar JM, Amici S, Rose K, Dronkers N, et al. Behavioral features in semantic dementia vs other forms of progressive aphasias. Neurology 2006; 67: 1752–1756.

Rosen HJ, Allison SC, Schauer GF, Gorno- ML, Weiner MW, Miller BL. Neuroanatomical correlates of behavioural disorders in dementia. Brain 2005; 128: 2612–2625.

Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 2002; 58: 198–208.

Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med 2004; 10: S10.

Ross CA, Poirier MA. What is the role of protein aggregation in neurodegeneration? Nat Rev Mol Cell Biol 2005; 6: 891–898.

Rosser A, Hodges JR. Initial letter and semantic category fluency in Alzheimer's disease, Huntington's disease, and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 1994; 57: 1389–1394.

Rouch I, Dorey JM, Padovan C, Trombert-Paviot B, Benoit M, Laurent B, et al. Does personality predict behavioral and psychological symptoms of Dementia? Results from PACO prospective study. J Alzheimer's Dis 2019; 69: 1099–1108.

Rowe JB. Parkinsonism in frontotemporal dementias. Int Rev Neurobiol 2019; 149: 249–275.

Royall DR. The FAB: A frontal assessment battery at bedside [1]. Neurology 2001; 57: 565.

Ruberg M, Javoy-Agid F, Hirsch E, Scatton B, Lheureux R, Hauw J -J, et al. Dopaminergic and cholinergic lesions in progressive supranuclear palsy. Ann Neurol 1985; 18: 523–529.

Rusz J, Bonnet C, Klempíř J, Tykalová T, Baborová E, Novotný M, et al. Speech disorders reflect differing pathophysiology in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. J Neurol 2015; 262: 992–1001.

Rutherford NJ, Heckman MG, DeJesus-Hernandez M, Baker MC, Soto-Ortolaza AI, Rayaprolu S, et al. Length of normal alleles of C9ORF72 GGGGCC repeat do not influence disease

phenotype. Neurobiol Aging 2012; 33: 2950.e5-2950.e7.

Sajjadi SA, Patterson K, Arnold RJ, Watson PC, Nestor PJ. Primary progressive aphasia: A tale of two syndromes and the rest. Neurology 2012; 78: 1670–1677.

Sakae N, Josephs KA, Litvan I, Murray ME, Duara R, Uitti RJ, et al. Neuropathologic basis of frontotemporal dementia in progressive supranuclear palsy. Mov Disord 2019; 34: 1655–1662.

Salthouse TA. What and when of cognitive aging. Curr Dir Psychol Sci 2004; 13: 140–144.

Sami S, Williams N, Hughes LE, Cope TE, Rittman T, Coyle-Gilchrist ITS, et al. Neurophysiological signatures of Alzheimer's disease and frontotemporal lobar degeneration: Pathology versus phenotype. Brain 2018; 141: 2500–2510.

Sanacora G, Mason GF, Rothman DL, Krystal JH. Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. Am J Psychiatry 2002; 159: 663–665.

Sánchez-Valle R, Forman MS, Miller BL, Gorno-Tempini ML. From progressive nonfluent aphasia to corticobasal syndrome: A case report of corticobasal degeneration. Neurocase 2006; 12: 355–359.

Santillo AF, Englund E. Greater loss of von Economo neurons than loss of layer II and III neurons in behavioral variant frontotemporal dementia. Am J Neurodegener Dis 2014; 3: 64–71.

Santillo AF, Nilsson C, Englund E. von Economo neurones are selectively targeted in frontotemporal dementia. Neuropathol Appl Neurobiol 2013; 39: 572–579.

Santos-Santos MA, Mandelli ML, Binney RJ, Ogar J, Wilson SM, Henry ML, et al. Features of patients with nonfluent/agrammatic primary progressive aphasia with underlying progressive supranuclear palsy pathology or corticobasal degeneration. JAMA Neurol 2016; 73: 733–742.

Sarac H, Zagar M, Davorka V, Henigsberg N, Bilic E, Pavlisa G, et al. Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy in a Patient with Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. Coll Antropol 2008; 32: 205–210.

Sawle G V, Brooks DJ, Marsden CD, Frackowiak RSJ. Corticobasal degeneration - A unique pattern of regional cortical oxygen hypometabolism and striatal fluorodopa uptake demonstrated by positron emmission tomography. Brain 1991; 114: 541 LP – 556.

Scaravilli T, Tolosa E, Ferrer I. Progressive supranuclear palsy and corticobasal degeneration: Lumping versus splitting. Mov Disord 2005; 20

Schmaal L, Goudriaan AE, van der Meer J, van den Brink W, Veltman DJ. The association between cingulate cortex glutamate concentration and delay discounting is mediated by resting state functional connectivity. Brain Behav 2012; 2: 553–562.

Schmaal L, Veltman DJ, Nederveen A, Van Den Brink W, Goudriaan AE. N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: A randomized crossover magnetic resonance spectroscopy study. Neuropsychopharmacology 2012; 37: 2143–2152.

Schmidt-Wilcke T, Fuchs E, Funke K, Vlachos A, Müller-Dahlhaus F, Puts NAJ, et al. GABA—from Inhibition to Cognition: Emerging Concepts. Neuroscientist 2018; 24: 501–515.

Schmotz C, Richinger C, Lorenzl S. High Burden and Depression among Late-Stage Idiopathic Parkinson Disease and Progressive Supranuclear Palsy Caregivers. J Geriatr Psychiatry Neurol 2017; 30: 267–272.

Schroeter ML, Raczka K, Neumann J, Yves von Cramon D. Towards a nosology for frontotemporal lobar degenerations-A meta-analysis involving 267 subjects. Neuroimage 2007; 36: 497–510.

Schumacher R, Halai AD, Lambon Ralph MA. Assessing and mapping language, attention and executive multidimensional deficits in stroke aphasia. Brain 2019; 142: 3202–3216.

Schwartz JC, Cech TR, Parker RR. Biochemical Properties and Biological Functions of FET Proteins. Annu Rev Biochem 2015; 84: 355–379.

Sedaghat F, Gotzamani-Psarrakou A, Dedousi E, Arnaoutoglou M, Psarrakos K, Baloyannis I, et al. Evaluation of dopaminergic function in frontotemporal dementia using I-FP-CIT single photon emission computed tomography. Neurodegener Dis 2007; 4: 382–5.

Seelaar H, Rohrer JD, Pijnenburg YAL, Fox NC, Van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: A review. J Neurol Neurosurg Psychiatry 2011; 82: 476–486.

Seeley WW. Selective functional, regional, and neuronal vulnerability in frontotemporal dementia. Curr Opin Neurol 2008; 21: 701–707.

Seeley WW, Bauer AM, Miller BL, Gorno-Tempini ML, Kramer JH, Weiner M, et al. The natural history of temporal variant frontotemporal dementia. Neurology 2005; 64: 1384–1390.

Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL, et al. Early frontotemporal dementia targets neurons unique to apes and humans. Ann Neurol 2006; 60: 660–667.

Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol 2008; 65: 249–255.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative Diseases Target Large-Scale Human Brain Networks. Neuron 2009; 62: 42–52.

Senderecka M, Grabowska A, Szewczyk J, Gerc K, Chmylak R. Response inhibition of children with ADHD in the stop-signal task: An event-related potential study. Int J Psychophysiol 2012; 85: 93–105.

Seo SW, Thibodeau MP, Perry DC, Hua A, Sidhu M, Sible I, et al. Early vs late age at onset frontotemporal dementia and frontotemporal lobar degeneration. Neurology 2018; 90: e1047–e1056.

Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016; 537: 50–56.

Sevinçer GM, İpekçioglu DY, Konuk N, Ertan T. The relationship between the premorbid personality traits and the behavioral and psychological symptoms of Alzheimer disease. Neurol Psychiatry Brain Res 2017; 24: 20–25.

Shaikh AG, Factor SA, Juncos JL. Saccades in Progressive Supranuclear Palsy–Maladapted, Irregular, Curved, and Slow. Mov Disord Clin Pract 2017; 4: 671–681.

Shen IH, Lee DS, Chen C ling. The role of trait impulsivity in response inhibition: Event-related potentials in a stop-signal task. Int J Psychophysiol 2014; 91: 80–87.

Shepard RN. Multidimensional scaling, tree-fitting, and clustering. Science (80-) 1980; 210: 390–398.

Shinagawa S, Nakajima S, Plitman E, Graff-Guerrero A, Mimura M, Nakayama K, et al. Psychosis in frontotemporal dementia. J Alzheimer's Dis 2014; 42: 485–499.

Silveri MM, Sneider JT, Crowley DJ, Covell MJ, Acharya D, Rosso IM, et al. Frontal lobe γ-aminobutyric acid levels during adolescence: Associations with impulsivity and response inhibition. Biol Psychiatry 2013; 74: 296–304.

Singh TD, Duffy JR, Strand EA, Machulda MM, Whitwell JL, Josephs KA. Neuropsychiatric symptoms in primary progressive aphasia and apraxia of speech. Dement Geriatr Cogn Disord 2015; 39: 228–238.

Siuda J, Fujioka S, Wszolek ZK. Parkinsonian syndrome in familial frontotemporal dementia. Park Relat Disord 2014; 20: 957–964.

Skippen P, Fulham WR, Michie PT, Matzke D, Heathcote A, Karayanidis F, et al. Reconsidering electrophysiological markers of response inhibition in light of trigger failures in the stop-signal task. bioRxiv 2019: 658336.

Skippen P, Matzke D, Heathcote A, Fulham WR, Michie P, Karayanidis F. Reliability of triggering inhibitory process is a better predictor of impulsivity than SSRT. Acta Psychol (Amst) 2019; 192: 104–117.

Skodda S, Visser W, Schlegel U. Acoustical analysis of speech in progressive supranuclear palsy. J Voice 2011; 25: 725–731.

Smith JL, Mattick RP, Jamadar SD, Iredale JM. Deficits in behavioural inhibition in substance abuse and addiction: A meta-analysis. Drug Alcohol Depend 2014; 145: 1–33.

Snaar JEM, Teeuwisse WM, Versluis MJ, van Buchem MA, Kan HE, Smith NB, et al. Improvements in high-field localized MRS of the medial temporal lobe in humans using new deformable high-dielectric materials. NMR Biomed 2011; 24: 873–879.

Snowden J, Neary D, Mann D. Frontotemporal lobar degeneration: Clinical and pathological relationships. Acta Neuropathol 2007; 114: 31–38.

Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. J Neurol Neurosurg Psychiatry 2001; 70: 323–332.

Snowden JS, Kobylecki C, Jones M, Thompson JC, Richardson AM, Mann DMA. Association between semantic dementia and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 2019; 90: 115–117.

Snowden JS, Pickering-Brown SM, Mackenzie IR, Richardson AMT, Varma A, Neary D, et al. Progranulin gene mutations associated with frontotemporal dementia and progressive non-

fluent aphasia. Brain 2006; 129: 3091–3102.

Soliveri P, Piacentini S, Girotti F. Limb apraxia in corticobasal degeneration and progressive supranuclear palsy. Neurology 2005; 64: 448–453.

Sparks DL, Markesbery WR. Altered Serotonergic and Cholinergic Synaptic Markers in Pick's Disease. Arch Neurol 1991; 48: 796–799.

Spinelli EG, Mandelli ML, Miller ZA, Santos-Santos MA, Wilson SM, Agosta F, et al. Typical and atypical pathology in primary progressive aphasia variants. Ann Neurol 2017; 81: 430–443.

Staekenborg SS, Su T, Van Straaten ECW, Lane R, Scheltens P, Barkhof F, et al. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. J Neurol Neurosurg Psychiatry 2010; 81: 547–551.

Staffaroni AM, Ljubenkov PA, Kornak J, Cobigo Y, Datta S, Marx G, et al. Longitudinal multimodal imaging and clinical endpoints for frontotemporal dementia clinical trials. Brain 2019; 142: 443–459.

Stagg CJ. Magnetic Resonance Spectroscopy as a tool to study the role of GABA in motor-cortical plasticity. Neuroimage 2014; 86: 19–27.

Stagg CJ, Bachtiar V, Johansen-Berg H. What are we measuring with GABA Magnetic Resonance Spectroscopy? Commun Integr Biol 2011; 4: 573–575.

Stagg CJ, Bachtiar V, Johansen-Berg H. The role of GABA in human motor learning. Curr Biol 2011; 21: 480–484.

Stagg CJ, Wylezinska M, Matthews PM, Johansen-Berg H, Jezzard P, Rothwell JC, et al. Neurochemical Effects of Theta Burst Stimulation as Assessed by Magnetic Resonance Spectroscopy. J Neurophysiol 2009; 101: 2872–2877.

Stahl SM. Mechanism of Action of Trazodone: a Multifunctional Drug. CNS Spectr 2009; 14: 536–546.

Stamelou M, Alonso-Canovas A, Bhatia KP. Dystonia in corticobasal degeneration: A review of the literature on 404 pathologically proven cases. Mov Disord 2012; 27: 696–702.

Stamelou M, Diehl-Schmid J, Hapfelmeier A, Kontaxopoulou D, Stefanis L, Oertel WH, et al. The frontal assessment battery is not useful to discriminate progressive supranuclear palsy from frontotemporal dementias. Park Relat Disord 2015; 21: 1264–1268.

Stamelou M, Höglinger G. A Review of Treatment Options for Progressive Supranuclear Palsy. CNS Drugs 2016; 30: 629–636.

Di Stasio F, Suppa A, Marsili L, Upadhyay N, Asci F, Bologna M, et al. Corticobasal syndrome: neuroimaging and neurophysiological advances. Eur J Neurol 2019; 26: 701-e52.

Steele JC, Richardson JC, Olszewski J. Progressive Supranuclear Palsy: A Heterogeneous Degeneration Involving the Brain Stem, Basal Ganglia and Cerebellum With Vertical Gaze and Pseudobulbar Palsy, Nuchal Dystonia and Dementia. Arch Neurol 1964; 10: 333–359.

Steenwijk MD, Geurts JJG, Daams M, Tijms BM, Wink AM, Balk LJ, et al. Cortical atrophy

patterns in multiple sclerosis are non-random and clinically relevant. Brain 2016; 139: 115–126.

Di Stefano F, Kas A, Habert M-O, Decazes P, Lamari F, Lista S, et al. The phenotypical core of Alzheimer's disease-related and nonrelated variants of the corticobasal syndrome: A systematic clinical, neuropsychological, imaging, and biomarker study. Alzheimer's Dement 2016; 12: 786–795.

Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. BMJ 2009; 339: 157–160.

Stezin A, Lenka A, Jhunjhunwala K, Saini J, Pal PK. Advanced structural neuroimaging in progressive supranuclear palsy: Where do we stand? Park Relat Disord 2017; 36: 19–32.

Stopford CL, Thompson JC, Neary D, Richardson AMT, Snowden JS. Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia. Cortex 2012; 48: 429–446.

Suárez-Calvet M, Dols-Icardo O, Lladó A, Sánchez-Valle R, Hernández I, Amer G, et al. Plasma phosphorylated TDP-43 levels are elevated in patients with frontotemporal dementia carrying a C9orf72 repeat expansion or a GRN mutation. J Neurol Neurosurg Psychiatry 2014; 85: 684–691.

Suzuki M, Desmond TJ, Albin RL, Frey K a. Cholinergic vesicular transporters in progressive supranuclear palsy. Neurology 2002; 58: 1013–8.

Swann N, Tandon N, Canolty R, Ellmore TM, McEvoy LK, Dreyer S, et al. Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci 2009; 29: 12675–12685.

Tan KR, Rudolph U, Lüscher C. Hooked on benzodiazepines: GABAA receptor subtypes and addiction. Trends Neurosci 2011; 34: 188–197.

Tan RH, Guennewig B, Dobson-Stone C, Kwok JBJ, Kril JJ, Kiernan MC, et al. The underacknowledged PPA-ALS: A unique clinicopathologic subtype with strong heritability. Neurology 2019; 92: E1354–E1366.

Tao JJ, Schram AM, Hyman DM. Basket Studies: Redefining Clinical Trials in the Era of Genome-Driven Oncology. Annu Rev Med 2018; 69: 319–331.

Terpstra M, Cheong I, Lyu T, Deelchand DK, Emir UE, Bednařík P, et al. Test-retest reproducibility of neurochemical profiles with short-echo, single-voxel MR spectroscopy at 3T and 7T. Magn Reson Med 2016; 76: 1083–1091.

Tharwat A. Independent component analysis: An introduction. Appl Comput Informatics 2018: 1–15.

Thompson CK, Mack JE. Grammatical impairments in PPA. Aphasiology 2014; 28: 1018–1037.

Thompson CK, Meltzer-Asscher A, Cho S, Lee J, Wieneke C, Weintraub S, et al. Syntactic and morphosyntactic processing in stroke-induced and primary progressive aphasia. Behav Neurol 2013; 26: 35–54.

Thompson PD, Day BL, Rothwell JC, Brown P, Britton TC, Marsden CD. The myoclonus in corticobasal degeneration: Evidence for two forms of cortical reflex myoclonus. Brain 1994; 117: 1197–1207.

Tkac I. Shimming and MRS. Proc Intl Soc Mag Reson Med 2010; 18: 18–20.

Tkáč I, Gruetter R. Methodology of 1H NMR spectroscopy of the human brain at very high magnetic fields. Appl Magn Reson 2005; 29: 139–157.

Tkac I, Starcuk Z, Choi I-Y, Gruetter R. In vivo1H NMR spectroscopy of rat brain at 1 ms echo time. Magn Reson Med 1999; 41: 649–656.

Tognarelli JM, Dawood M, Shariff MIF, Grover VPB, Crossey MME, Cox IJ, et al. Magnetic Resonance Spectroscopy: Principles and Techniques: Lessons for Clinicians. J Clin Exp Hepatol 2015; 5: 320–328.

Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F. A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. Brain 2009; 132: 1299–1309.

Torralva T, Roca M, Gleichgerrcht E, López P, Manes F. INECO Frontal Screening (IFS): A brief, sensitive, and specific tool to assess executive functions in dementia. J Int Neuropsychol Soc 2009; 15: 777–786.

Tremblay R, Lee S, Rudy B. GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. Neuron 2016; 91: 260–292.

Tsai RM, Miller Z, Koestler M, Rojas JC, Ljubenkov PA, Rosen HJ, et al. Reactions to Multiple Ascending Doses of the Microtubule Stabilizer TPI-287 in Patients with Alzheimer Disease, Progressive Supranuclear Palsy, and Corticobasal Syndrome: A Randomized Clinical Trial. JAMA Neurol 2019; 94158: 1–10.

Tsuboi Y, Josephs KA, Boeve BF, Litvan I, Caselli RJ, Caviness JN, et al. Increased tau burden in the cortices of progressive supranuclear palsy presenting with corticobasal syndrome. Mov Disord 2005; 20: 982–988.

Tsvetanov KA, Gazzina S, Jones SP, Swieten J van, Borroni B, Sanchez-Valle R, et al. Brain functional network integrity sustains cognitive function despite atrophy in presymptomatic genetic frontotemporal dementia. medRxiv 2019: 19012203.

Tsvetanov KA, Ye Z, Hughes L, Samu D, Treder MS, Wolpe N, et al. Activity and connectivity differences underlying inhibitory control across the adult life span. J Neurosci 2018; 38: 7887–7900.

Tuite PJ, Clark HB, Bergeron C, Bower M, St George-Hyslop P, Mateva V, et al. Clinical and pathologic evidence of corticobasal degeneration and progressive supranuclear palsy in familial tauopathy. Arch Neurol 2005; 62: 1453–1457.

Tun SM, Murman DL, Long HL, Colenda CC, Von Eye A. Predictive validity of neuropsychiatric subgroups on nursing home placement and survival in patients with alzheimer disease. Am J Geriatr Psychiatry 2007; 15: 314–327.

Turken AU, Swick D. Response selection in the human anterior cingulate cortex. Nat Neurosci 1999; 2: 920–924.

Turner BM, Sederberg PB, Brown SD, Steyvers M. A Method for efficiently sampling from distributions with correlated dimensions. Psychol Methods 2013; 18: 368–384.

Tykalova T, Rusz J, Klempir J, Cmejla R, Ruzicka E. Distinct patterns of imprecise consonant articulation among Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. Brain Lang 2017; 165: 1–9.

Uitti RJ, Ahlskog JE, Maraganore DM, Muenter MD, Atkinson EJ, Cha RH, et al. Levodopa therapy and survival in idiopathic Parkinson's disease: Olmsted County project. Neurology 1993; 43: 1918–1926.

Upadhyay N, Suppa A, Piattella MC, Bologna M, Di Stasio F, Formica A, et al. MRI gray and white matter measures in progressive supranuclear palsy and corticobasal syndrome. J Neurol 2016; 263: 2022–2031.

Utianski RL, Botha H, Martin PR, Schwarz CG, Duffy JR, Clark HM, et al. Clinical and neuroimaging characteristics of clinically unclassifiable primary progressive aphasia. Brain Lang 2019; 197: 104676.

Valente ES, Caramelli P, Gambogi LB, Mariano LI, Guimarães HC, Teixeira AL, et al. Phenocopy syndrome of behavioral variant frontotemporal dementia: A systematic review. Alzheimer's Res Ther 2019; 11: 1–15.

Verbruggen F, Aron AR, Band GPH, Beste C, Bissett PG, Brockett AT, et al. A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. Elife 2019; 8: 1–26.

Vercelletto M, Boutoleau-Bretonnière C, Volteau C, Puel M, Auriacombe S, Sarazin M, et al. Memantine in behavioral variant frontotemporal dementia: Negative results. J Alzheimer's Dis 2011; 23: 749–759.

Vermeiren Y, Le Bastard N, Van Hemelrijck A, Drinkenburg WH, Engelborghs S, De Deyn PP. Behavioral correlates of cerebrospinal fluid amino acid and biogenic amine neurotransmitter alterations in dementia. Alzheimer's Dement 2013; 9: 488–498.

Vermeiren Y, Janssens J, Aerts T, Martin JJ, Sieben A, Van Dam D, et al. Brain Serotonergic and Noradrenergic Deficiencies in Behavioral Variant Frontotemporal Dementia Compared to Early-Onset Alzheimer's Disease. J Alzheimer's Dis 2016; 53: 1079–1096.

Vinceti G, Olney N, Mandelli ML, Spina S, Hubbard HI, Santos-Santos MA, et al. Primary progressive aphasia and the FTD-MND spectrum disorders: clinical, pathological, and neuroimaging correlates. Amyotroph Lateral Scler Front Degener 2019; 20: 146–158.

Viviani R, Grön G, Spitzer M. Functional principal component analysis of fMRI data. Hum Brain Mapp 2005; 24: 109–129.

De Vivo DC, Johnston M V. Pediatric neurotransmitter diseases: Foreword. Ann Neurol 2003; 54: 1–2.

Voon V, Napier TC, Frank MJ, Sgambato-Faure V, Grace AA, Rodriguez-Oroz M, et al. Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. Lancet Neurol 2017; 16: 238–250.

Walls AB, Waagepetersen HS, Bak LK, Schousboe A, Sonnewald U. The Glutamine–

Glutamate/GABA Cycle: Function, Regional Differences in Glutamate and GABA Production and Effects of Interference with GABA Metabolism. Neurochem Res 2014; 40: 402–409.

Walsh CM, Ruoff L, Walker K, Emery A, Varbel J, Karageorgiou E, et al. Sleepless Night and Day, the Plight of Progressive Supranuclear Palsy. Sleep 2017; 40

Ward LM. Synchronous neural oscillations and cognitive processes. Trends Cogn Sci 2003; 7: 553–559.

Warmus BA, Sekar DR, McCutchen E, Schellenberg GD, Roberts RC, McMahon LL, et al. Tau-mediated NMDA receptor impairment underlies dysfunction of a selectively vulnerable network in a mouse model of frontotemporal dementia. J Neurosci 2014; 34: 16482–16495.

Warren JD, Hardy CJ, Fletcher PD, Marshall CR, Clark CN, Rohrer JD, et al. Binary reversals in primary progressive aphasia. Cortex 2016; 82: 287–289.

Warren NM, Piggott MA, Perry EK, Burn DJ. Cholinergic systems in progressive supranuclear palsy. Brain 2005; 128: 239–249.

Waschkies CF, Bruns A, Müller S, Kapps M, Borroni E, Von Kienlin M, et al. Neuropharmacological and neurobiological relevance of in vivo 1 H-MRS of GABA and glutamate for preclinical drug discovery in mental disorders. Neuropsychopharmacology 2014; 39: 2331–2339.

Wear HJ, Wedderburn CJ, Mioshi E, Williams-Gray CH, Mason SL, Barker R a, et al. The Cambridge Behavioural Inventory revised. Dement Neuropsychol 2008; 2: 102–107.

Wei W, Keogh MJ, Aryaman J, Golder Z, Kullar PJ, Wilson I, et al. Frequency and signature of somatic variants in 1461 human brain exomes. Genet Med 2019; 21: 904–912.

Weigard A, Heathcote A, Matzke D, Huang-Pollock C. Cognitive Modeling Suggests That Attentional Failures Drive Longer Stop-Signal Reaction Time Estimates in Attention Deficit/Hyperactivity Disorder. Clin Psychol Sci 2019; 7: 856–872.

Weigelt B, Horlings H, Kreike B, Hayes M, Hauptmann M, Wessels L, et al. Refinement of breast cancer classification by molecular characterization of histological special types. J Pathol 2008; 216: 141–150.

Wenning GK, Litvan I, Jankovic J, Granata R, Mangone CA, McKee A, et al. Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. J Neurol Neurosurg Psychiatry 1998; 64: 184–189.

Whelan R. Effective analysis of reaction time data. Psychol Rec 2008; 58: 475–482.

Whitwell JL, Höglinger GU, Antonini A, Bordelon Y, Boxer AL, Colosimo C, et al. Radiological biomarkers for diagnosis in PSP: Where are we and where do we need to be? Mov Disord 2017; 32: 955–971.

Whitwell JL, Jack CR, Boeve BF, Parisi JE, Ahlskog JE, Drubach DA, et al. Imaging correlates of pathology in corticobasal syndrome. Neurology 2010; 75: 1879–1887.

Whitwell JL, Jack CR, Parisi JE, Gunter JL, Weigand SD, Boeve BF, et al. Midbrain atrophy is not a biomarker of progressive supranuclear palsy pathology. Eur J Neurol 2013; 20: 1417–1422.

Whitwell JL, Jack CR, Senjem ML, Parisi JE, Boeve BF, Knopman DS, et al. MRI correlates of protein deposition and disease severity in postmortem frontotemporal lobar degeneration. Neurodegener Dis 2009; 6: 106–117.

Whitwell JL, Josephs KA. Neuroimaging in frontotemporal lobar degeneration - Predicting molecular pathology. Nat Rev Neurol 2012; 8: 131–142.

Whitwell JL, Josephs KA, Murray ME, Kantarci K, Przybelski SA, Weigand SD, et al. MRI correlates of neurofibrillary tangle pathology at autopsy: A voxel-based morphometry study. Neurology 2008; 71: 743–749.

Whitwell JL, Josephs KA, Rossor MN, Stevens JM, Revesz T, Holton JL, et al. Magnetic resonance imaging signatures of tissue pathology in frontotemporal dementia. Arch Neurol 2005; 62: 1402–1408.

Whitwell JL, Lowe VJ, Tosakulwong N, Weigand SD, Senjem ML, Schwarz CG, et al. [18F]AV-1451 tau positron emission tomography in progressive supranuclear palsy. Mov Disord 2017; 32: 124–133.

Whitwell JL, Przybelski SA, Weigand SD, Ivnik RJ, Vemuri P, Gunter JL, et al. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: A cluster analysis study. Brain 2009; 132: 2932–2946.

Whitwell JL, Tosakulwong N, Schwarz CG, Botha H, Senjem ML, Spychalla AJ, et al. MRI Outperforms [18F]AV-1451 PET as a Longitudinal Biomarker in Progressive Supranuclear Palsy. Mov Disord 2019; 34: 105–113.

Whitwell JL, Weigand SD, Boeve BF, Senjem ML, Gunter JL, Dejesus-Hernandez M, et al. Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. Brain 2012; 135: 794–806.

Wijtenburg SA, Rowland LM, Oeltzschner G, Barker PB, Workman CI, Smith GS. Reproducibility of brain MRS in older healthy adults at 7T. NMR Biomed 2019; 32: 1–8.

Willette AA, Calhoun VD, Egan JM, Kapogiannis D. Prognostic classification of mild cognitive impairment and Alzheimer's disease: MRI independent component analysis. Psychiatry Res - Neuroimaging 2014; 224: 81–88.

Williams DR, Holton JL, Strand C, Pittman A, De Silva R, Lees AJ, et al. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. Brain 2007; 130: 1566–1576.

Williams DR, Holton JL, Strand K, Revesz T, Lees AJ. Pure akinesia with gait freezing: A third clinical phenotype of progressive supranuclear palsy. Mov Disord 2007; 22: 2235–2241.

Williams DR, Lees AJ. What features improve the accuracy of the clinical diagnosis of progressive supranuclear palsy-parkinsonism (PSP-P)? Mov Disord 2010; 25: 357–362.

Williams DR, De Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain 2005; 128: 1247–1258.

Williams DR, Watt HC, Lees AJ. Predictors of falls and fractures in bradykinetic rigid syndromes: A retrospective study. J Neurol Neurosurg Psychiatry 2006; 77: 468–473.

Wilson M, Andronesi O, Barker PB, Bartha R, Bizzi A, Bolan PJ, et al. Methodological consensus on clinical proton MRS of the brain: Review and recommendations. Magn Reson Med 2019; 82: 527–550.

Wilson SM, Brambati SM, Henry RG, Handwerker DA, Agosta F, Miller BL, et al. The neural basis of surface dyslexia in semantic dementia. Brain 2009; 132: 71–86.

Wilson SM, Henry ML, Besbris M, Ogar JM, Dronkers NF, Jarrold W, et al. Connected speech production in three variants of primary progressive aphasia. Brain 2010; 133: 2069–2088.

Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimer's Dement 2017; 13: 1–7.

Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: A priority for European science and society. Lancet Neurol 2016; 15: 455–532.

Wood PL, Etienne P, Lal S, Nair NPV, Finlayson MH, Gauthier S, et al. A post-mortem comparison of the cortical cholinergic system in Alzheimer's disease and Pick's disease. J Neurol Sci 1983; 62: 211–217.

Worthington A, Wood RL. Apathy following traumatic brain injury: A review. Neuropsychologia 2018; 118: 40–47.

Wszolek ZK, Tsuboi Y, Ghetti B, Pickering-Brown S, Baba Y, Cheshire WP. Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Orphanet J Rare Dis 2006; 1: 706–715.

Xie SX, Forman MS, Farmer J, Moore P, Wang Y, Wang X, et al. Factors associated with survival probability in autopsy-proven frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry 2008; 79: 126–129.

Xu L, Groth KM, Pearlson G, Schretlen DJ, Calhoun VD. Source-based morphometry: the use of independent component analysis to identify gray matter differences with application to schizophrenia. Hum Brain Mapp 2009; 30: 711–724.

Yang W, Lui RLM, Gao JH, Chan TF, Yau ST, Sperling RA, et al. Independent component analysis-based classification of Alzheimer's disease MRI data. J Alzheimer's Dis 2011; 24: 775–783.

Yang Y, Halliday GM, Hodges JR, Tan RH. Von Economo Neuron Density and Thalamus Volumes in Behavioral Deficits in Frontotemporal Dementia Cases with and without a C9ORF72 Repeat Expansion. J Alzheimer's Dis 2017; 58: 701–709.

