DEFINING THE NEUROPSYCHOLOGICAL AND NEUROIMAGING PHENOTYPE OF

BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA

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DECLARATION STATEMENT

I, Laura Emily Downey, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Frontotemporal dementia (FTD) is the second most common cause of early-onset dementia after Alzheimer's disease (AD). There exists a paucity of quantifiable, sensitive, and specific biomarkers to detect this disease and track its manifestation and progression. The primary aim of this thesis was to develop and investigate new biomarkers for FTD, and focused on the examination of neuropsychological biomarkers in the behavioural variant of FTD (bvFTD) and their neuroanaotmical correlates.

Chapters 4 and 5 explored social cognition in patients with FTD and the neural correlates of this behaviour. bvFTD patients displayed gross dysfunction in the perception of sarcasm and the ability to understand basic social signals, and this mapped onto a larger social cognition neural network that has previously been defined in the literature. These findings delineate a brain network substrate for the social impairment that characterises FTD syndromes. In Chapters 6 and 7, I explored the executive functions of task switching, reaction time, and neural timing in patients with FTD. Results indicated several dissociable executive capacities, which mapped onto discrete neural areas as part of a larger executive function network, suggesting that structures implicated in aspects of executive functioning can be targeted by FTD and may underpin aspects of the bvFTD phenotype. In the final Chapter, I devised a novel battery to examine the bases of psychosis in FTD patients with the C9ORF72 mutation, which demonstrated a specific and unique impairment in the ability to interpret somatosensory proprioceptive information in these patients, which may represent a candidate mechanism for psychosis.

The studies described in this thesis contribute to the growing interest in characterising and understanding the neuropsychological phenotypes of bvFTD. Improved understanding of the anatomical associations of neuropsycholgical performance in this patient population could potentially facilitate earlier and more accurate diagnosis and symptom management.

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The Problem

Dementia is rapidly becoming one of the major health concerns of our time, with neurodegenerative diseases estimated to affect 81.1million people worldwide by 2040 (Ferri et al., 2005). Frontotemporal dementia (FTD) is the second most common cause of early-onset dementia after Alzheimer's disease (AD). As yet, no treatments are available for this disorder. There exists a paucity of quantifiable, sensitive, and specific biomarkers to detect this disease and track its manifestation and progression. With a number of therapeutic interventions and disease-modifying drugs in the early stages of development, such biomarkers become increasingly important.

Aims

The primary aim of this thesis is to develop and investigate new biomarkers for FTD in order to improve diagnosis and understanding of how the disease manifests and develops. Specifically, this thesis aims to achieve the following:

1) To investigate the nature of the social cognitive processing deficits observed in FTD, specifically in behavioural variant FTD (bvFTD) and semantic dementia (SD) subtypes, and explore the neuroanatomical correlates underlying this dysfunction.

 2) To develop a novel auditory neuropsychological tool to further explore this social-cognitive deficit in bvFTD, in order to reduce linguistic demands common to contemporary assessment tools and provide a more ecologically-valid means of social-cognitive assessment.

3) To investigate the nature of executive processing deficits in FTD and explore the underlying neuroanatomical correlates of this dysfunction

4) To explore neural timing function in FTD and assess the patterns of neural connectivity and crucial cortical network hubs underlying this ability

5) To assess the novel neuropsychiatric phenotype of psychosis in C9ORF72-defined FTD and explore its underling neurophysiological, neuropsychological, and neuroanatomical bases.

List of abbreviations

ACC - anterior cingulate cortex

ACR – anterior corona radiata

AD - Alzheimer's disease

AX – axial diffusivity

BPVS – British picture vocabulary scale

bvFTD – behavioural variant frontotemporal dementia

C9ORF72 – chromosome 9 open reading frame 72

CI - confidence interval

CSF – cerebrospinal fluid

DARTEL – differomorphic anatomical registration through exponentiated lie algebra

DLPFC/DMPFC - dorsolateral/dorsomedial prefrontal cortex

DMN – default mode network

DTI - diffusion tensor imaging

DWI – diffusion weighted image

EEG - electroencephalography

fMRI - functional magnetic resonance imaging

FA – Fractional anisotropy

FTD – frontotemporal dementia

FTLD - frontotemporal lobar degeneration

FDR – false discovery rateFMRIB – functional MRI of the brain

FSL – FMRIB software library

FEW - family-wise error

G – Spearman's 'g' of general intelligence

GLM – general linear model

GNT – graded naming test

GRN- progranulin

GM – grey matter

HG - Heschl's gyrus

IGT – iowa gambling task

ILF – inferior longitudinal fasciculus

IFL - inferior frontal lobe

IPL- inferior parietal lobe

IPS - intra-parietal sulcus

ISI - inter-stimulus interval

ITG - inferior temporal gyrus

LPA - logopenic (phonological) aphasia

MATLAB - matrix laboratory

MAPT – microtubule associated protein tau

MD – mean diffusivity

MMSE - mini-mental state examination

MNI – Montreal neurological institute

MRI - magnetic resonance image

MTG - medial temporal gyrus

NART – national adult reading test

OFC - orbitofrontal cortex

PFC - pre-frontal cortex

PNFA - progressive non-fluent aphasia

PPA - primary progressive aphasia

PSP – progressive supranuclear palsy

PT - planum temporale

ROI – region of interest

RD – radial diffusivity

RT - reaction time

SAS - supervisory attention system

SCR – superior corona radiata

SLF – superior longitudinal fasciculus

SMN – salience mode network

SD - semantic dementia

SMA – supplementary motor area

SPM – statistical parametric mapping

STC –striato-cortical-cerebellar network

STG - superior temporal gyrus

TASIT – the affective social inference test

TBSS – tract based spatial statistics

TDP43 – tar DNA binding protein 43

TIV – total intracranial volume

TL - temporal lobe

TR – trace anisotropy

ToM – theory of mind

TPJ - temporo-parietal junction

VBM - voxel-based morphometry

VEN – von economo neuron

WM – white matter

1. INTRODUCTION

1.1. Chapter introduction

Chapter 1 will focus on outlining the clinical and pathological features of the key dementias of interest to this thesis in order to give an overview of the pathological, neuroimaging, neuropsychological, genetic, and clinical hallmarks of these diseases. Chapter 2 will focus more precisely on outlining the behavioral and neuroimaging features specific to bvFTD in line with the primary aims of this thesis.

This thesis will primarily focus on FTD, however AD participants are used for the purpose of providing a neurologically-compromised behavioural comparison group in Chapters 6 and 7, and thus the pathological and clinical features of AD will also be outlined in brief in this Chapter.

1.2. Dementia

Dementia can be defined as an acquired deficit involving multiple domains of cognitive function, including memory, in the presence of normal consciousness, and sufficient to impact normal activities of daily living (Ball et al., 1993). AD represents the most common pathological dementia disease. Frontotemporal lobar degeneration (FTLD) represents the most common non-Alzheimer early-onset dementia disease. Other non-AD dementia diseases are also common, such as vascular dementia, dementia with Lewy bodies, and Creutzfeld Jakob disease.

Clinical distinction between these different diseases is often difficult, and neuropsychometry and clinical imaging can prove vital in assisting this differentiation.

Dementia is one of the leading public health issues of our time: it has a great effect on the quality of life for the patient and the caregivers and it places heavy demands on health care systems. FTD represents the second most common cause of early-onset dementia after Alzheimer's disease. With ageing populations, the number of patients with degenerative dementias such as FTD will rise dramatically, estimated to affect 81.1 million people worldwide by 2040 (Ferri et al., 2005)

Dementia is presently an incurable disease. While some disease-associated symptoms can be treated, such as psychosis, agitation, and anxiety, available treatments targeted at the dementia process itself remain largely ineffective. However, potential therapeutic agents are currently being developed, and early research suggests that these drugs have the greatest efficacy when administered in the earliest stages of disease before gross neuronal atrophy and extensive cognitive deficits develop. As such, sensitive metrics to detect the manifestation of the disease process and track its progress are of great importance in aiding early diagnosis.

1.2.1. Frontotemporal lobar degeneration (FTLD)

FTLD is a clinically, pathologically, and genetically heterogeneous disorder. FTLD is the most common underlying pathology of clinical FTD subtypes. The major pathological hallmark of FTLD is the selective erosion of the frontal and temporal cortices, with neuronal loss, gliosis and spongiosis of the superficial layers (Seeley, 2011).

1.2.1.1. Pathology

FTLD can be divided into two major pathological subtypes: FTLD with tau-positive inclusions (FTLD-tau), and FTLD with ubiquitin-positive and TDP-43-positive, but tau-negative, inclusions (FTLD-TDP; Seelaar et al. 2011). FTLD-tau is acommon pathological cause of both sporadic and genetic FTD, including those with Tau mutations. Tau inclusions may be observed in the form of Pick bodies, neurofibrillary tangles, and pretangles, and predominantly aggregate in the frontal and temporal cortex, hippocampus and subcortical nuclei, and occasionally in the midbrain, brainstem, cerebellum, and spinal cord (Mackenzie et al., 2008). TDP-43 proteinopathies represent the second major pathological cause of FTLD, and these have been subdivided into four different FTLD-TDP subtypes, depending on the morphology and distribution of the inclusions. Type A is characterised by abundant dystrophic neurites; type B with numerous neuronal cytoplasmic inclusions in both superficial and deep cortical laminae; type C with cytoplasmic inclusions, dystrophic neurites, and neuronal intranuclear inclusions (Mackenzie et al., 2011). Logopenic aphasia (LPA) is one of the more recently defined clinical subtypes of the primary progressive aphasia FTD syndromes, and in this case, Alzheimer's pathology of amyloid deposits and neurofibrillary tangles is usually the responsible pathology underlying this

subtype, despite its aphasic presentation and classification under the primary progressive aphasia (PPA) syndromes within the FTD clinical spectrum.

1.2.1.2.   Epidemiology and genetic risk factors

Around a third to a half of FTD patients have an autosomal dominant pattern of inheritance. Heritability varies across the different clinical phenotypes – bvFTD being the most heritable (Rohrer et al., 2009; Seelaar et al., 2011). The most common genetic causes of FTD are mutations in the microtubule-associated protein tau (MAPT), and progranulin (GRN) genes. More recently, pathogenic expansions in the chromosome nine open reading frame 72 (C9ORF72) have also been found to account for a significant proportion of inherited FTD (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Mutations in four other genes, including valosin-containing protein (VCP), chromatin modifying protein 2B (CHMP2B), transactive DNA-binding protein (TARDP) and fused-in-sarcoma (FUS) have been identified in a minority of cases.

1.2.1.2.1.   MAPT

The most common clinical MAPT-associated syndrome is bvFTD. MAPT-associated FTD is associated with a characteristic pattern of bilateral symmetrical atrophy of the medial temporal lobes with an anterior gradient, and atrophy of the frontal cortices. This pattern of atrophy often causes semantic as well as behavioural problems, and as such, those with MAPT mutations often display a characteristic neuropsychological profile of profound anomia, semantic deficits, and executive dysfunction(Rohrer et al., 2010). Over 45 mutations are currently described in the MAPT gene (Rohrer and Warren, 2011).

1.2.1.2.2.   GRN

The most common clinical diagnosis of those with a GRN mutation is bvFTD and progressive nonfluent aphasia PNFA (Chen-Plotkin et al. 2011). Mutations in GRN are characterised neuroanatomically by marked asymmetry of atrophy in the non-dominant hemisphere of the temporo-parietal junction and parietal cortices relative to the dominant hemisphere, with more frontal and temporal involvement as the disease progresses (Rohrer et al., 2010b). There are over 70 GRN mutations currently described, and these account for only a small proportion of cases (Rohrer, 2011).

1.2.1.2.3.   C9ORF72

A hexanucleotide repeat expansion of C9ORF72 is the most recently described pathogenic mutation within the FTD clinical literature. C9ORF72 mutations are estimated to account for up to 11% of familial FTD, and up to 40% of familial amyotrophic lateral sclerosis (ALS). This pathogenic expansion is characterised by depositions of TDP-43 (DeJesus-Hernandez et al., 2011). This mutation causes the loss of one or more alternatively spliced transcript(s) of unknown function and the formation of nuclear RNA foci, suggesting multiple disease mechanisms (DeJesus-Hernandez et al., 2011; Arighi et al., 2012). Wild-type alleles contain no more than 23–30 repeats, whereas mutated alleles have hundreds to thousands of repeats. A relationship between expansion length and disease penetrance and phenotype is yet to be defined. Further investigation into the neuroanatomical signature of C9ORF72 – defined FTD needs to be carried out, however preliminary investigation suggests the greatest loci of change within this clinical subgroup to be within the cerebellum, with atrophy of the parietal and frontal cortices also apparent (Mahoney et al., 2013).

1.2.1.3.   Clinical diagnostic criteria for FTLD

1.2.1.3.1.   Behavioural variant FTD (bvFTD)

bvFTD is a clinical FTD syndrome characterised by a progressive deterioration of personality, social comportment, and cognition (Rascovsky et al., 2011). The International consensus criteria for bvFTD (see Table 1) offer three possible levels of diagnostic certainty; i) definite bvFTD, which can only be established by post-mortem or biopsy histopathological examination, or by the presence of a known pathogenic mutation ii) probable bvFTD, which is made upon fulfilment of a certain set of criteria established by clinical and neuropsychological examination, functional decline, and the presence of frontal and/or atrophy on MRI, and iii) possible FTD, whereby one meets a number of specific behavioural and neuropsychological criteria. Exclusion criteria are that the pattern of deficits observed must not be better accounted for by other non-degenerative medical or psychiatric disorders, nor can there be a presence of biomarkers strongly indicative of AD or any other neurodegenerative disease.

Table 1. International consensus criteria for a diagnosis of bvFTD (Rascovsky et al., 2011)

International consensus criteria for bvFTD
I. Neurodegenerative disease
The following symptom must be present to meet criteria for bvFTD
A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).
II. Possible bvFTD
Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent
A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
A.1. Socially inappropriate behaviour
A.2. Loss of manners or decorum
A.3. Impulsive, rash or careless actions
B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
B.1. Apathy
B.2. Inertia
C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
C.1. Diminished response to other people's needs and feelings
C.2. Diminished social interest, interrelatedness or personal warmth
D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
D.1. Simple repetitive movements
D.2. Complex, compulsive or ritualistic behaviours
D.3. Stereotypy of speech
E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:

E.1. Altered food preferences
E.2. Binge eating, increased consumption of alcohol or cigarettes
E.3. Oral exploration or consumption of inedible objects
F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following
symptoms (F.1–F.3) must be present]:
F.1. Deficits in executive tasks
F.2. Relative sparing of episodic memory
F.3. Relative sparing of visuospatial skills
III. Probable bvFTD
All of the following symptoms (A–C) must be present to meet criteria.
A. Meets criteria for possible bvFTD
B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
C.1. Frontal and/or anterior temporal atrophy on MRI or CT
C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT
IV. Behavioural variant FTD with definite FTLD Pathology
Criterion A and either criterion B or C must be present to meet criteria.
A. Meets criteria for possible or probable bvFTD
B. Histopathological evidence of FTLD on biopsy or at post-mortem
C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD
Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD
A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
B. Behavioural disturbance is better accounted for by a psychiatric diagnosis
C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

1.2.1.3.2.   Primary Progressive Aphasia (PPA)

The consensus criteria for PPA stipulate that establishing an accurate clinical
diagnosis involves a two-step process, by which patients should first meet basic
PPA criteria (Mesulam, 2001) and then be further sub-classified according to sub-
classification clinical diagnostic criteria (Gorno-Tempini et al., 2011). In order to
meet current consensus criteria for a diagnosis of PPA, one must answer
positively to: i) most prominent clinical feature is difficulty with language, ii)
these deficits are the principal cause of impaired daily living activities, and iii)
aphasia should be the most prominent deficit at symptom onset and for the initial
phases of disease. Exclusion criteria are that one must answer negatively to the
following: i) pattern of deficits is better accounted for by other non-degenerative
nervous system or medical disorders, ii) cognitive disturbance is better
accounted for by a psychiatric disturbance, iii) prominent initial episodic
memory, visual memory and visuoperceptual impairment, iv) prominent, initial
behavioural disturbance. If these criteria are met, one is further diagnosed
according to the following PPA syndromic diagnostic criteria. There are three
levels of diagnostic certainty for each of the syndromic PPA variants: i) clinical
diagnostic criteria, ii) imaging-supported diagnosis, iii) definite pathological
diagnosis.

1.2.1.3.3.   Semantic variant PPA (Semantic Dementia, SD)

The consensus criteria for a diagnosis of SD are presented in Table 2. This
disorder is defined by poor confrontation naming and impaired single-word

comprehension. In order to meet clinical diagnosis, both of these must be present, in conjunction with a number of other behavioural features. Imaging must show predominant anterior temporal lobe atrophy on MRI or hypoperfusion or hypometabolism in this area on single-photon emission computed tomography (SPECT) or positron emission tomography (PET). Histopathological evidence of specific neurodegenerative pathology (i.e. FTLD-tau, FTLD-TDP, other) or the presence of a known pathogenic mutation is needed for definite diagnosis.

Table 2. Diagnostic features of semantic dementia (Gorno-Tempini et al., 2011)

Diagnostic features of semantic variant PPA
I. Clinical diagnosis of semantic variant PPA
Both of the following core features must be present:
1. Impaired confrontation naming
2. Impaired single-word comprehension
At least 3 of the following other diagnostic features must be present:
1. Impaired object knowledge, particularly for low frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)
II. Imaging-supported semantic variant PPA diagnosis
Both of the following criteria must be present:
1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one or more of the following results:
a. Predominant anterior temporal lobe atrophy
b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET
III. Semantic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of semantic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLDTDP, AD, other)
3. Presence of a known pathogenic mutation

1.2.1.3.4. Nonfluent variant PPA (Progressive Non Fluent Aphasia, PNFA)

The consensus criteria for a diagnosis of progressive nonfluent aphasia are presented in Table 3. PNFA is characterised by agrammatism in language production and effortful, halting speech with inconsistent speech sound errors and apraxia of speech. In order to meet clinical diagnosis, both of these must be present, in conjunction with a number of other behavioural features. Imaging must show predominant left posterior fronto insular atrophy on MRI or hypoperfusion or hypometabolism in this area on SPECT or PET. Histopathological evidence of specific neurodegenerative pathology (i.e. FTLD-tau, FTLD-TDP, other) or the presence of a known pathogenic mutation is needed for definite diagnosis.

Diagnostic features for the nonfluent/agrammatic variant of PPA
I. Clinical diagnosis of nonfluent PPA
At least one of the following core features must be present:
1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)
At least 2 of 3 of the following other features must be present:
1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge
II. Imaging-supported nonfluent/agrammatic variant diagnosis
Both of the following criteria must be present:
1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
a. Predominant left posterior fronto-insular atrophy on MRI or
b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET
III. Nonfluent/agrammatic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLDTDP, AD, other)
3. Presence of a known pathogenic mutation

1.2.1.3.5. Logopenic variant PPA (LPA)

The consensus criteria for a diagnosis of logopenic variant PPA are presented in Table 4. LPA is the most recently described of the PPA syndromic variants and is characterised by impaired single-word retrieval in spontaneous speech and naming, and impaired repetition of sentences and phrases. In order to meet

clinical diagnosis, both of these must be present, in conjunction with a number of other behavioural features. Imaging must show predominant left posterior perisylvian or parietal atrophy on MRI or hypoperfusion or hypometabolism in this area on SPECT or PET. Histopathological evidence of specific neurodegenerative pathology (i.e. AD, FTLD-tau, FTLD-TDP) or the presence of a known pathogenic mutation is needed for definite diagnosis.

Table 4. Diagnostic criteria for the diagnosis of logopenic aphasia (Gorno-Tempini et al., 2011)

Diagnositic criteria for logopenic variant PPA
I. Clinical diagnosis of logopenic variant PPA
Both of the following core features must be present:
1. Impaired single-word retrieval in spontaneous speech and naming
2. Impaired repetition of sentences and phrases
At least 3 of the following other features must be present:
1. Speech (phonologic) errors in spontaneous speech and naming
2. Spared single-word comprehension and object knowledge
3. Spared motor speech
4. Absence of frank agrammatism
II. Imaging-supported logopenic variant diagnosis
Both criteria must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results:
a. Predominant left posterior perisylvian or parietal atrophy on MRI
b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET
III. Logopenic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2
or 3 must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. AD, FTLD-tau, FTLD-TDP, other)
3. Presence of a known pathogenic mutation

1.2.2. Alzheimer's disease (AD)

1.2.2.1. Pathology

AD is characterized by two neuropathological hallmarks: extracellular deposits of amyloid (Aβ plaques) and intracellular neurofibrillary tangles (Braak and Braak, 1991). AD is characterized by a marked loss of neurons and synapses in many areas of the central nervous system, particularly in areas such as the basal forebrain and hippocampus. This neuronal loss is accompanied by gross atrophy.

1.2.2.2. Clinical diagnostic criteria for AD

AD is most commonly characterized by an insidious onset of memory impairment which progresses to involve multiple cognitive domains (McKhann et al., 1984). This amnestic presentation is in accordance with histopathological evidence for early medial temporal lobe involvement described above. The NINCDS-ADRDA criteria offer three categories of diagnostic certainty for AD: i) definite AD, which can only be established by post-mortem or biopsy examination; ii) probable AD, which is made upon fulfilment of a certain set of criteria established by clinical and neuropsychological examination, and iii) possible AD when there is an atypical onset, presentation or progression, without a known aetiology, and absence of co-morbid diseases capable of producing dementia (McKhann et al., 2011). Research criteria (Dubois et al., 2007) stipulate that a diagnosis of AD can be made when a patient presents with memory impairment and has supportive evidence of one of the following: medial temporal lobe atrophy from structural imaging, reduced glucose metabolism in bilateral temporal parietal regions on PET, or markers of pathology including evidence of amyloid deposition using

either PET imaging (Klunk et al., 2004) or reduced amyloid and increased tau levels obtained from a cerebrospinal fluid (CSF) sample.

1.3. CHAPTER CONCLUSION

This chapter has summarized the pathological, neuroimaging, neuropsychological, genetic, and clinical hallmarks of the key dementias of interest to this thesis, with particular focus on the syndromic variants of FTD. The following chapter will provide a more detailed summary of the behavioural and neuroimaging hallmark features of bvFTD in line with the primary aims of this thesis.

2. BEHAVIOURAL AND NEUROIMAGING FEATURES OF bvFTD

2.1. Chapter introduction

This chapter will focus on the behavioural and neuropsychological features of bvFTD and their neuroanaotmical correlates. bvFTD is primarily characterised by gross dysfunction within the areas of executive processing and social function (Rascovsky et al., 2011), and as such, this chapter will focus on investigating these two areas of cognition. In addition, the recent discovery of the C9ORF72-associated FTD has brought to light the unusual and unique phenotype of psychosis. As bvFTD is the most common phenotype of c9ORF72-associated FTD, this chapter will also explore the manifestation of psychosis in this population.

The function of neuropsychology within the context of neurodegenerative disease is to clinically assess cognitive function in order to characterise disease-specific cognitive phenotypes. This is useful in order to assess whether any cognitive decline is apparent from pre-morbid estimates or previous assessment, to measure any decline over time, and to qualitatively characterise clinical phenotypes of disease. Indeed, each of the consensus criteria for FTLD is based primarily upon neuropsychological characteristics (see Tables 1-4). In the consensus criteria for PPA (Gorno-Tempini et al., 2011), the authors include a table of psychological tasks to assess disease-specific phenotypic features to aid diagnostic certainty (see Table 5).

Table 5. Tasks that may be used to assess speech and language function in PPA (*Taken from* Gorno-Tempini et al., 2011)

Speech/language function	Task	Behavioral measures	Variant in which impaired
Speech production			
Grammar	Picture description task; story retelling (e.g., picture aided); constrained-syntax sentence production task	Grammatical structure; mean length of utterance; speech rate; accuracy of content; melody; prosody; specific error types in word selection; articulation	Nonfluent/agrammatic variant
Motor speech	Motor speech evaluation, including multiple repetitions of multisyllabic words; diadochokinesis of speech articulators; spontaneous speech	Effortfulness; hesitations; presence of apraxia of speech or dysarthria; specific types of speech sound errors; factors that affect articulation (e.g., word length in syllables)	Nonfluent/agrammatic variant
Confrontation naming	Single-word retrieval in response to pictures, sounds, foods, and odors	Error rate; delay in naming; factors that affect naming accuracy (e.g., familiar vs unfamiliar items, nouns vs verbs, semantic category); error types (e.g., semantic errors, phonemic errors)	Severe deficit in semantic variant with semantic errors; moderate impairment in logopenic variant with phonemic errors
Repetition	Oral repetition of words, pseudowords, phrases, and sentences	Factors that affect repetition accuracy (e.g., predictability of the phrase, sentence length, grammatical complexity); error types	Logopenic variant with phonological errors
Sentence comprehension	Matching orally presented sentences to pictures; answering yes/no questions; following directions	Factors that affect comprehension (e.g., grammatical complexity; reversibility of the sentence, e.g., The boy was kicked by the girl vs The ball was kicked by the girl)	Nonfluent/agrammatic variant, effect of grammatical complexity; logopenic variant, length and frequency effect
Single-word comprehension	Word-to-picture matching; Word-to-definition matching; Synonym matching	Factors that affect comprehension (e.g., familiarity; frequency; grammatical word class)	Semantic variant
Object/people knowledge	Picture-picture matching; odd-one-out; semantic associations; gesture-object matching; sound-picture matching	Factors that affect object knowledge (e.g., familiarity, semantic category)	Semantic variant
Reading/spelling	Lists including regular and irregular word lists, from various word classes, matched for other factors; pseudowords matched to words in length	Factors that affect reading/spelling accuracy (e.g., regularity, frequency, word class); error types (e.g., regularization, phonologically plausible errors; articulatory distortions)	Semantic variant with "regularization" errors; logopenic variant phonologic errors

Neuroimaging and neuropsychology work in tandem to inform our understanding of specific neural correlates to neuropsychological performance. Indeed, analysis of group-wise structural imaging has allowed novel insight into the neurological bases for different neuropsychological phenotypes of dementia. Elucidating the neural correlates for such phenotypes may prove highly useful in being able to better understand and potentially treat different clinical syndromes. Many different analysis techniques for correlating neural structures with performance are emerging, which allow us to examine not only the implicated grey matter structures, but the networks or white matter fiber pathways that connect them.

One of the primary difficulties presented in the study and understanding of FTD is the clinical, neuroimaging, pathological, and neuropsychological heterogeneity of the FTD-associated clinical syndromes. In the last decade, this disease has been broken-down into behavioural and language phenotypes, and more recently, the language phenotype has been further sub-classified into three dissociable aphasic phenotypes. A number of clinical research groups within the field have recently proposed that the behavioural phenotypes may be further sub-classified on the basis of clinical phenotype into apathy or disinhibition, or by differing neuroimaging phenotypes (Josephs et al., 2011). While such extensive sub-classification may prove more confusing than useful, understanding atypical forms of FTD and the factors driving the heterogeneity in this disease may lead to a better understanding of FTD as a whole, and will improve the support, care and education that can be given to the patients, carers and healthcare professionals. This chapter describes the clinical, pathological, epidemiological, genetic and

neuropsychological characteristics of the main dementias assessed in this thesis, and the utility of neuroimaging and neuropsychology in informing our knowledge of these.

This chapter will focus on summarising the neuropsychological and behavioural features of bvFTD by reviewing the literature relating to the most commonly reported areas of neuropsychological and behavioural dysfunction in this population and the neural correlates of these.

2.2. Social cognition

Social cognition broadly defined as the ability to meaningfully understand and engage in social interaction, is a multi-dimensional and still poorly understood aspect of human brain function (Zahn et al., 2007; Adolphs 2009; Kennedy & Adolphs 2012). It typically entails emotional, semantic, mnestic and evaluative processing of sensory signals, and specialised brain systems underpinning social cognition have been inferred from evidence in both the healthy brain and in disease states, suggesting that it might be a useful paradigm for detecting and tracking the clinical course of diseases in the FTLD spectrum. Indeed, the multi-dimensionality of social cognition is reflected in the diverse deficits described in bvFTD, including emotion recognition (Kipps et al., 2009b; Rosen et al., 2005; Omar et al., 2011), empathic concern and perspective taking (Rankin et al., 2006; Eslinger et al., 2011; Lough et al., 2006), perception of humour and sarcasm (Snowden et al., 2003; Kosmidis et al., 2008; Kipps et al., 2009b), and affective decision making (Torralva et al. 2007).

Whilst SD is more commonly conceptualised as a pervasive degradation of semantic knowledge, a disruption in normal social functioning is increasingly being reported within this population (Rankin et al., 2009; Duval et al. 2012). Formal investigation into social functioning within the context of SD in recent years has revealed significant under-functioning within the domains of theory of mind and attribution of intention (Duval et al., 2012), and detection of sarcastic intent (Rankin et al., 2009). Indeed, Rankin and colleagues (2009) observed a

significant impairment in the ability of those with SD to interpret simple sarcastic statements above that observed in those with bvFTD, and more interestingly, that this deficit was independent of language deterioration. The overlapping phenomenology of interpersonal difficulties exhibited by patients with bvFTD and SD might reflect underlying brain substrates that are at least partly shared: this in turn would be consistent both with profiles of regional brain damage in these syndromes (McGinnis, 2012; Warren et al., 2013) and with functional imaging evidence in the healthy brain, implicating distributed neural networks including ventro-medial prefrontal cortex, orbitofrontal cortex and anterior temporal lobes in processing social signals and programming social behaviours (Zahn et al., 2007; Adolphs, 2009; Carrington & Bailey, 2009).

2.2.1. Theory of mind (ToM)

Theory of mind (ToM), defined as the ability to represent others' mental states (Frith & Frith, 2000), is one of the primary cognitive skills required in order to meaningfully engage in social interaction. This complex cognitive function requires the representation, analysis and integration of a variety of social signals. ToM capacity can be further subclassified as ToM for the attribution of beliefs and intentions ('cognitive' ToM) and ToM for the attribution of feeling states ('affective' ToM), though these separable capacities frequently interact in everyday life (Poletti et al., 2012). Widely used tests of theory of mind such as the 'Mind in the Eyes' task (Baron-Cohen et al., 2001) largely index affective ToM using stimuli derived from other humans, however it has been repeatedly shown that intentionality can be attributed even to abstract, inanimate stimuli (e.g:

cartoon shapes: Castelli et al., 2000; Blakemore et al., 2004). Neuroimaging studies in healthy individuals have linked ToM with a network of brain regions, in particular ventro-medial PFC and frontal pole, OFC (Gallagher and Frith, 2003; Carrington and Bailey, 2009; Moll et al., 2011) and the anterior temporal lobes (Fumagalli and Priori, 2012).

The study of disease states potentially allows identification of brain areas critical for ToM. Impaired ToM occurs on a developmental basis as a hallmark of autism (Baron-Cohen et al., 1985; Baron-Cohen et al., 1999) and may also develop in association with a variety of focal brain lesions (Martin-Rodriguez and Leon-Carrion, 2010). Deficits of ToM in neurodegenerative disease have attracted much recent attention and on clinical and neuroanatomical grounds may be particularly relevant to bvFTD (Schroeter, 2012). Patients with bvFTD frequently have difficulty with aspects of social cognition that are likely to be relevant to ToM, including emotion recognition (Kipps et al., 2009b; Rosen et al., 2005; Omar et al., 2011), empathic concern and perspective taking (Rankin et al., 2006; Eslinger et al., 2011; Lough et al., 2006), and perception of humour and sarcasm (Snowden et al., 2003; Kosmidis et al., 2008; Kipps et al., 2009b). A specific ToM deficit may be an early feature of bvFTD (Adenzato et al., 2010; Gregory et al., 2002) and neuroanatomical substrates for this deficit have been proposed. bvFTD is associated with disintegration of a distributed neural network including anterior cingulate, insula, medial PFC and OFC (Seeley et al., 2007); (Zhou et al., 2010; Zhou et al., 2012; Raj et al., 2012) that overlaps brain areas previously implicated in ToM (Gallagher and Frith, 2003;Carrington and Bailey, 2009). Impaired ability to experience social emotions has been linked to frontopolar damage in bvFTD

(Moll et al., 2011). In addition, bvFTD is often associated with damage involving anterior temporal lobe regions that represent social concepts underpinning normal mentalising (Zahn et al., 2009a): these anterior temporal areas interact with medial PFC during moral reasoning (Fumagalli and Priori, 2012), while anterior temporal lobe damage has been implicated in the pathogenesis of cognitive and affective ToM deficits in another FTD syndrome, semantic dementia (Duval et al., 2012).

2.2.2. Neurobiology of social cognition

Elucidating the neurobiological bases to social cognitive impairment has received much attention in recent years. While functional imaging studies in healthy individuals provide invaluable information about the brain areas implicated within normal operation of social conduct, neurological diseases that selectively target predictable brain regions, such as in frontotemporal dementia, provide a unique and important opportunity to investigate key structures and their dissociable roles within a larger social-cognitive framework. There exists some debate as to which neural structures are important for particular aspects of social functioning, however general consensus indicates that the medial prefrontal, orbitofrontal, and anterior temporal structures are pertinent to normal social cognition (Adenzato et al., 2010; Abu-Akel and Shamay-Tsoory; Schroeter et al., 2008). Lateralization to the right hemisphere is also commonly reported (Zahn et al., 2009b; Zahn et al., 2007; Rankin et al., 2006; Seeley, 2011). The orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) appear to be a central to the cognitive interpretation of incoming social information (Kipps et al., 2009b;

Murphy et al., 2009; Schroeter et al., 2008), while anterior temporal structures are commonly conceptualised as key stores of social conceptual knowledge (Zahn et al., 2009b; Zahn et al., 2007; Duval et al., 2012). Rankin and colleagues (2009) have recently proposed that within the unique social context of sarcasm perception, the bilateral temporal lobes, and in particular the parahippocampal gyri, and the temporal poles, as well as the superior frontal gyrus, are all important. It is well known that the temporal poles have strong bidirectional connections with the mPFc and the OFC (Kondo et al., 2003), and thus it is more than likely that the ability to disentangle social concepts is subserved by a richly interconnected network of fronto-temporal structures (Saxe et al., 2006; Seeley et al., 2008; Abu-Akel and Shamay-Tsoory, 2011).

Neuroimaging studies in healthy individuals have linked the ability to mentalise, broadly defined as the cognitive capacity by which we interpret the behaviour of oneself and others in terms of mental states (Frith and Frith, 2003), with a network of distributed brain regions, in particular ventro-medial PFC and frontal pole, OFC (Gallagher and Frith, 2003; Carrington and Bailey, 2009; Moll et al., 2011), and the anterior temporal lobes (Fumagalli and Priori, 2012; see 2.2.1 for further details). In their recent meta analyses, Abu-Akel and Shamay Tsoory (2011) propose that mental states are first detected by the TPJ (Saxe et al., 2006; Abu-Akel and Shamay-Tsoory, 2011), which creates representations to be relayed though the superior temporal sulcus (STS) of the paracingulate cortex (PCC) to limbic and paralimbic regions for the emotional input and integration of that emotional input with incoming parasensory information. Seeley and colleagues (2008) highlight the role of such an anterior paralimbic frontal-subcortical

network as crucial for the processing of emotional stimuli in healthy individuals, and suggest that this is selectively damaged in bvFTD. These authors also illuminate the role of the Von Economo neurons (VEN), which have been identified as integral to social functioning, and the selective degradation of these in those with bvFTD, which may leave the social cognition network vulnerable within this disease. bvFTD is associated with disintegration of a distributed neural network including anterior cingulate, insula, mPFC and OFC (Seeley et al., 2007)(Zhou et al., 2010; Zhou et al., 2012; Raj et al., 2012) that overlaps brain areas previously implicated in ToM (see 2.2.1; Gallagher and Frith, 2003; Carrington and Bailey, 2009). Furthermore, bvFTD has been demonstrated to be vulnerable to selective degradation of the so called 'emotional salience network' (Zhou et al., 2010; Seeley et al., 2007, 2009), which is proposed to comprise of a functionally interconnected network subserving frontal and anterior temporal structures and serves as a critical network to support social-emotional processing, and mirrors the atrophy pattern seen in bvFTD (Seeley et al., 2011). In light of this, social cognitive deficits within the context of FTD, and in particular bvFTD, can be attributed to a large-scale neural network encompassing orbitofrontal, medial frontal, superior temporal regions (Eslinger et al., 2007).

