Exploration of novel biomarkers in frontotemporal lobar degeneration

Yun Tae Hwang

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Statement of Originality

I, Yun Tae Hwang, declare that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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Authorship Attribution Statements

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I designed the study, analysed the data and wrote the drafts of the manuscript.

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I conceptually developed and planned the review and wrote the drafts of the manuscript.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Abstract

Frontotemporal lobar degeneration is a neurodegenerative disorder characterised by progressive deterioration of frontal and anterior temporal lobes of the brain. It can be divided into a number of distinct clinical syndromes including semantic variant of primary progressive aphasia, non-fluent variant of primary progressive aphasia, progressive supranuclear palsy, corticobasal syndrome and behavioural variant frontotemporal dementia.

Currently, there are no available treatments for these clinical syndromes. Previous efforts to investigate and develop targeted disease modifying therapies for these conditions have been hampered by a lack of biomarkers that would aid in diagnosis and assessment of disease progression. In this work, I have focused on identifying and examining potential biomarkers across frontotemporal lobar degeneration syndromes.

Chapter 1 provides an overview of frontotemporal lobar degeneration syndromes covered in this thesis. In Chapter 2, I present the experimental methods and techniques used in subsequent experiments. Chapter 3 presents the development of a novel combination of existing methods to detect changes in written text output of an individual with semantic variant of primary progressive aphasia. In Chapter 4, I explored whether a right-sided clinical phenotype, defined according to imaging characteristics, exists for non-fluent variant of primary progressive aphasia. Chapter 5 demonstrates the utility of midbrain-pons ratio and magnetic resonance parkinsonism index in distinguishing different histopathological subtypes found in frontotemporal lobar degeneration syndromes – PSP-tau, CBD-tau and TDP-43 – from the control group, those with Alzheimer's Disease, and from each other. In Chapter 6, I attempted to examine the prevalence and the nature of sleep disturbance in behavioural variant frontotemporal dementia and how this may differ from those with amnestic Alzheimer's Disease.

Two of the biomarkers explored in Chapter 5, midbrain-pons ratio and magnetic resonance parkinsonism index, may have potential utility as a diagnostic biomarker and aid in identifying individuals with PSP for further study, including clinical trials. Language analysis, presented in Chapter 3, may have utility as a biomarker to aid in diagnosis and disease progression and ultimately improve our understanding of cerebral network disruptions in neurodegenerative disorders. The utility of the other biomarkers were not definitively established, but the results suggest that these biomarkers, particularly sleep analysis, warrant further characterisation and study.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACE	Addenbrooke's cognitive examination
AD	Alzheimer's Disease
AgRP	agouti related peptide
ANOVA	analysis of variance
API	apnoea/hypnoea index
ApoE	apolipoprotein E
ARC	arcuate nucleus
BNC	British national corpus
bvFTD	behavioural variant frontotemporal dementia
C9ORF72	chromosome 9 open reading frame 72
CBD	corticobasal disease (pathological entity)
CBS	corticobasal syndrome (clinical entity)
CCV	control corpus variability
CHMP	chromatin-modifying protein
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
DAT	dopamine transporter scan
DMN	dorsomedial nucleus
DQoL-OC	dementia quality of life scale for older family carers
FADT	facial affect discrimination test
FAST	facial affect selection test
FDG	18F-2-fluoro-2-deoxy-D-glucose
FIDT	face identity discrimination test
FPT	face perception test

FRS	functional rating scale
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
FUS	fused in sarcoma protein
GFAP	glial fibrillary acidic protein
GLM	general linear model
GRN	progranulin
GSAQ	global sleep assessment questionnaire
HC	healthy control
hnRPNA	heterogeneous nuclear ribonucleoprotein
LBD	Lewy body dementia
LH	lateral hypothalamus
lvPPA	logopaenic variant of primary progressive aphasia
MAPT	microtuble associated protein tau
MCI	mild cognitive impairment
MCP	middle cerebellar peduncle
Min	minutes
MMSE	Folstein's mini mental status examination
MND	motor neuron disease
MOS	medical outcome study
MP	midbrain-pons
MRC	Medical Research Council
MRI	magnetic resonance imaging
MRPI	magnetic resonance parkinsonism index
MSA	multisystem atrophy

NA	not applicable
NAc	nucleus accumbens
NfL	Neurofilmanent light chain
nfvPPA	non fluent variant of primary progressive aphasia
NMDA	N-methyl-D-aspartate
OPTN	optineurin
OSA	obstructive sleep apnoea
PAL	progressive aphasia language scale
PD	Parkinson's disease
PDSS	Parkinson's disease sleep scale
PET	position emission tomography
PFN	prefrontal nucleus
PPA	primary progressive aphasia
PSG	polysomnography
PSP	progressive supranuclear palsy
PSQI	Pittsburgh sleep quality index
RCF	Rey-Osterrieth complex figure
REM	rapid eye movement
ROC	receiver operating characteristic
ROI	region of interest
QoL-AD	quality of life in Alzheimer's Disease questionnaire
RCF	Rey complex figure test
REM	rapid eye movement
SCN	suprachiasmatic nucleus of the hypothalamus
SCP	superior cerebellar peduncle
SPZ	supraventricular zone

SQSTM	sequestome
st.dev	standard deviation
svPPA	semantic variant primary progressive aphasia
SYDBAT	Sydney language battery
TAACO	tool for the automatic analysis of cohesion
TAALES	tool for the automatic analysis of lexical sophistication
TARDBP	transactive response DNA-binding protein
TBK	TANK binding kinase
TBT	total bed time
TDP-43	TAR DNA binding protein 43
TMT	trail making test
TROG	test for reception of grammar
TST	total sleep time
UK	United Kingdom
USA	United States of America
VCP	valoisin containing protein
VTA	ventral tegmental area
WASO	wakefulness after sleep onset

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Chapter 3

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Chapter 5

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Chapter 1

Introduction to

frontotemporal lobar degeneration

Introduction

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disorder characterised by progressive deterioration of frontal and anterior temporal lobes of the brain[1-3]. The main clinical syndromes include behavioural variant frontotemporal dementia (bvFTD) and two variants of primary progressive aphasia, the semantic (svPPA) and non-fluent (nfvPPA) variants. Other clinical syndromes associated with FTLD include atypical parkinsonian syndromes such as progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS).

Accurate syndromic classification of these disorders is challenging due to clinical heterogeneity, symptom overlap across presentations, and variable evolution over time. For instance, it is widely accepted that PSP and CBS can be very difficult to distinguish from each other, and both can initially present with language abnormalities resembling nfvPPA[4, 5]; meanwhile not all cases of nfvPPA will develop clinical features suggestive of PSP or CBS.

Within-syndrome clinicopathological correlations, while variable across syndromes, is also generally poor. For example, the clinical diagnosis of nfvPPA has been associated with primarily tau pathology but also TDP-43 pathology and Alzheimer's Disease (AD) pathology[6]. Meanwhile, bvFTD has been associated with TDP-43, tau, fused-in-sarcoma protein and rarely, ubiquitin and AD pathologies[7, 8]. In contrast, identification of svPPA is highly predictive of TDP-43 pathology[9].

An ideal biomarker would be sensitive, specific, and therefore highly predictive of an individual pathological entity. Biomarkers might also aid staging, prognostication, and assessment of response to treatment. Currently, there is no single or composite biomarker that is sensitive or specific enough for routine clinical use in FTLD. What follows is a brief description of individual clinical syndromes associated with FTLD and an exploration of currently available biomarkers.

Behavioural variant frontotemporal dementia

Clinical and pathological features

Patients with bvFTD present with variable degrees of apathy, loss of empathy, disinhibition, changes in appetite, altered food preferences and executive dysfunction[10]. It is associated with progressive frontal and temporal lobe atrophy. It is the most common subtype of FTLD accounting for ~50% of presentations, with an estimated incidence of ~4/100,000 and prevalence of ~13/100,000[11, 12].

Current consensus diagnostic criteria for bvFTD emphasises 'possible' to 'probable' to 'definite' categories (Table 1-1)[13] based on the presence of cardinal clinical features, the results of supportive investigations, progressive deterioration, and exclusion of other potential causes. The underlying pathological substrate is highly variable and includes tau and TDP-43, as well as rarer entities such as FUS and ubiquitin[7, 8] (Table 1-2). While there are some clinical features that are associated with or predict specific pathology – for example, physical examination findings suggestive of motor neurone disease are associated with TDP-43[14] – core clinical features of bvFTD such as apathy and disinhibition occur with all known pathological substrates[12]. Consequently, the underlying pathological cause of bvFTD is difficult to determine reliably[15].

Stage	Feature	Manifestations
Possible: three of following features	• Behavioural disinhibition	• Socially inappropriate behaviour • Loss of manners and decorum • Impulsive, rash or careless action
	• Apathy or inertia	• Lack of initiative and spontaneity • Decreased initiation and maintenance of activities
	• Loss of sympathy/empathy	• Diminished responsiveness to other people's need and feelings • Diminished social interest or personal warmth
	• Hyperorality and dietary changes	• Altered food preference • Binge consumption of food, alcohol or cigarettes • Oral exploration/consumption of inedible objects
	• Executive dysfunction with sparing of memory and visuospatial function on neuropsychology tests	
Probable: possible + both of:	• Significant functional decline • Imaging features affecting frontal and/or anterior temporal lobe region	• Inability to remain employed or live independently • Atrophy on anatomical imaging (MRI/CT) • Hypometabolism/hypoperfusion on functional imaging (PET)
Definite: possible or probable and one of:	• Histopathology on biopsy or post-mortem • Presence of known pathogenic mutation	• See Table 1-2 • E.g.: *MAPT, GRN, C9ORF72, VCP, FUS*

Table 1-1. Current international consensus diagnostic criteria for bvFTD, adopted from Rascovsky et al[13]. *C9ORF72* = Chromosome 9 open reading frame 72; CT = computed tomography; *FUS* = Fused in sarcoma protein; *GRN* = progranulin; *MAPT* = microtubule associated protein tau; MRI = magnetic resonance imaging; PET = position emission tomography; *VCP* = valoisin containing protein

Abnormal Protein	Associated Clinical Syndrome	Proportion	Associated Gene mutation(s) in hereditary cases
Tau	bvFTD, nfvPPA, PSP, CBS	~30%	*MAPT*
TDP-43		~50%	
Type A	bvFTD, nfvPPA		*GRN*
Type B	bvFTD, bvFTD + MND		*C9ORF72*
Type C	bvFTD, svPPA		
Type D	Familial IBMPDBFTD		*VCP*
FUS	bvFTD with psychiatric and behavioural features, MND	~5-10%	*FUS*

Table 1-2. Current histological classification of FTLD[16, 17]**.** bvFTD = behavioural variant frontotemporal dementia; *C9ORF72* = chromosome 9 open reading frame; *FUS* = fused in sarcoma; *GRN* = progranulin; *IBMPDBFTD* = inclusion body myositis-Paget's disease of the bone-frontotemporal dementia; *MAPT* = microtuble associated protein tau; MND = motor neurone disease; nfvPPA = non-fluent variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia; TDP = TAR DNA binding protein; *VCP* = valoisin containing protein

Existing Biomarkers

Genetics

The most common genetic mutations associated with bvFTD are the *C9ORF72* repeat expansion (chromosome 9 open reading frame 72)[18, 19], *GRN* (progranulin)[20, 21], and *MAPT* (microtubule associated protein tau)[22]. While there are some characteristic features – for example, *MAPT* mutation carriers are thought to be more likely to develop prominent memory features and/or semantic deficits[23] – there is significant variation even within the same family (e.g., age of onset in a single *GRN* family[24]) and a number of different genetic mutations can be responsible for identical clinical presentations[25].

Numerous other mutations have been identified in bvFTD patients with much lower frequency. Specifically, mutations of *VCP* (valosin-containing protein)[26], *CHMP2B* (chromatin-modifying protein 2B)[27], *hnRNPA1* and *2B1 (*heterogeneous nuclear ribonucleoprotein)[28], *SQSTM1* (sequestome)[29], *TBK1* (TANK binding kinase)[30], *OPTN* (optineurin)[31], and *TARDBP* (transactive response DNA-binding protein)[31, 32] have all been reported. Together, all mutation carriers account for ~20% of bvFTD patients[33, 34], a higher proportion than that seen in other FTLD subtypes.

Fluid biomarkers

Currently, no specific fluid based biomarkers for specific proteinopathies exist[35]. While TDP-43 levels in CSF and blood can both be elevated in FTLD patients, the levels often overlap with those recorded in patients with tauopathy and controls[36]. CSF tau does not distinguish bvFTD patients from controls, nfvPPA, or svPPA[37] and does not differentiate between FTLD subtypes[38].

One intriguing, and novel, CSF and serum based biomarker in bvFTD is orexin, which is considered to be the most important neuro-hormonal regulator of sleep[39]. While a recent study found that CSF orexin levels were not significantly different between a bvFTD and control groups, there was a negative correlation between orexin levels and daytime somnolence in the bvFTD patients, suggesting that bvFTD patients may be more dependent on orexin levels for maintaining wakefulness[40]. In contrast, the levels of the precursor molecule, pro-orexin, in CSF were significantly elevated in the bvFTD cohort compared to controls[41]. Measuring orexin levels at a single time point, however, may not be an adequate indicator of orexinergic dysfunction since the orexin concentration in CSF of healthy humans is known to fluctuate throughout the day[42]. Serum levels of orexin, on the other hand, were reported to be reduced in a cohort of bvFTD patients compared to those with AD and PD, although there was a significant overlap of results at an individual level[43].

Imaging biomarkers

In bvFTD, atrophy detected on MRI typically begins in the anterior insula and cingulate cortex. Progression involves the orbitofrontal cortex, premotor cortex, and anterior temporal lobes before spreading to the entire frontal and temporal lobes bilaterally[44-46]. While different pathological subtypes can demonstrate slightly different atrophy patterns (e.g., TDP-43 pathology has been associated with parietal and posterior temporal involvement[47]), further study is required to determine if structural imaging alone can predict underlying pathologies[48].

FDG-PET findings can demonstrate hypometabolism in frontal and temporal lobes in bvFTD, consistent with established patterns of atrophy[49]. It may be most useful as an adjunct when structural imaging is equivocal to demonstrate underlying neuronal dysfunction[50] but challenges remain; for instance, metabolic disorders can lead to decreased FDG uptake[51] and, as yet, there is no data to confirm that FDG-PET can differentiate psychiatric disorders such as pseudodementia of depression from neurodegenerative disorders[52].

Clinical and neuropsychological biomarkers

Ongoing research efforts suggest that pathological processes underlying bvFTD significantly alter the reward and the hypothalamic circuits, which are responsible for fundamental, goal-driven homeostatic processes and autonomic functions[53, 54]. Several measures of autonomic function such as increased heart rate[53], pupillometry[55] and skin conductance[56] have been shown to be altered in bvFTD.

Another fundamental function regulated by hypothalamus, sleep[57], is also commonly disturbed in bvFTD[58-60] and worsens with disease progression along with other cardinal symptoms such as apathy and disinhibition[61]. There has been an increasing interest in sleep disturbance as a potential driver of pathogenesis in a multitude of neurodegenerative disorders including bvFTD[62]. However, at this stage,

the utility of sleep, metabolic, or autonomic analysis in determining the diagnosis, stage, prognosis, or treatment response in bvFTD has not been established.

Semantic variant of primary progressive aphasia

Clinical and pathological features

svPPA, also commonly referred to as semantic dementia, is a neurodegenerative syndrome characterised by progressive loss of semantic knowledge, resulting in 'specific terms replaced by commoner, more general terms'[63]. It is a rare disorder, with an estimated incidence of ~4/100,000[9, 11]. The defining clinical manifestation is impaired single word naming and comprehension[64, 65] which is accompanied by atrophy of the left anterior temporal lobe (Fig 1-1), although behavioural features such as disinhibition and hyper-religiosity can also emerge, particularly in those with involvement of the right temporal regions[66]. Other cognitive domains – particularly procedural memory, attention and visuospatial function, tend to remain comparatively preserved[9] (See Table 1-3). Pathologically, TDP-43 deposition, and specifically, type C with dystrophic neurites, is most commonly associated with svPPA[9]. However, this relationship is not exclusive or definitive and TDP types A and B, where TDP deposition is found in the cytoplasm, as well as tau and AD pathology, have been found in svPPA patients[67, 68].

Inclusion criteria	Language difficulty is the most prominent clinical feature Language difficulty is the primary cause of impaired activities of daily living Language difficulty is the most prominent symptom during the initial stages of the disease
Exclusion criteria	Pattern of deficits is better accounted by another, non-neurodegenerative, disorder including a psychiatric diagnosis Prominent, early episodic or visual memory or visuoperceptual impairments Prominent, early behavioural disturbance
Clinical diagnosis	Core features: • Impaired confrontational naming • Impaired single word comprehension

	Other diagnostic features (3/4 needs to be present): • Impaired object knowledge • Surface dyslexia or dysgraphia • Spared word and phrase repetition • Spared speech production (grammar and motor speech)
Supportive imaging features	In addition to clinical diagnosis: • Predominant anterior temporal atrophy (MRI/CT); or • Predominant anterior temporal hypometabolism (PET)
Definite pathology	In addition to clinical diagnosis: • Histopathological or genetic evidence of a specific neurodegenerative pathology

Table 1-3. Current diagnostic criteria for svPPA, adopted from Gorno-Tempini et al[64]. CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

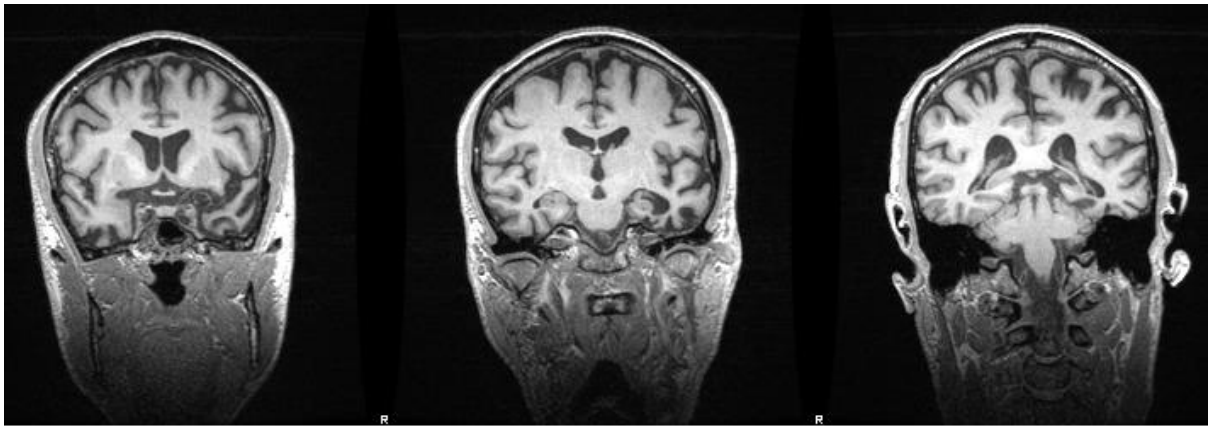

Figure 1-1. Coronal view of an MRI of a patient with svPPA. The images demonstrate characteristic temporopolar grey matter atrophy consistent with a diagnosis of left-lateralised svPPA.

Existing Biomarkers

Genetics

The detection of pathogenic mutations in individuals with svPPA is uncommon[9]. Specifically, there are reports of clinical presentations consistent with svPPA in individuals with *GRN*[69], *C9ORF72*[70] and *MAPT*[71] mutations but these cases account for a small fraction of svPPA cases. Only ~5% of affected individuals have a family history suggestive of an inherited disorder[9]. As such, genetic testing remains a biomarker of extremely limited utility in diagnosing svPPA.

Fluid biomarkers

Neurofilament light chain (NfL) levels in CSF of svPPA patients have been shown to be increased compared to healthy controls as well as those with AD[38]. Higher levels of NfL are associated with increased disease severity and worse performance on naming tasks as well as lower grey matter volume in the parahippocampus. However, these results do not distinguish svPPA from bvFTD and nfvPPA, nor do they correlate with survival or progression in grey matter atrophy[72, 73]. This suggests that while measurements of NfL in both CSF and serum may be useful in specific scenarios, its general utility is limited.

Imaging biomarkers

On structural imaging, such as in MRI, svPPA is characterised by atrophy of the left anterior temporal lobe. A radiologically and pathologically analogous scenario, with predominantly right rather than left temporal atrophy, is seen in ~30-40% of patients with focal anterior temporal lobe neurodegeneration[66, 74]; some refer to this syndrome as the right temporal variant of FTD to emphasise a different clinical profile to svPPA, while others use the term right svPPA to emphasise the shared imaging and pathological characteristics. In either variant, anterior temporal atrophy progresses over time and involves the contralateral temporal lobe as the disease progresses[75]. FDG-PET can demonstrate reduced metabolism in the temporal lobes[50] but usually unnecessary as atrophy is typically well established at diagnosis.

Neuropsychological biomarkers

A PPA phenotype predictor was recently developed using performance on items of the Addenbrooke's Cognitive Examination (ACE; see Chapter 2 for more information)[76]. This approach was reported to distinguish svPPA from nfvPPA and logopenic variant of PPA (lvPPA; pathologically a variant of AD[65])

with a sensitivity of 100% for svPPA. Whether this tool provides benefit over routine clinical assessment in the diagnosis of svPPA remains unknown at this stage.

Several studies have explored language analysis for predictors of subclinical neurodegenerative disease[77]. Previous studies in svPPA based on autobiographical narrative speech have demonstrated utilisation of fewer nouns, syntactic misordering, and a reduction in the complexity and variation of syntax[78, 79]. It is unclear whether this profile extends to unconstrained written language output. One study based on an individual's journal entries[80] demonstrated that the earliest changes in vocabulary – increased repetition and use of high frequency words – were detectable several years before the formal diagnosis of svPPA. Such an approach relies on a large volume of written text prior to the development of symptoms, making it difficult to apply in most clinical settings.

Non-fluent variant of primary progressive aphasia

Clinical and pathological features

nfvPPA, also referred to as progressive nonfluent aphasia, is a neurodegenerative syndrome characterized by slow, effortful, hesitant and distorted speech, which can present together with grammatical errors and orobuccal apraxia[65] (Table 1-4). Its incidence is similar to svPPA, occurring at ~3.5/100,000[81]. Patients presenting with nfvPPA may progress to develop clinical features of PSP or CBS[82, 83] and speech deficits consistent with nfvPPA can present along with other clinical features most consistent with diagnosis of PSP or CBS[84, 85]. Adding to the complexity, a number of rarer clinical variants of PPA – such as mixed progressive aphasia[86], dynamic aphasia[87], progressive dysprosodia[88] – have been grouped, at least for now, under nfvPPA based on clinical features, such as the presence of apraxia or imaging features, that overlap with nfvPPA.

Pathologically, nfvPPA is associated most commonly with a tauopathy consistent with PSP or CBD pathology[6] (*See below*). TDP-43[1] and AD pathology[89] have both been reported, although AD pathology, in particular, may be a concurrent, or a contributing, pathological finding rather than being the primary

pathology in these patients[4]. This may explain why lvPPA, which can also present with slow speech, frequent word-finding pauses and speech sound errors, was often diagnosed as nfvPPA[90] although its most characteristic feature is impaired sentence repetition progressing to impaired single word repetition[91].

There is a suggestion that certain clinical and imaging features can predict underlying pathology[92] – for instance, the presence of apraxia of speech has been associated with tau pathology[93]. However, this remains very much a work in progress and there is a need to improve our ability to clinically characterise these disorders.