Yang Y, Schmitt HP. Frontotemporal dementia: Evidence for impairment of ascending serotoninergic but not noradrenergic innervation. Immunocytochemical and quantitative study using a graph method. Acta Neuropathol 2001; 101: 256–270.

Yasen AL, Smith J, Christie AD. Reliability of glutamate and GABA quantification using proton magnetic resonance spectroscopy. Neurosci Lett 2017; 643: 121–124.

Ye Z, Altena E, Nombela C, Housden CR, Maxwell H, Rittman T, et al. Improving response inhibition in Parkinson's disease with atomoxetine. Biol Psychiatry 2015; 77: 740–748.

Ye Z, Rae CL, Nombela C, Ham T, Rittman T, Jones PS, et al. Predicting beneficial effects of atomoxetine and citalopram on response inhibition in Parkinson's disease with clinical and neuroimaging measures. Hum Brain Mapp 2016; 37: 1026–1037.

Yokoyama JS, Karch CM, Fan CC, Bonham LW, Kouri N, Ross OA, et al. Shared genetic risk between corticobasal degeneration, progressive supranuclear palsy, and frontotemporal dementia. Acta Neuropathol 2017; 133: 825–837.

Yoon WT, Chung EJ, Lee SH, Kim BJ, Lee WY. Clinical Analysis of Blepharospasm and Apraxia of Eyelid Opening in Patients with Parkinsonism. J Clin Neurol 2005; 1: 159.

Yoshiyama Y, Lee VMY, Trojanowski JQ. Therapeutic strategies for tau mediated neurodegeneration. J Neurol Neurosurg Psychiatry 2013; 84: 784–795.

Zadikoff C, Lang AE. Apraxia in movement disorders. Brain 2005; 128: 1480–1497.

Zamboni G, Huey ED, Krueger F, Nichelli PF, Grafman J. Apathy and disinhibition in frontotemporal dementia: Insights into their neural correlates. Neurology 2008; 71: 736–742.

Zarow C, Vinters H V., Ellis WG, Weiner MW, Mungas D, White L, et al. Correlates of hippocampal neuron number in Alzheimer's disease and ischemic vascular dementia. Ann Neurol 2005; 57: 896–903.

Zetterberg H, van Swieten JC, Boxer AL, Rohrer JD. Review: Fluid biomarkers for frontotemporal dementias. Neuropathol Appl Neurobiol 2019; 45: 81–87.

Zhang J. Mapping neuroinflammation in frontotemporal dementia with molecular PET imaging. J Neuroinflammation 2015; 12

Zhang J, Rittman T, Nombela C, Fois A, Coyle-Gilchrist I, Barker RA, et al. Different decision deficits impair response inhibition in progressive supranuclear palsy and Parkinson's disease. Brain 2016; 139: 161–173.

Zhang M, Ferrari R, Tartaglia MC, Keith J, Surace EI, Wolf U, et al. A C6orf10/LOC101929163 locus is associated with age of onset in C9orf72 carriers. Brain 2018; 141: 2895–2907.

Zhang W, Tarutani A, Newell KL, Murzin AG, Matsubara T, Falcon B, et al. Novel tau filament fold in corticobasal degeneration. Nature 2020; 53: 811703.

Zhang Z, Fan Q, Bai Y, Wang Z, Zhang H, Xiao Z. Brain gamma-aminobutyric acid (GABA) concentration of the prefrontal lobe in unmedicated patients with Obsessivecompulsive disorder: a research of magnetic resonance spectroscopy. Shanghai Arch Psychiatry 2016; 28: 263–270.

Zhao QF, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. J Affect Disord 2016; 190: 264–271.

Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. J Neural Transm 2014; 121: 799–817.

Zhu M, HajiHosseini A, Baumeister TR, Garg S, Appel-Cresswell S, McKeown MJ. Altered EEG alpha and theta oscillations characterize apathy in Parkinson's disease during incentivized

movement. NeuroImage Clin 2019; 23: 101922.

Zwergal A, La Fougère C, Lorenzl S, Rominger A, Xiong G, Deutschenbaur L, et al. Postural imbalance and falls in PSP correlate with functional pathology of the thalamus. Neurology 2011; 77: 101–109.

Appendices

Appendix 1: Diagnostic criteria

Behavioural variant frontotemporal dementia (Rascovsky *et al.*, 2011)

Possible bvFTD
Three of the following behavioural/cognitive symptoms (A-F)
A. Early behavioural disinhibition (one or more of A1-A3) A1. Socially inappropriate behaviour A2. Loss of manners or decorum A3. Impulsive, rash or careless actions
B. Early apathy or inertia (one or more of B1-B2) B1. Apathy B2. Inertia
C. Early loss of sympathy (one or more of C1-C2) C1. Diminished response to other people's needs and feelings C2. Diminished social interest, interrelatedness or personal warmth
D. Early perseverative, stereotyped or compulsive behaviour (one or more of D1-D3). D1. Simple repetitive movements D2. Complex, compulsive or ritualistic behaviours D3. Stereotypy of speech
E. Hyperorality and dietary changes (one or more of E1-E3) E1. Altered food preferences E2. Binge eating/increased consumption of alcohol or cigarettes E2. Oral exploration/consumption of inedible objects
F. Neuropsychological profile (all of F1-F3) F1. Deficits in executive tasks F2. Relative sparing of episodic memory F3. Relative sparing of visuospatial skills

Probable bvFTD
All of A-C must be present
A. Meets criteria for possible bvFTD
B. Significant functional decline
C. Imaging results consistent with bvFTD (one of C1-C2) C1. Frontal and/or anterior temporal atrophy on MRI or CT C2. Frontal and/or anterior temporal hypoperfusion/metabolism on PET/SPECT

Definite bvFTD
A must be present and B or C
A. Meets criteria for possible bvFTD B. Histopathological evidence of FTLD (biopsy or post-mortem)
C. Presence of a known pathogenic mutation *Early typically refers to symptom presentation within the first 3 years

Exclusion criteria: Pattern of deficits better accounted for by a non-degenerative nervous system or medical disorder, cognitive disturbance better accounted for by a psychiatric diagnosis or biomarkers indicative of Alzheimer's disease or other neurodegenerative process

Primary progressive aphasia (Gorno-Tempini *et al.*, 2011)

All of A-C must be present in all PPA subtypes
A. Most prominent clinical feature is difficulty with language
B. Language deficits are the principal cause of impaired activities of daily living
C. Aphasia is most prominent deficit at symptom onset and initial disease phases

Exclusion criteria
Pattern of deficits better accounted for by a non-degenerative nervous system or medical disorder
Cognitive disturbance better accounted for by a psychiatric diagnosis
Prominent initial episodic or visual memory or visuoperceptual impairments
Prominent initial behavioural disturbance

Non fluent variant primary progressive aphasia

At least one of A-B must be present
- A. Agrammatism
- B. Apraxia of speech

A least two of C-E must be present
- C. Impaired syntactic comprehension
- D. Spared single-word comprehension
- E. Spared object knowledge

Semantic variant primary progressive aphasia

Both A+B must be present
- A. Impaired confrontational naming
- B. Impaired single-word comprehension

At least three of C-F must be present
- C. Impaired object knowledge
- D. Surface dyslexia/dysgraphia
- E. Spared repetition
- F. Spared grammar and motor speech

Logopenic variant primary progressive aphasia

Both A+B must be present
- A. Impaired single word retrieval in spontaneous speech
- B. Impaired sentence repetition

At least three of C-F must be present
- C. Phonological errors
- D. Spared single word comprehension and object knowledge
- E. Spared motor speech
- F. Absence of frank agrammatism

Definite diagnosis requires a clinical diagnosis and either histopathological confirmation or presence of a known pathogenic mutation

Progressive supranuclear palsy (Höglinger *et al.*, 2017)

All of A-C must be present for all diagnoses
A. Sporadic occurrence B. Age greater than 40 at first symptom C. Gradual progression of symptoms

Possible PSP-RS
Both A+B must be present A. Slow velocity of vertical saccades B. More than two steps backwards on the pull test within 3 years of symptom onset

Probable PSP-RS
One of A-B must be present A. Vertical supranuclear gaze palsy B. Slow velocity of vertical saccades
One of C-D must be present C. Frequent unprovoked falls within 3 years D. Tendency to fall on pull test within 3 years

Probable PSP-F
One of A-B must be present
A. Vertical supranuclear gaze palsy
B. Slow velocity of vertical saccades
Three of C-G must be present C. Apathy D. Bradyphrenia E. Dysexecutive syndrome F. Reduced verbal fluency G. Impulsivity, disinhibition or perseveration

Possible PSP-CBS
One of A-B must be present A. Vertical supranuclear gaze palsy B. Slow velocity of vertical saccades
One of C-E must be present (asymmetric or symmetric) C. Orobuccal or limb apraxia D. Cortical sensory loss E. Alien limb phenomena
One of F-H must be present (asymmetric or symmetric) F. Limb rigidity G. Limb akinesia H. Limb myoclonus

Possible PSP-SL
One of A-B must be present A. Vertical supranuclear gaze palsy B. Slow velocity of vertical saccades
One of C-D must be present C. Meets criteria for non-fluent variant primary progressive aphasia D. Progressive apraxia of speech

Definite PSP
Neuropathological diagnosis with any clinical presentation

Exclusion criteria
There are 10 absolute and 25 relative exclusion criteria. See Höglinger et al. 2017 for details Important exclusion criteria include: A. Prominent episodic memory impairment suggestive of Alzheimer's Disease B. Prominent autonomic failure suggestive of multiple system atrophy of Lewy body disease C. Prominent, unexplained visual hallucinations or fluctuations in alertness D. Sudden onset or stepwise progression of symptoms suggestive of vascular aetiology

There are eight PSP subtypes, each with possible and probable criteria, only a selection are shown here. See Höglinger et al. 2017 for details

Patients may meet criteria for several PSP subtypes, in which case the Multiple Allocations eXtintion (MAX) rules criteria (Grimm et al. 2019) suggest that a diagnosis of PSP-RS and/or higher levels of diagnostic certainty are prioritised

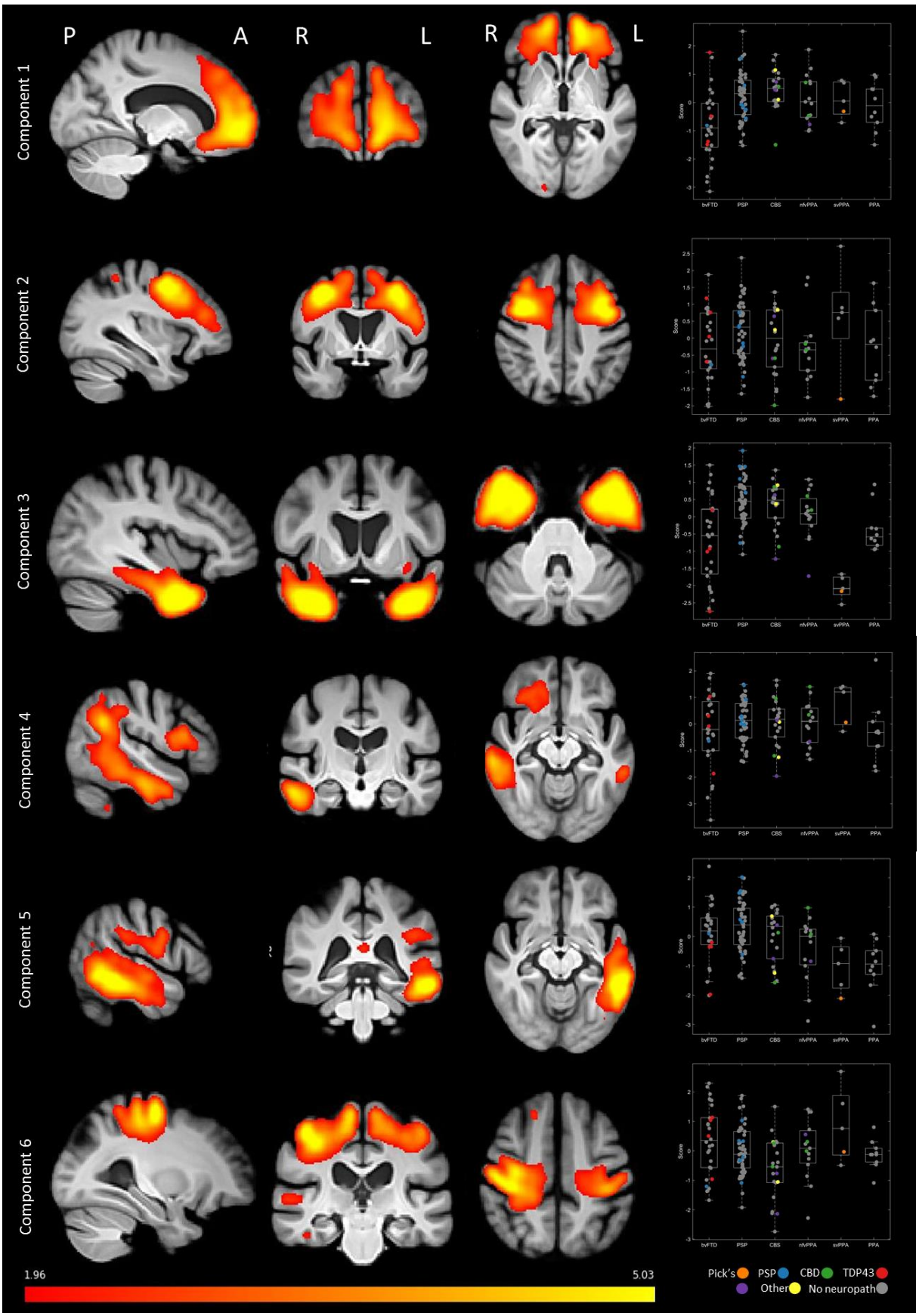
Corticobasal syndrome (Armstrong *et al.*, 2013*a*)

Probable CBS
Both A+B must be present A. Asymmetric presentation of two or more of A1-A3 A1. Limb rigidity or akinesia A2. Limb dystonia A3. Limb myoclonus B. Two or more of B1-3 B1. Limb or orobuccal apraxia B2. Cortical sensory deficit B3. Alien limb phenomena (more than simple levitation)

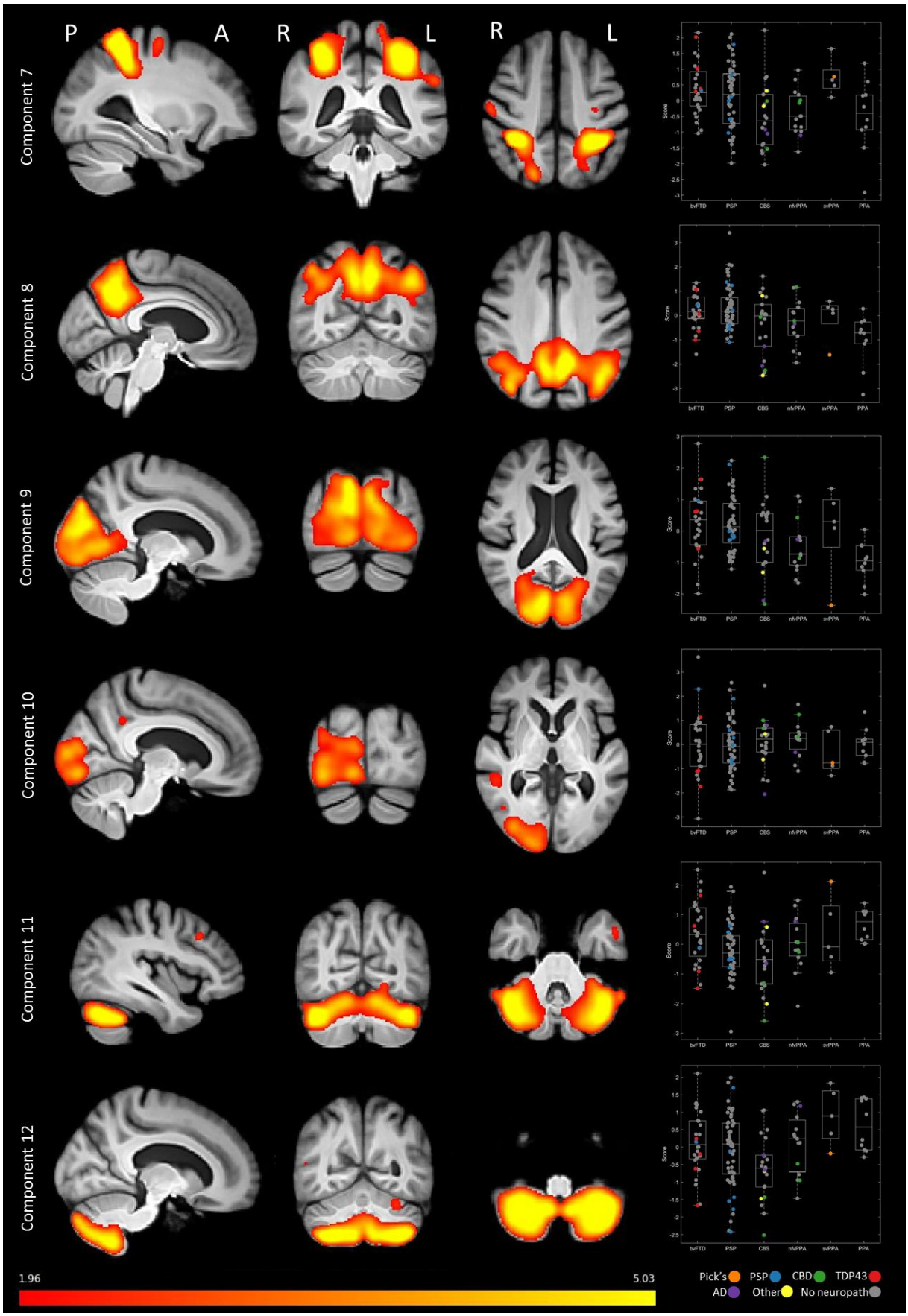
Possible CBS
Both A+B must be present A. Asymmetric or symmetric presentation of one or more of A1-A3 A1. Limb rigidity or akinesia A2. Limb dystonia A3. Limb myoclonus

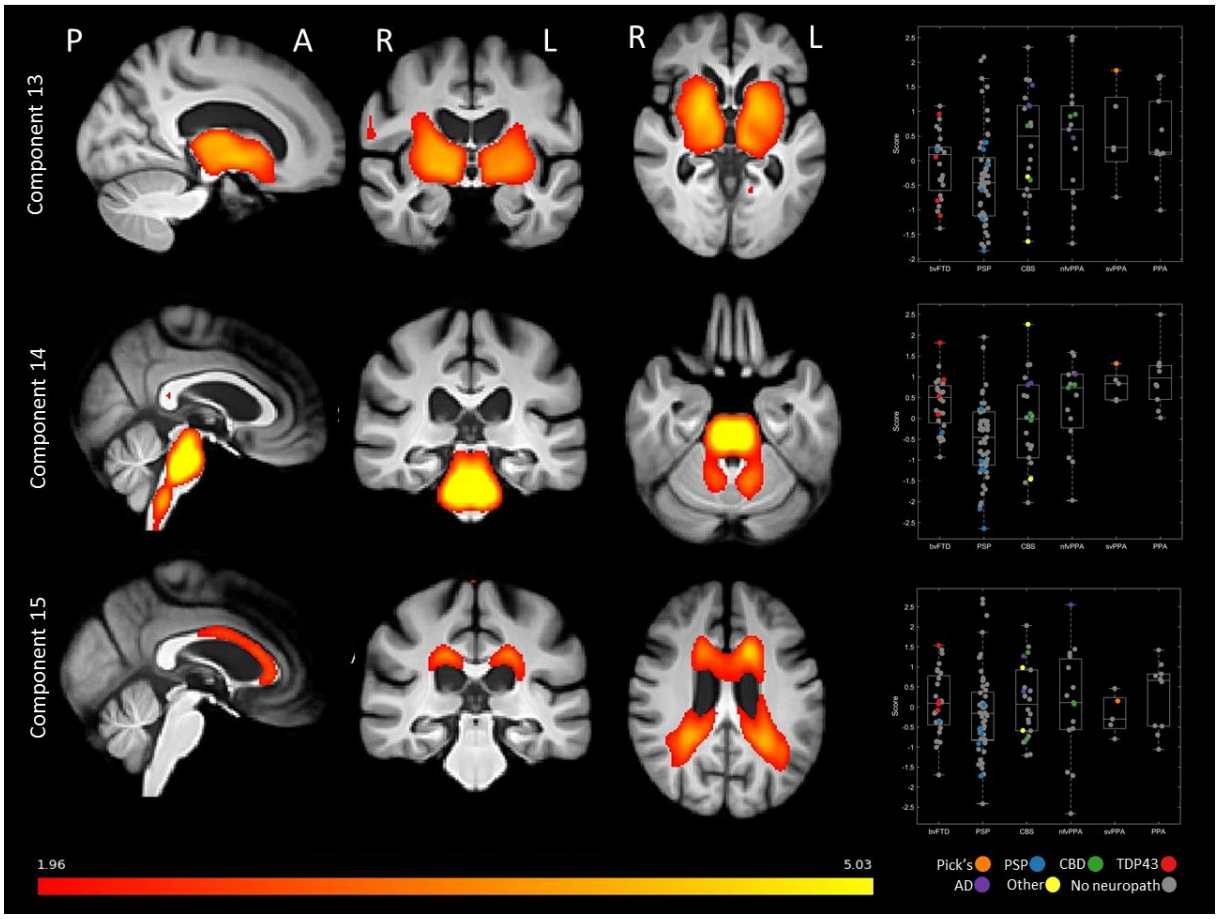
Definite Corticobasal degeneration (CBD)
Neuropathological diagnosis

Appendix 2: Neuropathology of imaging components

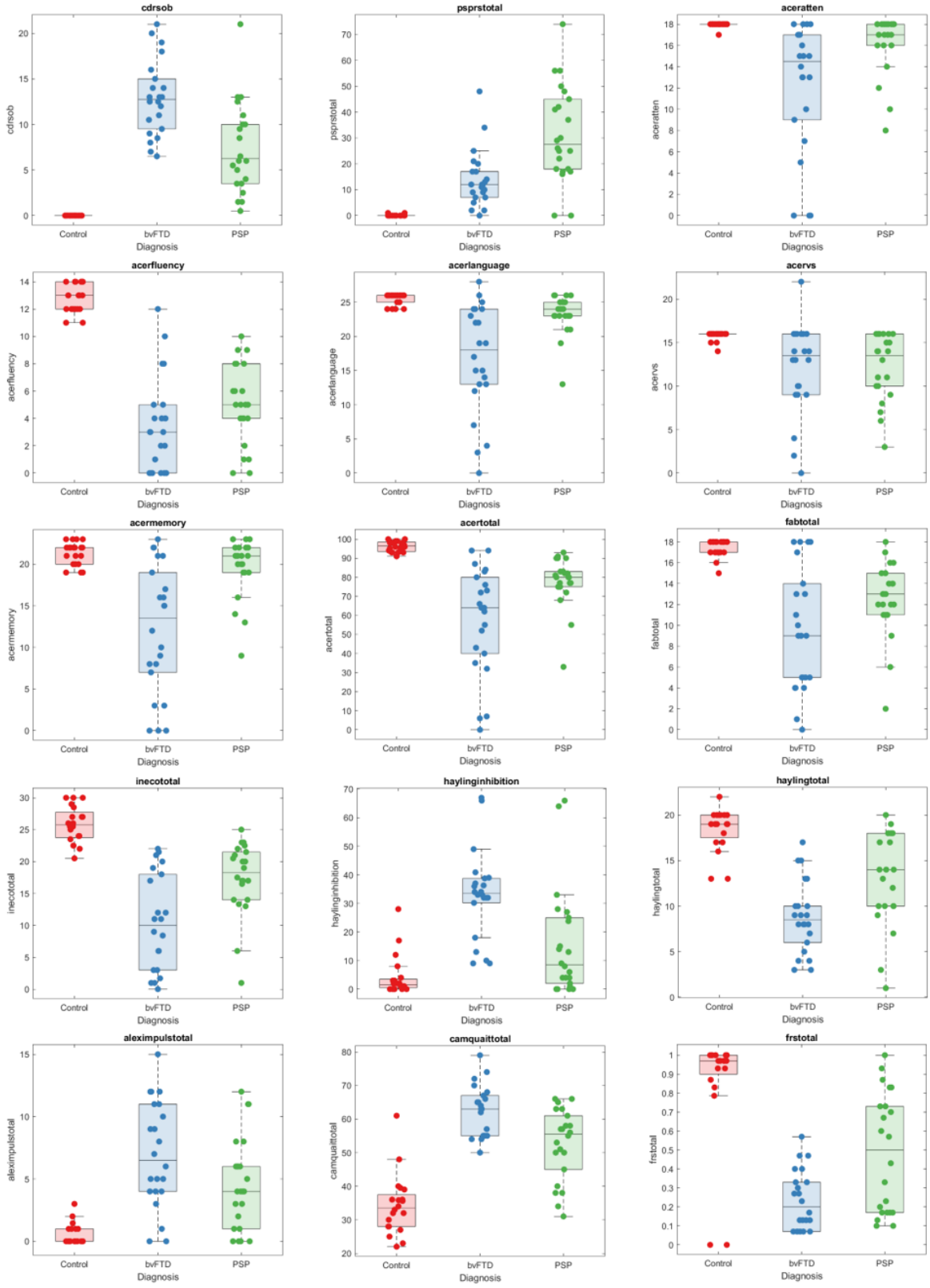

P
A
R
L
R
L
Component 1
Component 2
Component 3
Component 4
Component 5
Component 6
Score
bvFTD
PSP
CBS
nfvPPA
svPPA
PPA
1.96
5.03
Pick's
PSP
CBD
TDP43
Other
No neuropath

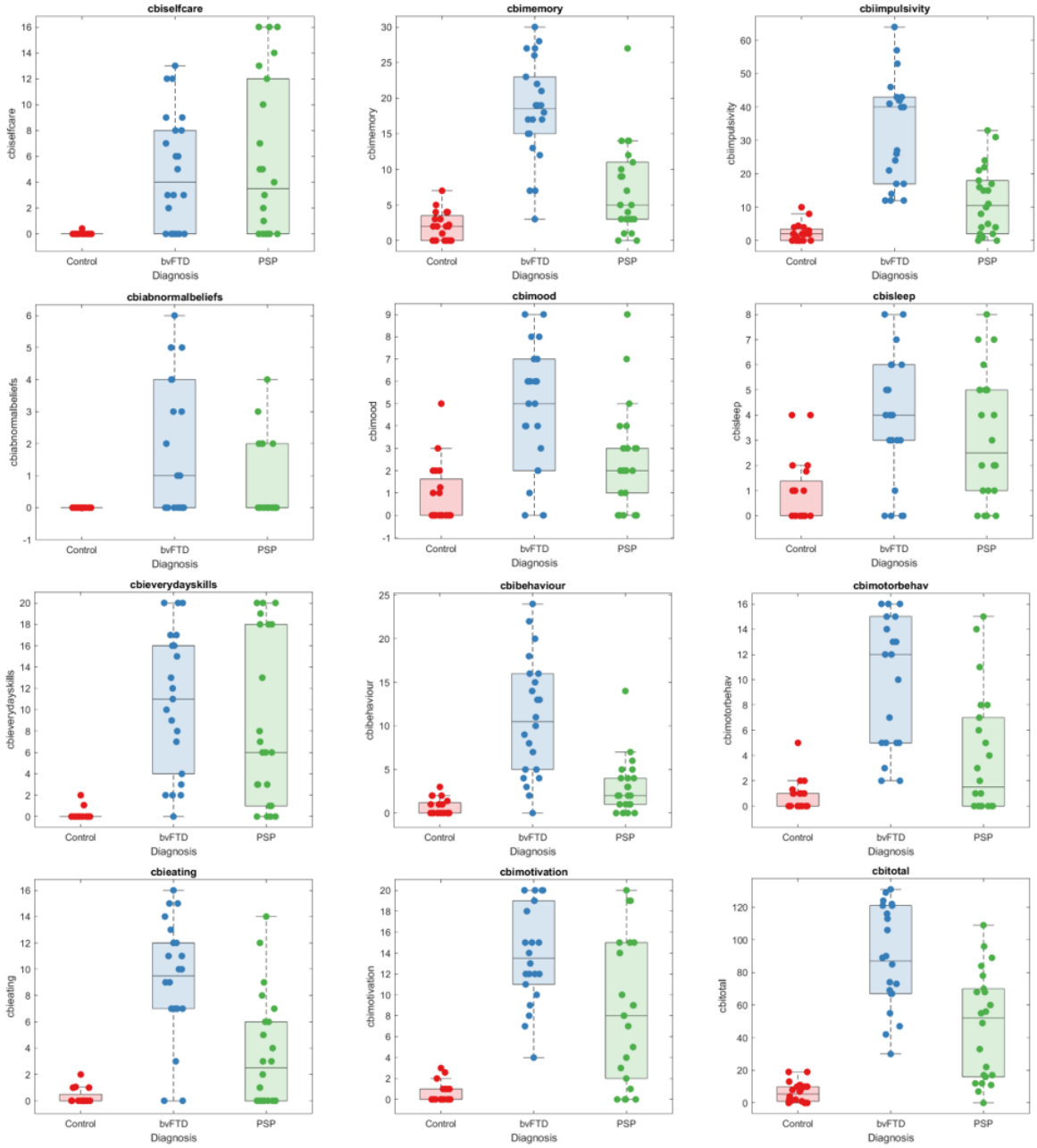
Appendix 2: Neuropathology of imaging components




P
A
R
L
R
L
Component 13
Component 14
Component 15
Score
bvFTD
PSP
CBS
nfvPPA
svPPA
PPA
1.96
5.03
Pick's
PSP
CBD
TDP43
AD
Other
No neuropath

Appendix 3: Neuropsychology results by FTLD subgroup




cbiselfcare
cbiselfcare
Control
bvFTD
PSP
Diagnosis
cbimemory
cbimemory
Control
bvFTD
PSP
Diagnosis
cbiimpulsivity
cbiimpulsivity
Control
bvFTD
PSP
Diagnosis
cbiabnormalbeliefs
cbiabnormalbeliefs
Control
bvFTD
PSP
Diagnosis
cbimood
cbimood
Control
bvFTD
PSP
Diagnosis
cbisleep
cbisleep
Control
bvFTD
PSP
Diagnosis
cbieverydayskills
cbieverydayskills
Control
bvFTD
PSP
Diagnosis
cbibehaviour
cbibehaviour
Control
bvFTD
PSP
Diagnosis
cbimotorbehav
cbimotorbehav
Control
bvFTD
PSP
Diagnosis
cbieating
cbieating
Control
bvFTD
PSP
Diagnosis
cbimotivation
cbimotivation
Control
bvFTD
PSP
Diagnosis
cbitotal
cbitotal
Control
bvFTD
PSP
Diagnosis