2.3. Executive function

Executive function can be defined as the ability to maintain an appropriate problem-solving set for attainment of a future goal (Welsh and Pennington, 1988). This cognitive capacity is classically assessed using tasks that require behavioural inhibition and control. There exists a reciprocal relationship between social cognition and the executive process of cognitive control, whereby one must

engage in cognitive control in order to flexibly adapt behavior toward social goals (Dumontheil et al., 2012), and both processes are mediated to some extent by the prefrontal cortices, an area commonly targeted by FTLD pathology (Seeley et al., 2008). Deficits in executive functioning represent one of the neuropsychological hallmarks of FTD. Such executive dysfunction is most prominent in bvFTD, and to a lesser extent, SD, and is at least partially responsible for the clinical characteristic of behavioural disinhibition that defines the clinical phenotype specific to this disease subtype.

Dysfunctions in executive processes in FTD, and in particular bvFTD, have been widely reported (Hornberger et al., 2008; Snowden et al., 2003; Lough et al., 2001; Gregory et al., 2002; Kipps and Hodges, 2006; Rabinovici et al., 2007). Widespread deficits in executive capacities have also been well-described in Alzheimer's disease (Stopford et al., 2012; Perry and Hodges, 2000; Baddeley et al., 2001), and many studies indicate that the two clinically- and pathologically-distinguishable disorders cannot be distinguished solely on the basis of performance in traditional executive function tasks (Stopford et al., 2012; Grossi et al., 2013; Nedjam et al., 2004), although this is not uniformly argued (Hornberger et al., 2010; Pachana et al., 1996). Indeed, Perry and colleagues (2000) propose executive and attentional deficits to be primary features of Alzheimer's disease, and evidence is mounting to suggest that executive deficits may be predictive preclinical features of AD (Albert et al., 2001). Neuroanatomically, Alzheimer's pathology targets medial temporal structures including the hippocampus and entorhinal cortex (Dubois et al., 2007). However recent research utilising advances in nuclear medicine suggests that pathological

depositions of amyloid are widespread within the frontal cortex in Alzheimer's

disease (Rowe et al., 2010; Klunk et al.), and furthermore, that this occurs early

within the disease (Rowe et al., 2010; Klunk et al., 2004). These two syndromes

represent quite phenotypically- and pathologically-distinct entities, but clinical

confusion and misdiagnosis remain a problem, highlighting the necessity of more

sensitive behavioural measures.

Recently, it has been suggested that FTLD may selectively target a large-scale

brain network including prefrontal cortex (PFC) and connecting WM pathways

(Seeley et al., 2007, 2012; Zhou et al., 2010, 2012; Raj et al., 2012; Mahoney et al.,

2013; Agosta et al., 2012). It is highly likely that frontotemporal and

frontoparietal grey matter regions and the connecting white matter pathways

implicated in the pathogenesis of FTD are also important to subserving aspects of

executive function such as task switching. Translation from functional imaging

studies in healthy adults to clinical findings is not always transparent, and

confirmatory convergences with findings in organic lesions models, such as that

represented by FTD, should clarify the significance of proposed theoretical

models proposed through image analysis and is the primary avenue for

understanding the true relevant consequences for a clinical population.

2.3.1. Task switching

One commonly-examined executive function that is of particular relevance to the

work presented in this thesis is that of task switching, which involves the ability

to cognitive shift between attention or task sets (Friedman et al., 2008). This

behaviour is proposed to require one to develop a stimulus-specific task-set, and continually re-configure and adapt, or 'switch', this task-set in order to engage with changing, or conflicting stimuli input (Aron et al., 2004). Many theoretical accounts as to the cognitive basis of task-switching exist, however the most influential stems from the supervisory attention system model of Norman and Shallice (1986), which has been incorporated and expanded into the model by the same name proposed by Stuss and Alexander (Stuss and Alexander, 2007). This model purports three primary processes in which one engages in executive functioning: energisation, whereby one initiates and sustains a response; monitoring of performance; and task-setting, in which one defines stimulus-response contingencies. Each of these processes has been associated with regionally-specific areas of the frontal lobe, such that energisation is proposed to be dependent upon superior medial areas (Stuss and Alexander, 2007; Alexander et al., 2005; Alexander et al. 2007; Picton et al. 2007; Stuss, 2011), monitoring is purported to require right lateral engagement (Alexander et al. 2007; Stuss et al., 2007; Stuss, 2011; Picton et al., 2007), and task-setting is proposed to be left-lateral dependent (Alexander et al., 2007; Stuss, 2011). Based on this evidence, Stuss (2011) proposes an executive function network, in which a dorsolateral circuit which projects to basal ganglia structures, is responsible for mediating the executive processes of task setting and monitoring, and a more superior medial circuit mediates energisation of performance. Such a model proposes key cortical and subcortical nodes within a flexible and dynamic network, whereby damage to any one node could cause variable deficit within the realm of executive functioning.

2.3.2. Neurobiological bases to task switching

Neuroantomical associations have been derived primarily from lesion studies and functional imaging experiments in healthy adults. Frontal lesion and functional imaging studies generally converge to suggest that the right inferior frontal cortex is important for inhibiting previous stimulus-response contingencies (Aron et al., 2003; Aron and Verbruggen, 2008), whereas the left medial frontal gyrus is important for setting task-set contingencies and engaging in top-down control (Aron et al., 2003; Aron and Verbruggen, 2008; Vallesi et al., 2007; Monsell, 2003). Right-lateralised superior medial areas, including the anterior cingulate cortex (ACC), supplementary motor area (SMA), and pre-SMA, and lateral areas, including the dorsolateral prefrontal cortex (DLPFC),have also been highlighted as imperative to normal task-switching ability (Stuss, 2011; van Veen et al., 2001; Picton et al., 2006). While distinct roles for each hemisphere in the process of task-switching have been proposed, it is likely that this complex behaviour requires bilateral recruitment of ventrolateral and superior medial frontal areas.

Although many studies have demonstrated associations between grey matter integrity and the ability to meaningfully engage in task-switching behaviour, fewer studies have examined the relationship between white matter microstructure and executive function. It is highly likely that rather than being subserved by single anatomical regions, executive functions such as task switching rely on a network of preferentially involved cortical and subcortical regions. Limited research into the relationship between white matter

microstructure and executive function suggest that frontoparietal pathways such as the corona radiata may be important (Aron et al., 2007). In a study examining cognitive control using a stop-signal task, Aron and colleagues used diffusion-weighted MRI to show that the inferior frontal cortex and sub thalamic nucleus are connected via a WM pathway that also connects these regions to the pre-SMA (Aron et al., 2007). These results were supported in the same study using a functional imaging paradigm and led to authors to suggest that a functional anatomical network in the right hemisphere may be responsible for braking or stopping an action. In another study, Seghete and colleagues (Seghete et al., 2013) examined the WM correlates of executive tasks in adolescents using DTI and concluded that greater FA and lower MD in the ACR, SCR, and precentral gyrus were associated with better task-switching performance. This was supported by recent research in patients with traumatic brain injury, in which FA in the SCR was correlated with switch task performance (Leunissen et al., 2013). Other research suggests task switching to be broadly mediated by frontoparietal WM (Gold et al., 2010). Further work needs to be done in order to more fully elucidate which WM tracts are necessary in the execution of efficient task-switching.

2.4. Psychosis

While dysfunction in social cognition and executive function are by far the most widely reported neuropsychological features of bvFTD, the discovery of the FTD mutation on C9ORF72 highlighted a novel and highly interesting genotype-phenotype relationship unique to FTD-affected carriers of this gene, of which bvFTD is the most common syndromic diagnosis. Perhaps the most interesting

phenotypic manifestation of C9ORF72-associated FTD to have been identified is that of psychosis. The presence of psychotic features in C9ORF72 carriers has been estimated to be anywhere from 38% in a UK cohort (Snowden et al., 2012b), to up to 56% in an Australian cohort (Dobson-Stone et al., 2012). This has been reported by a number of research groups (Mahoney et al., 2012a; Galimberti et al., 2013; Larner, 2013; Arighi et al., 2012), and appears highly selective to C9ORF72 carriers. It has been suggested that the presence of psychosis within the context of FTD dramatically increases the chance of carrying a C9ORF72 mutation (Floris et al., 2012), suggesting the characterisation of psychotic features as a valuable diagnostic tool. Psychotic delusions documented in patients with C9ORF72 mutations appear to be reminiscent of those observed in disorders such as schizophrenia, including delusions of persecution and aberrant self-perception (Mahoney et al., 2012a; Snowden et al., 2012b; Larner, 2013; Floris et al., 2012; Takada and Sha, 2012). The apparent specificity of this psychosis to C9ORF72-defined FTD raises the question of its unique neuroanatomical and neurobiological bases.

Although detailed neuroanatomical-phenotypic correlation has yet to be undertaken in the C9ORF72 mutation spectrum, a cortico-thalamo-cerebellar network has been identified as a potential substrate for certain clinical features, in particular, for neuropsychiatric symptoms (Mahoney et al., 2012a; Mahoney et al., 2012b). Snowden and colleagues (2012) describe a number of cases in which psychotic experiences in their sample of C9ORF72 cases appear to be self-referent in nature, including experiences of parasitosis, delusions of plastic objects stemming from one's skull, and feeling of loss of anal muscular control.

Another case study describes delusions of pregnancy (Larner, 2013). Aberrant self-schema representation has been consistently implicated in the pathogenesis of psychotic disorders (Blakemore et al., 2003; Blakemore et al., 2000; Frith et al., 2000; Synofzik et al. 2008), and the nature of the psychotic disturbances observed in C9ORF72 cases suggests that such self-schema aberrations may also play a causative role in the phenomena in these carriers.

From a pathophysiological perspective, the neuropsychiatric features of C9ORF72-FTD might be interpreted as arising from aberrant body (or self) schema processing. The concept of 'body schema' was first defined by Head and Holmes (1911) as the internalised, combined postural and spatial model of ourselves that provides a standard against which sensory changes can be calibrated and incorporated. These authors proposed a number of key properties that the body schema should possess, including multiplicity (representation in more than one sensory modality), hierarchy (differential engagement of attention and conscious awareness according to circumstances) and plasticity (continual updating by sensory experience). Head and Holmes further emphasised the key role of the somatosensory cortex and its interactions with subcortical structures (including thalamus and cerebellum) in the physiology and pathophysiology of the body schema. The concept has since been extensively studied and has become widely accepted by neurophysiologists, neurologists and psychiatrists (for example, (Goodwin et al., 1972; Lackner, 1988; Botvinick and Cohen, 1998; Blakemore et al., 2000; Creem-Regehr et al., 2007; Goble, 2010; Hauser et al., 2011; Moseley et al., 2012). Body schema processing and self / non-self differentiation are closely related perceptual and cognitive operations:

disambiguation of self from non-self frequently depends on stable and accurate body schema boundaries, modulated by the effects of one's own and external actions.

Altered body schema processing has been implicated in the pathogenesis of somatising symptoms (Miles et al., 2011), anxiety (Paulus and Stein, 2010), psychotic disorders and altered states of bodily awareness (Blakemore et al., 2000; Blakemore et al., 2003; Frith et al., 2000; Synofzik et al., 2008). The culprit cortico-thalamo-cerebellar network implicated in neuroimaging and neuropathological studies of C9ORF72-FTD is a potential substrate for the neuropsychiatric symptoms exhibited by these patients (Mahoney et al., 2012).

Neuroimaging research investigating various components of self-referent information processing, and in particular, ascription of agency to action, has implicated the cerebellum ,parietal lobes, and right prefrontal cortex (Jeannerod, 2009; Frith et al., 2000; Blakemore et al., 2000, Blakemore et al., 2003) as potential loci subserving this ability, suggesting the possibility of a 'self-other differentiation' network. The cortical components of this network have been specifically implicated in a range of phenomena associated with body schema alteration or distortion in health and disease states (Naito et al., 1999; Creem-Regehr et al., 2007; Moseley et al., 2012), consistent with the concept of multiple sensory and homeostatic representations that together must be integrated into a coherent 'body matrix'.

These structures represent a constellation of the atrophic regions targeted by C9ORF72-FTD pathology (Whitwell et al., 2012; Mahoney et al., 2012a), which may then play a causative role in the psychotic symptoms observed in these patients. Blakemore and colleagues (2000, 2003) posit the ability to differentiate self from other as dependent upon forward-model of action attribution in which one must make predictions about the sensory consequences of action, compare incoming perceptual information with such a prediction, and then ascribe agency based upon this comparison. The cerebellum has been purported as a potential comparator within this model, as evidenced by neuroimaging studies in both healthy individuals and those with psychiatric dysfunction or neurological damage (see Jeannerod, 2009 for review). The parietal lobes have been highlighted as crucial to accurate interpretation of incoming somatosensory proprioceptive information and outgoing self-generated action (Jeannerod, 2009). Further investigation into such mechanisms may enable an increased understanding of the neuroanatomical bases to psychotic features observed in C9ORF72 carriers.

2.5. CHAPTER CONCLUSION

The use of neuropsychological and behavioural tasks within the context of FTD has proved highly useful in terms of diagnosis and disease classification. Tasks that are particularly sensitive to executive and social dysfunction are of the greatest utility in the diagnosis of bvFTD. Patients affected with this syndrome have shown to display pervasive dysfunction in these areas of cognition, which may be useful in differentiating those affected by bvFTD from other dementia

diseases, such as the primary progressive aphasias and AD, as well as from other non-degenerative mental-health disorders. Exploration of the features of psychosis within the context of those affected by a mutation in the C9ORF72 may also prove useful in terms of predicting this underlying genetic diagnosis.

3. METHODS OVERVIEW

3.1. Chapter introduction

This chapter provides a general overview of the participants and the methods used in the experiments presented in this thesis. Deviations from the procedures described here as well as relevant additional details are provided in the corresponding chapters.

3.2. Participants

3.2.1. Healthy controls

Neurologically-healthy participants without a family history of dementia were recruited as controls. These were both volunteers from the community, and spouses of affected individuals. Individuals had a detailed history taken and underwent neurological exam by a clinical neurologist and detailed neuropsychological examination by a research psychologist. If there was no evidence to suggest cognitive problems and no contraindications to MRI, participants underwent MR scanning. The spouses of study participants were usually assessed and scanned on the same day as their partners.

3.2.2. Patients

All clinically-affected participants had attended the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. This is a secondary/tertiary referral centre and consequently these individuals tend to represent younger patients and those in whom there is more

diagnostic uncertainty, compared with more typical older-age dementia presentations. The participants recruited from the clinic included patients with sporadic FTD, genetically-defined FTD, and sporadic AD. All patients underwent full clinical and neuropsychological assessment as part of their research assessment, as well as imaging. Each patient scan was reviewed by a team of neurologists, psychologists, and radiologists to determine the presence and location of cortical atrophy. A cognitive neurologist carried out the clinical examination, and neuropsychological assessment was carried out for all patients by a research psychologist. No patient had radiological evidence of a substantial concomitant vascular burden.

3.2.3. Genetically-proven cases

All patients were screened for pathogenic mutations in genes causing the FTD syndrome, comprising MAPT, GRN, PSEN1, PSEN2 and pathogenic expansions of C9ORF72. If a mutation in the MAPT or GRN gene had been established in the family, this was confirmed in the patient by Sanger sequencing of the specific exon. For the C9ORF72 hexanucleotide repeat, the presence of a large expansion was confirmed by repeat-primed PCR, and subsequently the size was approximated by Southern blot if sufficient DNA was available (methods described in Renton et al. 2011; Beck et al., 2013). In patients with sporadic disease the absence of a mutation in 17 genes causing dementia was confirmed by targeted next generation sequencing using the MRC dementia gene panel (Beck et al., 2013).

Of the patients included in this thesis, five patients were found to have pathogenic C9ORF72 expansions; of these, three had sufficient DNA for repeat size confirmation (3472, 3501 and 3600 base pairs respectively). A further seven patients had a pathogenic mutation in the MAPT gene (four exon10+16, two exon13 c.1212C>T; one novel presumptively pathogenic mutation c.1052A>G in exon12). All other patients were deemed to have sporadic disease due to the absence of known mutations.

3.2.4. Ethical issues

All participants gave written informed consent. No payment was given for participation in any research study; however reimbursement was given for any expense incurred during the visit, including travel and lunch costs.

3.3. Clinical assessment

All participants attending the Specialist Cognitive Disorders Clinic undergo comprehensive diagnostic evaluation. A full history is taken from the patient and (usually separately) from a close informant. A neurologist under the supervision of a consultant neurologist performed a full clinical assessment. This typically includes:

1) Standard screening blood tests to exclude other treatable causes of cognitive problems such as impaired renal or liver function, B12 and thyroid function.

2) EEG to exclude seizures, or identify patterns indicative of a particular type of dementia.

3) Neuroimaging, typically MRI, in order to exclude other treatable causes such as tumours and subdural haematomas and assess patterns of atrophy and vascular disease.

In addition to the routinely administered assessments above, patients may also undergo:

1) Genetic testing: in affected individuals with an age at onset or family history suggestive of an autosomal dominant inheritance, screening for known genetic mutations (AD or FTLD as appropriate) may be undertaken. In at-risk cases where individuals have a known mutation in their family, genetic testing may be offered to determine whether the participant is carrying the mutation. This is supported by a genetic counselling service.

2) Lumbar puncture and CSF analysis: this investigation may be used to detect evidence of inflammation and to measure neuron-specific proteins (tau and $A\beta 1$-42).

3.4. Neuropsychological assessment

All study participants, including patients and healthy controls, underwent a full neuropsychological investigation that was carried out by a single psychologist (L.E.D.). This battery of tests was identical for each participant and typically carried out in a single session over a period of roughly two and a half hours and consisted of the following: The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) - an abbreviated version of the Wechsler Adult Intelligence Scale, yielding a global measure of intelligence represented by a verbal and performance IQ score; The Recognition Memory Test for faces/words (RMT; Warrington, 1984) – which presents 50 faces/word with an orienting question,

after which the participant is presented with the target paired with an unfamiliar face/word and asked to judge which they have seen before. The British Picture Vocabulary Scale (BPVS; Dunn, Dunn & Whetton, 1982) - which tests comprehension of a picture stimulus with a non-verbal output whereby participants must match one of four pictures to a target word of increasing difficulty; The Graded Naming Test (GNT; McKenna & Warrington, 1983) - which requires participants to name line drawings that become increasingly less common; The Object Decision subtest of the Visual Object and Space Perception battery (VOSP; Warrington & James, 1991) – in which participants are asked to identify the silhouette of a 75 degree rotated real object from three nonsense silhouettes of similar complexity; Digit Span task (DS; Wechsler, 1987) - which was used to assess working memory by repeating number strings of increasing length; The D-KEFS Colour Word Interference Test (DKEFS Stroop; Delis, Kaplan & Kramer, 2001) - which is an adaptation of the Stroop test, where colour words are presented in a conflicting ink colour and participants are timed naming the colour of the ink for 50 of these words.

3.5. Patient inclusion Criteria

Patient diagnosis was determined by a consultant neurologist on the basis of the results of the above investigations (section 3.3). All FTLD and AD patients included in research studies described in this thesis had to fulfil a number of stringent inclusion criteria (see tables 1 to 4) based on performance on specific neuropsychological tests and specific patterns of cortical loss on MRI. These are

designed to minimize the overlap between these diseases whilst excluding any non- FTLD or AD pathologies where possible.

All FTD patients were enrolled in a larger longitudinal research study which examined the clinical ,neuroimaging, blood, and CSF biomarkers of FTD. This study required participants to return to the center once annually for a review over a period of three years. The experimental assessments that are discussed in this thesis (chapters 4 – 8) were most often conducted during this longitudinal study visit. As such, participants were seen over a number of years, and included in a number of experimental studies. Each experimental study presented in this chapter includes patients that have contributed data to more than one experimental study. The majority of participants included in any experimental chapter (>75%) contributed to all experimental studies presented in this thesis.

3.5.1.   FTLD

3.5.1.1.   bvFTD

All bvFTD patients fulfilled consensus criteria for a diagnosis of probable bvFTD (Rascovsky et al., 2011, see Table 1), and showed structural MRI evidence of atrophy of the frontal and/or temporal lobes with a history of marked changes in behaviour and personality.

3.5.1.2.   SD

All SD patients fulfilled consensus criteria for a diagnosis of probable semantic dementia (Gorno-Tempini et al., 2011, see Table 2), and showed structural evidence of predominant temporal atrophy on MRI, with a history of pervasive anomia and degraded semantic knowledge.

3.5.1.3. PNFA

All PNFA patients fulfilled consensus criteria for progressive nonfluent aphasia (Gorno-Tempini et al., 2011, see Table 3), and showed structural MRI evidence of atrophy within the frontal and/or temporal regions, with a history of progressive speech-output difficulty.

3.5.2. Typical, amnestic AD

Typical AD patients had to fulfill current research criteria for probable AD (Dubois et al., 2007), and had to have a history suggestive of an amnestic presentation.

3.6. Participant exclusion criteria

Patients were excluded from any study if they did not meet the inclusion criteria. Furthermore, participants were excluded from any study if English was not their first language and they had lived in the United Kingdom for less than fifteen years. Healthy control participants were excluded from any study if they had a history of neurological or psychiatric disturbance. Participants were excluded from neuroimaging studies if they had any contraindication for scanning (e.g. pacemaker) or an abnormal scan due to reasons beyond the dementia diagnosis, including but not restricted to: abnormal growth such as tumor or meningioma, or vascular damage beyond that expected for the participants age. Further study-specific exclusion criteria are listed in the appropriate chapters.

3.7. Experimental task software

3.7.1. Superlab

Superlab (www.superlab.com) is an experimental lab software for building experiments, running experiments, and collecting data. This software can be used to present visual stimuli on a computer screen, and auditory stimuli via speakers. Data collected by Superlab includes measures such as reaction time and simple behavioural responses, such as button press. This software was used to deliver experimental stimuli and collect behavioural data in Chapters 6 and 7 of this thesis.

3.7.2. Cogent

Cogent (http://www.vislab.ucl.ac.uk/cogent_2000.php) is a Matrix laboratory (MATLAB, see 3.8.2.1) toolbox which can be used to deliver pictorial and auditory stimuli and record behavioural response data, such as reaction time or keypad press response. This software was used to deliver experimental stimuli and collect behavioural data in Chapter 4.

3.8. Imaging

MR imaging was undertaken in all patients, except in those that had contraindication, such as a pacemaker. MR images were not collected, however, in healthy control participants. Control scans were not collected, nor included in any anatomical analyses, as it is questionable how one would interpret a volume-score association in a healthy group of people who in theory don't have any atrophy in comparison to those who do, in that we cannot make the assumption that more cortexes equals better score in a healthy population.

3.8.1. MRI acquisition

All scans were acquired on a 3T Signa MRI scanner (General Electric, Milwaukee, Wisconsin, USA) using a spoiled gradient echo (SPGR) technique. Scans included a sagittal T1 weighted scout sequence, an axial dual-echo sequence (T2- weighted and proton-density weighted) and a T1- weighted volumetric image (124 contiguous 1.5mm slices). All preprocessing and statistical analysis of imaging data was carried out by a single experimenter (L.E.D.).

3.8.2. Image processing software

Digitised images were transferred to a Linux workstation. A number of different software packages and programs were used for image and statistical analyses.

3.8.2.1. MATLAB

Matlab (matrix laboratory) is a high-level language and interactive computing environment developed by MathWorks (Sherborn, Massachusetts). It allows matrix manipulations, plotting of functions and data, implementation of algorithms, creation of user interfaces, and interfacing with programs written in other languages.

3.8.2.2. Statistical Parametric Mapping (SPM)

The Statistical parametric mapping (SPM) software package (version 8) (Ashburner & Friston, 2000) was used in this thesis, implemented in Matlab to carry out voxel-based morphometry (VBM) analyses (see 3.8.3.1.1). SPM is used to identify and characterize functional or structural anatomy of changes in the brain by conducting voxel-wise statistical analyses to allow inference about regionally specific correlates between areas of the brain and experimental factors.

3.8.2.3. FSL

FMRIB software library (FSL)(Smith et al., 2004) is a comprehensive library of analysis tools for the processing and analysis of functional, structural, and diffusion imaging data. FSL was used in this thesis in order to implement tract based spatial statistics (TBSS) on the diffusion imaging data.

3.8.2.4. Tract based spatial statistics (TBSS)

TBSS (Smith et al., 2006) allows the statistical analysis of multi-subject diffusion data. TBSS is used to identify and characterize the integrity of white matter tracts by conducting voxel-wise cross-subject statistical analyses. This allows inferences to be made about the anatomical connectivity in the brain, by measuring the anisotropic diffusion of water in white matter tracts.

3.8.2.5. MRICron

MRICron ® (http://www.sph.sc.edu/comd/rorder/mricron.html) is a cross-platform image viewer. This program allows the importation, viewing, rendering, and drawing of anatomical regions of interest on brain images. MRICron was used within this thesis to import and draw anatomical regions of interest to be used as volumes of interest to mask data and restrict statistical analyses to pre-defined areas of interest within VBM and DTI analyses.

3.8.3. Image analysis techniques

3.8.3.1. Image processing for voxel-wise analyses

3.8.3.1.1. Voxel based morphometry

Voxel based morphometry (VBM) allows grey and white matter and cerebrospinal fluid within the brain to be segmented and matched between multiple inter-individual scans. This allows statistical comparison at each voxel

within the brain across all participants of any group differences in volume, or associations between volume at each voxel and other metrics. VBM allows the alignment of each participants' MRI scan into the same spatial framework so that large numbers of scans can be statistically compared. Statistical analysis can be performed to localize group differences in patterns of atrophy in dementia or to correlate areas of neuronal atrophy with neuropsychological test scores.

VBM was carried out using SPM8. Scans were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using SPM8's new segment toolbox with default settings (Ashburner & Friston, 2005). Segmentations were produced with rigid alignment to MNI space and resampled to 1.5mm isotropic voxels for use with DARTEL (Ashburner, 2007). DARTEL then iteratively registered the grey and white matter segments to an evolving estimate of their group-wise average (Ashburner & Friston, 2009). The native space tissue segments were then normalized to MNI space using the DARTEL transformations and DARTEL to MNI SPM function, and modulated to account for local volume changes. A 6mm full width at half maximum (FWHM) Gaussian smoothing kernel was applied. Total intracranial volume (TIV) for each participant was estimated using Jacobian integration of deformation fields from the GM, WM and CSF segments (Ridgway et al., 2009). Prior to analysis n explicit mask was applied to include only voxels for which the intensity was at least 0.1 in at least 80% of the images (Ridgway et al., 2009). Significant results were displayed as overlays on a study-specific template, which was created by putting all the original images into standard (MNI) space using the parameters derived from the DARTEL transformations and averaging them.

3.8.3.1.2. DTI

Diffusion tensor imaging (DTI) allows the investigation of the integrity of white matter microstructure by assessing the diffusion displacement and directionality of water molecules within cerebral white matter fibers.

A number of outcome variables are generated from DTI analyses, commonly including fractional anisotropy, (FA) axial diffusivity (AX), trace diffusivity (TR), and radial diffusivity (RD). FA provides a metric of the anisotropy or directionality of water diffusion, whereby higher FA values reflect higher axonal calibre in WM pathways, and lower FA values reflect poorly organized tissue (Alexander et al., 2007). AX quantifies the amount of water diffusion along the primary axis, whereas RD measures the perpendicular dispersion to the primary axis of diffusion (Alexander et al., 2007). TR provides a measure of the magnitude of diffusion and is rotationally invariant (Alexander et al., 2007). Understanding such a relationship is of great interest, as the greater the integrity of the white matter through myelination, the faster signals are transported, thus allowing for more efficient communication of executive signals between neural regions (Seghete et al., 2013).

Image analysis was implemented using TBSS, and involved the following steps: (i) non-linear alignment of all participants' fractional anisotropy images into common FMRIB58 FA template space; (ii) affine-transformation of the aligned images into standard MNI152 1 mm space; (iii) averaging of the aligned fractional anisotropy images to create a 4D mean FA image; (iv) thinning of the mean FA

image to create a mean FA 'skeleton' to represent the centre of all white matter

tracts. Significant results were projected onto a study-specific mean brain

registered to standard (MNI) space.

3.8.4. Statistical software and models

3.8.4.1. STATA

Statistical analyses in this thesis were conducted in STATA (STATA Corporation,

College Station, TX, USA). STATA version 12 was used for the statistical analyses

in this thesis. Appropriate parametric or non-parametric tests were used for

continuous and categorical data, adjusting for covariates where necessary;

specific details are given in each chapter.

3.8.4.2. Analysis of background neuropsychological performance

All analysis of background neuropsychological data (section 3.4) was done in

STATA (see 3.8.4.1). Regression models were used to examine group differences

in each behavioural metric, adjusting for age and gender. Group differences in

demographic information (e.g. years of disease duration, and age) were assessed

using t tests, and differences in gender and handedness were examined using chi^2

tests.

3.8.4.3. Voxel and vertex-wise analyses

3.8.4.3.1. VBM statistical analysis

Typically, a general linear model (GLM) was used to assess group differences in

grey matter volume controlling for age, gender and TIV. Where multiple patient

groups were included in an analysis, group-membership was also controlled for.

Other covariates such as level of comprehension, or executive function were

included in statistical models where appropriate and these are outlined in each

Chapter,. Statistical significance of between-group differences was tested using family-wise error rate (FWE) correction at p<0.05. Maps showing statistically significant differences between patients, or groups of patients are shown in the relevant Chapters.

3.8.4.3.2. DTI statistical analyses

A GLM was used to assess group differences in white matter tract integrity controlling for age, gender and TIV. Where multiple patient groups were included in an analysis, group-membership was also controlled for. Other covariates such as level of comprehension, or executive function were included in statistical models where appropriate and these are outlined in each Chapter, where appropriate. The same model was fitted separately to FA, RD, TR, and AX. Statistical analysis was implemented using the permutation-based (non-parametric) randomise tool within FSL with 5000 permutations generated for each test. A significance threshold (p <0.05) was applied following correction for multiple comparisons using false discovery rate (FDR) correction with threshold-free cluster enhancement (Smith and Nichols, 2009). Further information on significance level and number of significant voxels was obtained from the already thresholded significant (FDR corrected) results within each anatomical mask using the FSLstats tool.

4. SOCIAL COGNITIVE PROCESSING IN FRONTOTEMPORAL DEMENTIA

4.1. Introduction

As described in Chapter 2 (2.2), social dysfunction is a hallmark feature of bvFTD (Kipps et al., 2009b; Rosen et al., 2005; Omar et al., 2011). Deficiencies in empathic concern and perspective taking (Rankin et al., 2006; Eslinger et al., 2011; Lough et al., 2006), perception of humour and sarcasm (Snowden et al., 2003; Kosmidis et al., 2008; Kipps et al., 2009b), and affective decision making (Toralva et al., 2006) have been described. Studies of social cognition in SD are fewer; a number of studies have reported abnormal social functioning within this group, (Rankin et al., 2009; Duval et al 2012), particularly in the realm of identification of paralinguistic cues (Rankin et al., 2009). The overlap in social dysfunction seen in both bvFTD and SD may suggest that there is breakdown within a common fronto-temporal social cognitive network (see 2.2 for further explanation). I utilized the imaging modalities of VBM and DTI to explore the cortical components of this social cognitive network and the underlying connections between them.

Social cognition is likely underpinned by a distributed network which in healthy individuals has been associated with ventro-medial prefrontal cortex, frontal pole, orbitofrontal cortex (OFC;(Gallagher and Frith, 2003; Carrington and Bailey, 2009;Moll et al., 2011)); and the anterior temporal lobes (Fumagalli and Priori,

2012); areas which lie within the Salience network and show selective vulnerability in FTD. Given that social dysfunction is a key criterion of bvFTD establishing the neural correlates of these behaviours may offer a powerful way of establishing the structural underpinnings of these complex behaviours. Furthermore as social dysfunction is common across this pathologically-heterogeneous disease it may have validity in establishing common structural changes which cut across the spectrum of FTD.

Whilst several studies have established the neural correlates of some aspects of social dysfunction in FTD, there are no studies assessing white matter correlates of social cognition in FTD nor have there been studies comparing changes in white matter with grey matter in relation to social dysfunction. White matter tracts bind together functional networks providing the structural interconnectivity needed for normal cognitive processes. Diffusion Tensor Imaging (DTI) and processing pipelines such as Tract Based Spatial Statistics (TBSS) are powerful neuroimaging tools allowing us to study structural connections by measuring the microstructual properties within white matter tracts. This allows us to build a profile of structural network changes, which is particularly relevant in understanding the neurobiology of neurodegenerative conditions such as FTLD (Agosta et al., 2012, Mahoney et al., 2012; Zhang et al 09).

This Chapter aims to further elucidate the neural mechanisms of social dysfunction in two canonical syndromes of FTD - bvFTD and SD - by correlating function with both grey matter volume and white matter tract integrity. The key

hypothesis was that performance on tasks with high ecologic validity relating to

emotion recognition, sarcasm perception and risk aversion (three key social

cognitive processes) would overlap with neural circuits within the distributed

fronto-temporal salience network (Zhou et al., 2010). A secondary hypothesis

was that the integrity of the white matter tracts supporting social cognition

within each of the FTD subtypes would be more widely damaged than the parallel

grey matter neural correlates, as white matter damage has been shown to

precede structural atrophy in FTD (Agosta et al., 2012).

4.2. Methods

4.2.1. Participants

Twenty-nine consecutive patients with a diagnosis of bvFTD (Rascovsky et al.,

2011), 15 patients with a diagnosis of SD (Gorno-Tempini et al., 2011), and 37

healthy individuals were recruited according to criteria outlined in Chapter 3 (see

section 3.2). Details are provided in Table 6.

4.2.2. Neuropsychometry

All study participants completed a standard battery of neuropsychological tests,

as outlined in Chapter 3.4.

4.2.3. Experimental tasks

Comprehension of task requirements was assessed using the practice question of

the TASIT sarcasm. It was up to the experimenter's discretion to decide whether

the participant adequately understood the task requirements based on the

answers given to the practice questions. If participants were deemed to not

comprehend this task adequately, assessment was terminated and the IGT was

not administered, as this task requires comprehension of an A4 instruction page and is highly linguistically demanding.

4.2.3.1.   The Emotion Evaluation and Test of Social Inference (TASIT) - Emotional inference

The TASIT (Macdonald et al., 2007) emotional inference task was used in order to assess the ability to recognize basic emotion and sarcastic intent. The emotion evaluation component comprises of participants being shown short scenes (15-20s) of professional actors displaying either positive (surprised, happy, neutral) or negative (anger, disgust, sadness, anxiety) emotions. The participant is presented with a card with each of the above emotive words printed on it once each vignette has completed, and asked to identify which of those emotions was most dominantly shown within the scene. A total of five different cards were changed in between each scene presentation so that order of printed emotive stimuli was randomised between trials. Clarity was given prior to the commencement of the assessment for the following emotions: anxious, which participants were told could be used to describe anything from worried, right up to being fearful; revolted, which participants were told could encompass anything from feeling disgusted, right up to feeling like they might be sick; and neutral, which it was explained to participants could be used when no clear emotion was being shown. One practice scene in which feedback was given, and fourteen emotive vignettes were shown to each participant, and answers were scored online at the time of assessment.