Inclusion criteria	Language difficulty is the most prominent clinical feature Language difficulty is the primary cause of impaired activities of daily living Language difficulty is the most prominent symptom during the initial stages of the disease
Exclusion criteria	Pattern of deficits is better accounted by another, non-neurodegenerative, disorder including a psychiatric diagnosis Prominent, early episodic or visual memory or visuoperceptual impairments Prominent, early behavioural disturbance
Clinical diagnosis	At least one of: • Agrammatism in language production • Effortful, halting speech with inconsistent sound errors/distortions In addition, at least 2 of: • Impaired comprehensions of complex sentences • Spared single-word comprehension • Spared object knowledge
Supportive imaging features	In addition to the clinical diagnosis: • Predominant left posterior fronto-insular atrophy (MRI); or • Predominant left posterior fronto-insular hypometabolism (PET)
Definite pathology	In addition to clinical diagnosis: • Histopathological or genetic evidence of a specific pathology

Table 1-4. Current diagnostic criteria for nfvPPA, adopted from Gorno-Tempini et al[64]. CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

Existing Biomarkers

Genetics

nfvPPA has been infrequently reported as a presenting clinical phenotype of *MAPT*[94], *GRN*[95, 96] and *C9ORF72*[97] mutations, but these pathogenic mutations present more commonly with another FTLD phenotype such as bvFTD[81].

Fluid biomarkers

Serum NfL has been reported to differentiate logopenic variant of PPA[65] from nfvPPA and svPPA, but not to distinguish nfvPPA from svPPA[98]. Measuring amyloid-β levels in CSF may be useful in distinguishing nfvPPA from lvPPA since it will be low in lvPPA as a variant of AD[99], but amyloid-β is unable to differentiate FTLD syndromes from healthy controls[37, 38].

Imaging biomarkers

The defining imaging feature of nfvPPA is atrophy of the peri-sylvian region[64], specifically involving the left inferior frontal gyrus (pars opercularis), the insula, the supplementary motor area and the inferior parietal regions[92]. These imaging features, when present, may help secure a syndromic diagnosis of nfvPPA, but are not helpful in distinguishing specific neuropathological substrates.

Tau specific PET ligands have successfully demonstrated location of tau deposition in nfvPPA patients. However, one of the most promising tau ligands, 18F-flortaucipir, which was specifically developed to demonstrate tau deposition in AD, demonstrates low affinity for tauopathy in FTLD[100].

Neuropsychological biomarkers

Neuropsychological approaches have been developed to diagnose nfvPPA. For example, the PPA phenotype predictor described earlier identified the nfvPPA with sensitivity of ~80%[76].

Progressive Supranuclear Palsy

Clinical and pathological features

The term PSP is used to describe a clinical syndrome characterised by supranuclear gaze palsy, postural instability and progressive axial rigidity[101] (Table 1-5), though these features are not invariably present. The 'classic' clinical presentation of PSP is known as Richardson syndrome; it has a reported incidence of ~6/100,000[102, 103]. In addition, the term PSP can be used to describe a specific 4 repeat domain tauopathy ("4R tau"), where the tau protein is organised in straight filament conformations and subcortical regions and brainstem are more severely affected; there are also tufted astrocytes which distinguishes it from other tauopathies[101, 104]. Despite the use of the term PSP to describe clinical and pathological entities, clinicopathological correlation is imprecise.

Specifically, a number of clinical phenotypes, in addition to Richardson syndrome, have been recognised or associated with PSP pathology. These include PSP with predominant parkinsonism, with gait freezing, with corticobasal syndrome, with cerebellar ataxia, with behavioural features and predominant speech language disorder[84]. These variants, when combined, can make up to ~2/3 of initial presentations of PSP and correctly revising the diagnosis clinically to PSP can be challenging when the clinical features of Richardson syndrome are absent[105]. Such clinical heterogeneity arises from regional distribution of tau pathology[106] emerging from preferential spread through different functional networks[107].

Inclusion criteria	Sporadic occurrence First symptom onset at age > 40 Gradual progression of symptoms
Exclusion criteria	Must rule out following conditions based on clinical + imaging + other biomarker testing as indicated: • Neurodegenerative disorders: e.g., AD, multisystem atrophy, LBD, MND, leukoencephalopathy/leukodystrophy • Cerebrovascular disease/previous strokes • Prion diseases • Autoimmune/paraneoplastic encephalitis

	• Encephalopathies (e.g., metabolic, Wilson's disease) • Infections (e.g., neurosyphilis, Whipple's Disease) Presence of any genetic mutation other than *MAPT*, *LRRK2*, and *Parkin*
Core clinical features presented in decreasing order of certainty	Oculomotor dysfunction: 1. Vertical supranuclear gaze palsy 2. Slow velocity of vertical saccades 3. Square wave jerks or 'eyelid opening apraxia' Postural instability – developing within 3 years of first symptom onset 1. Repeated, unprovoked falls 2. Falling on the pull test 3. More than 2 steps backwards on the pull test Akinesia 1. Progressive gait freezing within 3 years 2. Parkinsonism, predominantly axial akinetic rigidity; levodopa unresponsive 3. Parkinsonism with tremor; levodopa responsive Cognitive dysfunction 1. Features of nfvPPA or progressive apraxia of speech 2. Frontal cognitive/behavioural abnormalities 3. Corticobasal syndrome
Supportive features	Clinical • Levodopa resistance • Hypokinetic, spastic dysarthria and dysphagia • Photophobia Imaging • Midbrain atrophy/hypometabolism (MRI/PET) • Post-synaptic striatal dopaminergic degeneration (DAT)

Table 1-5: Current diagnostic criteria for PSP, adopted from Hoglinger et al[84]. Once the inclusion criteria and the exclusion criteria are satisfied, the clinical features determine the diagnostic category as 'possible' or 'probable' PSP. The diagnosis of definite PSP requires neuropathological confirmation. AD = Alzheimer's disease; DAT = dopamine transporter scan; LBD = Lewy body dementia; MND = motor neuron disease; MRI = magnetic resonance imaging; PET = position emission tomography

Existing Biomarkers

Genetics

Although there are reports of *MAPT* mutations in familial PSP[1, 108], PSP is generally considered a sporadic disease[109]. There are also 2 haplotypes of *MAPT* and the presence of the H1 variant increases risk of PSP[110] but this should be best considered as a risk assessor, similar to *ApoE* genotype in AD[111], rather than a predictor or a diagnostic biomarker of PSP, given the rarity of PSP.

Fluid biomarkers

In PSP, despite increased level of tau deposition in the brain, the CSF levels of tau are not consistently elevated, unlike in AD[112]. However, measurement of CSF tau may have a role in distinguishing PSP from CBS, since the latter demonstrates much higher levels[113, 114].

On the other hand, NfL levels in both CSF and serum are significantly elevated in PSP individuals compared to healthy controls and PD; but the levels are not distinguishable from those with CBS or multisystem atrophy[72, 115]. While this limits the utility of NfL as a diagnostic biomarker, NfL levels also change over time, suggesting that it may have a role as a surrogate biomarker for disease progression and assessing treatment outcome[105].

Imaging biomarkers

MRI in PSP patients can demonstrate atrophy of the midbrain. This can result in the 'hummingbird' sign – where the atrophied midbrain resembles the head of a bird with a long beak, and the relatively preserved pons being the body with wings – which, when present, has high specificity (~1) but low sensitivity (<0.7) for PSP[116]. This finding has been developed further into midbrain- pons ratio (MP ratio) and magnetic resonance parkinsonism index (MRPI) involving both the MP ratio and the measurements of superior and middle cerebellar peduncles, both of which have been shown to predict PSP pathology compared to healthy controls and patients with PD and MSA[117, 118]. Both

measures have been explored in the clinical diagnosis of FTLD syndromes[119] but not as markers of FTLD pathologies. FDG-PET can demonstrate hypometabolism in the frontal cortex, caudate, midbrain and thalamus[120]. Dedicated dopamine transporter scan (DAT) is available overseas to demonstrate nigrostriatal neurodegeneration[121] but neither currently adds additional value over MRI in making the diagnosis of PSP[109].

Clinical and neuropsychological biomarkers

Restriction and slowing of vertical eye movement is a pathognomonic feature of PSP, or at least of the Richardson syndrome. Understandably there have been efforts to quantify changes in eye movements, and decreased vertical saccadic velocity can differentiate tau pathology from AD and other FTLD pathology[122]. This approach requires specialised equipment and is not currently used in clinical practice.

Corticobasal Syndrome

Clinical and pathological features

CBS is characterised by combination of extrapyramidal signs – most commonly parkinsonism and dystonia – as well as cortical features – typically apraxia, sensory deficits and alien limb phenomena[123]. It is considered much rarer than PSP with estimated incidence of 0.6-0.9/100,000[102]. The term corticobasal degeneration (CBD) refers to the specific pathological entity first described in association with CBS. CBD is characterised by 4R tau deposits similar to PSP, but with plaques found predominantly in astrocytes[104, 123, 124]. These deposits also have predominantly cortical distribution unlike in PSP[125].

Clinicopathological correlation between CBS and CBD is poor. In addition to CBS, three other clinical syndromes have been associated with CBD; the frontal behavioural-spatial syndrome, nfvPPA, and PSP syndrome. Conversely, several different pathological entities have been associated with CBS. Specifically, in addition to CBD, PSP, AD, and TDP-43 pathology have been reported in CBS patient

cohorts[126, 127]. There are no clinical features sufficiently specific to distinguish CBD pathology from other FTLD pathologies[85].

Inclusion criteria	Insidious onset and gradual progression Symptom duration of at least 1 year First symptom onset at age > 50 Gradual progression of symptoms
Exclusion criteria	Must rule out following conditions based on clinical + imaging + other biomarker testing as indicated: • Neurodegenerative disorders: e.g., AD, multisystem atrophy, LBD, MND, leukoencephalopathy/leukodystrophy • Cerebrovascular disease/previous strokes • Other focal structural lesions 2 or more relatives diagnosed with CBS Positive genetic mutation affecting tau
Core clinical features for diagnosis of probable CBS	Asymmetric presentation of at least 2 limb features: • Limb rigidity/akinesia • Limb dystonia • Limb myoclonus In addition, 2 cortical features from: • Apraxia – limb or orobuccal • Cortical sensory deficit • Alien limb phenomenon
Clinical variants	Frontal behavioural-spatial variant requires 2 of: • Executive dysfunction • Behavioural or personality changes • Visuospatial deficits • One core clinical feature nfvPPA variant requires • Clinical features of nfvPPA as outlined in Table 1-4 • One core clinical feature PSP variant (only for diagnosis of possible CBS) requires: • Clinical features of PSP as outlined in Table 1-5 • One core clinical feature of CBS

Table 1-6: Diagnostic criteria for probable sporadic CBS, adopted from Armstrong et al[85]. The diagnosis of possible CBS suggests overlap with other tauopathies and requires 1 each of limb and

cortical features, or clinical variants without a core clinical feature. There is also no constraint on age or family history/genetic testing results for a 'possible' diagnosis of CBS. AD = Alzheimer's Disease; CBS = corticobasal syndrome; LBD = Lewy body dementia; MND = motor neuron disease; nfvPPA = non fluent variant of primary progressive aphasia; PSP = progressive supranuclear palsy

Existing Biomarkers

Genetics

There are only rare reports of families and individuals with mutations in *MAPT*, *C9ORF72*, and *presenilin 1* presenting with CBS clinical phenotype[123]. CBS is generally considered to be sporadic, and genetic testing does not have an established role in the diagnosis – and in fact, positive genetic testing affecting tau is classified as an exclusion criterion for probable CBD in the current diagnostic criteria.

Fluid biomarkers

CSF tau levels have been reported to be significantly elevated in CBS compared to PSP as well as PD[113, 114] although amyloid levels can also be reduced and it is important to exclude co-existing AD pathology[128, 129]. However, low amyloid has not been a consistent finding across studies[130], perhaps reflecting underlying pathological heterogeneity. CSF and serum NfL levels are elevated in CBS individuals compared to healthy controls, although these results are not necessarily distinguishable from those with other FTLD syndromes[72, 115].

Imaging biomarkers

MRI can demonstrate asymmetric cortical atrophy particularly involving peri-rolandic region, posterior frontal and parietal lobes[123]. CBS associated with TDP-43 pathology tends to involve the frontotemporal regions as well as the prefrontal cortex while those with AD pathology demonstrate greater parietal lobe atrophy[131].

The pattern of hypometabolism on FDG-PET may also differ in clinically defined CBS according to the underlying pathology. For example, several studies have demonstrated differing patterns of hypometabolism in CBS due to underlying AD pathology compared to CBS due to non-AD pathologies (e.g., PSP or CBD)[132]. Furthermore, Pardini et al[133] demonstrated differing patterns of hypometabolism on FDG-PET according to underlying pathology, not only between CBS due to underlying AD pathology compared to non-AD pathology, but also between CBS caused by CBD and PSP pathologies[134]. Currently available evidence is insufficient to determine the sensitivity and specificity of FDG-PET in making these distinctions. As amyloid based therapies are developed and deployed, it may prove advantageous to distinguish CBS cases caused by AD pathology, but it remains unclear whether distinguishing CBS caused by CBD from CBS caused by PSP, both 4R tauopathies, is useful at a clinical level.

Putative biomarkers in FTLD

Genetic testing

Genetic testing, when abnormal, can provide a specific diagnosis and indicate the underlying pathological substrate. Unfortunately, highly penetrant autosomal dominant mutations are identified only in ~25% of FTLD patients; a further ~15% of patients have an affected first degree relative, potentially suggesting as yet unidentified genetic mechanisms of disease[135, 136]. More than half of FTLD cases remain unexplained by known genetic factors or strong family history, potentially limiting the utility of genetic markers as diagnostic tools in FTLD as a whole. Genetic testing currently remains predominantly diagnostic, as opposed to a prognostic, biomarker, although there is emerging evidence that measurements of progranulin levels in blood[36, 137] in *GRN* mutation carriers, may have a role in staging, prognostication and assessing response to treatment.

Fluid biomarkers

Cerebrospinal fluid (CSF) has been investigated as a source of potential biomarkers, but the results thus far have been disappointing. Unlike in AD, where a combination of CSF amyloid and tau levels provide direct evidence of AD pathology with clinically acceptable sensitivity and specificity[138], no specific CSF based biomarker has been shown to distinguish specific FTLD syndromes[35, 139]. CSF NfL, an important contributor to axonal and neuronal stability as well as neuronal function[140], has been identified as a potential marker of disease activity in established FTLD (i.e., for disease staging) and potentially for assessment of response to treatment[72, 141, 142]. However, altered CSF NfL levels indicate presence of axonal injury and are not specific to FTLD[140, 143] precluding its use as a diagnostic biomarker. Nevertheless, NfL is emerging as a promising diagnostic and staging serum biomarker[144-146], albeit with limited specificity.

The investigation of potential blood/serum biomarkers is even more challenging. Potential biomarkers may not cross the blood brain barrier. Alternatively, serum levels could be affected by production outside the CNS, increased systemic metabolism, or interaction with other serum components[147]. Nevertheless, recently serum levels of glial fibrillary acidic protein (GFAP) have been identified as a potential biomarker of FTLD, with serum levels elevated compared to healthy controls[148] and patients with psychiatric disorders[149], as well as correlating with disease severity. However, further work is required to validate the utility of GFAP – for instance, it is unclear whether serum GFAP levels can differentiate AD from FTLD[150] or not[148].

Imaging Biomarkers

Brain neuroimaging has an established role in diagnosis of FTLD. The diagnostic criteria often incorporate imaging to confirm characteristic patterns of cortical atrophy (i.e., MRI) or hypometablism (i.e., FDG-PET) and to exclude other conditions that may be responsible or contribute to the clinical picture[50]. Over time, as our understanding of cerebral alterations with FTLD has improved, such that

tracking of regional brain atrophy over time may even lead to a revision of the original clinical diagnosis[151].

Another imaging modality commonly deployed in the initial diagnostic process for FTLD is positron emission tomography, or PET. Several PET ligands have been studied in a research setting, but only two approaches are used clinically in the diagnosis of FTLD: 18F-2-fluroro-2-deoxy-D-glucose (i.e., FDG-PET) and amyloid imaging, with one of several commercially available amyloid PET ligands. FDG-PET can demonstrate regional hypometabolism to support a clinical diagnosis of FTLD[152] and distinguish it from AD. Amyloid-PET is useful in discriminating or excluding AD from FTLD, but since amyloid pathology is not a key feature of FTLD, it has no further role in differentiating FTLD subtypes[138]. Despite being in development over the last 10 years, tau specific ligands have not yet translated to clinical practice and what role they have in the diagnosis of FTLD is yet to be clarified. I am not aware of any specific PET ligands for TDP-43 for use in humans.

Conclusion

As this chapter illustrates, the absence of biomarkers significantly hampers our ability to further delineate FTLD syndromes and assess disease progression. This absence provides a significant barrier to the identification of potential targets for therapeutic interventions and measuring successful response to potential disease modifying treatments.

Existing biomarkers reviewed in the previous sections of this chapter provide a foundation for exploration of neurodegenerative disorders. They are, however, not without shortcomings. Genetic markers, when positive in a symptomatic individual, provide a definitive diagnosis. However, even when positive, these genetic markers do not aid in assigning staging or assessing disease progression. Fluid and imaging-based biomarkers may assist in assessing disease severity and, particularly in the case of the latter, rates of progression, as previously discussed in this Chapter. However, there is scope

for further exploration of current biomarker utility and identification of new biomarkers – Chapters 4 and 5 attempt to add to the existing work in this field.

In addition, no current biomarkers reflect the presence or severity of symptoms or disease progression particularly well. Capturing the complexity of variable and evolving symptoms with reliable biomarkers is a focus of ongoing study. In Chapters 3 and 6, I focused on the application of technology to provide further insight into symptom progression (i.e., language changes and sleep disturbances in svPPA and bvFTD respectively) and utility as biomarkers.

In the subsequent chapters of this thesis, I explore novel biomarkers that could aid in further distinguishing, as well as capturing the symptoms and progression of specific FTLD syndromes. Chapter 2 outlines the methods and techniques used to distinguish FTLD subtypes in subsequent chapters. The first study explores language changes in svPPA as a marker of disease progression (Chapter 3). This approach was chosen, because of a serendipitous opportunity to analyse a large quantity of text (>100,000 words) produced by an individual with svPPA ~2 years apart. While svPPA is characterised by specific language deficits (e.g. difficulties with confrontational naming)[153] that are relatively well characterised at presentation, it is not yet well understood how language output evolves as the disease progresses.

The next two studies focus on detailed analysis of specific regions of the brain on volumetric MRI to distinguish different types of (mostly) tauopathies. Chapter 4 focuses on nfvPPA patients who appear to have predominantly right sided perisylvian atrophy and a somewhat distinct clinical phenotype. The chapter utilises volumetric MRI as well as more advanced imaging analysis to explore whether a 'right' variant of nfvPPA can be separated from the standard, or 'left' variant nfvPPA, akin to svPPA which has established left- and right- variants[74].

Chapter 5 focuses on delineating pathologically defined PSP and CBD from each other, as well as from pathologically confirmed TDP-43 cases and clinically identified healthy controls and Alzheimer's Disease using the MP ratio and MRPI from MRI performed at diagnosis. PSP and CBD have many overlapping clinical features and demonstrate poor clinicopathological correlation[154]; improving our ability to distinguish PSP and CBD could have significant implications of diagnosis and recruitment into clinical trials.

Finally, in Chapter 6, I investigate the utility of sleep as a biomarker for diagnosis, prognosis, and disease progression in bvFTD. Recently, it was proposed that sleep disturbance is a driver of neurodegeneration[62], and there has been an increasing interest in charactering the nature of sleep disturbances in bvFTD and the potential underlying mechanisms[155]. With this work, I attempted to provide a comprehensive characterisation of sleep disturbance in bvFTD utilising several different sleep assessment tools (e.g., sleep questionnaire, sleep diary, actigraphy and polysomnography) as a prelude to the development of sleep as a diagnostic bvFTD biomarker bvFTD.

Chapter 2

Methods

Introduction

All participants were recruited via FRONTIER, a clinical research program focusing on frontotemporal dementia and related younger-onset dementias, based at the Brain and Mind Centre, University of Sydney. Participants underwent detailed clinical assessment including history and examination as well as neuropsychological assessment and MRI. Based on these results, each participant was diagnosed and classified into a FTLD syndrome – bvFTD, svPPA, nfvPPA, PSP, CBS – based on the current clinical and research diagnostic criteria[13, 64, 105, 123]. A proportion of patients donated their brain for pathological examination. In addition, various, and distinct, methods were deployed, based on specific characteristics of each clinical syndrome, to identify potential novel biomarkers and assess their utility. FRONTIER also recruits and assesses healthy individuals and patients with AD to function as controls.

Clinical Assessment

Clinical assessment involved interviews with patients and their informants, as well as a broad assessment of the main cognitive domains – attention, memory, visuospatial function, language and executive function, followed by a neurological examination[156]. Noted items in history included the nature of the symptoms, their duration, family history as well as functional and social capacity as well as the patient's degree of insight. Much of the language function was assessed during this process, taking note of speech fluency, word finding difficulties, use of grammar, presence of dysarthria, dysphasia, and paraphasia. There was also more structured assessment of semantic knowledge via confrontational naming of animals as well as word and sentence repetition. Neurological examination specifically looked for signs of parkinsonism, motor dysfunction, cerebellar dysfunction, eye movement deficits, visuospatial dysfunction as well as limb and orobuccal apraxia.

Neuropsychological Assessment

Addenbrooke's Cognitive Examination

Addenbrooke's Cognitive Examination (ACE) was used as a screening test of global cognition. ACE assesses five cognitive domains – attention, memory, verbal fluency, language and visuospatial ability and produces a total score of 100. The revised version (ACE-R)[157] was used for patients assessed prior to 2013, and Version 3 (ACE-III)[158] thereafter. When required, ACE-R score was converted to ACE-III equivalent using a calculator available at https://www.sydney.edu.au/brain-mind/resources-for-clinicians/dementia-test.html#calculator[159].

Formal neuropsychological evaluation

Formal neuropsychological assessments testing various cognitive domains were also performed including, but not limited to, memory, visuospatial function, language abilities, executive function and emotional recognition and processing.

Visuospatial and episodic memory functions were assessed using the Rey-Osterrieth Complex Figure (RCF) task[160]. There are two components to the test – the first component requires the participant to copy a complex design presented in front of them. The accuracy, and the organisation of the act of copying, are scored. The second task asks the participant to produce a copy of the complex figure from memory after a short delay (usually ranging from 5-20 minutes), as a test of non-verbal memory.

Language abilities were tested using four components of Sydney Language Battery (SYDBAT) which consists of polysyllabic nouns of decreasing frequency and graded broadly into 3 difficulty levels[161] across four constructs: naming, comprehension, word repetition and semantic association. Syntactic

comprehension was tested with Test for Reception of Grammar (TROG)[162] and sentence repetition was assessed using the 'sentence repetition' subset of the Multilingual Aphasia Examination[163].

Executive function was assessed with letter fluency[164], the Trail Making Test (TMT) Parts A and B[165] . In letter fluency, the participant is required to produce as many words, but not proper nouns, and avoid repetitions or words with the same stem beginning with the letters "F", "A", and "S" within 1 minute each. The number of words generated is recorded, with a reduced number indicating executive impairment[166]. In the TMT, the participant is asked to join circles according to a sequence that they must determine given only a brief example. In part A, the circles are labelled with ascending numbers. In part B, the circles are labelled with a mix of numbers and letters and the subject is required to alternate between numbers and letters (e.g., start with "1", then "A", then "2", then "B" and so on). The time taken for both tests are recorded, and this assesses speed of information processing; the time differences between Part B and Part A indicate executive function, or dysfunction[167].