Test	Control	bvFTD	PSP	F	p value	bvFTD vs Control		PSP vs Control		bvFTD vs PSP	
	mean (SD)					mean diff	p value	mean diff	p value	mean diff	p value
FTLD CDR SOB	0 (0)	12.86 (4.09)	7.32 (4.9)	61.95	2.05E-15	12.86	**2.05E-15**	7.32	**1.00E-07**	5.55	**2.11E-05**
PSPRS Total	0.1 (0.31)	13.95 (10.98)	31.45 (18.59)	32.38	2.61E-10	13.85	**2.61E-10**	31.35	**1.08E-09**	-17.5	**6.86E-05**
ACER Attention	17.95 (0.22)	12.18 (6.12)	16.23 (2.79)	11.95	4.19E-05	-5.77	**4.19E-05**	-1.72	3.41E-01	-4.05	3.41E-03
ACER Memory	21.3 (1.38)	12.14 (7.78)	19.59 (3.58)	19.69	2.52E-07	-9.16	**2.52E-07**	-1.71	5.25E-01	-7.45	**2.49E-05**
ACER Fluency	12.85 (1.04)	3.55 (3.42)	5 (2.94)	70.45	1.40E-16	-9.3	**1.40E-16**	-7.85	**9.57E-10**	-1.45	1.85E-01
ACER Language	25.5 (0.83)	16.77 (7.97)	23.27 (2.91)	17.54	9.58E-07	-8.73	**9.58E-07**	-2.23	3.26E-01	-6.5	**1.76E-04**
ACER Visuospatial	15.8 (0.52)	12.18 (5.21)	12.14 (3.81)	6.32	3.19E-03	-3.62	3.19E-03	-3.66	7.59E-03	0.05	9.99E-01
ACER Total	96.2 (2.71)	57.68 (28.1)	77.91 (13.17)	23.36	2.93E-08	-38.52	**2.93E-08**	-18.29	5.42E-03	-20.23	1.46E-03
FAB	17.45 (0.83)	9.55 (5.89)	12.55 (3.57)	20.06	2.01E-07	-7.9	**2.01E-07**	-4.9	6.88E-04	-3	4.49E-02
Hayling (A+B score)	4.3 (7.12)	33.15 (15.41)	15.76 (19.03)	20.05	2.03E-07	28.85	**2.03E-07**	11.46	4.06E-02	17.38	7.78E-04
Hayling Total	18.45 (2.28)	8.82 (3.94)	13 (5.14)	30.38	7.01E-10	-9.63	**7.01E-10**	-5.45	**1.27E-04**	-4.18	2.78E-03
INECO	25.78 (2.83)	10.44 (7.49)	17.45 (5.7)	37.39	2.51E-11	-15.34	**2.51E-11**	-8.33	**4.58E-05**	-7.01	**4.29E-04**

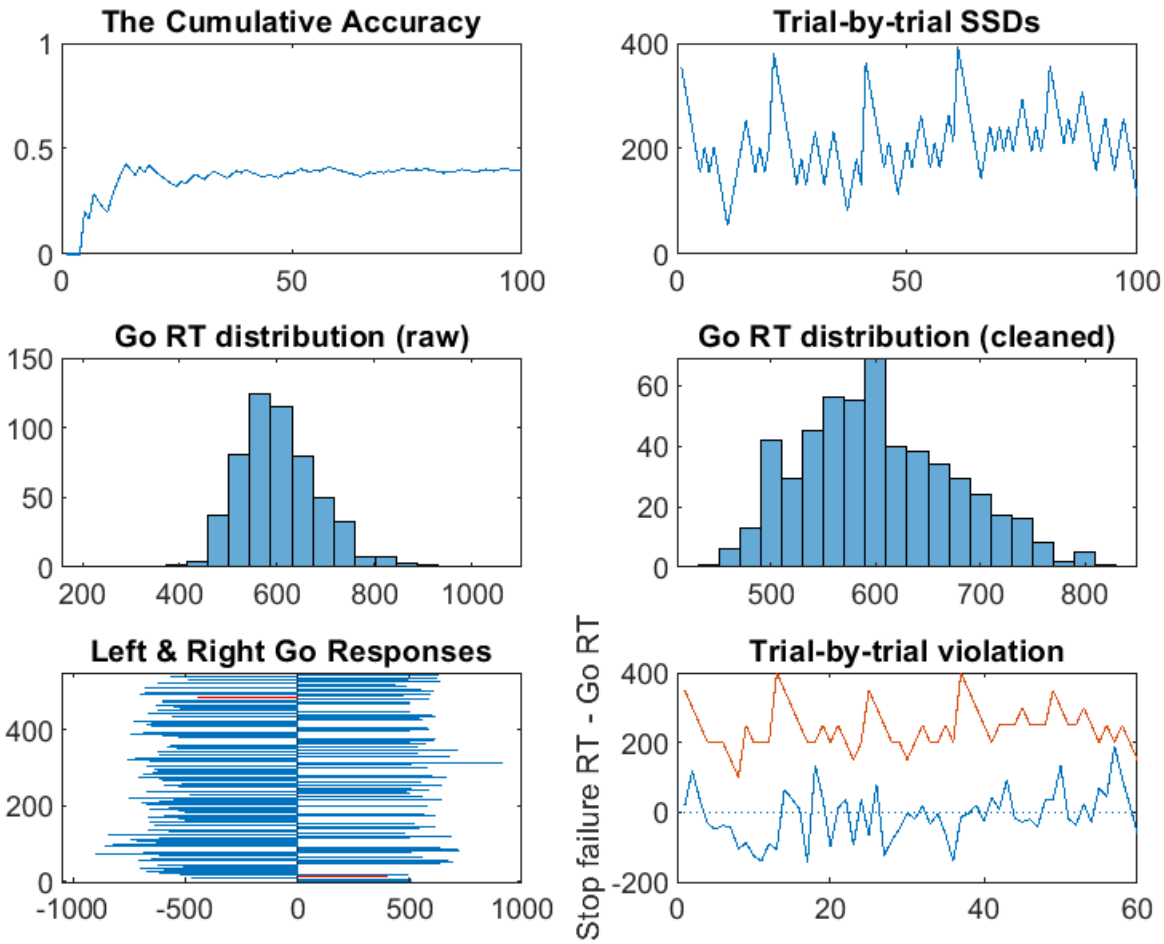
CBI Memory	2.06 (2.01)	18.27 (7.14)	7.18 (6.44)	44.08	1.43E-12	16.21	**1.43E-12**	5.12	1.49E-02	11.09	**7.61E-08**
CBI Everyday skills	0.15 (0.5)	10.68 (6.51)	8.64 (7.9)	17.81	8.10E-07	10.53	**8.10E-07**	8.48	**7.27E-05**	2.05	5.01E-01
CBI Selfcare	0.02 (0.09)	4.82 (4.44)	5.64 (6.2)	9.5	2.56E-04	4.8	**2.56E-04**	5.62	**4.08E-04**	-0.82	8.17E-01
CBI Behaviour	0.72 (0.93)	10.86 (6.79)	3.05 (3.18)	30.72	5.89E-10	10.14	**5.89E-10**	2.33	2.14E-01	7.82	**6.20E-07**
CBI Mood	0.86 (1.35)	4.64 (2.89)	2.55 (2.3)	14.29	8.15E-06	3.77	**8.15E-06**	1.68	5.34E-02	2.09	1.01E-02
CBI Abnormal beliefs	0 (0)	1.82 (2.13)	0.68 (1.21)	8.64	4.97E-04	1.82	**4.97E-04**	0.68	2.81E-01	1.14	2.93E-02
CBI Eating	0.3 (0.57)	9.18 (4.43)	3.68 (4.21)	32.78	2.15E-10	8.88	**2.15E-10**	3.38	9.66E-03	5.5	**1.18E-05**
CBI Sleep	0.89 (1.28)	3.77 (2.51)	3.18 (2.54)	9.81	2.02E-04	2.88	**2.02E-04**	2.29	3.85E-03	0.59	6.51E-01
CBI Motor behaviour	0.77 (1.21)	10.27 (4.99)	3.86 (4.79)	29.47	1.11E-09	9.51	**1.11E-09**	3.1	4.61E-02	6.41	**8.26E-06**
CBI Motivation/apathy	0.58 (0.94)	13.86 (4.7)	8.32 (6.78)	39.17	1.14E-11	13.28	**1.14E-11**	7.74	**8.93E-06**	5.55	1.04E-03
CBI Impulsivity*	2.32 (2.73)	33.91 (16.21)	11.82 (10.12)	43.63	1.73E-12	31.59	**1.73E-12**	9.5	2.30E-02	22.09	**5.56E-08**
CBI Total	6.35 (6.13)	88.18 (31)	46.77 (33.24)	48.58	2.40E-13	81.83	**2.40E-13**	40.42	**2.48E-05**	41.41	**1.02E-05**
FRS Total (Logit)	0.86 (0.3)	0.23 (0.16)	0.48 (0.31)	29.3	1.21E-09	-0.62	**1.21E-09**	-0.37	**7.25E-05**	-0.25	7.34E-03

Neuropsychological tests: Neuropsychology of FTLD syndromes (bvFTD and PSP). CDR-FTLD SOB: Clinical Dementia Rating scaling sum of boxes modified for FTLD. PSPRS: Progressive Supranuclear Palsy rating scale. ACER: Addenbrooke's Cognitive Examination-Revised. FAB: Frontal Assessment Battery. CBIR: Cambridge Behavioural Inventory Revised. FRS: Frontotemporal Dementia Rating Scale. *CBI Impulsivity score calculated from all items from the disinhibited, challenging, motor, eating and insight subscales and the euphoria items from the mood subscale (Borroni *et al*, 2012). P values in bold remain significant ($p<0.05$) after Bonferroni correction ($6.6x10^{-04}$).

Appendix 4: Stop No-Go Task Results

	Control	FTLD (bvFTD+PSP)	bvFTD	PSP
Total trials (n)	670.05 (92.36)	663.14 (97.91)	636.47 (122.34)	687 (63.76)
Go correct (n)	520.7 (68.56)	489.00 (81.90)	467.77 (99.91)	508 (57.99)
Go incorrect (n)	6.8 (6.13)	29.28 (42.16)	27.88 (53.34)	30.53 (30.4)
Go Omission (n)	0.05 (0.22)	4.42 (15.52)	7.53 (22.31)	1.63 (2.99)
NoGo Correct (n)	45.4 (7.98)	42.11 (15.61)	37.53 (15.24)	46.21 (15.17)
NoGo incorrect (n)	2.1 (3.6)	6.08 (9.06)	6.88 (10.21)	5.37 (8.12)
Stop correct (n)	41.45 (8.78)	30.64 (10.43)	31.47 (12.02)	29.9 (9.04)
Stop failed/incorrect (n)	53.55 (8.19)	61.61 (11.66)	57.41 (11.95)	65.37 (10.29)
Go correct reaction time (ms)	641.77 (124.3)	1082.64 (344.61)	1023.6 (335.87)	1135.46 (352.71)
Go error rate	0.01 (0.01)	0.06 (0.09)	0.07 (0.12)	0.06 (0.06)
NoGo error rate	0.04 (0.07)	0.14 (0.22)	0.18 (0.27)	0.11 (0.16)
Stop accuracy rate	0.43 (0.04)	0.33 (0.09)	0.35 (0.1)	0.31 (0.08)

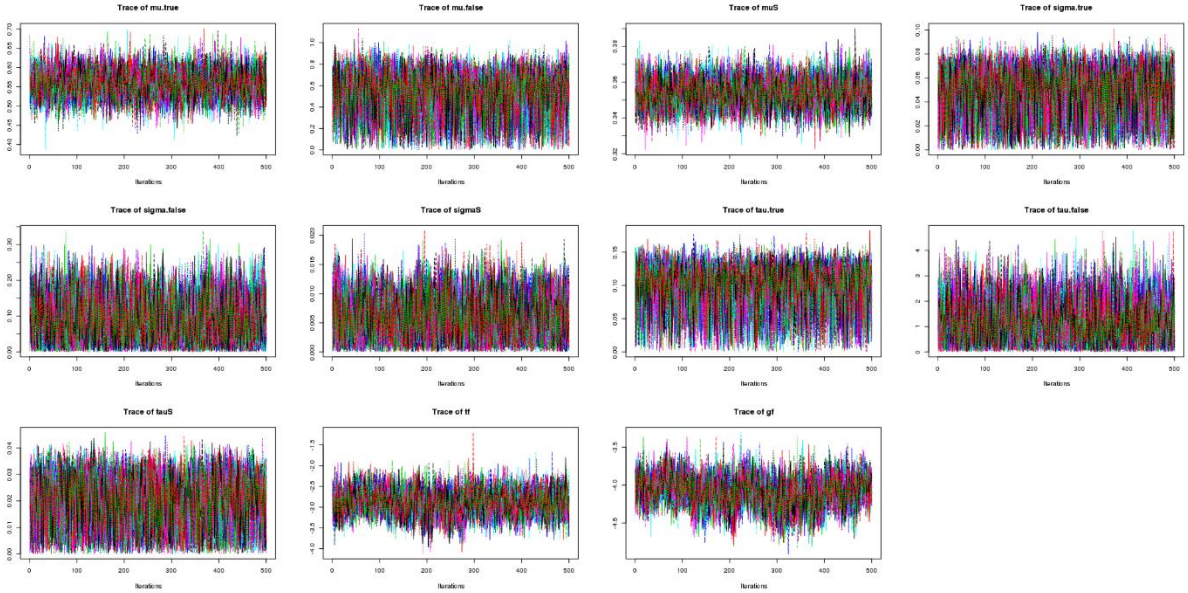
Table of stop no-go behavioural results. Each cell contains mean and (standard deviation).



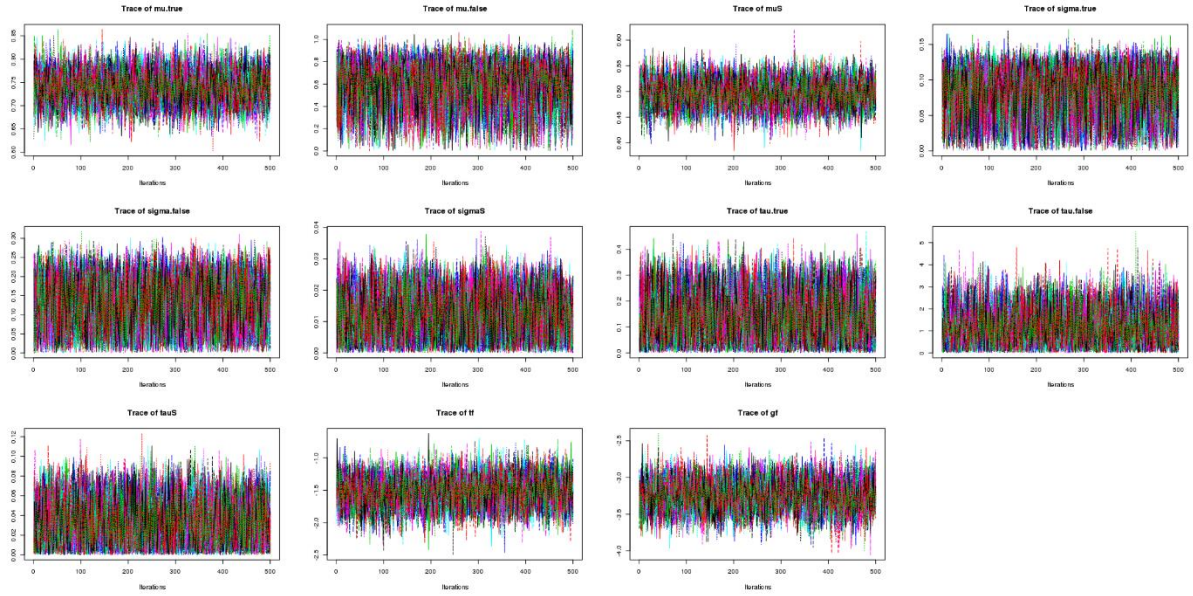
Example quality assurance plot for one FTLD participant. Top left: Cumulative accuracy (x axis: trial number, y axis: accuracy). Top right: Trial by Trial stop signal delay (SSD) (x axis: trial number, y axis: SSD). Middle left: Go reaction time distribution, unedited. Middle right: Go reaction time distribution after outliers removed. Bottom right: Trial-by-trial go responses (correct=blue, incorrect=red). Bottom right: Test of trial-by-trial violations, red line=SSD, blue line=stop failure reaction time- preceding go reaction time.

Appendix 5: Dynamic models of choice model fits

MCMC chains – Control model

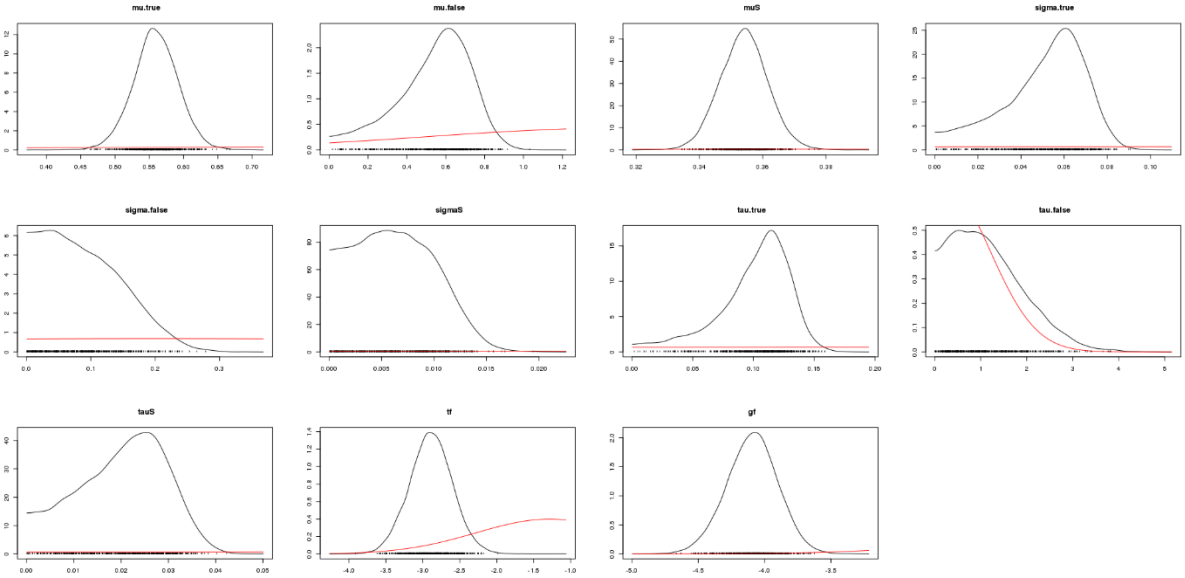


MCMC chains – FTLD model

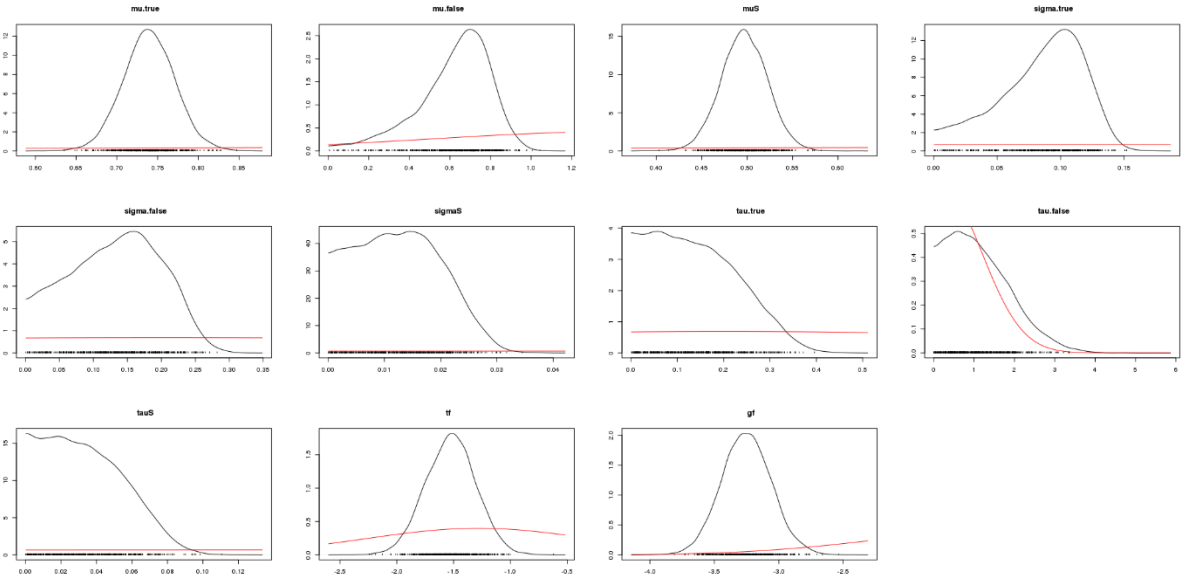


Prior and posterior density plots

Controls

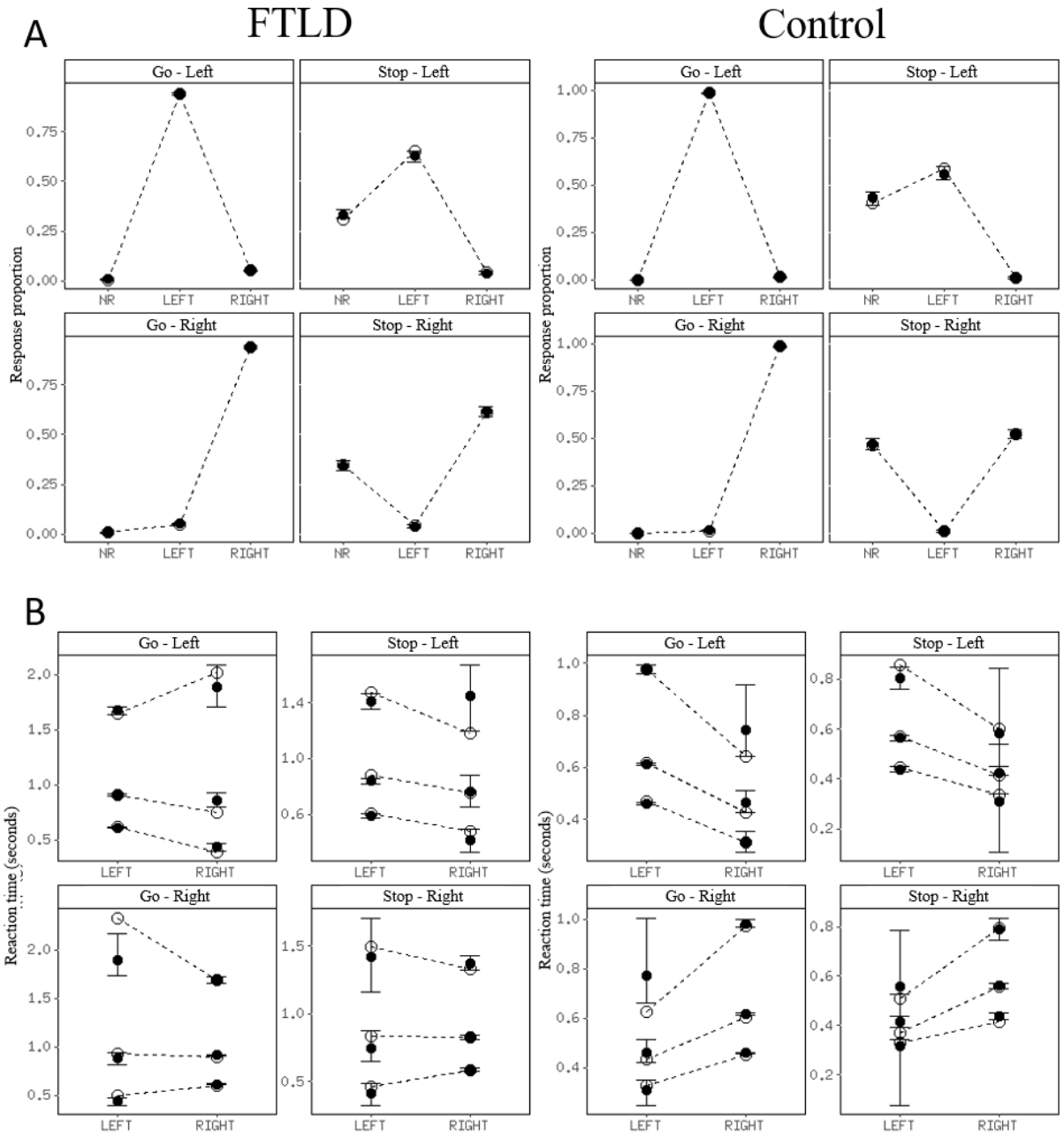


FTLD

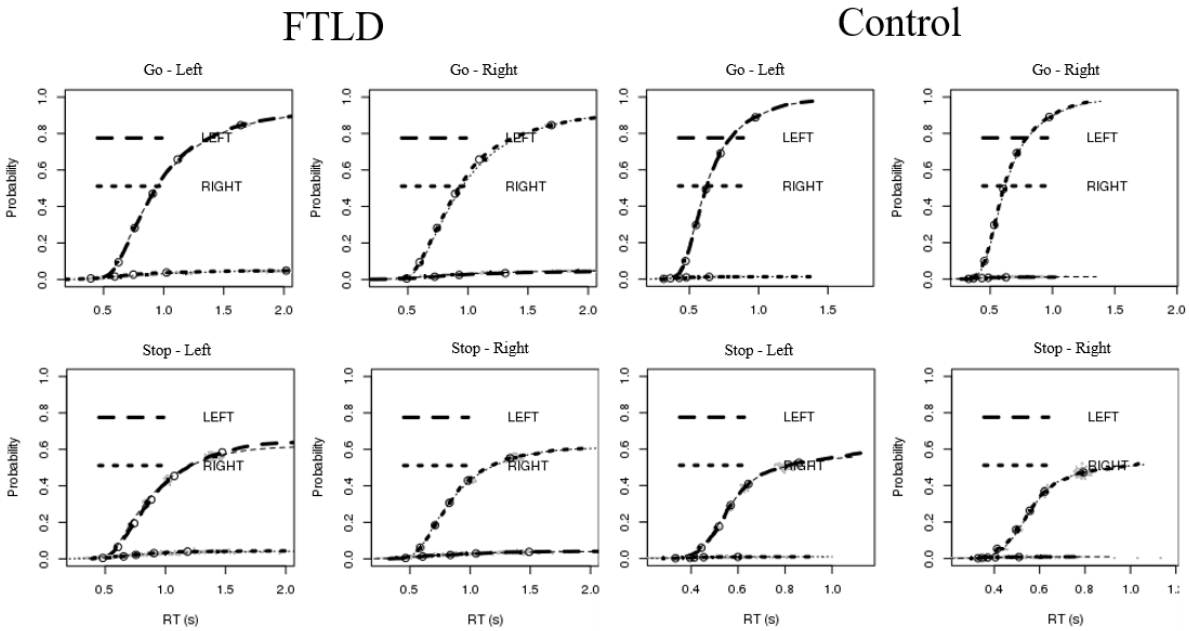


Hyper-prior (red lines) and posterior (black peaked lines) distributions for the population means.

Goodness of fit results

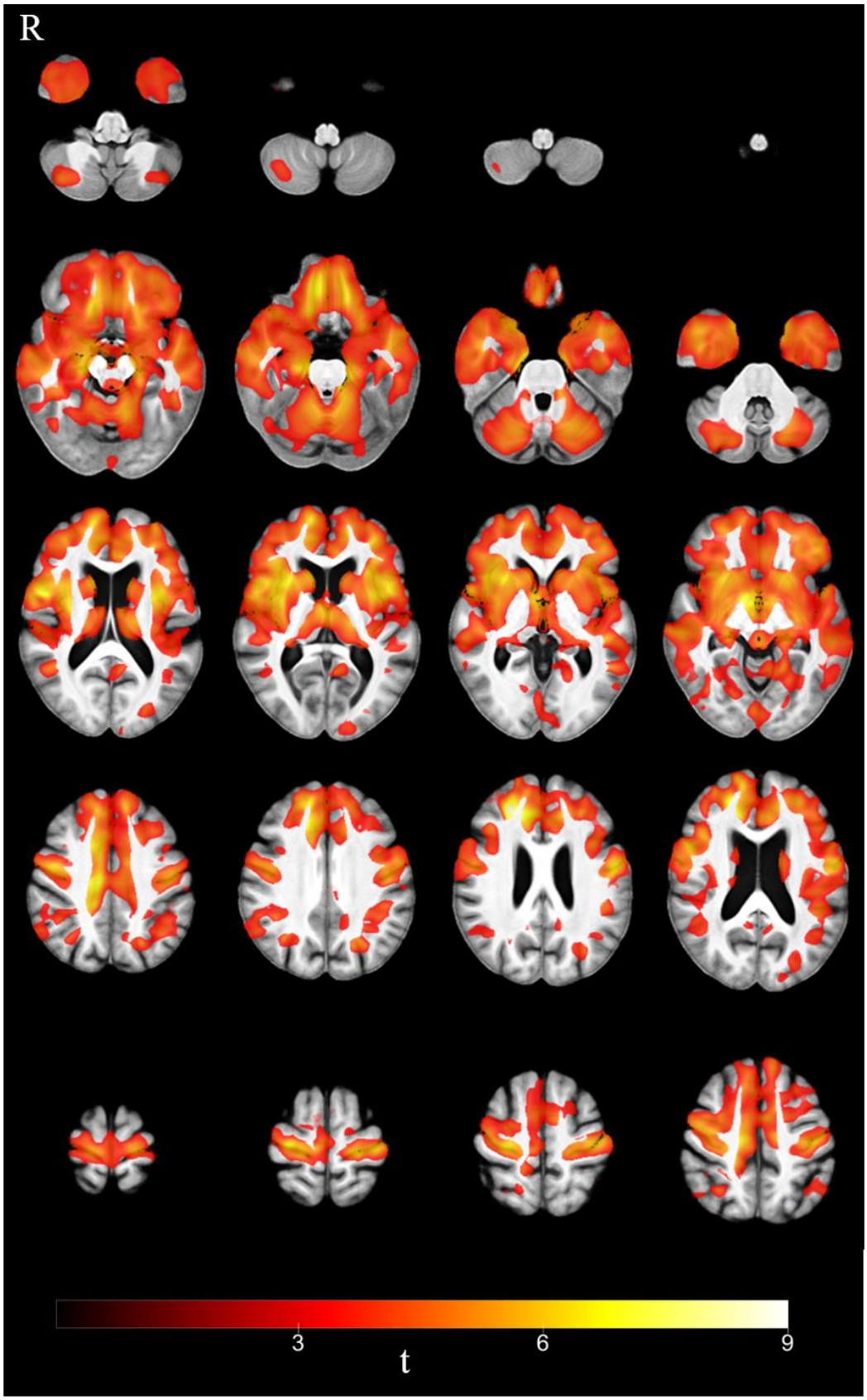


Goodness of fit functions test if the model accurately represents the data by comparing experimentally acquired data to simulated results from the model. A: Response proportions (NR=non-response). B: Response time percentiles. The three lines correspond to the 10th, 50th, and 90th percentiles. Dashed line and open points represent the data. Solid points represent medians of the model prediction. Error bars show the 95% credible intervals. The figures show average results over all participants.