4.2.3.2.   TASIT – Sarcasm Detection

Subsequent to the emotion evaluation task, a total of nine video vignettes of the same actors displaying three scenes depicting each of sincere intent, simple sarcasm, or paradoxical sarcasm were presented to each participant. Participants were informed that they would again be shown a series of short scenes, and that after each scene, they would be asked four questions relating to how those within the scene felt, how they were trying to make others feel, and the underlying intent of their interactions or statements. Furthermore, it was emphasized to participants that if they understood the protagonist within the vignette to be saying something that was different to what they were actually feeling, to answer the questions based on what they believed the actor to be feeling. In sincere scenes, exchanges of honesty were displayed. In simple sarcastic vignettes, there was incongruence between what the actor said and what they actually meant such that an actor says one thing, but it is clear that he or she means the opposite to those that have detected the sarcastic intent. Within scenes displaying paradoxical sarcasm, sarcastic statements require a more thorough understanding of human social interaction and intent, as these statements reflect more than just the opposite of what has been stated, but rather an elaboration or exaggeration of this. For example in one scene, when a teenager is asked if he has his train ticket, he replies "no, I've torn it up and thrown it away".   If one does not perceive the sarcastic intent to such a statement, it would seem nonsensical. One practice item was administered to gauge whether each individual could reliably understand the task requirements, and no feedback was given. Each scene was presented once, and participants could request to view the scene once more

should they require it. Participants were excluded from the TASIT sarcasm perception task if it was clear at practice that they did not comprehend the depicted scenario, or the corresponding task questions. Number of participants per group, per task, is labelled accordingly in Table 6.

4.2.3.3.   The Iowa Gambling Task (IGT)

The IGT (Bechara et al., 1994) is a computer-based gambling task in which participants are presented with a total of four decks of cards on a computer screen (A, B, C, and D), and told that they must select a card from any deck by using the mouse. It is explained to participants prior to commencement of the task, that once a card is selected, they will 'win' some money, which is pictorially represented in the green bar at the top of the screen. Every time money is won, the size of the green bar increases. Participants are further told that every so often, they may also lose some money, in which case, the size of the green bar will decrease in penalty. Participants are told that the aim of the game is to win as much money as possible, and avoid losing as much as possible, and further, that some decks of cards are indeed better to achieve this than others. A total of one hundred trials are administered. Card choices from decks A and B generate large wins, however these decks also generate substantive losses, and are thus classed as 'high risk' decks. Card choices from decks C and D generate relatively smaller wins, however, these decks confer significantly smaller penalties, and as such, are the 'safe' decks. Continuously choosing cards from the safe decks is required in order to finish with the highest monetary outcome. The dependant variable is the

final net score, which is calculated by subtracting the number of choices from the high risk decks (A + B) from the number of selections from the safe decks (C + D). The IGT requires participants to comprehend an entire A4 page of task instructions, and participants were excluded from this task if it was clear that they could not comprehend these instructions and the multi-component task requirements. Number of participants per group, per task, is labelled accordingly in Table 6.

4.2.4. MRI acquisition

Images were acquired as described in Chapter 3 (section 3.8.1)

4.2.5. Image Processing

Structural images were pre-processed using the methods described in Chapter 3 (3.8.1) for VBM and DTI data separately. Before processing all images were visually inspected for obvious signs of motion artefact in both T1 MPRAGE and DTI sequences. Two participants with SD were excluded from the imaging analysis due to poor image quality causing poor segmentations. No imaging data were collected for healthy control participants.

4.2.6. Statistical analysis

4.2.6.1. Neuropsychological performance

Neuropsychological data were analysed according to methods described in Chapter 3 (see 3.8.4.2).

4.2.6.2.   Statistical analysis of experimental data

Analysis of covariance (ANCOVA) models were used to examine the relationship between group membership and behavioural performance. The behavioural metric score was regressed on group membership with either i) TASIT - emotion recognition or ii) TASIT - sarcasm evaluation or iii) IGT as the dependent variable, and age, gender, and level of comprehension (BPVS), included as nuisance covariates. The TASIT sarcasm evaluation task was also broken down in order to examine group differences in performance of simple sarcasm and paradoxical sarcasm tasks separately. Group by task interactions were also examined.

Table 6. Demographic and neuropsychological characteristics of patient and healthy control

General characteristics	bvFTD	SD	Healthy controls
No.	29	15	37
Age (yrs)	64(7.1)	65(6.6)	63(7.8)
Sex (F:M)	4:25	5:10	19:18
Symptom duration (yrs)	7.8(5.3)	6.2(1.9)	NA
Neuropsychological assessment			
IQ			
WASI vocab (/80)	**40 (24)**	**26 (24)****	71 (5.3)
WASI blocks (/48)	**23 (19)**	**29 (19)**	46 (11.2)
WASI similarities (/71)	**22 (13)**	**16 (16)**	46 (6.0)
WASI matrices (/32)	**15 (8.5)**	**18 (8.7)**	27 (7.5)
NART (/50)	**26 (15)**	**26 (16)**	42 (5.9)
Episodic memory			
RMT Words (/50)	**35 (10)**	**33 (6.0)**	48 (2.6)
RMT Faces (/50)	**35 (8.0)**	**34 (8.7)**	43 (4.5)
Semantic processing			
BPVS (/150)	**119 (35)**	**76 (56)****	147 (2.1)
GNT (/30)	**11 (9.3)**	**3.4 (5.8)****	26 (3.0)
Executive function:			
D-KEFS Stroop inhibition (sec)	**137 (98)****	**108 (70)**	55 (13)
Digit span reverse (/12)	5.6 (2.9)	6.1 (3.2)	7.3 (1.9)
Social cognition - TASIT			
Emotion (/14)	**7.1 (2.9)**	**5.8 (2.8)**	11 (1.3)
Total sarcasm (/24)	13 (6.7) [¥]	**11 (5.9)**	22 (2.3)
Simple sarcasm (/12)	**7.4 (3.5)**	**5 (3.5)**	10 (1.4)
Paradoxical sarcasm (/12)	**7 (2.9)**	**5.7 (2.9)**	11 (1.3)
Other skills			
DS forward (/12)	8.8 (1.6)	6.8 (2.6)	8.9 (1.7)
VOSP (/20)	16 (3.8)	15 (3.5)	18 (1.6)

Mean (standard deviation) values shown; maximum scores are shown in parentheses after names of tests. ¥ data from 27 patients (two unable to understand task). Significant group differences in t tests p<0.05 relative to the healthy control group are shown in bold; ** denotes significant difference between bvFTD and SD patients. BPVS, British picture vocabulary scale; D-KEFS, Delis-Kaplan Executive Function System; GNT, Graded Naming Test; n/a, not available; NART, National Adult Reading Test; RMT, recognition memory test; sec, seconds; TASIT, the Awareness of Social Inference Test; VOSP, Visual Object and Space Perception; WASI, Wechsler Abbreviated Scale of Intelligence.

4.2.6.3.   Statistical analysis of Grey Matter and DTI metrics

Preprocessing for both VBM and DTI data were carried out as described in Chapter 3 (3.8.3.1.1 and 3.8.3.1.2) VBM typically implements parametric statistical analysis on grey matter data, however, the FSL randomize tool was implemented in the current dataset in order to conduct non-parametric statistical analysis on both white matter (DTI data) and grey matter (VBM). This allows a more general inference of the relationship between the two tissue classes and the behavioural measures of interest by ensuring statistical methodological homogeneity. Both image analyses were carried out according to methods described for the analysis of DTI data outlined in Chapter 3 (3.8.4.3.2). In essence, both grey matter and white matter data were analysed by implementing the permutation-based (non-parametric) randomise tool within FSL with 5000 permutations generated for each test. A significance threshold ($p < 0.05$) was applied following correction for multiple comparisons using false discovery rate (FDR) correction.

ANCOVA models were used to examine the relationship between behavioural measures and both GM volume and WM tract microstructure. GM volume (or WM microstructure metrics) was regressed on the behavioural metric score and , group membership and their interaction for either i) TASIT - emotion recognition or ii) TASIT - sarcasm evaluation or iii) IGT as the variable of interest, and age, level of comprehension (BPVS), total intracranial volume, included as nuisance

covariates. All analyses examined the neuroanatomical correlates across all groups (total effect), in bvFTD group only (whilst adjusting for group membership), and in SD group only (whilst adjusting for group membership). Grey matter volume and each white matter DTI metric (FA/AX/RD) were analysed separately using the above model. The experimental model can be represented as:

GM (or WM DTI metric) = f [(bvFTD behavioural score of interest x group membership) + (SD behavioural score of interest x group membership) + age + BPVS + TIV + group + mean + error]

4.3. Results

4.3.1. Demographics and general neuropsychological performance

General characteristics of participants are summarized in Table 6. The patient and healthy control groups were well matched for mean age (p=0.74) and patient groups had similar mean disease durations (p=0.86). Male participants were over-represented in the bvFTD group (p=0.009) compared to healthy controls. The bvFTD and SD groups each showed the anticipated profile of cognitive deficits relative to the healthy control group and to the other syndromic group (see Table 6). The SD group showed significantly more impaired performance on measures of single word comprehension, naming and vocabulary, and the bvFTD group showed significant impairment in the Stroop inhibition task (all p<0.05; see Table 6).

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4.3.2. Experimental task performance

All patients within the present study completed the TASIT emotional inference task, however a small number of both SD and bvFTD patients did not complete either the TASIT sarcasm task, or both the TASIT sarcasm and IGT tasks, due to an inability to comprehend the more linguistically-demanding task instructions.

Scores for both FTD and control groups in each subtest are displayed in Table 6. There was a significant deficit in both FTD groups relative to healthy controls in the total TASIT emotion recognition condition ($p<0.001$, for both bvFTD and SD respectively). There was no significant group performance difference between all groups in the perception of sincere statements ($p>0.05$). After adjusting for verbal comprehension and sincere statement TASIT score there was a significant deficit in both FTD groups relative to healthy controls in the total TASIT sarcasm condition ($p<0.001$ for both FTD groups).Further sub-component analyses revealed similar deficits in both FTD groups, compared to controls, in the perception of simple sarcastic statements ($p<0.001$ for both groups) and paradoxical sarcastic statements ($p<0.001$ and $p<0.008$, for bvFTD and SD respectively). No significant group by task interaction was found. A trend toward a significant deficit in the bvFTD group relative to healthy controls in the net IGT score was observed ($p<0.07$; $p>0.05$ for SD).

4.4. Neuroanatomical associations

4.4.1. Grey matter performance correlates

Statistical parametric maps of regional grey matter volume associated with performance on sarcasm detection tasks are shown in Figure 1; local maxima and clusters of regional grey matter voxels associated with social cognition performance in general are summarised in Table 7, at the same FDR corrected threshold (p=0.05) adopted for DTI data. There were no significant grey matter correlations with performance on the TASIT emotion identification task. Across both patient groups, TASIT total sarcasm identification score was positively correlated with regional grey matter in right anterior temporal and orbitofrontal cortex. Within the bvFTD group alone, TASIT total sarcasm identification score was correlated with regional grey matter volume in bilateral orbitofrontal cortex and anterior temporal lobes. No significant grey matter correlations with sarcasm identification were observed in the SD group alone. Comparing disease groups, TASIT total sarcasm identification score was significantly more strongly correlated with grey matter in left parahippocampus and fusiform gyri in the bvFTD group than the SD group.. No significant associations between grey matter volume and performance metrics were observed in the SD group compared to the bvFTD group.

Table 7. Summary of VBM correlates of sarcasm perception in patient groups

Behavioural correlate	Brain region	Cerebral hemisphere	Cluster size (voxels)	P value
Combined groups	Anterior TL, OFC	R	107453	0.02
bvFTD only	Anterior TL, OFC	Bilateral	318805	0.01
bvFTD > SD	Parrahippocampal, fusiform gyri	L	61222	0.03

Voxel-based morphometry (VBM) associations of TASIT total sarcasm identification score are summarised. All correlations shown are positive and significant after family-wise error correction for multiple comparisons at whole brain level (p<0.05). bvFTD, behavioural variant frontotemporal dementia; L, left hemisphere; OFC, orbitofrontal cortex; R, right hemisphere; SD; semantic dementia; TL, temporal lobe.

Figure 1. Grey matter correlates of sarcasm perception in patient groups
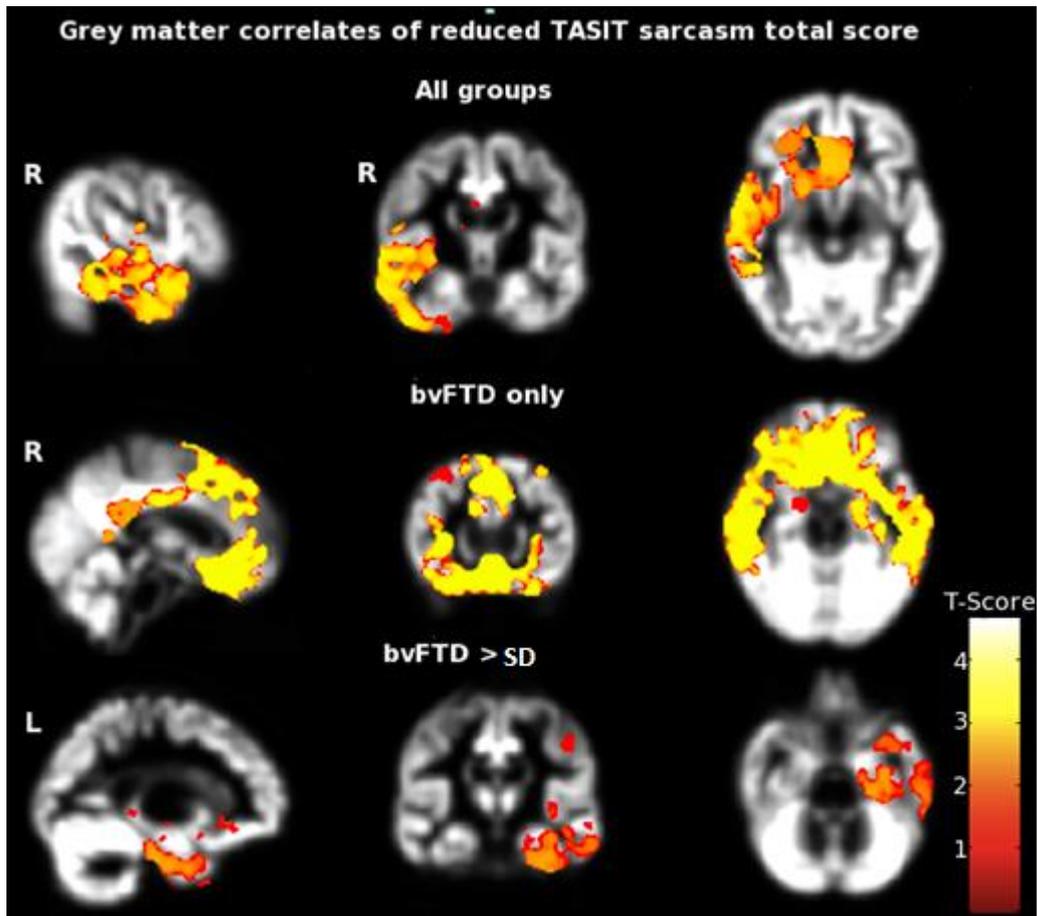
Grey matter correlates of sarcasm identification across both bvFTD and SD participant groups. Results are overlaid on a customised group template brain image and displayed in MNI standard space; the right hemisphere (R) is displayed on the left. The colour scale indexes p-value after family-wise error correction over the whole brain at p <0.05. Key: bvFTD, behavioural variant frontotemporal dementia; SD, semantic variant of primary progressive aphasia.

4.4.2. White matter tract integrity performance correlates

Maps of DTI metric alterations associated with performance on social cognition tasks are shown in Figure 2 and Figure 3; data for peak co-ordinates and clusters of white matter alterations associated with task performance are summarised in Table 8 and Table 9. All results are reported thresholded at p=0.05 after FDR error correction for multiple comparisons over the whole brain.

Across both patient groups, TASIT emotion identification score was inversely correlated with AX, RD and TR and positively correlated with FA extensively over dorsal, ventral and commissural white matter tracts in both cerebral hemispheres (Figure 2); the largest effects (Table 8) were demonstrated in frontal subcortical projection pathways (right anterior thalamic radiation) and fornix. Within the bvFTD group alone, emotion identification impairment was associated with white matter alterations predominantly in corpus callosum and fornix. Within the SD group alone, emotion identification score was inversely correlated with increased AX and RD predominantly in right anterior thalamic radiation. Comparing syndromic groups, the correlation between higher total emotion score and decreased RD was significantly stronger in right anterior thalamic radiations and right inferior longitudinal fasciculus in the SD group than the bvFTD group; the reverse contrast did not identify any significant white matter associations in the bvFTD group compared to the SD group.

Across both patient groups, TASIT total sarcasm (simple sarcasm + paradoxical sarcasm) identification score was inversely correlated with AX, RD and TR in bi-hemispheric but predominantly right temporal and inferior frontal white matter tracts; the largest effects in terms of statistical significance and extent (Table 9) were demonstrated in right uncinate fasciculus (Figure 3). Within the bvFTD group, sarcasm identification score correlated with predominantly right-sided but bilateral temporal and inferior frontal white matter alterations; largest effects were demonstrated in right uncinate fasciculus and right anterior thalamic radiation. Within the SD group, sarcasm identification score correlated with more discrete right temporal white matter alterations; the largest effects were demonstrated in right inferior longitudinal fasciculus. Contrasts regressing total simple sarcasm score and total paradoxical sarcasm score did not identify any additional significant white matter associations. Comparisons between syndromic groups did not identify any significant differential white matter associations.

Across both syndromic groups (Table 8 and Table 9), white matter correlates of emotion identification and sarcasm identification were signalled by AX, RD and TR alterations, with partial convergence among these metrics. However, the signal with FA was much less extensive and less consistent.

The grey matter associations with social cognition performance from the VBM analysis were only partly convergent with the white matter correlates identified in the DTI analysis (Figure 2 and Figure 3). Convergence between the grey and white matter modalities was most clearly shown in the regional emphasis of the

changes associated with sarcasm identification in right anterior temporal and

inferior frontal lobes. In contrast, no grey matter associations with emotion

identification were identified to sit beside the white matter correlates.

Table 8 Summary of DTI correlates of emotion identification in patient groups

↑ **Axial Diffusivity**							
Contrast	**Cluster No.**	**Voxels**	**x**	**y**	**z**	**p-value**	**White matter tract**
All patients	1	58082	3	-4	10	<0.001	Fornix
bvFTD only	1	50442	2	2	15	<0.001	Fornix
SD only	1	27988	12	-7	3	0.002	Right anterior thalamic radiation
	2	2852	-38	1	27	0.02	Left precentral gyrus white matter
	3	36	37	-79	-2	0.05	Right inferior occipital gyrus white matter
	4	33	40	-68	-4	0.05	Right inferior occipital gyrus white matter
↑ **Radial Diffusivity**							
All patients	1	68045	3	-10	11	<0.001	Right anterior thalamic radiation
bvFTD only	1	45523	2	4	16	<0.001	Fornix
SD only	1	48721	4	-11	9	0.001	Right anterior thalamic radiation
bvFTD>SD*	1	443	22	-6	14	0.04	Right anterior thalamic radiation
	2	361	46	-10	-22	0.05	Right inferior longitudinal fasciculus
	3	82	32	-31	9	0.05	Right inferior fronto-occipital fasciculus
↑ **Trace Diffusivity**							
All patients	1	63092	3	-7	10	<0.001	Right anterior thalamic radiation
↓ **Fractional Anisotropy**							
bvFTD only	1	1557	-3	29	5	0.02	Genu corpus callosum

Diffusion tensor tractography (DTI) associations of altered white matter diffusivity metrics associated with TASIT emotion identification score are summarised. Cluster numbering indexes statistically independent anatomical associations within each contrast generated using the FSL cluster command. Results are corrected for multiple comparisons at whole brain level using family-wise error correction (p=0.05) and ordered by statistical significance and size (number of voxels in the cluster). Peak co-ordinates and anatomical associations are based on centre-of-gravity of cluster and are displayed in MNI standard space. *note that here and in Figure 1, this group interaction contrast is based on an *inverse* correlation with RD; bvFTD, behavioural variant frontotemporal dementia; SD, semantic dementia

Table 9. DTI correlates of sarcasm perception in patient groups

Contrast	Cluster No.	Voxels	x	y	z	p-value	White matter tract
↑ Axial Diffusivity							
All patients	1	10986	33	2	-7	0.005	Right uncinate fasciculus
bvFTD only	1	23527	11	10	0	0.004	Right anterior thalamic radiation
	2	565	32	-49	38	0.05	Right superior parietal lobule
	3	247	14	-67	48	0.05	Right superior parietal lobule
	4	111	36	-62	40	0.05	Right superior parietal lobule
	5	92	36	-65	31	0.05	Right angular gyrus white matter
	6	76	-56	-29	-10	0.05	Right superior longitudinal fasciculus: temporal part
	7	29	23	-55	53	0.05	Right angular gyrus white matter
SD only	1	389	48	-12	-22	0.04	Right inferior longitudinal fasciculus
↑ Radial Diffusivity							
All patients	1	9125	33	3	-8	0.009	Right uncinate fasciculus
	2	1183	47	-47	2	0.03	Right superior longitudinal fasciculus: posterior part
bvFTD only	1	4686	24	24	-5	0.02	Right uncinate fasciculus
	2	3209	43	-16	-18	0.03	Right inferior longitudinal fasciculus
	3	1127	-16	29	-12	0.04	Left anterior corona radiata
	4	56	45	-54	-8	0.05	Right inferior temporal gyrus white matter
SD only	1	156	53	-11	-22	0.05	Right inferior longitudinal fasciculus
↑ Trace Diffusivity							
All patients	1	9436	33	4	-8	0.007	Right uncinate fasciculus
	2	42	53	-48	6	0.05	Right superior longitudinal fasciculus: posterior part
bvFTD only	1	9436	32	9	-8	0.02	Right uncinate fasciculus
	2	869	-13	30	-12	0.04	Left anterior corona radiata
	3	145	-26	23	-14	0.05	Left uncinate fasciculus
SD only	1	154	53	-10	-22	0.05	Right inferior longitudinal fasciculus

Diffusion tensor tractography (DTI) associations of altered white matter diffusivity metrics associated with TASIT total sarcasm identification score are summarised. Cluster numbering indexes statistically independent anatomical associations within each contrast generated using the FSL cluster command. Results are corrected for multiple comparisons at whole brain level using family-wise error correction (p=0.05) and ordered by statistical significance and size (number of voxels in the cluster). Peak co-ordinates and anatomical associations are based on centre-of-gravity of cluster and are displayed in MNI standard space. bvFTD, behavioural variant frontotemporal dementia; SD, semantic dementia

Figure 2. White matter correlates of emotion recognition in patient groups
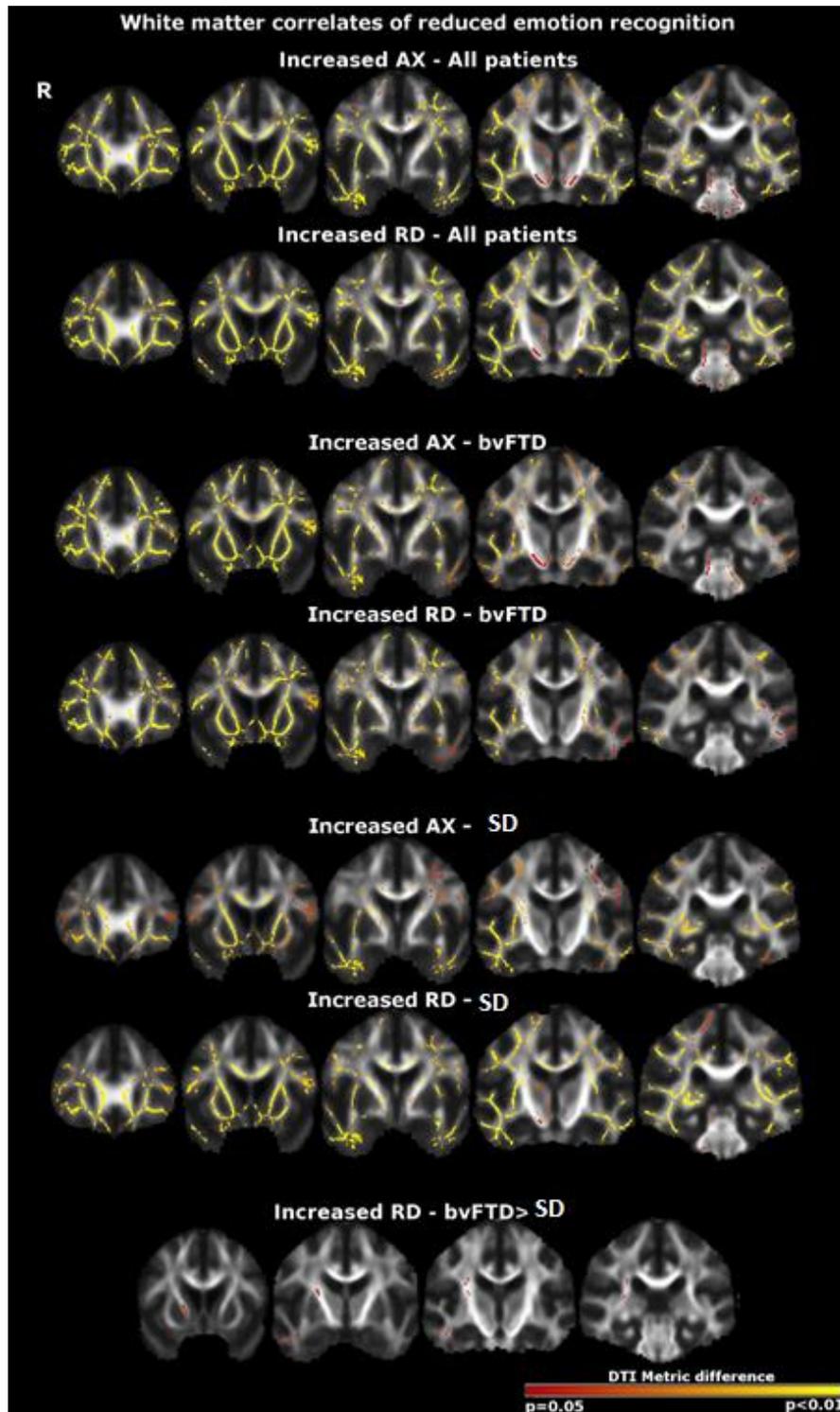
White matter correlates of reduced emotion identification performance in both patient groups (top panels), the bvFTD alone (middle panels) and the SD group alone (bottom panels). Results are overlaid on a customised group template brain image and displayed in MNI standard space; the right hemisphere (R) is displayed on the left. The colour scale indexes p-value after family-wise error correction over the whole brain at p < 0.05. Key: AX, axial diffusivity; bvFTD, behavioural variant frontotemporal dementia; RD, radial diffusivity, SD, semantic dementia

Figure 3. White matter correlates of sarcasm detection in patient groups
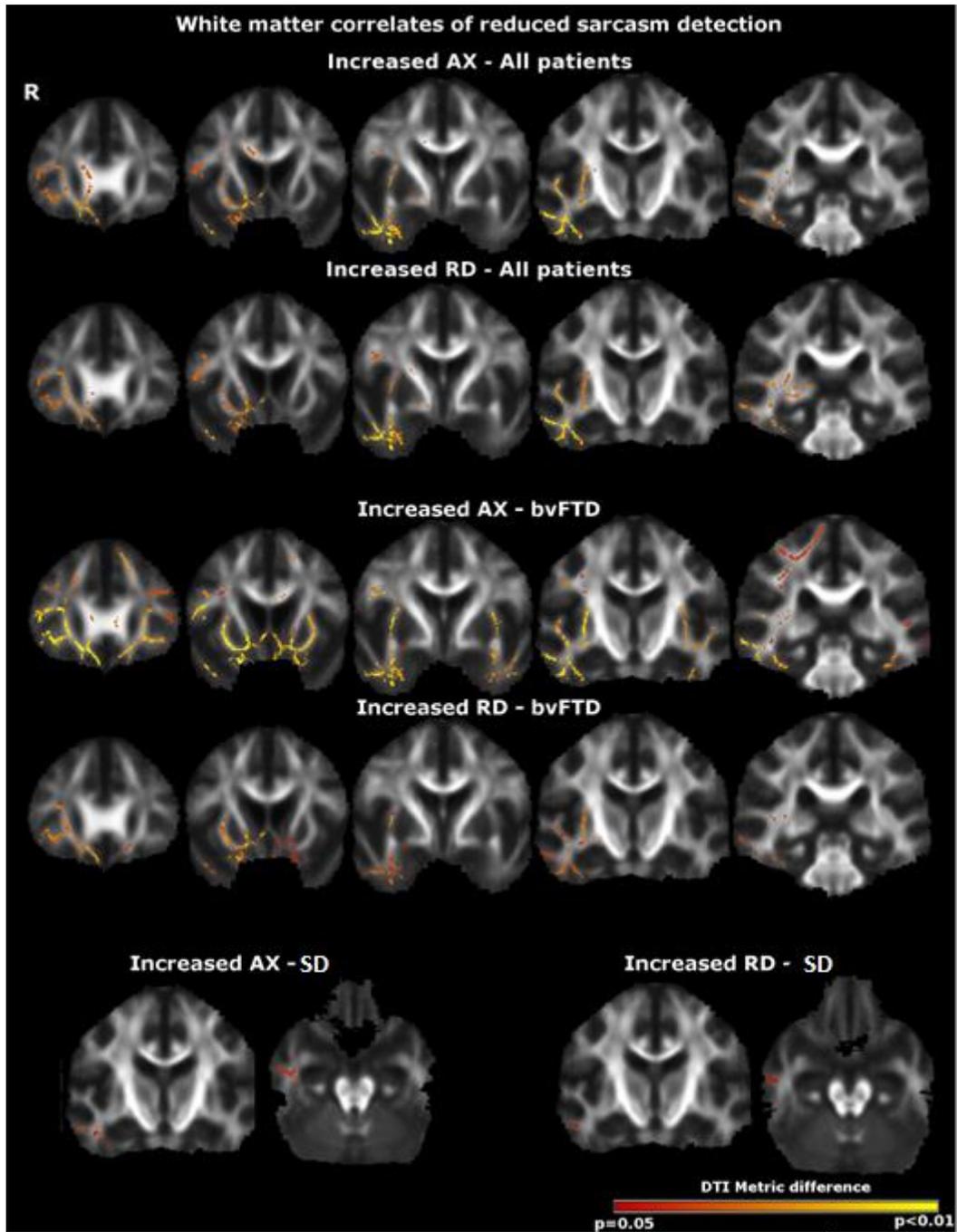
White matter tract correlates of reduced sarcasm identification across both patient groups (top panels), in the bvFTD group alone (middle panels) and in the SD group alone (bottom panels). Results are overlaid on a customised group template brain image and displayed in MNI standard space; the right hemisphere (R) is displayed on the left. The colour scale indexes p-value after family-wise error correction over the whole brain at p < 0.05. Key: AX, axial diffusivity; bvFTD, behavioural variant frontotemporal dementia; RD, radial diffusivity, SD, semantic dementia.

4.5. Discussion

Here I have used anatomically-unbiased VBM and DTI protocols to delineate grey and white matter associations of cognitive processes relevant to social signal encoding (canonical emotion identification) and interpretation (sarcasm identification) in two canonical FTD syndromes with prominent social difficulties. In line with previous work (Kipps et al., 2008b; Torralva et al., 2009; Rankin et al., 2009; Duval et al., 2012; Shany-Ur et al., 2012), both the bvFTD and SD groups exhibited deficits of emotion identification and sarcasm interpretation and deficits were comparably severe in both groups. White matter signatures of brain network damage underpinning these social cognition deficits were widely distributed albeit with an anterior frontotemporal and right hemispheric emphasis, overlapping networks implicated in social cognition in the healthy brain (Adolphs, 2009; Kennedy and Adolphs, 2012; Zahn et al., 2009a; Carrington and Bailey, 2009) and in association with focal brain damage (Mahoney et al., 2011; Rankin et al., 2006; Rankin et al., 2009; Moll et al., 2011). Furthermore, there was extensive overlap of white matter tract signatures between the bvFTD and SD groups: the evidence for separable, syndrome-specific signatures (i.e., profiles of neuroanatomical associations that differed between syndromes) was relatively sparse. This suggests that bvFTD and SD involve common large-scale networks mediating social cognition processes, albeit with different regional emphases; and that social cognition processes may constitute 'trans-syndromic' signatures of brain dysfunction in FTD. Moreover, white matter tract correlates of social cognition impairment here were only partly convergent with (and more

consistent than) the grey matter correlates identified in the corresponding VBM analyses: this underlines both the potential of DTI to reveal disease signatures that may not be fully delineated using grey matter imaging techniques, and the critical role of white matter pathway integrity in maintaining normal brain network function.

The most robust white matter associations of emotion and sarcasm processing here were identified within tracts previously implicated in linking cognitive and evaluative processing with emotional responses. Abnormal diffusivity in anterior thalamic radiation was identified as a correlate of emotion identification in the combined group and within the SD group; and a correlate of sarcasm identification within the bvFTD group. The anterior thalamic radiation participates in thalamo-fronto-striatal re-entrant circuits and has widespread projections to prefrontal cortex and basal forebrain regions; both in the healthy brain and in a range of neuropsychiatric disorders, this tract has been implicated in various cognitive operations that mediate the social context of emotional signals, including reward and punishment potential, gating and cognitive meaning of affective signals and pervasive induced mood states that may promote evaluation of emotional experiences (Cheon et al., 2011; Erpelding and Davis, 2013; Fujino et al., 2014; Han et al., 2013; Haxby et al., 2002; Joutsa et al., 2011; McIntosh et al., 2008). Impaired emotion identification in the combined cohort and within the bvFTD group was strongly associated with altered diffusivity in fornix, consistent with other work in FTD syndromes (Kumfor et al., 2013). Fornix is a core limbic tract that links primitive affective, autonomic and homeostatic mechanisms with cortical evaluative mechanisms, and has

previously been associated with altered hedonic valence of sensory stimuli and abnormal emotional behaviours (Kazlouski et al., 2011; Maier-Hein et al., 2014; Modi et al., 2013). Impaired sarcasm detection in the combined cohort and within the bvFTD group was strongly associated with abnormal diffusivity in uncinate fasciculus: this tract is part of the 'extended limbic system' (Pugliese et al., 2009) and plays a key role in associating linguistic and paralinguistic information coded in anterior superior temporal cortices with affective, motivational, evaluative and mentalising mechanisms in rostral frontal cortices (Von Der Heide et al., 2013). Uncinate fasciculus has been identified previously as a key locus of pathology in DTI studies of bvFTD and SD (Agosta et al., 2012; Mahoney et al., 2013) and damage involving this tract has been associated with altered social behaviour and abnormal evaluation of affective states (Pugliese et al., 2009; Tartaglia, 2012; Phan et al., 2009). The grey matter (VBM) and white matter (DTI) correlates identified here together support previous evidence implicating the right temporal lobe in sarcasm detection (Kipps et al., 2009b; Rankin et al., 2009) and further define the brain network underpinning the processing of sarcasm: in particular, the present data are consistent with a model in which anterior temporal lobe structures process associative meaning and affective tone of speech signals, inferior frontal cortices disambiguate paralinguistic intent and uncinate fasciculus acts as the key route of reciprocal information transfer between these grey matter 'hubs' (Von der heide et al., 2013).