Emotion recognition and processing was assessed using the face perception (FPT), face identity discrimination (FIDT), facial affect discrimination tests (FADT), and facial affect selection (FAST)[168] FADT was performed using 60 black and white photographs showing one of 6 emotions (anger, disgust, fear, happiness, sadness, surprise) displayed on a computer screen for 5 seconds in a pseudorandom order; the participants were instructed to select best label for the picture using a mouse, pointing or verbally based on their preference. FAST is an untimed task requiring participants to select the face that most closely corresponded to the emotion spoken by the examiner, from an array of 7 faces of the same person (6 emotions and a neutral face); the face positions varied from trial to trial.

The digit span test was used as a test of attention and working memory. Participants are read a sequence of digits and asked to recite them back in the order they were heard. If completed successfully, the number sequence becomes longer by a digit and this continues until two errors are made at a specific span length. The second part of the test asks the participant to repeat the digits in the reverse order; the span increases in length by a digit until two errors are made at a particular span[169].

Language assessment

This was performed using recordings of spontaneous speech and description of Boston Cookie Theft picture[170] based on progressive aphasia language scale (PAL)[171]. PAL divides into motor speech disorder into 4 categories – presence of distortions (or lack of accurate articulation), effortful speech, articulatory groping and loss of normal prosody (incorrect placement of stress and intonation) – and errors in syntax, inflection or omission of grammatical features (i.e., agrammatism). Each of these variables were graded as 'questionable', 'definite' or 'severe'.

Imaging Acquisition

Magnetic resonance imaging (MRI) was performed to obtain volumetric T1 sequences. Participants assessed between November 2007 and December 2016 were scanned with a 3 Tesla Philips MRI scanner (Koninklije Philips NV, Amsterdam, Netherlands) with a standard 8-channel head coil at Neuroscience Research Australia (NeuRA). Participants assessed after December 2016 were scanned on a 3T GE MR750 MRI scanner (General Electric, Boston, Mass, USA) with a standard 8-channel head coil at the Brain and Mind Centre. The 3D T1-weighted images across both scanning sites were acquired with the following parameters: coronal orientation, matrix 256 x 256, 200 slices, 1 x 1 mm in-plane resolution, slice thickness = 1mm, echo time/repetition time = 2.6/5.8ms, flip angle α = 8 degrees.

For analysis of cortical thickness, T1 images were processed using FreeSurfer version 6.0, following several pre-processing steps, including skull stripping, Talairach transformations, atlas registration, and spherical surface maps and parcellations (http://surfer.nmr.mgh.harvard.edu/)[172] and Cortical thickness was smoothed with a 20 mm full-width at half-height Gaussian kernel.

For analysis of brainstem volumes, the acquired T1 images were analysed using RadiAnt Dicom Viewer (version 2020.2.3; Medixant, Poznan, Poland) to calculate the MP ratio and MPRI. First, each T1 coronal scans underwent multiplanar reconstruction, orientated via visual inspection to midline (Fig 2-1a) then the pons and the midbrain were manually traced as previously described[173]. Briefly, a first line was drawn through the superior pontine notch and the inferior edge of the quadrigeminal plate; a second line was drawn through the inferior pontine notch, parallel to the first line. The left MCP was measured parasagittally as the distance between the superior and the inferior borders of the MCP from the image that best showed the MCP between the pons and the cerebellum; and the left SCP was measured coronally from the first image where the inferior colliculus and SCP were clearly distinct[174] (Fig 2-1b, c and d). The area enclosed by the tracing was automatically calculated by the software. MP ratio is calculated as ratio of midbrain area/pontine area; MRPI was calculated as (area of pons/midbrain)*(MCP/SCP)[117]

Textual Analysis

The Tool for the Automatic Analysis of Cohesion (TAACO)[175] was used to count lexical components (e.g., nouns, verbs, adjectives and adverbs) while the Tool for the Automatic Analysis of Lexical Sophistication (TAALES)[176] was used to extract established lexical parameters such as concreteness and imageability from the Medical Research Council Psycholinguistic database[177] and age of acquisition[178]. An average score was calculated for each text based on the sum of all the scores of the individual word divided by the total number or words in the text with an assigned score. Examples of

lexical parameters analysed and the example scores are shown in Tables 2-1 and 2-2 respectively. Both software packages were obtained from https://linguisticanalysistools.org/tools/html.

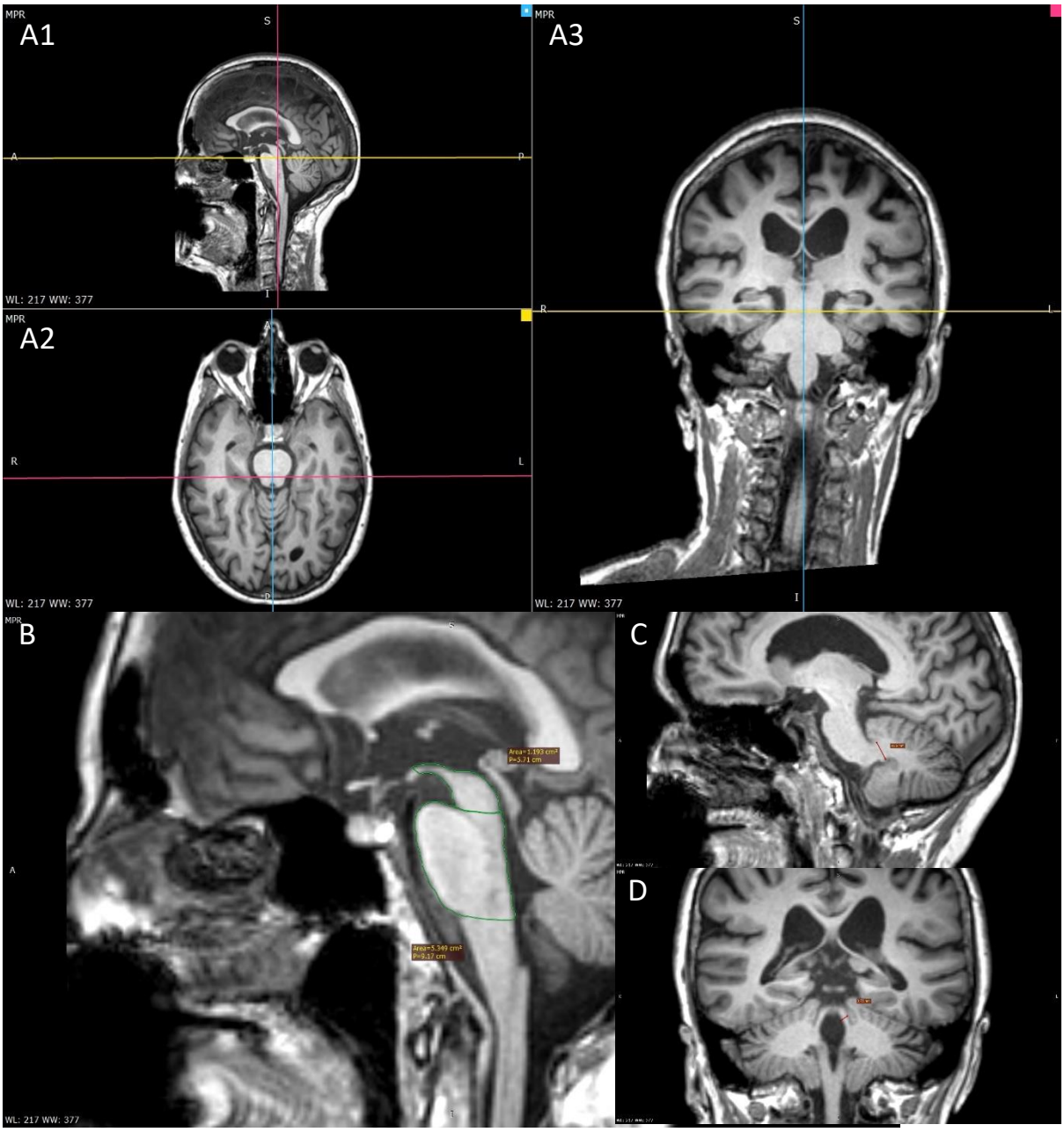

Figure 2-1. An example of manual orientation and alignment of T1 volumetric images. A: Composite T1 images in the sagittal, coronal and axial planes to identifying midline. B: T1 image in the sagittal plane with midbrain and pons trace out. C: T1 image in sagittal plane identifying MCP. D: T1 image in coronal plane identifying SCP. MCP = middle cerebellar peduncle; SCP = superior cerebellar peduncle

Pathological Specimen Preparation and Examination

The pathological information was provided by the Sydney Brain Bank. The brain tissue immunoblotting was performed from sarkosyl-insoluble, urea soluble fractions extracted from frozen tissue and processed as previously described[179]. Standardized neuropathologic characterization starting with examination of the middle frontal gyrus, superior temporal gyrus, parietal lobe, hippocampus and cingulate gyrus with haematoxylin and eosin, tau, ubiquitin and alpha-synuclein stains were conducted as previously described[180-184]. Broadly, the brain was classified as tauopathy and then subdivided on the basis of 3-repeat tau (Pick disease) or 4-repeat tau with presence of tufted astrocytes and 35 kDa tau band (PSP) or 4-repeat tau with astrocytic plaques (CBD). Tau negative samples were subdivided into TDP-43 positive or negative cases.

Category	*Description*	*Derivation*	*Corpus*	*References*
Familiarity	How commonly a word is encountered	Sum of familiarity scores/number of words in text with familiarity scores	MRC	[185]
Concreteness	How concrete/abstract a word is	Sum of concreteness scores/number of words in text with concreteness scores	MRC	[185]
Imageability	How easily one can construct a mental image of the word	Sum of imageability scores/number of words in text with imageability scores	MRC	[185]
Meaningfulness	How many associations a word has	Sum of meaningfulness scores/number of words in text with meaningfulness scores	MRC	[185]
Age of Acquisition	Age at which a word was learned	Sum of age of acquisition scores/number of words in text with age of acquisition scores	Kuperman	[178]
Polysemy	How many meanings a word can have	Sum of polysemy scores/number of words with polysemy score	Wordnet	[186]
Co-occurrence Probability	Probability of words occurring together	Kullback-Leibler divergence relative entropy	BNC	[187]
Semantic distinctiveness	Ambiguity of words, based on context	Natural log of mean LSA cosine of similarity	BNC	[187]

Table 2-1. Glossary of Lexical Parameters from Tool for the Automatic Analysis of Lexical Sophistication (TAALES).

Category	Word	Score	Category	Word	Score
Concreteness	Clarinet	633	*Imageability*	Kitten	639
	Harvest	535		President	572
	Osculation	410		Citizen	445
	Issue	338		Osculation	318
	Etiquette	252		Here	278
	However	186		Incursion	164
Familiarity	Coffee	625	*Meaningfulness*	Children	608
	Engineer	514		Ocean	522
	Abdomen	426		Fact	463
	Hexagon	387		Auditorium	380
	Enigma	290		Protocol	229
	Osculation	138		Calix	158

Table 2-2: Examples of Medical Research Council Psycholinguistic Parameters. Taken from MRC Psycholinguistic Database: Machine Usable Dictionary, Version 2.00[177] available at https://websites.psychology.uwa.edu.au/school/MRCDatabase/uwa_mrc.htm (accessed 6 November 2020). Maximum score for all these parameters is 700 while the lowest score is 100. Higher scores indicate stronger characteristic, for example, a word with a higher familiarity score represents a more familiar word (e.g., 'coffee'). Note that there is no meaningfulness scored assigned to the word 'osculation' in this dictionary. As an example of an average score, the phrase 'ocean children' (or any of the variants such as 'ocean's children' or 'children's ocean') would have meaningfulness score of (522 + 608)/2 = 565.

Sleep Assessment

Sleep Questionnaire

There are no currently validated methods to document sleeping habits of an individual with a neurodegenerative disorder that could be completed by a partner/carer while also encompassing the experience of the carer as well. Therefore, I created a novel sleep questionnaire covering sleep patterns of the preceding 4 weeks, and a sleep diary to prospectively document sleep behaviour of the individual with dementia and its effect on their carer.

The first section of the sleep questionnaire consisted of 19 questions about the sleep behaviour of the affected individual which incorporated elements from a number of existing sleep assessment tools – Pittsburgh Sleep Quality Index (PSQI)[188], sleep questionnaire from Medical Outcome Study (MOS)[189], global sleep assessment questionnaire (GSAQ)[190], SLEEP-50[191] and Parkinson's disease sleep scale (PDSS-2)[192]. The second section of the sleep questionnaire consisted of 8 questions focusing on the quality of sleep and its impact on the quality of the life of the carer and incorporated elements adopted and modified from Quality of Life in Alzheimer's Disease questionnaire (QoL-AD)[193], Dementia Quality of Life Scale for Older Family Carers (DQoL-OC)[194], and quality of life measure to assess partner morbidity in benign prostatic enlargement[195]. Sleep specific elements common to every questionnaire were selected as important (e.g., about snoring, naps during the day), and the phrasing was modified appropriately for the intended responder. Some questions, thought to be less relevant to the study population (e.g., about somnolence during driving or recent travel history) were excluded.

The sleep diary was designed to be completed prospectively. The questionnaire covers sleep disturbances at night, as well as excessive somnolence, mood, and factors that would adversely impact on sleep during the day, of the affected individual as well as its impact on the carer's sleep. It is also derived from the existing sleep assessment tools mentioned in the previous paragraph. The sleep questionnaire and the sleep diary can be found in Appendix 2-1 and Appendix 2-2 respectively.

Actigraphy

Actigraphy utilises biological (e.g., heart rate + movement) and external parameters (e.g., presence of light) to infer sleep/wake durations while the participant is wearing the actigraphy device. For this study, I utilised the Actiwatch Spectrum Pro (Koninklije Philips NV, Amsterdam, Netherlands) (Figure 2-2). The participants were asked to wear the Actiwatch for 7 days, taking it off during planned exposure to water such as shower or swimming. The participant's carer recorded a sleep diary in

parallel and both were returned by mail. The data were extracted and analysed using Actiware software (Koninklije Philips NV, Amsterdam, Netherlands).

Figure 2-2: An image of Actiwatch Spectrum Pro. The device is battery powered, rechargeable, water resistant and it is encased in hypoallergenic plastic material.

Polysomnography

Polysomnography (PSG) is a simultaneous recording of numerous parameters including electroencephalogram, electro-oculogram, electromyogram of submentalis muscle, electrocardiogram, respiratory effort, oxygen saturation, air flow and limb movements overnight[196], ideally while the participant sleeps. PSG is considered the gold standard for assessing many aspects that impact sleep, from limb movements, the presence and severity of breathing disorders such as apnoea, arousal from sleep as well as information on duration and progression through different stages of sleep.

The sleep studies were performed at a dedicated sleep laboratory at Woolcock Institute of Sleep Research, Glebe, NSW, Australia, using Grael v2 PSG system with Profusion scoring software (Compumedics Limited, Abbotsford, VIC, Australia) and scored as outlined in the American Academy of Sleep Medicine Manual for Scoring of Sleep and Associated Events, version 2.2[197].

Summary

Subsequent chapters will utilise techniques outlined in this chapter to explore potential biomarkers in various clinical syndromes and pathological entities encountered within the spectrum of frontotemporal lobar degeneration. In chapter 3, textual analysis techniques were used to characterise written output changes in a patient with svPPA, along with clinical and neuropsychological techniques. In chapter 4, detailed clinical and imaging techniques were used to classify and delineate two distinct syndromes in nfvPPA. In chapter 5, pathological specimen and imaging analysis established the utility of measuring the volumes of midbrain and pons in differentiating pathologically confirmed PSP and other FTLD. In chapter 6, sleep analysis techniques were used to document changes in sleep patterns of individuals with bvFTD and how sleep disturbances differ in bvFTD from controls and those with AD.

Chapter 3

Textual analysis of

longitudinal linguistic changes in

semantic variant of primary progressive aphasia

Introduction

Language is a complex cognitive function facilitating representational thought and underwriting personal and cultural development and societal organisation[198]. A couple of papers from the early 1990s provided some evidence that alterations in language output in later years could be a potential harbinger of neurodegenerative diseases[77, 199], but the issue remains largely unexplored.

The first detailed demonstration of this phenomenon in an individual is that of Dame Iris Murdoch, a prolific Anglo-Irish author diagnosed with Alzheimer's disease at 77 years of age in 1996[200]. A predominantly manual text analysis of excerpts from three of her novels revealed a significantly reduced number of unique words in her last published work, *Jackson's Dilemma*. In contrast, word length, use of different word classes, overall structure and syntactic composition were not found to differ across the selected excerpts. One limitation of this manual approach, however, is that analyses were restricted to select passages in certain chapters from her books, given the volume of the words – the analysed books have average word counts of ~150,000 words. It is noteworthy that this last work of Dame Iris's was received only "respectfully" on publication[200], suggesting that the quality of the novel, as judged by her readership, was below her previous standards. It seems likely, therefore, that the original text analysis of her works failed to capture the many facets of language, aside from vocabulary, that influence the overall quality of her work.

Subsequent re-analysis of Dame Iris' work, deploying automated analysis of entire texts have since revealed a marked decline in grammatical complexity in addition to a reduction in vocabulary[201]. This fully automated approach was also able to distinguish, albeit in a post-hoc manner, between healthy aging and Alzheimer's disease in three authors (Dame Iris Murdoch, Agatha Christie and PD James) based purely on linguistic features, particularly vocabulary, word repetition and noun use[202].

These language changes, if confirmed, would seem to be an obvious way to identify and develop a biomarker in primary progressive aphasia, the collective term for the neurodegenerative syndrome of the language domain. Most work in this area has occurred in svPPA. These studies have demonstrated utilisation of fewer nouns, syntactic misordering, and a reduction in the complexity and variation of syntax[78, 79]. It remains unclear, however, whether this profile extends to unconstrained and unprompted language output, which can take place over a longer time interval.

There are reports of some patients with FTD whose creativity 'blossoms' in the lead up to their diagnosis[203, 204]. This has manifested most commonly in visual or musical form, but a few patients, particularly those with svPPA, have demonstrated 'verbal creativity'[205]. None of the reported texts (a collection of poems, short compositions, and a book) were analysed in detail however and it is unknown how their lexical outputs compared to routine, or "normal", language use, or how they changed over time.

Only one study has explored longitudinal written language changes in svPPA from the diary of a single case[80]. Analyses focused on one week's worth of entries every six months, which were manually scored by two independent, trained raters and comparisons made between blocks of text written two years apart. While constrained by the limited pool of text excerpts analysed, this study suggests that the earliest changes in vocabulary – increased repetition and use of high frequency words – were detectable several years before the formal diagnosis of svPPA[80].

In this chapter, I explore the writings of patient WR, who experienced a burst of creativity near the symptom onset of his svPPA and proceeded to write and self-publish two coherent and independent works of literary fiction unrelated to each other following the onset of svPPA. Leveraging recent developments in computing power and automated linguistic analysis tools, I endeavour to demonstrate how unconstrained written language production changed across WR's works of literary

fiction in their entirety (>100,000 words each) and confirm previously described language changes in svPPA.

Case Synopsis

WR is a left-handed male, retired shipping industry executive with 13.5 years of formal education. In 2014, WR took up writing historical fiction, self-publishing his first novel at the age of 62 (2015), and the second novel 3 years later (2018). In 2017, WR presented to the FRONTIER research clinic at the University of Sydney with a four-year history of word-finding difficulties, poor comprehension, slowed reading, and difficulty recalling facts, in the context of preserved day-to-day memory and topographical orientation. Importantly, WR's history, corroborated by his spouse, clearly indicates the onset of svPPA symptoms at least 2 years prior to publication of his first novel.

Methodological Considerations

WR kindly provided the final, pre-editorial drafts of his two works (in chronological order, henceforth Book 1 and Book 2), ensuring that the linguistic output being analysed belonged to WR as much as possible. These drafts were typed and revised entirely by WR himself. WR's spouse advised that there were occasions when WR would ask for an alternate word, or suggestions on phrasing. However, these occurrences were not frequent, and while she was not keeping an event diary, she did not feel that the frequency of these occurrences were noticeably different between the two books; we judged that these occurrences would be within the boundaries of the 'normal' writing process.

No literary outputs from WR exist that clearly predate the onset of his symptoms for comparison, and a direct comparison between Book 1 and Book 2 cannot, on its own, indicate significant differences between the two books, given the inherent variation in the lexical and linguistic features of novels. A control corpus was therefore created from the first 5 works of adult fiction, written originally in English, of 20 male authors based in the United States of America (USA) and the United Kingdom (UK) in the

19th and early 20th century (see Supplementary Table 3-1 in Appendix for names of the authors and the books utilised). Novels written early in the author's careers were chosen to minimise the chance that the control authors had an undiagnosed neurodegenerative process at the time of writing. The size of the control corpus was selected to sufficiently capture the lexical variation at the individual author level, whilst ensuring a broad sampling of writing styles and language usage across authors as a representative sample of 'normal' Enlgish language used in novels aimed at adults, WR's intended target audience. Texts were obtained from Project Gutenberg (https://www.gutenberg.org/), an open online repository of texts in the public domain. Prior to analysis, texts were pruned of extraneous 'non-fiction' text (e.g., dedication, forwards from other contributors). It was not possible to control for external editorial input in the control texts; however, any such input would have contributed to their further 'normalisation'.

All the texts were analysed as per protocol outlined in Chapter 2. The control texts were first analysed at the level of individual authors to calculate the range, mean and standard deviation (st.dev) for each parameter across each author's five works. The st.dev provided a metric of the expected within-author variability across texts and was used here as the 'yardstick' to compare the change between WR's two novels. Per author results were then pooled to calculate the mean of the st.dev values within the control corpus, as well as the overall st.dev across the 20 authors' standard deviation values to provide an index of Control Corpus Variability (CCV). The change, or the absolute values of the differences for each parameter between WR's Book 1 and Book 2, were compared to the CCV using a modified t-test procedure described by Crawford et al[206]. We pre-specified a threshold of $t>3$ with $p<0.003$ (Bonferroni corrected for 16 comparisons), to identify parameters that differed significantly from the inherent variation within the control pool (i.e., a value that lies outside 99% of the variability in the Control corpus).

WR also underwent neuropsychological assessment and structural imaging as per the imaging protocol outlined in Chapter 2 on two separate occasions in 2017 and 2018.

Results

Neuropsychology

Formal neuropsychological testing in 2017 confirmed the canonical svPPA cognitive profile in WR. Relative to a demographically matched group of 10 Controls, WR displayed impaired confrontation naming and verbal fluency, with mild deficits in comprehension, semantic association and verbal memory, in the context of relatively intact single-word and sentence repetition, visual episodic memory, and visuospatial and executive functions. Follow-up assessment in 2018 revealed a significant decline in comprehension, semantic association, and verbal fluency, while performance in other cognitive domains remained relatively stable (Table 3-1).

Neuroimaging

Visual inspection of structural MRI from 2017 demonstrated left-predominant anterior temporal atrophy, in the absence of obvious frontal, parietal, or occipital atrophy (Figure 3-1A), consistent with the diagnosis of svPPA. At 12-month follow-up (2018), atrophy was observed to have progressed into adjacent left and right temporal regions (Figure 3-1B).