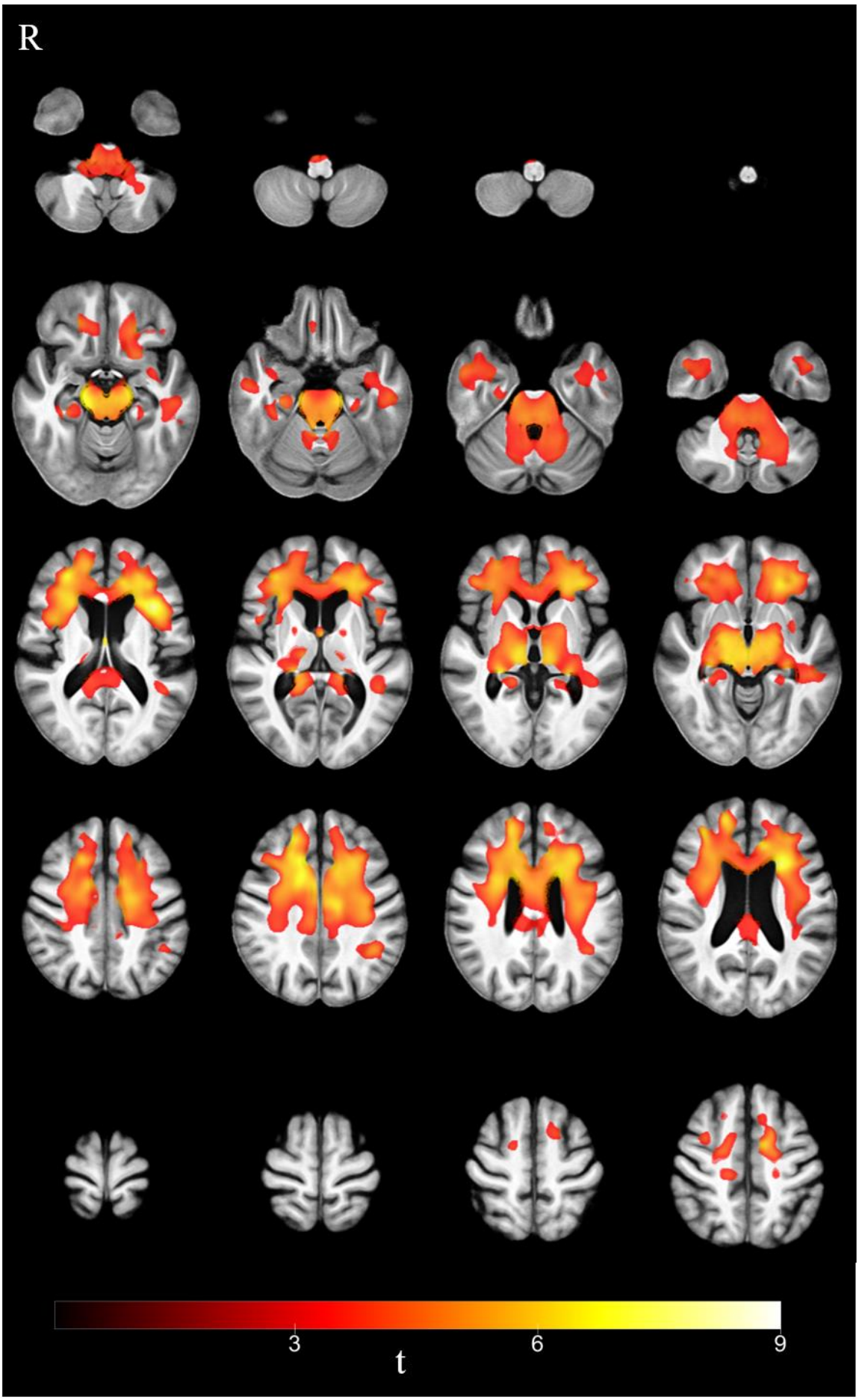


Cumulative distribution probability functions. Thick lines represent the data, thin lines represent model predictions. Open points mark the 10th, 30th, 50th, 70th, and 90th percentiles. The clusters of gray dots represent the uncertainty in the percentiles from 100 randomly selected samples from the joint posterior

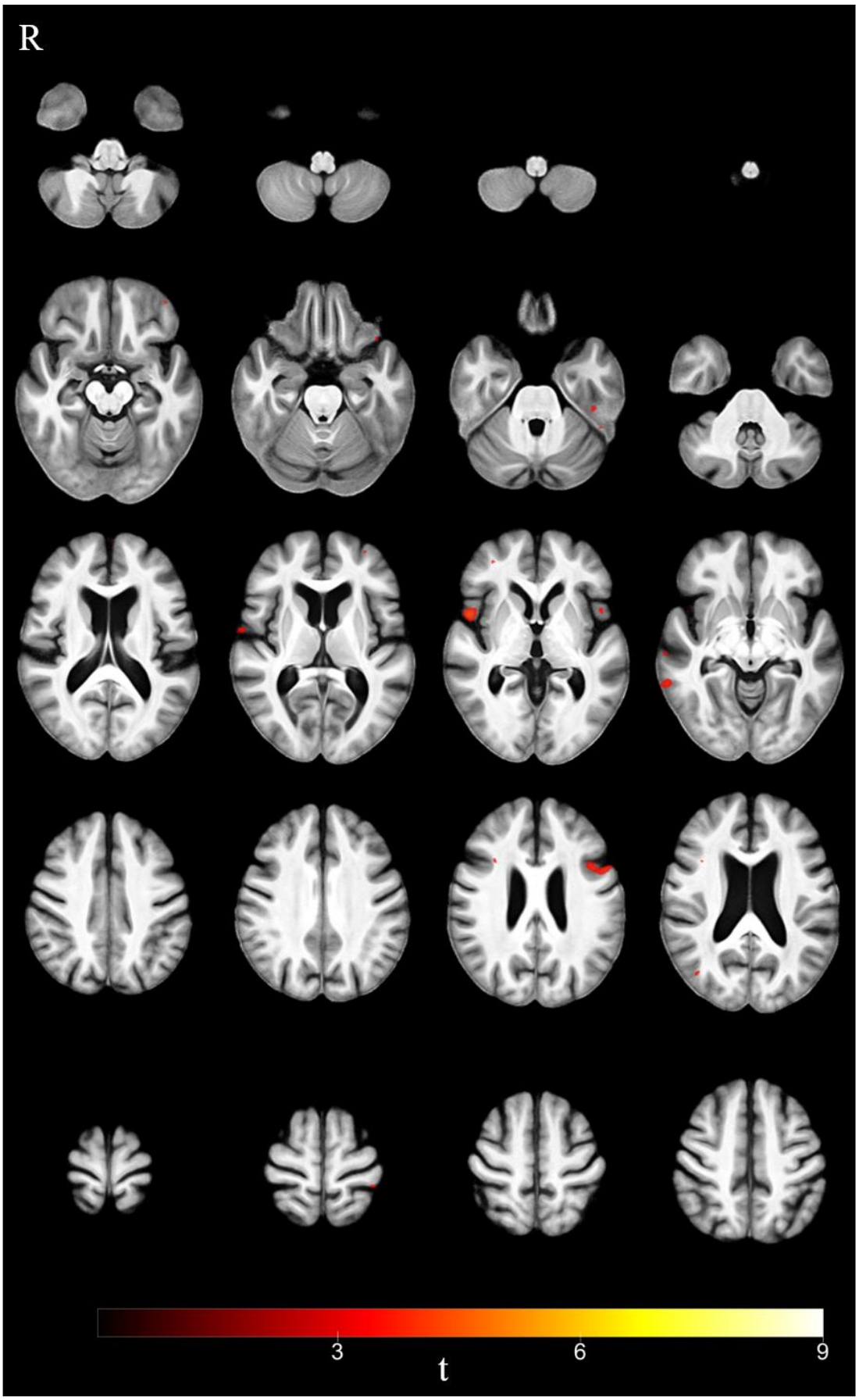
Appendix 6: 7T Voxel Based Morphometry



Axial view of grey matter volume Control>FTLD

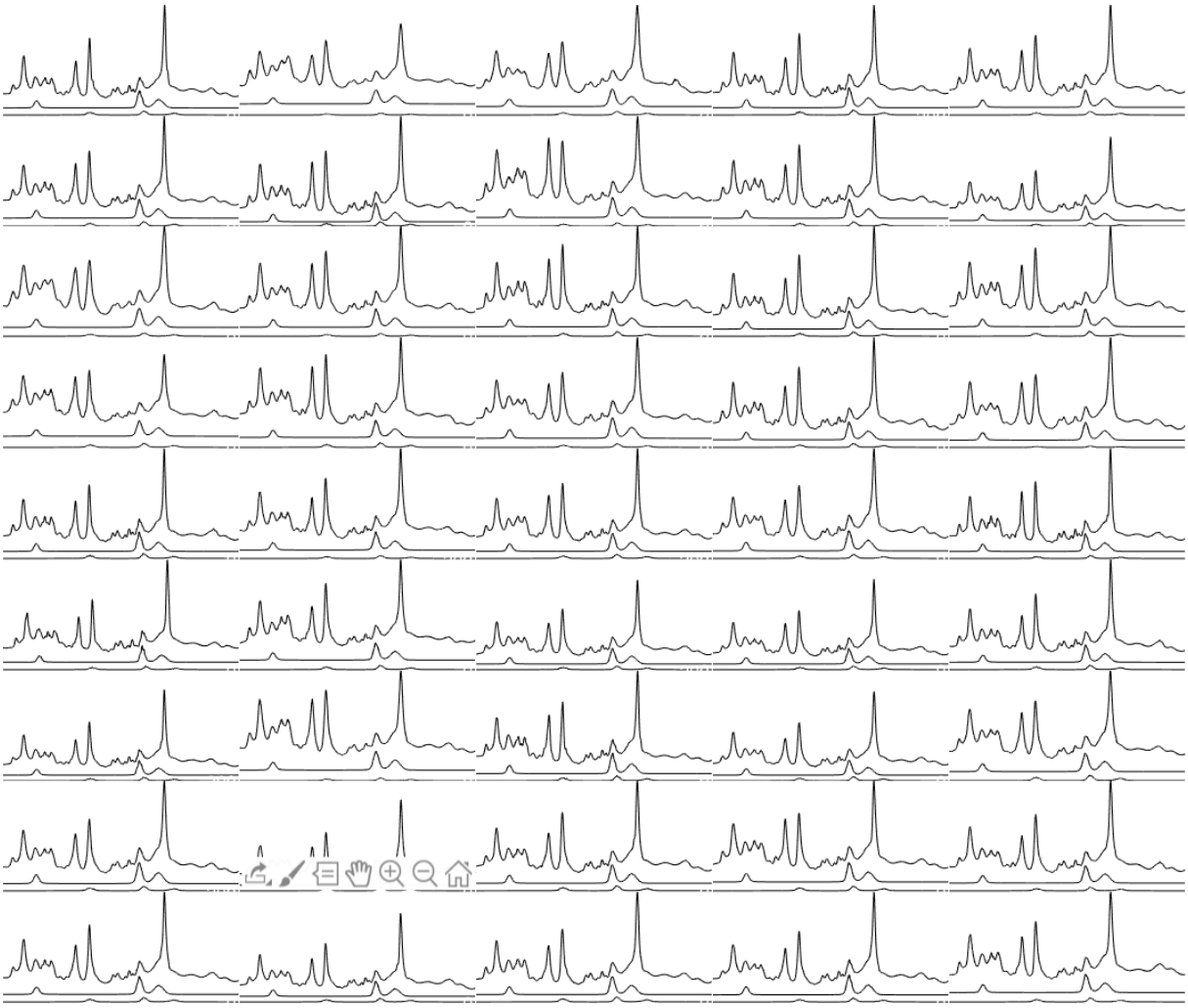


Axial view of white matter volume Control>FTLD

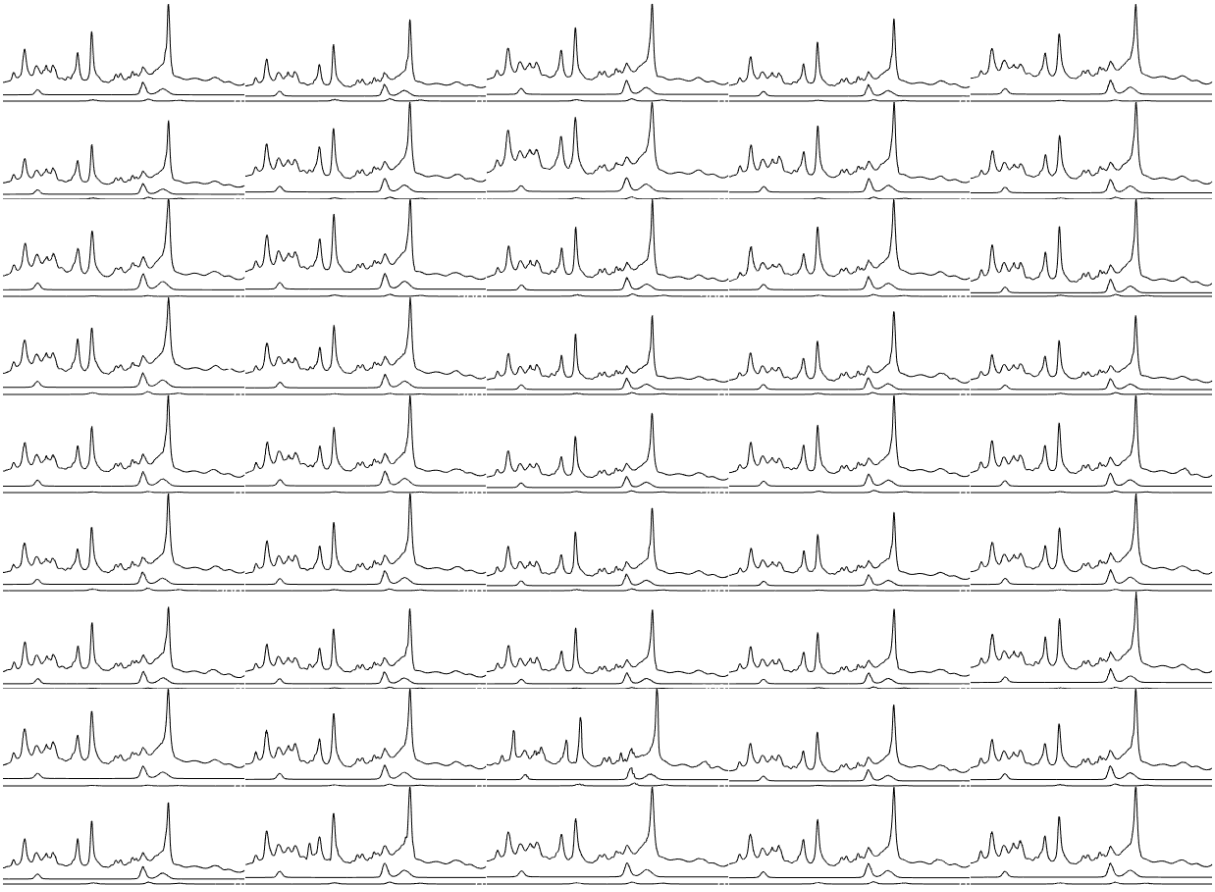


Axial view of grey matter volume conjunction of Control>bvFTD and Control>PSP. Voxels are p<0.001 uncorrected

Appendix 7: Individual MRS spectra

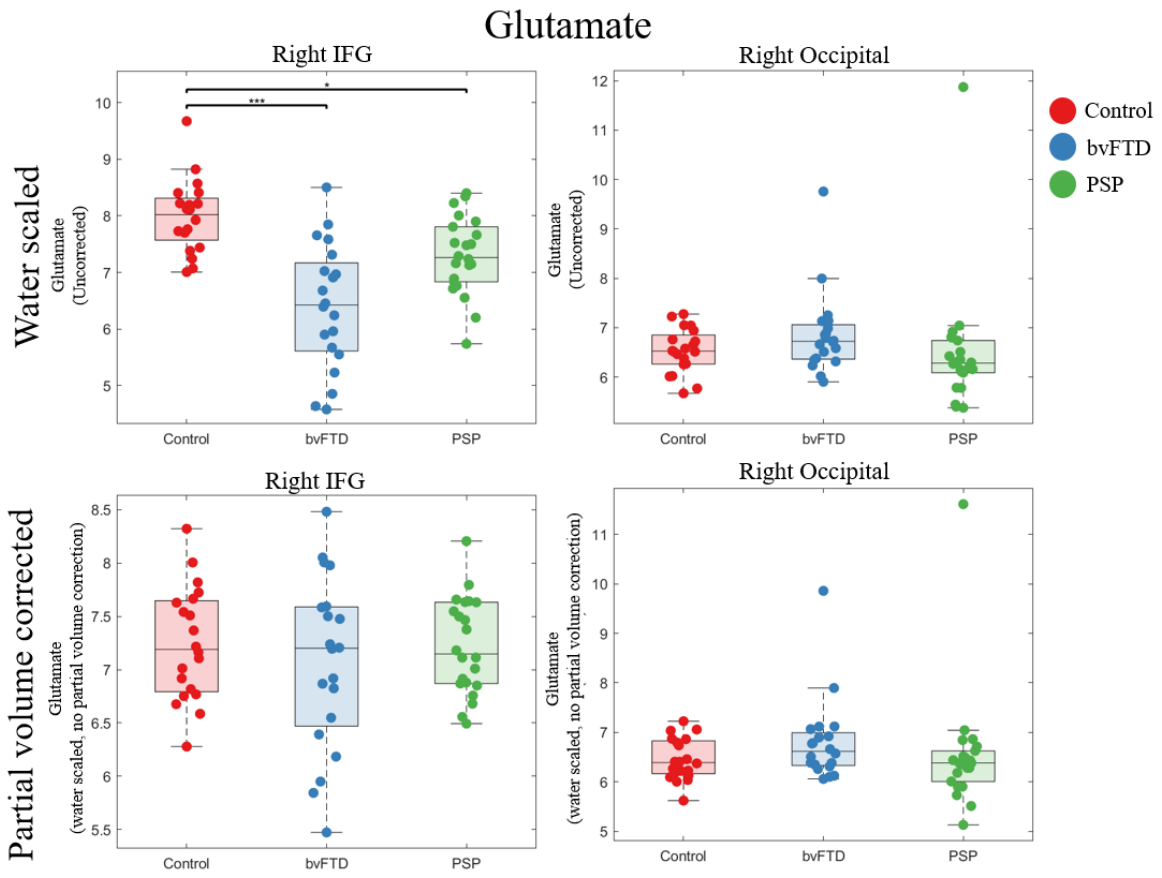


All individual spectra from the right inferior frontal gyrus voxel. Top line is the whole fit, the middle line is the glutamate fit and the bottom line the GABA fit.

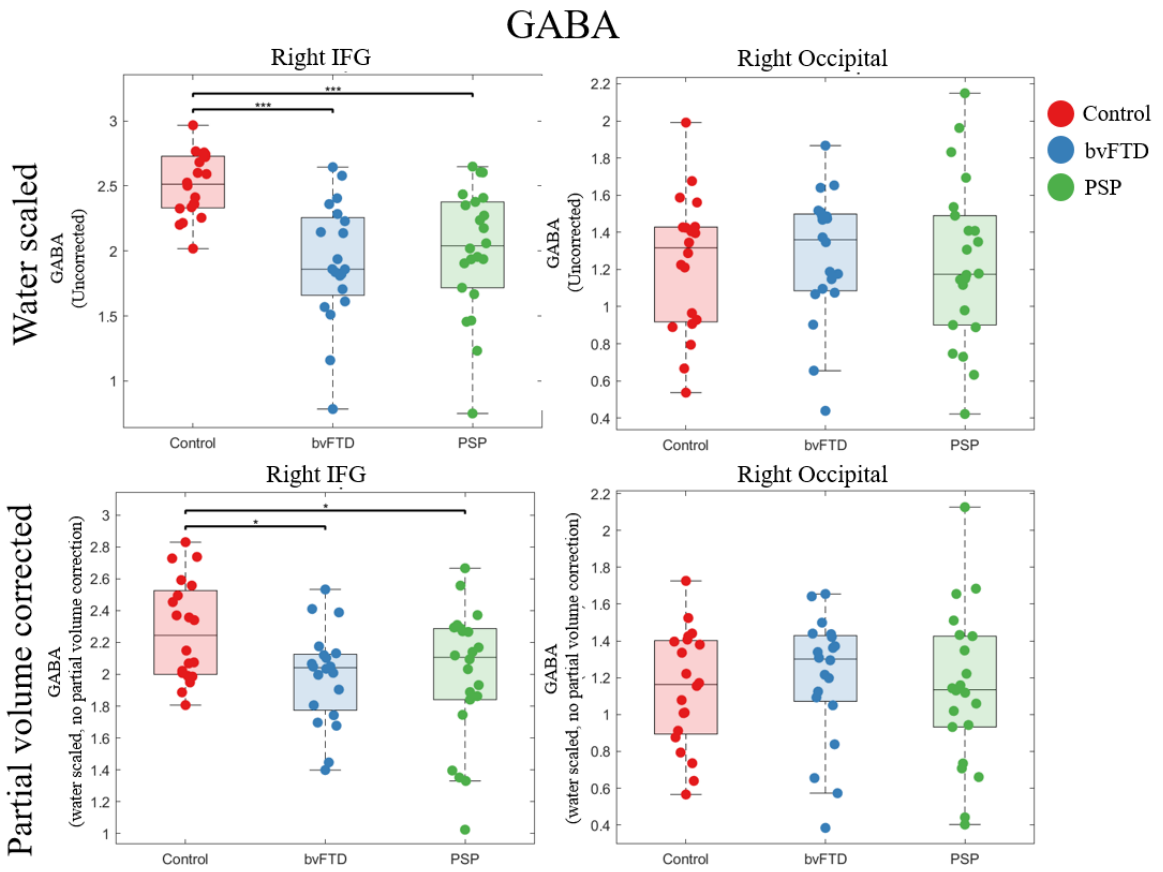


All individual spectra from the right inferior frontal gyrus voxel. Top line is the whole fit, the middle line is the glutamate fit and the bottom line the GABA fit.

Appendix 8: MRS results by FTLD syndrome subgroup



MRS measurement of glutamate, results by FTLD syndrome subtype. bvFTD: behavioural variant frontotemporal dementia, PSP: progressive supranuclear palsy (including PSP-RS and PSP-F subtypes). Top row: water scaled values with no partial volume correction for the right inferior frontal gyrus (IFG) and primary visual cortex (occipital) voxels. Bottom row: The same data after age, sex and partial volume (grey and white matter) correction. On each boxplot, the middle line is the median and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Whiskers include any data not considered an outlier (within 2.7 standard deviations of the mean). Each dot represents the value from an individual participant, colour coded by group. *=p<0.05, *=p<0.05, **=p<0.01, ***=p<0.001 (after Bonferroni correction).



MRS measurement of GABA, results by FTLD syndrome subtype. bvFTD: behavioural variant frontotemporal dementia, PSP: progressive supranuclear palsy (including PSP-RS and PSP-F subtypes). Top row: water scaled values with no partial volume correction for the right inferior frontal gyrus (IFG) and primary visual cortex (occipital) voxels. Bottom row: The same data after age, sex and partial volume (grey and white matter) correction. On each boxplot, the middle line is the median and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Whiskers include any data not considered an outlier (within 2.7 standard deviations of the mean). Each dot represents the value from an individual participant, colour coded by group.

Appendix 9: Publications

Publications arising from my PhD at the time of printing

Murley AG, Rowe JB. Neurotransmitter deficits from frontotemporal lobar degeneration. *Brain* 2018;**141**:1263–85.

Murley AG, Coyle-Gilchrist I, Rouse MA, *et al.* Redefining the multidimensional clinical phenotypes of frontotemporal lobar degeneration syndromes. *Brain* 2020;**143**:1555–71.

Murley AG, Rouse MA, Jones PSJ, *et al.* GABA and glutamate deficits from frontotemporal lobar degeneration are associated with disinhibition. *Brain* 2020;**In press**.

Murley AG, Jones PS, Coyle Gilchrist I, *et al.* Metabolomic changes associated with frontotemporal lobar degeneration syndromes. *J Neurol* 2020;**267**:2228–38.

Murley AG, Rouse MA, Coyle-Gilchrist I, *et al.* Predicting loss of independence and mortality in frontotemporal lobar degeneration syndromes. *medRxiv* 2020

doi:10.1093/brain/awx327 BRAIN 2018: 141; 1263–1285 | 1263

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Neurotransmitter deficits from frontotemporal lobar degeneration

Alexander G. Murley[1] and James B. Rowe[1,2,3]

Frontotemporal lobar degeneration causes a spectrum of complex degenerative disorders including frontotemporal dementia, progressive supranuclear palsy and corticobasal syndrome, each of which is associated with changes in the principal neurotransmitter systems. We review the evidence for these neurochemical changes and propose that they contribute to symptomatology of frontotemporal lobar degeneration, over and above neuronal loss and atrophy. Despite the development of disease-modifying therapies, aiming to slow neuropathological progression, it remains important to advance symptomatic treatments to reduce the disease burden and improve patients' and carers' quality of life. We propose that targeting the selective deficiencies in neurotransmitter systems, including dopamine, noradrenaline, serotonin, acetylcholine, glutamate and gamma-aminobutyric acid is an important strategy towards this goal. We summarize the current evidence-base for pharmacological treatments and suggest strategies to improve the development of new, effective pharmacological treatments.

1 Department of Clinical Neurosciences, University of Cambridge, Herchel Smith Building, Robinson Way, Cambridge, CB2 0SZ, UK
2 MRC Cognition and Brain Sciences Unit, University of Cambridge, 15 Chaucer Road, Cambridge, CB2 7EF, UK
3 Behavioural and Clinical Neurosciences Institute, University of Cambridge, Sir William Hardy Building, Downing Street, Cambridge, CB2 3EB, UK

Correspondence to: Alexander Murley
Herchel Smith Building, Forvie Site, Robinson Way, Cambridge, CB2 0SZ, UK
E-mail: am2505@medschl.cam.ac.uk

Keywords: frontotemporal dementia; progressive supranuclear palsy; corticobasal degeneration; neurotransmitters; dementia

Abbreviations: AMPA = α-amino-3-hydroxyl-5-methyl-isoxazolepropionic acid; bvFTD = behavioural variant frontotemporal dementia; CBD = corticobasal degeneration; CBS = corticobasal syndrome; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; NMDA = *N*-methyl D-aspartate; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy; SPECT = single photon emission computed tomography

Introduction

Frontotemporal lobar degeneration (FTLD) causes diverse clinical syndromes, including frontotemporal dementia (FTD), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) (MacKenzie *et al.*, 2010; Riedl *et al.*, 2014). In recent years there has been marked progress in defining these syndromes in terms of their clinical diagnostic criteria (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011; Armstrong *et al.*, 2013; Höglinger *et al.*, 2017), genetic association (Seelaar *et al.*, 2011; Baizabal-Carvallo and Jankovic, 2016), pathology (MacKenzie *et al.*, 2010), and clinical and imaging biomarkers (Whitwell *et al.*, 2005; Hughes *et al.*, 2013; Skillback *et al.*, 2014; Rohrer *et al.*, 2015*b*; Ranasinghe *et al.*, 2016). These advances have supported the development of candidate disease-modifying therapeutics (Boxer and Boeve, 2007; Tsai and Boxer, 2014; Stamelou and Höglinger, 2016). However, treatments that slow or halt disease progression after symptoms begin must be accompanied by more effective treatment of

Received July 5, 2017. Revised September 5, 2017. Accepted October 3, 2017. Advance Access publication January 24, 2018

symptoms to reduce the overall burden of disease. One strategy is to reverse neurotransmitter deficits, similar to dopaminergic therapy of Parkinson's disease or cholinergic therapy for Alzheimer's disease. Novel symptomatic drug treatment would improve patients' and their families' quality of life.

Recent changes in the clinical and pathological characterization of the major clinical syndromes caused by FTLD give anatomical and pharmacological insights that call for a reappraisal of the neurotransmitter literature. We adopt the clinical labels as set out in current consensus diagnostic criteria for the behavioural variant FTD (bvFTD) (Rascovsky *et al.*, 2011), semantic variant of primary progressive aphasia (svPPA) (Gorno-Tempini *et al.*, 2011), logopenic variant of PPA (lvPPA) (Gorno-Tempini *et al.*, 2011), non-fluent agrammatic variant PPA (nfvPPA) (Gorno-Tempini *et al.*, 2011), CBS (Armstrong *et al.*, 2013) and PSP (Höglinger *et al.*, 2017). However, older studies may have used different terms or overlooked the evolution of phenotype that obscures the boundaries between groups as the disease progresses (Coyle-Gilchrist *et al.*, 2016). Where these changes are relevant to the interpretation of neurotransmitter effects, we make variations from the current standard classification explicit, but otherwise consider semantic dementia as semantic variant PPA and progressive non-fluent aphasia as non-fluent agrammatic variant PPA.

Here we review the pharmacological abnormalities associated with FTLD in terms of regional changes in neurotransmitter synthesis, release, reuptake, catabolism, and synaptic binding. We focus on the major neurotransmitter systems, dopamine, noradrenaline, serotonin, acetylcholine, glutamate and gamma aminobutyric acid (GABA) both individually (including their receptor subtypes) and the interactions between them. Table 1 provides a summary of the available evidence, with full information on references by disease and by neurotransmitter in Supplementary Table 1.

Table 1 Summary of neurotransmitter deficits in FTLD

Neurotransmitter pathway	FTD	PSP	CBS
Dopamine			
Dopaminergic neurons	↓↓	↓↓	↓↓
Dopamine receptors	↓	↓↓[a]	↔
Noradrenaline			
Noradrenergic neurons	↔	↓↓	na
Noradrenergic receptors	na	na	na
Serotonin			
Serotonergic neurons	↓↓	↓	↓
Serotonergic receptors	↓↓	↑	na
Acetylcholine			
Cholinergic neurons	↔[b]	↓↓	↓↓
Cholinergic receptors	↔/↓	↔/↓	na
Glutamate			
Glutamatergic neurons	↓↓	↓↓	na
Glutamatergic receptors	↓↓	↔	na
GABA			na
GABAergic neurons	↓	↓↓	na
GABA receptors	na	↓	na

A more detailed table, including references, is included as Supplementary Fig. 1.
↓↓ = moderate/severe deficit; ↓ = mild deficit; ↑/↔/↓ = conflicting or inconsistent results; ↔ = no significant change; ↑ = mild increase; na = no available evidence.
[a]In PSP D2 receptors are reduced in the striatum and basal ganglia but D1 receptors appear to be preserved.
[b]Cholinergic neurons are reduced in the nucleus basalis but are preserved in the cerebral cortex in bvFTD. In nfvPPA there is greater evidence of a cholinergic deficit with atrophy of basal forebrain cholinergic nuclei.

Dopamine

Dopaminergic deficits are widely associated with Parkinson's disease but are also a common feature of FTLD. The majority of dopaminergic neurons originate in the ventral midbrain and form nigrostriatal, mesolimbic and mesocortical projections (Fig. 1A). Nigrostriatal neurons from the substantia nigra pars compacta terminate in the striatum, regulating cortico-striato-thalamo-cortical loops for motor, oculomotor and cognitive control (Rowe and Rittman, 2016). The motor circuit regulates movement, both in facilitating (via the direct pathway) and inhibiting (via the indirect pathway) actions. Loss of dopaminergic neurons in the nigrostriatal pathway causes parkinsonism in Parkinson's disease, but also in FTLD. Additional mesolimbic and mesocortical dopaminergic neurons from the ventral tegmental area regulate reward, learning and motivation-related behaviour (Wise, 2004). The mesolimbic tract projects principally to the nucleus accumbens in the striatum and to the amygdala and hippocampus, affecting motivation, hedonia and reward (incentive salience). Changes to the mesolimbic tract may also exacerbate compulsion and impulsivity. The mesocortical tract (which projects to the prefrontal, cingulate and perirhinal cortices) regulates motivation, emotion, reward and desire, including learning of the value of goal-directed actions. Dopamine binds to five types of G protein coupled receptors; D_1-class (D_1 and D_5) and D_2-class (D_2, D_3 and D_4), which differ in their response to dopamine agonists and antagonists (Beaulieu and Gainetdinov, 2011; Southan *et al.*, 2016). The different receptor subtypes have distinct distribution densities across brain regions and are associated with different, although overlapping, effects on cognition and movement (Beaulieu and Gainetdinov, 2011), and may be differentially affected by FTLD.