White matter associations of social cognitive performance were not restricted to anterior frontotemporal tracts: diffusivity correlates were also identified within long intra-hemispheric pathways including inferior and superior longitudinal and

fronto-occipital fasciculi. These pathways have been associated previously with general measures of social cognition such as 'emotional intelligence' (Takeuchi et al., 2013), and may link sensory processing mechanisms with limbic and motor output mechanisms including those that mediate social 'mirroring' actions (Hecht et al., 2013). These long tract associations underline the distributed nature of the brain networks that support social cognition processes (Kennedy and Adolphs, 2012; Kumfor et al., 2013; Mahoney et al., 2013; Chiong et al., 2013; Phan et al., 2009). Of note, correlates of social cognition here did not include fronto-insular connections within the salience network previously implicated as central both to the pathogenesis of bvFTD and to processes supporting human social cognition (Seeley et al., 2009; Zhou et al., 2010). The present data suggest that additional, specific pathways and networks may be critical in supporting social cognition in FTD as the core network disintegrates, while providing potential sites of anatomical convergence (such as orbitofrontal cortex) where these networks might interact. A role for abnormal network interactions would be consistent with other work in FTD syndromes (Chioing et al., 2013), while also allowing that extensive white matter pathway damage in other diseases (such as AD) may leave social capacities relatively unscathed (Acosta-Cabonero et al., 2010).

While much of the neuroimaging evidence converged for both SD and bvFTD groups, neural correlates which differentiated these two syndromes were also observed. VBM analyses revealed grey matter associations between the anterior temporal lobe and OFC and sarcasm in the bvFTD group only. Furthermore, the parahippocampal and fusiform gyri revealed differences in sarcasm perception between bvFTD and SD groups. Such a pattern of differential association may reflect the nature and underlying bases of the social cognitive deficits

experienced by either patient population. The parrahippocampal and fusiform areas are well established cortical areas within a semantic storage system, and as such, may reflect a greater social semantic loss in the SD patients above that experienced by the bvFTD group. The fusiform area in particular is associated with the perception and storage of facial information, and such information is important in order to meaningfully interpret social signals (Critchley et al., 2000). In contrast, the greater association between social impairment and degradation of the OFC and anterior temporal lobe in bvFTD patients may reflect a more fundamental loss of social conceptual knowledge and information transfer between key nodes within a social cognitive network (Zahn et al., 2009; Kennedy and Adolphs, 2012).

These findings illustrate the potential value of DTI as a functional and disease metric in FTD. Neuroanatomical data derived from DTI and VBM should be compared with caution, given the different properties and technical bases of these modalities; with these caveats in mind, we analysed the present DTI and VBM data in a common pre-processing and statistical framework. Considering both social cognition metrics here, white matter associations were extensive and more consistent than regional grey matter associations, in line with other neuroimaging and neuropathological evidence for extensive white matter pathology in FTD syndromes (Agosta et al., 2011; Mahoney et al., 2013; Whitwell et al., 2010; Neumann et al., 2007; Hiji et al., 2008; Galantucci et al., 2011). The data corroborate previous work suggesting that DTI may generate sensitive, clinically relevant biomarkers of FTD syndromes with potential to inform grey matter metrics (Borroni et al., 2007). White matter signatures based on the FA

metric were substantially less extensive than for other diffusivity metrics here (Table 8 and Table 9). Information about the specific sensitivities and specificities of particular DTI metrics in disease states and more particularly, as correlates of clinical dysfunction remains very limited. The data from this study raise the possibility that certain DTI metrics may reflect functionally-relevant alterations in white matter microarchitecture.

Taken together, these findings further define neurobiological signatures for the social impairment that characterises FTD syndromes, grounded in the emerging neural network paradigm of neurodegenerative disease (Warren et al., 2012, 2013). The findings suggest that certain DTI metrics provide sensitive and functionally relevant indices of white matter damage in FTD and support the further assessment of sarcasm as a useful model for probing social and other cognitive functions that depend on large-scale brain networks. This study has several limitations that suggest directions for future work. The findings should be corroborated in larger cohort studies comparing other neurodegenerative diseases and mimic syndromes such as primary psychiatric disorders for which differentiating biomarkers are particularly required (Niida et al., 2013) and targeting candidate white matter pathways for more detailed tractographic analysis. Longitudinal studies will be essential to establish the sequence of alterations in candidate behavioural and neuroimaging biomarkers, ideally including pre-symptomatic individuals with genetic forms of FTLD, in order to capture very early disease effects. Subsequent histopathological correlation will be required to assess the molecular specificity of biomarker signatures (Rohrer et al., 2011; Whitwell et al., 2011; Warren et al., 2013; Warren et al., 2012). In the

face of these challenges, the present work suggests that white matter metrics of complex behavioural deficits can yield robust signatures of brain network disintegration in FTD that may transcend conventional clinical and imaging markers.

4.6. CHAPTER CONCLUSIONS

These findings further define neurobiological signatures for the social impairment that characterises FTD syndromes, grounded in the emerging neural network paradigm of neurodegenerative disease (Warren et al., 2013). The findings suggest that certain DTI metrics provide sensitive and functionally-relevant indices of white matter damage in FTD and support the further assessment of sarcasm as a useful model for probing social and other cognitive functions that depend on large-scale brain networks.

5. AUDITORY EXPLORATION OF MENTALISING IN bvFTD

5.1. Chapter introduction

One criticism of the experimental investigation of social cognition is that tasks lack ecological validity and relevance to real-world social interaction. This Chapter sought to develop a novel auditory social cognition task which would perhaps bear more ecological validity than standard social cognition tasks by requiring participants to derive social cues by engaging in an everyday activity – listening to music. bvFTD participants were selected as the population of interest for this task due to the pervasive social deficits that are characteristic of this population (see 2.2). There is an extensive literature surrounding the cortical correlates of social cognition (see 2.2.2), and I utilized VBM in the present chapter to examine whether any neural areas previously implicated in social cognition would be associated with performance in the present experimental task.

Mentalising can be broadly defined as the cognitive capacity by which we interpret the behaviour of ourselves and others in terms of mental states (Frith and Frith, 2003) and is an important area of interest within social cognition (see 2.2). The term 'theory of mind' (ToM; see 2.2.1) is often used interchangeably with mentalising, but can be defined more precisely as a crucial component of the mentalising process whereby mental states are explicitly attributed to others (Frith and Frith, 2003). ToM and mentalising in the broader sense together constitute a key capacity within the wider domain of social cognition.

Relations between mentalising, ToM and music processing have not been widely studied; however, music is likely *a priori* to engage brain processes relevant to ToM and it is an attractive candidate stimulus for probing such processes in bvFTD. Music typically entails decoding of an emotional 'message' and music-making generally has a strong social context across human societies (Levitin, 2008). Music has been shown to modulate semantic information in other cognitive systems, such as language (Koelsch et al., 2004). Deficits in processing emotion information in music have been demonstrated in various disease states, notably the frontotemporal dementias, and are dissociable from the processing of other kinds of musical perceptual information (Stewart et al., 2006; Omar et al., 2011; Omar et al., 2010; Johnson et al., 2011; Hsieh et al., 2012). The brain mechanisms of music processing in health and disease and the brain substrates for processing emotional information in music have received considerable attention (Blood et al., 1999; Blood and Zatorre, 2001; Stewart et al., 2006; Gosselin et al., 2006; Koelsch et al., 2006; Mitterschiffthaler et al., 2007; Mizuno and Sugishita, 2007; Caria et al., 2011; Brattico et al., 2011): previous work has implicated a distributed network of cortical and subcortical (in particular, limbic) areas in mediating the emotional response to music, suggesting that music processing unites cognitive representational and evaluative mechanisms with the more 'primitive' neural mechanisms of reward and biological drives (Blood and Zatorre, 2001; Salimpoor et al., 2011; Omar et al., 2011). From this perspective, music might therefore be regarded as a comprehensive and biologically-relevant model stimulus for assessing human frontal lobe functions.

More specifically, recognition of emotion in music engages prefrontal and anterior temporal components of the brain network previously implicated in ToM processing (see 2.2.1; Blood et al., 1999; Rankin et al., 2006; Mizuno and Sugishita, 2007; Eslinger et al., 2011; Rankin et al., 2006; Zahn et al., 2009a; Zahn et al., 2007) and damage involving this network has been linked specifically to deficits of music emotion recognition as well as ToM in bvFTD (Omar et al., 2011). Most previous studies of music emotion processing in the normal brain and in disease states have assessed the processing of elementary or canonical emotions (e.g., 'happiness', 'sadness', 'anger') or basic affective dimensions such as consonance – dissonance in music (e.g. Gosselin et al., 2006; Koelsch et al., 2006; Mitterschiffthaler et al., 2007; Omar et al., 2011; Omar et al., 2010; Caria et al., 2011; Brattico et al., 2011). There is a sense in which all emotional attributions to music involve some degree of mentalising, since musical emotions must be inferred rather than existing explicitly in the stimuli as do animate emotions in facial and vocal expressions. However, behavioural and neuroimaging findings in autism and other disorders of social conduct suggest that music has complex interactions with mentalising (Bhatara et al., 2009; Heaton and Allen, 2009). In particular, it has been demonstrated directly that normal listeners are able to make mentalising judgments about composer agency from musical pieces, and such judgments have functional MRI correlates in the same medial prefrontal and anterior temporal network mediating other kinds of ToM attributions (Steinbeis and Koelsch, 2009). Music is an abstract stimulus yet is widely accessible and highly effective in conveying certain kinds of emotional signals: whereas actual social interactions are often highly complex with many potentially relevant variables, music might allow such interactions to be presented in a reduced,

surrogate form that isolates elements critical for mentalising (Warren, 2008). In particular, music may code multi-component or ambiguous feeling states as abstract representations. Taken together the available evidence suggests that music may probe the interface between ToM, knowledge of social concepts and biological reward (Omar et al., 2011; Blood and Zatorre, 2001); this complex interface is characteristic of 'real world' social interactions, but difficult to access using conventional neuropsychological stimuli.

In this study I assessed mentalising in music using a novel paradigm based on the attribution of affective mental states in a cohort of patients with bvFTD and in healthy control participants. Neuroanatomical correlates of mentalising ability in the patient group were assessed using VBM on structural brain MRI data. Based on previous evidence concerning ToM processing in FTLD (Adenzato et al., 2010; Gregory et al., 2002; Kipps and Hodges, 2006), I hypothesised that attribution of mental states (but not other kinds of attributions) to musical stimuli would be selectively vulnerable in bvFTD. I further hypothesised that performance on the mentalising task would correlate with grey matter volume in medial PFC, OFC and anterior temporal regions previously implicated in both ToM and emotion recognition in music, in FTLD and in the healthy brain (Menon and Levitin, 2005; Eslinger et al., 2011; Zahn et al., 2009a; Zahn et al., 2007; Omar et al., 2011). Consequently, neuroanatomical correlates were assessed firstly across the whole brain, and secondly in smaller regions encompassing these [bilateral and and ventro-medial PFC, and bilateral anterior temporal lobes] specific regions.

5.2. Methods

5.2.1. Participants

Twenty consecutive patients with a diagnosis of bvFTD and twenty healthy control participants were recruited (details summarised in Table 10) according to the methods outlined in Chapter 3 (see section 3.2). No participant had a history of clinically significant hearing loss. All participants had an assessment of general neuropsychological functions (as outlined in 3.4; and shown in Table 10), including the Awareness of Social Inference Test (TASIT; McDonald et al., 2003), which will be utilized in this chapter in a slightly different capacity to the experimental investigation of this task carried out in Chapter 4 Patients' carers completed the Cambridge Behavioural Inventory (CBI; Wedderburn et al., 2008) as an index of behavioural symptoms; item 78 on the CBI ('Appears indifferent to the worries and concerns of family members') was selected for further analysis as the item most relevant to theory of mind. All participants were native to Britain, except one participant who had been resident within the United Kingdom for 15 years, and all had lifelong exposure to Western music. Most participants had fewer than two years formal music training, corresponding to the 'least trained' (novice, non-musician) category of musical experience described by Halpern and colleagues (Halpern et al., 1995).

Table 10. Demographic and neuropsychological characteristics of bvFTD patients and healthy control participants

	bvFTD[§]	<10th Percentile[¶]	Controls	P value
No.	20		20	n/a
Age (years)	64(9.3)		65(8.5)	0.70
Sex (F:M)	4:16		11:9	**0.009**
Education (yrs)	13(3)		15(2)	0.06
Non-musicians†	19		19	ns
CBI (/324)	110(55)		n/a	n/a
CBI (item 78; /4)∞	2.25 (1.5)		n/a	n/a
Symptom duration(yrs)	5.5 (5.4)		n/a	n/a
IQ				
WASI vocab	46.16(16.9)		71.6(4.2)	**0.001**
WASI blocks	22.3(15.0)		48.3(12.5)	**0.0001**
WASI similarities	23.7(10.9)		40.95(6.3)	**0.0001**
WASI matrices	14.11(6.7)		27.5(9.7)	**0.0001**
NART (/50)	28(3.1)	12/28	48(1.6)	0.0001
Episodic memory				
RMT Words (/50)	36.25(7.9)	11/16	47.5(3.6)	**0.0001**
RMT Faces (/50)	35.47(8.4)	11/16	45.2(4.3)	**0.0001**
Executive function				
D-KEFS Stroop word (s)	28(17.6)	6/18	21.5(4.3)	0.65
D-KEFS Stroop inhibition (s)	90.8(34.9)	16/18	55.5(10.1)	**0.0001**
IGT (net total)	-11.1(20.5)		n/a	
Semantic processing				
BPVS (/150)	124.1(20.1)	19/20	147.8(1.9)	**0.0001**
Social cognition				
TASIT emotion (/14)	7.9(2.5)	16/18	11.75(1.2) [§§]	**0.0001**
Other skills				
GNT (/30)	11.6(8.6)	18/18	27(2.7)	**0.0001**
Forwards DS (/12)	8(2.7)	6/18	8(2.7`)	ns
Backwards DS (/12)	6.5(2.6)	8/18	6.5(2.5)	ns
Addition (/12)	5.7(3.5)	7/18	7.1(2.5)	ns
Subtraction (/12)	5.7(3.4)	8/18	8.2(2.4)	**0.01**
VOSP (/20)	15(4.4)	5/18	18(1.6)	**0.002**

Mean (standard deviation) values shown. Significant group differences in t tests *P*<0.05 relative to the present control group and results <5th percentile of published norms are shown in bold. BPVS, British picture vocabulary scale; CBI, Cambridge Behavioural Inventory (Item 78 refers to 'Appears indifferent to the worries and concerns of family members'); D-KEFS Stroop (word and inhibition), Delis-Kaplan Executive Function System; DS, digit span; GNT, Graded Naming Test; IGT, Iowa Gambling Task; n/a, not available; NART, National Adult Reading Test; ns, not significant; RMT, recognition memory test; TASIT, The Awareness of Social Inference Test; VOSP, Visual Object and Space Perception; WASI, Wechsler Abbreviated Scale of Intelligence. ∞ CBI information was collected for only 12 participants. †Defined as <2 years musical training; one control participant had a grade 8 qualification in piano; one patient had a grade 5 qualification in piano. §One bvFTD patient completed only the mentalising condition of the experimental test and the BPVS; two other patients completed only the experimental test and

5.2.2. Experimental behavioural assessment

5.2.2.1.   Structure of the experimental test.

In order to assess mentalising on musical stimuli, we designed a novel behavioural paradigm to assess affective ToM based on forced-choice cross-modal matching of musical samples to word-picture combinations. The paradigm incorporated two conditions that were administered sequentially as separate subtests. In the 'mentalising' condition, music stimuli represented particular affective mental states. In the other 'non-mentalising' condition (designed as a control for the 'mentalising' condition), music stimuli represented non-mental objects and events. Music stimuli were all short non-vocal excerpts derived from the Western classical corpus, including solo instrumental, chamber and orchestral pieces; the complete list of stimuli and foils for each subtest is presented below in Table 11 and Table 12. Musical excerpts were selected from the longer source piece based on the effectiveness of the particular excerpt in representing the mental state or the non-mental object or event, rather than from a fixed section or segment of every source piece. On each trial, the task was to decide which of three word – picture combinations best described the musical sample; each word – picture triad comprised the target, a close foil and a more distant foil (for example, in the mentalising condition, 'dreamy' [target] – 'dreading' [close foil] – 'adventurous' [distant foil]; in the non-mentalising condition, 'raindrops' [target] – 'birdcall' [close foil] – 'train ' [distant foil]). In the mentalising condition, stimuli

and foils were designed to reduce reliance on elementary emotion judgements that could be based on simple perceptual cues (for example, 'dreamy' does not have a close elementary emotional analogue, and would not be distinguished from the close foil 'dreading' based on a single perceptual cue such as 'slow tempo') ; the word choices were in most cases synonyms of those used to designate affective mental states in a standard test of ToM, the Baron-Cohen 'Reading the Mind in the Eyes' test (Baron-Cohen et al., 2001).

Music stimuli for both conditions were chosen based on pilot data in a separate group of 25 young healthy control participants; all musical samples included in the final test were matched to the target word – picture combination by at least 80% of participants in the pilot control group. As a further criterion used in selecting musical examples for the pilot study, pieces with strong prior semantic associations were avoided (in particular, descriptive titles) likely to be widely familiar to musically untrained listeners and implying by association a particular mental or non-mental representation. The musical stimulus sets in the mentalising and non-mentalising conditions were closely comparable in duration, tempo, harmonic and timbral characteristics (solo instrument, chamber or orchestral texture – see Table 11 and Table 12. Pictorial stimuli for the matching task were selected from public internet databases.

5.2.2.2. Experimental procedure.

The experimental test was administered under Matlab7 © (*www.mathworks.com*) running the Cogent1.25 toolbox (*www.vislab.ucl.ac.uk/cogent*) on a notebook computer. Music stimuli were presented in free-field at a comfortable listening

level for each participant (at least 70 dB). Participants were first familiarised with the paradigm using musical examples not subsequently presented in the actual test. Twenty test trials were administered in each condition; conditions were presented in fixed order (non-mentalising followed by mentalising). Combinations of words and pictures (high quality colour images) were simultaneously presented on the computer monitor; target and foil triads were presented in a fixed order, and the relative screen positions of targets and foils were randomised from trial to trial. Participant selections were recorded and stored for offline analysis. In addition, on each trial the participant was asked if they were familiar with the piece, and this information was also recorded. Each piece was presented once; a single repeat of a trial was allowed if the examiner considered that the participant had been distracted during the original presentation. No time limit was imposed and no feedback about performance was given during the test.

Table 11. Music stimuli and foils presented in the experimental behavioural test – Mentalising

Trial	Musical target (Composer)	duration (sec)	target	close foil	distant foil	tempo	type
1	Arcana (Varèse)	30	adventurous	scolding	dreamy	Moderato	Orchestral
2	BWV 847 (Bach)	30	stressed	secretive	mysterious	Adagio	Piano
3	Etudes op.10 n°4 (Chopin)	30	stressed	secretive	mysterious	Allegro	Piano
4	Sonate 2 Scherzo (Chopin)	29	scolding	adventurous	melancholy	Allegro	Piano
5	Piano quintet: molto moderato (Fauré)	31	mysterious	begging	playful	Allegro	Chamber
6	Tallis Fantasia (Vaughan Williams)	32	mysterious	begging	stressed	Adagio	Orchestral
7	Phantasiestücke: Langsam (Schumann)	30	comforting	upset	heroic	Adagio	Chamber
8	Lieder Ohne Worte: n°1 (Mendelssohn)	33	comforting	upset	heroic	Moderato	Piano
9	Symphony n°3: 2nd mov (Gorecki)	30	dreamy	dreading	adventurous	Adagio	Orchestral
10	Piano Concerto 1: Larghetto (Chopin)	31	dreamy	dreading	adventurous	Adagio	Orchestral
11	Mantra (Stockhausen)	30	dreading	dreamy	comforting	Moderato	Chamber
12	Music for Strings, Percussion & Celesta: Adagio (Bartok)	31	dreading	dreamy	comforting	Adagio	Chamber
13	Magnificat 1 (Bach)	29	heroic	friendly	lazy	Allegro	Orchestral
14	Gymnopédie 1 (Satie)	27	lazy	melancholy	heroic	Adagio	Piano
15	Appassionata sonata: Andante (Beethoven)	32	lazy	melancholy	heroic	Adagio	Piano
16	Sospiri (Elgar)	31	melancholy	lazy	scolding	Adagio	Orchestral
17	Plink Plank Plunk (Leroy Anderson)	28	playful	seductive	begging	Allegro	Orchestral
18	Tic Toc Choc (Couperin)	30	playful	seductive	begging	Allegro	Harpsichord
19	Piano Concerto 1: Larghetto (Chopin)	30	secretive	stressed	seductive	Adagio	Orchestral
20	Violin Sonata: Blues (Ravel)	32	seductive	playful	secretive	Adagio	Chamber
Mean (std)		30 (1.4)					

Table 12. Music stimuli and foils presented in the experimental behavioural test – world event

Trial	Musical target (Composer)	duration (sec)	target	close foil	distant foil	tempo	type**
1	Petite suite en bateau (Debussy)	26	bird calls	raindrops	waves	Adagio	Piano
2	Symphony no 6 Mov 2 (Beethoven)	18	bird calls	raindrops	waves	Allegro	Orchestral
3	Symphony No. 6 opening (Haydn)	33	sunrise	waves	storm	Adagio	Orchestral
4	Ma Mere L'Oye: Le jardin Féerique (Ravel)	27	sunrise	waves	storm	Adagio	Orchestral
5	Revolutionary Etude (Chopin)	32	waterfall	flying	horse	Allegro	Piano
6	Daphnis et Chloé: Suite n°3 (Ravel)	29	flying	waterfall	donkey	Adagio	Orchestral
7	Romeo and Juliet: Death of Tybalt (Prokofiev)	31	machinery	car horns	snow	Moderato	Orchestral
8	Koyaanisqatsi The Grid (Glass)	34	machinery	car horns	snow	Allegro	Chamber
9	Koyaanisqatsi Cloudscape (Glass)	30	carhorns	machinery	snow	Adagio	Chamber
10	Symphony n°4 Scherzo (Tchaïkovsky)	31	raindrops	train	bird calls	Allegro	Orchestral
11	String quartet n°4, mov 4 (Bartok)	30	raindrops	train	bird calls	Allegro	Chamber
12	The Keel Row (Trad)	29	horse	donkey	waterfall	Moderato	Piano
13	German Dance No 3 K605 (Mozart)	32	horse	donkey	waterfall	Moderato	Chamber
14	D'un Jardin Clair (Boulanger)	31	snow	waves	machinery	Adagio	Piano
15	Doctor Gradus ad Parnassum (Debussy)	24	snow	waves	machinery	Allegro	Piano
16	Rite du Printemps: Danse de la terre (Stravinsky)	23	storm	train	sunrise	Adagio	Orchestral
17	The Chairman Dances: Foxtrot (Adams)	30	train	storm	sunrise	Moderato	Orchestral
18	Pacific 231 (Honneger)	30	train	storm	sunrise	Adagio	Orchestral
19	Caravan (Adler)	15	wind	waves	car horns	Moderato	Harmonica
20	Tolstoy farm from Satyagraha (Glass)	28	wind	waves	car horns	Allegro	Chamber
Mean (std)*		28 (4.9)					

Trials in each subset were presented in randomised order *mean stimulus duration, tempo and type did not differ significantly (p > 0.05) between subtests**'type' here summarises the harmonic and timbral texture of the excerpt (solo instrument, chamber or orchestra.

5.2.3. MRI acquisition

Images were acquired as described in Chapter 3 (section 3.8.1).

5.2.4. Image Processing

Structural images were pre-processed using the methods described in Chapter 3 (section 3.8.4.3.1) for VBM data.

5.3. Analysis

5.3.1. Analysis of neuropsychological performance

Neuropsychological data were analysed according to methods described in Chapter 3 (see 3.4).

5.3.2. Analysis of behavioural data.

Behavioural data were analysed using STATA 12©. Experimental data were analysed using repeated-measures regression models incorporating participant scores in the mentalising or non-mentalising condition as a within-subject variable, group (bvFTD or control) as a between-subjects variable; and participant age, gender, and scores on the colour-word inhibition Stroop task, the BPVS, and the NART as covariates of no interest (to adjust for possible performance effects of demographic bias, general executive capacity, single-word comprehension, and premorbid IQ, respectively). Imageability and lexical frequency of the words presented in both conditions were calculated using the N-Watch psycholinguistic research database

(), in order to examine whether such characteristics could be contributing to the results. Population averaged models for repeated measures were used to examine the group by task interaction, with and without adjustment for word imageability and lexical frequency.

In order to assess how well mentalising and non-mentalising conditions were able to discriminate bvFTD patients from healthy controls we constructed receiver operating characteristic (ROC) curves whereby the discriminatory ability of each task was quantified using the area under the curve (AUC). The AUC is the probability that in a randomly selected patient/control pair, the patient has a lower score than the control (Hanley & McNeil, 1982); perfect discrimination between patient and control groups would correspond to an AUC of 1, whilst the same distribution of scores in patients and controls would correspond to an AUC of 0.5.. Correlations between experimental tasks and between each experimental task and potentially relevant demographic, behavioural (CBI) and general neuropsychological variables were assessed using Spearman's rho in the patient group.

5.3.3. Image analysis.

MRI images were analysed according to methods described in Chapter 3 (3.8.3). Linear regression models were used to examine regional grey matter volume associations with performance on each of the experimental subtests; voxel intensity (an index of grey matter volume) was modelled as a function of subtest score in all patients, including participant's age, TIV and Stroop inhibition score (a measure of general executive performance) as covariates of no interest. Separate

models were used to assess grey matter associations of each experimental task separately and after combining task regressors in a common design matrix (to allow neuroanatomical associations of each task to be compared directly). Statistical parametric maps of regional grey matter volume associations with score on each experimental subtest were first examined at threshold $p<0.05$ after family-wise error (FWE) correction for multiple comparisons over the whole brain, and then after small volume correction using anatomical regions based on our *a priori* hypotheses if whole-brain analysis did not yield a significant result.

Anatomical small volumes were derived by manual tracing from the template brain image using MRIcron ® (http://www.sph.sc.edu/comd/rorder/mricron.html) and comprised a prefrontal (combined OFC – ventro-medial PFC) region and left and right anterior temporal lobe regions . The prefrontal region included bilateral OFC (including the orbital surface of both frontal lobes and the lateral orbital gyri below the inferior frontal sulcus bilaterally) and ventro-medial PFC (the medial inter-hemispheric surface of both frontal lobes, extending superiorly to the apex of the callosal genu). Each anterior temporal lobe volume extended from the temporal pole posteriorly to the most anterior extension of Heschl's sulcus (Kim et al., 2000). These volume boundaries were intentionally generous, to ensure that individual variations in brain anatomy were all fully encompassed, however, all anatomical attributions within these volumes were subsequently checked visually in order to ensure accurate localisation to particular regions within the volume.

5.4. Results

5.4.1. Demographic characteristics

The bvFTD and control groups were well matched for age (p=0.7); males were over-represented in the patient group (p=0.009), and gender accordingly was included as a covariate of no interest in all analyses. Patients and controls did not differ significantly in educational background, though there was a trend to longer time spent in formal education in the control group (p=0.06).

5.4.2. General neuropsychological performance

As a group the bvFTD patients showed the anticipated profile of deficits relative to healthy control participants, showing impaired performance on measures of executive function, memory and naming (Table 11). Relative to this control group (who displayed well above average neuropsychological performance), patients also showed reduced single word comprehension and visual object perception. However, it is of note that these scores did not fall within the impaired range (<5th %ile) based on published norms.

5.4.3. Experimental task performance

Scores for the bvFTD and control groups in each subtest are displayed in Figure 4. No significant group by task interaction was found. Healthy control participants performed comparably on both experimental tasks. A repeated measures regression model (adjusted for verbal comprehension, general executive performance, premorbid IQ, age, and gender) revealed a significant deficit in the bvFTD group relative to healthy controls in the mentalising

condition (p<0.003); there was no significant group performance difference in the non-mentalising condition, though there was a non-significant trend to worse performance in the bvFTD group on this subtest (p=0.08). No significant group by task interaction was found. However, after adjustment for word imageability and frequency the estimated group by task interaction was of similar magnitude, suggesting that these components had little impact on the findings.

Figure 4. Task performance in patients and healthy controls for both experimental tasks
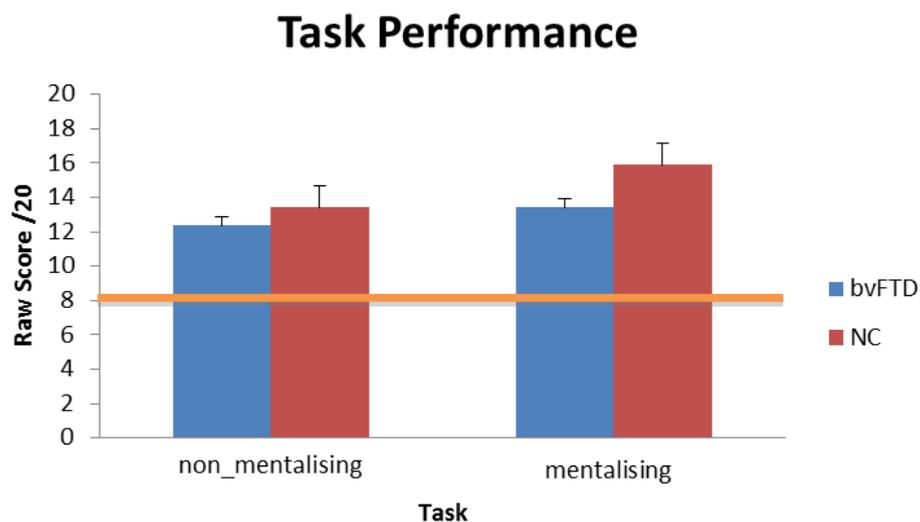
Task Performance

Performance (mean + S.E.M) on musical mentalising and non-mentalising tasks for the behavioural variant frontotemporal dementia (bvFTD) and normal control (NC) groups. Orange line represents chance score.

Spearman correlation analyses revealed that scores on the two experimental tasks were significantly correlated (p=0.003). Scores on the TASIT were found to be significantly selectively correlated with performance on the mentalising task, (p=0.002) though not the non-mentalising task (p=0.067). In addition, scores on the selected CBI item ('Appears indifferent to the worries and concerns of family members') were significantly negatively correlated with performance on the

mentalising task (p=0.03), but not the non-mentalising task (p =0.67). There were no correlations between performance on either experimental task and executive function, single word comprehension, clinical disease duration, years of education, or premorbid intelligence estimates. Only two control participants reported prior familiarity with over half the musical examples used; most participants reported no prior familiarity with the musical examples. Accordingly we did not perform a formal regression analysis of performance on prior musical familiarity. However, a separate analysis excluding the two control participants who reported higher prior familiarity with the musical examples did not materially change the findings.

ROC curves based on each of the experimental tasks discriminated between bvFTD patients and healthy controls (Figure 5). A comparison of mentalising and non-mentalising AUC performance is presented in Figure 5. No significant AUC difference was found between the mentalising and non-mentalising tasks, however mentalising task performance showed a trend toward greater sensitivity and specificity (AUC coefficient 0.88 (95%: CI 0.73, 0.95) compared with the non-mentalising task (AUC coefficient 0.73 (95% CI: 0.57, 0.90). Further binomial breakdown of the AUCs revealed that a cutpoint raw score of 15 on the mentalising task correctly classified 85% of participants as being either a patient or a control, whereas this was reduced to 71% for the non-mentalising task using the same cut-point value.

Figure 5. Comparison of musical mentalising and non-mentalising performance AUC: prediction of disease by task performance
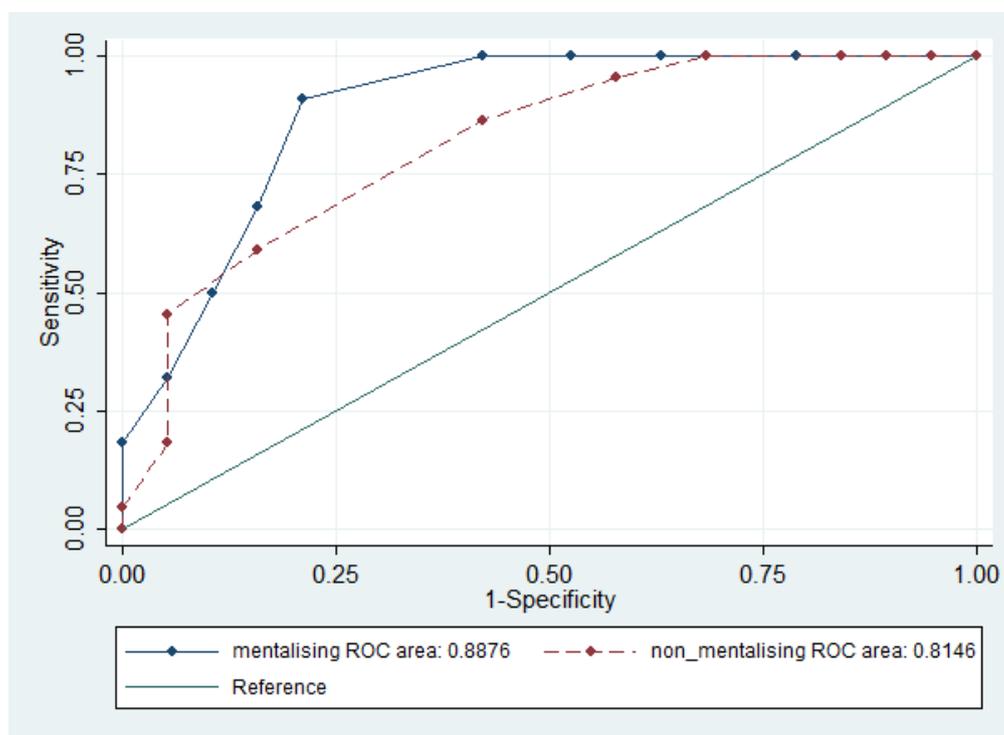
The ROC curves use total scores (/20) in each task to discriminate between bvFTD patients and normal controls.

Examining individual participant performance profiles (Figure 6), five patients showed a clear (>4 point) discrepancy in favour of superior performance on the non-mentalising task. However, two patients showed the reverse pattern, with superior performance on the mentalising task. No similarly marked discrepancies were seen for individuals in the healthy control group (Figure 6).