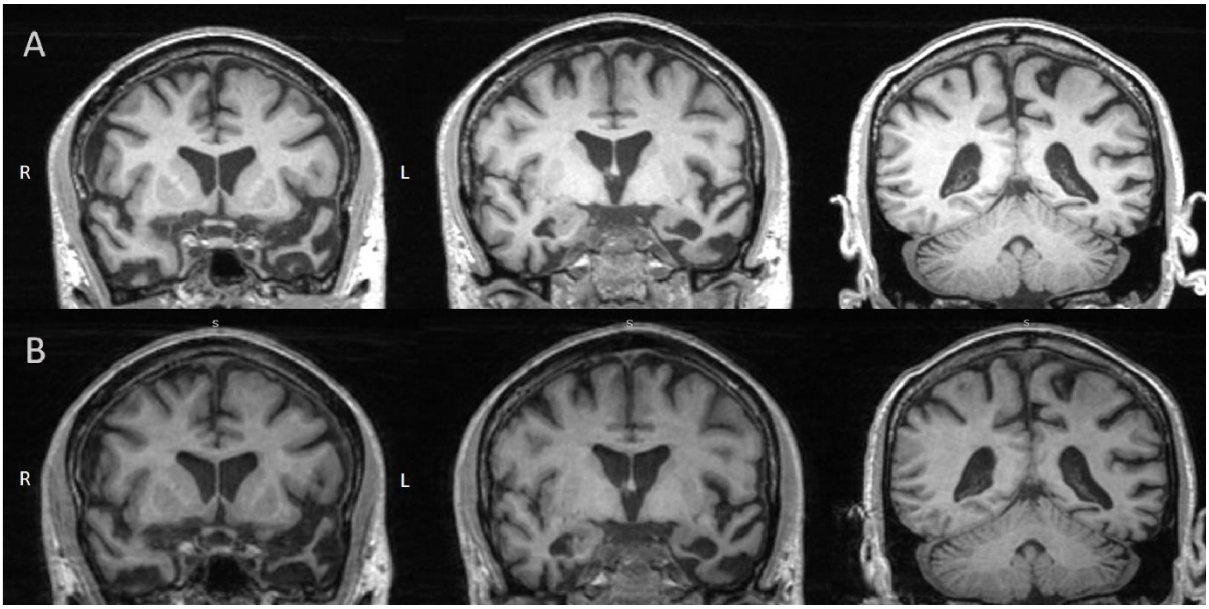

Figure 3-1. Coronal view of WR's MRI. These imagines demonstrate characteristic left anterior temporal pole grey matter atrophy consistent with a diagnosis of left-lateralised svPPA in Patient WR. Panel A displays WR's scan from his initial clinical visit in 2017, while Panel B shows WR's follow-up scan one year later in 2018.

	Controls (5M, 5F)	**WR Visit 1 (2017)**	**Difference at Time 1**	**WR Visit 2 (2018)**	**Difference at Time 2**
Demographics					
Age (years)	63.4 (2.0)	63.4	*t* = 0	64.5	*t* = 0.5
Education (years)	14.2 (1.0)	13.5	*t* = -0.67	13.5	*t* = -0.7
Disease staging					
FRS Rasch[†]	n/a	2.9 (Mild)	n/a	1.7 (Moderate)	n/a
Cognitive screening					
ACE-III Total (100)	94.9 (2.9)	71	***t* = -7.9*** **	67	***t* = -9.2*** **
Semantic processing					
SYDBAT Naming (30)	27.2 (2.1)	8	***t* = -8.7*** **	6	***t* = -9.6*** **
SYDBAT Comprehension (30)	29.4 (1.1)	25	***t* = -3.8** **	20	***t* = -8.1*** **
SYDBAT Semantic Association (30)	28.4 (1.2)	24	***t* = -3.5** **	19	***t* = -7.5*** **
SYDBAT Repetition (30)	29.9 (0.3)	30	*t* = 0.3	30	*t* = 0.3
Executive function					
Letter Fluency (FAS)	48.2 (11.0)	35	*t* = -1.1	23	*t* = -2.2
Digit Span Forwards (9)	10.5 (2.2)	7	*t* = -1.5	6	*t* = -1.9
Digit Span Backwards (8)	7.1 (1.8)	5	*t* = -1.1	4	*t* = -1.6
TMT B-A (seconds)	51.2 (20.9)	42	*t* = -0.4	73	*t* = 1.0
Non-verbal episodic memory					
RCF 3-minute recall (36)	17.8 (3.4)	13.5	*t* = -1.2	15	*t* = -0.8

Table 3-1. Demographics, clinical, and cognitive variables for patient WR relative to an age- and education-matched Control group (n=10). Maximum test score depicted in brackets where appropriate. Raw scores presented for patient WR. Control group values represent means and standard deviations (in brackets). Bolded values indicate a significant difference between WR's test performance and that of the Control group, based on case-control comparisons using Crawford's modified t-statistic. * = $p < .05$; ** = $p < .01$; *** = $p < .0001$. n/a = not applicable. ACE-III = Addenbrooke's Cognitive Examination-Third Edition; FTD-FRS = Frontotemporal Dementia Functional Rating Scale; RCF = Rey Complex Figure; SYDBAT = Sydney Language Battery; TMT = Trail Making Test.

[†]Lower scores on FRS denote greater functional impairment.

Literary Output

Vocabulary Components

Table 3-2 presents an overview of key facets of WR's literary output from Book 1 to Book 2. The most significant alteration was observed in relation to adverb usage, which was comparable to Controls in Book 1 (0.067; Control mean = 0.062; range = 0.049 - 0.074) yet increased considerably in Book 2 (0.082). This change (0.015) is over 8.1 st.dev greater than CCV (mean = 0.004; st.dev = 0.001; $p < 0.001$). The proportion of unique adverbs, however, was not significantly different to that used by Controls (Book 1 = 0.0049; Book 2 = 0.003; Control mean = 0.006; range: 0.003 - 0.010; T = -0.207; p = 0.838). Verb and adjective usage, both in general and unique words, did not deviate significantly from the Control corpus, nor between Books 1 and 2 (Table 3-2).

The number of unique lemmas (from 0.054 to 0.037) and lexical density (from 0.528 to 0.513) decreased from Book 1 and Book 2, but this was not found to be statistically significant relative to the Control cohort (unique lemmas: t = 0.523; p =0.607; lexical density: t = 0.122 and p = 0.904). Noun utilisation was higher in Book 1 (0.248) yet declined to within normal ranges in Book 2 (0.222; Control mean = 0.209; range: 0.193 – 0.242); the absolute change in proportions between Book 1 and Book 2 (0.026) was 2.8 st.dev higher than the Control st.dev (mean = 1.1; st.dev = 0.5, p = 0.01; not significant as $p > 0.003$ corrected). The proportion of unique nouns also decreased from Book 1 to Book 2 (0.03 to 0.021); however, this difference (0.009) was within the limits of CCV (mean = 0.006; st.dev = 0.003).

	Book 1	*Book 2*	*Difference*	*Control Corpus Variation*		*T score*	*p value*	*Control Corpus Parameters*			
TAALES			*(Absolute)*	Mean	st.dev			Mean	st.dev	Range Low	Range High
Word Count	103625	133217	29592	30768.39	15151.05	-0.08	0.470	103614.5	40351.64	43678.2	196938.4
MRC Familiarity Score	587.657	592.837	5.179	1.288	0.665	5.7	*#	590.638	2.114	586.642	593.232
MRC Concreteness	312.954	309.313	3.640	2.945	1.323	0.5	0.307	310.375	6.185	300.863	323.022
MRC Imageability	334.313	333.750	0.563	2.672	1.213	-1.7	0.053	335.131	6.516	325.082	344.290
MRC Meaningfulness	343.813	353.421	9.608	2.819	1.488	4.5	*#	353.725	6.972	341.685	368.061
Age of Acquisition	5.432	5.085	0.347	0.084	0.058	4.4	*#	5.205	0.175	4.997	5.561
Co-occurrence Probability	0.880	0.824	0.056	0.020	0.009	4.1	*#	0.890	0.037	0.836	0.976
Semantic Distinctiveness	2.092	2.118	0.026	0.010	0.005	3.3	0.00195#	2.094	0.014	2.079	2.124
TAACO											
Unique Lemmas	0.054	0.037	0.017	0.013	0.008	0.5	0.304	0.073	0.017	0.037	0.104
Lexical Density	0.528	0.513	0.015	0.014	0.006	0.1	0.452	0.484	0.011	0.462	0.503
Total Nouns	0.248	0.222	0.026	0.011	0.005	2.9	0.005	0.209	0.014	0.193	0.242
Unique nouns	0.030	0.021	0.009	0.006	0.003	1.6	0.060	0.039	0.009	0.020	0.052
Total Adverbs	0.067	0.082	0.016	0.004	0.001	8.1	*#	0.062	0.006	0.049	0.074
Unique Adverbs	0.004	0.003	0.001	0.001	0.001	-0.2	0.419	0.006	0.002	0.003	0.010
Total Verbs	0.159	0.155	0.004	0.006	0.002	-1.0	0.170	0.153	0.009	0.133	0.167
Unique Verbs	0.013	0.008	0.005	0.003	0.002	0.7	0.235	0.016	0.004	0.008	0.027
Total Adjectives	0.062	0.060	0.002	0.005	0.003	-1.2	0.123	0.068	0.008	0.048	0.088
Unique Adjectives	0.011	0.007	0.004	0.003	0.002	0.6	0.290	0.017	0.004	0.009	0.024

Table 3-2. Summary Results of Textual Analysis. Control Corpus Variation (CCV) is mean and st.dev of standard deviation of each parameter across twenty control authors. All TAACO figures are given as a proportion of the total word count of the respective books. The absolute difference between Book 1 and Book 2 was compared to CCV using Crawford's modified t-statistic for case-control comparisons[206] to derive t-score and the p value. Control corpus mean, st.dev and range values are provided for comparison with WR's works. *p = <0.001; # = significant after Bonferroni correction at p < 0.0028. MRC = Medical Research Council; st.dev = standard deviation. TAALES = Tool for the Automatic Analysis of Lexical Sophistication. TAACO = Tool for the Automatic Analysis of Cohesion.

Lexical Parameters

WR displayed a shift towards the use of familiar words, with a significant (corrected p<0.001) increase in MRC familiarity scores from Book 1 (587.657) to Book 2 (592.837). While both these scores are within the Control corpus range (Range: 586.642 – 593.232; mean = 590.638), the magnitude of the change in the two books is significant, being 5.7 st.dev from CCV (mean = 1.288; st.dev = 0.665; p < 0.001).

WR's meaningfulness score increased from Book 1 (343.813) to Book 2 (353.421). While both scores are again within the Control corpus range (Range: 341.685 – 368.061; mean = 353.725), the difference of 9.608 is 4.5 st.dev from CCV (mean = 2.819; st.dev = 1.488; p < 0.001) suggesting a shift towards the more frequent use of more abstract or general words.

The reduction in age of acquisition scores from Book 1 (5.4) to Book 2 (5.1) is 4.4 st.dev from CCV (mean = 0.084; st.dev =0.058; p <0.001), representing an increased reliance on words that were acquired at an earlier age, and therefore more accessible, in Book 2 compared to Book 1. This is independent of their familiarity or length[178].

WR's co-occurrence probability decreased significantly from Book 1 (0.880) to Book 2 (0.824) by 4.1 st.dev (CCV mean = 0.020; st.dev = 0.009; p < 0.001). Since co-occurrence probability examines semantic representations by taking context into account and indicates lexical processing effort[207], this reduction indicates that WR's narrative structure became progressively simpler, lexically less sophisticated and words commonly associated together no longer appear in close proximity. This decline parallels WR's diminishing performance on single item association as reflected on the semantic association subscale of the SYDBAT (Table 3-1).

While the semantic distinctiveness scores of Book 1 (2.092) and Book 2 (2.118) both fall within the control range (range: 2.079-2.124; mean = 2.094), the difference between the two scores (0.03) deviates by 3.3 st.dev from CCV (mean = 0.010; st.dev = 0.005; p = 0.004). Semantic distinctiveness quantifies subtle context dependent variations in word meaning, and while this result is not statistically significant at the corrected threshold of $p < 0.003$, the increased score may reflect the increasing ambiguity or more 'general' language use, characteristic of svPPA[63, 208].

Aside from these changes, a number of parameters were observed to remain stable over the time period assessed. Concreteness, imageability and total word count did not change or deviate in a significant manner from the control group (Table 3-2).

Discussion

In this chapter, using automated language analysis tools, and an independent control corpus, I demonstrate utility of certain lexical and linguistic characteristics as potential biomarkers of disease progression in svPPA as these parameters shift toward simpler vocabulary and language structure with advancing deterioration of the conceptual knowledge base.

The study demonstrated a significant increase in adverb usage between Books 1 and 2, despite a numerical decrease in the number of unique adverbs. This pattern is consistent with previous reports describing a qualitative increase in the use of adverbs in spoken speech in svPPA compared to healthy controls[209, 210]. These previous studies do not specify whether the number of unique adverbs were examined, or the trajectory of adverb usage over time. Overall, verb usage remained comparable across WR's two books, although there was a numerical reduction in unique verbs from Book 1 to Book 2. The relatively stable verb usage from Book 1 to Book 2 likely reflects the centrality of action words in conveying meaning in phrases, compared with nouns[211] and is also consistent with findings of retention of verbs over at least some types of nouns in svPPA[212].

Increased adverb usage and the suggestion of decreased unique adverb and unique verb usages may be interpreted as a compensatory strategy in the face of progressive degradation of the semantic knowledge base. For example, svPPA patients may employ adverbs to modify simpler verbs which are often repeated, in place of more unique verb usage. For example, 'he then hurried home' could be supplanted by 'he then went home quickly' manifesting in circumlocutious speech, a characteristic feature of this disorder[9, 91, 213-215]. Other examples of adverb usage are presented in Table 3-3 for illustrative purposes although these are not necessarily examples of 'pathology' since the intent behind word selection and phrasing is the sole privilege and discretion of the author.

Example text	Comment….
Over the next weeks, he thought about it *a lot*, and *finally* decided to go ahead with that.	'A lot' modifies the verb 'thought'
The ship was *entirely* of timber construction, and so, a piece of railing, a spar, some decking, the hatch covers *all* may have needed *some* small repairs from time to time.	'Entirely' modifies 'of timber construction', an adjectival clause applying to 'ship'; 'all' modifies the verb 'may'; 'some' modifies the adjective 'small' modifying 'repairs'
The only girl he had *sometimes* gone out with *previously*…	'Sometimes' modifies the verbal phrase 'gone out'
…became *very* keen on this lady, and wanted to get to know her *a lot better*. He also *certainly* got the impression that she wanted to see him *again*.	'Very' modifies the verb 'became keen'; 'a lot better' modifies the verb 'know'; 'again' modifies the verb 'see'
Just a few days after their arrival, the team from (place name) had *already* sold most of the products they had brought with them, and for *quite* good prices.'	'Just' modifies 'a few', a quantifier adjective modifying the noun 'days'; 'quite' modifies 'good' which is acting as an adjective modifying the noun 'prices'

Table 3-3. Representative examples of adverb usage in WR's writings extracted from Book 2. Excerpts from WR's Book 2 illustrating adverb usage. Adverbs are shown in *underscored italics* for emphasis. Adverbs modify verbs; additionally, words modifying adjectives are also classified as adverbs. In English, words with suffix '-ly' are almost always adverbs. Adverbs that do not end with suffix '-ly' are explained in the Comments section. Note the grammatically coherent sentence structure.

Familiarity, meaningfulness scores and age of acquisition were found to differ between Books 1 and 2 (Table 3-2), indicating an increased reliance on words that are encountered and used more commonly – i.e. more deeply integrated into the semantic language network. These findings are consistent with previous reports that such words are relatively preserved in svPPA, and that the words used become less specific[63, 80]. This analysis also uncovered alterations in WR's context dependent lexical processing and variation, as assessed by co-occurrence probability and semantic distinctiveness, across the two books. These latter findings resonate with previous studies suggesting that disruptions in svPPA extend beyond the semantic network into linguistic and lexical systems[78, 210]. These results also support the future use of age of acquisition as an indicator of semantic degradation, independent of, or in addition to, familiarity or word frequency[216] in svPPA.

While the changes across Books 1 and 2 of adverb usage, familiarity and meaningfulness scores, age of acquisition, co-occurrence probability, and semantic distinctiveness are significant, most of the absolute values of these lexical parameters continued to lie within the Control ranges. This suggests that despite clear disease progression and intra-individual alterations in written output over time, it is possible for patients with svPPA to produce language that appears to sit within 'normal' limits for some years after diagnosis. This has broad implications for studies on language output – a cross-sectional study analysing lexical and linguistic parameters at a single time point, particularly those aimed at identifying subtle prodromal features of dementia, may fail to identify significant alterations.

A number of parameters remained relatively stable in the ~3 years separating Book 1 and Book 2, perhaps against initial expectations. Firstly, concreteness was not observed to change significantly over time. Previous studies have reported impaired comprehension and concrete concept processing in svPPA[217-219], although some studies demonstrate that concrete words are better comprehended relative to abstract words, at least in written language processing tasks[220]. Given his relatively mild disease staging, and clear affinity for writing, it may be that WR compensated for his primary language

deficit by steering his written language output towards more familiar, and thereby more accessible, themes and topics, as has previously been demonstrated in the context of event-based narratives in svPPA[213, 221]. This may serve to maintain the concreteness of the text while increasing the average familiarity score and decreasing the age of acquisition, as demonstrated in our analysis.

Imageability was also not found to change significantly between WR's two literary works. This finding stands in contrast with a previous study reporting a reduction in imageability scores of spoken prompted language with disease progression in svPPA[222]. Efforts have also been made to tease out the independent effects of concreteness and imageability in svPPA, which revealed a decreased ability to associate abstract, or low imageability, words in stimulus-based association tasks[223]. However, imageability and concreteness are likely to be highly interdependent in normal language usage[224, 225], in which case the stability of imageability between the two books, given the stability of the concreteness, is not necessarily unexpected.

A number of methodological issues warrant consideration. Computer algorithms are by no means perfect and are subject to classification errors. However, they are also more consistent than humans, and an automated approach to text analysis enables the screening of large volumes of texts with any errors interspersed consistently across each analysed text. Because there was no comparable literary output from WR prior to disease onset, it was necessary to create a large independent control corpus to act as a reference point in order to contextualise the magnitude of these changes. While the selection of the authors and texts into the control corpus was somewhat arbitrary, the results were expressed as relative values to the control corpus rather than as absolutes, which should remain similar across different control corpora. This novel approach permits investigation of naturalistic language production compared to lexical outputs initiated by a fixed prompt such as a 'Cookie Theft' picture. In addition, creation of a control cohort affords an empirical 'standard' for comparison that incorporates the normal range of intra-individual variations in lexical use that naturally occurs over

time with experience, thematic changes and the evolving nature of languages[77] that could be utilised across many assessments and provides consistency across different neurodegenerative syndromes.

The intra-individual alterations in linguistic and lexical features identified through automated text analysis, if confirmed in other individuals with svPPA, may have a role as a potential marker of disease progression and treatment response. Furthermore, text analysis represents a potential method for screening and monitoring for svPPA. With an appropriate control corpus, automated statistical text analysis could be applied to any lexical output of individuals – scripts, non-fiction writings, newspapers and magazine articles, reports, emails and perhaps even free speech – to quantify alterations in vocabulary and lexical parameters to detect statistically significant deviations from the control corpus and identify these individuals for early assessment.

Chapter 4

Case series of right hemispheric

nonfluent variant of primary progressive aphasia

Introduction

Initial descriptions of nfvPPA exclusively reported marked asymmetric focal atrophy of the left hemispheric brain structures on brain imaging, particularly the peri-insular cortex[226]; this imaging feature is currently a core component of the current diagnostic criteria for nfvPPA[153].

In the svPPA, however, both left- and right-hemisphere subtypes are recognised, presenting with overlapping as well as distinct clinical features. Specifically, patients with right-svPPA, sometimes referred to as the right temporal variant of FTD, exhibit prominent and early behavioural disturbances such as dietary changes and disinhibition[66] are seen in addition to the cardinal features of anomia and impaired semantic knowledge. Prosopagnosia[227] and increased religiosity[66, 227] have also been reported in this group. Despite these clinical and radiological distinctions, both left- and right-svPPA syndromes demonstrate the same TDP-43 Type C pathology[9].

The presence of left- and right- anterior temporal lobe atrophy presentations with distinct clinical features in svPPA raises the question as to whether a similar process can occur in nfvPPA – does a specific clinical phenotype exist with individuals presenting with predominantly *right-,* rather than left-sided peri-insular involvement? Although right predominant peri-insular atrophy has previously been reported in nfvPPA, the clinical profile has been described in only a few single case reports[88, 228, 229]; whether these clinical features overlap with, or are distinct from, the typical nfvPPA presentation with left peri-insular atrophy remains unknown. Of particular interest is whether emotional processing and facial recognition, abilities commonly associated with the right peri-insular region[230], could serve as cognitive biomarkers of right peri-insular disease involvement.

The research presented in this chapter aimed to identify the presence of right peri-insular atrophy in patients diagnosed with nfvPPA, characterise the clinical and neuroimaging features associated with right peri-insular atrophy, and examine the hypothesis that such patients would exhibit clinical

similarities as well as differences that would distinguish them from patients with nfvPPA with left dominant peri-insular atrophy.

Methodological Considerations

Participants

I reviewed clinical records and images of 67 consecutive research participants at the FRONTIER frontotemporal dementia research clinic at the Brain and Mind Centre, the University of Sydney, between January 2008 and September 2019 fulfilling the relevant clinical diagnostic criteria for nfvPPA[153]. Participants with incomplete data, concomitant motor neuron disease, a past history of stroke, epilepsy, alcoholism, or significant traumatic brain injury were excluded, as were patients with unavailable brain MRI, leaving 55 participants eligible for screening of hemispheric asymmetries.

Two independent raters, blind to the clinical information identified right-predominant asymmetric cases after visual inspection of coronal sections of T_1-weighted brain MRI. This procedure identified 7 participants with right predominant peri-insular atrophy. To validate this finding, those MRI scans were anonymized and age- and sex-matched with 7 healthy controls and 7 nfvPPA patients with left dominant peri-insular atrophy. All coronal images (i.e., cases and controls, total 42 images) were randomly ordered and inspected at the temporal-frontal junction and categorised by three independent raters as symmetric, right or left dominant peri-insular atrophy. Complete inter-rater concordance of right dominant peri-insular atrophy was achieved in 4 of the 7 cases; these 4 participants were labelled right-nfvPPA (Fig 4-1) for the purpose of this study.

For comparison of clinical findings, these four right-nfvPPA participants were re-matched for disease duration and ACE scores as well as age and sex with 8 left-nfvPPA participants, and 12 age- and sex-matched healthy control participants.

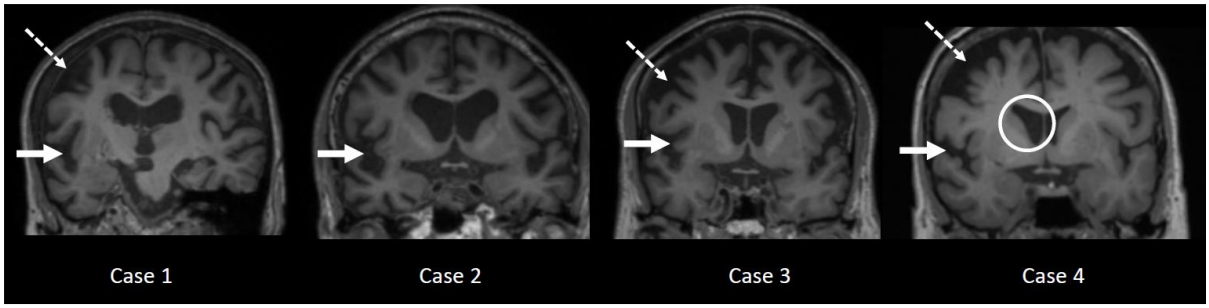

Figure 4-1. Coronal MRI images of the four right-nfvPPA participants. The sections are located at the temporal-frontal junction and demonstrates prominent atrophy in the right hemisphere (arrow).