Frontotemporal dementia

There is clinical and experimental evidence of a nigrostriatal deficit in many cases of FTD, with loss of pre-synaptic dopaminergic neurons, reduced dopamine levels, reduced dopamine transporter binding, and abnormal dopamine receptor binding. Extrapyramidal symptoms of bradykinesia, rigidity and gait dysfunction are seen in up to 70% of patients at some stage during the disease course (Rinne *et al.*, 2002; Padovani *et al.*, 2007; Kertesz *et al.*, 2011;

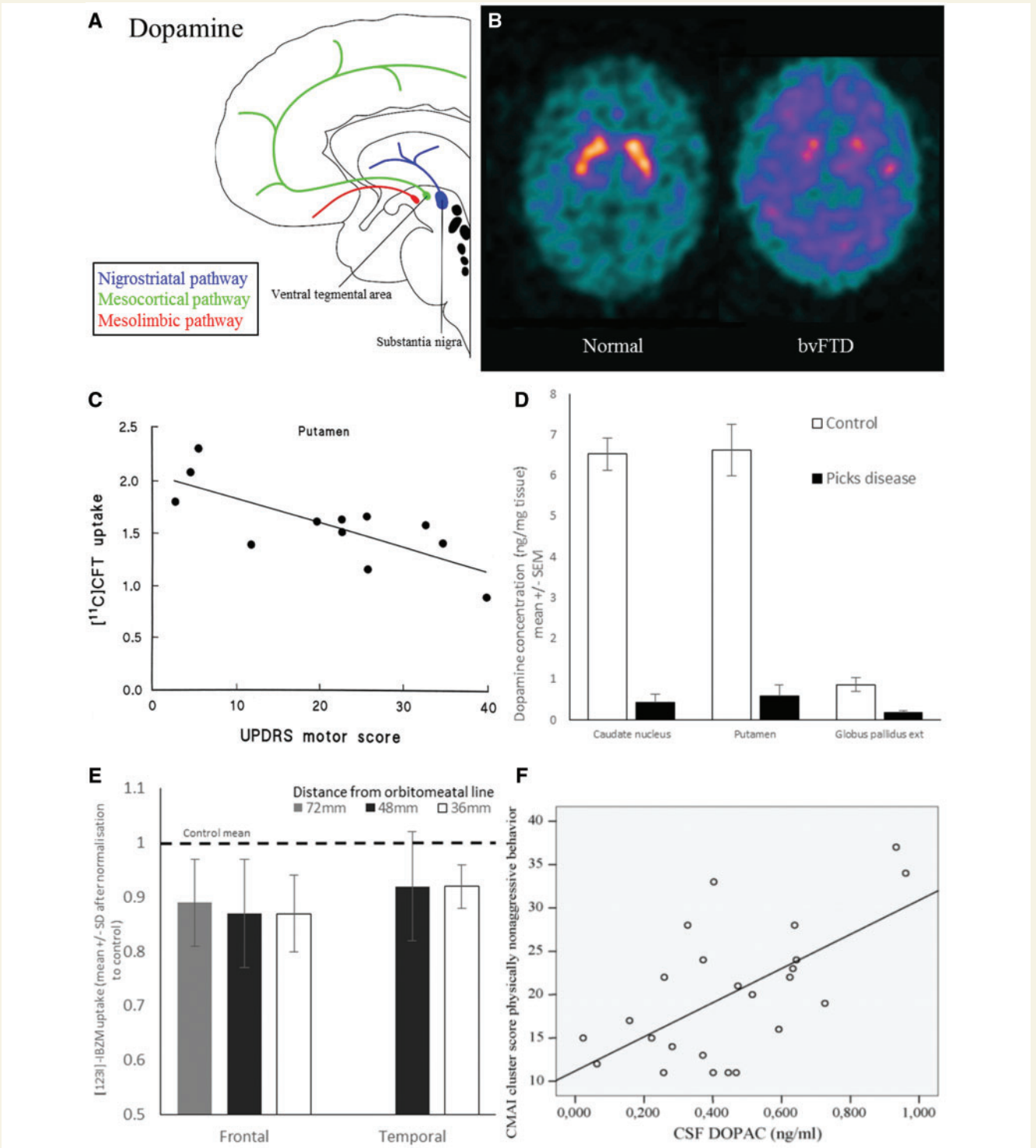


Figure 1 Dopamine deficits in FTD. (**A**) Schematic illustration of dopaminergic pathways. (**B**) Ioflupane SPECT scan showing loss of presynaptic dopaminergic neurons in the striatum of FTD compared with normal scan. (**C**) Loss of dopaminergic neurons in the putamen (measured by ^{11}C-CFT-PET) correlates with severity of extra-pyramidal motor symptoms (Unified Parkinson's Disease Rating Scale motor score). From Rinne *et al.* (2002). Reprinted with permission from Wolter Kluwer. (**D**) Dopamine levels are reduced in the caudate, putamen and globus pallidus. Graph of data from Kanazawa *et al.* (1988). Reprinted with permission from Elsevier. (**E**) There is loss of D2 dopamine receptors in the frontal lobes (as measured by ^{123}I-IBZM-PET). Graph of data from Frisoni *et al.* (1994). Reprinted with permission from Elsevier. (**F**) CSF DOPAC levels (3,4-dihydroxyphenylacetic acid, a dopamine metabolite) correlate with behavioural disturbance. From Engelborghs *et al.* (2008). Reprinted with permission from Elsevier.

Gil-Navarro *et al.*, 2013). *In vivo* imaging reveals that dopamine transporter levels (a marker of presynaptic neuron integrity in the striatum) are reduced in the caudate and putamen (Fig. 1B) (Rinne *et al.*, 2002; Sedaghat *et al.*, 2007). The degree of this loss correlates with extra-pyramidal symptom severity (Fig. 1C) (Rinne *et al.*, 2002; Sedaghat *et al.*, 2007).

In bvFTD there are low levels of dopamine, measured by high performance liquid chromatography, in the putamen, caudate and substantia nigra (Kanazawa *et al.*, 1988; Nagaoka *et al.*, 1995) (Fig. 1D). Parkinsonism is commonly seen in bvFTD, especially when caused by certain genetic mutations (Baizabal-Carvallo and Jankovic, 2016). Mutations on chromosome 17, including in the *MAPT* (Hutton *et al.*, 1998) and *PGRN* (Baker *et al.*, 2006) genes, are associated with rigidity, akinesia and neuronal loss in the substantia nigra, although symptom onset and severity vary with each specific mutation (Foster *et al.*, 1997; Pickering-Brown *et al.*, 2002; Le Ber *et al.*, 2008; Siuda *et al.*, 2014; Baizabal-Carvallo and Jankovic, 2016). For example, an early PET study in three patients with FTD associated with a chromosome 17 mutation found severe reduction in presynaptic dopaminergic neurons with normal D2 receptor levels in the striatum (Pal *et al.*, 2001). The hexanucleatide expansion in the *C9orf72* gene on chromosome 9 is most typically associated with FTD with amyotrophic lateral sclerosis (Rohrer *et al.*, 2015*a*), but up to half of patients have parkinsonism, with decreased dopamine transporter levels in the basal ganglia (Boeve *et al.*, 2012; O'Dowd *et al.*, 2012). Extrapyramidal symptoms are also seen with mutations in *CHMP2B*, *FUS*, *TARDBP*, *TREM2* and *VCP* (Siuda *et al.*, 2014; Baizabal-Carvallo and Jankovic, 2016). In non-fluent agrammatic variant PPA, there is frequent loss of dopaminergic neurons in the striatum (Gil-Navarro *et al.*, 2013), which underlies the frequent progression of motor symptoms in this disorder, and its clinical overlap with CBS and PSP (Rohrer *et al.*, 2010). Parkinsonism in bvFTD and non-fluent agrammatic variant PPA appears to occur with all types of underlying pathology; tau (Hutton *et al.*, 1998), TDP-43 (Boeve *et al.*, 2012) and FUS pathology (Deng *et al.*, 2014) are all associated with motor symptoms (Baizabal-Carvallo and Jankovic, 2016).

In addition to extrapyramidal motor features, degeneration of dopaminergic tracts, especially the mesocortical pathway, could contribute to behavioural symptoms of FTD. For example, D2 dopamine receptors are reduced in the frontal lobes of patients with FTD (Frisoni *et al.*, 1994) (Fig. 1E), while CSF levels of dopamine and its metabolites are reduced in some (Sjogren *et al.*, 1998) but not all studies (Vermeiren *et al.*, 2013). CSF levels of dopamine correlate with agitation and caregiver burden in FTD (Fig. 1F) (Engelborghs *et al.*, 2008). However, these findings contrast with a study that found higher dopamine levels in the prefrontal cortex at post-mortem (Vermeiren *et al.*, 2016). Such inconsistencies may result from technological or methodological differences in tissue preparation or analysis, but they may also reflect true heterogeneity in the FTD population, especially in small post-mortem analyses.

Aggression, agitation and psychosis are distressing and burdensome aspects of FTD. Antipsychotic medications with dopaminergic receptor affinity are often used to treat them but patients can be extremely sensitive to the extrapyramidal side effects due to pretreatment nigrostriatal deficits (Pijnenburg *et al.*, 2003). Atypical antipsychotics such as quetiapine, olanzapine or clozapine cause fewer extrapyramidal side effects (Moretti *et al.*, 2003*b*) while noting that there is less evidence for their efficacy in dementia. In an open label, non-randomized study, olanzapine improved behavioural fluctuations, wandering and irritability (Moretti *et al.*, 2003*b*). An alternative strategy using methylphenidate, a noradrenaline and dopamine reuptake inhibitor, reduced risk-taking behaviour in a small double-blind, placebo-controlled study, but without effects on a wide range of cognitive tasks (Rahman *et al.*, 2006). There is a case report of improved behaviour with methylphenidate and bupropion (another noradrenaline and dopamine reuptake inhibitor) in one patient with FTD (Goforth *et al.*, 2004). In addition to the uncertainty over dopaminergic strategies to treat cognitive and behavioural symptoms in FTD, systematic evidence is lacking of the efficacy of levodopa or dopamine agonists to ameliorate parkinsonism in FTD, with only case reports of benefit in some patients (Chow, 2002; Tsai and Boxer, 2014).

Progressive supranuclear palsy

In vivo and post-mortem studies show that the extrapyramidal features of PSP are associated with a severe loss of dopaminergic neurons and changes in dopamine receptors, particularly D2 receptors. Pathological tau aggregates, including neuronal tangles and glial inclusions, develop in areas with a high density of dopaminergic neurons including the substantia nigra and striatum (Litvan *et al.*, 1996; Hardman *et al.*, 1997). There is marked loss of pigmented dopaminergic neurons in the substantia nigra pars compacta on examination post-mortem (Hardman *et al.*, 1997; Oyanagi *et al.*, 2001). There is also loss of both dopaminergic neurons and dopamine receptors in the striatum (Baron *et al.*, 1986; Kim *et al.*, 2002; Oyanagi, 2002; Im *et al.*, 2006; Oh *et al.*, 2012). Dopamine transporter binding is reduced in the caudate, putamen and globus pallidus at post-mortem (Warren *et al.*, 2007*b*) and *in vivo* (Fig. 2A) (Seppi *et al.*, 2006). Dopamine levels are reduced in the putamen, caudate nucleus, substantia nigra and globus pallidus at post-mortem (Fig. 2C) (Ruberg *et al.*, 1985; Hornykiewicz and Shannak, 1994). *In vivo* PET and single photon emission computed tomography (SPECT) studies indicate reduced levels of D2 receptors in the basal ganglia (Fig. 2D) (Brooks *et al.*, 1992; Arnold *et al.*, 2002; Oyanagi, 2002) while post-mortem studies show corresponding loss of D2 receptors in the putamen, caudate and substantia innominata (Ruberg *et al.*, 1985; Pierot *et al.*, 1988; Pascual *et al.*, 1992; Landwehrmeyer

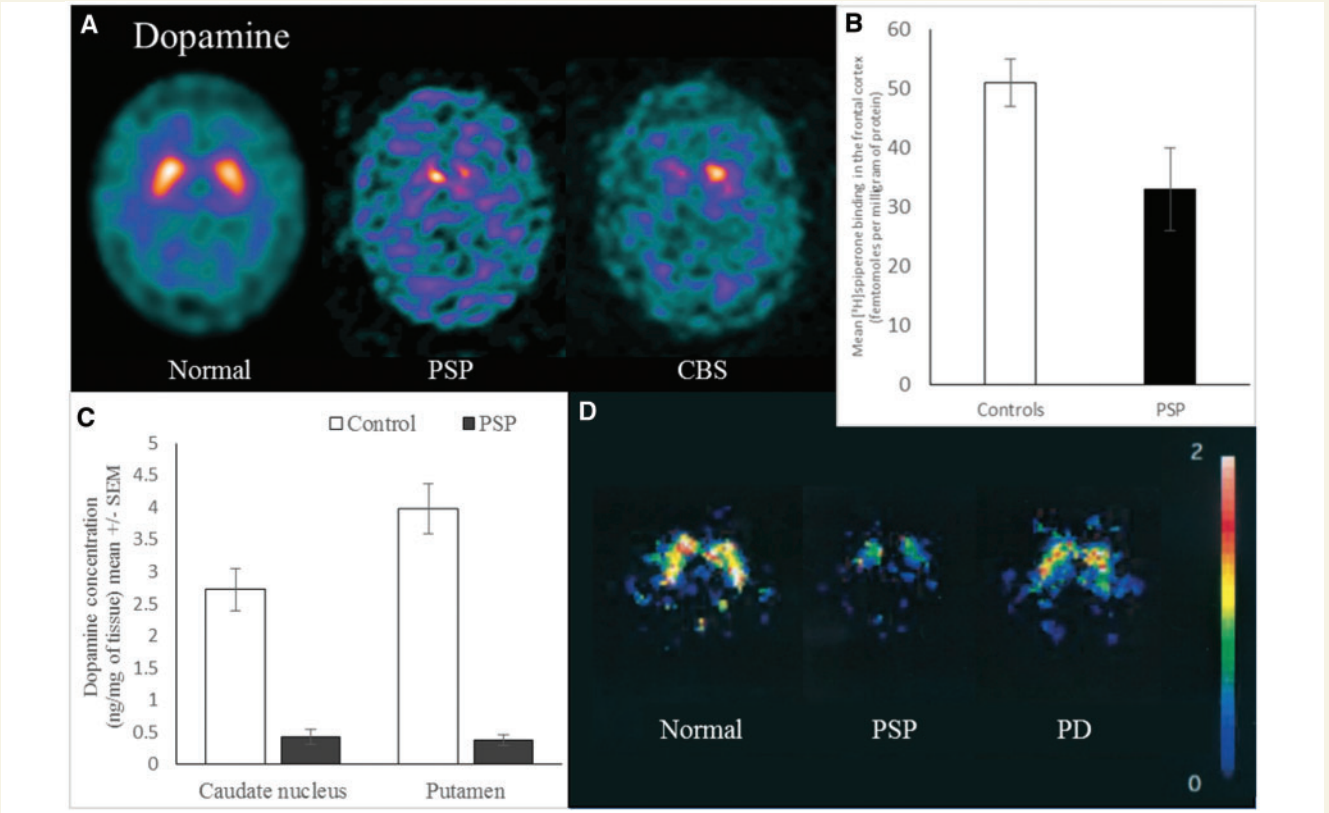


Figure 2 Dopamine deficits in PSP and CBS. (**A**) Ioflupane SPECT scan showing reduced pre-synaptic dopaminergic neurons in the striatum of PSP and CBS compared to a normal scan. (**B**) Post-mortem dopamine receptor levels (measured by spiperone binding) are reduced in the frontal cortex in PSP. Graph of data from Ruberg *et al.* (1985). Reprinted with permission from Wiley. (**C**) Dopamine levels are reduced in the caudate nucleus and putamen in PSP. Graph of data from Ruberg *et al.* (1985). (**D**) D2 dopamine receptor levels (measured by ^{123}I-iodobenzofuran SPECT) are reduced in the striatum of PSP when compared with healthy controls and Parkinson's disease. From Oyanagi (2002). Reprinted with permission from Wiley.

and Palacios, 1994). One study reported higher D2 receptor binding in the striatum compared with controls (Warren *et al.*, 2007*a*), which might represent receptor upregulation in response to loss of presynaptic dopaminergic neurons. In contrast D1 receptors appear relatively well preserved (Pierot *et al.*, 1988). There is also evidence that the mesocortical pathway is impaired in PSP, with degeneration of dopaminergic neurons in the ventral tegmental area (Murphy *et al.*, 2008) and loss of dopamine receptors in the frontal cortex, measured post-mortem with ^{3}H-spiperone (Fig. 2B) (Ruberg *et al.*, 1985). This is especially relevant to the often profound change in motivation and apathy in PSP.

In contrast to Parkinson's disease, motor symptoms in typical clinical presentations of PSP (increasingly known as progressive supranuclear palsy-Richardson's syndrome, or PSP-RS, to distinguish it from other phenotypes of PSP pathology) (Höglinger *et al.*, 2017) typically do not respond well to dopaminergic therapy. This may be because in PSP there is loss of both dopaminergic neurons and receptors in the basal ganglia and cerebral cortex. This contrasts with Parkinson's disease, in which predominant loss of presynaptic nigrostriatal dopaminergic neurons is greater than the relative preservation, or even upregulation, of post-synaptic dopamine receptor densities (Olanow, 2004).

Corticobasal syndrome

CBS is caused by corticobasal degeneration (CBD) pathology in about 60% of cases, the remainder being due to PSP, FTD, Alzheimer's disease and other pathology (Boeve *et al.*, 1999; Alexander *et al.*, 2014). Patients with CBD have pathological neuroglial tau deposits, severe neuronal loss and gliosis in the substantia nigra and striatum, typically with a history of extrapyramidal signs (Oyanagi *et al.*, 2001; Armstrong *et al.*, 2013; Coyle-Gilchrist *et al.*, 2016). Despite this, the *in vivo* imaging evidence of dopaminergic deficits is inconsistent. Fluorodopa PET indicates presynaptic dopaminergic reductions in the caudate, putamen and frontal cortex (Sawle *et al.*, 1991; Nagasawa *et al.*, 1996; Laureys *et al.*, 1999; Klaffke *et al.*, 2006; Pirker *et al.*, 2015), but with wide variation and surprisingly no correlation with disease duration or severity (Cilia *et al.*, 2011). Indeed some patients with autopsy-confirmed CBD have had a normal dopamine transporter SPECT scan despite prominent parkinsonian features (Chaal and Rowe, 2013;

Kaasinen *et al.*, 2013), and D2 receptor levels can be unchanged (Klaffke *et al.*, 2006; Pirker *et al.*, 2013). These conflicting results may partly reflect the poor clinicopathological correlation of CBS with CBD (Boeve *et al.*, 1999; Cilia *et al.*, 2011; Alexander *et al.*, 2014). This is arguably a greater problem in the older literature, which often used CBD when referring to CBS, and therefore may include a high proportion of Alzheimer's disease in their cases. We suggest that future studies of CBS need corollary pathological or biomarker evidence to distinguish CBD and non-CBD causes of CBS. The current evidence suggests a complex and inconsistent relationship between nigrostriatal dopamine deficiency and symptoms in patients with CBS, but evidence is scarce in comparison to other disorders.

Noradrenaline

The locus coeruleus in the pons is the principle site of noradrenaline synthesis in the brain and contains the soma of noradrenergic neurons that project to the forebrain (Fig. 3A). Different subpopulations of neurons within the locus coeruleus project to the orbitofrontal, medial prefrontal, anterior cingulate and motor cortices (Chandler *et al.*, 2014). These noradrenergic pathways have an important role in regulating the function of the prefrontal cortex (McGaughy *et al.*, 2008; Chandler *et al.*, 2014), while in contrast to dopamine, there is minimal noradrenergic innervation of the striatum. Noradrenaline acts via α and β G protein coupled receptor families, each of which comprise subtypes that have different responses to ligand binding (Sara, 2009). The effect of noradrenaline depends on the relative densities of these receptors (Aston-Jones and Cohen, 2005). For example, noradrenergic input to the basal forebrain can promote arousal by activating cholinergic neurons through α1 and β1 receptors and inhibiting GABAergic neurons through α2 receptors (Schwarz and Luo, 2015), while presynaptic auto-inhibitory α2 receptors may paradoxically enhance noradrenergic transmission in response to antagonists (Invernizzi and Garattini, 2004). Noradrenaline is involved in regulating a range of behaviours including wakefulness, attention, memory and decision-making (Rowe *et al.*, 1996; Sara, 2009; Dalley *et al.*, 2011; Aston-Jones and Waterhouse, 2016). In comparative

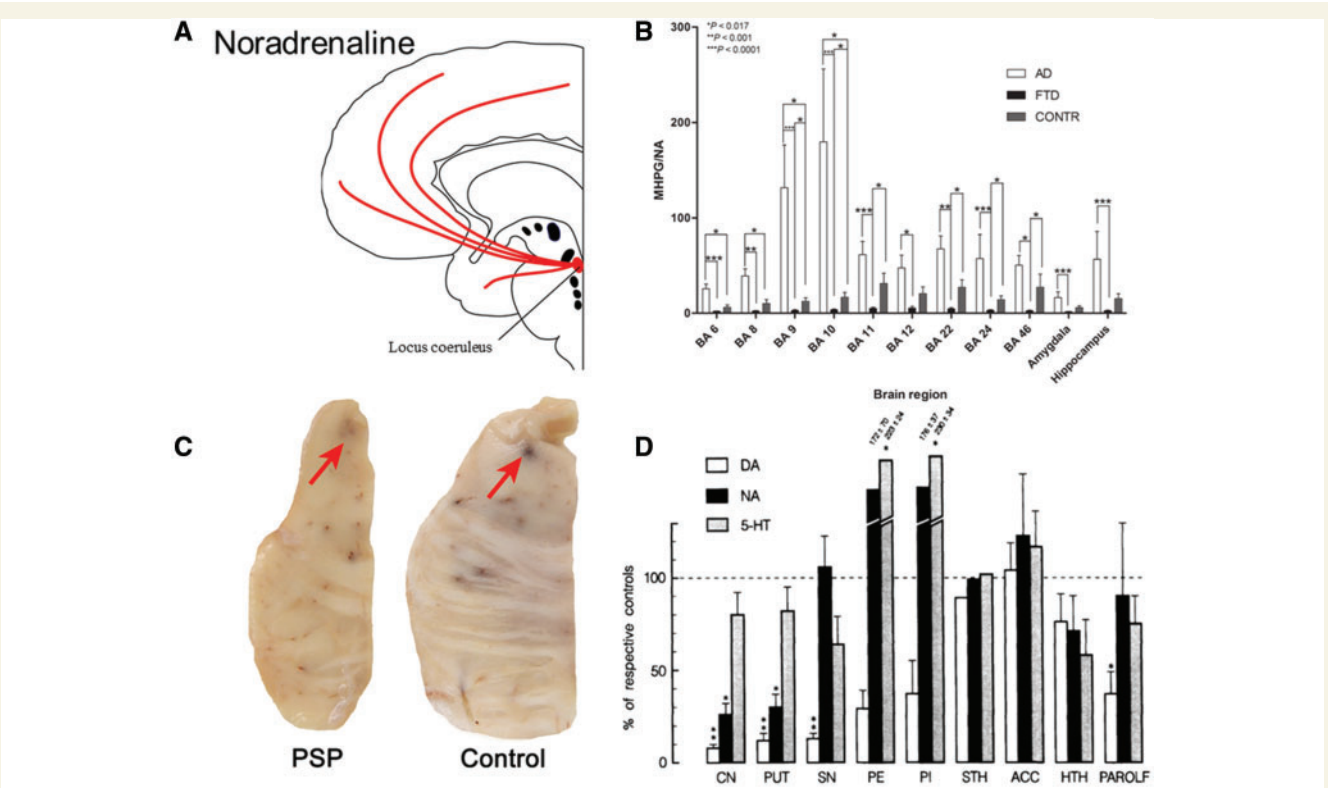


Figure 3 Noradrenergic deficits in FTD and PSP. (**A**) Schematic illustration of noradrenergic pathways. (**B**) MHPG/noradrenaline ratios, indicative of catabolic noradrenergic turnover, are reduced in Brodmann areas 11, 22, 24 and 46 in FTD. From Vermeiren *et al.* (2016). Reprinted with permission from the authors and IOS Press. The publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-160320. (**C**) Post-mortem brainstem tissue from control and PSP brains. There is a paler locus coeruleus suggesting loss of melatonin-containing noradrenergic neurons. Courtesy of Kieran Allison, Cambridge Brain Bank. (**D**) Noradrenaline levels are reduced in the caudate (CN), putamen (PUT), hippocampus (HTH) and parolfactory cortex (PAROLF). Serotonin levels are reduced in those areas as well as in the subthalamic nucleus (SN). Dopamine levels are reduced in those areas as well as the globus pallidus externa (GPe) and interna (GPi). From Hornykiewicz and Shannak (1994). Reprinted with permission from Springer.

models, for example rats, limiting noradrenergic transmission results in impaired executive function (Newman *et al.*, 2008; Chandler *et al.*, 2014) and increasing noradrenaline levels reduces impulsivity (Robinson *et al.*, 2008). Computational and neurophysiological models suggest noradrenergic pathways mediate salience and shift in attention (Aston-Jones and Cohen, 2005).

Frontotemporal dementia

There is limited evidence for noradrenergic changes in FTD but in many respects, the noradrenergic pathways appear to be normal or near normal, relative to the marked deficits seen in other neurotransmitter pathways. For example, neuropathological studies of FTD suggest the preservation of cell density in the locus coeruleus, and noradrenaline levels are normal or even elevated in the frontal lobe (Vermeiren *et al.*, 2016), despite the presence of pathological tau inclusions (Nagaoka *et al.*, 1995; Yang and Schmitt, 2001; Brunnström *et al.*, 2011; Irwin *et al.*, 2016). However, there may be reduced noradrenaline catabolism and turnover. For example, one study found low 3-methoxy-4-hydroxyphenylglycol (MHPG) to noradrenaline ratios, a proposed marker of noradrenergic turnover, in the frontal and temporal lobes, anterior cingulate, amygdala and hippocampus (Fig. 3B) (Vermeiren *et al.*, 2016). In contrast, several studies show normal levels of noradrenaline and MHPG in CSF (Sjogren *et al.*, 1998; Engelborghs *et al.*, 2008; Vermeiren *et al.*, 2013). However, in one of these studies there was a correlation between CSF levels of noradrenaline and disease severity, even though overall levels were unchanged (Engelborghs *et al.*, 2008). The enzyme monoamine oxidase, which metabolizes noradrenaline, is reduced in some areas of the brain (including the temporal lobe) although levels are unchanged in the frontal lobe (Sparks *et al.*, 1991). This anatomical heterogeneity may be one reason for the inconsistent reports of MHPG/noradrenaline levels. However, an alternative explanation is that the locus coeruleus receives inhibitory serotoninergic innervation from the upper raphe nuclei (Yang and Schmitt, 2001) such that the major loss of serotonergic projections in FTD (see below) serves indirectly to increase noradrenaline signalling to the frontal lobe.

Idazoxan is an α2 adrenoceptor antagonist that increases synaptic noradrenaline levels by antagonism of inhibitory autoreceptors on noradrenergic neurons. Idazoxan improved attention, planning and problem-solving in a small group of patients with FTD (Sahakian *et al.*, 1994; Coull *et al.*, 1996). Looking ahead to candidate symptomatic therapies, selective noradrenergic reuptake inhibitors such as atomoxetine and reboxetine, or combined serotonin and noradrenaline reuptake inhibitors like venlafaxine and duloxetine, may provide better tolerated augmentation of noradrenergic neurotransmission in FTD building on the evidence of their safety and efficacy in other disorders (Wang *et al.*, 2011; Cubillo *et al.*, 2014; Kehagia *et al.*, 2014; Ye *et al.*, 2015; Rae *et al.*, 2016).

Progressive supranuclear palsy and corticobasal syndrome

Evidence is emerging of an early noradrenergic deficit in PSP, with loss of noradrenergic neurons and low noradrenaline levels in the basal ganglia. There is significant pathology in the locus coeruleus with both tau deposition (Dickson, 1999; Arnold *et al.*, 2013), and neuronal loss (Fig. 3C) (Hauw *et al.*, 1994; Mori *et al.*, 2002; Dickson *et al.*, 2010). A single post-mortem study also found reduced levels of noradrenaline in the caudate and putamen (Hornykiewicz and Shannak, 1994) (Fig. 3D), although noradrenergic receptor density is normally low in the striatum compared to cortex. These early and sometimes severe noradrenergic changes may be directly linked to cognitive and behavioural manifestations of PSP, such as rigidity and impulsivity, analogous to the treatable noradrenergic deficit underlying aspects of impulsivity in Parkinson's disease (Kehagia *et al.*, 2014; Rae *et al.*, 2016). In keeping with this, a double-blind cross-over study of the α2 antagonist idazoxan showed improvement in motor function in PSP (Ghika *et al.*, 1991). However a larger study with a more potent α2 antagonist (efaroxan) found no effect (Rascol *et al.*, 1998). Atomoxetine has been shown to reduce impulsivity and executive deficits in Parkinson's disease (Marsh *et al.*, 2009; Kehagia *et al.*, 2014; Ye *et al.*, 2015), but evidence is lacking in PSP. Evidence is also lacking for noradrenergic changes in CBS, although tau pathology is present in the locus coeruleus (Dickson, 1999).

Serotonin

Serotonin (5-HT) is synthesized mainly by two groups of neurons in the raphe nuclei in the brainstem, which project widely (Fig. 4A) (Charnay and Léger, 2010). The rostral group, comprising 85% of serotonergic neuron cell bodies, project to the cerebral cortex, thalamus, hypothalamus and basal ganglia (Hornung, 2003). The caudal group project mainly to the brainstem and spinal cord (Hornung, 2003). With these widespread projections, serotonin regulates many higher brain functions related to cognitive control, learning, and affect (Harvey, 2003; Ciranna, 2006; Canli and Lesch, 2007; Artigas, 2013). There are seven different serotonin receptor families (5-$HT_{1–7}$), which are neuromodulatory G protein coupled receptors except for the 5-HT_3 receptor family, which includes ligand-gated ion channels (Barnes and Sharp, 1999; Southan *et al.*, 2016). To add to this complexity, genetic polymorphisms within a receptor subtype (Barnes and Sharp, 1999) and presynaptic transporter (Porcelli *et al.*, 2012), influence serotonergic function.