Figure 6. Raw performance across tasks in bvFTD and healthy control participants
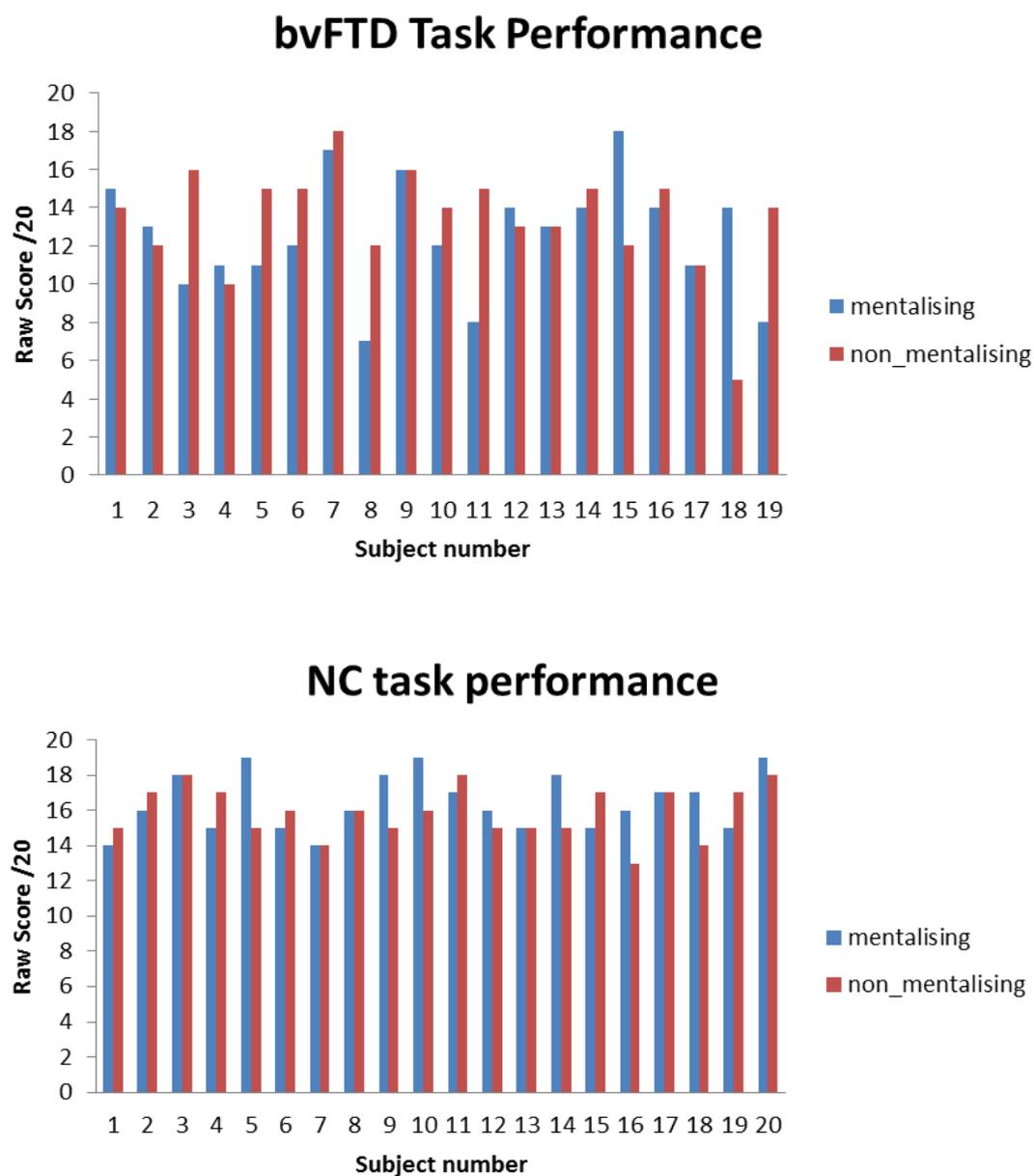
Individual performance profiles for participants in the behavioural variant frontotemporal dementia (bvFTD) and normal control (NC) groups. (A). Patients 3, 5, 8, 11 and 19 showed a >4 point discrepancy between subtest scores, with superior performance on the musical non-metalising task; patients 15 and 18 showed the reverse performance pattern. (B) For individuals in the NC group, the discrepancy between scores on each subtest was never >3 points.

5.4.4. Neuroanatomical associations

Statistical parametric maps of grey matter volume associations with performance in the mentalising and non-mentalising conditions are shown in Figure 7; data for local maxima of grey matter change are summarised in Table 13.

At the level of the whole brain: No significant positive or negative associations between performance on the mentalising task and grey matter volume were identified. Performance on the non-mentalising task showed no significant positive associations with grey matter volume. However, better performance on the non-mentalising task was associated with less grey matter volume in ventromedial PFC ($p<0.05$ after FWE correction for multiple comparisons over the whole-brain). When neuroanatomical associations of performance in each task were compared in a combined design, performance on the mentalising task was significantly more strongly associated with grey matter in ventromedial PFC than was performance on the non-mentalising task ($p<0.05$ after FWE correction for multiple comparisons over the whole-brain); there were no regions in which the association between volume and score was greater for the non-mentalising than for the mentalising task.

At the level of small volume correction: Performance on the mentalising task was positively associated with grey matter volume in right entorhinal cortex ($p<0.05$ after FWE correction for multiple comparisons within the anatomical small volume of interest). No significant negative associations between performance on the

mentalising task and grey matter volume were identified. Performance on the non-mentalising task showed no significant positive associations with grey matter volume. There were no regions in which the association between volume and score was greater for the non-mentalising than for the mentalising task after correction for multiple comparisons within the small volume of interest.

Statistical parametric maps (SPMs, shown in white) of regional grey matter volume positively correlated with performance on the musical mentalising task (above) and significantly more strongly correlated with performance on the mentalising than the non-mentalising task (below) in the bvFTD group. SPMs are rendered on the mean customised template image in MNI space; sagittal (left) and axial (right) sections are shown, and the left hemisphere is shown on the left in axial sections. For display purposes, SPMs have been thresholded at p<0.001 uncorrected; however, the grey matter correlations shown were also present thresholded at p<0.05 after correction for multiple comparisons (see Table 14).

Table 13. Summary of VBM findings in bvFTD group

Behavioural correlate	Direction of correlation	Brain region	Cerebral hemisphere	Peak coordinates	Z-score
Mentalising	+	Anterior entorhinal	Right	26 -3 -35	4.09*
Non-mentalising	_	Ventro-medial PFC	Left	-12 69 -9	6.1**
Mentalising > Non-mentalising	+	Ventro-medial PFC	Left	-12 69 -9	5.4**

Coordinates (mm) of local maxima for grey matter volume change correlating with behavioural performance in the patient group are shown in Montreal Neurological Institute standard sterotactic space. All results listed were significant at threshold $p<0.05$ corrected for multiple comparisons *within the prespecified anatomical small volume of interest (see text), or ** over the whole brain. PFC, prefrontal cortex

5.5. Discussion

Here I have presented evidence that ability to attribute surrogate affective mental states to music may be impaired in bvFTD. These findings move beyond previous work demonstrating that the ability to label simple emotions in music is impaired in bvFTD as part of a more general multimodal impairment of emotion processing (Omar et al., 2011; Hsieh et al., 2012): the deficit demonstrated here lay with attribution of more complex feeling states to music, and furthermore, the deficit may be at least partly specific for the attribution of mental states versus other, non-mental representations within the domain of music, although a statistically significant interaction effect was not found. This musical mentalising deficit was not attributable to general executive dysfunction, premorbid intelligence or other potentially relevant confounding factors, but did correlate specifically with performance on a test of social inference (TASIT) requiring interpretation of others' mental states, as well as with carer-reported real-world quantitative estimates of patients' ability to interpret others' mental states on the Cambridge Behavioural Inventory (an index shown previously to be sensitive to functional behavioural changes in bvFTD: (Kipps et al., 2009a). I cannot completely exclude the possibility that performance on the musical mentalising task was driven by processing of word and picture labels rather than musical pieces per se: however, a musical mentalising deficit was demonstrated after adjusting for certain relevant characteristics of the labels in each condition and adjusting for general verbal semantic capacity. The specific correlation of experimental mentalising task performance here with standard measures of mentalising performance

provides further evidence that our mentalising task here did, indeed, index musical mentalising capacity. The results of the mentalising deficit shown may suggest relative specificity, which could potentially be in keeping with previous evidence that patients with bvFTD can exhibit dissociable impairments of theory of mind function independent of general executive capacity (Lough et al., 2001). The present findings show that, remarkably, the mentalising deficit in bvFTD extends to the abstract realm of music. Because music is a somewhat unusual vehicle for attributions of this kind, the question arises whether the results could simply reflect a task difficulty effect. This explanation is unlikely: attribution of non-mental characteristics to music is, if anything, intrinsically even more demanding, and indeed, single participant performance profiles here revealed individual patients who had selective difficulty with non-mental musical attributions. Furthermore, healthy control participants showed no such task-specific effect that is suggested by the performance of bvFTD participants, although it must be noted that the observed deficit was weak and occurred in the absence of a robust interaction effect.

The behavioural mentalising deficit here was associated with grey matter changes in brain regions (the anterior temporal lobe and ventro-medial PFC) previously implicated in mentalising both in the healthy brain and in disease (Gallagher and Frith, 2003; Carrington and Bailey, 2009). In particular, the anterior medial prefrontal and right anterior temporal cortical associations here were in proximity to areas identified in a previous study of mentalising in music (Steinbeis and Koelsch, 2009). Furthermore, the neuroanatomical associations I have identified are in line with previous evidence for the brain substrates of

mentalising in other modalities in bvFTD (Gregory et al., 2002; Kipps et al., 2009b). The positive correlation of grey matter in anterior temporal cortex with musical mentalising ability accords with previous evidence that this region abstracts information relevant to social concept processing (Zahn et al., 2009); while the correlation between reduced grey matter in PFC with better performance in the non-mentalising condition may imply that relative sparing of mentalising regions (in the context of more widespread associated brain damage) interferes with analysis of music for non-mental representations. Atrophy of inferior frontal lobe cortex has previously been shown to be an early feature of bvFTD (Perry et al., 2006): though detailed longitudinal behavioural studies are presently lacking, a strong *prima facie* case could be made on both clinical and neuroimaging grounds that mentalising ability may be a sensitive and early indicator of incipient bvFTD. Caution is needed in interpreting the present VBM results, since the patient cohort was relatively small in relation to the known clinical and anatomical heterogeneity of bvFTD (Rohrer et al., 2011). However, acknowledging this caveat, I would argue based on the present evidence that music is a promising model system to capture theory of mind dysfunction and perhaps thereby assist in the early detection of bvFTD: musical mentalising requires representation of abstract qualities from a complex stimulus, for which (unlike real-life social scenarios) stimulus properties can be manipulated relatively precisely.

Aside from their clinical implications, our findings speak to certain key issues in the neurobiology of music and social cognition more generally. The neurobiological study of music is challenging, as there are currently no adequate

non-human models of music processing and music is typically invested with extensive socio-cultural associations that are at least partly learned. Indeed, music constitutes a universal human artefact that (along with other artefacts) can be invested with social signals such as agency (Steinbeis and Koelsch, 2009). Functional imaging of the healthy brain can delineate correlates of music processing but cannot distinguish critical correlates from those that may be epiphenomenal. Human diseases that affect music processing therefore constitute potentially informative 'experiments of nature'; however, most diseases produce substantial associated brain damage impacting on non-musical functions or (like stroke) they affect musical processing mechanisms stochastically. bvFTD is an ideal model system with which to address core biological functions of music: this disease selectively affects complex human social behaviours while sparing many other aspects of cognition, and targets a large-scale intrinsic brain network that links sensory experience with affective, semantic and reward processing (Seeley et al., 2007; Zhou et al., 2010, 2012; Raj et al., 2012). It has been demonstrated that neural structures predominantly implicated in bvFTD comprise long Von Economo projection neurons linking insular, cingulate and prefrontal cortices and subcortical centres (Seeley et al., 2012): humans are one of a small number of species that possess these neurons and they appear to serve as a critical substrate for complex social behaviour. The network bound by these neurons has also been shown to be integral to music processing (Blood and Zatorre, 2001; Omar et al., 2011): previously this was somewhat paradoxical, as the evolutionary value of music remains speculative (Mithen, 2005). The present findings in bvFTD raise the possibility that the modelling of mental states may be a core neurobiological function of music.

This interpretation is in line with accumulating neurobiological and ethnographic evidence (Levitin, 2008). It has been proposed that music played a specific role in decoding others' emotion states during human evolution (Mithen, 2005). Recognition of emotion in music engages components of the brain network previously implicated in mentalising (Rankin et al., 2006; Zahn, et al. 2007, 2009; Eslinger et al., 2011) and behavioural findings in autism and other disorders of social conduct have previously suggested that music has complex interactions with mentalising (Bhatara et al., 2009; Heaton and Allen, 2009). I propose that, precisely on account of its abstract, inanimate nature, music may be highly effective in conveying certain kinds of signals relevant to mentalising: whereas actual social interactions are often highly complex with many potentially relevant variables, music might allow such interactions to be presented in a reduced, surrogate form that isolates elements critical for mentalising with low behavioural cost (Warren, 2008). A capacity to use music in this way would likely enhance empathy and pair-bonding and might therefore have been selected during human evolution (Mithen, 2005; Warren, 2008). This hypothesis requires further examination with a more comprehensive behavioural examination of musical mentalising in the healthy brain as well as disease states, and with correlative structural and functional imaging to establish the underlying brain mechanisms in detail.

This study has several limitations. Clearly, a key issue for the strength of interpretation of these results is the lack of a significant interaction effect between performance in the mentalising task versus performance in the non-

mentalising task. The fact that the results of the mentalising task correlate with real-world measures of affective ToM, where the non-mentalising task did not, give strength to the possibility of a selective mentalising deficit, however we cannot prove this here. Future work may benefit from larger sample sizes to increase power of the results and the potential likelihood of finding a significant interaction. There is a need to further substantiate the validity and limitations of the mentalising paradigm as applied to music, and the relation between elementary emotion processing and the attribution of more complex or ambiguous affective states to music. There is no universally agreed 'lexicon' of musical emotions and more information is needed about musical mentalising in the healthy brain. Mentalising in music should ideally be studied in the context of a more comprehensive assessment of mentalising abilities in different modalities; this would enable evaluation of the specificity and sensitivity of the music-associated deficit. In a related vein, it would be relevant to manipulate musical stimulus parameters such as familiarity, valence and complexity as well as perceptual characteristics to assess the extent to which these may modulate mentalising on musical stimuli. From a clinical perspective, there is a need for detailed neuropathological correlation in bvFTD populations, both to establish disease associations and to correlate behavioural deficits with histopathological features. It would, for example, be intriguing to evaluate the role of Von Economo neurons in this very specifically human ability (Seeley et al., 2006). In addition, the promise of early disease detection requires further substantiation of the timing of development of mentalising deficits in the course of bvFTD evolution. It would be of great interest, for example, to establish whether such deficits (and particularly, deficits of more abstract theory of mind processes, such as those

embodied in music) might lead other features in presymptomatic carriers of mutations causing bvFTD. This will require longitudinal study of individuals affected and at-risk of developing bvFTD. Furthermore, the stimuli were presented in a fixed order, such that practice or fatigue may have played a role in performance based on that fixed order. Future work may benefit from randomizing presentation to account for this. Taking these caveats into account, the present findings provide evidence that music can represent surrogate mental states and that the ability to construct such mental representations is impaired in bvFTD. The findings have potential implications for our understanding of the biology of this disease and human social cognition more broadly.

5.6. CHAPTER CONCLUSIONS

To conclude, in this Chapter I have explored metalising ability in a cohort of bvFTD patients using a novel auditory task. Results from this task suggest the possibility of a specific deficit in the ability to extract emotive information from auditory excerpts in bvFTD patients disproportionate to their ability to extract other meaningful information from similar excepts, and to the overall performance of matched healthy controls. This behavioural deficit was found in the absence of a significant group by task interaction, however, and as such must be interpreted with caution. The specificity of this behavioural deficit requires further examination. This performance deficit was localised using VBM to the right entorhinal cortex and ventromedial PFC, areas previously implicated within a broad 'mentalising network'. Together, these findings suggest the use of such an auditory task as a valid and potentially useful tool in assessing mentalising.

6. NEURAL TIMING IN BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA

6.1. Chapter introduction

Precise timing is essential for many human behaviours (Bueti et al., 2008). Timing has been claimed to be integral not only in making sense of the temporal course of events but also in planning and attention (Grondin, 2010; Allman et al., 2011; Allman and Meck, 2012), and is also postulated to contribute to ToM (Baron-Cohen et al., 2001). Each of these processes are deficient in bvFTD to some extent (see 2.2 and 2.3 for more detail), and thus it may be possible that such hallmark deficits observed in this heterogeneous syndrome are at least partially mediated by loss of/impairments in/changes to a subjective sense of time and the ability to meaningfully perceive and monitor behaviour according to an implicit timing mechanism (Buonomano and Karmarkar, 2002; Allman and Meck, 2012). These cognitive capacities remain relatively intact in AD and the primary progressive aphasia syndromes of SD and PNFA, and as such it was postulated that timing would be relatively preserved in these populations. However, these patient groups were included in the present chapter for a more comprehensive evaluation of timing in this neurodegenerative disease and as neurologically compromised comparator populations against the bvFTD group. This chapter will explore neural timing function in bvFTD in order to investigate whether any neural timing deficits exist in this population. In the next chapter, neural timing will be further discussed within the broad context of executive function and the executive processes that may contribute to timing ability. Much work has been

done to elucidate the cortical basis of timing, however little is known about the role of white matter inthis cognitive capacity. The present study utilized VBM in order to explore the grey matter correlates of timing, and DTI was utilized to elucidate whether white matter pathways are important for intact timing function.

Timing has been used as a model system of cognitive dysfunction in neurological disease states because it is involved in many important mental functions: perception and encoding of temporal information, attention shifting, storage and retrieval from long-term memory, and comparison of the temporal memory with other stored templates (Rowe et al., 2010). Disorders of time and perturbations in timing mechanisms have been observed in a number of different neurological conditions including Parkinson's disease (O'Boyle et al., 1996; Perbal et al., 2005), Huntington's disease (Rowe et al., 2010; Hinton et al., 2007), schizophrenia (Davalos et al., 2005), frontal lesion patients (Picton et al., 2006) and a single case study of a patient with frontotemporal dementia (Wiener and Coslett, 2008).

Much work has been done to elucidate the neuroanatomical bases underlying human timing in both healthy individuals as well as those with focal and degenerative brain lesions. Recent functional meta-analyses (Ortuno et al., 2011; Coull et al., 2012) highlight the role of the motor and supplementary motor areas as integral components of a larger thalamo-cortico-striatal neural timing circuit. Couell and colleagues (2012) draw attention to the necessity of differentiating between implicit and explicit timing requirements when examining the neurological substrates of these supposedly biologically separable concepts.

These authors postulate that participants form a temporal template of the timing information presented and when using this to predict the onset of a stimulus, such as is required in a self-paced finger tapping task, they engage the parietal cortex, left premotor areas, and the cerebellum (Couell et al., 2012). This was also supported by a study of self-paced tapping in HD patients in which the supplementary motor area (SMA), premotor cortex (PMC), dorsolateral prefrontal cortex (DLPFC), and basal ganglia (BG) were found to subserve this function (Bechtel et al., 2010; Rowe et al., 2010). Indeed, results from studies in Parkinson's disease (O'Boyle et al., 1996; Harrington and Haaland, 1999) and cerebellar lesion patients (Spencer et al., 2003), as well as in healthy controls (Coull et al., 2012; Lewis and Miall, 2003) are often interpreted as reflecting the involvement of both the cerebellum and BG in timekeeping operations (Bueti et al., 2008), suggesting a common subcortical network of timing-related areas underpinning the use of time both for action and perception. This is further supported by investigation of self-paced timing in the context of manifest Huntington's disease (Rowe et al., 2010) and Parkinson's disease (Harrington and Haaland, 1999), which has shown impaired performance worsening with progressive degeneration of the BG and other disease-associated structures. It is likely that timing is subserved by a widespread network of connected structures and that damage to any one of these components of the neural timing circuit could cause dysfunction in timing ability.

Many of the aforementioned structures implicated in paced neural timing ability (Witt et al., 2008; Coull et al., 2012) represent a constellation of anatomical regions that are consistently targeted by FTD pathology, suggesting that paced

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timing tasks may be sensitive to FTD-related dysfunction. One of the earliest sites of pathological involvement in bvFTD is the striatum (Snowden et al., 2003), which has also been proposed as the core timer within a cortico-thalamo-striatal neural timing network (Allman and Meck, 2012). The cerebellum further represents a common focus of timing literature, and although not commonly conceptualised as a centre of pathology in bvFTD, this structure has recently been implicated in the pathogenesis of the FTD-MND gene c9ORF72 (Mahoney et al., 2012a; Majounie et al., 2012a; DeJesus-Hernandez et al., 2011). Indeed a recent report suggests that the cerebellum in cases with c9ORF72 mutations, of which bvFTD is the most common phenotype, is one of the earliest and most prominent sites of pathological deposition and subsequent degradation (Mahoney et al., 2012b).

Although bvFTD is phenotypically, pathologically and genetically highly heterogeneous, imaging studies suggest that the underlying neurodegeneration and spread of pathological deposition follows a somewhat predictable trajectory (Hornberger et al., 2012). Neuroimaging studies using techniques such as diffusion tensor imaging (DTI) also suggest that the integrity of white-matter tracts in those with bvFTD are compromised before the degradation of grey matter macrostructure (Agosta et al., 2011) and that such tract degradation also follows a somewhat predictable atrophic trajectory (Agosta et al., 2012; Zhang et al., 2013). Grey matter structures particularly relevant to the proposed neural timing circuitry, including the basal ganglia and cerebellum, are spread within cerebral white matter; however, to the best of our knowledge, no group study has identified an association between neural timing ability and integrity of underlying

white-matter tracts, nor has neural timing been examined within the context of bvFTD.

The current study employed a finger-tapping paradigm to examine neural timing in bvFTD. Finger-tapping tasks require participants to button-press in time with a paced metronome (externally-paced), or to keep that beat once the metronome has ceased (self-paced), and are often used to assess timing ability. Such tasks have been shown to provide invaluable metrics to tracking the manifestation and progression of disease in persons prodromal to and affected by both Huntington's disease (HD) (Betchel et al., 2010; Rowe et al., 2010) and Parkinson's disease (O'Boyle et al., 1996), and have also been used to explore the differential effects of focal frontal lesions on timing performance (Picton et al., 2006). Several statistical models have been proposed to evaluate performance on such timing tasks. The most widely-accepted approach is that offered by Wing and Kristofferson (1973), which purports that time can be parcelled out at the neural level into clock and motor contributions to timing ability and variability. Studies of patients with neurological damage have provided some evidence that the two processes of motor and clock variance can be dissociated and mapped onto discrete neural systems (Ivry and Spencer, 2004; Spencer et al., 2003). Continued investigation of timing in neurological populations may further elucidate both neurological timing mechanisms as well as provide novel metrics of understanding manifestation and progression of disease.

This study aimed to assess the ability of a cohort of patients with bvFTD to keep time under externally-paced and self-paced conditions. Grey and white matter

correlates of timing ability in bvFTD were assessed using VBM and DTI. It was hypothesized that in comparison to both healthy individuals, and a population of neurologically-compromised disease controls, bvFTD participants would be able to keep the beat with an externally-paced tone, but would show a deficiency in their ability to maintain a regular supra-second beat without the aid of external cues in a self-paced task. Should such a dysfunction be observed, it was hypothesized to emanate from a disruption of the underlying cortical-subcortical circuit subserving time mechanisms and the white matter tracts underlying this, which I propose to be degraded in bvFTD. The present study therefore assessed grey and white matter integrity across the whole brain, and in addition the left portion of the SMA was used as an area of small volume correction for the grey matter analyses, according to *a priori* hypotheses in connection with this area (Couell et al., 2012), which indicate the SMA to be a crucial structure to neural timing ability.

6.2. Methods

6.2.1. Participants

Twenty two participants with a diagnosis bvFTD, 12 participants with a diagnosis of SD, eight participants with a diagnosis of PNFA , eight participants fulfilling consensus criteria for AD, and 35 healthy control participants were recruited according to methods outlined in Chapter 3 (sections 3.2; 3.5). Demographic details are summarised in Table 14.

6.2.2. Experimental behavioural assessment

6.2.2.1. Externally-paced tapping task

Participants were informed that they would hear a series of tones, and that these would be played according to a regular beat [1500ms intervals; 0.67Hz]. Participants were instructed to use the index finger of their dominant hand to tap in pace with these tones, and further, that because the tones were produced according to a regular beat, that they should start to be able to predict when each tone was to be played and thus tap at the same time as the production of the tone. Participants were given a practice session in which a series of six auditory stimuli separated by the fixed interval of 1500ms was presented, and subsequently presented with a total of 50 auditory stimuli.

6.2.2.2. Self-Paced tapping task

After the completion of the paced tapping task, participants were instructed that they would be presented with a short succession of tones, to which they should similarly keep the pace using the index finger of the dominant hand. Participants were informed that these tones would cease after a short period and that they would be required to keep the beat going by continuing to tap at the same pace until they were instructed to stop. The synchronization phase consisted of 6 auditory stimuli separated by a fixed interval of 1500ms, following which participants were required to continue tapping at the established pace for a further 50 taps.

6.2.3. Experimental procedure

The experimental test was administered under Superlab © on a Dell OptiPlex 960 computer. Tone stimuli were presented in free field at a comfortable listening

level for each participant (at least 70 dB). The timing of finger taps was recorded

using a Cedrus® RB-730 Response Pad . Conditions were presented in fixed order

(externally-paced followed by self-paced). Participant responses were recorded

and stored for offline analysis. A single repeat of task was allowed if the examiner

considered that the participant had been distracted during the original

presentation or did not adequately understand the task requirements. No

feedback about performance was given during the session.

6.2.4.   Analysis of neuropsychological performance

Neuropsychological data were analysed according to methods described in

Chapter 3 (see 3.4)

6.2.5.   Analysis of behavioural data.

Behavioural data were analysed using STATA 12©. The data were analysed

according to the Wing and Kristofferson (1973) model of motor response timing.

This model proposes that each inter-response interval is determined by two

processes: a central timekeeper or clock that provides the trigger to initiate the

response at intervals C, and a motor system delay, D, between the clock trigger

and the response. It is assumed that both clock interval and motor delay vary

between responses and that these two processes are independent. A further

assumption is that each inter-response interval is determined by only the clock

interval C for that response and the motor delay D both for that response and for

the preceding response, so for the jth response:

$$I_j = C_j - D_{j-1} + D_j$$

The dependence of the inter-response interval on the motor delay of the previous response imposes a negative correlation between successive inter-response intervals: a short inter-response interval will be expected to follow a long inter-response interval, or a long interval is expected follow a short interval. This negative lag one autocorrelation, ρ(1), allows separation of the clock and motor delay components of the timing process. It is defined as:

$$\rho(1) = \frac{G(1)}{G(0)}$$

Where, G(1) is the lag 1 covariance and G(0) is the lag 0 covariance (i.e. equivalent to variance of the inter-response interval). It is assumed that for lag greater than 1 the autocorrelations are zero, since there should be no dependence between responses separated by more than 1 interval. Based on this assumption, the variance in the motor delay and clock process can then be estimated as:

$$\sigma_D^2 = -G(1)$$

$$\sigma_C^2 = G(0) + 2G(1)$$

If there is no motor delay $\rho(1)$ will be 0, since there will be no lag 1 covariance, and G(1) will also equal zero. If there is no clock variability $\rho(1)$ will be -0.5 (half the variability determined by the motor delay of the j-1th response and half by the motor delay of the jth response).

Data were analysed following a modification of the Wing and Kristofferson (1973) model, to allow for change over time (drift) in the inter-response interval and for missing values. For each task for each participant the *arima* command in STATA was used to fit an autoregressive model with lag 1 autocorrelation, with

drift in the inter-response interval modelled using stimulus number. To allow for relatively complex drifts in the self-paced tapping task, linear, quadratic and cubic terms were fitted for stimulus number. Since observed drifts were simpler in the paced task, only linear and quadratic terms were fitted for stimulus number. Any inter-response intervals that were more than two standard deviations from the predicted value of the model were excluded, since these were thought to be due to error in data collection (missed taps or accidental double taps).

6.2.6. MRI acquisition

Brain MRI data were acquired for all participants as outlined in Chapter 3 (3.8.1)

6.2.7. Image analysis.

Due to low patient numbers and the associated lack of statistical power to detect anatomical-behavioral correlation, image analyses was conducted in the bvFTD group only. Image analyses were conducted to examine the correlations between those behavioural metrics where bvFTD participants performed significantly poorer than controls (see Table 16 and Table 17) and the neural areas or underlying connections important to these metrics. Therefore, for both paced and self-paced imaging analyses, clock variance and absolute drift metrics were examined as the covariates of interest in linear regression models.

Total variance was not examined separately to clock variance in the analysis of self-paced timing metrics as the contribution of motor variance to total variance

in the Wing and Kristofferson model was found to be negligible, suggesting all variance to stem from the 'clock' component of the model (see 6.3.3.2 for further explanation).

6.2.7.1.   VBM analysis

Pre-processing of patient brain MR images was performed according to methods outlined in Chapter 3 (3.8.3.1.1).

Linear regression models were used to examine regional grey matter volume correlates with performance on each of the experimental subtests; voxel intensity (an index of grey matter volume) was modelled as a function of subtest score across the group, including participant's age, TIV and Stroop inhibition score (a measure of executive function) as covariates of no interest. Separate models were used to assess grey matter associations of each experimental task separately (i.e. four separate models: paced clock variance; paced absolute drift,; self-paced clock variance; and self-paced absolute drift).

An anatomical small volume of the SMA was derived in FSL using the John Hopkins University (JHU) cortical atlas tool (Desikan et al., 2006). This small volume was then transferred into MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html) where it was divided into left and right cortices by manually tracing down the midline. The left portion of the SMA was used as an area of small volume correction for the

grey matter analyses, according to *a priori* hypotheses in connection with this area (Couell et al., 2012).

6.2.7.2. DTI analysis

Raw diffusion weighted images were processed according to the methods described in Chapter 3 (0). Linear regression models were used to examine regional white matter tract correlates with performance on each of the experimental subtests; tract diffusivity measures (indexing the integrity of white matter tracts) were modelled as a function of subtest score across the group, including participant's age, TIV and Stroop inhibition score (a measure of executive function) as covariates of no interest. The same model was fitted separately to FA, RD and AX, and each behavioural measure was modelled separately (i.e. four separate models: paced clock variance; paced absolute drift; self-paced clock variance; and self-paced absolute drift). Statistical analysis of the DTI data was implemented according to methods described in Chapter 3 (3.8.4.3.2).

6.3. Results

6.3.1. Demographic characteristics

Demographic and task-related information is presented in Table 14. The patient and control groups were well matched for age (p=0.9); males were over-represented in the bvFTD group (p=0.0004).

Table 14. Demographic and neuropsychological characteristics of participants

	bvFTD	SD	PNFA	AD	Controls
No.	22	12	7	8	35
Age (years)	62(9.9)	64(6.8)	66 (8.6)	65(7.7)	62(7.8)
Sex (M:F)	16:6	7:5	2:5	7:1	15:20
IQ					
WASI vocab (80)	42(19.8)	27.9(21.8)	33.8(11.8)	53.75(12.7)	70.4(4.8)
WASI blocks (/71)	22.5(16.2)	33.9(16.3)	27.1(17.9)	20.8(13.6)	46.6(11.56)
WASI similarities (48)	22.4(12.6)	16(16.3)	23(17.9)	26.8(9.2)	40.7(6.3)
WASI matrices (/32)	14.6(7.3)	19.9(8.01)	16.7(8.4)	14.4(8.1)	27.5(8.3)
NART total (/50)	27.5(14.8)	24(18)	17(5.8)	33.3(9.6)	41.3(5.8)
Episodic memory					
RMT Words (/50)	36.25(7.9)	32.7(8.4)	42.5(4.2)	34.7(8.6)	47.5(2.6)
RMT Faces (/50)	35.47(7.0)	34(8.4)	37.7(7.0)	38.2(4.7)	43.2(4.0)
Executive function					
D-KEFS Stroop inhibition (s)	**131.8(96.0)**	110.6(49.4)	126.1(50.4)	**134.5(48.5)**	55.3(14.1)
Semantic processing					
BPVS (/150)	129.0(24.1)	**85.8(53.2)**	128.5(31.6)	131.1(22.7)	147.5(1.5)
Other skills					
GNT (/30)	13.2(8.2)	**2.7(4.9)**	13.2(9.4)	18(5.4)	24.8(3.4)
Forwards DS (/12)	6.0(1.3)	6.2(1.5)	5(1.2)	5.7(1.6)	7.0(0.89)
Backwards DS (/12)	4.13(1.5)	4.5(1.5)	3(1.6)	3.8(1.8)	5.1(0.95)
Addition(/12)	5.18(3.5)	4.7(4.1)	2.7(2.6)	3.5(1.5)	7.3(2.3)
Subtraction(/12)	5.3(3.8)	5.1(4.4)	2.7(2.6)	4.1(2.6)	7.3(2.3)
VOSP (/20)	15.8(3.6)	15.5(3.9)	17.7(1.9)	16.8(1.8)	18.4(1.6)

Mean (standard deviation) values shown. Results where patients in one group performed significantly poorer than the other patient groups are shown in bold and underlined. AD, Alzheimer's disease; BPVS, British picture vocabulary scale; bvFTD, behavioural variant frontotemporal dementia; D-KEFS Stroop (word and inhibition), Delis-Kaplan Executive Function System; DS, digit span; GNT, Graded Naming Test; n/a, not available; NART, National Adult Reading Test; PNFA, progressive nonfluent aphasia; RMT, recognition memory test; SD, semantic dementia; VOSP, Visual Object and Space Perception – object decision task; WASI, Wechsler Abbreviated Scale of Intelligence.

6.3.2. General neuropsychological performance

Neuropsychological performance is presented in Table 15. Each patient group showed the anticipated profile of deficits relative to healthy control participants; bvFTD participants exhibited impaired performance on measures of executive function, memory and naming; SD patients showed significantly reduced word comprehension and naming; AD patients also showed a significant executive impairment as assessed by the Stroop inhibition task.

6.3.3. Experimental task performance

A number of patients completed only the paced component of the task due to an inability to sustain attention on the self-paced task without the external guidance of the tone stimuli. The number of participants included in each analysis is thus included in the corresponding results figures.

6.3.3.1. Externally-Paced Tapping

Figure 10 shows the inter-response intervals by stimulus for each participant in each group. Table 15 gives the summary statistics from the autocorrelation model and variances calculated according to the Wing and Kristofferson model. In all groups most participants' inter-response intervals during paced tapping started close to the fixed interval of 1500ms and showed little drift over the task. The lag 1 autocorrelation for the majority of participants was within the range of -0.5 to 0, as would be expected from theoretical assumptions of the Wing and

Kristofferson model. The negative clock or motor variances noted in Table 15

result from lag 1 autocorrelation outside of this range.

The results of the multiple regression model are given in Table 16. In comparison

to controls, mean clock variance was higher for participants with bvFTD

(adjusted difference 11473; 95% CI: 3028 to 26643ms^2) but not significantly

different in any of the other patient groups. Motor variance was similar to

controls in all patient groups.

There were no differences in drift between the controls and the patient groups.

Patients with bvFTD showed greater absolute drift in comparison to controls but

the difference was relatively small (mean adjusted difference 38ms; 95% CI: 13 to

90ms). All other patients groups had similar mean absolute drift to controls.

Table 15. Mean differences between controls and patient groups on paced tapping derived from the regression model.