Clinical and Cognitive assessment

Participants underwent comprehensive clinical assessment and relevant clinical features (e.g., dysarthria, apraxia, tremor, parkinsonism, behavioural changes, visuospatial disturbance, hallucinations) were scored as either present or absent (Table 4-1). Two independent raters performed assessment of expressive language utilising simplified PAL[171] rubric as outlined in Chapter 2, where features such as distortion and syntax were scored as either 'present' or 'absent' rather than utilising 3 categories[171]. Neuropsychology assessment was performed as outlined in Chapter 2.

Imaging acquisition and pre-processing

Whole brain T_1-weighted MRI images were acquired and then processed utilising FreeSurfer for all participants according to the protocols outlined in Chapter 2. No participant was excluded due to excessive surface or subcortical segmentation errors following visual inspection. Cortical thickness was smoothed with a 20 mm full-width at half-height Gaussian kernel. This level of blurring kernel was selected to reduce the impact of imperfect alignment between cortices and thereby improving the signal-to-noise ratio[231].

Imaging data analyses

An exploratory analysis was first conducted to explore differences in cortical atrophy between diagnostic groups by using a one-factor general linear model (GLM) design implemented with mri_glm

program from FreeSurfer and modelling cortical thickness as the response variable and diagnostic groups as a three-level explanatory factor (right-nfvPPA, left-nfvPPA, and healthy controls). Four hypotheses were tested by contrasting cortical thickness of both nfvPPA (right and left-nfvPPA) altogether against healthy controls (A), each nfvPPA group separately against healthy controls (B, C) and both nfvPPA groups against to each other (D) (Fig 4-2). For each contrast, significance maps were generated for visualization and mapped onto FreeSurfer standard inflated cortical model (fsaverage) assuming a non-corrected level of statistical significance of $p < 0.01$.

To further explore regional and hemispheric differences between groups, a region of interest (ROI) confirmatory analysis was conducted by using the average cortical thickness of parcellations selected from the **Desikan-Killiany Atlas**[232]. The ROI selection was based on the evidence of atrophy in both right and left nfvPPA, and key epicentres of atrophy reported previously[233].

A repeated-measures ANOVA was conducted to explore differences in cortical thickness within-subjects' hemispheres and between diagnostic groups. The average of cortical thickness for each ROI was used as the dependent variable, while the hemispheric laterality (left, right) and group (right-nfvPPA, left-nfvPPA, healthy controls), as the predictor variables. Post-hoc analyses were conducted in case a significant omnibus effect was detected in the model followed by pair-wise contrasts corrected using the Tukey method. Statistical significance was set at $p < 0.05$, unless otherwise stated.

Statistical analyses were performed using JASP (University of Amsterdam, Amsterdam, Netherlands) and R (R Foundation for Statistical Computing, Vienna, Austria). Fisher's exact tests were conducted to estimate differences between categorical variables between groups.

Results

Of the 55 nfvPPA participants, 4 (7.3%) were unanimously identified as having right predominant peri-insular atrophy (labelled as right-nfvPPA). Their clinical profiles are displayed in Table 4-1. All 4 participants presented with articulation problems (i.e., dysarthria), agrammatism, and behavioural features but did not uniformly demonstrate apraxia. The frequency of clinical features such as visuospatial dysfunction, hallucinations, apraxia, tremor, or parkinsonism were similar in both groups.

Cognitive profile

Baseline cognitive profiles for the right- and left-nfvPPA groups are presented in Table 4-2. No significant differences emerged between the two groups on any cognitive tests.

Assessment of spontaneous speech video samples

Ratings were consistent between the two raters (Cohen's $\kappa = 0.864$, $z = 3.30$, $p = <0.01$). There were no differences between right-nfvPPA participants and left-nfvPPA individuals in all assessed speech components (Table 4-3).

Imaging Analysis

The GLM analyses identified a distinctive distribution of atrophy across groups. The contrast of both nfvPPA groups combined against healthy controls showed bi-hemispheric regions of atrophy (Figure 4-2A) distributed in the superior and inferior frontal gyri, insula, supramarginal, posterior-parietal inferior and part of entorhinal cortices. This pattern largely overlapped with the distribution found in each nfvPPA group (Fig 4-2B and Fig 4-2C). As expected, the right-nfvPPA group displayed more predominant atrophy in the right peri-insular region than the left-nfvPPA group. The right-nfvPPA group showed additional atrophy located in the right anterior, medial and inferior temporal lobe which was confirmed in the contrast analysis between the two nfvPPA groups (Figure 4-2D). Interestingly, cingulate gyrus involvement was only detected in the left-nfvPPA group (Fig 4-2C).

	P01	P02	P03	P04
Age at assessment (y)	77.9	75.7	70.3	73.8
Sex	Male	Female	Female	Male
Disease Duration (y; estimated)	3	4	7	5
Handedness	Right	Left	Right	Right
Presenting symptoms				
	Distorted speech Word-finding difficulties Dysarthria	Distorted speech Word-finding difficulties Dysarthria	Articulation Slow speech	Stuttering Dysarthria
Clinical examination				
Dysphagia	-	-	-	-
Behavioural changes	+	+	+	+
Appetite change	-	-	-	-
Parkinsonism	+	+	-	-
Orobuccal apraxia	+	+	-	+
Limb apraxia	-	+	-	-
Articulatory errors	+	+	+	+
Reading difficulties	+	-	-	-
Spelling errors	+	+	-	-
Agrammatism	+	+	+	+

Table 4-1. Clinical profiles of the four right-nfvPPA patients. Note: '+' = feature is present; '-' = feature is absent. Agrammatism was defined as errors in syntax, word order or sentence structure during free speech.

	P01	P02	P03	P04	Left-nfvPPA	Right-nfvPPA	*p*-value	Control
ACE-III								
Total	66	74	87	95	81.1 (9.8)	80 (13.3)	0.853	92.8 (3.5)
Attention	14	18	16	16	16.2 (1.1)	15.5 (1.7)	0.445	17 (1.6)
Memory	15	18	24	25	23.4 (2.5)	20.5 (4.8)	0.193	24 (1.8)
Fluency	5	1	8	14	5.6 (3.9)	7 (5.5)	0.625	11.9 (1.3)
Language	20	21	23	23	20.9 (2.5)	22.3 (2.2)	0.383	24.8 (1.6)
Visuospatial	12	16	16	15	15.3 (1)	14.8 (1.9)	0.557	15.1 (1.3)
Rey Complex Figure								
Copy	25.5	33	32	27.5	30 (3.4)	29.5 (3.6)	0.818	30.7 (5.2)
3-min recall	5	23.5	19	21.5	11.9 (3.2)	17.25 (8.4)	0.131	14.5 (4.2)
Trail-making Test								
Part A	62	105	43	36	58.1 (20.1)	61.5 (31)	0.822	34.7 (5.4)
Part B*	Discontinued	Discontinued	86	89	182.8 (95.6)	87.5 (2.12)	0.215	77.4 (19.8)
SYDBAT								
Naming	18	9	26	29	19.4 (6.7)	20.5 (9)	0.811	26.2 (2.1)
Repetition	13	0	8	27	20.8 (10.8)	12 (11.3)	0.223	29.6 (0.7)
Comprehension	28	25	30	28	27.8 (1.7)	27.8 (2.1)	1.000	28.7 (1.5
Semantic Association	23	27	30	26	25.3 (5.1)	26.5 (2.9)	0.663	28.4 (1.1)
TROG								
% Correct	69	62	71	20^	63.9 (15.6)	67.3 (4.7)	0.723	77.8 (1)
Sentence Repetition*	Not offered	Discontinued	11	12	7.2 (3.7)	12 (0.7)	0.164	11.8 (1.2)
Emotion recognition								
FPT	35	39	40	38	37.9 (2.5)	38 (2.2)	0.927	39 (1.2)
FIDT*	27	Discontinued	36	29	32.1 (4.7)	31 (4.7)	0.664	35.3 (4.7)
FADT*	26	Discontinued	36	33	33.3 (4.1)	32 (5.1)	0.607	35.5 (1.6)
FAST	24	33	36	36	34 (5.9)	32 (5.7)	0.643	37.4 (2.8)

Table 4-2. Individual neuropsychological assessment scores for the four right PNFA patients and group averages. *When a specific test result was not available this was not included in the calculation of the group averages.

	Left-nfvPPA (N = 8)	Right-nfvPPA (N = 4)	*P values*
N impaired (%)			
Distortion	5 (63%)	4 (100%)	0.143
Stress	5 (63%)	3 (75%)	0.414
Syntax^	1 (13%)	1 (33%)	0.458
Grammar^	2 (25%)	2 (50%)	0.177
Naming^	6 (75%)	3 (100%)	0.853
Word Repetition	3 (38%)	3 (75%)	0.249
Sentence Repetition	5 (63%)	2 (50%)	0.857

Table 4-3. Speech rating comparisons between left and right nfvPPA groups. ^Syntax, grammar and naming of one right-nfvPPA participant was unable to be assessed due to severe speech distortion.

REGIONS OF INTEREST	**OVERALL EFFECT OF DIAGNOSTIC GROUPS ON CORTICAL THICKNESS**		**BRAIN HEMISPHERE DIFFERENCES WITHIN SUBJECTS**		**INTERACTION EFFECT BETWEEN DIAGNOSTIC GROUPS AND BRAIN HEMISPHERE**	
	$F_{(2,17)}$	*p*	$F_{(1,17)}$	*p*	$F_{(2,17)}$	*p*
PARS OPERCULARIS	2.73	*.0938*	1.77	*.2013*	4.14	*.0342*
PSTG	0.61	*.5568*	4.92	*.0405*	1.01	*.3867*
INSULA	3.06	*.0731*	0.02	*.8858*	3.00	*.0767*
ANTERIOR CINGULATE	2.78	*.0902*	18.22	*.0005*	1.10	*.3562*
SUPRAMARGINAL	5.48	*.0145*	0.11	*.7497*	0.37	*.6934*

Table 4-4. Repeated Measures ANOVA of averaged cortical thickness in the regions of interest.

Region of interest analyses

Based on key epicentres of atrophy identified in nfvPPA[233] and areas of maximal cortical thinning found in the GLM analysis (Figure 4-3), the average cortical thickness of the pars opercularis, insula, rostral anterior cingulate, banks of the superior temporal sulcus, and supramarginal gyrus bilaterally were selected as ROIs (Table 4-4). Separate repeated-measures ANOVAs were conducted for each ROI, using hemispheric laterality as a within-subject factor and diagnostic group as a between-subject factor. Left-nfvPPA and right-nfvPPA shared the more thinning in the left anterior cingulate than in the right anterior cingulate. A distinctive ROI affected in the left-nfvPPA group was the thinning in the left pSTG, whereas for the right-nfvPPA, the main group effect was driven by atrophy in both supramarginal ROIs (overall difference from healthy control ($p < .0133$). The right-nfvPPA and left-nfvPPA groups tended to show more thinning in the ipsilateral rather than contralateral pars opercularis, but this difference did not survive statistical correction. The only ROI that showed no differences across groups was the insula.

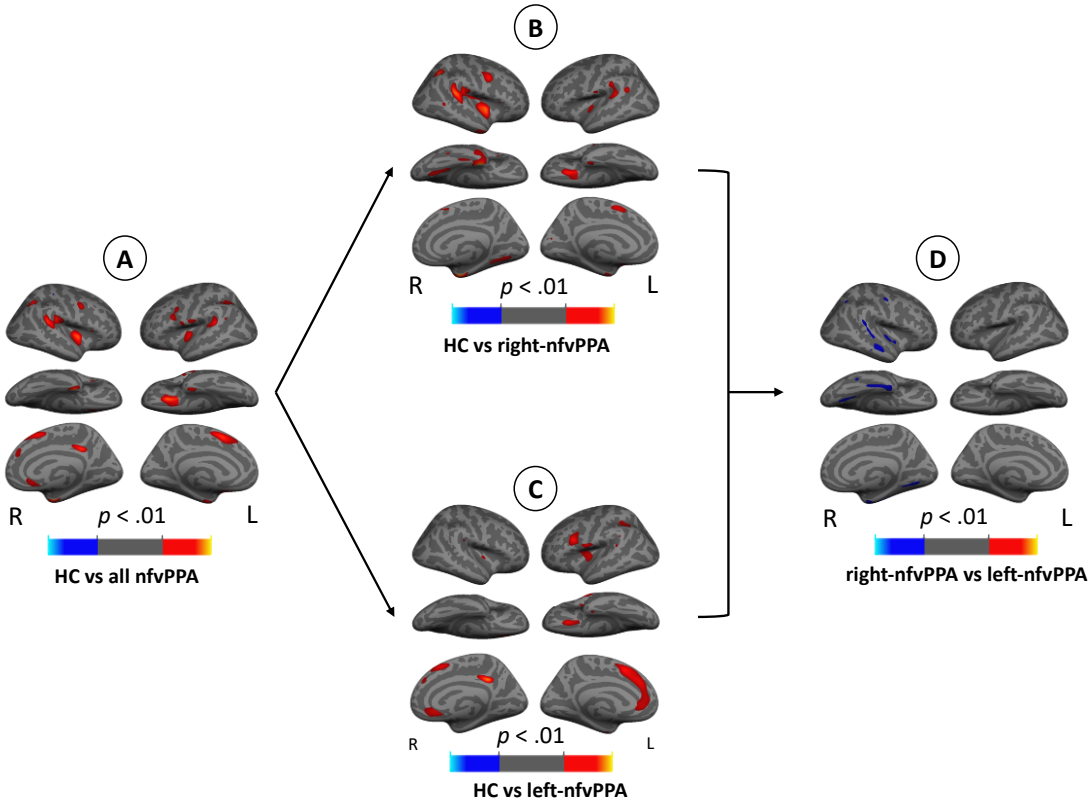

Figure 4-2. Distribution of cortical atrophy from GLM analysis. A) A contrast of all nfvPPA participants and healthy controls demonstrated atrophy in the superior and inferior frontal gyri, insula, supramarginal, posterior-parietal inferior temporal lobe and part of the entorhinal cortices. B) A contrast of right-nfvPPA and healthy controls confirmed right peri-insular atrophy. C) A contrast of left-nfvPPA and healthy controls confirmed atrophy of left peri-insular region as well as anterior cingulate gyrus in the left hemisphere. D) A contrast of right-nfvPPA and left-nfvPPA demonstrated right temporal atrophy in right-nfvPPA only. HC = healthy controls; nfvPPA = non fluent variant of primary progressive aphasia; L = left; R = right.

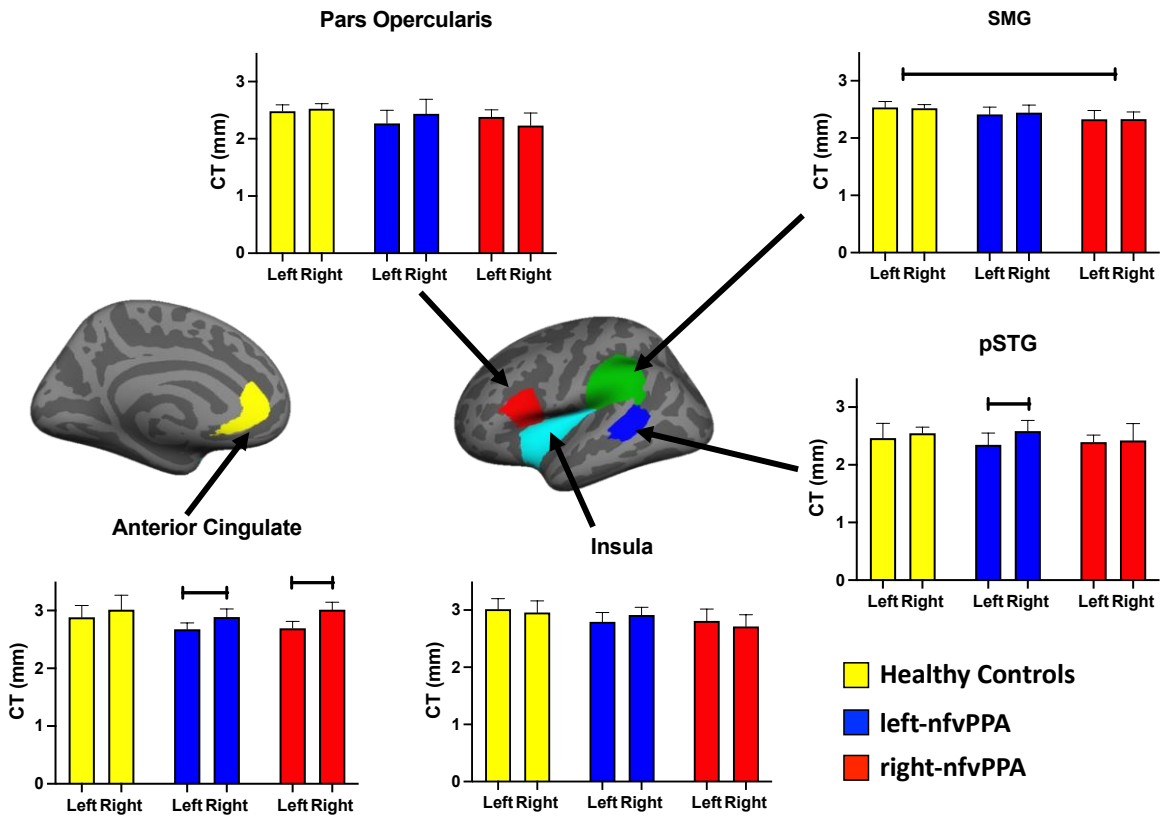

Figure 4-3. Region of interest analysis. There is significant cortical thinning at the left anterior cingulate and right supramarginal gyrus and posterior superior temporal sulcus. * = $p < 0.05$; ** = $p < 0.01$. CT = cortical thickness; pSTG = posterior superior temporal sulcus; SMG = supramarginal gyrus.

Discussion

In a large nfvPPA cohort from a single centre, we identified 4 individuals who met the clinical requirements of current diagnostic criteria for nfvPPA but demonstrated right dominant peri-insular atrophy on MRI. The clinical, cognitive and linguistic profiles of these right-nfvPPA cases, including emotional processing, were broadly similar to those of left-nfvPPA.

Despite the lack of distinct differences, there are two interesting findings worth noting for further study. At the time of assessment, although not statistically significant, the frequency of grammatical errors and impairment in fluency was more prevalent in the right-nfvPPA group. Previous work has suggested that grammatical function is localised to the left hemisphere, particularly the left posterior inferior frontal cortex[234] while the motor speech network, as mentioned, is distributed relatively symmetrically[235]. It is possible these two patients demonstrated more prominent bilateral atrophy (though more predominantly right sided) which resulted in syntactic deficits. Further analysis of the connection between those regions, including subcortical-cortical loops using functional neuroimaging techniques, could also provide further clarification on this point.

Another interesting finding was the prominent atrophy of the left anterior cingulate in left-nfvPPA and in right-nfvPPA. The anterior cingulate cortex is involved in volitional control of emotional states and innate motor patterns rather than in the production of linguistic vocalisation[236], and therefore, atrophy in that area may contribute to overall reduction in vocal output in nfvPPA but not necessarily in right-nfvPPA. This finding needs to be explored in larger cohorts.

Although this study is the first to investigate clinical and neuroimaging profiles of nfvPPA patients presenting with predominant right-sided atrophy, our findings need to be examined with caution. Indeed, only four patients with right dominant peri-insular atrophy were identified who were suitable for detailed analysis. I have tried to counter this limitation of the sample size by careful case selection

and comprehensive clinical and neuroimaging examination, which was performed consistently across all participants included in this study.

In addition, I relied on participants' self-report of handedness which is – at best – an indirect proxy of hemispheric dominance. Consequently, the proportion of right-nfvPPA in our cohort (<10%) could simply reflect the population prevalence of right hemisphere dominance[237]. In that case, these individuals would be expected to possess a clinical profile analogous to left-nfvPPA. However, if true, this would not explain the subtle differences in the clinical features and pattern of cortical atrophy between the two nfvPPA groups. Future study may benefit by including specialised procedures such as the Wada test[238] and/or transcranial doppler ultrasound[239] to establish hemispheric dominance.

Another noteworthy aspect is the variation in clinical phenotype arising from pathological heterogeneity underlying nfvPPA, where both tau and TDP-43 type A pathology have been reported. Recent literature suggests that different pathological substrates may be responsible for slightly different clinical manifestations[92] – for instance, tauopathy is more likely to be associated with motor speech deficits[93]. Even in our small cohort, there is potential evidence of substrate heterogeneity – P02 particularly struggled with fluency, naming, repetition, face matching and Trails assessment despite a relatively short disease duration and moderate ACE score. While it remains to be seen if any other clinical features can be associated with specific proteinopathies, the outcome of *postmortem* analyses are not currently available for the four right-nfvPPA participants.

My study identified and examined the nfvPPA cases with predominant right hemisphere atrophy based on imaging with a closely matched group of typical nfvPPA. We were unable to identify a specific collection of clinical features that distinguished right-nfvPPA from nfvPPA; the immediate next step will be examining changes over time to determine patterns of change and whether the disease evolution differs between these two presentations. Another consideration would be to explore other

clinical features such as production and perception of prosody and complex non-verbal auditory perception.

Chapter 5

Assessing the utility of imaging based biomarkers

to differentiate pathologically classified

frontotemporal lobar degeneration syndromes

Introduction

As discussed in Chapter 1, FTLD is a neurodegenerative entity presenting as several distinct but overlapping clinical syndromes including bvFTD, PPA, PSP, and CBS[1-3]; distinguishing between each of these syndromic entities, which may evolve over time, is challenging. Clinicopathological correlation is poor[240] – for example, tau deposition has been reported in individuals diagnosed clinically with PSP, CBS, bvFTD as well as nfvPPA[241]. The inverse scenario is also true – for example, bvFTD has been associated with pathological deposits of tau, TDP-43 and fused-in-sarcoma protein. The underlying pathological substrate can be predicted with only about 60% accuracy even with careful clinical phenotyping and multi-factor analysis[8]. Sensitive and specific biomarkers of pathology are desperately needed to improve diagnosis and selection of patients for clinical trials.

One potential biomarker of tau pathology, and more specifically the progressive supranuclear palsy – tau subtype (PSP-tau), is morphometric assessment of the brainstem, often examined using a ratio of midbrain area to other brain structures on MRI. Two measures have been studied; the midbrain to pons ratio (MP ratio) and the magnetic resonance parkinsonism index (MRPI). Both measures have been shown to differentiate clinically defined PSP from Parkinson's disease and multisystem atrophy-parkinsonism (MSA-P)[117, 242, 243], a finding that was verified in a pathological cohort[118]. Within the FTLD spectrum, the MP ratio has been shown to distinguish clinically defined PSP from nfvPPA [119].

In this chapter, I examined three specific hypotheses – firstly, that the MP ratio and/or MRPI differ in pathologically confirmed PSP-tau from controls and clinically defined AD. Secondly, that these measures distinguish PSP-tau from other FTLD pathologies such as CBD; and, thirdly, whether the MP ratio, as a simpler measurement, is more reliable than the MRPI.

Methodological Considerations

Participants

Participants in a brain bank program at ForeFront Aging and Neurodegeneration between 2003 and 2020 with FTLD – i.e., pathological features of PSP-tau, CBD-tau and TDP-43 – were identified. Those without MRI and clinical assessment were excluded from the study. AD and Control participants were recruited through the FRONTIER frontotemporal dementia research clinic at Neuroscience Research Australia (2008-2016) and later the Brain and Mind Centre, the University of Sydney (2017-2020). AD participants were matched to FTLD participants for age, disease duration, years of education and ACE scores; the Control participants were matched to the FTLD group for age and years of education. Pathological confirmation of AD pathology and normality was not a requirement for the AD and control groups respectively.

Pathological specimen preparation and examination was provided by the Sydney Brain Bank, following the protocol outlined in Chapter 2.