Serotonin receptors are among the most complex and varied of neurotransmitter receptors, and while there is clear evidence of serotonergic deficits in FTLD, studies to date mainly lack a detailed breakdown of receptor

subtypes, or focus on 1A and 2A receptors. Serotonin has important roles in synaptic plasticity and as a neuromodulator of the direct effects of other neurotransmitters (Celada *et al.*, 2013). For example, serotonin inhibits dopamine release and modulates glutamate and GABA transmission (Ciranna, 2006). In the hippocampus serotonin receptors reduce glutamate and stimulate GABA from inhibitory interneurons, reducing long term potentiation (Ciranna, 2006). In the frontal cortex glutamate release is inhibited by serotonin whereas in the prefrontal cortex serotonin enhances glutamate transmission (Dawson *et al.*, 2001; Ciranna, 2006). This suggests that FTLD-induced serotonin

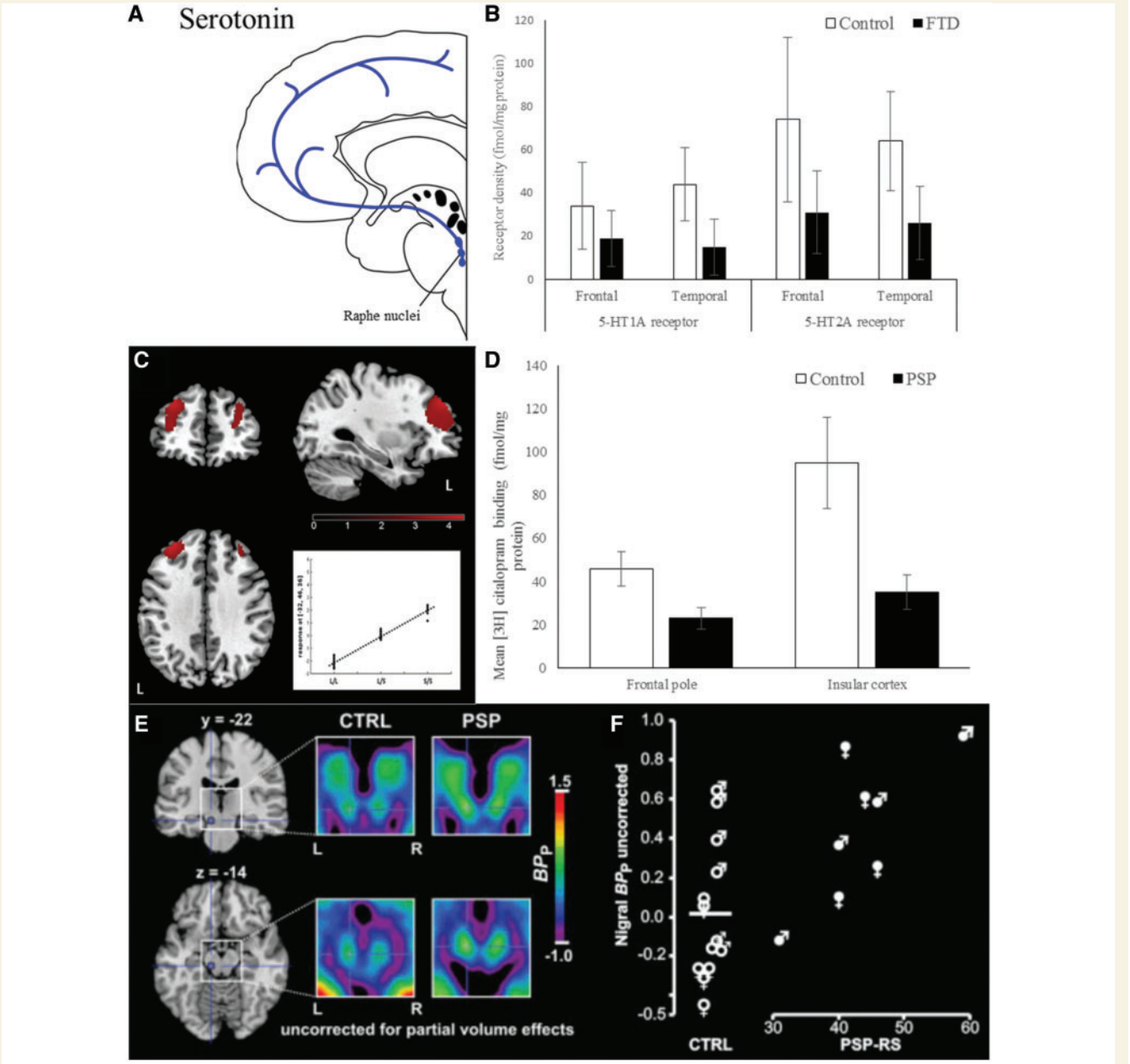


Figure 4 Serotonergic deficits in FTD and PSP. (**A**) Schematic illustration of serotonin pathways. (**B**) 5-HT1 and 2A receptor density is reduced in the frontal and temporal lobe in FTD. Graph of data from Bowen *et al.* (2008). Reprinted with permission of the authors and Springer. (**C**) Effect of 5-HTTLPR genotype on brain perfusion in FTD patients. Comparison of long (L/L) versus short (S/S) carriers at the same disease stage showing reduced perfusion of some areas of the frontal lobe in L/L carriers. From Premi *et al.* (2015). Reprinted with permission from Elsevier. (**D**) Presynaptic serotonergic neurons (measured by citalopram binding to post-mortem tissue) are reduced in the frontal and insular cortices in PSP. Graph of data from Chinaclia and Landwehrmeyer (1993). Reprinted with permission from Elsevier. (**E**) 5-HT2A receptor PET binding is increased bilaterally in the striatum and substantia nigra compared with controls. In the same study (**F**) disease severity positively correlated with 5-HT2A binding potential in the striatum. From Stamelou *et al.* (2009). Reprinted with permission from Wiley.

deficiency could cause widespread cognitive, motor and affective symptoms, directly and through the disruption of its modulation of other systems.

Frontotemporal dementia

Serotonin dysfunction is a significant contributor to the behavioural and cognitive symptoms seen in bvFTD (Huey *et al.*, 2006; Hughes *et al.*, 2015). Reductions in serotonin transmission or postsynaptic receptor densities are associated with several symptoms seen in FTD including aggression, impulsivity, increased appetite and depression (Huey *et al.*, 2006). At post-mortem examination, 5HT1A and 2A receptors are reduced in the frontal and temporal lobes and the hypothalamus (Fig. 4B) (Sparks and Markesbery, 1991; Francis *et al.*, 1993; Procter *et al.*, 1999; Bowen *et al.*, 2008). *In vivo* PET studies corroborate the post-mortem findings with the 5-HT2A receptor binding potential reduced in the midbrain and medial frontal cortex (Franceschi *et al.*, 2005) and the 5-HT1A binding potential reduced across all cortical areas (Lanctôt *et al.*, 2007).

Evidence for actual serotonergic neuronal cell loss is less conclusive. One post-mortem study found loss of neurons in the raphe nucleus and their projections to the cerebral cortex, which correlated with disease duration (Yang and Schmitt, 2001). There is also pathological tau deposition in the raphe nuclei (Irwin *et al.*, 2016). This contrasts with other studies that report no change in imipramine binding, proposed as a measure of presynaptic serotonergic terminals (Sparks and Markesbery, 1991), while post-mortem biochemical assays of serotonin are normal or elevated in FTD (Bowen *et al.*, 2008; Vermeiren *et al.*, 2016) and CSF measures of serotonin and its metabolites are unchanged (Engelborghs *et al.*, 2008). Nonetheless, CSF homovanillic acid/5-hydroxyindoleacetic acid (HVA/5-HIAA) levels (a proposed marker of the serotonergic modulation of dopaminergic neurotransmission) correlate with aggressive behaviour in FTD (Engelborghs *et al.*, 2004, 2008). 5-HIAA/5-HT ratios (a proposed marker of serotonergic turnover) are also lower in FTD compared to controls in the frontal and temporal lobes (Vermeiren *et al.*, 2016). It is possible that these apparent inconsistencies between biochemical assays and receptor or neuronal markers result from different stages of serotonergic cell loss and downstream functional compensation. To test this hypothesis would require the comparison of methods within the same pathological cohort, preferably one that includes patients with a wide range of neurocognitive severity.

There appears to be an association between FTD and length polymorphism in the gene promotor S(5-HTTLPR) of the serotonin transporter gene (SLC6A4) which suggests serotonin may be involved in the pathogenesis of FTD. A short allele (5-HTTLPR-s) was associated with a greater susceptibility to FTD in one study (Albani *et al.*, 2008) although this was not replicated (Yokoyama *et al.*, 2015). The 5-HTTLPR variant also affects brain atrophy in FTD. Patients with a long 5-HTTLPR allele have correspondingly greater atrophy and lower perfusion at equivalent disease stages (Fig. 4C) (Premi *et al.*, 2015) while the short allele is associated with more atrophy in the left inferior frontal gyrus and less in the right temporal lobe (Yokoyama *et al.*, 2015). The long allele may have a protective effect on cognitive presentation but is not associated with better prognosis (Borroni *et al.*, 2010).

In bvFTD there are reduced neurophysiological markers of inhibitory control and prefrontal cortical function, which are restored with the selective serotonin reuptake inhibitor citalopram in a placebo-controlled double-blind assessment (Hughes *et al.*, 2015). Several open label studies without placebo-control have shown improvement in behavioural symptoms with serotonergic drugs. For example, citalopram reduced disinhibition, irritability and depression (Herrmann *et al.*, 2012) and improved Frontal Assessment Battery test scores (Herrmann *et al.*, 2012) and inappropriate sexual behaviour (Anneser *et al.*, 2007). Paroxetine improved behavioural symptoms in an open label study (Moretti *et al.*, 2003*a*) but this was not supported by a subsequent placebo-controlled blinded study (Deakin *et al.*, 2004). Trazodone may improve behavioural symptoms in bvFTD based on a randomized control cross-over study (Lebert *et al.*, 2004). Interestingly, trazodone differs from selective serotonin reuptake inhibitors (SSRIs): it is an antagonist of a range of serotonin receptors apart from 5HT1A where it is an agonist, and it inhibits the serotonin transporter. A meta-analysis of antidepressants in FTD showed a combined mean reduction of 15 points on the Neuropsychiatric Inventory, noting, however, that the evidence was mainly from small, non-placebo controlled trials (Huey *et al.*, 2006).

Progressive supranuclear palsy and corticobasal syndrome

Pathological tau inclusions are found post-mortem in the raphe nuclei with PSP (Revesz *et al.*, 1996) while presynaptic serotonergic neurons are reduced in the caudate nucleus, frontal and temporal cortex (Fig. 4D) (Chinaclia and Landwehrmeyer, 1993). Serotonin levels were not significantly reduced in one post-mortem study (Hornykiewicz and Shannak, 1994). PET and post-mortem studies have both shown upregulation of 5-HT1B and 2A receptors in the substantia nigra and striatum (Fig. 4E) (Castro *et al.*, 1998; Stamelou *et al.*, 2009), which might represent compensation for loss of presynaptic serotonergic neurons. This upregulation correlated with severity of motor impairment (Fig. 4F) (Stamelou *et al.*, 2009), but information on the correlation with cognitive, affective or associative functions is also needed.

There have been case reports of patients with PSP showing some improvements in motor function with an SSRI (Miyaoka *et al.*, 2002), and anecdotal reports of serotonergic reuptake inhibition as an effective treatment for emotional lability (Rittman *et al.*, 2016). Overall there is not strong evidence for the efficacy of serotonergic drugs in PSP

(Stamelou and Höglinger, 2016). This lack of evidence may be because studies have focussed on depression and anxiety as outcomes of treatment, rather than impulsivity, disinhibition or cognitive change (Rittman *et al.*, 2016).

There is neuronal loss and gliosis in the raphe nucleus in CBD (Gibb *et al.*, 1989). However *in vivo* data are lacking on the serotonergic pathways and receptor density in CBS, and there are no systematic trials of serotonin reuptake inhibitors.

Acetylcholine

Acetylcholine is neuromodulatory on many areas of the forebrain (Everitt and Robbins, 1997), and influences a wide range of cognitive functions including attention, memory and emotion, but also motor control, through cortical and subcortical transmission in the cortico-striato-thalamocortical circuits (Picciotto *et al.*, 2012). The major cholinergic inputs to the cerebral cortex originate in the nucleus basalis of Meynert and adjacent nuclei in the basal forebrain (Fig. 5A) (Selden, 1998). Two other cholinergic nuclei in the brainstem, the pedunculopontine and lateral dorsal tegmental nuclei, project to the thalamus. Acetylcholine acts on two main receptor classes in the brain; muscarinic G protein coupled receptors (M1–5) and nicotinic ligand-gated ion channels (Picciotto *et al.*, 2012). Cholinergic receptors can have excitatory or inhibitory effects depending on their subtype and pre- versus postsynaptic location (Picciotto *et al.*, 2012).

Cholinergic drugs are in widespread use clinically, although not specifically in FTLD. For example, anti-cholinergic drugs reduce tremor and dystonia in movement disorders (Rifkin *et al.*, 1978), although they can cause impairments in learning and memory (Everitt and Robbins, 1997). The loss of cholinergic neurons and reduced choline acetyltransferase in Alzheimer's disease (Francis *et al.*, 1999) lies behind the widespread use of cholinesterase inhibitors to enhance cholinergic transmission and thereby alleviate cognitive symptoms in Alzheimer's disease (Rogers *et al.*, 1998). This cholinergic hypothesis has led to research into the role of cholinergic therapies in other dementias, including syndromes arising from FTLD.

Frontotemporal dementia

Cholinergic pathways are affected in FTD but not to the same extent as in Alzheimer's disease. While there is some loss of cholinergic neuronal markers in the nucleus basalis, overall cholinergic pathways to the cortex appear unaffected. Choline acetyltransferase, the enzyme for the synthesis of acetylcholine, can be used as a marker of presynaptic cholinergic neuron integrity. Post-mortem levels of choline acetyltransferase are reduced in the nucleus basalis of Meynert and the hypothalamus but are normal in the frontal, temporal and parietal lobes (Wood *et al.*, 1983; Hansen *et al.*, 1988; Sparks and Markesbery, 1991; Procter *et al.*, 1999). Acetylcholinesterase, which catalyses the breakdown of acetylcholine, is predominantly located on the presynaptic cholinergic neurons. Levels are reduced in the nucleus basalis at post-mortem (Sparks and Markesbery, 1991) but have been normal in the thalamus and cerebral cortex when measured *in vivo* with ^{11}C-MP4A PET (Fig. 5B and C) (Hirano *et al.*, 2010) or at post-mortem (Meier-Ruge *et al.*, 1984; Sparks and Markesbery, 1991).

Studies are inconsistent on cholinergic receptors in bvFTD. ^{123}IQNB SPECT imaging of two patients with Pick's disease indicated reduced muscarinic receptor density in the frontal and temporal cortex (Weinberger *et al.*, 1991) consistent with autoradiography in a case report (Yates *et al.*, 1980). In contrast two studies found no significant change in muscarinic receptor density post-mortem (Wood *et al.*, 1983; Procter *et al.*, 1999).

There is evidence of a cholinergic deficit in primary progressive aphasia. In patients with semantic dementia there was loss of muscarinic receptors in the temporal lobe (Odawara *et al.*, 2003). Disproportionate atrophy of the basal forebrain nuclei was identified in a high resolution MRI study, most evidently in the semantic variant, and to a lesser extent the non-fluent variant (Teipel *et al.*, 2016). This is relevant in view of the evidence that the frontotemporal language networks of a healthy brain receive significant cholinergic inputs (Amunts *et al.*, 2010). The logopenic variant had minimal structural change, despite its strong clinicopathological correlation with Alzheimer's disease.

Despite the possible cholinergic deficits in bvFTD and PPA, cholinesterase inhibitors do not convincingly improve cognitive function. An open label non-randomized study found that behavioural changes improved with rivastigmine, in comparison to a group that took antipsychotics and benzodiazepines (Moretti *et al.*, 2004). In contrast bvFTD patients taking donepezil had worsening disinhibition and compulsive behaviour (Mendez *et al.*, 2007). A randomized, double-blind trial of galantamine versus placebo found no effect on cognitive function or activities of daily living (Kertesz *et al.*, 2008).

Progressive supranuclear palsy and corticobasal syndrome

There are marked cholinergic deficits in PSP, which may contribute not only to cognitive impairment but also postural instability via the pedunculopontine nucleus (Jellinger, 1988; Warren *et al.*, 2005). There is loss of cholinergic neurons and their presynaptic terminals in many subcortical regions in PSP. Choline acetyltransferase is reduced in the nucleus basalis of Meynert, midbrain nuclei and pedunculopontine nucleus (Fig. 5D) (Juncos *et al.*, 1991; Javoy-Agid, 1994; Kasashima and Oda, 2003) as well as the putamen, caudate and pallidum (Ruberg *et al.*, 1985;

Pierot *et al.*, 1988; Javoy-Agid, 1994). Presynaptic acetylcholine transporters are reduced in the putamen and substantia nigra, while sparing the globus pallidus and cerebral cortex (Fig. 5F) (Suzuki *et al.*, 2002). ^{123}I-IBVM SPECT, which binds to acetylcholine transporters, reveals reduced signal in the thalamus of PSP patients (Fig. 5E) (Mazere *et al.*, 2012) and PET studies show reduced acetylcholinesterase binding in the pons, basal ganglia and thalamus (Shinotoh *et al.*, 1999; Gilman *et al.*, 2010; Hirano *et al.*, 2010).

There is loss of cholinergic projections from the brainstem (pedunculopontine and laterodorsal tegmental nuclei)

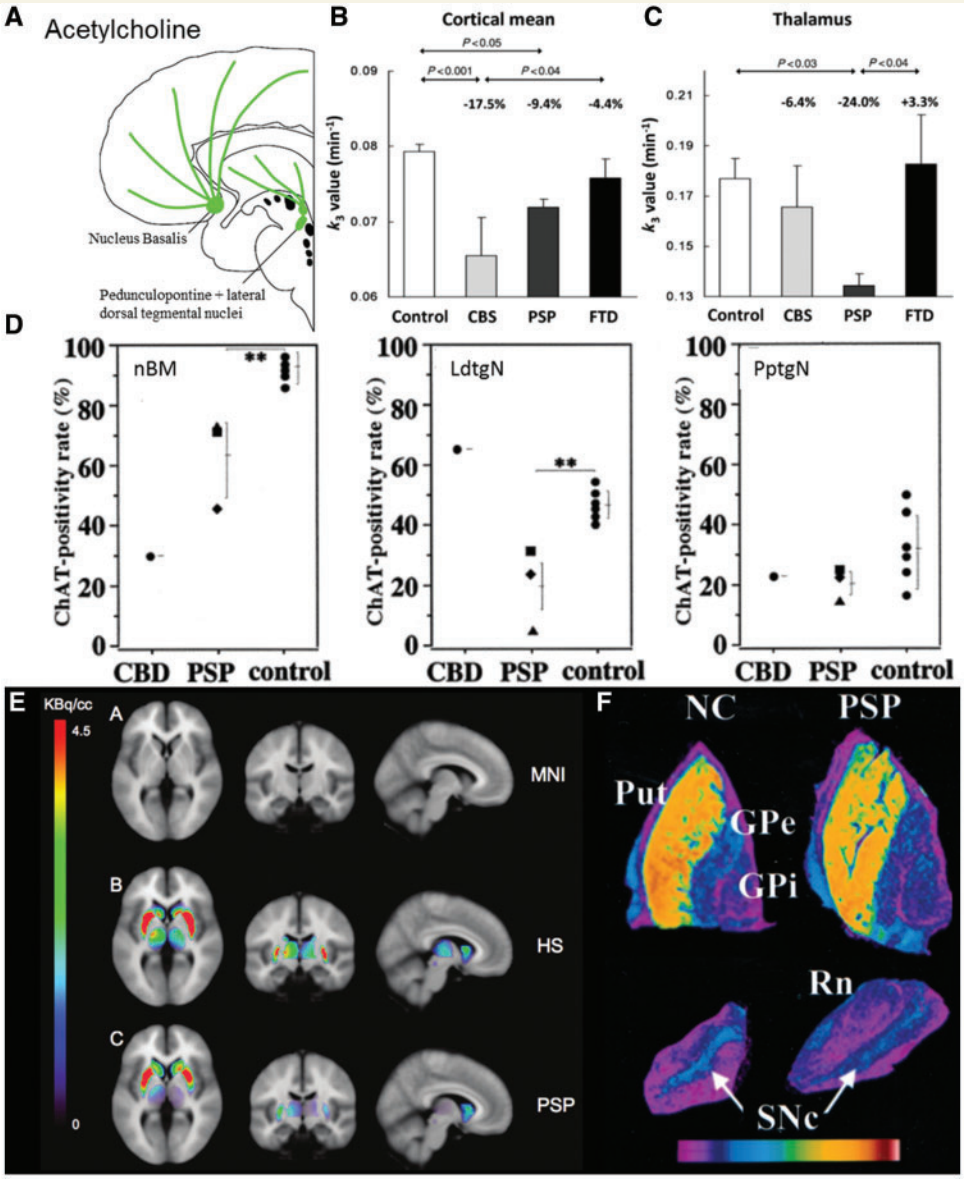


Figure 5 Cholinergic deficits in FTD, PSP and CBS. (**A**) Schematic illustration of cholinergic pathways. (**B** and **C**) ^{11}C-MP4A PET, a measure of acetylcholinesterase activity, in healthy controls, CBS, PSP and FTD. Cortical k_3 (a measure of PET ligand binding) is reduced in CBS and PSP but not FTD. Thalamic mean k_3 is reduced in PSP but not CBS or FTD. From Hirano *et al.* (2010). Reprinted with permission from Oxford University Press. (**D**) Quantitative estimation of choline acetyltransferase (ChAT) positivity rate (%) in the nucleus basalis of Meynert (nBM), laterodorsal tegmental (LdtgN) and pedunculopontine tegmental (PptgN) nuclei. From Kasashima and Oda (2003). Reprinted with permission of Springer. (**E**) SPECT of acetylcholine transporter. MNI = MRI template; HS = healthy subject. Specific binding in the striatum, thalamus and pedunculopontine nucleus extracted by subtracting reference from region of interest binding. Binding is lower in the thalamus and pedunculopontine nucleus. From Mazere *et al.* (2012). Reproduced with permission from the Radiological Society of North America. (**F**) Autoradiogram of brain tissue from a healthy control (NC) and PSP. ^{3}H-vesamicol binding to acetylcholine transporter (VAChT). There is reduction in binding in the putamen (Put) and substantia nigra pars compacta (SNc). Rn = red nucleus. Image intensity converted to pseudocolour representation according to key. From Suzuki *et al.* (2002). Reproduced with permission from Wolters Kluwer.

to the thalamus (Hirsch *et al.*, 1987; Jellinger, 1988; Kasashima and Oda, 2003). The pedunculopontine loss is especially relevant to the impairment of movement, gait and muscle tone in PSP (Benarroch, 2013). Deep brain stimulation of the pedunculopontine nucleus has been reported to improve PSP motor symptoms in selected cases, but definitive trials are lacking (Hazrati *et al.*, 2012; Servello *et al.*, 2014). One study reported that acetylcholine receptors are relatively well preserved in the striatum (Ruberg *et al.*, 1985) while other studies report a reduction in muscarinic and nicotinic receptors in the striatum (Landwehrmeyer and Palacios, 1994; Warren *et al.*, 2007*b*). With such small series, and variable methods, it is unclear if technical or phenotypic differences account for these inconsistencies.

There is also some limited evidence for cholinergic deficits in the cerebral cortex. Acetyltransferase levels are reduced in frontal cortex of PSP patients compared with controls both at post-mortem and with *in vivo* PET imaging (Ruberg *et al.*, 1985; Javoy-Agid, 1994; Hirano *et al.*, 2010). However, cortical muscarinic receptor levels appear to be unaffected in PSP, with levels similar to controls in PET studies (Ruberg *et al.*, 1985; Asahina *et al.*, 1998).

In clinical practice, cholinergic blockade with hyoscine is sometimes used for sialorrhoea and drooling, but it may worsen gait and memory in PSP (Litvan *et al.*, 1994). Despite this deleterious effect of anti-cholinergic medication, the converse 'pro-cholinergic' treatment by cholinesterase inhibitors is typically ineffective (Stamelou and Höglinger, 2016). A case series of rivastigmine in five patients found that it improved working memory, memory and verbal fluency but worsened motor function (Liepelt *et al.*, 2010). A randomized, placebo-controlled crossover study of donepezil showed no effect on quality of life, Progressive Supranuclear Palsy Rating Scale or global cognitive function (Litvan *et al.*, 2001). This study did find a slight improvement in one memory task but also worsened motor activities of daily living (Litvan *et al.*, 2001). Interestingly, the syndrome of pure akinesia and gait freezing, now recognized as a prodromal variant of PSP (Höglinger *et al.*, 2017) has been reported to improve after cholinesterase inhibition in an open case series (Kondo, 2006). Despite this encouraging study, replication in a placebo controlled trial is awaited.

In a post-mortem study of a single case of CBD the number of cholinergic acetyltransferase positive neurons in the nucleus basalis of Meynert was reduced (Kasashima and Oda, 2003). This was replicated *in vivo*, with reduced acetylcholinesterase levels in the frontal, parietal and occipital cortex (Hirano *et al.*, 2010). There is insufficient data on cholinergic treatment of patients with CBS, although it should be noted that ~20–40% of patients with CBS have Alzheimer's-type pathology not CBD (Boeve *et al.*, 1999; Alexander *et al.*, 2014). It is plausible, but not proven, that the Alzheimer pathology cases of CBS would respond better to cholinesterase inhibitors despite appearing similar to CBD cases in other clinical features. We therefore anticipate that clinical trials of CBS will stratify treatment according to biomarkers, such as amyloid PET imaging or CSF, to distinguish CBD from Alzheimer's disease aetiology.

Glutamate

Glutamate is the principle excitatory neurotransmitter in the brain. Glutamate acts on fast, short acting ionotropic receptors and slower but longer acting metabotropic glutamate receptors (mGluR) (Meldrum, 2000). The three main ionotropic glutamate receptors are named after the selective agonists *N*-methyl D-aspartate (NMDA), α-amino-3-hydroxyl-5-methyl-isoxazolepropionic acid (AMPA) and kainite (Meldrum, 2000). Glutamate has an important role in learning and memory formation. For example, NMDA receptors in the hippocampus regulate long term potentiation (Morris *et al.*, 1986; Rowland *et al.*, 2005) while sustained activation of the dorsolateral prefrontal cortex during working memory requires NMDA stimulation (Wang *et al.*, 2013). NMDA receptor antagonists impair attention, reaction time, processing speed and working memory in healthy humans (Malhotra *et al.*, 1996; Newcomer *et al.*, 2000), and may exacerbate psychotic symptoms (Gilmour *et al.*, 2012). Glutamate signalling through NMDA receptors is required to create and maintain gamma oscillations (Carlé *et al.*, 2011), which support many higher cognitive functions (Lange *et al.*, 1997; Bartos *et al.*, 2007; Williams and Boksa, 2010; Gaetz *et al.*, 2012; Gorelova *et al.*, 2012).

While glutamatergic transmission is essential for cognition, excessive glutamatergic transmission may also be harmful, promoting excitotoxic neuronal death (Mark *et al.*, 2001) that contributes to neurodegeneration in models of Alzheimer's disease (Danysz *et al.*, 2000; Kalia *et al.*, 2008). It is possible that FTLD is similarly affected. Functionally, continuous overactivation of NMDA receptors alters the efficacy of information processing by reducing the sensitivity of neural networks and impairing their ability to detect a relevant signal from upstream neurons (Danysz *et al.*, 2000). Memantine is a low affinity NMDA receptor antagonist and selectively blocks pathological tonic NMDA receptor activation (associated with amyloid plaques) without preventing NMDA-mediated synaptic transmission. In addition to potential symptomatic effects on cognition (Reisberg *et al.*, 2003), it might therefore also reduce chronic glutamatergic excitotoxicity (Danysz and Parsons, 2012).

Frontotemporal dementia

There is preclinical and clinical evidence that glutamate is important in the pathogenesis of FTD. For example, transgenic mice that express pathological human tau have repetitive and disinhibited behaviour, coupled with NMDA receptor hypofunction (Warmus *et al.*, 2014). Treatment with an NMDA agonist restores their behaviour. Transgenic mice expressing mutations in the FTD-

associated gene *CHMP2B*, have altered AMPA receptor composition (Gascon *et al.*, 2014), with impaired sociability, which can be reversed if normal AMPA receptor composition is restored (Gascon *et al.*, 2014). Mouse models expressing pathological human tau suggest glutamate mediated excitotoxicity could accelerate neuronal loss in tauopathies such as FTD (Decker *et al.*, 2016). These preclinical studies raise the possibility that pharmacological glutamatergic treatments might reduce symptom severity and improve prognosis.

In patients, glutamatergic pyramidal neurons are reduced in the thalamus, frontal and temporal cortex (Ferrer, 1999). Magnetic resonance spectroscopy of patients with FTD has found glutamate/glutamine levels are reduced in the frontal and temporal lobes (Fig. 6A) (Ernst *et al.*, 1997; Sarac *et al.*, 2008). There is an inverse correlation between CSF glutamate levels and verbal agitation (Vermeiren *et al.*, 2013).

Both ionotropic and metabotropic glutamate receptors are affected in FTD. For example, AMPA and NMDA receptor densities are reduced in the frontal and temporal lobes of patients at post-mortem (Francis *et al.*, 1993; Procter *et al.*, 1999; Bowen *et al.*, 2008), while AMPA receptor composition is also abnormal (Fig. 6B) (Gascon *et al.*, 2014). Using the ligand ^{11}C-ABP688, PET of patients with bvFTD found reduced availability of metabotropic glutamate receptors (mGluR5) in the frontal and temporal lobes, basal ganglia and thalamus (Leuzy *et al.*, 2016). However, one study found that post-mortem levels of metabotropic glutamate receptors type 1 and 5 (mGluR1 and 5) are increased in the frontal cortex (Dalfo *et al.*, 2005).

A phase II randomized placebo-controlled trial of memantine showed no benefit in patients with bvFTD (Boxer *et al.*, 2013). A double-blind placebo-controlled crossover trial of memantine in PPA was also negative (Johnson *et al.*, 2010). However, these studies were not powered to detect small treatment effects. While there may be no true benefit, it remains possible that small treatment effects exist which would be amplified if other neurotransmitter deficits were also normalized, in particular GABAergic impairments. The GABA–glutamate interaction is of particular relevance because it supports precisely tuned oscillatory dynamics of neural circuits for cognition (Bastos *et al.*, 2012).

Progressive supranuclear palsy and corticobasal syndrome

Loss of glutamatergic neurons in the basal ganglia may partly explain why dopaminergic therapy is ineffective in PSP. Glutamate modulates dopamine release and loss of glutamatergic neurons may prevent patients compensating for dopaminergic neuron loss (Lange *et al.*, 1997). Glutamatergic neurons from the caudal intralaminar nuclei that form the thalamostriatal pathway are reduced in PSP (Fig. 6C) (Henderson *et al.*, 2000). However, the severity of this neuronal loss does not correlate with disease duration or severity (Henderson *et al.*, 2000). In contrast, NMDA receptor levels are preserved in the frontal and temporal lobes and striatum (Holemans *et al.*, 1991).

Glutamatergic over-activity is implicated in Parkinson's disease and by analogy has been considered a candidate mechanism of accelerated neurodegeneration in PSP (Lange *et al.*, 1997). Amantadine is an NMDA receptor antagonist that is often used to treat motor symptoms (Kompoliti *et al.*, 1998; Stamelou and Höglinger, 2016), although there is no randomized controlled trial evidence of efficacy in PSP. Gabapentin has complex pharmacodynamics and in part acts by increasing GABA and reducing glutamate levels (Sills, 2006). A randomized blinded trial of gabapentin in 14 patients found no effect on motor function but improved outcome in anti-saccade control (Poujois *et al.*, 2007), which is associated with frontal lobe integrity (Mirsky *et al.*, 2011; Perneczky *et al.*, 2011) and commonly impaired in PSP (Garbutt *et al.*, 2008; Zhang *et al.*, 2016). There are no reports of post-mortem or *in vivo* glutamate measurements in CBS.