		Control (N=35)	BvFTD (N=23)	PNFA (N=8)	SD (N=12)	AD (N=8)
Autocorrelation model statistics						
Intercept (ms)	Mean (SD)	1475 (44.2)	1480 (41.2)	1505 (50.6)	1482 (19.2)	1490 (53.2)
	Min, max	1324, 1583	1384, 1570	1444, 1567	1433, 1499	1428, 1605
Drift (ms per stimulus)	N (%) negative drift	11 (31)	7 (30)	3 (38)	4 (33)	2 (25)
	Mean (SD) drift	18 (34.1)	7 (93.3)	-4 (54.1)	7 (26.0)	6 (40.4)
	Mean (SD) absolute drift	28 (26.4)	60 (70.3)	41 (31.7)	21 (16.6)	30 (25.2)
Modelled end IRI (ms)	Mean (SD)	1492 (24.8)	1487 (112.4)	1492 (80.5)	1490 (26.0)	1496 (24.9)
	Min, max	1438, 1551	1073, 1692	1363, 1635	1423, 1520	1451, 1522
Modelled mean IRI (ms)	Mean (SD)	1494 (7.1)	1492 (33.8)	1490 (12.7)	1497 (5.3)	1497 (8.8)
	Min, max	1473, 1507	1389, 1604	1463, 1500	1486, 1505	1485, 1511
Lag 1 autocorrelation	Number between -0.5 and 0	25 (71)	18 (78)	4 (50)	8 (67)	8 (100)
	Mean (SD)	-0.29 (0.2)	-0.18 (0.21)	-0.16 (0.38)	-0.42 (0.14)	-0.24 (0.13)
	Min, max	-0.66, 0.34	-0.51, 0.21	-0.61, 0.45	-0.61, -0.10	-0.46, -0.08
Variances						
Inter-response interval variance (ms^2)	Mean (SD)	9701 (6916)	16934 (19929)	23050 (21570)	7020 (10168)	9628 (6042)
	Min, max	600, 32862	885, 73334	1804, 56864	937, 38342	2393, 18054
Clock variance (ms^2)	Mean (SD)	3799 (5633)	14206 (25678)	20549 (35413)	1069 (2187)	5256 (3937)
	Min, max	-3705, 25426	-255, 104232	-10098, 96870	-1684, 7211	406, 11654
Motor variance (ms^2)	Mean (SD)	2951 (3447)	1364 (5387)	1251 (15685)	2976 (4168)	2186 (1716)
	Min, max	-2470, 15865	-15449, 12918	-23022, 33481	122, 15566	696, 4777

Abbreviations: N, number; SD, standard deviation; min, minimum value; max, maximum value; bvFTD, behavioural variant frontotemporal dementia; PNFA, progressive nonfluent aphasia; SD, semantic dementia; AD, Alzheimer's disease. All effect sizes are versus control

Table 16. Mean differences between controls and patient groups on paced tapping, with and without adjustment for expected performance estimates derived from the Wing & Kristofferson model

	Estimate (and 95% CI)	bvFTD	PNFA	SD	AD
Clock variance (ms^2)	Unadjusted	10407 (2614 to 26475)	5846 (-4435 to 26195)	-2731 (-5151 to -654)	1457 (-1961 to 4564)
	Adjusted	**11473 (3028 to 26643)**	6551 (-4935 to 27721)	-2249 (-5826 to 1666)	2853 (-1210 to 9391)
Motor variance (ms^2)	Unadjusted	-1587 (-4524 to 602)	1768 (-4243 to 20333)	25 (-1866 to 4115)	-765 (-2368 to 898)
	Adjusted	-1887 (-4910 to 753)	1526 (-4441 to 18277)	-106 (-1964 to 3374)	-1146 (-3131 to 1017)
Accuracy (ms)	Unadjusted	-2 (-15 to 14)	-4 (-18 to 2)	3 (-1 to 7)	3 (-3 to 10)
	Adjusted	-4 (-19 to 11)	-2 (-15 to 8)	1 (-5 to 6)	-1 (-10 to 5)
Continual Drift (across time) (ms per stimulus)	Unadjusted	-10 (-59 to 23)	-22 (-74 to 14)	-10 (-31 to 7)	-12 (-57 to 10)
	Adjusted	-16 (-74 to 22)	-22 (-71 to 18)	-13 (-35 to 5)	-20 (-66 to 6)
Drift (absolute value) (ms per stimulus)	Unadjusted	33 (10 to 77)	13 (-12 to 43)	-7 (-20 to 5)	2 (-13 to 26)
	Adjusted	**38 (13 to 90)**	11 (-13 to 38)	-4 (-18 to 11)	11 (-9 to 40)

Abbreviations: CI, confidence interval; bvFTD, behavioural variant frontotemporal dementia; PNFA, progressive nonfluent aphasia; SD, semantic dementia. All effect sizes are versus control. Statistically significant group differences are underlined.

Table 17. Mean differences between controls and patient groups on self-paced tapping, with and without adjustment for expected performance estimates derived from the Wing and Kristofferson model.

	Estimate (and 95% CI)	bvFTD	PNFA	SD	AD
Clock variance (ms^2)	Unadjusted	6976 (117 to 19301)	-2340 (-5488 to 617)	-2404 (-5602 to 52)	10307 (-3715 to 39422)
	Adjusted	**8019 (132 to 21162)**	-1514 (-5201 to 5522)	-2023 (-5868 to 1327)	11376 (-2715 to 39740)
Motor variance (ms^2)	Unadjusted	404 (-2072 to 7625)	987 (-230 to 2174)	49 (-618 to 847)	-2202 (-8858 to 1030)
	Adjusted	703 (-2134 to 8082)	618 (-1891 to 2112)	290 (-587 to 2160)	-1605 (-8334 to 1711)
Total variance (ms^2)	Unadjusted	7785 (294 to 24461)	-366 (-3553 to 2335)	-2305 (-5680 to -537)	5904 (-1919 to 20715)
	Adjusted	**9426 (133 to 26600)**	-278 (-5414 to 3959)	-1442 (-5277 to 3029)	8166 (-393 to 23310)
Accuracy (ms)	Unadjusted	-135 (-292 to -0)	-47 (-310 to 195)	-141 (-296 to 16)	-126 (-383 to 56)
	Adjusted	-127 (-274 to 10)	-14 (-296 to 275)	-144 (-329 to 4)	-130 (-384 to 29)
Continual drift (across time) (ms per stimulus)	Unadjusted	-113 (-287 to 89)	49 (-187 to 264)	-49 (-159 to 64)	-172 (-607 to 52)
	Adjusted	-78 (-261 to 142)	74 (-189 to 337)	-36 (-182 to 105)	-134 (-491 to 83)
Drift (absolute value) (ms per stimulus)	Unadjusted	155 (42 to 301)	43 (-76 to 154)	-41 (-115 to 30)	132 (-27 to 592)
	Adjusted	**163 (39 to 326)**	44 (-101 to 149)	-37 (-127 to 38)	142 (-20 to 582)

Abbreviations: CI, confidence interval; bvFTD, behavioural variant frontotemporal dementia; PNFA, progressive nonfluent aphasia; SD, semantic dementia; AD, Alzheimer's disease.

All effect sizes are versus control. Statistically significant group differences are underlined. All effect sizes are versus control.

6.3.3.2.   Self-Paced tapping

Figure 8 shows the inter-response intervals by stimulus for each group. Most participants' inter-response intervals at the start of self-paced tapping were relatively close to the fixed interval of 1500ms. However, there were more participants in the patient groups with inter-response intervals noticeably shorter than 1500ms at the start of the task. A large number of participants in all groups showed drift during the task, with more participants showing negative drift (getting faster) than positive drift (getting slower). The average lag 1 autocorrelation was close to zero, with many participants having positive lag 1 autocorrelation resulting in estimated negative motor variance. The average motor variance was close to zero in most patient groups, which suggests that in the self-paced task motor variance had little impact on the overall variance of the inter-response intervals.

The results of the multiple regression model are given in Table 17. Separation of motor and clock variance may have limited validity for the self-paced task, as descriptive analysis suggested that the motor component was minimal. However, results are provided on between-group comparisons for information purposes. In comparison to controls, patients with bvFTD had higher variance of inter-response intervals (9426; 95% CI: 133 to 26600ms^2). There was evidence of a trend for lower accuracy in bvFTD patients than controls (-127; -274 to 10ms), SD (-144; -329 to 4ms) and AD (-130; -384 toms 29). There were no significant differences between any of the patient groups and controls in drift. Participants with bvFTD showed greater absolute drift in comparison to controls with an

adjusted average of 163ms greater drift by the end of the task (95% CI: 39 to 326ms). No other patient groups showed evidence of a difference from controls in absolute drift.

Figure 8. Plots of paced (LHS) and self-paced (RHS) raw responses (in seconds) across time, for controls, bvFTD, PNFA, SD, and AD respectively
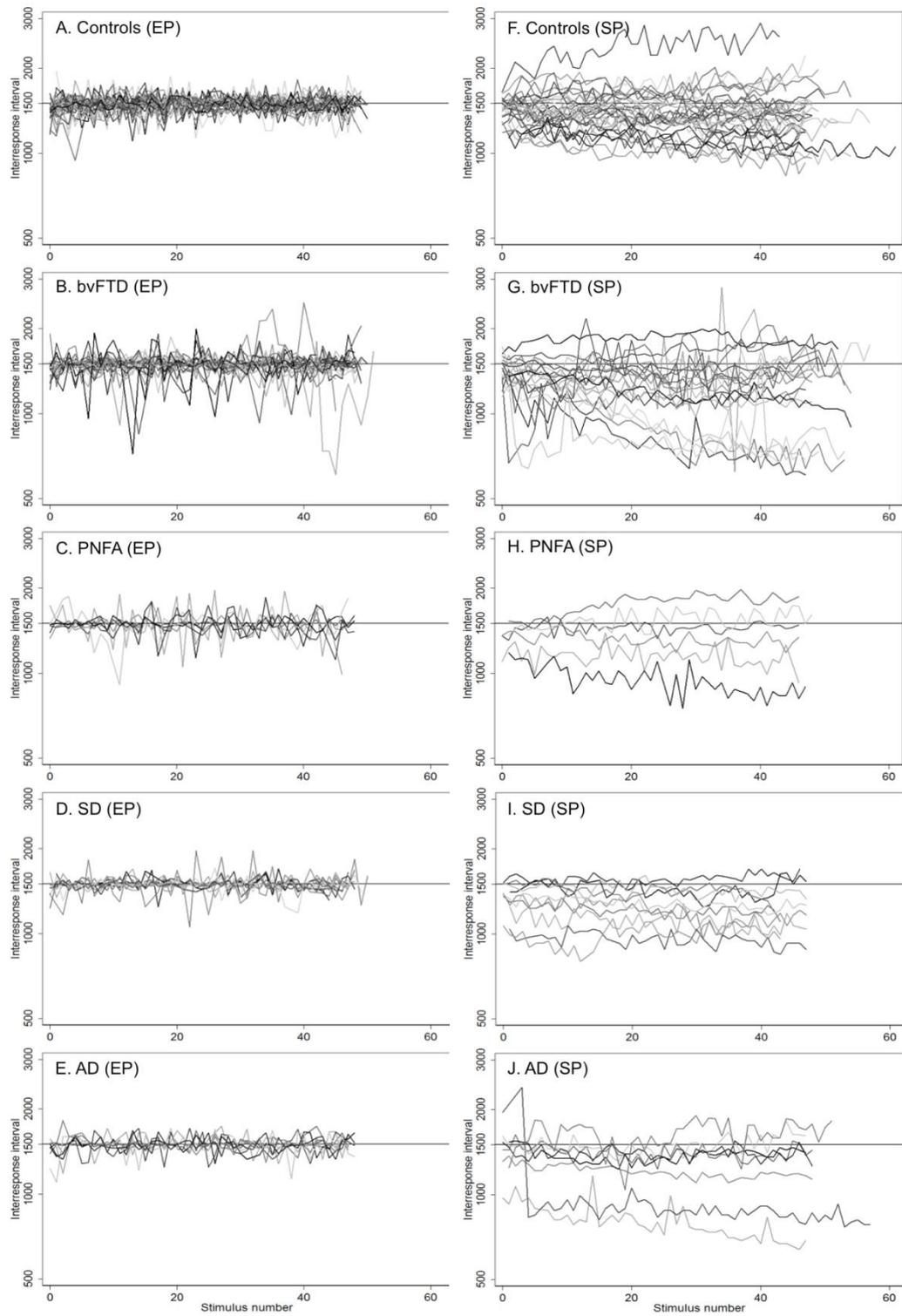
6.3.4. Neuroanatomical associations

6.3.4.1. VBM findings

Statistical parametric maps of grey matter volume associations with performance in the externally-paced and self-paced conditions are shown in Figure 9 and Figure 10; data for local maxima of grey matter change are summarised in Table 18.

With the externally-paced task, no significant neuroanatomical correlates were observed at the level of the whole-brain, nor after small volume correction, for clock variance and drift metrics. However, there was a trend toward a significant single peak voxel at the level of the whole-brain in the left parietal cortex that did not reach statistical significance.

In the self-paced task, no significant neuroanatomical correlations were observed at the level of the whole-brain. After small volume correction, a significant negative correlation of absolute drift performance was observed in the left supplementary motor area (p<0.045 after FWE correction for multiple comparisons within the anatomical small volume of interest). A similarly significant negative correlation of clock variance was observed in the left supplementary motor area (p<0.044 after FWE correction for multiple comparisons within the anatomical small volume of interest). No significant correlations were observed in the positive direction for any contrast.

6.3.4.2.   DTI findings

TBSS-DTI nonparametric analyses revealed a significant correlation between absolute drift behavioural score and decreased fractional anisotropy (FA) within the bilateral cerebellum, brain stem superior to the medial cerebellar peduncle within the vicinity of the basal ganglia structures, and a small portion of the left SLF (p<0.04 at peak voxel, mean voxel size 30.00). These findings are represented in Figure 11. No significant neuroanatomical correlations with clock variance within either the externally-paced or self-paced tasks were observed.

Table 18. Summary of voxel-based morphometry findings in the bvFTD group

Behavioural correlate	Direction of correlation	Brain region	Cerebral hemisphere	Peak coordinates	T-score
Externally-Paced: clock variance	inverse	Parietal lobe	L	-73 -33 29	3.65~
Self-Paced: drift	inverse	SMA	L	3 -6 - 46	4.64**
Self-Paced: clock variance	Inverse	SMA	L	-9 3 49	4.66**

Coordinates (mm) of local maxima for grey matter volume change correlating with behavioural performance in the patient group are shown in Montreal Neurological Institute standard stereotactic space. **Reached statistical significance at p<0.05 at Peak-level. ~Did not reach statistical significance.

Figure 9. VBM grey matter correlates of response drift in the bvFTD patient group
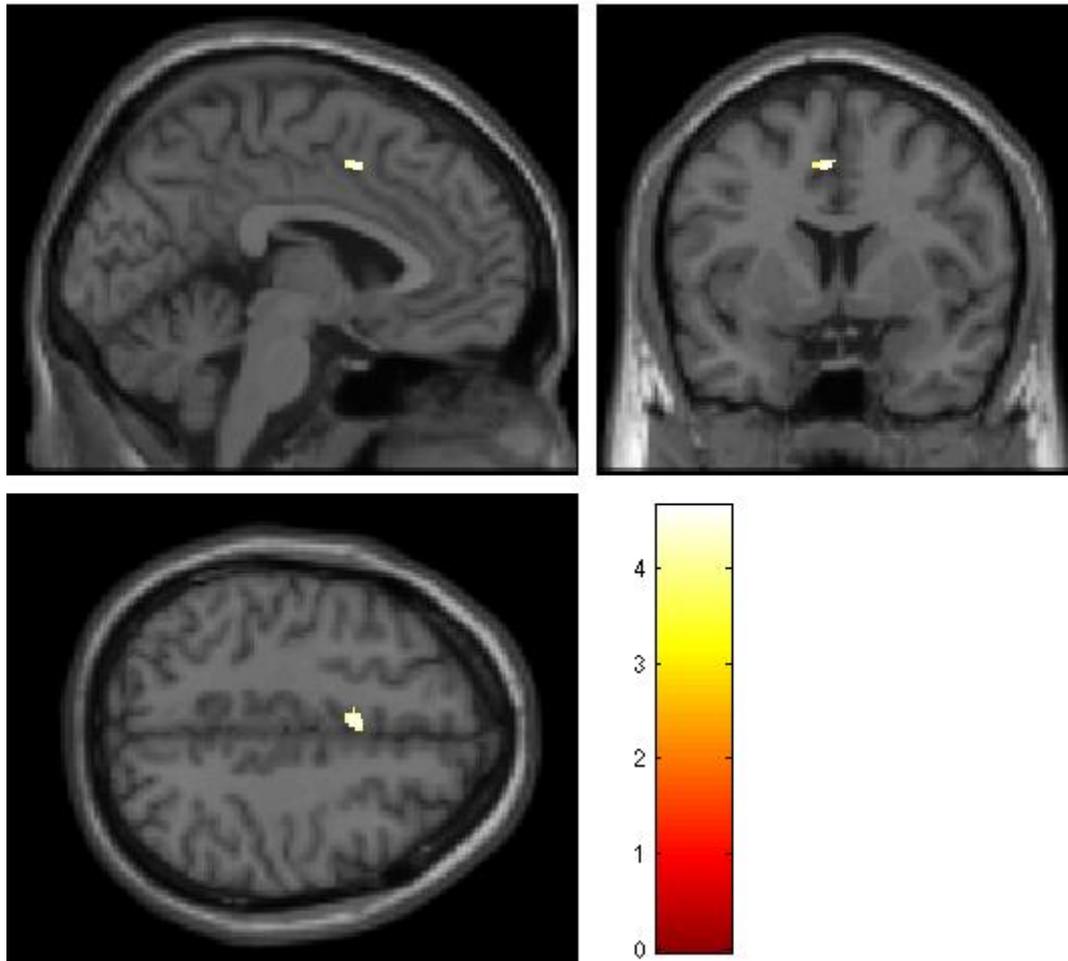
VBM: Self-Paced task absolute mean drift score negative grey matter correlates in the left supplementary motor area (SMA). Negative correlation indicates higher absolute drift, and thus poorer performance, is correlated with reduced grey matter in the left PMC. Images are presented in anatomical space (L=L) on a study-specific mean brain image. The colour scale indexes p-value after family-wise error correction for the small volume of interest at p < 0.05

Figure 10. VBM grey matter correlates of timing variance in the bvFTD patient group
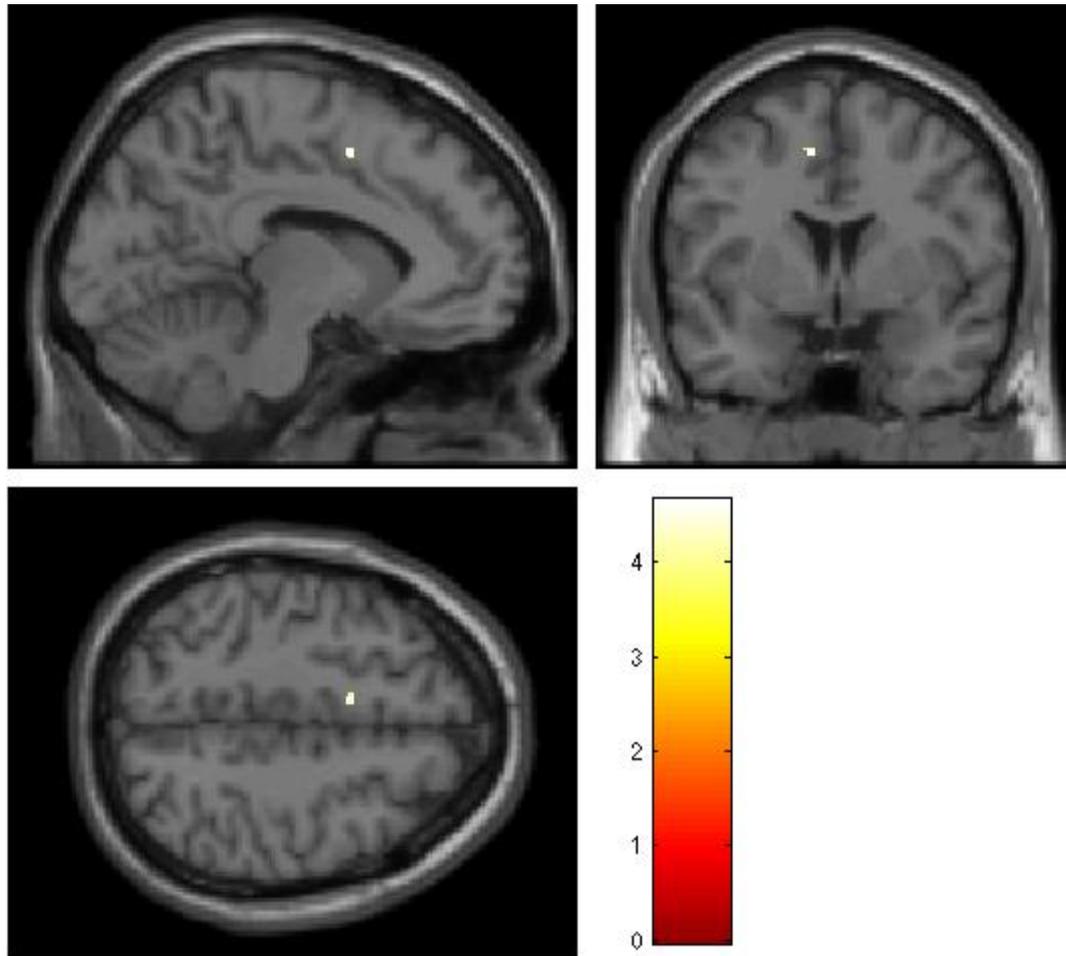
VBM: Self-Paced task mean clock variance score negative grey matter correlates in the left supplementary motor area (SMA). Negative correlation indicates higher clock variance, and thus poorer performance, is correlated with reduced grey matter in the left SMA. Images are presented in anatomical space (L=L) on a study-specific mean-brain image. The colour scale indexes p-value after family-wise error correction over the small volume of interest at p < 0.05

Figure 11. DTI white matter correlates of response drift in the bvFTD patient group
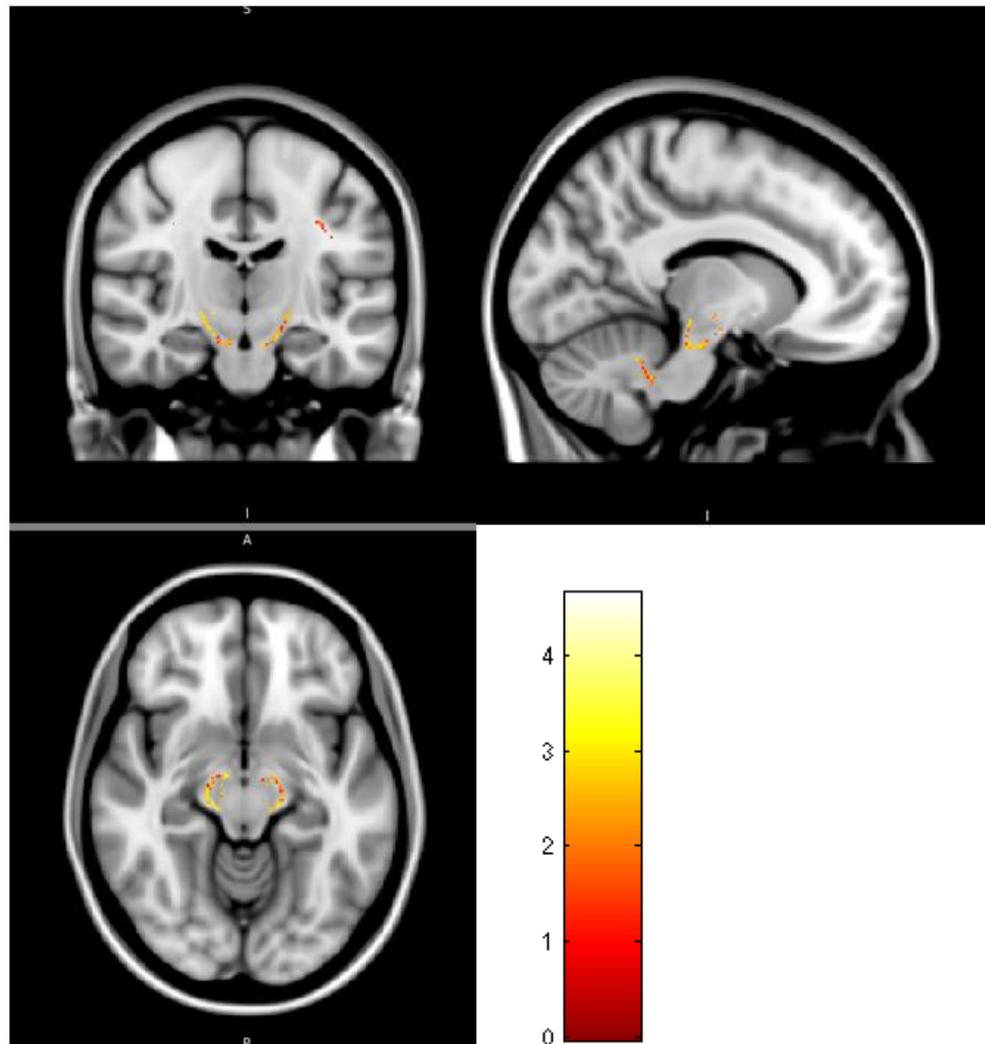
DTI: Self-Paced task absolute mean drift score white matter Fractional Anisotropy (FA) correlates in the brainstem, cerebellum, and left superior longitudinal fasiculus. Images are displayed in radiological space (L=R) on the standard 1mm voxel size MNI-152 brain in FSL. The colour scale indexes p-value after family-wise error correction over the specified tracts of interest at $p < 0.05$

6.4. Discussion

I present evidence that neural timing is disrupted in bvFTD, and that this timing dysfunction is attributable to degradation of the cortical and subcortical grey matter structures and interconnecting white matter tracts previously implicated in a neural timing network. These cortical correlates are located in areas previously identified as crucial to neural timing ability, and the implicated white matter tracts were found to be in areas highly relevant to those pre-defined cortical areas of interest and their projections., This is the first cohort study to demonstrate neural timing dysfunction in individuals with bvFTD, and perhaps more importantly, the first study to identify the white matter tracts which support specific aspects of neural timing ability using DTI. This data has important clinical and theoretical implications.

The present behavioural findings will be first discussed in terms of their relevance to the existing behavioural literature, and the neuroimaging findings will subsequently considered in terms of the implications to proposed models of neural timing networks. Timing data were analysed according to the Wing and Kristofferson timing model (1973) which parcels time into separable clock and motor components and thus examines the contributions of both facets of timed performance simultaneously. Using this model I was able to determine that a deficit in the 'clock' component of timing was present in the bvFTD group, evidenced by their inability to tap in time to an externally-paced stimuli with negligible influence of any motor abnormalities. This 'clock' deficit was observed to be selective to the bvFTD participants, with healthy controls, and

neurologically compromised PNFA and AD patient groups performing within normal limits on this task. Self-paced timing was similarly assessed using the Wing and Kristoffersen model and was also found to be selectively impaired in those with bvFTD. In order for the assumptions of this model to apply, there must be some contribution above zero for both clock and motor components. In many participants, the motor timing component was found to be negative, and thus the model was unable to examine clock and motor contributions to timed performance separably and total variance was taken as a measure of total clock variance. bvFTD patients showed greater total variance over the course of the self-paced finger tapping task, and also showed a significantly higher absolute drift across the span of the task. These deficits were again selective to the bvFTD participant group and were not observed in any of the other healthy control or patient groups. Together, and in the context of the present findings of intact accuracy about the 1500ms target during both externally-paced and self-paced tapping tasks, these results suggest a selective deficit in the ability to carry out precisely timed motor actions in those with bvFTD.

These behavioural findings complement evidence of timing abnormalities in other neurological populations, such as Parkinson's disease (PD)(O'Boyle et al., 1996) and Huntington's disease (HD) (Rowe et al., 2010) and strengthen the hypotheses first raised by Wiener and Coslett in a case study of a single patient with bvFTD, that neural timing may be selectively disrupted within this FTLD disease variant (Wiener and Coslett, 2008). The strongest behavioural finding in the present research was the significantly increased absolute drift over time in the bvFTD patients, who tended to gradually accelerate. This behaviour has also

been observed in PD patients, who similarly tended to execute timed responses at an accelerated rate over time in a tapping task (Ivry & Keele, 1989;Picton et al. 2006). Wiener and Coslett (2008) postulated that this migration from the target over time emanates from a 'fast clock'. In terms of the information processing model of timing (Gibbon et al., 1984), this corresponds to the creation of a speeded template of the original timed interval and thus timed motor responses are increased at the rate at which this time-keeper beats. This may account for the observed acceleration over time in the present data as emanating from an inability to lay down an accurate timing template from which to compare consecutive responses (Coull et al., 2012).

The present neuroimaging findings have important implications for contemporary models of the neuroanatomical circuitry of neural timing networks. VBM was used to examine the grey matter correlates of the mean behavioural scores in those components that were found to be abnormal at the level of behaviour in the bvFTD group. No grey or white matter correlates of clock variability during externally-paced tapping were found, however a non-significant cluster of voxels within the left parietal cortex was of note. Conversely, grey matter correlates for measures of both response variance and absolute drift over time in the self-paced tapping tasks were found within the left supplementary motor area (SMA). Furthermore, examination of the white matter tracts selectively supporting the observed response drift using DTI illuminated a highly significant network of tract-based FA correlates within the cerebellum and brain stem areas within the vicinity of basal ganglia structures and the left SLF – a structure crucial in connecting frontotemporal and frontoparietal regions.

Together these neuroimaging findings converge to highlight a neural timing network supporting timed motor output, and in particular, response-drift over time, within areas that have previously been identified as crucial to neural timing ability. These results suggest further support for the purported cerebellar-striato-cortical (STC) timing network (Coull et al., 2012) and re-confirm what has been observed in both PD (O'Boyle et al., 1996), and HD (Rowe et al., 2010; Hinton et al., 2010), which indicated worsening timed performance with progressive degeneration of the basal ganglia. Significant correlations between abnormal timing performance and the basal ganglia have also been reported in schizophrenic populations (Ortuno et al., 2011). The basal ganglia have been suggested to monitor activity in striato-thalamo-cortical circuits and perform coincidence detection of signal-specific patterns of activity in working memory (Buhusi and Meck, 2005; Teki et al., 2011). Furthermore, the SMA has been implicated widely in time processing (Macar et al 2002.; Macar et al. 2004) and plays a key role in time perception as part of this STC pathway (Teki et al., 2011). The SMA is one of the primary projection sites of the striatum to the cortex via the globus pallidus and thalamus and its suggested role in perceptual timing is further supported by its direct connections with the caudate and putamen, both basal ganglia structures, and dentate nucleus of the cerebellum (Akkal et al., 2007). Several EEG and MEG studies have revealed ramp-shaped contingent negative variation over the SMA during timing tasks (Macar et al., 2002), leading Ortuno and colleagues in their recent meta-analyses to hypothesize that the SMA serves as temporal accumulator (Ortuno et al., 2011). These authors found the greatest number of significant voxels within an activation likelihood estimate study within the SMA, providing highly compelling evidence of the importance of

this area to neural timing and strengthening the significance of the present results.

These results have important clinical implications. The observation that specific neural timing abilities are damaged in bvFTD, and that this maps onto neural correlates that have been consistently identified in both neurologically-compromised (Bechtel et al. 2010; O'Boyle et al. 1996; Rowe et al. 2010; Picton et al. 2006) and healthy control (Coull et al., 2012; Ortuno et al.2010) populations provides further support for the existence of an STC network that supports neural timing ability. The demonstration that this network appears to be damaged in bvFTD suggests that dysfunction in neural timing capability may contribute to a number of phenotypic features particular to bvFTD. Dysfunctional social cognition is a hallmark behavioural feature of bvFTD recognised in diagnostic criteria (Rascovsky et al., 2011), and neural timing has been highlighted as an important contributing factor to social cognitive processes, such as in theory of mind (Baron-Cohen et al. 2001), or making sense of the temporal course of events (Allman et al., 2011; Grondin, 2010; 2011). More general investigation into how precise timing may be key to many different types of actions may also prompt developments in models of neural timing. For example, this study implicates the SMA within the confines of a primarily motor task. Had the paradigm somehow involved, for example, 'comic timing', we propose that that anatomical correlation with different hubs within the same timing network (e.g. cerebellum, basal ganglia and their inter-connections) plus other prefrontal regions more strongly implicated in social interaction, ToM and perspective taking may have been observed. Thus, the identification of timing deficits in bvFTD may develop our

clinical understanding of the condition as subtle timing deficits may contribute to many of the more recognised social and behavioural features.

These results also have important theoretical implications for understanding the neurobiological basis of neural timing ability. The degradation of white matter tracts appeared far more widespread than atrophic cortical correlates, supporting the notion that white matter may be disproportionately damaged over grey matter in the earlier stages of the disease (Agosta et al., 2012), and highlighting the possibility that it is the integrity of those implicated white matter tracts that is crucial in supporting neural timing ability, rather than the cortical structures which they connect.. The tracts that connect cortical areas such as the SMA with basal ganglia subcortical structures, such as the SLF within the present research, appear vital to maintain accurate timed motor output according to a predefined timing interval. Such evidence suggests that methods of examining neuroanatomical correlates of timing performance which allow examination of white matter microstructure, such as DTI, are vital if we are to further disentangle the complex neuroanatomical network that supports timing behaviour and the many different components that make up this intricate behaviour.

Genetic mutations account for up to 40% of all cases of FTD (Rohrer et al., 2010a), and thus identifying novel non-invasive and low-cost metrics of early detection of disease manifestation is of great importance. Within the highly heterogeneous framework of phenotypic expression and pathological bases present in bvFTD, such a metric may also prove of use in differentiating between responsible

pathological subtypes or pathogenic mutations. For example, the cerebellum is not commonly conceived as a locus of pathology within bvFTD, however extensive investigation into the neuropathological phenotype of those with a mutation of the newly discovered C9ORF72 gene responsible for many cases of bvFTD has identified the cerebellum as the greatest locus of pathological deposition and atrophy within those carrying this mutation (Mahoney et al., 2012a; DeJesus-Hernandez et al. 2012). The brainstem and basal ganglia structures are similarly ill-conceived as structures that are specifically targeted by bvFTD pathology; however brain stem degeneration is a hallmark of PSP which can present as an extrapyramidal syndrome co-morbidly with bvFTD. Indeed, recent evidence of a case with pathologically-proven PSP whom presented with a typical bvFTD syndrome (Hassan et al., 2012) suggests that there may be a greater degree of brain stem dysfunction in FTD, and perhaps a greater likelihood of the development of pyramidal features in bvFTD when brain stem degradation is observed.

6.5. CHAPTER CONCLUSIONS

In conclusion, the present study presents novel insights into the disruption of neural timing ability selective to those with bvFTD in the context of intact performance in several other neurologically-compromised disease controls and healthy individuals. This deficit correlated with discrete cortical correlates in previously implicated areas to neural timing, and a widespread network of white matter tracts. These data have important clinical and theoretical implications and suggest that deficits in neural timing may contribute to many of the behavioural abnormalities observed within bvFTD, and that the integrity of the white matter

connecting previously implicated cortical and subcortical structures may be
crucial in supporting intact timing ability.

7. EXECUTIVE FUNCTION IN FRONTOTEMPORAL DEMENTIA

7.1. Chapter introduction

In the previous chapter, I have used a finger-tapping task to demonstrate that neural timing is grossly disrupted in bvFTD, and that this is mediated by a network of cortical and subcortical regions and their interconnecting fiber pathways. Executive dysfunction is a hallmark behavioural characteristic of bvFTD (Rascovsky et al., 2011), and it is likely that a number of reported executive processes , including energisation, monitoring of response, and task-setting to define a temporal schedule, (Norman and Shallice, 1986; see 2.3.1) are required to effectively engage in the cognitive skill of timing. As such, the general investigation of neural timing in bvFTD will be further explored here, along with more specific executive tasks, in the wider context of executive function. .At the time of devising this behavioral battery, a paper was published which reported that executive dysfunction in bvFTD could be entirely explained by a reduction in fluid intelligence, or 'g' (Roca et al., 2013). As such, intelligence was included as a covariate in all analyses in this chapter in order to investigate the relationship between executive function and intelligence further. As in the previous chapter, AD, SD, and PNFA patient groups were included in the present chapter as neurologically compromised comparator populations against the bvFTD group of interest for a more comprehensive evaluation of executive function. The cortical correlates of the executive functions examined in this chapter were investigated using VBM. The relationship between grey matter, executive function, and

intelligence was of primary interest in this chapter, rather than the white matter

tracts that connect cortical areas, which are widely distributed throughout the

brain.