Clinical assessment, imaging acquisition, and analysis were performed as outlined in Chapter 2. For the assessment of intra-observer reliability, 2 random images were selected from each diagnostic category and re-traced in a blind fashion.

Statistical Analysis

The Shapiro-Wilk tests were used to confirm that all the variables in each group were normally distributed. Group comparisons were performed using Brown-Forsyth ANOVA. Subgroup pairwise comparisons were performed using unpaired T-tests with Welch's correction. Bonferroni correction was applied to all results, with corrected p threshold set as $p = 0.05/10 = 0.005$. Correlation was calculated using Spearman non-parametric test. All statistical analyses were performed using Prism (version 9, GraphPad Software, San Diego, CA, USA).

Results

In total, 65 participants were included in the study. There were 42 participants with pathologically confirmed FTLD; 13 had PSP, 6 had CBD and 23 had TDP-43 pathology. No individuals with pathologically confirmed FUS met the study inclusion criteria. In addition, 11 AD and 12 matched control participants were included. Their demographic and clinical profiles are displayed in Table 5-2.

Illustrating the poor clinicopathological correlation commonly reported in this population, only 6/13 PSP-tau participants had a clinical diagnosis of PSP. Remaining participants with PSP-tau had clinical diagnoses of CBS (N = 5), nfvPPA (N = 1) and bvFTD (N = 1). For CBD-tau patients, only one participant had a clinical diagnosis of CBS; other clinical diagnoses included nfvPPA (N = 2) and bvFTD (N = 3). Of the 23 participants with TDP-43, the majority were diagnosed with bvFTD (N = 5), svPPA (N = 2), FTD-MND (N = 10) and 'mixed FTD' (N = 1); the remainder were diagnosed clinically with nfvPPA (N = 1) and CBS (N = 4).

Out of the clinical features examined, only 3 features – parkinsonism and gait disorder for PSP-tau and sleep disturbance for TDP-43 – were present in more than half of the PSP-tau and TDP-43 cohorts respectively, but these features were also present in a significant proportion of other syndromes.

The areas of the midbrain and pons as well as the length of the MCP and the SCP along with the pairwise comparisons of MP ratio and MRPI are displayed in Table 5-2. These results suggest that PSP-tau can be successfully differentiated from healthy controls ($p < 0.0001$ for both) and AD ($p < 0.0001$ for MP ratio and $p = 0.0004$ for MRPI). Both the MP and MRPI can also distinguish PSP-tau from CBD-tau ($p = 0.0017$ and $p = 0.0004$ respectively) and TDP-43 ($p < 0.0001$ for both). Both the MP ratio and MRPI distinguished CBD-tau ($p = < 0.0001$ and $p = 0.0003$ respectively) and TDP-43 from controls ($p < 0.0001$ for both).

The optimal receiver operating characteristic (ROC) curve cut-off for the significant pairwise group comparisons based on the highest likelihood ratio are presented in Tables 5-3 and 5-4 respectively. The actual curves are presented in Fig 5-1 and 5-2 for MP and MRPI respectively. Based on these results, an MP ratio < 0.244 would predict PSP-tau over CBD-tau with a sensitivity of 92% and specificity of 85%, and a likelihood ratio of 6.5. Alternatively, an MRPI >10.8 would predict PSP-tau over CBD-tau with a sensitivity of ~85% and specificity of 100%. Post-hoc analysis of the MP ratio revealed the following pattern: PSP-tau < CBD-tau < control = AD = TDP (where "<" indicates a significant difference and "=" indicates no significant difference). Post-hoc analysis of the MRPI revealed the following pattern: Control = AD = TDP < CBD < PSP.

Scenarios in which the MP ratio and MRPI may have clinical utility are considered in Table 5-5 and significant ROC curves are presented in Fig 5-3. The MP ratio and MRPI could be used to distinguish PSP from a cohort of mixed CBD and TDP-43, whereas CBD could not be reliably distinguished from a cohort of mixed PSP and TDP-43.

Finally, intra-rater measurements were highly correlated for measurements of the midbrain, pons and SCP, but not the MCP (Table 5-1). The intra-rater correlation was high for the MP ratio, but not the MRPI, perhaps because the MCP is used in the calculation of the MRPI, but not the MP ratio.

	Midbrain	Pons	MCP	SCP	MP Ratio	MRPI
R value	0.8424	0.9636	0.3939	0.9758	0.9152	0.5897

Table 5-1. R values demonstrating intra-rater correlation of the blinded repeat measures of midbrain, pons, MCP and SCP in 10 MRIs, 2 randomly selected from each of the 5 groups. There is a high correlation between the repeat measures in the midbrain, the pons and the SCP, but not in the MCP and MRPI.

		PSP		CBD		Control		AD*		TDP-43*		
Sex	F:M	6:7		2:4		8:4		6:5		12:11		
In Vivo Diagnosis (%correct)		6/13		1/6		N/A		11/11		18/23		
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age at Diagnosis (Y)		66.3	5.3	66.1	14.1	66.2	2.0	60.9	2.4	64.1	8.8	p = 0.078
Est Dis Duration (Y)		4.3	3.2	2.8	1.2	N/A		4.3	2.6	3.3	2.5	p = 0.320
Age at Death (Y)		71.2	4.4	71.5	13.7	N/A		N/A		66.8	8.8	p = 0.227
Interval b/w MRI and Death (Y)*		4.9	2.4	5.6	0.8	N/A		N/A		2.6	1.9	p = 0.002
Education (Y)		12.7	4.1	12.4	2.5	13.6	1.9	10.7	1.8	12.2	3.2	p = 0.106
ACE Score at Diagnosis		77.5	10.6	83.3	5.1	96.8	2.1	76.1	10.6	67.9	13.5	p = 0.020#
Clinical Features												
Behavioural features												
• Disinhibition		1/13		1/6				1/11		10/21		
• Apathy		5/13		3/6				1/11		8/13		
• Perseveration		0/13		0/6				0/11		3/14		
• Diet changes		1/13		2/6				0/11		6/13		
Hallucinations		0/13		0/6				0/11		3/21		
Memory Impairment		2/13		1/6				4/6		7/20		
Parkinsonism		9/13		1/6				0/6		7/21		
Apraxia (limb and orobuccal)		8/13		2/6				2/6		10/21		
Language Impairment^		9/13		4/6				1/6		17/21		
Visuospatial Impairment		2/13		0/6				2/6		5/20		
Gait Disorder		8/13		1/6				0/6		9/21		
Eye Movements		4/13		1/6				0/6		5/21		
Sleep Disturbance		5/13		1/6				1/11		14/17		

Table 5-2. Demographic and clinical findings in assessed individuals. *The denominator for the AD and the TDP-43 cohort is variable due to incomplete data. #This p value was calculated excluding the ACE scores from the control group. ^Language impairment refers to any language disturbance – e.g., dysarthria, anomia and agrammatism.

	PSP	CBD	Control	AD	TDP	Groupwise p-test
Sample N	13	6	12	11	23	
Midbrain area (cm^2)	1.11+/- 0.28	1.56 +/- 0.19	1.88 +/- 0.12	1.65 +/- 0.21	1.58 +/- 0.27	<0.0001
Pons area (cm^2)	5.60 +/- 0.54	6.18 +/- 0.77	5.79 +/- 0.53	5.77 +/- 0.41	5.80 +/- 0.70	0.5293
MP Ratio	0.20 +/- 0.04	0.25 +/- 0.02	0.33 +/- 0.03	0.29 +/- 0.05	0.27 +/- 0.04	<0.0001
MCP (mm)	9.49 +/- 1.37	10.68 +/- 2.22	9.95 +/- 1.05	10.04 +/- 0.75	10.87 +/- 1.2	0.0712
SCP (mm)	3.42 +/- 0.66	4.59 +/- 0.40	5.33 +/- 0.30	4.41 +/- 0.75	5.40 +/- 0.43	<0.0001
MRPI	14.97 +/- 4.28	9.20 +/- 1.38	5.74 +/- 0.64	8.54 +/- 3.15	7.52 +/- 1.30	<0.0001

MP Ratio pairwise comparison p-test

PSP					
CBD	0.0017				
Control	<0.0001	<0.0001			
AD	<0.0001	0.0411	0.0244		
TDP	<0.0001	0.0862	<0.0001	0.35252	

MRPI pairwise comparison p-test

PSP					
CBD	0.0004				
Control	<0.0001	0.0003			
AD	0.0004	0.5532	0.0149		
TDP	<0.0001	0.0177	<0.0001	0.3198	

Table 5-3. Areas of midbrain and pons and lengths of the MCP and the SCP. These values were used to calculate MP ratio and MRPI of each individual case; these values were then pooled to calculate the overall mean and SD of MP ratio and MRPI. The post-hoc pairwise t-tests were performed using unpaired two way T-test with Welch's correction with significance threshold of p = 0.005 following Bonferroni correction.

		p value	Threshold	Sensitivity	95% Confidence		Specificity	95% Confidence		Likelihood ratio
PSP	CBD	0.0017	<0.244	0.923	0.667	0.996	0.857	0.487	0.993	6.5
	Control	<0.0001	<0.263	1	0.772	1	1	0.758	1	
	AD	<0.0001	<0.252	1	0.772	1	0.909	0.623	0.995	11
	TDP	<0.0001	<0.229	0.692	0.424	0.873	0.96	0.805	0.998	17.3
CBD	Control	<0.0001	<0.286	0.857	0.487	0.993	0.917	0.646	0.996	10.23
Control	TDP	<0.0001	>0.328	0.583	0.32	0.807	0.96	0.805	0.998	14.6

Table 5-4. Receiver operating characteristic (ROC) curve with threshold values and sensitivity and specificity with 95% confidence interval and likelihood ratio for pairwise comparison of MP ratio. MP ratio <0.244 would suggest underlying PSP pathology over CBD pathology with sensitivity of 92% and specificity of 85%. The actual ROC curves can be found in Fig 5-1.

		p value	Threshold	Sensitivity	95% Confidence		Specificity	95% Confidence		Likelihood ratio
PSP	CBD	0.0004	>10.8	0.846	0.578	0.973	1	0.646	1	
	Control	<0.0001	>8.39	1	0.772	1	1	0.758	1	
	AD	0.0004	>13.28	0.615	0.355	0.823	0.909	0.623	0.995	6.769
	TDP	<0.0001	>10.55	0.923	0.667	0.996	100	0.867	1	
CBD	Control	0.0003	>7.07	1	0.646	1	1	0.758	1	
Control	TDP	<0.0001	<6.09	0.833	0.552	0.97	0.92	0.75	0.986	10.42

Table 5-5. Receiver operating characteristic (ROC) curve with threshold, sensitivity and specificity with 95% confidence interval and likelihood ratio for pairwise comparison of MRPI. MRPI >10.8 would suggest underlying PSP pathology over CBD pathology with sensitivity of ~85% and specificity of 100%. The actual ROC curves can be found in Fig 5-2.

		p- value	Threshold	Sensitivity	95% Confidence		Specificity	95% Confidence		Likelihood ratio
MP Ratio										
PSP	CBD + TDP	<0.0001	<0.2440	0.8125	0.6469	0.9111	0.9231	0.6669	0.9961	10.56
CBD	PSP + TDP	0.8756	>0.2444	0.4737	0.3248	0.6274	0.8571	0.4869	0.9927	3.316
TDP	PSP + CBD	<0.0001	>0.229	0.5	0.2993	0.7007	0.96	0.8046	0.9979	12.5
MRPI										
PSP	CBD + TDP	<0.0001	>10.65	0.9688	0.8426	0.9984	0.9231	0.6669	0.9961	12.59
CBD	PSP + TDP	0.6611	<7.808	0.3947	0.256	0.5528	0.8571	0.4869	0.9927	2.763
TDP	PSP + CBD	<0.0001	<10.26	0.8	0.5284	0.9193	0.96	0.8046	0.9979	20

Table 5-6. Comparison of individual pathological entities in FTLD spectrum vs grouped cohort and receiver operating characteristic (ROC) curve with threshold, sensitivity and specificity with 95% confidence intervals and likelihood ratio. The ROC curves for PSP vs CBD + TDP and TDP vs PSP + CBD are presented in Fig 5-3.

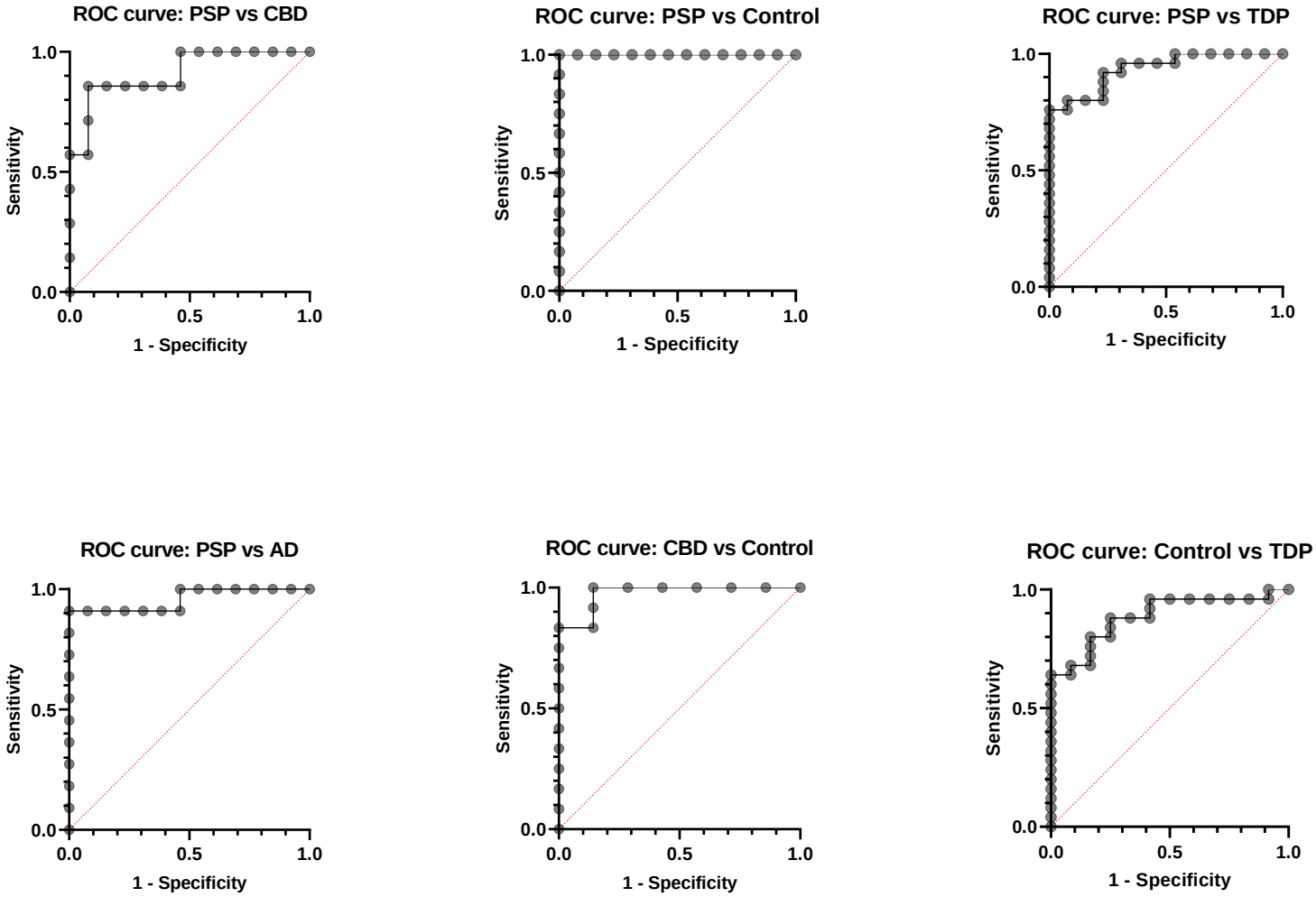

Figure 5-1. Receiver operating characteristic curves of significant MP comparisons at an individual diagnosis level.

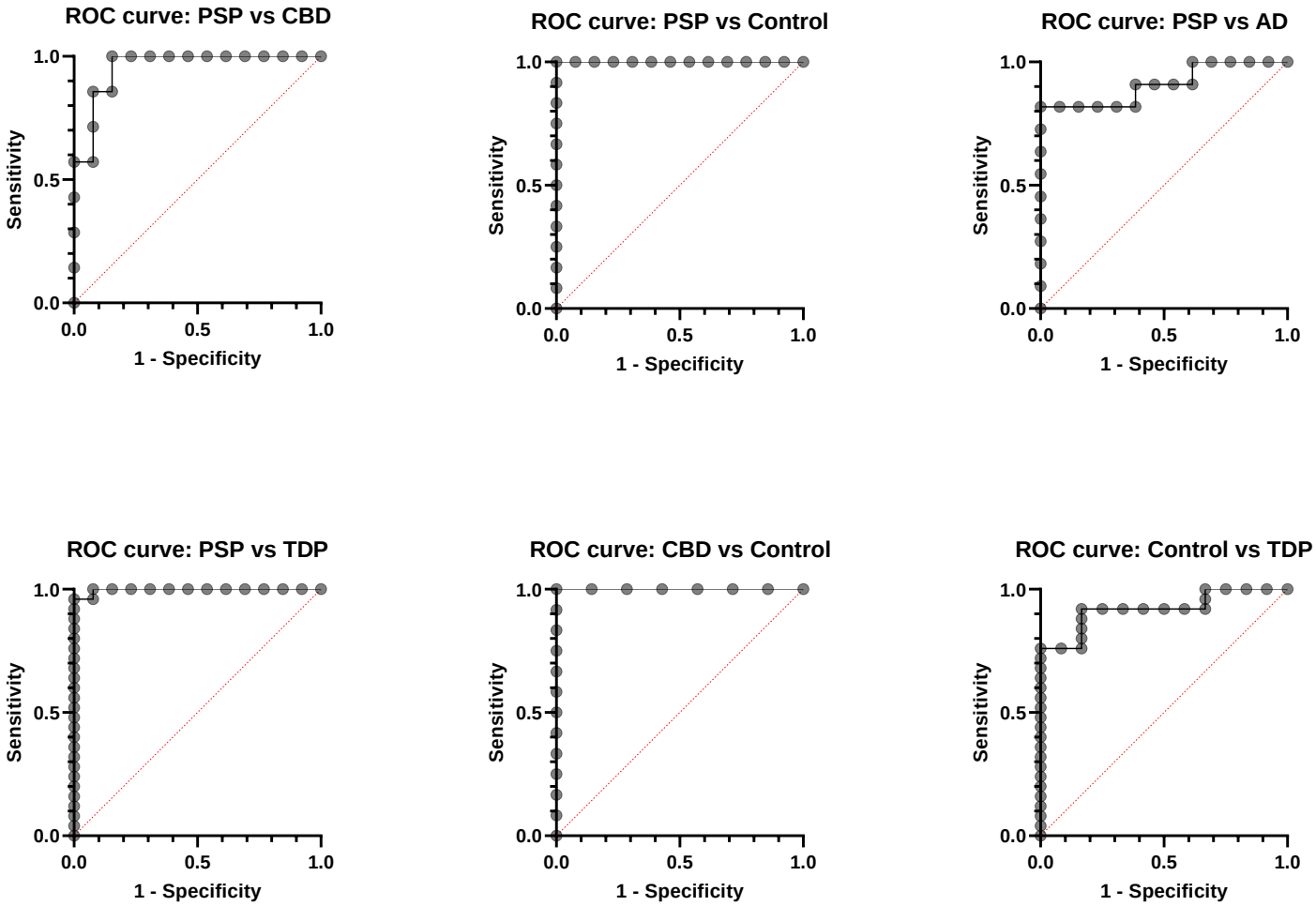

Figure 5-2. Receiver operating characteristic curves of significant MRPI comparisons at an individual diagnosis level.

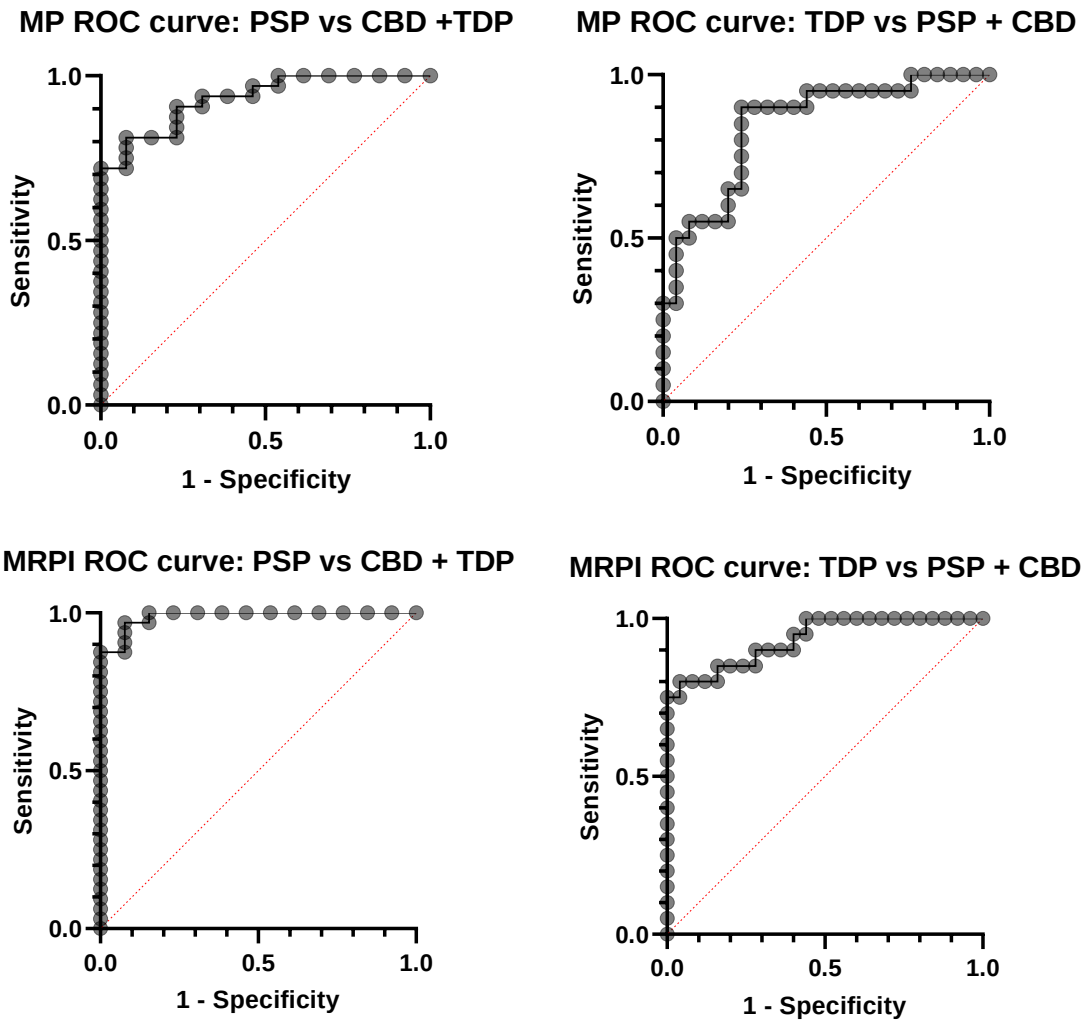

Figure 5-3. Receiver operating characteristic curves of significant MP and MRPI comparisons at individual diagnosis vs group.

Discussion

The results of the study highlight the difficulties encountered in the diagnosis of FTLD entities when relying on clinical features alone. Clinicopathological correlation was generally poor for PSP (<50%) in the present study, illustrating the need for reliable biomarkers. Depending on the chosen threshold, both the MP ratio and MRPI at presentation distinguished those with PSP-tau from controls and clinically defined AD, as well as from those with CBD-tau and TDP-43 with similar sensitivity and specificity.