Gamma-aminobutyric acid

GABA is the predominant inhibitory neurotransmitter in the brain, formed by glutamate decarboxylase conversion of glutamate to GABA in interneurons. There are two classes of GABA receptors: $GABA_A$ ligand-gated ion channels and $GABA_B$ G protein coupled neuromodulatory receptors. GABAergic inhibitory neurons dampen and balance excitation within neural circuits, but do more than simply counteract excitatory glutamatergic neurons. They have a key role in the regulation of oscillatory dynamics, including the generation of gamma oscillations and regulation of the magnitude and frequency of these oscillations (Owens and Kriegstein, 2002; Mann and Paulsen, 2007; Buzsáki and Wang, 2012). This is essential for coordinating information transfer and information processing in the brain (Fries, 2009; Bastos *et al.*, 2012). Increasing synaptic GABA levels increases gamma power during cognitive control tasks (Frankle *et al.*, 2009) whereas inhibiting GABA receptors reduces gamma oscillatory power and impairs inhibition and working memory (Hines *et al.*, 2013). Gamma oscillations correlate with GABA concentrations (as measured by magnetic resonance spectroscopy) in the visual (Muthukumaraswamy *et al.*, 2009), primary motor (Gaetz *et al.*, 2011) and dorsolateral prefrontal cortex (Kujala *et al.*, 2015) while $GABA_A$ receptor density (as measured by flumazenil-PET) correlates with gamma frequency and magnitude (Kujala *et al.*, 2015). Impaired GABA neurotransmission has been implicated in a

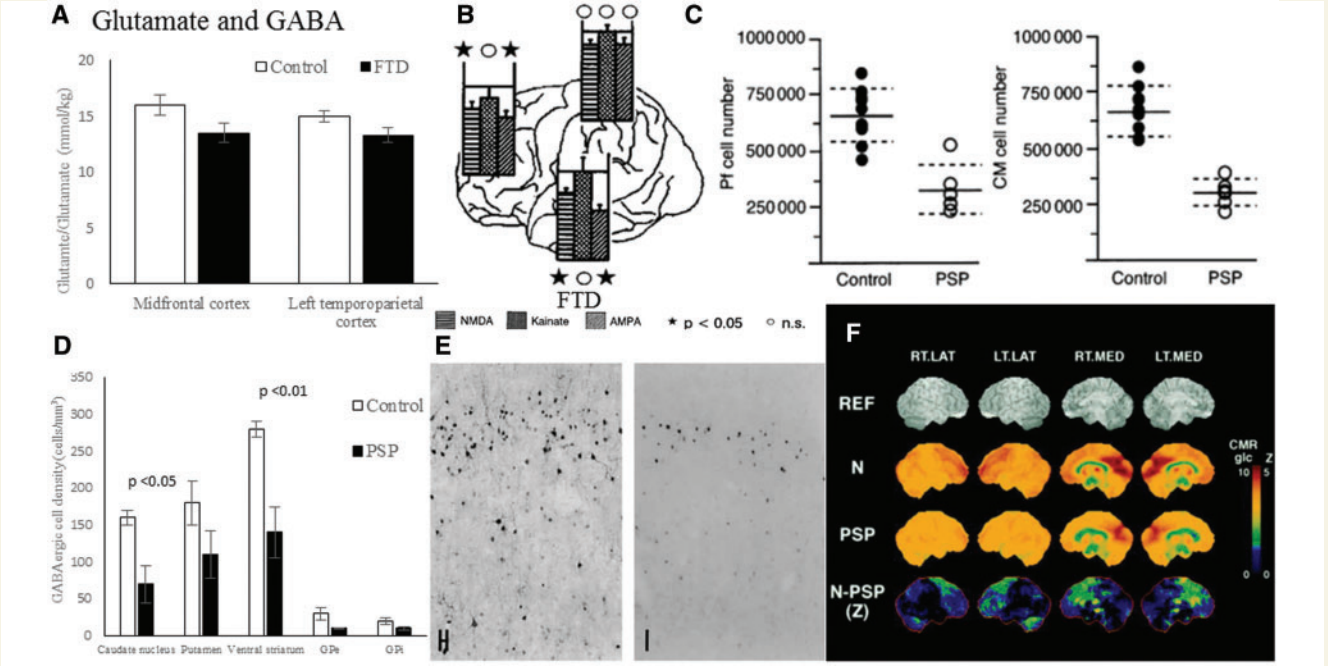


Figure 6 Glutamate and GABA deficits in FTD and PSP. (**A**) Mean metabolite concentrations using magnetic resonance spectroscopy. Glutamine–glutamate concentrations are reduced in the frontal cortex of FTD. Graph of data from Ernst *et al.* (1997). Reprinted with permission from the authors and the Radiological Society of North America. (**B**) Post-mortem glutamatergic receptor binding in FTD. Binding to NMDA and AMPA receptors is reduced in the frontal and temporal lobes. From Procter *et al.* (1999). Reprinted with permission from S. Karger AG. (**C**) Neuron number in two thalamic nuclei [parafascicular (Pf) and centromedian (CM)] that contain glutamatergic neurons is reduced in PSP compared with controls. Adapted from Henderson *et al.* (2000), with permission from the authors and Oxford University Press. (**D**) Numbers of GABAergic neurons (measured by glutamic acid decarboxylase mRNA expression) in the striatum and pallidum in controls and PSP patients. There is significant reduction in striatal GABAergic neurons in patients. Graph of data from Levy *et al.* (1995), reprinted with permission from the authors and Wolters Kluwer. (**E**) Calbindin immunohistochemistry of GABAergic cells in the frontal cortex of FTD and control brains. From Ferrer (1999). Reproduced with permission from Karger. (**F**) ^{11}C-flumazenil PET binding to benzodiazepine receptors in healthy controls (N), PSP and the group difference in cortical and subcortical areas. From Foster *et al.* (2000). Reproduced with permission from Wolters Kluwer.

number of brain disorders including schizophrenia (Gonzalez-Burgos *et al.*, 2011) and Huntington's disease (Reynolds and Sally, 1990) as well as the syndromes associated with FTLD.

Frontotemporal dementia

The subgroup of GABAergic neurons that bind calbindin-D28k are reduced in upper neocortical layers of the frontal and temporal cortex in FTD (Ferrer, 1999), especially in layers II and III (Fig. 6E) (Ferrer, 1999). However, in the same study, the subgroup of GABAergic basket and chandelier neurons that bind parvalbumin were preserved (Ferrer, 1999). The superficial layers II and III are the main source of cortico-cortical feedforward efferent projections and receive feedback projections from deep layers. Gamma oscillations and coherence are reduced between the frontal lobes of patients with bvFTD (Hughes *et al.*, 2013), which may relate to loss of cortical feedforward information processing and cognitive decline (Mann and Paulsen, 2007). GABA concentrations are also decreased in the basal ganglia in bvFTD (Kanazawa *et al.*, 1988). GABAergic approaches to treatment of FTD symptoms warrant further investigation, but evidence of their clinical efficacy is currently lacking.

Progressive supranuclear palsy and corticobasal syndrome

GABAergic interneurons are reduced in PSP. A post-mortem study found a 50–60% decrease in the number of GABAergic neurons (estimated from the number expressing glutamic acid decarboxylase mRNA, by *in situ* hybridization) in the caudate nucleus, putamen, ventral striatum and pallidum (Fig. 6D) (Levy *et al.*, 1995). Binding to $GABA_A$ receptors is reduced in the globus pallidus but preserved in the striatum (Landwehrmeyer and Palacios, 1994; Suzuki *et al.*, 2002). A flumazenil-PET study showed loss of $GABA_A$ receptors compared with controls (Fig. 6F) (Foster *et al.*, 2000).

There are case reports of GABA receptor agonists improving speech, eye movements, akinesia and rigidity in PSP (Daniele *et al.*, 1999; Cotter *et al.*, 2010; Dash, 2013; Chang and Weirich, 2014), but in the authors'

experience this phenomenon is very uncommon and there are no randomized placebo controlled studies. There are no reports of post-mortem or *in vivo* assessments of GABA in CBS.

Towards better symptomatic treatment in frontotemporal lobar degeneration

Despite their overlapping clinical phenotypes and pathological features, the major clinical syndromes associated with FTLD have different neurotransmitter deficits (summarized in Table 1). Restoring these deficits, individually or in combination, has the potential to improve cognitive, behavioural and motor symptoms. However, the evidence base for therapeutic effects is dominated by small, open-label studies in unstratified populations.

To summarize the evidence for selective deficits, FTD causes loss of serotonergic and dopaminergic neurons and receptor densities, whilst noradrenergic and cholinergic pathways are relatively preserved. There is loss of both glutamatergic and GABAergic neurons but the functional consequence of their deficits is unclear, in part because of the complex and dynamic interaction between GABAergic and glutamatergic neurons in cortical circuits. In PSP, the most evident neurotransmitter deficits are dopaminergic, noradrenergic and cholinergic, whilst serotonergic projections appear to be relatively preserved. There is evidence of a glutamatergic and GABAergic deficit, which provide potential avenues for non-dopaminergic therapy. There is limited evidence on the neurotransmitter deficits in CBS, with some evidence of deficits in both cholinergic and dopaminergic pathways.

Although clinical trials and cases series have not shown consistent benefits from the modulation of neurotransmitters in FTLD syndromes, this may be due to weaknesses in research methodology rather than a true lack of effect. For example, many studies use what would now be considered as outdated and inaccurate diagnostic criteria, which reduces the applicability to contemporary patient populations. Many clinical studies are open-labelled and in small series, sometimes fewer than 10 patients, giving little power to detect benefits, let alone guide therapeutic stratification. There is a paucity of replication studies, and where studies contain a 'conceptual replication', details in research methodology confound the interpretation of seemingly conflicting results. Much of the research comes from post-mortem brain tissue, which has the advantage of providing concurrent pathological validation of the disorder. However, post-mortem studies have tended to use small series ($n < 10$), and by the nature of post-mortem material, they cannot provide insights into the early or sequential changes in neurotransmitter systems. Future work will benefit from longitudinal and *in vivo* studies, exploiting advances in PET ligands (Finnema *et al.*, 2015), ultra-high field MRI and spectroscopy (Agarwal and Renshaw, 2012), and CSF biomarkers. Early PET studies of necessity used non-specific ligands, which may not correspond to the receptor specificities of psychopharmacological agents. This is not to criticise either body of work, but it does impair the direct comparison of imaging and pharmacological studies, even where comparable patient groups are studied. Similarly, future preclinical studies would benefit from within-sample comparisons of different methods, seeking not only cross-validation of biochemical or receptor assays, but also the relationship between different measures, for example neuronal loss, receptor density, and biochemical turnover of a neurotransmitter. Such cross-modal studies would provide a powerful resource to model disease progression and functionally relevant compensatory changes in FTLD.

Further research is required into the effect of FTLD on different neurotransmitter receptors and their subtypes, not only to guide candidate drug selection, but also to determine the progression of changes from early to late stage disease. Without this detailed knowledge, there is a risk that a given drug may be effective at one stage of disease but be counterproductive at another. Such non-linear dose-response effects are common in dopaminergic treatments of Parkinson's disease (Cools, 2006; Rowe *et al.*, 2008), but the principal of 'U-shaped' responses to drug treatment also affect serotonergic (Macoveanu *et al.*, 2013; Hughes *et al.*, 2015) and noradrenergic drugs (Ye *et al.*, 2015). Where drug effects follow a 'U-shaped' response, the focal nature of FTLD presents a special challenge. Take the behavioural variant of FTD as an example. If prefrontal and temporal cortex are deficient in a given neurotransmitter (whether neuronal density, receptor density, or afferent projections), but motor, parietal and occipital cortex are not, then any systemic treatment based on restoring that neurotransmitter in frontal and temporal cortex will risk 'overdosing' the unaffected areas. This problem is well established in Parkinson's disease, in the sometimes difficult balance between motor disability and impulse control disorders (Napier *et al.*, 2015). The application of focal treatments to restore biochemical function, such as dopaminergic stem cell transplants or gene therapy to induce dopamine synthesis in striatal cells, can overcome some of the adverse consequences of systemic drug treatment in Parkinson's disease. However, such localized treatments seem even more challenging in a diffuse lobar cortical disorder. Similarly, the use of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to restore or enhance focal and selective neurotransmitter systems is having a major impact in drug discovery and systems neuroscience (Roth, 2016), but seems far from direct clinical applications. For the time being, systemic drug delivery is likely to be the mainstay of clinical therapeutics.

We suggest three steps to improve the likelihood of new and effective pharmacological treatments. First, clarification of the links between individual neurotransmitters and specific clinical end-points. We suggest that identifying the

neurotransmitter deficits that correlate with clinical severity is essential to guide treatment studies. This evidence may draw on *in vivo* imaging and CSF studies and post-mortem immunohistochemistry of cases that have been regularly phenotyped during disease progression. This would be a considerable undertaking, but possible if added to existing longitudinal studies (Rohrer *et al.*, 2015*b*; Woodside *et al.*, 2016).

Second, it is essential to implement stratification of patients in future trials, selecting participants for their relevant symptoms rather than the diagnosis alone. For example, in a trial to demonstrate a clinical effect of serotonergic treatment on impulsivity in bvFTD, based on experimental medicines evidence (Hughes *et al.*, 2015), participants should not merely have bvFTD by consensus criteria, but also have impulsivity; noting that disinhibition is one of six criteria whereas only three are required for the diagnosis. Including patients with bvFTD who are not disinhibited is likely to reduce the power of a symptomatic treatment trial. Moreover, it may be better to include all patients with disinhibition arising from syndromes associated with FTLD in which disinhibition is common but not a diagnostic criterion (including semantic variant PPA, CBS and PSP) (Lansdall *et al.*, 2017). This would increase the power and relevance of the trial to a wider patient group.

Third, future clinical trials need careful selection of relevant outcome tools, especially where drugs are repurposed for new end-points. For example, selective serotonin reuptake inhibitors are licenced for affective disorders but it would be wrong to use a depression rating scale in bvFTD or PSP where the expected effect is on impulsivity. Similarly, cholinesterase inhibitors are licenced for Alzheimer's disease for their effect on cognition but cognitive function scales would be inappropriate if the intended effect in say PSP were on gait and balance.

For each of the disorders associated with FTLD, it is likely that experimental medicines studies with biomarker based surrogate end-points are needed before randomized placebo controlled clinical trials are started. The evidence presented in this review suggests that there are strong grounds to pursue such experimental medicine studies, drawing on the preclinical psychopharmacology models and patient data, to minimize the risks of clinical trials. There are many candidate end-points, to demonstrate human target engagement and efficacy in the CNS. These may be used singly or in combination, including functional imaging; magnetic resonance spectroscopy (Cai *et al.*, 2012; Muthukumaraswamy *et al.*, 2013); PET imaging of neurotransmitters receptors and occupancy; magneto-/electro-encephalographic physiological indices of oscillatory dynamics (Muthukumaraswamy, 2014), focal function (Hughes *et al.*, 2015) and network interactions (Moran *et al.*, 2011, 2013; Hughes *et al.*, 2013; Gilbert *et al.*, 2016); CSF biomarkers; and neurocognitive batteries (Kehagia *et al.*, 2014).

This review has focused on the symptomatic benefits of restoring neurotransmitters. However, some of these agents, like trazodone, have wider effects on pathogenesis and neuronal survival that may also lead to disease modification or slowing of disease progression (Halliday *et al.*, 2017). Even where the principal effect is symptomatic, this may improve survival, such as the impact of dopaminergic therapy in Parkinson's disease after its introduction in the late 1960's (Uitti *et al.*, 1993). Relief of apathy, disinhibition, falls, and dementia in syndromes associated with FTLD might therefore improve survival as well as interim quality of life.

Finally, we note that there has been recent concern regarding international pharma investment in disorders of the CNS (Fineberg *et al.*, 2013). However, we suggest that there is scope and grounds for optimism for progress towards effective symptomatic pharmacological therapies. Such treatments, based on restoring neurotransmitter deficits, would reduce the cost, social and health burden of FTLD.

Funding

This review was funded by the Holt Fellowship (A.M.), the Wellcome Trust (JBR 103838), and the National Institute for Health Research Cambridge Biomedical Research Centre and Cambridge Brain Bank.

Supplementary material

Supplementary material is available at *Brain* online.

References

Agarwal N, Renshaw PF. Proton MR spectroscopy—detectable major neurotransmitters of the brain: biology and possible clinical applications. AJNR Am J Neuroradiol 2012; 33: 595–602.

Albani D, Prato F, Fenoglio C, Batelli S, Dusi S, De Mauro S, et al. Association study to evaluate the serotonin transporter and apolipoprotein E genes in frontotemporal lobar degeneration in Italy. J Hum Genet 2008; 53: 1029–33.

Alexander SK, Rittman T, Xuereb JH, Bak TH, Hodges JR, Rowe JB. Validation of the new consensus criteria for the diagnosis of corticobasal degeneration. J Neurol Neurosurg Psychiatry 2014; 85: 925–9.

Amunts K, Lenzen M, Friederici AD, Schleicher A, Morosan P, Palomero-Gallagher N, et al. Broca's region: novel organizational principles and multiple receptor mapping. PLoS Biol 2010; 8: e1000489.

Anneser JM, Jox RJ, Borasio GD. Inappropriate sexual behaviour in a case of ALS and FTD: successful treatment with sertraline. Amyotroph Lateral Scler 2007; 8: 189–90.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013; 80: 496–503.

Arnold G, Schwarz J, Tatsch K, Kraft E, Wächter T, Bandmann O, et al. Steele-Richardson-Olszewski-syndrome: the relation of dopamine D2 receptor binding and subcortical lesions in MRI. J Neural Transm 2002; 109: 503–12.

Arnold SE, Toledo JB, Appleby DH, Xie SX, Wang LS, Baek Y, et al. Comparative survey of the topographical distribution of signature molecular lesions in major neurodegenerative diseases. J Comp Neurol 2013; 521: 4339–55.

Artigas F. Serotonin receptors involved in antidepressant effects. Pharmacol Ther 2013; 137: 119–31.

Asahina M, Suhara T, Shinotoh H, Inoue O, Suzuki K, Hattori T. Brain muscarinic receptors in progressive supranuclear palsy and Parkinson's disease: a positron emission tomographic study. J Neurol Neurosurg Psychiatry 1998; 65: 155–63.

Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 2005; 28: 403–50.

Aston-Jones G, Waterhouse B. Locus coeruleus: from global projection system to adaptive regulation of behavior. Brain Res 2016; 1645: 75–8.

Baizabal-Carvallo JF, Jankovic J. Parkinsonism, movement disorders and genetics in frontotemporal dementia. Nat Rev Neurol 2016; 12: 175–85.

Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006; 442: 916–19.

Barnes NM, Sharp T. A review of central 5_HT receptors and their function. Neuropharmacology 1999; 38: 1083–152.

Baron JC, Maziere B, Loc'h C, Cambon H, Sgouropoulos P, Bonnet AM, et al. Loss of striatal [76Br]bromospiperone binding sites demonstrated by positron tomography in progressive supranuclear palsy. J Cereb Blood Flow Metab 1986; 6: 131–6.

Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci 2007; 8: 45–56.

Bastos AM, Usrey WM, Adams RA, Mangun GR, Fries P, Friston KJ. Canonical microcircuits for predictive coding. Neuron 2012; 76: 695–711.

Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 2011; 63: 182–217.

Benarroch EE. Pedunculopontine nucleus: functional organization and clinical implications. Neurology 2013; 80: 1148–155.

Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, et al. Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. Brain 2008; 131: 732–46.

Boeve BF, Boylan KB, Graff-Radford NR, Dejesus-Hernandez M, Knopman DS, Pedraza O, et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain 2012; 135: 765–83.

Boeve BF, Maraganore DM, Parisi JE, Ahlskog JE, Graff-Radford N, Caselli RJ, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. Neurology 1999; 53: 795.

Borroni B, Grassi M, Agosti C, Premi E, Archetti S, Alberici A, et al. Establishing short-term prognosis in frontotemporal lobar degeneration spectrum: role of genetic background and clinical phenotype. Neurobiol Aging 2010; 31: 270–9.

Bowen DM, Procter AW, Mann DMA, Snowden JS, Esiri MM, Neary D, et al. Imbalance of a serotonergic system in frontotemporal dementia: implication for pharmacotherapy. Psychopharmacology. 2008; 196: 603–10.

Boxer AL, Boeve BF. Frontotemporal dementia treatment: current symptomatic therapies and implications of recent genetic, biochemical, and neuroimaging studies. Alzheimer Dis Assoc Disord 2007; 21: S79–87.

Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2013; 12: 149–56.

Brooks DJ, Ibanez V, Sawle GV, Playford ED, Quinn N, Mathias CJ, et al. Striatal D2 receptor status in patients with Parkinson's disease, striatonigral degeneration, and progressive supranuclear palsy, measured with 11C-raclopride and positron emission tomography. Ann Neurol 1992; 31: 184–92.

Brunnström H, Friberg N, Lindberg E, Englund E. Differential degeneration of the locus coeruleus in dementia subtypes. Clin Neuropathol 2011; 30: 104–10.

Buzsáki G, Wang XJ. Mechanisms of gamma oscillations. Annu Rev Neurosci 2012; 4: 203–25.

Cai K, Nanga RP, Lamprou L, Schinstine C, Elliott M, Hariharan H, et al. The impact of gabapentin administration on brain GABA and glutamate concentrations: a 7T 1H-MRS study. Neuropsychopharmacology 2012; 37: 2764–71.

Canli T, Lesch KP. Long story short: the serotonin transporter in emotion regulation and social cognition. Nat Neurosci 2007; 10: 1103–9.

Carlé NM, Meletis K, Siegle J, Cardin J, Futai K, Vierling-Claassen D, et al. A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. Mol Psychiatry 2011; 17: 537–48.

Castro ME, Pascual J, Romon T, Pazos A. 5-HT 1B receptor binding in degenerative movement disorders. Brain Res 1998; 790: 323–8.

Celada P, Puig MV, Artigas F. Serotonin modulation of cortical neurons and networks. Front Integr Neurosci 2013; 7: 25.

Chaal S, Rowe J. Dopamine Transporter (DAT) imaging can be normal with neuropathologically confirmed Cortiobasal Degeneration. J Neurol Neurosurg Psychiatry 2013; 84: e2.59.

Chandler DJ, Gao WJ, Waterhouse BD. Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. Proc Natl Acad Sci USA 2014; 111: 6816–21.

Chang AY, Weirich E. Trial of zolpidem, eszopiclone, and other GABA agonists in a patient with progressive supranuclear palsy. Case Rep Med 2014; 2014: 107064.

Charnay Y, Léger L. Brain serotonergic circuitries. Dialogues Clin Neurosci 2010; 12: 471–87.

Chinaclia G, Landwehrmeyer B. Serotoninergic terminal transporters are differentially affected in Parkinson's disease and progressive supranuclear palsy: an autoradiographic study with [3H] citalopram. Neuroscience 1993; 54: 691–9.

Chow TW. Goals in symptomatic pharmacologic management of frontotemporal lobar degeneration. Am J Alzheimer's Dis Other Dementias 2002; 17: 267–72.

Cilia R, Rossi C, Frosini D, Volterrani D, Siri C, Pagni C, et al. Dopamine transporter spect imaging in corticobasal syndrome. PLoS One 2011; 6: e18301.

Ciranna L. Serotonin as a modulator of glutamate- and GABA-mediated neurotransmission: implications in physiological functions and in pathology. Curr Neuropharmacol 2006; 4: 101–14.

Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006; 30: 1–23.

Cotter C, Armytage T, Crimmins D. The use of zolpidem in the treatment of progressive supranuclear palsy. J Clin Neurosci 2010; 17: 385–6.

Coull JT, Sahakian BJ, Hodges JR. The α2 antagonist idazoxan remediates certain attentional and executive dysfunction in patients with dementia of frontal type. Psychopharmacology 1996; 123: 239–49.

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

Cubillo A, Smith AB, Barrett N, Giampietro V, Brammer MJ, Simmons A, et al. Shared and drug-specific effects of atomoxetine and methylphenidate on inhibitory brain dysfunction in medication-naive ADHD boys. Cereb Cortex 2014; 24: 174–85.

Dalfo E, Albasanz JL, Rodriguez A, Martín M, Ferrer I. Abnormal group I metabotropic glutamate receptor expression and signaling in the frontal cortex in Pick disease. J Neuropathol Exp Neurol 2005; 64: 638–47.

Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron 2011; 69: 680–94.

Daniele A, Moro E, Bentivoglio AR. Zolpidem in progressive supranuclear palsy. N Engl J Med 1999; 341: 543–4.

Danysz W, Parsons CG. Alzheimer's disease, β-amyloid, glutamate, NMDA receptors and memantine—searching for the connections. Br J Pharmacol 2012; 167: 324–52.

Danysz W, Parsons CG, Mobius HJ, Stoffler A, Quack G. Neuroprotective and symptomatological action of memantine relevant for Alzheimer's disease–a unified glutamatergic hypothesis on the mechanism of action. Neurotox Res 2000; 2: 85–97.

Dash SK. Zolpidem in progressive supranuclear palsy. Case Rep Neurol Med 2013; 2013: 250865.

Dawson LA, Nguyen HQ, Li P. The 5-HT6 receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. Neuropsychopharmacology 2001; 25: 662–8.

Deakin JB, Rahman S, Nestor PJ, Hodges JR, Sahakian BJ. Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial. Psychopharmacology 2004; 172: 400–8.

Decker JM, Krüger L, Sydow A, Dennissen FJA, Siskova Z, Mandelkow E, et al. The Tau/A152T mutation, a risk factor for frontotemporal spectrum disorders, leads to NR2B receptor mediated excitotoxicity. EMBO Rep 2016; 17: 552–69.

Deng H, Gao K, Jankovic J. The role of FUS gene variants in neurodegenerative diseases. Nat Rev Neurol 2014; 10: 337–48.

Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. J Neurol 1999; 246 (Suppl 2): II6–15.

Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA. Neuropathology of variants of progressive supranuclear palsy. Curr Opin Neurol 2010; 23: 394–400.

Engelborghs S, Vloeberghs E, Le Bastard N, Van Buggenhout M, Mariën P, Somers N, et al. The dopaminergic neurotransmitter system is associated with aggression and agitation in frontotemporal dementia. Neurochem Int 2008; 52: 1052–60.

Engelborghs S, Vloeberghs E, Maertens K, Marescau B, De Deyn PP. Evidence for an association between the CSF HVA:5-HIAA ratio and aggressiveness in frontotemporal dementia but not in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004; 75: 1080.

Ernst T, Chang L, Melchor R, Mehringer CM. Frontotemporal dementia and early Alzheimer disease: differentiation with frontal lobe H-1 MR spectroscopy. Radiology 1997; 203: 829–36.

Everitt BJ, Robbins TW. Central cholinergic systems and cognition. Annu Rev Psychol 1997; 48: 649–84.

Ferrer I. Neurons and their dendrites in frontotemporal dementia. Dement Geriatr Cogn Disord 1999; 10: 55–60.

Fineberg NA, Haddad PM, Carpenter L, Gannon B, Sharpe R, Young AH, et al. The size, burden and cost of disorders of the brain in the UK. J Psychopharmacol 2013; 27: 761–70.

Finnema SJ, Scheinin M, Shahid M, Lehto J, Borroni E, Bang-Andersen B, et al. Application of cross-species PET imaging to assess neurotransmitter release in brain. Psychopharmacology 2015; 232: 4129–57.

Foster NL, Minoshima S, Johanns J, Little R, Heumann ML, Kuhl DE, et al. PET measures of benzodiazepine receptors in progressive supranuclear palsy. Neurology 2000; 54: 1768–73.

Foster NL, Wilhelmsen K, Sima AAF, Jones MZ, Damato CJ, Gilman S, et al. Frontotemporal dementia and parkinsonism linked to chromosome 17. Ann Neurol 1997; 41: 706–15.

Franceschi M, Anchisi D, Pelati O, Zuffi M, Matarrese M, Moresco RM, et al. Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. Ann Neurol 2005; 57: 216–25.

Francis PT, Holmes C, Webster MT, Stratmann GC, Procter AW, Bowen DM. Preliminary neurochemical findings in non-Alzheimer dementia due to lobar atrophy. Dementia 1993; 4: 172–7.

Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer' s disease: a review of progress. J Neurol Neurosurg Psychiatry 1999; 66: 137–47.

Frankle WG, Cho RY, Narendran R, Mason NS, Vora S, Litschge M, et al. Tiagabine increases [11C]flumazenil binding in cortical brain regions in healthy control subjects. Neuropsychopharmacology 2009; 34: 624–33.

Fries P. Neuronal gamma-band synchronization as a fundamental process in cortical computation. Annu Rev Neurosci 2009; 32: 209–24.

Frisoni GB, Pizzolato G, Bianchetti A, Chierichetti F, Ferlin G, Battistin L, et al. Single photon emission computed tomography with [99Tc]-HM-PAO and [123I]-IBZM in Alzheimer's disease and dementia of frontal type: preliminary results. Acta Neurol Scand 1994; 89: 199–203.

Gaetz M, Edgar J, Wang D, Roberts P. Relating MEG measured motor cortical oscillations to resting γ- aminobutyric acid (GABA) concentration. Neuroimage 2011; 15: 616–21.

Gaetz W, Roberts TP, Singh K, Muthukumaraswamy SD. Functional and structural correlates of the aging brain: relating visual cortex (V1) gamma band responses to age-related structural change. Hum Brain Mapp 2012; 33: 2035–46.

Garbutt S, Matlin A, Hellmuth J, Schenk AK, Johnson JK, Rosen H, et al. Oculomotor function in frontotemporal lobar degeneration, related disorders and Alzheimer's disease. Brain 2008; 131: 1268–81.

Gascon E, Lynch K, Ruan H, Almeida S, Verheyden JM, Seeley WW, et al. Alterations in microRNA-124 and AMPA receptors contribute to social behavioral deficits in frontotemporal dementia. Nat Med 2014; 20: 1444–51.

Ghika J, Tennis M, Hoffman E, Schoenfeld D, Growdon J. Idazoxan treatment in progressive supranuclear palsy. Neurology 1991; 41: 986–91.

Gibb WR, Luthert PJ, Marsden CD. Corticobasal degeneration. Brain 1989; 112: 1171–92.

Gilbert JR, Symmonds M, Hanna MG, Dolan RJ, Friston KJ, Moran RJ. Profiling neuronal ion channelopathies with non-invasive brain imaging and dynamic causal models: case studies of single gene mutations. Neuroimage 2016; 124: 43–53.

Gilman S, Koeppe RA, Nan B, Wang CN, Wang X, Junck L, et al. Cerebral cortical and subcortical cholinergic deficits in parkinsonian syndromes. Neurology 2010; 74: 1416–23.

Gilmour G, Dix S, Fellini L, Gastambide F, Plath N, Steckler T, et al. NMDA receptors, cognition and schizophrenia—testing the validity of the NMDA receptor hypofunction hypothesis. Neuropharmacology 2012; 62: 1401–12.

Gil-Navarro S, Lomeña F, Cot A, Lladó A, Montagut N, Castellví M, et al. Decreased striatal dopamine transporter uptake in the non-fluent/agrammatic variant of primary progressive aphasia. Eur J Neurol 2013; 20: 1459–66.

Goforth HW, Konopka L, Primeau M, Ruth A, O'Donnell K, Patel R, et al. Quantitative electroencephalography in frontotemporal dementia with methylphenidate response: a case study. Clin EEG Neurosci 2004; 35: 108–11.

Gonzalez-Burgos G, Fish KN, Lewis DA. GABA neuron alterations, cortical circuit dysfunction and cognitive deficits in schizophrenia. Neural Plast 2011; 2011: 723184.

Gorelova N, Mulholland PJ, Chandler LJ, Seamans JK. The glutamatergic component of the mesocortical pathway emanating from different subregions of the ventral midbrain. Cereb Cortex 2012; 22: 327–36.

Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology 2011; 2: 1006–14.