Executive function is broadly defined as the ability to maintain an appropriate

problem-solving set for attainment of a future goal (Welsh & Pennington, 1988).

As explored in Chapter 2, (see 2.3), dysfunctions in executive processes in FTD,

and in particular bvFTD, have been widely reported (i.e. Hornberger et al., 2008;

Snowden et al., 2003; Lough et al., 2001; Gregory et al., 2003; Kramer et al., 2003;

Kipps and Hodges, 2006; Rascovsky et al., 2007). In the context of phenotypic

confusion between FTD and other neurodegenerative and psychiatric illnesses,

increased understanding of the precise nature of these executive deficits may

provide a useful neuropsychological tool for more precise diagnosis.

An issue of contention exists within the executive function literature in terms of

how this cognitive capacity is conceptualised. Some authors conceive of executive

function as a collection of related, but fundamentally dissociated cognitive

processes (Norman and Shallice, 1986; Aron et al., 2004; Stuss and Alexander,

2007), while others report a view of executive function as being a unitary entity

or resource which may be partially related to the much older concept of general

intelligence (Roca et al., 2010; 2013). The latter argument suggests that the

deficits in executive function observed after frontal lobe damage can be explained

almost entirely by a reduction in general intelligence, or Spearman's 'g' (Roca et

al., 2010; 2013). This research suggests that deficits in traditional executive tasks

after frontal lobe lesions appear on the background of reduced fluid intelligence,

and that when patients and controls are matched for fluid intelligence, no frontal

executive deficit remains (Roca et al., 2010; 2013). Such data are in contrast to

the more traditional conception of executive function as a conglomerate of

distinct functionally-dissociable processes, and instead puts forward a view of

executive function as a unitary resource. Further examination of the role of

general intelligence in executive function is needed in order to understand and

clarify the relationship between frontal lobe damage, executive function, and fluid

intelligence, and the neural correlates of these cognitive capacities.

An influential theoretical account of executive function stems from the

supervisory attention system (SAS) model of Norman and Shallice (1986), which

has been incorporated and expanded into the model by the same name proposed

by Stuss and Alexander (2002). This model purports three primary processes of

executive function: energisation; monitoring of performance; and task-setting

(see 2.3 for further explanation and Table 19 for a list of these processes and

corresponding definitions). Each of these processes has been associated with

regionally-specific areas of the frontal lobe, such that energisation is proposed to

be dependent upon superior medial areas (Stuss & Alexander, 2007; Alexander et

al 05; 07; Picton et al 07; Stuss et al 05; Stuss 2011), monitoring is purported to

require right lateral engagement (Alexander et al 08; Stuss et al 05; Stuss 2011;

Picton et al 06), and task-setting is proposed to be left-lateral dependant

(Alexander et al., 2005; 2007; 09; Stuss 2011).

A sub-skill of executive function is that of task switching, which involves the

ability to cognitively shift between attention or task sets (Friedman et al., 2008).

This behaviour is discussed in detail in Chapter 2 (see 2.3) and is proposed to require one to develop a stimulus-specific task-set, and continually re-configure and adapt, or 'switch', this task-set in order to engage with changing, or conflicting stimuli input (Aron et al., 2004). Neuroantomical associations have been derived primarily from lesion studies and functional imaging experiments in healthy adults and suggest successful task switching to be mediated by: the right inferior frontal cortex for inhibiting previous stimulus-response contingencies (Aron et al., 2003; 2004; Aron 2008), and the left medial frontal gyrus for setting task-set contingencies and engaging in top-down control (Aron et al., 2003; 2004; Aron, 2008; MacDonald et al., 2000; Monsell et al 2003; Raver et al., 2003). Right-lateralised superior medial areas, including the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, SMA, and pre-SMA, have also been highlighted as imperative to normal task-switching ability (Alexander et al., 2011; MacDonald et al.,2000; Van Veen V et al., 2001; Picton et al., 2006) .

Table 19. Definitions of tasks and processes derived from the Supervisory Attention System model (Stuss et al., 2005)

TASKS	DEFINITION
Sustaining	Required for tasks when targets occur at a relatively slow rate over a long period of time
Concentrating	Necessary for demanding tasks involving rapidly occurring stimuli
Sharing	Necessary when two or more unrelated tasks have to be carried out at the same time
Suppressing	Required when automatic responses need to be inhibited
Switching	Demands shifting attention between tasks requiring different stimulus-response pairings
Preparing	Involves getting ready for a task that follows soon after a warning signal
Setting	Requires establishing a set and sequence of appropriate processes to complete a task

PROCESSES	
Energizing	Initiation and constant activation of the strength of the selected response mode
Inhibiting	Preventing a pre-potent behavioural response
Monitoring	Process of checking the task over time for 'quality control' and the adjustment of behaviour
contention scheduling	Process of preparing for and making decision for behaviour
Task setting	Requires the ability to set a stimulus–response relationship

The primary aim of the present study was to investigate whether a behavioural switching task could be used as a paradigm to explore the dissociable facets of executive function as outlined by the SAS model (Norman & Shallice, 1986; Stuss & Alexander, 2002), and further, whether any observed deficits would correlate with level of general intelligence as reported by Roca and colleagues (2010). Secondly, the present study aimed to use voxel-based morphometry to investigate how these specific facets of executive function correlate with regions of grey matter damage in this patient group. The behavioural switching task utilized in this study was based on a task used by Aron and colleagues (Aron et al., 2004), which engages essential cognitive operations with minimal extraneous task demands. This task involves overriding a pre-potent response when faced with incongruent information and has been shown to be broadly reliant on inferior frontal, supplementary motor, and midbrain subcortical regions (Aron et al., 2007). A full list of the tasks utilized within this chapter, the relationship between the present tasks and the proposed component processes, and the anatomical predictions for these is presented in   Table 20. Basic latency of response (with and without the presence of distractors) was also measured, as was externally-paced, and self-paced neural timing using a standard finger-tapping paradigm (see Chapter 6) In order to further explore the relationship between executive dysfunction and general intelligence, we also analysed all measures with and without a general intelligence covariate. We hypothesized that these executive capacities of task-switching, reaction time, and neural timing would show a relationship with the integrity of the network of aforementioned frontal lobe cortical and subcortical structures, particularly the inferior frontal

and frontoparietal areas, which are most degraded by this disease, and that such executive dysfunction would be apparent even after adjusting for level of general intellect.

Table 20. Relationship between tasks in present study to SAS tasks and component processes, and the anatomical predictions for these based on the literature

TASK /PERFORMANCE METRIC	UNDERLYING TASK TYPE	HYPOTHESIZED COMPONENT PROCESS	ANATOMICAL PREDICTION
REACTION TIME TASKS			
Simple RT	Sustaining*	Energizing	R SC [a]; SM [c]
Choice RT	Sustaining*, suppressing	Energizing, monitoring, inhibiting	R SC, R anteromedial, RL, SM [a] OF, RL [b]
Preparation effect	Preparing	Task-setting	RTL [a]
Choice effect	sustaining*, suppressing	monitoring, inhibiting	SM [a]
SWITCH TASK			
Short switch	Sustaining, preparing, switching, suppressing	Energizing, monitoring, inhibiting, contention scheduling	RSM, RL [b, g], IM [c]
Long switch	Sustaining, preparing, switching, suppressing	Energizing, monitoring, inhibiting, contention scheduling	SM [a, c], RSM, RL [b, g], IM [c]
Preparation effect	Preparing	Energizing	RL [b]
Congruency effect	Suppressing	Inhibiting	pre-SMA, dmPFC [b, e, h] SM, ACG [g]
Switch cost	Switching	Inhibiting, energizing	SM [c], RL, LL [b], vlPFC [d]
TIMING TASKS			
Externally-paced Absolute drift	Sustaining, concentrating	Energizing, monitoring	SM, RL [b]
Self-paced Absolute drift	Sustaining, concentrating, setting	Energizing, monitoring, task setting	SM, RL [b]
Self-paced Clock variance	Sustaining, concentrating, setting	Energizing, monitoring, task setting	LSMA [f]

Key: [a] Stuss et al.,2005; [b] Aron et al., 2004; [c] Shallice et all., 2008; [d] Braver et al., 2004; [e] Ridderhinkoff et al.,2004; [f] Couell et al., 2012; [g] Stuss and Alexander, 2011; [h] Botvinicnk and Cohen, 2004; [i] Picton et al., 2007. Abbreviations: R =right, SC= superior cingulate; RL = right lateral; SM = superior medial; OF = orbitofrontal; TL = temporal lobe; IM = inferior medial; SMA = supplementary motor area; ACG = anterior cingulate gyrus; LL = left lateralised; dmPFC= dorsomedial prefrontal cortex; STG, superior temporal gyrus; PCG, pre-central gyrus

7.2. Methods

7.2.1. Participants

Twenty seven participants with a diagnosis of bvFTD, 15 participants with a diagnosis of SD, nine participants with a diagnosis of PNFA, nine participants with a diagnosis of AD, and 37 healthy control participants were recruited according to the methods described in Chapter 3 (3.2; presented in Table 22).

7.2.2. Experimental investigation

For all tasks, participants were asked to respond with the index finger of their dominant hand. Where more than one response was required, participants were asked to respond using the index fingers of both hands.

7.2.2.1. Reaction time task

The reaction time (RT) task used here was based on a previous study (Stuss et al., 2005). The task consisted of two blocks:

(a) Simple RT task, in which participants were instructed to make a speeded response to the letter A,

(b) Choice RT task in which participants were instructed to respond to the same target letter A in the context of distractors B, C, and D. The latency between the presentation of each stimulus varied such that stimuli were presented after either a 3-, 4-, 5-, 6-, or 7-second inter-stimulus interval (ISI).

A response box with two central response keys was placed in front of

participants. At the Simple RT task, an instruction page was presented which

stated that participants would see the letter A on the screen, and that they must

press the left response button as quickly as possible when they see this letter. At

the start of the Choice RT task, the participants were presented with a second

instruction page, in which they were told that they would now be presented with

either an A, to which they again must press the left button as quickly as possible,

or a letter B, C, or D, to which they must respond by pressing the right button of

the response pad as quickly as possible. Six practice trials were administered,

followed by 48 stimuli trials for both the Simple and Choice RT tasks. Stimuli

were presented in Arial font, size 16, in the centre of the screen. The tasks were

presented in a fixed order: Simple RT followed by Choice RT.

7.2.2.2.   Task switching

The switch task used here was based on a previous study (Aron et al., 2004) and

utilized a computer screen for cue delivery and a button-press mechanism for

recording response, as described above for the Simple and Choice RT tasks (see

7.2.2.1). The task required participants to press either a left or right button,

depending on the task instruction and requirements, whereby stimulus and cue

demands differed between each trial. The switch task was comprised of four

blocks:

(a) Arrow only, in which the cue "Arrow" was displayed to instruct participants to

respond to arrow direction, then following a delay of 1000ms a left or right

pointing arrow stimulus appeared (see Figure 12).

(b) Word only, in which the cue "Word" was displayed to instruct participants to respond to word direction, then following a delay of 1000ms either the stimulus "LEFT" or "RIGHT" appeared (see Figure 12).

(c) Short switch, in which either the cue "Arrow" or "Word" was displayed, then following a delay of 200ms both a combined arrow and word stimulus appeared (see Figure 12).

(d) Long switch, in which either the cue "Arrow" or "Word" was displayed, then following a delay of 1500ms both a combined arrow and word stimulus (identical stimuli to those used in the Short switch block) appeared.

Figure 12 . Simple Arrow and simple word stimuli in switch task
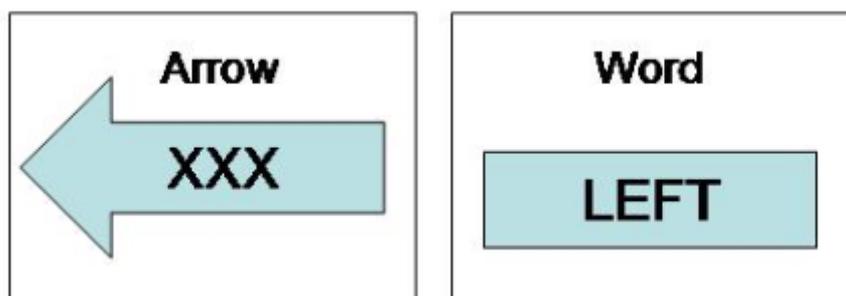
In the Short and Long switch conditions, the word and arrow stimulus were presented as a combination of the stimuli above, and could either be congruent (agree on direction, e.g., a left-pointing arrow with the word "LEFT" inside it; (see lefthand panel of Figure 13) or incongruent (indicating different directions, e.g., a left-pointing arrow with the word "RIGHT" inside it; see righthand panel of

Figure 13). Trials in the switching task were also categorised into switch or non-switch. A non-switch trial was one in which the cue was the same as for the immediately preceding trial. A switch trail was one in which the cue differed from the immediately preceding trial. For example, if a block commenced with 3 trials in the order 'Arrow'-'Word'-'Word', trial 2 ('Word') would be considered a switch trial (as the previous item had the 'Arrow' cue), while trial 3 ('Word') would be considered a non-switch trial (as the previous item also had a 'Word' cue). For the Arrow only and Word only blocks, six practice stimuli were presented followed by 24 stimuli trials per block. For the Short switch and Long switch blocks, six practice stimuli were presented followed by 48 stimuli trials per block. Each block was separated by an instruction page, detailing the task requirements for the next task. When participants made an incorrect response, a tone stimulus sounded to indicate that an error had been made.

All arrow/word stimuli comprised of a 3cm by 1cm text box (with or without arrow header) with Arial font size 16 text and were presented in the centre of the computer screen. The 'Arrow' and 'Word' task cues were printed 0.5cm above the stimuli in Arial font, size 16 (see Figure 13).
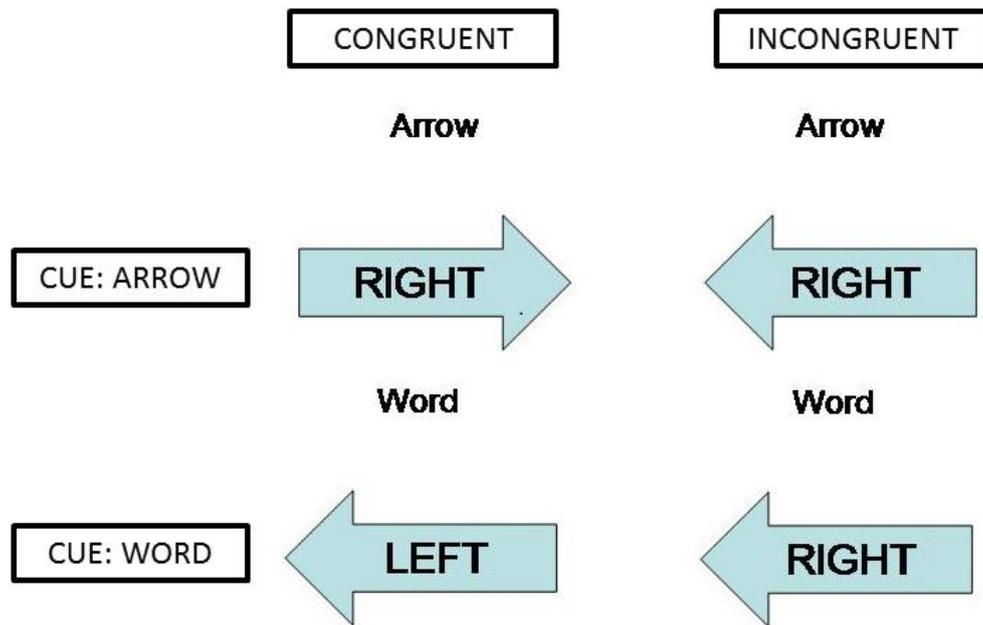
Figure 14: Example of stimuli in the switch task. Top left: congruent stimulus pair with 'Arrow' cue; Top right: incongruent stimulus pair with 'Arrow' cue; Bottom left: congruent stimulus pair with 'Word' cue; Bottom right: incongruent stimulus pair with 'Word' cue.

7.2.2.3.   Finger tapping timing task

All participants completed the two tests of neural timing detailed in Chapter 6:

A) Externally-paced finger tapping

B) Self-paced finger tapping

For the experimental set-up of the timing tasks, see section 6.2.2.

7.2.3. Experimental Procedure

The experimental tasks were administered under Superlab © on a Dell OptiPlex 960 computer. Tone stimuli (switch and finger tapping tasks) were presented in free field at a comfortable listening level for each participant (at least 70 dB). Tasks were presented in a fixed order (RT tasks followed by switching task followed by finger tapping tasks). Participant responses were recorded and stored for offline analysis. A single repeat of experimental block was allowed if the examiner considered that the participant had been distracted during the original presentation or did not adequately understand the task requirements. No feedback about performance was given during the session.

7.2.4. MRI acquisition

Images were acquired as described in Chapter 3 (section3.8.1).

7.2.5. Imaging processing

Structural images were pre-processed using the methods described in Chapter 3 (section 3.8.4.3.1) for VBM analysis.

An anatomical small volume of the frontal lobes in their entirety was derived in FSL using the John Hopkins University (JHU) cortical atlas tool (Desikan et al., 2006). This frontal lobe mask was then transferred into MRIcron (http://www.sph.sc.edu/comd/rorder/mricron.html) where it was saved as a volume of interest. This mask was chosen because it offers a more standardised alternative to personal manual segmentation, and is defined by very generous

volume boundaries, which ensures that the frontal lobes in their entirety are captured. This mask was applied to all contrasts such that only voxels included within the mask were examined.

7.2.6. Statistical analysis

7.2.6.1. Analysis of neuropsychological performance

Neuropsychological data were analysed according to methods described in Chapter 3 (see section 3.4).

7.2.6.2. Behavioural analysis

Behavioural data were analysed using STATA 12©. Data were analysed separately for each task using generalised estimating equations (GEE) to account for clustering of data by participant. For all analyses, models were analysed with (i) adjustment for gender and age, and (ii) adjustment for age, gender, and a measure of general intelligence (WASI matrices test raw score). Data will be presented for each task separately, and further broken down into each effect of interest for clarity of presentation. A full summary of each performance metric derived from the experimental tasks, and method of calculation for each of these, is presented in Table 21. For the purpose of clarity, reaction time (RT) here is used in reference to the Simple RT and Choice RT tasks, whereas latency is used as the behavioural metric to measure speeded response.

Table 21. Method of calculation of the relevant performance metric for each task in the present study

TASK/PERFORMANCE METRIC	RELEVANT PERFORMANCE METRIC	HOW CALCULATED
REACTION TIME TASKS		
Simple RT	Simple RT latency	Mean Simple RT latency
	Simple RT proportion correct	Mean Simple RT proportion correct
Choice RT	Choice RT latency	Choice RT latency (targets only)
	Choice RT proportion correct	Choice RT proportion correct (targets only)
Derived performance metrics	Preparation effect (latency)	Choice RT & Simple RT (long delay) – Choice RT & Simple RT (short delay) (targets only, data collapsed across the 2 conditions)
	Choice effect (latency)	Mean Choice RT (targets only) - mean Simple RT
SWITCH TASK		
Arrow only	Arrow only latency	Mean Arrow only latency
	Arrow only proportion correct	Mean Arrow only proportion correct
Word only	Word only latency	Mean Word only latency
	Word only proportion correct	Mean Word only proportion correct
Short switch	Short switch latency	Latency correct across all correct response preceded by short delay
	Short switch proportion correct	Proportion correct across all correct response preceded by short delay
Long switch	Long switch latency	Latency across all correct response preceded by long delay
	Long switch proportion correct	Proportion correct across all correct response preceded by long delay
Derived performance metrics	Preparation effect (latency)	Long switch latency - Short switch latency
	Preparation effect (proportion correct)	Short switch proportion correct - long switch proportion correct
	Congruency effect (latency)	Incongruent item latency - Congruent item latency (correct items only)
	Congruency effect (proportion correct)	Congruent item proportion correct - Incongruent item proportion correct
	Switch cost (latency)	Odds ratio: Switch item latency - non-Switch item latency
	Switch cost (proportion correct)	Odds ratio: Non-switch proportion correct - Switch proportion correct

TIMING TASKS		
Externally-paced tapping	Externally-paced Absolute drift	Drift from target 1500ms in externally-paced task
Self-paced tapping	Self-paced Absolute drift	Drift from target 1500ms in self-paced task
	Self-paced Clock variance	Clock variance from W&K model in self-paced task

7.2.6.2.1. Reaction time tasks

7.2.6.2.1.1. RT – Simple and Choice

Simple RT data were derived from response to the 'A' stimuli in the first block. Choice RT data were derived from latency to the 'A' stimuli only (not B, C, D distractors) in the second condition. The first two trials for each participant were discarded. To exclude atypical responses, for each participant the mean and standard deviation of natural log latency was calculated and trials were then excluded where log latency was more than two standard deviations from the mean. Latency was analysed using a GEE model with identity link and Gaussian family, with exchangeable correlation structure and robust standard error. This approach is similar to linear regression in that it models the mean response, but allows responses by the same individual to be correlated rather than assuming independence. The outcome variable in the model was natural log of latency. Results are presented as exponentiated coefficients, rather than difference in log latency, as the exponential of the coefficient reflects the ratio of latency between the groups being compared.

7.2.6.2.1.2. Proportion Correct

Proportion correct was derived by dividing the total number of responses by the number of correct responses made. As the proportion of correct responses was close to 100% for this task, analysis focused on the latency to correct responses.

7.2.6.2.1.3.   Preparation effect

Inter-stimulus interval (ISI) (3, 4, 5, 6, and 7 seconds) and the interaction between group and inter-stimulus interval were examined. ISI was divided into short and long categories, whereby an ISI of 3 or 4 seconds was classified as short, and an ISI of 5, 6, or 7 seconds was defined as a long ISI. Latency to the A stimulus was collapsed across the two conditions and separated into whether it was preceded by a short or long ISI. A 'preparation effect' metric was then generated by subtracting the mean latency to the stimuli preceded by a short ISI from the mean latency to the same stimulus when preceded by a long ISI in order to examine the effect of ISI on latency of response.

7.2.6.2.1.4.   Choice effect – latency

The difference in latency of response between the simple and choice RT tasks was examined. A 'latency choice effect' metric was generated by subtracting the mean latency to the target stimulus in the choice RT task (distractors present) from the mean RT to the target stimuli in the simple RT task (no distractors).

7.2.6.2.2.   Switching task

Data for the long and short switch blocks were analysed together. The first two trials for each participant were discarded. To exclude atypical responses, for each block for each participant the mean and standard deviation of natural log reaction time was calculated and trials were then excluded where log reaction time was more than two standard deviations from the mean. The predictor variables of interest in analysis of switching were: participant group (control, bvFTD, PNFA, SD and AD), compatibility of word and arrow stimuli (congruent and

incongruent), switch (switch or non-switch), the interaction between switch and compatibility, the interaction between group and switch, the interaction between group and compatibility and the interaction between group, switch and compatibility.

7.2.6.2.2.1. Latency

Latency in the long and short switch blocks of the switch task was analysed using a GEE model with identity link and Gaussian family, with exchangeable correlation structure and robust standard error. This approach is similar to linear regression and models the mean response, but allows responses by the same individual to be correlated rather than assuming independence. The outcome variable in the model was natural log of reaction time. Results are presented as exponentiated coefficients, as these reflect the ratio of reaction time between the groups being compared.

7.2.6.2.2.2. Proportion correct

The proportion of correct responses was analysed using a GEE model with logit link and binomial family, with independent correlation structure and robust standard error. This modelling approach is similar to logistic regression and models difference in log odds of correct response, while allowing for non-independence of responses by the same participant. Results from this model are expressed as odds ratios for ease in interpretation

7.2.6.2.2.2.1. Preparation effect

Response following cue in the short delay and long delay switch conditions and the interaction between group and delay (short vs long) was examined. Data were collapsed across both compatibility conditions. A ' latency preparation effect' metric was then generated by subtracting the mean latency to the correct stimuli in the short switch condition from the mean latency to correct stimuli in the long switch condition. . A 'proportion correct preparation effect' was generated by subtracting the proportion of correct responses in the short delay condition from the proportion of correct data in the long delay condition (see Table 21).

7.2.6.2.2.2.2.   Congruency effect

Analysis was conducted in order to examine the effect of stimuli compatibility on both the proportion correct and reaction time to correct response. In order isolate the compatibility effect, trials were only included where the participant had correctly responded to the preceding stimulus. RT and proportion correct to both congruent and incongruent stimuli presentations were analysed as above (see 7.2.6.2.2.1 and 7.2.6.2.2.2)

7.2.6.2.2.2.3.   Switch cost

 In order to isolate the switching effect, trials were only included where the participant had correctly responded to the preceding stimulus. The main interest for the switch analysis was whether the effect of stimuli compatibility differed between switch and non-switch tasks, as this is thought to most accurately reflect the transient competition from the most recent task rather than the generic effect of suppressing response activation from the irrelevant task (Aron, 2004).

7.2.6.2.3. Finger tapping timing tasks

There were two timing tasks: externally-paced tapping, and self-paced tapping. The data from these tasks was analysed according to the neural timing model of Wing and Kristofferson (1973), which generates the following variables of interest: Clock variability, motor variability; response drift over time; accuracy of response to target; mean interresponse interval.

For an explanation of the analysis of the timing task data, see Chapter 6 (see section 6.2.4).

7.2.6.3. Imaging analysis

MR images were analysed according to methods described in Chapter 3 (3.8.3.1.1). Linear regression models were used to examine regional grey matter volume correlates with performance on each of the experimental subtests; voxel intensity (grey matter volume) was modeled as a function of subtest score, including group membership, participant's age, TIV, and gender as covariates of no interest, with and without the inclusion of a measure of intelligence (the matrices subtest of the WASI).

7.3. Results

7.3.1. Participants characteristics

Demographic and task-related information is presented in Table 22. The patient and control groups were well matched for age (p=0.9); males were over-

represented in the bvFTD group (p=0.0004). Neuropsychological performance is presented in Table 22. On average, patient groups performed significantly worse than control subjects in each test, except in the visual object perception task (VOSP), where all groups showed normal visual perception. Patients showed the anticipated profile of deficits relative to healthy control participants and each other; bvFTD participants exhibited impaired performance on measures of executive function; SD patients showed significantly reduced word comprehension and naming; AD patients also showed a significant executive impairment as assessed by the Stroop inhibition task.

Table 22. Demographic and neuropsychological characteristics of participants

	bvFTD	SD	PNFA	AD	Controls
No.	27	15	9	9	37
Age (years)	65(7.2)	64(6.2)	66 (8.1)	65(7.2)	64(7.8)
Sex (Male)	18	9	3	7:1	16
IQ					
WASI vocab (80)	42.3(20.2)*	29.2(26.1)*	28.3(16.8)*	54.2(12.0)*	70.9(4.9)
WASI blocks (/71)	21.1(15.6)*	29.4(17.2)*	27.3(17.6)*	20.1(12.9)*	46.5(11.5)
WASI similarities (48)	21.8(11.9)*	16.2(16.6)*	21.3(10.8)*	26.4(8.7)*	40.5(6.0)
WASI matrices (/32)	13.6(7.0)*	17.9(8.7)*	19.6(7.8)*	14.8(7.7)*	26.7(7.2)
NART total (/50)	27.8(14.4)*	24.1(17/1)*	14.7(10.0)* [b c d]	34.6(9.8)*	41.6(5.7)
Episodic memory					
RMT Words (/50)	36.3(8.0)*	33.1(7.5)*	39.3(4.2)*	33.3(8.8)*	47.9(2.6)
RMT Faces (/50)	34.4(6.7)*	30.3(11.5)*	30.3(11.5)*	37.6(4.7)*	43.0(4.4)
Executive function					
D-KEFS Stroop inhibition (s)	118.7(72.2)*[c]	114.7(53.0)*	N/A	134.8(45.6)*[c b]	55.4(13.3)
Semantic processing					
BPVS (/150)	128.8(23.6)*	88.6(55.2)* [a b d]	123.3 (33.7)	132.6(21.5)	147.5(1.7)
Other skills					
GNT (/30)	12.5(8.4)*	4.5(7.4)[a b d]	11.0(10.7)*	17.4(5.3)*	25.2(3.4)
Forwards DS (/12)	7.1(2.5)*	7.4(2.5)*	5.0(3.4)* [b c d]	7.0(2.2)*	9.1(1.5)
Backwards DS (/12)	5.5(2.7)*	6.2(3.0)	3(1.6)* [b c d]	4.4(2.4)*	7.5(1.9)
Addition(/12)	4.6(3.6)*	4.6(3.6)*	2.1(2.9)* [b c d]	3.4(1.5)*	7.3(2.3)
Subtraction(/12)	5.0(4.1)*	5.0(4.1)*	2.7(2.9)* [b c]	3.8(2.7)* [b c]	8.1(2.5)
VOSP (/20)	15.5(3.0)	15.6(3.4)	17.9(1.2)	16.3(2.3)	18.2(1.7)

Mean (standard deviation) values shown. AD, Alzheimer's disease; BPVS, British Picture Vocabulary Scale; bvFTD, behavioural variant frontotemporal dementia; D-KEFS Stroop (word and inhibition), Delis-Kaplan Executive Function System; DS, digit span; GNT, Graded Naming Test; n/a, not available; NART, National Adult Reading Test; PNFA, progressive nonfluent aphasia; RMT, Recognition Memory Test; SD, semantic dementia; VOSP, Visual Object and Space Perception – object decision task; WASI, Wechsler Abbreviated Scale of Intelligence. Key: * significantly poorer performance than healthy controls; [a] = significantly poorer performance than PNFA patients; [b] = significantly poorer performance than bvFTD patients; [c] = significantly poorer performance than SD patients; [d] = significantly poorer performance than patients with AD

7.3.2. Behavioural results

Results of the behavioural analyses are presented below. Data from these analyses are presented in Table 23. Comparisons where performance in one group differed to another are indicated (see Table 23 legend). Unless stated otherwise the direction and significance (p greater or less than 0.05) of the results reported below are equivalent for the two models covarying for age and gender, or age, gender, and general intelligence.

7.3.2.1.   Simple and Choice RT task

No significant group by task interactions were observed for the outcomes of latency, proportion correct, or preparation effect in the Simple and Choice RT task.

7.3.2.1.1.   Response latency

Response latencies collapsed across conditions were significantly slower for all patient groups in comparison to controls on both Simple and Choice RT tasks. Patients with SD showed the longest latencies, but there were no significant differences between between patient groups.

7.3.2.1.2.   Proportion correct

All participants made very few errors with the Simple RT task and only a small number of errors in the Choice RT task (not significantly different to controls).

7.3.2.1.3.   Preparation effect

Longer ISI was associated with a faster latency (p=0.007 for <=4 versus 5/6/7 seconds) but there was no interaction between ISI and participant group (p=0.15).

7.3.2.1.4.   Choice effect

The presence of distractors in the Choice RT task was associated with an increase in latency of response in all groups. There were no significant group differences in the difference in latency between choice and Simple RT tasks (p>0.05 for all comparisons).

Table 23. Behavioural results across all tasks

	Controls	bvFTD	PNFA	SD	AD
REACTION TIME					
Simple RT latency (ms)	300(32.7)	668(619.2)*	434(92.8)*	688(607.9)*	367(88.3)*
Simple RT proportion correct	100(0.0)	99.6(1.1)	100(0.0)	99.8(0.8)	100(0.0)
Choice RT latency (ms)	528(56.6)	833(455.9)*	790(194.8)*	992(559.8)*	728(114.7)*
Choice RT proportion correct	98.0(2.1)	95.1(12.3)	99.3(1.2)	97.5(3.8)	99.4(1.2)
Short ISI latency (ms)	540(57.7)	849(461.9)*	814(176.5)*	936(559.7)*	733(127.7)*
Long ISI latency (ms)	512(58.2)	806(436.6)*	757(191.6)*	899(522.2)*	720(92.3)*
choice effect latency difference (ms)	228(44.65)	165(537.3)	356(143.7)	304(583.1)	361(101.6)
Preparation effect latency difference(ms)	27(31.2)	42(117.1)	57(46.5)	37(160.6)	13(67.8)
SWITCH TASK					
Simple arrow latency (ms)	533(59.2)	717(217.9)*	874(281.4)*	748(281.0)*	660(134.2)*
Simple arrow proportion correct (%)	98(3.3)	98(3.2)	99(2.1)	98(3.7)	99(1.6)
Simple word latency (ms)	571(71.9)	746(197.8)*	1915(196.6)*	790(303.5)*	698 (86.5)*
Simple word proportion correct (%)	98(2.2)	98(3.2)	100(0.0)	99(2.2)	99(2.1)
Short switch latency (ms)	1597(386.1)	2110(882.8)*	2478 (750.8)*	1961(730.8)*	3151(927.1)*
Short switch proportion correct (%)	95(6.6)	82(12.1)*[a]	86(13.4)	79(14.2)*[a]	79(10.2)*[a]
Long switch latency (ms)	1054(371.5)	1673 (751.2)*	1851(449.1)*[b c]	1516(672.0)	2464(927.3)*[b c]
Long switch proportion correct (%)	97(3.6)	88(10.2)*[a]	93(12.5)	82(14.9)*[a]	90(8.1)*[a]
Preparation effect latency difference (ms)	-543(378.3)	-437(826.35)*	- 627 (610.95)	- 445(614.8)	-687(927.2)
Preparation effect proportion correct difference	2(4.5)	6(11.6) *[a]	6(13.1)	3(14.6) *[a]	11(9.1) *[a]
Congruent latency [#]	NA	1.215	1.565*	1.185	1.545*
Congruent proportion correct (%)	100(0.0)	97(1.3)	98.8(0.9)	99.8(0.8)	96.7(1.3)
Incongruent latency [#]	NA	1.36*	1.51*	1.205	1.79*

Incongruent proportion correct (%)	85(7.6)	81(15.2) *[a]	86(8.3)	80(15.3) *[a]	80(10.1) *[a]
Congruency effect – latency (ms)	NA	23.3(19.1)*	10.2(17.9)*	11.5(20.2)	23.7(17.7)*
Congruency effect – proportion correct (%)	7(9.8)	23(18.4) *[a]	15(17.0)	29(19.3) *[a]	34(19.1) *[a]
Switch cost – latency [#]	1	1.14*	0.97	1.08	1.05
Switch cost – proportion correct [#]	2.1	0.17* [a c]	0.51	NA	NA
TIMING TASKS					
Externally-paced Absolute drift (ms per stimulus)	25.4(18.3)	63.44(71.15)*[a c d]	40.8(29.3)	23.19(15.9)	30.1(23.5)
Self-paced Absolute drift (ms per stimulus)	169.3(166.1)	328.7(281.5)*[a c d]	207.4(110.8)	108.9(41.9)	296.2(321.9)
Self-paced Clock variance (ms[2))]	6411(6992.8)	12691(20331.2)* [a c d]	4062.9(2379.4)	3374.3(2373.6)	1670.5(24211.4)

Table 23: Experimental behavioural results. Key: * significantly poorer performance than healthy controls; [a] = significantly poorer performance than PNFA patients; [b] = significantly poorer performance than bvFTD patients; [c] = significantly poorer performance than SD patients; [d] = significantly poorer performance than patients with AD; [#] = results are presented as an odds ratio. Abbreviations: AD, Alzheimer's disease; bvFTD, behavioural variant frontotemporal dementia; PNFA, progressive nonfluent aphasia; SD, semantic dementia; ms, milliseconds; NA = not available; s, seconds

7.3.2.2.   Switching task

Data for the switch task are given in Table 23.