Quantification of midbrain atrophy is a reliable marker of FTLD pathology, regardless of the clinical diagnosis. Specifically, the MP ratio and MRPI both distinguished the control group from PSP-tau (thresholds of <0.263 and >8.39 respectively), CBD-tau (thresholds of <0.286 and >7.07 respectively) and TDP-43 pathology (thresholds of <0.328 and >6.09 respectively). These results aligns with known pathological characteristics of PSP-tau which features significant midbrain atrophy[101]. The reduction in midbrain volumes in CBD-tau and TDP-43 cohorts may be due to anterograde degeneration of the midbrain secondary to cortical neuron loss, although there is increasing interest in primary brainstem involvement in FTLD, particularly of the superior colliculus controlling the oculomotor system[244].

Quantification of midbrain atrophy is a useful marker of PSP-tau pathology, even when used among a cohort of mixed FTLD pathologies. The present study showed that more severe midbrain atrophy (i.e., low MP ratio and high MRPI) distinguished PSP-tau from the combined CBD-tau + TDP-43 cohort (MP ratio <0.244 and MRPI >10.65) while preserved midbrain volume (i.e., high MP ratio and low MRPI) distinguished TDP-43 pathology from a mixed tau cohort (MP ratio >0.229 and MRPI <10.26). In this context, the MRPI demonstrated higher sensitivity with similar specificity. These measures may also be useful in establishing a diagnosis when an FTLD syndrome is suspected but pathognomonic features of PSP and CBS (e.g., supranuclear palsy or alien limb phenomenon) are not present.

These results are consistent with previous studies examining brainstem volumes in patients with parkinsonism, rather than a clinical syndrome associated with FTLD pathologies. Using a similar methodology, where all regions of interests were traced manually[245] – both MRPI and MP ratio were shown to distinguish PSP from CBS. A study examining MRPI in a pathologically defined cohort of PSP-tau and CBD-tau using an automated tracing algorithm also confirmed the utility of MRPI in this context[246]. The same study also confirmed the utility of the MRPI in distinguishing PSP from other pathologies (including CBD-tau, TDP-43 and PD) as well as PSP-tau and CBD-tau from other pathologies[246]. The MP ratio was not specifically examined in this study.

The MP ratio offers several advantages over the MRPI. The MP index can be measured on a single midline sagittal MRI image, while the MRPI requires the same measurements for MP ratio as well as SCP and MCP measurements on different image sections. The increased number of measures required to calculate the MRPI increase the tracing time and may increase the risk of systematic error. Both tools provide excellent sensitivity and specificity. Only in one specific scenario - the distinction PSP-tau from TDP-43 pathology – did the MRPI offer higher sensitivity and specificity.

There are number of ways this study could have been improved. A bigger cohort, particularly in the CBD-tau group, and biomarker confirmation of AD (e.g., amyloid imaging, CSF analysis, or pathological examination) and exclusion of subclinical pathology in the control group by similar means, would strengthen the results. Disease duration varied between the PSP and the CBD cohorts. However it seems unlikely that the differences in imaging parameters observed between these two groups reflected a difference in disease duration as the mean disease duration was not significantly different. Larger studies of pathologically confirmed cohorts could clarify this point. An interesting aspect that I was unable to explore in this study due to inadequate clinical information, was whether different clinical variants – corticobasal, ataxic, frontal or language – with proven PSP pathology, have different

MP ratios or MRPI at presentation. In another words, do measures of midbrain atrophy predict PSP pathology regardless of the presenting clinical phenotype?

Also, all measurements and tracings on the MRI images were performed manually using a mouse on a conventional computer screen. A dedicated tracing set up – for example displaying the images on a touch screen and tracing using a stylus – or use of an automated tracing algorithm such as one reported by Nigro et al[247] could have produced even more reliable results. On the other hand, the present study showed that excellent results can be obtained with simple and widely available image viewing software, and without the need for specialised equipment or software.

The results of the present study represent a significant step towards development of *in vivo* biomarkers for PSP-tau pathology in the assessment of patients with FTLD syndromes. The sensitivities and specificities of the MP ratio and the MRPI are comparable to the sensitivities and specificities of amyloid pathology detection in the cerebrospinal fluid (80-96% and 77-82% respectively) and amyloid positron emission tomography (91-97% and 87-100% respectively)[138]. CSF examination and amyloid imaging are currently used as diagnostic biomarkers in clinical practice and as screening tools for clinical trials in AD. The present study demonstrates that the MP ratio could provide similar diagnostic certainty for the identification of PSP-tau, either in clinical or research settings, at an even more affordable price.

Chapter 6

Sleep disturbances in

behavioural variant frontotemporal dementia

Note to the Chapter

The research activities and results presented in this chapter were severely curtailed by the impact of the global COVID-19 pandemic. Specifically, the FRONTIER Research Group (Brain Mind Centre, University of Sydney) was not performing face to face assessments between 18 March 2020 and September 2020, nor between 26 June 2021 and 14 Feb 2022 in response to lockdowns imposed by the Government of New South Wales (18 March 2020 – 1 July 2020 and 26 June 2021 – 11 Oct 2021). Additionally, restrictions on inter-state travel imposed by various Australian state governments also significantly impacted research participant recruitment.

Introduction

As discussed in Chapter 1, individuals diagnosed with bvFTD present with variable degrees of apathy, loss of empathy, disinhibition, changes in appetite, altered food preferences and executive dysfunction[10]. There are currently no reliable diagnostic or staging biomarkers of bvFTD, which limits our ability to develop and assess appropriate disease modifying treatments. While FDG-PET and MRI have utility in the assessment and management of patients with bvFTD, neither modalities can reliably predict specific pathological entities (i.e., tau or TDP-43 pathology) causing the bvFTD syndrome[48].

Ongoing research efforts aim to improve understanding of bvFTD by focusing on the characteristic symptoms of bvFTD – particularly behavioural and eating disturbances. Previous studies suggest that pathological processes underlying bvFTD significantly alter the reward and the hypothalamic circuits[54], which are responsible for fundamental, goal-driven homeostatic processes and autonomic functions[53, 54]. Sleep is another essential homeostatic process regulated by the hypothalamus,[248, 249] but very little is currently known about sleep profiles in bvFTD. If disturbed, sleep assessment may be developed as an early diagnostic or a prognostic marker in bvFTD.

There is limited evidence to show that sleep disturbance may be an integral component of bvFTD[62]. Up to 80% of the participants diagnosed with bvFTD reported difficulty sleeping, as well as disruptive sleep events and excessive daytime somnolence[60]. Daytime hypersomnolence appears to be the most frequent manifestation affecting 47-64% of those surveyed[58, 59], a higher proportion than that found in AD. In a longitudinal study of 204 patients, sleep disturbance was found to worsen in parallel to disease progression, similar to other cardinal features of bvFTD mediated by hypothalamic involvement (i.e., apathy, disinhibition, and eating changes[61]). In the same study, sleep disturbances appeared to worsen earlier in the course of the disease than in AD, although the differences had disappeared in the advanced stage of both diseases[61].

Actigraphy has been used to characterise sleep and circadian rhythm disturbance of bvFTD in two studies of nine institutionalised[250] and 13 community dwelling[251] patients. These studies demonstrated presence of sleep fragmentation and alteration in circadian sleep cycle, with preserved circadian temperature cycle[250]. In the setting of AD there is evidence of a direct and general disruption of suprachiasmatic nucleus, the central circadian pacemaker[252]. Whether this is the mechanism of sleep disturbance in bvFTD, or another neural substrates are implicated, is currently unknown.

Finally, polysomnography (PSG) investigations have identified changes in sleep architecture in bvFTD with a reduction in total and REM sleep duration and increased sleep fragmentation, or frequent interruptions to sleep[253-255]. These changes appear to occur earlier in the disease process than in AD, consistent with findings of Ranasinghe et al[61]. However, the clinical significance of the PSG findings is unclear, as these studies did not correlate sleep abnormalities with severity of the disease or caregiver distress, reducing their utility and impact in clinical practice.

In this chapter, I aimed to confirm the finding from previous studies that sleep is disturbed in bvFTD, and to extend this work by investigating the nature of sleep disturbance in bvFTD through a combination of a novel survey, actigraphy, and polysomnography. This knowledge could lead to significant improvements in clinical care, given that sleep disturbance in bvFTD has been significantly associated with caregiver distress[256] and appropriately targeted interventions may be able to provide symptomatic relief to the patient as well as to their carers. Addressing sleep disturbance may also delay the transition to residential care, since the development of sleep disturbance is considered to be a reliable predictor of increasing care needs and nursing home admission in the subsequent twelve months[257, 258]. There are also a range of pharmacological treatments already available to manage sleep disturbances[259] which makes sleep disturbance a novel, but a potentially amenable and therefore an attractive therapeutic target in bvFTD.

Methodological Considerations

Participants

Participants diagnosed with probable bvFTD as per the current diagnostic criteria[13] were recruited from those enrolled in the longitudinal cohort study at FRONTIER frontotemporal dementia research clinic at the Brain and Mind Centre, the University of Sydney, between 2018 and 2020. Individuals with a known diagnosis of a sleep disorder such as obstructive sleep apnoea were excluded from the study. Clinical assessments, assessment of caregiver burden via sleep questionnaire, actigraphy with sleep diary, and PSG were performed as outlined in Chapter 2.

There were two independent control groups for this study; one provided control data for a newly developed sleep questionnaire and the other for actigraphy and PSG. The healthy control group and AD participants for the sleep questionnaire were recruited from the same longitudinal cohort study at FRONTIER. The disease control (i.e., amnestic MCI/early AD) participants for the actigraphy and the PSG studies were recruited through the Healthy Brain Aging Clinic at Brain and Mind Centre, the University of Sydney, between 2015 and 2020. These individuals did not complete the sleep questionnaires or the sleep diary but actigraphy and PSG were performed with only minor differences to the protocol as outlined in Chapter 2. Specifically, the only difference between the two actigraphy protocols was duration, which ranged between 7-14 days in the disease control cohort and 7 days for the bvFTD cohort; PSG was performed according to an identical protocol in both disease groups.

Each response item of the sleep questionnaire was classified as 'normal' if symptoms were absent for 2 nights or less. The sleep diary was used predominantly as an attempt to validate the actigraphy results in the bvFTD; no sleep diary was available from MCI/AD group for comparison.

All statistical analyses were performed using Prism (version 9, GraphPad Software, San Diego, CA, USA). The groupwise comparisons were performed using one way Welch's ANOVA; pairwise tests were

performed using unpaired t-test with Welch's correction. Chi-square test was used to test the significance of each questionnaire item. Two-tailed correlation was calculated using non-parametric Spearman method.

Results

Sleep Questionnaire

The questionnaire was obtained from 26 probable bvFTD participants – 25 completed by a study partner, and 1 completed by the patient – 12 individuals with AD, and 19 healthy controls; 8 control participants (5 males and 3 females) completed the questionnaire themselves. Their demographic profiles are displayed in Table 6-1. Male participants outweighed female participants in all three groups, but there were no significant differences in sex across the three groups.

	AD		**bvFTD**		**HC**		**p value**
M:F	9:3		20:6		14:5		0.969
	Mean	st.dev	Mean	st.dev	Mean	st.dev	
Age^ (y)	63.34	7.83	62.86	8.34	65.26	3.93	0.412
Education^ (y)	11.48	2.26	13.51	3.13	15.22	2.37	0.0006
ACE-III*	64.83	10.65	76.63	17.08	95.63	2.95	0.0162
Sleep Time^ (h)	9.31	1.77	8.52	3.04	7.63	0.97	0.0127
Dis Dur* (y)	4.76	3.59	6.24	4.73	NA		0.306

Table 6-1. Demographic Profile of the cohort. Note – after Bonferroni correction, significance threshold p = 0.05/ = 0.01. Education years of AD < bvFTD < HC was the only significant comparison. ^Groupwise comparison for age, education and the sleep times were compared using one way Welch's ANOVA; *ACE and disease duration comparisons were between the AD and the bvFTD group only, performed using unpaired t-test with Welch's correction. ACE-III = Addenbrooke's Cognitive Examination version 3; AD = Alzheimer's Disease; bvFTD = behavioural variant frontotemporal dementia; Dis Dur = disease duration; F = female; HC = healthy control; M = male; NA = not applicable; st.dev = standard deviation.

Several questionnaire responses differed significantly across the groups (Table 6-2), even after correcting for multiple comparisons (Bonferroni corrected p = 0.05/16 = 0.00313). Specifically, there was a groupwise difference in Q4 "How often does s/he feel drowsy or sleepy during the day?". Pairwise comparisons of the groups for Q4 demonstrated that the bvFTD group responses differed from the HC group (p = 0.0003), and there was a trend for difference compared to the AD group (p = 0.01). The AD group responses did not differ from the HC group responses (p = 0.2194). 8/26 bvFTD study partners and 4/14 AD study partners and 3/19 healthy controls reported sleeping in a different room to their partner; often the reasons given were partner rather than patient related (e.g., the partner snored), but this may have led to underestimation of nocturnal sleep disturbance.

		bvFTD	**AD**	**HC**	**p^**
Asleep in <15 min		0.308	0.572	0.684	0.0352
Q1	Slept noisily	0.545	0.273	0.133	0.030
Q2	Rested in morning	0.375	0.083	0.111	0.0532
Q3	Waking up short of breath	0.143	0.000	0.000	0.102
Q4	Drowsy/sleep during the day	0.760	0.462	0.158	**0.0004**
Q5	Difficulty falling asleep	0.320	0.000	0.053	0.016
Q6	Difficulty returning to sleep	0.348	0.091	0.105	0.088
Q7	Difficulty staying awake	0.462	0.308	0.053	0.012
Q8	Get out of bed at night	0.680	0.636	0.556	0.705
Q9	Snore during sleep	0.750	0.385	0.308	0.015
Q10	Stop breathing during sleep	0.063	0.125	0.071	0.304
Q11	Acting out dreams	0.333	0.167	0.063	0.133
Q12	Temperature complaints	0.391	0.250	0.158	0.236
Q13	Bad dreams	0.200	0.071	0.053	0.268
Q14	Medications for sleep	0.200	0.071	0.000	0.088
Q15	Obtain sufficient sleep	0.292	0.000	0.000	0.010

Table 6-2. Proportion of individuals with sleep disturbances. The questionnaire can be found in Appendix 2-1. ^p values were calculated using chi-square tests for each question, with Bonferroni corrected p = 0.05/16 = 0.00313 set as threshold for significance. The 'Don't Know' answers for each question were excluded from the analysis. For Q4, the only significant item, there were 2 'Don't Know' answers excluded – 1 from bvFTD and 1 from HC group.

Actigraphy

13 bvFTD patients, from 26 that answered the questionnaires, underwent actigraphy; only 7 of these individuals completed the sleep diary while undergoing actigraphy and 3 of these diaries were completed by the participant themselves, rather than their carer, as these individuals lived mostly by themselves. The demographic profiles and the results are displayed in Table 6-3. There were no significant differences between the age of the two control groups (63.34 years for the FRONTIER group vs 68.77; p = 0.0655), although the years of education was significant shorter in the FRONTIER group (11.48 years vs 13.48; p = 0.0418). ACE scores and disease duration data were not available from the second group for comparison.

	bvFTD		**MCI/AD**		**p-value**
M:F	10:3		13:10		0.292
	Mean	st.dev	Mean	st.dev	
Age (y)	64.97	8.89	68.77	7.98	0.2136
Education (y)	14.4	3.9	13.48	3.24	0.4756
ACE-III	80	15.08	NA		
MMSE	NA		27.1	3.13	
Dis Dur (y)	6.97	5.56	Not captured		
Actigraphy Results					
Total bed time (min)	612.14	129.18	508.18	67.73	0.0161
Total sleep time (min)	492.79	101.11	448.57	67.04	0.1767
Onset latency (min)	39.28	26.72	35.19	13.71	0.6153
Sleep efficiency (%)	81.05	6.57	88.29	6.31	0.0038
WASO	57.25	25.21	59.6	30.83	0.8086
Number of naps	2.86	1.64	Not captured		
% time not captured	0.07	0.15	5.03	5.13	0.0002

Table 6-3. Demographic profile and actigraphy results. Bonferroni corrected significance threshold: p = 0.05/7 = 0.0071. *Sleep efficiency was significantly reduced in the bvFTD group compared to the MCI/AD group. %MCI/AD group had significantly longer duration that was not captured. No other significant differences between groups were detected. ACE-III = Addenbrooke's Cognitive Examination version 3; Dis Dur = disease duration; min = minutes; y = years; WASO = Wakefulness After Sleep Onset. There was no significant difference in age or years of education between the two control groups. The sex ratio across groups was also not significantly different.

The only significant difference in actigraphy metrics between the bvFTD and MCI/AD groups was sleep efficiency (see Chapter 2). Specifically, sleep efficiency was reduced in bvFTD compared to AD (81% vs 88%, p = 0.0038). There was a trend (p = 0.0161) towards increased total bed time in bvFTD compared to AD. The onset latency and WASO were similar in the two groups; actigraphy is unable to identify or distinguish different causes of reduced sleep efficiency. The number of daytime naps were not captured in the MCI/AD group as daytime naps were manually scored only in the bvFTD cohort. Compliance with actigraphy, as indicated by "% time not captured" was superior in the bvFTD group compared to the MCI/AD group.

Correlations between the total bed time (TBT) between the actigraphy results and the sleep diary results were generally poor (Table 6-4) calling in to question the reliability the sleep diary data. However, two participants returned acceptable r values suggesting that suitably dedicated individuals may be able to produce reliable sleep diaries.

Participant	r	p-value
1	0.9258	0.0143
2	-0.3472	0.4714
3	0.2041	0.8571
4	0.7968	0.0381
5	0.07485	0.8762
6	0.3714	0.4972
7	0.22646	0.5714

Table 6-4. Correlation of total bed time of the 7 individual participants as captured by the actigraphy and the sleep diary. After Bonferroni correction, p = 0.05/7 = 0.00714 was specified as the significant value. R values suggest generally poor correlation, although Participants 1 and 4 demonstrates that sleep diary is not necessarily universally or entirely unreliable.

Polysomnography

Six bvFTD individuals from the actigraphy cohort proceeded to sleep study which was performed at Woolcock Institute of Sleep Research as described in Chapter 2. The sleep study results were compared with the data from the MCI/AD group. Their demographic profiles and sleep parameters are presented Table 6-5.

No statistically significant differences were observed between the two groups, even though 3 of the 6 bvFTD individuals were found to have obstructive sleep apnoea. Surprisingly, the number of apnoea and hypopnoea episodes per hour, measured as high apnoea-hypopnoea index (AHI), did not significantly differ in the bvFTD group compared to controls.

The 6 individuals who underwent overnight PSG also completed actigraphy. 4 parameters were measured by both test modalities, although PSG data were collected during a single night, while actigraphy results were individualised averages, with the data collected over 7 nights. None of the PSG participants were wearing an actigraph during their PSG session due to logistic and scheduling challenges. There were no statistically significant correlations between parameters measured at PSG over 1 night and actigraphy metrics averaged over 7 nights (Table 6-6).

	bvFTD		MCI/AD		p value
Sex (M:F)	4:2		13:10		0.9999
	mean	st.dev	mean	st.dev	
Age (y)	67.81	9.7	68.77	7.98	0.8303
Education (y)	14.21	5.17	13.48	3.24	0.7528
ACE-III	89.33	7.58	Not available		
MMSE	Not available		27.1	3.13	
TST (min)	332.1	62.3	339.4	91.65	0.8218
Sleep Latency (min)	15.73	15.52	34.85	53.99	0.1507
WASO (min)	121.17	109.13	118.67	91.73	0.9604
Sleep Efficiency (%)	72.4	18.42	67.64	22.45	0.6038
N1 (min)	79.33	37.62	54.85	40.49	0.1986
N2 (min)	141.33	53.2	149	61.04	0.7665
N3 (min)	61.08	28.15	81.57	48.83	0.2035
REM (min)	50.42	27.83	45.28	27.66	0.6976
AHI (/h)	25.47	11.17	27.13	18.76	0.7866

Table 6-5. Polysomnography results. There were no significant differences between the bvFTD group and the MCI/AD group for the standard PSG parameters examined. ACE-III = Addenbrooke's cognitive examination version 3; AD = Alzheimer's Disease; AHI = apnoea hypnoea index = number of apnoea/hypnoea episodes per hour; bvFTD = behavioural variant frontotemporal dementia; F = female; min = minutes; MCI = mild cognitive impairment; MMSE = Folstein's mini mental examination; M = male; N = non-rapid eye movement sleep; REM = rapid eye movement sleep; st.dev = standard deviation; TST = total sleep time; WASO = wake after sleep onset; y = years.

	PSG		Actigraphy			
	mean	st.dev	mean	st.dev	r	p
TST (min)	332.1	62.3	437.5	72.38	0.143	0.803
WASO (min)	121.17	109.13	44.08	22.87	0.6	0.2417
Sleep latency (min)	15.73	15.52	29.14	23.42	0.371	0.497
Sleep Efficiency (%)	72.4	18.42	84.22	5.96	0.2	0.714

Table 6-6. Correlation of common parameters from PSG and actigraphy. There was no significant correlation between parameters measured at PSG over 1 night and actigraphy metrics averaged over 7 nights.

Discussion

The present study revealed evidence of disturbed sleep in bvFTD, but further study is needed. In particular, this study was limited by a small sample size which is especially important given the clinical, neuroanatomical and pathological heterogeneity of bvFTD. Nonetheless, the sleep questionnaire data suggest that there is a sleep disturbance, with increased day time somnolence, in patients with bvFTD. PSG diagnosed OSA for the first time in *half* of the bvFTD participants. Actigraphy demonstrated reduced sleep efficiency, while data regarding sleep latency was conflicting; actigraphy and questionnaire data suggest that bvFTD patients experience difficulty falling asleep, although this finding was not confirmed on PSG. Finally, the previous PSG findings – reduction in total REM and increased sleep fragmentation[253-255] – were not replicated in the present study.

PSG results, while generally considered definitive, need to be interpreted cautiously. PSG assessments in the present study were performed in a dedicated sleep laboratory, as is the usual practice. However, such a testing parameter may have influenced the results of the PSG. For example, 4/6 bvFTD participants in the present study had to travel over 2 hours to the sleep laboratory, potentially inducing disproportionate fatigue with consequent effects on sleep parameters. The foreign environment and need for sensing apparatus may have artificially affected sleep quality (e.g., lower TST and higher WASO). Other disadvantages of PSG – such as complex technique, monitoring requirements and the necessity of sleeping in an unfamiliar laboratory setting are also well documented[260]. One approach to nullify these potential confounding variables is the use of domiciliary PSG, however existing systems still require attachment to the same number of monitoring leads.

The present study encountered several challenges. In particular, adequate recruitment and consistent data collection was severely curtailed by the impacts of the COVID-19 pandemic and government responses to it. On review of existing PSG studies in bvFTD[253-255] the recruitment target at study commencement was at least 20 individuals with bvFTD, 10 individuals with AD, and 10

healthy control individuals. Due to COVID-19 affected recruitment, disease control data was sought from a separate study performed under similar though not identical study conditions. While necessary for the completion of the present study, the impact of including comparative groups recruited under another study protocol is unknown. Finally, consistent data on psychiatric status was not available for the complete cohort, making it difficult to determine the impact of mood on sleep disturbance.