Halliday M, Radford H, Zents KAM, Molloy C, Moreno JA, Verity NC, et al. Repurposed drugs targeting eIF2α-P-mediated translational repression prevent neurodegeneration in mice. Brain 2017: 1768–83.

Hansen LA, Deteresa R, Tobias H, Alford M, Terry RD. Neocortical morphometry and cholinergic neurochemistry in Pick's disease. Am J Pathol 1988; 131: 507–18.

Hardman CD, Halliday GM, McRitchie DA, Cartwright HR, Morris JG. Progressive supranuclear palsy affects both the substantia nigra pars compacta and reticulata. Exp Neurol 1997; 144: 183–92.

Harvey JA. Role of the serotonin 5-HT2A receptor in learning. Learn Mem 2003; 10: 355–62.

Hauw J, Daniel SE, Dickson D, Horoupian DS. Preliminary NINDS neuropathologic criteria for Steele- Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 1994; 44: 2015–19.

Hazrati LN, Wong JC, Hamani C, Lozano AM, Poon YY, Dostrovsky JO, et al. Clinicopathological study in progressive supranuclear palsy with pedunculopontine stimulation. Mov Disord 2012; 27: 1304–7.

Henderson JM, Carpenter K, Cartwright H, Halliday GM. Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and therapeutic implications. Brain 2000; 123 (Pt 7): 1410–21.

Herrmann N, Black SE, Chow T, Cappell J, Tang-Wai DF, Lanctôt KL. Serotonergic function and treatment of behavioral and psychological symptoms of frontotemporal dementia. Am J Geriatr Psychiatry 2012; 20: 789–97.

Hines RM, Hines DJ, Houston CM, Mukherjee J, Haydon PG, Tretter V, et al. Disrupting the clustering of GABAA receptor α2 subunits in the frontal cortex leads to reduced γ-power and cognitive deficits. Proc Natl Acad Sci USA 2013; 110: 16628–33.

Hirano S, Shinotoh H, Shimada H, Aotsuka A, Tanaka N, Ota T, et al. Cholinergic imaging in corticobasal syndrome, progressive supranuclear palsy and frontotemporal dementia. Brain 2010; 133: 2058–68.

Hirsch EC, Graybiel AM, Duyckaerts C, Javoy-Agid F. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proc Natl Acad Sci USA 1987; 84: 5976–80.

Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy—the movement disorder society criteria. Mov Disord 2017; 32: 853–64.

Holemans S, Javoy F, Agid Y, Laterre EC, Maloteaux JM. [3H]MK-801 binding to NMDA glutamatergic receptors in Parkinson's disease and progressive supranuclear palsy. Brain Res 1991; 565: 154–7.

Hornung JP. The human raphe nuclei and the serotonergic system. J Chem Neuroanat 2003; 26: 331–43.

Hornykiewicz O, Shannak K. Brain monoamines in progressive supranuclear palsy–comparison with idiopathic Parkinson's disease. J Neural Transm Suppl 1994; 42: 219–27.

Huey E, Putnam K, Grafman J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. Neurology 2006; 66: 17–22.

Hughes LE, Ghosh BC, Rowe JB. Reorganisation of brain networks in frontotemporal dementia and progressive supranuclear palsy. Neuroimage Clin 2013; 2: 459–68.

Hughes LE, Rittman T, Regenthal R, Robbins TW, Rowe JB. Improving response inhibition systems in frontotemporal dementia with citalopram. Brain 2015; 138: 1961–75.

Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998; 393: 702–5.

Im JH, Chung SJ, Kim JS, Lee MC. Differential patterns of dopamine transporter loss in the basal ganglia of progressive supranuclear palsy and Parkinson's disease: analysis with [(123)I]IPT single photon emission computed tomography. J Neurol Sci 2006; 244: 103–9.

Invernizzi RW, Garattini S. Role of presynaptic a2-adrenoceptors in antidepressant action: recent findings from microdialysis studies. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 819–27.

Irwin DJ, Brettschneider J, McMillan CT, Cooper F, Olm C, Arnold SE, et al. Deep clinical and neuropathological phenotyping of Pick disease. Ann Neurol 2016; 79: 272–87.

Javoy-Agid F. Cholinergic and peptidergic systems in PSP. J Neural Transm Suppl 1994; 42: 205–18.

Jellinger K. The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 1988; 51: 540–3.

Johnson NA, Rademaker A, Weintraub S, Gitelman D, Wienecke C, Mesulam M. Pilot trial of memantine in primary progressive aphasia. Alzheimer Dis Assoc Disord 2010; 24: 308.

Juncos JL, Hirsch EC, Malessa S, Duyckaerts C, Hersh LB, Agid Y. Mesencephalic cholinergic nuclei in progressive supranuclear palsy. Neurology 1991; 41: 25–30.

Kaasinen V, Gardberg M, Röyttä M, Seppänen M, Päivärinta M. Normal dopamine transporter SPECT in neuropathologically confirmed corticobasal degeneration. J Neurol 2013; 260: 1410–11.

Kalia L, Kalia SK, Salter M. NMDA receptors in clinical neurology: excitatory times ahead. Lancet Neurol 2008; 7: 742–55.

Kanazawa I, Kwak S, Sasaki H, Muramoto O, Mizutani T, Hori A, et al. Studies on neurotransmitter markers of the basal ganglia in Pick's disease, with special reference to dopamine reduction. J Neurol Sci 1988; 83: 63–74.

Kasashima S, Oda Y. Cholinergic neuronal loss in the basal forebrain and mesopontine tegmentum of progressive supranuclear palsy and corticobasal degeneration. Acta Neuropathol 2003; 105: 117–24.

Kehagia AA, Housden CR, Regenthal R, Barker RA, Müller U, Rowe J, et al. Targeting impulsivity in Parkinson's disease using atomoxetine. Brain 2014; 137: 1986–97.

Kertesz A, McMonagle P, Jesso S. Extrapyramidal syndromes in frontotemporal degeneration. J Mol Neurosci 2011; 45: 336–42.

Kertesz A, Morlog D, Light M, Blair M, Davidson W, Jesso S, et al. Galantamine in frontotemporal dementia and primary progressive aphasia. Dement Geriatr Cogn Disord 2008; 25: 178–85.

Kim YJ, Ichise M, Ballinger JR, Vines D, Erami SS, Tatschida T, et al. Combination of dopamine transporter and D2 receptor SPECT in the diagnostic evaluation of PD, MSA, and PSP. Mov Disord 2002; 17: 303–12.

Klaffke S, Kuhn AA, Plotkin M, Amthauer H, Harnack D, Felix R, et al. Dopamine transporters, D2 receptors, and glucose metabolism in corticobasal degeneration. Mov Disord 2006; 21: 1724–7.

Kompoliti K, Goetz CG, Litvan I, Jellinger K, Verny M. Pharmacological therapy in progressive supranuclear palsy. Arch Neurol 1998; 55: 1099–102.

Kondo T. Drug intervention for freezing of gait resistant to dopaminergic therapy: a pilot study. Park Relat Disord 2006; 12: 63–6.

Kujala J, Jung J, Bouvard S, Lecaignard F, Lothe A, Bouet R, et al. Gamma oscillations in V1 are correlated with GABAA receptor density: a multi-modal MEG and Flumazenil-PET study. Sci Rep 2015; 5: 16347.

Lanctôt KL, Herrmann N, Ganjavi H, Black SE, Rusjan PM, Houle S, et al. Serotonin-1A receptors in frontotemporal dementia compared with controls. Psychiatry Res Neuroimaging 2007; 156: 247–50.

Landwehrmeyer B, Palacios JM. Alterations of neurotransmitter receptors and neurotransmitter transporters in progressive supranuclear palsy. J Neural Transm Suppl 1994; 42: 229–46.

Lange KW, Kornhuber J, Riederer P. Dopamine/glutamate interactions in Parkinson's disease. Neurosci Biobehav Rev 1997; 21: 393–400.

Lansdall CJ, Coyle-Gilchrist IT, Jones PS, Rodriguez PV, Wilcox A, Wehmann E, et al. Apathy and impulsivity in frontotemporal lobar degeneration syndromes. Brain 2017; 140: 1792–807.

Laureys S, Salmon E, Garraux G, Peigneux P, Lemaire C, Degueldre C, et al. Fluorodopa uptake and glucose metabolism in early stages of corticobasal degeneration. J Neurol 1999; 246: 1151–8.

Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. Dement Geriatr Cogn Disord 2004; 17: 355–9.

Leuzy A, Zimmer ER, Dubois J, Pruessner J, Cooperman C, Soucy JP, et al. *In vivo* characterization of metabotropic glutamate receptor type 5 abnormalities in behavioral variant FTD. Brain Struct Funct 2016; 221: 1387–402.

Levy R, Ruberg M, Herrero MT, Villares J, Javoy-Agid F, Agid Y, et al. Alterations of GABAergic neurons in the basal ganglia of patients with progressive supranuclear palsy: an in situ hybridization study of GAD67 messenger RNA. Neurology 1995; 45: 127–34.

Liepelt I, Gaenslen A, Godau J, Di Santo A, Schweitzer KJ, Gasser T, et al. Rivastigmine for the treatment of dementia in patients with progressive supranuclear palsy: clinical observations as a basis for power calculations and safety analysis. Alzheimers Dement 2010; 6: 70–4.

Litvan I, Blesa R, Clark K, Nichelli P, Atack JR, Mouradian MM, et al. Pharmacological evaluation of the cholinergic system in progressive supranuclear palsy. Ann Neurol 1994; 36: 55–61.

Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol 1996; 55: 97–105.

Litvan I, Phipps M, Pharr VL, Hallett M, Grafman J, Salazar A. Randomized placebo-controlled trial of donepezil in patients with progressive supranuclear palsy. 2001; 57: 467–73.

MacKenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol 2010; 119: 1–4.

Macoveanu J, Hornboll B, Elliott R, Erritzoe D, Paulson OB, Siebner H, et al. Serotonin 2A receptors, citalopram and tryptophan-depletion: a multimodal imaging study of their interactions during response inhibition. Neuropsychopharmacology 2013; 38: 996–1005.

Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, et al. NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacology 1996; 14: 301–7.

Mann EO, Paulsen O. Role of GABAergic inhibition in hippocampal network oscillations. Trends Neurosci 2007; 30: 343–9.

Mark LP, Prost RW, Ulmer JL, Smith MM, Daniels DL, Strottmann JM, et al. Pictorial review of glutamate excitotoxicity: fundamental concepts for neuroimaging. Am J Neuroradiol 2001; 22: 1813–24.

Marsh L, Biglan K, Gerstenhaber M, Williams JR. Atomoxetine for the treatment of executive dysfunction in Parkinson's disease: a pilot open-label study. Mov Disord 2009; 24: 277–82.

Mazere J, Meissner WG, Mayo W, Sibon I, Lamare F, Guilloteau D, et al. Progressive supranuclear palsy: *in vivo* SPECT imaging of presynaptic vesicular acetylcholine transporter with [123I]-iodobenzovesamicol. Radiology 2012; 265: 537–43.

McGaughy J, Ross RS, Eichenbaum H. Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. Neuroscience 2008; 153: 63–71.

Meier-Ruge W, Iwangoff P, Reichlmeier K. Neurochemical enzyme changes in Alzheimer's and Pick's disease. Arch Gerontol Geriatr 1984; 3: 161–5.

Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. J Nutr 2000; 130: 1007S–15S.

Mendez MF, Shapira JS, McMurtray A, Licht E. Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. Am J Geriatr Psychiatry 2007; 15: 84–7.

Mirsky JB, Heuer HW, Jafari A, Kramer JH, Schenk AK, Viskontas IV, et al. Anti-saccade performance predicts executive function and brain structure in normal elders. Cogn Behav Neurol 2011; 24: 50–8.

Miyaoka T, Seno H, Inagaki T, Horiguchi J. Fluvoxamine for the treatment of depression and parkinsonism in progressive supranuclear palsy. Int J Psychiatry Clin Pract 2002; 6: 45–7.

Moran RJ, Campo P, Symmonds M, Stephan KE, Dolan RJ, Friston KJ, et al. Free energy, precision and learning: the role of cholinergic neuromodulation Europe PMC Funders Group. J Neurosci 2013; 33: 8227–36.

Moran RJ, Symmonds M, Stephan KE, Friston KJ, Dolan RJ. An *in vivo* assay of synaptic function mediating human cognition. Curr Biol 2011; 21: 1320–5.

Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Rivastigmine in frontotemporal dementia. Drugs Aging 2004; 21: 931–7.

Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms: a randomized, controlled, open 14-month study. Eur Neurol 2003a; 49: 13–19.

Moretti R, Torre P, Antonello RM, Cazzato G, Griggio S, Bava A. Olanzapine as a treatment of neuropsychiatric disorders of Alzheimer's disease and other dementias: a 24-month follow-up of 68 patients. Am J Alzheimers Dis Other Demen 2003b; 18: 205–14.

Mori H, Oda M, Komori T, Arai N, Takanashi M, Mizutani T, et al. Lewy bodies in progressive supranuclear palsy. Acta Neuropathol 2002; 104: 273–8.

Morris RGM, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 1986; 319: 774–6.

Murphy KE, Karaconji T, Hardman CD, Halliday GM. Excessive dopamine neuron loss in progressive supranuclear palsy. Mov Disord 2008; 23: 607–10.

Muthukumaraswamy SD. The use of magnetoencephalography in the study of psychopharmacology (pharmaco-MEG). J Psychopharmacol 2014; 28: 815–29.

Muthukumaraswamy SD, Edden RAE, Jones DK, Swettenham JB, Singh KD. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. Proc Natl Acad Sci USA 2009; 106: 8356–61.

Muthukumaraswamy SD, Myers JFM, Wilson SJ, Nutt DJ, Hamandi K, Lingford-Hughes A, et al. Elevating endogenous GABA levels with GAT-1 blockade modulates evoked but not induced responses in human visual cortex. Neuropsychopharmacology 2013; 38: 1105–12.

Nagaoka S, Arai H, Iwamoto N, Ohwada J, Ichimiya Y, Nakamura M, et al. A juvenile case of frontotemporal dementia: neurochemical and neuropathological investigations. Prog Neuropsychopharmacol Biol Psychiatry 1995; 19: 1251–61.

Nagasawa H, Tanji H, Nomura H, Saito H, Itoyama Y, Kimura I, et al. PET study of cerebral glucose metabolism and fluorodopa uptake in patients with corticobasal degeneration. J Neurol Sci 1996; 139: 210–17.

Napier TC, Corvol J, Grace AA, Roitman JD. Linking neuroscience with modern concepts of impulse control disorders in Parkinson's disease. Mov Disord 2015; 30: 141–9.

Newcomer JW, Farber NB, Olney JW. NMDA receptor function, memory, and brain aging. Dialogues Clin Neurosci 2000; 2: 219–32.

Newman LA, Darling J, McGaughy J. Atomoxetine reverses attentional deficits produced by noradrenergic deafferentation of medial prefrontal cortex. Psychopharmacology 2008; 200: 39–50.

O'Dowd S, Curtin D, Waite AJ, Roberts K, Pender N, Reid V, et al. C9ORF72 expansion in amyotrophic lateral sclerosis/frontotemporal dementia also causes Parkinsonism. Mov Disord 2012; 27: 1072–74.

Odawara T, Shiozaki K, Iseki E, Hino H, Kosaka K. Alterations of muscarinic acetylcholine receptors in atypical Pick's disease without Pick bodies. J Neurol Neurosurg Psychiatry 2003; 74: 965–7.

Oh M, Kim JS, Kim JY, Shin KH, Park SH, Kim HO, et al. Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. J Nucl Med 2012; 53: 399–406.

Olanow CW. The scientific basis for the current treatment of Parkinson's disease. Annu Rev Med 2004; 55: 41–60.

Owens DF, Kriegstein AR. Is there more to GABA than synaptic inhibition? Nat Rev Neurosci 2002; 3: 715–27.

Oyanagi C. Comparison of striatal dopamine D2 receptors in Parkinson's disease and progressive supranuclear palsy patients using [I] iodobenzofuran single-photon emission computed tomography. J Neuroimaging 2002; 12: 316–24.

Oyanagi K, Tsuchiya K, Yamazaki M, Ikeda K. Substantia nigra in progressive supranuclear palsy, corticobasal degeneration, and parkinsonism-dementia complex of Guam: specific pathological features. J Neuropathol Exp Neurol 2001; 60: 393–402.

Padovani A, Agosti C, Premi E, Bellelli G, Borroni B. Extrapyramidal symptoms in frontotemporal dementia: prevalence and clinical correlations. Neurosci Lett 2007; 422: 39–42.

Pal PK, Wszolek ZK, Kishore A, De La Fuente-Fernandez R, Sossi V, Uitti RJ, et al. Positron emission tomography in pallido-ponto-nigral degeneration (PPND) family (frontotemporal dementia with parkinsonism linked to chromosome 17 and point mutation in tau gene). Park Relat Disord 2001; 7: 81–8.

Pascual J, Berciano J, Grijalba B, del OE, Gonzalez AM, Figols J, et al. Dopamine D1 and D2 receptors in progressive supranuclear palsy: an autoradiographic study. Ann Neurol 1992; 32: 703–7.

Perneczky R, Ghosh BCP, Hughes L, Carpenter RHS, Barker RA, Rowe JB. Saccadic latency in Parkinson's disease correlates with executive function and brain atrophy, but not motor severity. Neurobiol Dis 2011; 43: 79–85.

Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron 2012; 76: 116–29.

Pickering-Brown SM, Richardson AMT, Snowden JS, McDonagh AM, Burns A, Braude W, et al. Inherited frontotemporal dementia in nine British families associated with intronic mutations in the tau gene. Brain 2002; 125: 732–51.

Pierot L, Desnos C, Blin J, Pierrot L, Scherman D, Javoy-agid F, et al. D1 and D2-type dopamine receptors in patients with Parkinson's disease and progressive supranuclear palsy. J Neurol Sci 1988; 86: 291–306.

Pijnenburg YAL, Sampson EL, Harvey RJ, Fox NC, Rossor MN. Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration. Int J Geriatr Psychiatry 2003; 18: 67–72.

Pirker S, Perju-Dumbrava L, Kovacs GG, Traub-Weidinger T, Asenbaum S, Pirker W. Dopamine D2 receptor SPECT in corticobasal syndrome and autopsy-confirmed corticobasal degeneration. Park Relat Disord 2013; 19: 222–6.

Pirker S, Perju-Dumbrava L, Kovacs GG, Traub-Weidinger T, Pirker W. Progressive dopamine transporter binding loss in autopsy-confirmed corticobasal degeneration. J Parkinsons Dis 2015; 5: 907–12.

Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol 2012; 22: 239–58.

Poujois A, Vidailhet M, Trocello JM, Bourdain F, Gaymard B, Rivaud-Péchoux S. Effect of gabapentin on oculomotor control and parkinsonism in patients with progressive supranuclear palsy. Eur J Neurol 2007; 14: 1060–2.

Premi E, Archetti S, Pilotto A, Seripa D, Paghera B, Padovani A, et al. Functional genetic variation in the serotonin 5-HTTLPR modulates brain damage in frontotemporal dementia. Neurobiol Aging 2015; 36: 446–51.

Procter AW, Qurne M, Francis PT. Neurochemical features of frontotemporal dementia. Dement Geriatr Cogn Disord 1999; 10: 80–4.

Rae CL, Nombela C, Rodríguez PV, Ye Z, Hughes LE, Jones PS, et al. Atomoxetine restores the response inhibition network in Parkinson's disease. Brain 2016; 139: 2235–48.

Rahman S, Robbins TW, Hodges JR, Mehta MA, Nestor PJ, Clark L, et al. Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. Neuropsychopharmacology 2006; 31: 651–8.

Ranasinghe KG, Rankin KP, Pressman PS, Perry DC, Lobach IV, Seeley WW, et al. Distinct subtypes of behavioral-variant frontotemporal dementia based on patterns of network degeneration HHS public access. JAMA Neurol 2016; 73: 1078–88.

Rascol O, Sieradzan K, Peyro-Saint-Paul H, Thalamas C, Brefel-Courbon C, Senard JM, et al. Efaroxan, an alpha-2 antagonist, in the treatment of progressive supranuclear palsy. Mov Disord 1998; 13: 673–6.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011; 134: 2456–77.

Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003; 348: 1333–41.

Revesz T, Sangha H, Daniel SE. The nucleus raphe interpositus in the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Brain 1996; 119 (Pt 4): 1137–43.

Reynolds G, Sally P. Brain GABA levels in asymptomatic Huntington's disease. N Engl J Med 1990; 323: 682–2.

Riedl L, Mackenzie IR, Forstl H, Kurz A, Diehl-Schmid J. Frontotemporal lobar degeneration: current perspectives. Neuropsychiatr Dis Treat 2014; 10: 297–310.

Rifkin A, Quitkin F, Kane J, Struve F, Klein DF. Are prophylactic antiparkinson drugs necessary? A Controlled Study of procyclidine withdrawal. Arch Gen Psychiatry 1978; 35: 483–9.

Rinne JO, Laine M, Kaasinen V, Norvasuo-Heila MK, Nagren K, Helenius H. Striatal dopamine transporter and extrapyramidal symptoms in frontotemporal dementia. Neurology 2002; 58: 1489–93.

Rittman T, Coyle-Gilchrist IT, Rowe JB. Managing cognition in progressive supranuclear palsy. Neurodegener Dis Manag 2016; 6: 499–508.

Robinson ESJ, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X, et al. Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology 2008; 33: 1028–37.

Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, Albala B, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with alzheimers-disease. Neurology 1998; 50: 136–45.

Rohrer JD, Isaacs AM, Mizlienska S, Mead S, Lashley T, Wray S, et al. C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis. Lancet Neurol 2015a; 14: 291–301.

Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the genetic frontotemporal dementia initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol 2015b; 14: 253–62.

Rohrer JD, Paviour D, Bronstein AM, O'Sullivan SS, Lees A, Warren JD, et al. Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: a neuropsychological and neuroimaging analysis. Mov Disord 2010; 25: 179–88.

Roth BL. DREADDs for neuroscientists. Neuron 2016; 89: 683–94.

Rowe J, Rittman T. The basal ganglia in cognitive disorders. In: Husain M, Schott J, editors. Oxford textbook of cognitive neurology and dementia. Oxford: Oxford University Press; 2016. p. 69–80.

Rowe JB, Hughes L, Ghosh BCP, Eckstein D, Williams-Gray CH, Fallon S, et al. Parkinson's disease and dopaminergic therapy—differential effects on movement, reward and cognition. Brain 2008; 131: 2094–105.

Rowe JB, Saunders JR, Durantou F, Robbins TW. Systemic idazoxan impairs performance in a non-reversal shift test: implications for the role of the central noradrenergic systems in selective attention. J Psychopharmacol 1996; 10: 188–94.
Rowland LM, Astur RS, Jung RE, Bustillo JR, Lauriello J, Yeo RA. Selective cognitive impairments associated with NMDA receptor blockade in humans. Neuropsychopharmacol 2005; 30: 633–9.
Ruberg M, Javoy-Agid F, Hirsch E, Scatton B, LHeureux R, Hauw JJ, et al. Dopaminergic and cholinergic lesions in progressive supranuclear palsy. Ann Neurol 1985; 18: 523–9.
Sahakian BJ, Coull JJ, Hodges JR. Selective enhancement of executive function by idazoxan in a patient with dementia of the frontal lobe type. J Neurol Neurosurg Psychiatry 1994; 57: 120–1.
Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 2009; 10: 211–23.
Sarac H, Zagar M, Davorka V, Henigsberg Ne, Bilic E, Pavlisa G. Magnetic resonance imaging and magnetic resonance spectroscopy in a patient with amyotrophic lateral sclerosis and frontotemporal dementia. Coll Antropol 2008; 32: 205–10.
Sawle GV, Brooks DJ, Marsden CD, Frackowiak RSJ. Corticobasal degeneration—a unique pattern of regional cortical oxygen hypometabolism and striatal fluorodopa uptake demonstrated by positron emmission tomography. Brain 1991; 114: 541–56.
Schwarz LA, Luo L. Organization of the locus coeruleus-norepinephrine system. Curr Biol 2015; 25: R1051–6.
Sedaghat F, Gotzamani-Psarrakou A, Dedousi E, Arnaoutoglou M, Psarrakos K, Baloyannis I, et al. Evaluation of dopaminergic function in frontotemporal dementia using I-FP-CIT single photon emission computed tomography. Neurodegener Dis 2007; 4: 382–5.
Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. J Neurol Neurosurg Psychiatry 2011; 82: 476–86.
Selden N. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. Brain 1998; 121: 2249–57.
Seppi K, Scherfler C, Donnemiller E, Al E, Contribution O. Topography of dopamine transporter availability in progressive supranuclear palsy: a voxelwise [123i]β-cit spect analysis. Arch Neurol 2006; 63: 1154–60.
Servello D, Zekaj E, Saleh C, Menghetti C, Porta M. Long-term follow-up of deep brain stimulation of peduncolopontine nucleus in progressive supranuclear palsy: report of three cases. Surg Neurol Int 2014; 5: S416–20.
Shinotoh H, Namba H, Yamaguchi M, Fukushi K, Nagatsuka SI, Iyo M, et al. Positron emission tomographic measurement of acetylcholinesterase activity reveals differential loss of ascending cholinergic systems in Parkinson's disease and progressive supranuclear palsy. Ann Neurol 1999; 46: 62–9.
Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 2006; 6: 108–13.
Siuda J, Fujioka S, Wszolek ZK. Parkinsonian syndrome in familial frontotemporal dementia. Park Relat Disord 2014; 20: 957–64.
Sjogren M, Minthon L, Passant U, Blennow K, Wallin A. Decreased monoamine metabolites in frontotemporal dementia and Alzheimer's disease. Neurobiol Aging 1998; 19: 379–84.
Skillback T, Farahmand B, Bartlett JW, Rosen C, Mattsson N, Nagga K, et al. CSF neurofilament light differs in neurodegenerative diseases and predicts severity and survival. Neurology 2014; 83: 1945–53.
Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SPH, et al. The IUPHAR/BPS guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucleic Acids Res 2016; 44: D1054–68.
Sparks DL, Markesbery WR. Altered serotonergic and cholinergic synaptic markers in Pick's disease. Arch Neurol 1991; 48: 796–9.
Sparks DL, Woeltx VM, Marksebery WR. Alterations in brain monoamine oxidase activity in aging, Alzheimer's Disease, and Pick's Disease. Arch Neurol 1991; 48: 718–21.
Stamelou M, Höglinger G. A review of treatment options for progressive supranuclear palsy. CNS Drugs 2016; 30: 629–36.
Stamelou M, Matusch A, Elmenhorst D, Hurlemann R, Eggert KM, Zilles K, et al. Nigrostriatal upregulation of 5-HT2A receptors correlates with motor dysfunction in progressive supranuclear palsy. Mov Disord 2009; 24: 1170–5.
Suzuki M, Desmond TJ, Albin RL, Frey KA. Cholinergic vesicular transporters in progressive supranuclear palsy. Neurology 2002; 58: 1013–18.
Teipel S, Raiser T, Riedl L, Riederer I, Schroeter ML, Bisenius S, et al. Atrophy and structural covariance of the cholinergic basal forebrain in primary progressive aphasia. Cortex 2016; 83: 124–35.
Tsai RM, Boxer AL. Treatment of frontotemporal dementia. Curr Treat Options Neurol 2014; 16: 319.
Uitti RJ, Ahlskog JE, Maraganore DM, Muenter MD, Atkinson EJ, Cha RH, et al. Levodopa therapy and survival in idiopathic Parkinson's disease: Olmsted County project. Neurology 1993; 43: 1918–26.
Vermeiren Y, Le Bastard N, Van Hemelrijck A, Drinkenburg WH, Engelborghs S, De Deyn PP. Behavioral correlates of cerebrospinal fluid amino acid and biogenic amine neurotransmitter alterations in dementia. Alzheimers Dement 2013; 9: 488–98.
Vermeiren Y, Janssens J, Aerts T, Martin JJ, Sieben A, Van Dam D, et al. Brain serotonergic and noradrenergic deficiencies in behavioral variant frontotemporal dementia compared to early-onset Alzheimer's disease. J Alzheimers Dis 2016; 53: 1079–96.
Wang LE, Fink GR, Diekhoff S, Rehme AK, Eickhoff SB, Grefkes C. Noradrenergic enhancement improves motor network connectivity in stroke patients. Ann Neurol 2011; 69: 375–88.
Wang M, Yang Y, Wang CJ, Gamo NJ, Jin LE, Mazer JA, et al. NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. Neuron 2013; 77: 736–49.
Warmus BA, Sekar DR, McCutchen E, Schellenberg GD, Roberts RC, McMahon LL, et al. Tau-Mediated NMDA receptor impairment underlies dysfunction of a selectively vulnerable network in a mouse model of frontotemporal dementia. J Neurosci 2014; 34: 16482–95.
Warren NM, Piggott MA, Greally E, Lake M, Lees AJ, Burn DJ. Basal ganglia cholinergic and dopaminergic function in progressive supranuclear palsy. Mov Disord 2007a; 22: 1594–600.
Warren NM, Piggott MA, Lees AJ, Burn DJ. The basal ganglia cholinergic neurochemistry of progressive supranuclear palsy and other neurodegenerative diseases. J Neurol Neurosurg Psychiatry 2007b; 78: 571–5.
Warren NM, Piggott MA, Perry EK, Burn DJ. Cholinergic systems in progressive supranuclear palsy. Brain 2005; 128: 239–49.
Weinberger DR, Gibson R, Coppola R, Jones DW, Molchan S, Sunderland T, et al. The distribution of cerebral muscarinic acetylcholine receptors in vivo in patients with dementia. A controlled study with 123IQNB and single photon emission computed tomography. Arch Neurol 1991; 48: 169–76.
Whitwell JL, Josephs KA, Rossor MN, Stevens JM, Revesz T, Holton JL, et al. Magnetic resonance imaging signatures of tissue pathology in frontotemporal dementia. Arch Neurol 2005; 62: 1402–8.
Williams S, Boksa P. Gamma oscillations and schizophrenia. J Psychiatry Neurosci 2010; 35: 75–7.
Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci 2004; 5: 483–94.
Wood PL, Etienne P, Lal S, Nair NP, Finlayson MH, Gauthier S, et al. A post-mortem comparison of the cortical cholinergic system in Alzheimer's disease and Pick's disease. J Neurol Sci 1983; 62: 211–17.
Woodside J, Lamb R, Chelban V, Burn D, Church A, Gerhard A, et al. PROSPECT: a UK-based longitudinal observational study of PSP, CBD, MSA and atypical Parkinsonism syndromes [abstract]. Mov Disord 2016; 31: S87–8.

Yang Y, Schmitt HP. Frontotemporal dementia: evidence for impairment of ascending serotoninergic but not noradrenergic innervation. Immunocytochemical and quantitative study using a graph method. Acta Neuropathol 2001; 101: 256–70.

Yates CM, Simpson J, Maloney AFJ, Gordon A. Neurochemical observations in a case or Pick's disease. J Neurol Sci 1980; 48: 257–63.

Ye Z, Altena E, Nombela C, Housden CR, Maxwell H, Rittman T, et al. Improving response inhibition in Parkinson's disease with atomoxetine. Biol Psychiatry 2015; 77: 740–8.

Yokoyama JS, Bonham LW, Sturm VE, Adhimoolam B, Karydas A, Coppola G, et al. The 5-HTTLPR variant in the serotonin transporter gene modifies degeneration of brain regions important for emotion in behavioral variant frontotemporal dementia Serotonin transporter in bvFTD. Neuroimage Clin 2015; 9: 283–90.

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