Inadequate recruitment had flow on effects for the PSG arm of the study. It is remarkable to note that *half* of the bvFTD participants in the present study were diagnosed with OSA, and that actigraphy data did not correlate with PSG data. The study was not specifically designed to determine the rate of or risk factors for OSA in bvFTD. As such, a limitation of the present study is that weight and BMI data were not included in the analysis. Furthermore, the small sample size (n=6) prevents any meaningful interpretation of the data, but several questions should be explored. For example, is OSA more common in bvFTD than matched controls or patients with MCI/AD? Could the sleep disturbances detected in the present study be solely due to OSA, or are other mechanism driven by neural pathways affected in bvFTD also contributing? Could bvFTD increase the risk of OSA, either directly or indirectly (e.g., via weight gain)? Would a larger study of concomitant PSG and actigraphy be able to demonstrate correlation of sleep metrics in bvFTD?

Despite the low enrolment and associated technical difficulties, this study was not completely futile. Actigraphy was tolerated in most individuals with bvFTD with reasonable compliance, subject to carer support; in fact compliance with actigraphy was superior in the bvFTD group compared to the MCI/AD group. There are several potential reasons for this outcome. Firstly, while the actigraph is splash resistant, study participants were instructed to remove the device for showering and other deliberate exposures to water (e.g., swimming). Could MCI/AD patients be more prone to forgetting to re-attach the device than bvFTD patients? Unfortunately, the present study data did not include a measure of

memory impairment used in both groups, making this possibility impossible to explore. Secondly, individuals in the MCI/AD group often participated independently, while individuals in the bvFTD group were supported by a carer, with separate information sheets for the participant and carer. This, combined with the fact that some patient-study partner dyads provided accurate sleep diary data, suggest that active involvement of a carer is critical to accurate data collection in patients with neurodegenerative cognitive impairment.

Further exploration on which sleep assessment tool – the questionnaire, the sleep diary, actigraphy or PSG – best correlates with clinically meaningful disease characteristics (e.g., carer burden) is important. While PSG provides the most definitive information about sleep quality, the significant investigative burden of PSG – specifically, attachment to cumbersome equipment and monitors, often in the unfamiliar surrounds of a sleep laboratory – in individuals exhibiting pronounced behaviour changes makes its routine use challenging. This challenge is borne out in the participation rate in the present study, where only ~6/26 participants, or just under a quarter of the cohort who began the study, ultimately completed the PSG.

A sleep questionnaire may be more accessible and easier to deploy in larger cohorts, but there are inherent weaknesses with relying on carer description of sleep disturbance in bvFTD patients. Specifically, sleep disturbances may occur when the carer is asleep and some carers may not share a bed or bedroom with the patient, meaning that relevant data may not be captured. Meanwhile, actigraphy, which can be utilised in a more naturalistic domiciliary setting over several days as well as nights[259, 261], could reflect real world sleep disturbances more accurately than PSG or sleep questionnaires. However, actigraphy also has limitations – reliance on movement-based algorithmic identification of sleep, and capturing limited number of parameters and may not generate sufficiently precise data for clinical and research purposes. Nonetheless, further study to determine is required to

determine if the longer and more ecologically valid characteristics of actigraphy offer advantages over PSG in the context of dementia despite these limitations.

Chapter 7

Conclusions:

Where have we come? And what's next?

My efforts at exploring potential novel biomarkers for FTLD have identified two entities – language disturbances and quantification of midbrain atrophy (i.e., the midbrain/pons ratio and magnetic resonance parkinsonism index (MP ratio and MRPI respectively)) – that have potential as a biomarker with utility in both clinical and research settings. The studies presented in this thesis also confirmed that much remains unknown with bvFTD, particularly regarding sleep disturbances. All these studies, including my unsuccessful search for 'right-nfvPPA', provide further, different but intriguing directions for exploration.

In Chapter 3, I combined the novel control dataset I compiled and the application of existing text analysis tools to demonstrate significant increase adverb usage, familiarity and meaningfulness scores as expected, as well as previously unreported changes age of acquisition, co-occurrence probability, and semantic distinctiveness in written language output of an individual with svPPA. All these alterations in the language, documented in granular detail, are consistent with our current understanding of the svPPA. This study also demonstrated an important fact – that these language alterations may still fall within the 'normal' ranges, some years into the disease process.

The next step is to assess whether examination of intra-individual alterations in linguistic and lexical features utilising automated tools and bulk analysis of texts can demonstrate similar language changes in other individuals with svPPA, to establish text analysis as a potential marker of disease progression and treatment response.

Text analysis may also be a useful tool to detect the presence of language alterations in other dementias that do not primarily involve, or are characterised by, language disturbance. This approach would maximise our capability to examine language disruptions in unique individuals with rare dementias such as Sir Terry Pratchett, a British author who was remarkably still writing best-selling novels after his diagnosis with posterior cortical atrophy[262] (which primarily disrupts visuospatial

function initially) and further our understanding of disruptions to the cerebral networks in these disorders.

Beyond the analyses of existing texts, I propose that text analysis represents a potential method for screening and monitoring of early cognitive changes. With a sufficiently large, appropriately validated control corpus, automated text analysis, along with appropriate statistical approaches such as Crawford's modified t-test[263], could be applied to any lexical output of individuals – scripts, non-fiction writings, newspapers and magazine articles, reports, emails and perhaps even free speech – to quantify alterations in vocabulary and lexical parameters to detect statistically significant deviations from the norm compared to the control corpus in an unbiased way. This approach opens the door for text analysis to be utilised more broadly, not just as an indicator of disease progression, but also as an algorithmic, probabilistic screening tool for dementia.

In Chapter 4, I investigated whether a distinct clinical phenotype of nfvPPA associated with right perisylvian atrophy exists. This would be analogous to svPPA where both 'left' and 'right' clinical phenotypes have been reported[9, 66]; the current diagnostic criteria recognise existence of the two hemispheric variants of svPPA but not for nfvPPA[64]. I was able to identify 4 nfvPPA cases with predominant right hemisphere atrophy but unable to identify a specific collection of clinical features that distinguished 'right-nfvPPA' from the typical nfvPPA. Although no clinical differences between right-nfvPPA and left-nfvPPA were found, subtle differences in the pattern of cortical atrophy were detected.

While the null result itself is in one sense surprising and unanticipated, the absence of 'right-nfvPPA' is still intriguing – what is different about nfvPPA from svPPA at a neuroanatomical or pathophysiological level that renders 'right-nfvPPA' non-existent, or at least, so difficult to identify?

One lead for further study could be the low prevalence of predominant right hemisphere atrophy which was only found in ~10% of our nfvPPA cohort when one may anticipate a proportion of ~30% based on the prevalence in svPPA, where hemispheric lateralisation is much better characterised. One possible explanation for such a large discrepancy in proportion of right and left nfvPPA is that nfvPPA patients presenting with right hemisphere dominant neurodegeneration may develop motor symptoms early on in the disease course and be diagnosed with a related motor syndrome, such as PSP, rather than nfvPPA. While the relationships between right-nfvPPA and these disorders are yet to be explored in detail, there is a recent report of an individual presenting with nfvPPA with predominantly right sided atrophy on imaging, who progressed over 9 years to develop motor features such as apraxia and supranuclear gaze palsy, and autopsy ultimately demonstrated PSP pathology[264], confirming that these two disorders can exist on a spectrum.

An additional focus of future studies could include the alien limb phenomenon in nfvPPA. Alien limb phenomenon manifests as a limb, often the upper limb, demonstrating apparently purposeful but unintended movements[265]. While alien limb phenomenon can occur following stroke, when present in a context of a suspected neurodegenerative disorder, it is considered a pathognomonic feature of CBS which share a common pathological substrate, tau, with nfvPPA[6]. In both scenarios, alien limb phenomenon occurs more commonly on the left side of the body, suggesting its origin in the right hemispheric dysfunction[266-268] and it would be important to investigate presence, or absence, of alien limb phenomenon in future investigations of nfvPPA cases presenting with predominant right hemispheric atrophy.

In Chapter 5, I examined the utility of the MP ratio and MRPI obtained from MRI at diagnosis in differentiating between FTLD pathologies, especially PSP-tau. Both the MP and MRPI distinguished PSP-tau pathology from CBD-tau pathology and TDP-43 pathology. These results adequate sensitivity

and specificity to predict pathological substrates of FTLD subtypes *in vivo*, with adequate sensitivity and specificity suggesting potential utility in both clinical and research settings.

Further work is required to validate these findings. Prospective validation (performed in individuals with suspected PSP but unconfirmed pathological diagnosis) as well as inter-observer validation (performed by a number of radiologists/neurologists measuring the MP ratio and MRPI in a blinded fashion) is required to further develop these tools. Future studies would also help determine whether the MP ratio or the MRPI is superior in terms of sensitivity, specificity and inter- as well as intra-observer correlation and identify specific scenarios better served by one measure or the other.

Another aspect to examine is longitudinal changes in the MP and the MRPI in these diseases, and whether the longitudinal alterations provide further clues about these syndromes and explore whether these may have a role as a marker of disease progression.

In Chapter 6, I attempted to characterise the nature of sleep disturbance in individuals with probable bvFTD. Ultimately, I was not able to identify any features associated with sleep that were significantly different from the MCI/AD group acting as 'disease-control' group on PSG; but actigraphy demonstrated insomnia with significantly higher sleep latency, and the sleep questionnaire supported this finding with increased time to sleep and significantly increased day time somnolence in individuals with bvFTD.

There are many 'known unknowns' regarding sleep disturbance in bvFTD. There is still limited information on the impact, if any, of sleep disturbances on the carers, symptom profile and progression of disease, neuropsychological profile, genetic status, and imaging features.

Most importantly, we still do not know whether improving sleep parameters is a relevant target of intervention for bvFTD modulation and management. Recently it was hypothesized that orexin, an important neuro-hormonal regulator of sleep[39], may be implicated in bvFTD[155]. My finding that insomnia is more common in bvFTD patients potentially support this hypothesis since elevated orexin levels are associated with insomnia[269]. This would require confirmation in another study, given the previously discussed limitations of my study, but orexinergic system has already shown to be an amenable and safe therapeutic target and modulating the orexinergic system with a receptor antagonist can increase the total sleep time with minimal side effects[270]. Ultimately, a randomised control trial would be needed to determine if sleep modulation via orexinergic pathway in bvFTD can provide any clinical benefit.

Altogether, the works presented in this thesis explores potential areas of focus for developing putative biomarkers in FTLD, and have even identified potentially promising leads – quantification of language changes and measures of midbrain atrophy. One consistent caveat throughout this thesis that must be acknowledged is the small number of participants in each study. Many FTLD syndromes, particularly bvFTD but also nfvPPA, PSP and CBS demonstrate significant clinical and/or pathological heterogeneity. Subclassification of cohorts according to clinical phenotype or underlying pathology further reduces power of each study and limits the ability to detect significant but small or subtle differences. The relative rarity of each FTLD syndromes and difficulties in recruitment due to COVID-19 lockdown further exacerbated this issue. The putative clinical utility of each potential biomarker presented in this thesis, their advantages and limitations as well as further work required to evaluate and/or validate each biomarker is summarised in Table 7-1.

While working on these projects, I reached an important realisation that while FTLD and the suffering they cause to the patient and those around them may not change, our ability to characterise and comprehend FTLD is rapidly evolving because of modern advances in technology. For example, there

has been a significant increase in accessible computational power for analysing large quantity of texts; 3T MRI scanners are becoming more ubiquitous, lowering the barrier to obtaining detailed volumetric imaging for differentiating FTLD syndromes in routine clinical practice; and development of wearable data collection devices such as an actigraph has simplified collection of many biological parameters such as heart rate and sleep. These advances in technology, and many others that are yet to be explored, provide an unprecedented opportunity to characterise the known, the novel, and as yet unknown cognitive and physiological alterations in FTLD, identify relevant biomarkers, and ultimately, and hopefully, development of treatments that would alleviate suffering and loss experienced by individuals afflicted with, and affected by, FTLD.

Biomarker	**Putative Role**	**Advantages**	**Limitations**	**Further Evaluation**
Text Analysis	Diagnostic aid Monitoring Functional stratification Treatment evaluation Disease detection/Screening	Can be automated Operate semi-real time	Required quantity of language output Not suitable for everyone	Confirm findings in a larger cohort Identify changes in other neurodegenerative disorders Establish specific changes unique to a single disorder
Volumetric Analysis	Diagnostic aid (?)	MRI easily accessible	Answer in search of a question	Further characterisation of neural circuitry
Brainstem Measurements	Diagnostic aid Disease detection Prognostication (?)	Accessibility	Time required for tracing	Validation in a larger cohort
Sleep Disturbances	Monitoring Functional stratification Treatment evaluation	Impacts carer burden Actigraphy Easily accessible Minimal patient burden Continuous monitoring	Actigraphy Reduced granularity re: sleep Incomplete capture of sleep disturbances PSG Significant investigative burden Not easy to repeat	Validation in a larger cohort Correlation with clinical profile Correlation with carer burden

Table 7-1: **Summary table of each biomarker examined in this project.**

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Appendix

Appendix to Chapter 2

Appendix 2-1

Sleep Questionnaire

FuTONS Sleep Questionnaire

Your name: _____

Participant's name: _____

Relationship: _____

Date of Completion: _____

Please answer the following questions about the sleeping habits of the study participant as best as you can based on what has happened in the **past 4 weeks.**

How much time, on average, did s/he take to fall asleep after s/he went to bed?

0-15 min 16-30 min 31-45 min 46-60 min More than 60 min

How many hours did s/he sleep on average each night? _____

What time did s/he normally go to bed? _____

What time did s/he normally wake up? _____

1. How often did s/he not sleep quietly (e.g., moving restlessly, speaking)

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

_____

2. How often did s/he appear rested after waking up in the morning?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

_____

3. How often did s/he wake up short of breath or with a headache?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

_____

4. How often did s/he feel drowsy or sleepy during the day?

Never *1-2 days/week* *3-5 days/week* *6-7 days/week* *Don't Know*

_____

5. How often did s/he have difficulty falling asleep?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

_____

6. How often did s/he wake up during sleep and have difficulty going to sleep again?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

---

7. How often did s/he have difficulty staying awake during the day?

Never *1-2 days/week* *3-5 days/week* *6-7 days/week* *Don't Know*

---

8. How often did s/he get out of bed at night (e.g., use the bathroom, or wander around)??

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

---

9. How often did s/he snore during sleep?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

---

10. How often does s/he briefly stop breathing multiple times during sleep?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

---

11. How often does s/he 'act out dreams' while asleep? (e.g., punching, kicking, moving legs)

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

---

12. How often did s/he complain of feeling too cold or too hot in bed?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

---

13. How often did s/he complain of having bad dreams?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

---

14. How often did s/he use medications to help her/him go to sleep?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

---

15. How often did s/he get sufficient sleep, in your opinion?

Never *1-2 nights/week* *3-5 nights/week* *6-7 nights/week* *Don't Know*

Please answer the following questions about **yourself.**

Where do you sleep, in relation to the person you care for?

Same bed Same room but different bed Different room

Approximately how long have you had this sleeping arrangement?

Less than 1 year Between 1 and 3 years More than 3 years

Could you provide a reason for the current sleeping arrangement?

_____

_____

_____

_____

For the following questions, please base your answer on what has happened in the **last 4 weeks**.

1. How often have you had to wake up at night because of the person you care for?

   Never *Once a week* *A few times per week* *Daily*

_____

2. Do you feel exhausted during the day because you had to wake up at night?

   Never *Once a week* *A few times per week* *Daily*

_____

3. Are you limited in your daily tasks and social activities during the day because you are tired?

   Never *Once a week* *A few times per week* *Daily*

_____

4. How often do you experience distress because the person you care for is sleeping poorly?

   Never *Once a week* *A few times per week* *Daily*

_____

5. How often have you thought that your life might be better if your study partner slept better?

   Never *Once a week* *A few times per week* *Daily*

_____

Appendix to Chapter 2

Appendix 2-2

Sleep Diary

FuTONS Sleep Diary - For Carer to Complete

Participant's Name: _____ Start Date: _____

Day of the Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	_____	_____	_____	_____	_____	_____	_____
Complete in the morning							
P went to bed at:	am/pm	am/pm	am/pm	am/pm	am/pm	am/pm	am/pm
P fell asleep: Easily	☐	☐	☐	☐	☐	☐	☐
After some time	☐	☐	☐	☐	☐	☐	☐
I was aware of P waking up during the night: (If unsure = U)							
P did not wake up	☐	☐	☐	☐	☐	☐	☐
If yes, number of times:							
I was aware of P getting out of the bed during the night: (If unsure = U)							
P did not get out of bed	☐	☐	☐	☐	☐	☐	☐
If yes, number of times:							
My sleep was disturbed by P, or P complaining of: (Please select all answers that apply)							
Bad dreams	☐	☐	☐	☐	☐	☐	☐
Snoring	☐	☐	☐	☐	☐	☐	☐
Going to the bathroom	☐	☐	☐	☐	☐	☐	☐
Being too cold/too hot	☐	☐	☐	☐	☐	☐	☐
Other							
After waking up, P returned to sleep:							
Easily	☐	☐	☐	☐	☐	☐	☐
After some time	☐	☐	☐	☐	☐	☐	☐
P got out of bed at:	am/pm	am/pm	am/pm	am/pm	am/pm	am/pm	am/pm
Last night, P slept:	hours	hours	hours	hours	hours	hours	hours
P woke up: Refreshed	☐	☐	☐	☐	☐	☐	☐
Somewhat refreshed	☐	☐	☐	☐	☐	☐	☐
Fatigued	☐	☐	☐	☐	☐	☐	☐
I woke up: Refreshed	☐	☐	☐	☐	☐	☐	☐
Somewhat refreshed	☐	☐	☐	☐	☐	☐	☐
Fatigued	☐	☐	☐	☐	☐	☐	☐
Complete before going to bed							
P took a nap during the day: (Nap = sleeping in bed; if unsure = U)							
P did not nap	☐	☐	☐	☐	☐	☐	☐
If yes, how long?	hours	hours	hours	hours	hours	hours	hours
P dozed during the day: (Dozing = sleeping briefly not in a bed; if unsure = U)							
P did not doze	☐	☐	☐	☐	☐	☐	☐
If yes, number of times:							
Throughout the day, P's mood was:							
Pleasant	☐	☐	☐	☐	☐	☐	☐
Unpleasant	☐	☐	☐	☐	☐	☐	☐
P consumed caffeinated beverages today:							
How many?							
P consumed alcoholic beverages today:							
How many?							
P required medications to help with sleep before going to bed:							
Yes	☐	☐	☐	☐	☐	☐	☐
Name:							
P's bedtime routine today included:							
(Eg: reading, bath)							

P = Participant

FuTONS Sleep Diary v 1. 0; 1 May 2018

Appendix to Chapter 3

Appendix 3-1

Supplementary Table 3-1

Author	Date of Birth	Date of Death	Age at Death	Title of the Book	Date of Publication	Age at Publication
James Matthew Barrie	9/5/1860	6/19/1937	77	Auld Licht Idylls	1888	28
				When a Man is Single	1888	28
				My Lady Nicotine	1890	30
				Little Minister	1891	31
				Sentimental Tommy	1896	36
Edgar Rice Burroughs	1/9/1875	3/19/1950	75	Tarzan of the Apes	1911	36
				Outlaw of Torn	1911	36
				Princess of Mars	1911	36
				Gods of Mars	1912	37
				Return of Tarzan	1912	37
Gilbert Keith Chesterton	29/5/1874	6/14/1936	62	Napoleon of Notting Hill	1906	32
				Man who was Thursday	1908	34
				Ball and the Cross	1909	35
				Manalive	1912	38
				Flying Inn	1914	40
James Fenimore Cooper	15/09/1789	14/09/1851	62	Precaution	1820	31
				The Spy: A Tale of the Neutral Ground	1821	32
				The Pioneers: or The Sources of the Susquehanna	1823	34
				The Pilot: A Tale of the Sea	1824	35
				The Last of the Mohicans	1826	37
Arthur Conan Doyle	22/05/1859	7/7/1930	71	A Study in Scarlet	1887	28
				Micah Clarke	1889	30
				The Mystery of Cloomber	1889	30
				The Firm of Girdleston	1890	31
				The Sign of the Four	1890	31
Henry Rider Haggard	22/06/1856	5/14/1925	69	Dawn	1884	28
				King Solomon's Mines	1885	29
				She: A History of Adventure	1886	30
				Allan Quatermain	1887	31
				Jess	1887	31

Thomas Hardy	2/6/1840	1/11/1928	88	Desperate Remedies	1871	31
				Under the Greenwood Tree	1872	32
				A Pair of Blue Eyes	1873	33
				Far from the Maddening Crowd	1874	34
				The Hand of Ethelberta	1876	36
Nathaniel Hawthorne	4/7/1804	19/5/1864	60	Fanshawe	1828	24
				The Scarlet Letter	1850	46
				The House of Seven Gables	1851	47
				The Blithedale Romance	1852	48
				The Marble Faun	1860	56
Henry James	15/04/1843	2/28/1916	73	Roderick Hudson	1875	32
				The American	1876	33
				The Europeans	1878	35
				Confidence	1879	36
				Washington Square	1880	37
Jerome K Jerome	2/5/1859	6/14/1927	68	Three Men in a Boat	1889	30
				Diary of a Pilgrimage	1891	32
				Novel Notes	1893	34
				Three Men on the Bummel	1900	41
				Paul Kelver	1902	43
David Herbert Lawrence	11/09/1885	3/2/1930	45	The White Peacock	1911	26
				The Trespasser	1912	27
				Sons and Lovers	1913	28
				The Rainbow	1915	30
				Women in Love	1920	35
Harry Sinclair Lewis	7/2/1885	1/10/1951	66	Our Mr Wrenn	1914	29
				The Trail of the Hawk	1915	30
				The Job	1917	32
				The Innocents	1917	32
				Main Street	1920	35
John Griffith London	12/1/1876	11/22/1916	40	The Cruise of the Dazzler	1902	26

				A Daughter of the Snows	1902	26
				The Call of the Wild	1903	27
				The Sea-Wolf	1904	28
				The Game	1905	29
William Somerset Maugham	25/01/1874	12/16/1965	91	Liza of Lambeth	1897	23
				The Making of a Saint	1898	24
				Orientations	1899	25
				The Hero	1901	27
				Mrs Craddock	1902	28
Herman Melville	1/8/1819	28/9/1891	72	Typee	1846	27
				Omoo	1847	28
				Mardi	1849	30
				Redburn	1849	30
				White-Jacket	1850	31
Walter Scott	15/08/1771	21/09/1832	61	Waverley	1814	43
				Guy Mannering	1815	44
				The Antiquary	1816	45
				Ivanhoe	1820	49
				Kenilworth	1821	50
Robert Louis Stevenson	13/11/1850	3/12/1894	44	Prince Otto	1885	35
				Kidnaped	1886	36
				The Black Arrow	1888	38
				The Master of Ballantrae	1889	39
				Catriona	1893	43
Anthony Trollope	24/04/1815	3/12/1882	67	The Macdermots of Ballycloran	1847	32
				The Kellys and the O'Kellys	1848	33
				The Three Clerks	1858	43
				The Bertrams	1859	44
				Castle Richmond	1860	45
Mark Twain	30/11/1825	4/21/1910	85	The Gilded Age	1873	48
Pen name of Samuel Langhorne Clemens				The Adventures of Tom Sawyer	1876	51

				The Prince and the Pauper	1881	56
				Adventures of Huckleberry Finn	1884	59
				A Connecticut Yankee in King Arthur's Court	1889	64
Herbert George Wells	21/09/1866	8/13/1946	80	The Time Machine	1895	29
				The Wonderful Visit	1895	29
				The Island of Doctor Moreau	1896	30
				The Wheels of Chance	1896	30
				The Invisible Man	1897	31

Supplementary Table 3-1: The titles of the books used to create the control pool, the names of the authors and the age of the author at publication.