7.3.2.2.1.   Higher-level interactions

Accuracy: There was a significant interaction between compatibility and cue type (OR words = 0.07; OR arrows = 0.11; p=0.015), such that accuracy was greatest for congruent stimuli when the cue was an arrow. Despite this finding, there was no evidence of a three-way interaction between cue type, compatibility and participant group in either of the adjusted models (p=0.35).

There was no significant group by switch and compatibility interaction (p=0.15). However, when intelligence was included in the model with age and gender, a significant group by switch interaction (p=0.03) and a trend towards a group by switch and compatibility interaction (p=0.07) was revealed, suggesting greater accuracy of response to congruent stimuli in the non-switch over the switch condition in the bvFTD patient group, disproportionate to that observed in the control and SD, PNFA, and AD groups.

Latency: From the analysis of the latency component of the switch task, there was a significant interaction between cue type and delay length (p<0.001), such that latency of response to word stimuli benefited more from an increased delay than arrow stimuli. A three-way interaction between group, cue and delay (p=0.003) was also observed, such that the control, SD, PNFA, and AD participants showed a greater benefit of delay to stimuli presentation which was not observed in the

bvFTD group. This disparity in the benefit of delay between the bvFTD group and the other participants was particularly evident when the cue was a word.

7.3.2.2.2. Latency

Latencies tended to be longer for patients than for controls in all conditions. Participants with bvFTD had significantly longer latency than controls in both the long switch (p=0.047) and short switch conditions (p=0.01), and similar latencies within both simple arrow and word conditions (p>0.05 for both comparisons). Participants with PNFA and AD had longer latencies than controls in all conditions (simple arrow, simple word, short switch, long switch; p<0.05 for all comparisons). Participants with SD had similar latencies to controls in all conditions (p>0.05 for all comparisons). Participants with bvFTD tended to have quicker latencies than those with AD or PNFA and similar latencies to those with SD.

7.3.2.2.3. Proportion correct

The overall effects of proportion correct for the simple arrow and word data indicated that all groups had a high proportion of correct response to the simple stimuli. Proportion correct data from the short and long switch conditions suggested that across both switch trials, control participants tended to have a higher proportion of correct response than any of the patient groups. As can be seen from more detailed reporting of experimental effects (see below), proportions of correct response were primarily moderated by cue compatibility and length of delay between cue and stimuli, such that responses were most

accurate following longer delay period and to congruent stimuli, and this was true for all participant groups.

7.3.2.2.4. Cue type

Accuracy: Participants made very few errors with the simple arrow and word conditions. For all patient groups there was no significant difference in correct response between words and arrows, although there was a trend towards lower odds of correct responses to the arrow condition in patients with SD (p=0.062).

In the short and long switch conditions all patient groups had significantly lower odds of being correct than controls when the cue was a word, although this difference was only borderline statistically significant for PNFA versus controls. There were no significant differences in the odds of being correct between any of the patient groups (p>0.05 for all comparisons). When the cue was an arrow, patients with PNFA did not have significantly lower odds of being correct than controls, however all other patient groups had significantly lower odds of being correct than controls.

Latency: Latency tended to be longer for patients than controls to both simple arrow and simple word stimuli (p<0.05 for all comparisons). There was no significant difference in latency between response to word and arrow cues in any of the groups (p>0.05 for all comparisons).

7.3.2.2.5. Delay and preparation effect

Accuracy: There were greater odds of a correct answer with long delay than short delay (p<0.001) and this was true for all groups. bvFTD, SD, and AD participants had significantly lower proportion of correct responses compared to controls in both the short and long switch conditions (p<0.05 for all comparisons). Patients with PNFA had a similar proportion of correct responses to controls in both short and long switch conditions.

Latency: There was a significant difference in the latency-based preparation effect measure between controls and patients with bvFTD (p=0.025); bvFTD patients gained a significantly smaller benefit from greater preparation time (smaller reduction in response latency going from the short delay to long delay condition) than controls. SD, PNFA, and AD patients showed no greater or lesser benefit of preparation than controls (p>0.05 for all comparisons).

7.3.2.2.6. Compatibility effect

Accuracy: Considering all groups together there was no significant group by compatibility interaction (p=0.15). The proportion of correct responses was high for all participant groups in the congruent condition with many participants having 100% correct responses. All participant groups had significantly lower odds of being correct for incongruent stimuli (p<0.05 all groups).

Latency: There was a significant interaction between group and compatibility in the latency-based measure (p=0.003). There was a significant difference in latency ratio (LR) between congruent and incongruent items for controls and

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patients with bvFTD, indicating that the bvFTD patients were relatively slower with incongruent than congruent cues (p=0.005). AD patients were also significantly slower with incongruent than congruent items relative to controls (p=0.03). However, SD and PNFA patients showed no such compatibility effect, with no significant difference in LRs between these patient groups and controls (SD: p=0.22; PNFA: p=0.77).

7.3.2.2.7. Switch cost

Accuracy: Results cannot be examined for patients with AD, as this group had 100% correct responses to congruent stimuli in the non-switch condition, making it impossible to model switch cost for these participants due to zero variance in this group. Considering all other groups (controls, bvFTD, SD, PNFA) together in the model with age and gender covariates, there was no significant group by switch interaction (p=0.11). However, a significant group by switch interaction was observed when level of general intelligence was included as a covariate (p=0.03). This overall switch cost effect appeared to relate largely to performance on incongruent trials, as the odds of a correct answer were not significantly different between switch and non-switch trials when stimuli were congruent (p>0.05 all patient groups for all models). Control participants and participants with SD, AD, and PNFA had a lower odds of correct response for switch compared to non-switch trials. This resulted in the odds ratio (OR) being significantly different for patients with bvFTD (switch OR=2.14) compared to both controls (switch OR =0.28, interaction p=0.04) and participants with PNFA (switch

OR=0.59, interaction = 0.036), as well as a trend towards a significant difference with patients with SD (switch OR=0.63, interaction p=0.1).

Latency: Considering all groups together, there was no significant group by switch interaction (p=0.053). The overall LR for switch cost was greatest for patients with bvFTD (LR=1.14, p=0.011), followed by patients with SD (LR=1.09, p=0.039). For patients with bvFTD the switch cost was significantly greater than for controls (interaction switch cost LR=1.15,p=0.020) and patients with PNFA (switch cost LR=0.85, interaction p=0.037). For participants with SD, although there was a trend towards higher switch cost, there were no significant differences with other groups. Participants with PNFA and AD showed no significant overall switch cost and did not differ in switch cost from controls.

When stimuli were congruent, controls and patients with PNFA showed significantly longer latencies in the switch compared to non-switch trials, and there was also a trend in the same direction for patients with SD (p=0.067). In contrast, there was little evidence that patients with bvFTD and AD had longer latencies in switch trials compared to non-switch trials when stimuli were congruent.

When stimuli were incongruent, all participant groups had significantly longer latencies in the switch compared to the non-switch trials (p<0.05, all groups).

7.3.2.3. Finger tapping timing tasks

The full report of results from the finger tapping timing tasks is presented in Chapter 6 (see section 6.3.3). The results of these analyses relevant to the current chapter are presented in Table 23.

7.3.3. Neuroimaging results

Data for local maxima of grey matter change are summarised in Table 24. A schematic of all areas where significant behavioural-anatomical correlations were observed is shown in Figure 14. All statistically significant results were obtained from analyses modeling the behavioural score of interest as a function of the participant's age, gender, TIV, group membership, and level of general intellect. When the intelligence covariate was removed from the analyses, only the 'preparation effect metric' results for both the Simple and Choice RT tasks and the switching task remained statistically significant (see Table 23).

7.3.3.1.1. Reaction time task

A positive correlation between preparation effect, measured by the latency of response in the short ISI condition in the Choice RT task minus the latency of response in the longer ISI condition in the Choice RT task, and increased grey matter volume in the right temporal pole was observed. No significant neuroanatomical correlations were observed for Simple or Choice latency, or for proportion correct, nor were any inverse associations found.

7.3.3.1.2.   Switch task

The same preparation metric was correlated with decreased grey matter in the orbitofrontal cortex in the switch task. A significant correlation between reduced grey matter in the right medial frontal gyrus (MFG) and increased response latency to congruent stimuli in the switch task was observed. No such correlation was observed for the proportion of correct responses to congruent stimuli. Similarly there was no significant anatomical correlation with response latency to incongruent stimuli, nor between reduced grey matter and the proportion of correct responses to incongruent stimuli in the switch task. No significant grey matter correlates of any compatibility metric, calculated by subtracting either the response latency or proportion of correct responses in the incongruent condition from the congruent condition, were observed. A trend for a significant correlation between reduced grey matter volume in the right superior medial frontal lobe (SMFL) and switch cost was observed, however this did not reach statistical significance. No inverse associations were observed between reduced grey matter and improved performance in any metric.

7.3.3.1.3.   Neural timing tasks

A correlation between drift in response in both the externally-paced and self-paced timing tasks and decreased volume in the right superior temporal gyrus was observed. This did reach statistical significance in the externally-paced condition, and a strong trend was observed for the self-paced condition. A significant correlation was observed between reduced grey matter volume in the left precentral gyrus of the frontal lobe and a clock variance metric. No significant

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neuroanatomical correlations were observed for the mean inter-response

interval in neither paced nor self-paced conditions. No inverse associations were

observed between reduced grey matter and improved performance in any metric.

7.3.3.1.4.   Relationship with general intelligence 'g'

All statistically significant results were obtained from analyses modeling the

behavioural score of interest as a function of the participant's age, gender, TIV,

group membership, and level of general intellect. When the intelligence covariate

was removed from the analyses, only the 'preparation effect metric' results for

both the Simple and Choice RT tasks and the switching task remained statistically

significant (see Table 24).

Table 24. Summary of voxel based morphometry findings when adjusting for age, gender, and general intelligence

Behavioural correlate	Brain region	Cerebral hemisphere	Peak coordinates	Anatomical prediction
RT Task				
Preparation effect*	Temporal pole	R	35, 21, -35	RTL [a]
Switch Task				
Preparation effect *	OFC, TPJ, TP	R, L	-17, -22, 15	RTL [a]
Congruent latency	MFG	R	39, -3, 58	SM, RACC [i]
Switch cost	SM	R	26, 23, 54	SM [c], RL, LL [b], vlPFC [d]
Timing Tasks				
Externally paced drift	MTG	R>L	18, 21, -11	SM, RL [b]
Self -paced drift	STG	R	56, 18, -11	SM, RL [b]
Clock variance effect	PCG	L	-45, -10, 7	LSMA [f]

Key: * Result remained statistically significant after removing the intelligence covariate from the analysis. [a] Stuss et al.,2005; [b] Aron et al., 2004; [c] Shallice et all., 2008; [d] Braver et al., 2004; [e] Ridderhinkoff et al.,2004; [f] Couell et al., 2012; [g] Stuss and Alexander, 2011; [h] Botvinicnk and Cohen, 2004; [i] Picton et al., 2007. Abbreviations: R =right, SC= superior cingulate; RL = right lateral; SM = superior medial; OF = orbitofrontal; MTG = medial temporal gyrus;TL = temporal lobe; TPJ= temporoparietal junction; TP = temporal pole; IM = inferior medial; SMA = supplementary motor area; ACG = anterior cingulate gyrus; LL = left lateralised; dmPFC= dorsomedial prefrontal cortex; STG, superior temporal gyrus; PCG, pre-central gyrus.

Figure 14. Schematic representation of neural correlates of behavioral performance
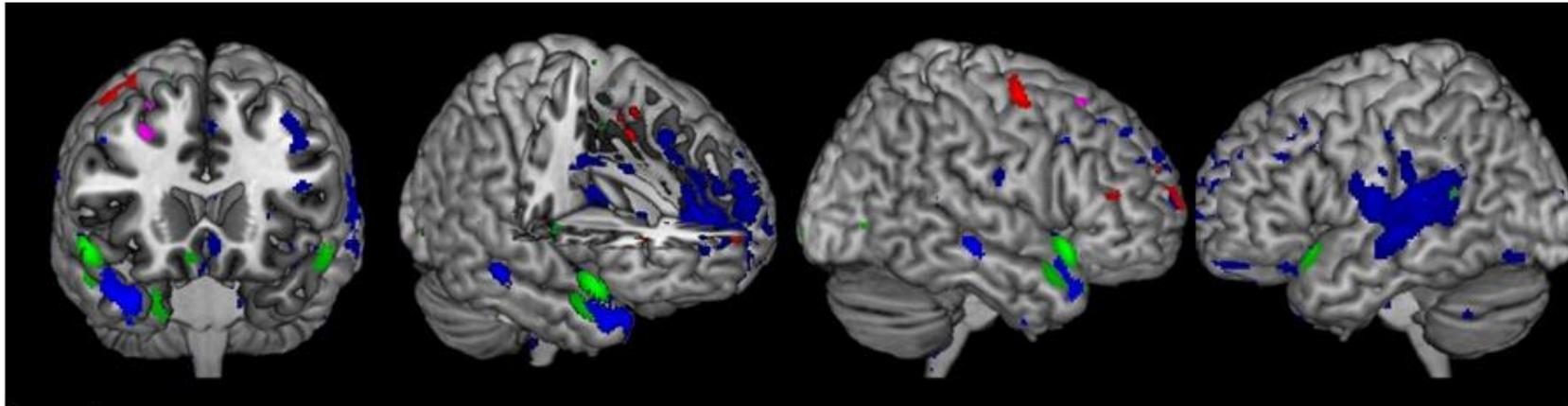
From L-R: Top view of template brain; frontal section cut-out of template brain; right section cut-out of template brain; right hemisphere; left hemisphere. Key: blue indicates neural correlates of 'preparation effect (see above for details); pink indicates neural correlates of switch cost (see text for details); green indicates neural correlates of response drift in externally-paced and self-paced finger tapping task (see text for details); red indicates neural correlates of latency to congruent stimuli.

7.4. Discussion

I present here evidence for dissociable executive capacities that cannot be explained by a general deficit in level of intelligence. Furthermore, I present evidence that dysfunction in any one of such capacities can be attributed to the degradation of a distinct network of grey matter structures within the frontal lobes. These cortical correlates are located in areas previously identified as crucial to dissociable components of executive cognition, and provide evidence to strengthen this literature by examining a neurodegenerative population with a heterogeneous profile of frontal and temporal lobe atrophy. These data have important clinical and theoretical implications.

7.4.1. Simple and Choice RT tasks

The present data from the Simple and Choice RT tasks indicated all patient groups to be slower than and comparable in accuracy of response to controls. Longer ISI was also associated with a reduction in latency in all groups, whilst the presence of distractors in the Choice RT task caused an increase in latency compared to the Simple RT task (no distracters). The observation that all patient groups were slower to respond than healthy controls is no surprise considering their neurological health, and may reflect a core slowing in their ability to process information and initiate response. The lack of difference in proportion of correct responses between all patient groups and the controls, however, serves to highlight the fact that these patients did adequately understand the task requirements.

7.4.2. Switch task

A number of interesting results emerged from the analysis of the switch task data. As was observed in the Simple and Choice RT tasks, latency of response tended to be longer for all patient groups in all conditions compared to controls. All groups also had a similarly high rate of correct responses to the simple stimuli. In general, all groups made more accurate responses to the congruent stimuli, and in the non-switch conditions, however accuracy of response was worsened by the presence of incongruent stimuli and even more so if this was paired with a switch in cue. Interestingly, all patient groups were less accurate in their response when the cue was a word. This likely reflects the core language dysfunction common to FTD, and the increased linguistic difficulties that arise as part of this disease. When the delay between cue and stimulus presentation was long, control, SD, AD, and PNFA groups benefited in terms of both accuracy and latency of response. By contrast, bvFTD participants exhibited a significantly smaller reduction in response latency in the long delay compared to the short delay condition, seemingly failing to capitalise on the preparatory opportunity afforded by the longer delay. Switch cost analysis confirmed the original hypothesis that participants would be slower and less accurate in trials where there was a switch from the preceding cue, however different profiles of response emerged for each of the patient groups.

7.4.3. bvFTD performance profile

The most interesting response profile emerged in the behavioural variant group. This is unsurprising considering the syndromic profile of bvFTD, which is most commonly defined by a deficit in executive capacity and greater atrophy of the frontal lobes compared to those with primary progressive aphasia and Alzheimer's disease. Patients with bvFTD tended to have faster response latencies than those with AD or PNFA and similar response latencies to those with SD. This most likely reflects an attentional dysfunction and failure to monitor response, whereby patients with bvFTD are impulsive and quick to respond before checking their pre-potent response against the task requirements. This is also directly in line with the findings of Stopford and colleagues (2012), who reported bvFTD patients to respond at a comparable speed to healthy controls, despite significantly poorer accuracy. Patients with bvFTD showed a significant switch cost, suggesting that these participants experienced greater difficulty than their patient and healthy control counterparts in suppressing the transient effects of the most recent task requirements. All other patient groups showed no such switch cost, and this increased cost in the bvFTD group was observed even after adjusting for general intelligence. The response latency to switch trials was also greater in the bvFTD group compared to controls. Together, these behavioural results suggest that the bvFTD participants showed gross abnormalities in many different facets of executive function required by the switch task, including selecting the appropriate response, switching between response rules, speed of response, and the interplay between delay of cue and response requirements, and this dysfunction was disproportionate to performance in both neurologically-compromised and healthy counterparts.

7.4.4. SD performance profile

Participants with SD responded comparably to controls in terms of general accuracy in the Simple and Choice RT tests and the word and arrow only conditions of the switch task (only falling down in the difficult short and long switch conditions). However the latency of response in this group was highly dependent upon the condition requirements. SD participants showed the longest latencies in the simple and choice reaction time tasks and the short switch condition. This group of patients showed no increase in latency, however, in the compatibility effect metric, suggesting that they were abnormally slow to initiate their response irrespective of whether the stimuli were congruent or incongruent.

7.4.5. PNFA performance profile

Participants with PNFA had longer latencies than controls in all conditions. However, in measures of accuracy, PNFA participants responses were comparable to the control group, and indeed, were the only patient group that were not significantly less accurate than controls in their responses regardless of cue type or delay length to cue. This group of participants showed no overall cost in terms of latency or accuracy in comparison to the control group in terms of stimulus compatibility or task switch.

7.4.6. AD performance profile

Participants with AD showed a high concordance with the control group in terms of accuracy of response across the Simple and Choice RT tests and the word and arrow only conditions of the switch task (like SD patients, only falling down in the difficult short and long switch conditions). Indeed, data from this group of participants could not be analysed for the switch cost condition because they had 100% correct responses to congruent stimuli in the non-switch condition. Unfortunately, as perfect accuracy equates to zero variance in response, this group was precluded from the switch cost analyses and thus was not able to be statistically compared to performance in the other groups. This is a major limitation of this model. Conversely, this group also exhibited longer latencies to response compared to controls in all conditions (and unlike SD patients, did show the expected congruency effect). This mirrors the findings of Stopford and colleagues (2012), who reported that participants with AD have significantly slower response latencies, though comparable accuracy to control participants. This pattern of behavior suggests that the AD patients prioritized accuracy of response over latency and were able to consider their response before initiating.

7.4.7. Neuroanatomical associations

The neuroimaging analysis revealed a number of interesting results in consensus with the current literature suggesting that different areas of the frontal cortices support dissociable executive capacities (Stuss et al., 2005; 2007; Shallice et al., 2008; Aron et al., 2004). Right lateralization of anatomical executive associations is commonly reported in the executive function literature (Picton et al., 2006; Garavan et al., 2006; Kelly et al., 2004), however the present study shows

bilateral involvement, which supports the findings of Stuss and colleagues (2004), and the neuroanatomical associations proposed by the supervisory attentional systems model (SAS: Norman & Shallice., 1986; Stuss & Alexander, 2001; Alexander et al., 2005; 2007; Stuss, 2011).

Congruency can be likened to the proposed SAS executive process of inhibition, which has previously been associated with integrity in the SMA (Aron et al., 2004), dorsomedial PFC (Aron et al ., 2004; Ridderhinkoff et al., 2004; Botvinicnk and Cohen, 2004), the superior medial frontal lobe (Stuss & Alexander, 2011), and the anterior cingulate gyrus (Stuss & Alexander, 2011). The VBM analysis revealed no significant correlates of the main congruency effect in terms of either latency or accuracy of response. However, response latency to congruent stimuli in the present study was found to be correlated with grey matter in the right medial frontal gyrus in the switch task. This is similar to previous literature which has implicated similar structures in response latency to simple stimuli (Shallice et al., 2007; Stuss et al., 2005). The present results, in line with previous studies, highlight the importance of superior and ventro-medial frontal structures in the successful inhibition of incorrect responses.

The present analysis revealed switch cost, a measure of behavioural inhibition, to be associated with the integrity of grey matter in the right superior medial frontal lobe, although this finding did not reach statistical significance after FWE correction. This lends support to the findings of a previous study, in which behavioural inhibition in task switching was found to be dependent upon both right lateral and left lateral frontal lobes (Aron et al., 2004), however these

findings must be interpreted with the caution as they did not reach statistical significance . Other studies have also shown this ability to be associated with the integrity of the superior medial frontal lobe (Shallice et al., 2008), and the ventrolateral prefrontal cortex (Braver et al., 2004), none of which were observed in the present study. Disparity in anatomical localization of inhibition may be due to differences in populations assessed and the intricacies of how the different tasks were operationalized.

The most striking result in the neuroanatomical analyses was observed for the 'preparation effect' metric. This effect was found to be strongly correlated with integrity of the grey matter in the right temporal pole in the Simple and Choice RT tasks, and more strongly in the orbitofrontal cortex and left superior medial areas in the switch task, where there is a higher cognitive demand due to extraneous interference of multiple cues. The preparation effect here can be likened to the SAS process of task-setting. Task-setting is proposed to be left-lateral dependent (Alexander et al., 2007; 2009; Stuss et al., 2011), which is reflected in the current results for the preparation effect in the switch task.

An examination of the neural correlates of timing metrics revealed that the right superior temporal gyrus was found to be integral to both externally-paced and self-paced timing. The precentral gyrus in the left hemisphere was found to be correlated with clock variability. In all, this is largely consistent with the neural timing literature, in which there is strong evidence for timing to be supported by a striato–thalamo-cortical circuit, particularly involving the supplementary motor area and pre-SMA bilaterally (Coull et al., 2012; Teki et al., 2011; Ortuno et al.,

2011), which are both in the close vicinity to the present results. A number of the SAS executive processes (Norman & Shallice., 1986; Stuss & Alexander, 2002) can be conceptualized as contributing to timing ability, such as the act of monitoring timed performance, or energisation of continual finger-tapping response. As such, it is no surprise that many of the neural areas that contribute to timing performance are also involved in executive processing.

7.4.8. Relationship with general intelligence 'g'

The findings of the present study do not support the notion that a reduction in 'g' can account for the patterns of executive dysfunction observed in FTD. Results of the behavioural analysis with the inclusion of the 'g' covariate did not cause any marked reduction in significant patient-control differences. In fact, the inclusion of the intelligence covariate served to strengthen the effect size of the group by compatibility by switch interaction, suggesting a greater accuracy of response to congruent stimuli in the non-switch over the switch condition in the bvFTD patient group is dependent upon adjustment of general level of intellect. Furthermore, when intelligence was included as a covariate within the voxel based morphometry (VBM) analysis, many significant neuroanatomical correlates of the different facets of executive function were derived nonetheless. However, when the intelligence covariate was removed from the analyses, a reduction in the number of contrasts that reached statistical significance was observed. This suggests that in controlling for level of intellect, we were able to remove some noise from the data that may have been contributing to reduce the statistical power of finding a direct correlation between the behavioural covariate of

interest and its neuroanatomical bases. The difference between the present study and the study by Roca and colleagues (2010) may lie in the patient populations observed. Where the current study examined frontotemporal dementia patients as an organic lesion model of the frontal and temporal lobes, Roca and colleagues tested a cohort of patients with discrete isolated lesions. The heterogeneity of the neuronal loss in the FTD patients may have allowed for a greater variance in the anatomical dataset than is afforded when using discrete lesion mapping. While I recognise that general intelligence, or 'g' may be involved in some executive processes, I have found no evidence to support the notion that a reduction in 'g' on its own can account for the patterns of executive dysfunction observed in FTD, and therefore, no evidence in support of executive function as a unitary resource.

7.4.9. Theoretical implications

The present results have a number of important theoretical implications. The data support the conceptualization of executive function as a collection of related, but fundamentally dissociable cognitive processes (Norman and Shallice, 1986; Aron et al., 2004; Stuss & Alexander, 2007), rather than as a unitary entity or resource which may be partially related to the much older concept of general intelligence (Roca et al., 2010; 2013).

Figure 14 highlights a prefrontal, ventromedial, and superior medial network of frontal areas that subserve these dissociable processes of speeded response, response to conflict, preparation of response, and timing functions. This is similar

to the network proposed by Stuss (2011) in which a dorsolateral circuit which projects to basal ganglia structures is responsible for mediating the executive processes of task setting and monitoring, and a more superior medial circuit mediates energisation of performance. Latency metrics in the present study were found to be correlated with the right temporal pole and right superior medial areas, and can be likened to Stuss and colleagues' process of energisation, which the authors propose to be dependent upon superior medial areas (Alexander et al., 2005; 2007; Stuss, 2011). The SAS model (Norman & Shallice, 1986; Stuss & Alexander, 2007) process of monitoring is purported to require right lateral engagement (Alexander et al., 2005; 2007 Stuss, 2011); this is mirrored by the congruency effect in the present study, whereby one must monitor outgoing responses against task-requirements, and its association with atrophy in right-lateral areas. Furthermore, the preparation effect metric in the present results for which I found strong prefrontal and left superior medial neural correlates can be viewed as in line with the process of task-setting in the SAS model, which is proposed to be left-lateral dependant (Alexander et al., 2005; 2007; Stuss, 2011). The present data highlight key cortical areas within a flexible and dynamic network previously implicated in the literature and in line with the SAS model of executive control (1986; 2007), whereby damage to any one node could cause variable deficits within the realm of executive functioning.

7.4.10. Clinical implications

These results have important clinical implications. The results support the conceptualization of executive function as a collection of related, but

fundamentally dissociated cognitive processes (Norman and Shallice, 1986; Aron et al., 2004; Stuss and Alexander, 2007), which appear to be disproportionately dysfunctional in bvFTD compared to other FTD and AD patient groups and healthy controls. This collection of cognitive capacities was found to map onto a network of neural correlates that have been consistently identified in both neurologically-compromised (Stuss et al., 2005; Stuss and Alexander, 2007; Shallice et al., 2007) and healthy populations (Stuss and Alexander, 2007; Braver et al., 2009), although it must be noted that some neuroanatomical correlations did not reach statistical significance, and therefore must be interpreted with caution. If executive functions can be dissociated and do have distinguishable anatomical correlates, as suggested by the present data, then we can potentially discriminate more precisely the nature of executive dysfunction in different clinical phenotypes, and use tests sensitive to the different executive processes to help us better understand the complex relationships between phenotype, genotype and pathology within the FTD spectrum. bvFTD has a highly heterogeneous phenotypic profile in terms of underlying pathology, behavioral manifestation, and neuroanatomical involvement. There is currently considerable interest in understanding how behavioural phenotypes map onto brain networks, and the degradation of differing neural areas within the executive function network may shed some light on how this disease manifests behaviourally. Thus, the identification of dissociable executive deficits in bvFTD may develop our clinical understanding of the condition through increasing our understanding of the way in which subtle executive deficits may contribute to the wider social and behavioural features of this disease.

The use of reaction-based tasks to investigate executive capacity in a cognitively diminished population, such as that represented by FTD and AD here, also suggests potential clinical utility. Such tasks are simple to carry out and require minimal instruction, therefore reducing linguistic demands. The more complex switch task used in the present study utilized response to a single arrow or word stimuli as an effective base to expand upon and control for the more complex demands of the switch conditions. There is great difficulty in designing effective tasks that can accurately capture the executive capacity of all FTD patients due to the heterogeneity of deficits inherent within the FTD syndrome spectrum. For example, while a slow response to incongruent stimuli in the Stroop task may reflect executive dysfunction in bvFTD patients, the same slowed response in PNFA patients may more likely reflect an inability to form and pronounce the words. The reaction-based executive tasks used in the present study may provide a better means of examining executive function in which performance is less confounded by the collateral deficits experienced by these different patient groups.

7.5.   CHAPTER CONCLUSION

In this chapter I have provided evidence that executive function can be broken down into dissociable capacities, which are subserved by dissociable cortical areas that make up a larger executive function networkSuch executive capacities are particularly degraded in bvFTD, and cannot be explained by a general reduction in intelligence. This work has important theoretical implications for the

understanding of executive function and its neural bases, and to the clinical

understanding of FTD and its heterogeneous behavioural profile.

8. PHYSIOLOGICAL BASES TO PSYCHOSIS IN C9ORF72-DEFINED FTD

8.1. Chapter introduction

In the previous experimental chapters (Chapters 4 – 7) within this thesis I have demonstrated gross dysfunction in social cognition, executive function, and neural timing mechanisms which may contribute to these dysfunctions in bvFTD participants. A lesser-explored facet of the bvFTD phenotype is the recently reported psychosis which can accompany those affected by C9ORF72-defined FTD (see 2.1.3), of which bvFTD is the most common syndromic diagnosis. As the focus of this thesis is to extensively investigate the neuropsychological phenotype of bvFTD, this chapter will focus on the novel C9ORF72-bvFTD phenotype of psychosis.

Recent advances in histopathology and genetics have transformed our picture of the molecular substrates of FTD (Seelaar et al., 2011; Rohrer and Warren, 2011). In large series, a high proportion (approximately 40%) of cases of FTD have been linked to mutations in one of three major causative genes (see 1.2.1.2 for more detail): the microtubule-associated binding protein tau gene (MAPT, causing MAPT-associated genetic FTD, MAPT-FTD); the progranulin gene (GRN, causing GRN-FTD); and expanded hexanucleotide (GGGGCC) repeat insertions in a non-coding promoter region of open reading frame 72 on chromosome 9 (C9ORF72, causing C9ORF72-FTD). C9ORF72-FTD has recently been identified as a major cause of familial FTD (around 12% of cases), FTD in association with motor

neuron disease (around 40% of cases) and apparently sporadic FTD (around 8% of cases: (Mahoney et al., 2012a; Snowden et al., 2012b; DeJesus-Hernandez et al., 2011; Majounie et al., 2012b). Pathological C9ORF72 expansions lead to loss of one or more alternatively spliced RNA transcripts of unknown function and formation of nuclear RNA foci, suggesting several candidate molecular disease mechanisms (Arighi et al., 2012; DeJesus-Hernandez et al., 2011; Gijselinck et al., 2012). Histopathologically, C9ORF72-FTD has been associated with cellular inclusions containing TAR-DNA-binding protein 43 (TDP-43) subtypes A and B and protein p62 (Whitwell et al., 2012). However, despite these substantial genetic and pathological advances, our understanding of the pathophysiological mechanisms that translate molecular pathology to clinical phenotype in FTD remains very limited (Warren et al., 2013).

The pathophysiological mechanisms of C9ORF72-FTD are of particular clinical and neurobiological interest on account of its wide phenotypic heterogeneity coupled with certain specific phenotypic features. Neurologically, the development of motor neuron signs is an important harbinger of the diagnosis, however this is not a uniform finding (Mahoney et al., 2012a). The neuropsychological profile of C9ORF72-FTD overlaps extensively with other cases of FTD (Mahoney et al., 2012b; Snowden et al., 2012b). However, memory and dominant parietal dysfunction are relatively prominent in group studies; and early, salient neuropsychiatric disturbances appear to be a hallmark of C9ORF72-FTD, reported in approximately 40 - 60% of cases across published series, albeit with variability between studies (Snowden et al., 2012a; Dobson-Stone et al., 2012; Floris et al., 2012). These disturbances include anxiety, agitation and

psychotic symptoms of hallucinations and delusions (Mahoney et al., 2012a; Galimberti et al., 2013; Larner, 2013; Arighi et al., 2012; Snowden et al., 2012b; Snowden et al., 2012a). Phenomenologically, hallucinations and delusions in C9ORF72-FTD share features with primary psychiatric illnesses such as schizophrenia but often have a somatic focus or include prominent elements of disordered awareness of self in relation to others, including themes of paranoia, infestation, bodily distortion or invasion, pregnancy, or loss of voluntary or sphincteric muscle control (Mahoney et al., 2012a; Larner, 2013; Snowden et al., 2012a; Snowden et al., 2012b; Takada and Sha, 2012). Although detailed neuroanatomical-phenotypic correlation has yet to be undertaken in the C9ORF72 mutation spectrum, a distributed profile of brain atrophy has been identified in group neuroimaging studies of C9ORF72-FTD with prominent involvement of the frontal and parietal lobes, thalamus and cerebellum (Mahoney et al., 2012a; Whitwell et al., 2012; Boeve et al., 2012). This profile contrasts with the relatively focal involvement of antero-medial temporal structures characteristic of MAPT-FTD and the highly asymmetrical inter-hemispheric atrophy profile of GRN-FTD (Rohrer et al., 2010b; Whitwell et al., 2012). Cerebellar atrophy is a prominent longitudinal signal of advancing disease (Mahoney et al., 2012b) and the cerebellum is also a key locus of tissue pathology in C9ORF72-FTD (Mahoney et al., 2012b; Al-Sarraj et al., 2011; King et al., 2013). This neuroanatomical evidence suggests that involvement of a cortico-thalamo-cerebellar network may play an important and potentially defining role in the pathogenesis of C9ORF72-FTD in relation to other pathologies causing FTD.

From a pathophysiological perspective, the neuropsychiatric features of C9ORF72-FTD might be interpreted as arising from aberrant body (or self) schema processing, which was first defined by Head and Holmes (1911) as the internalised, combined postural and spatial model of ourselves that provides a standard against which sensory changes can be calibrated and incorporated (see 2.4 for further explanation). The concept has since been extensively studied and has become widely accepted by neurophysiologists, neurologists and psychiatrists (e.g. Goodwin et al., 1972; Lackner, 1988; Botvinick and Cohen, 1998; Naito et al., 1999; Blakemore et al., 2000; Creem-Regehr et al., 2007; Sachdev et al., 2008; Goble, 2010; Hauser et al., 2011; Moseley et al., 2012; Aybek et al., 2013). Body schema processing and self / non-self differentiation are closely related perceptual and cognitive operations: disambiguation of self from non-self frequently depends on stable and accurate body schema boundaries, modulated by the effects of one's own and external actions. Altered body schema processing has been implicated in the pathogenesis of many psychiatric conditions (see 2.4 for a more detailed discussion) .

 The culprit cortico-thalamo-cerebellar network implicated in neuroimaging and neuropathological studies of C9ORF72-FTD is a potential substrate for the neuropsychiatric symptoms exhibited by these patients (Mahoney et al., 2012a). Previous neuroimaging work in healthy individuals and patients with psychosis has implicated a distributed neural network including the cerebellum, parietal lobes, posterior insula and prefrontal cortex in self-referent information processing, particularly ascription of agency to actions (Jeannerod, 2009; Blakemore et al., 2000; Frith et al., 2000; Blakemore et al., 2003; Tsakiris et al.,

2007). The cortical components of this network have been specifically implicated in a range of phenomena associated with body schema alteration or distortion in health and disease states (Naito et al., 1999; Creem-Regehr et al., 2007; Moseley et al., 2012), consistent with the concept of multiple sensory and homeostatic representations that together must be integrated into a coherent 'body matrix'.

Here I investigated systematically the physiological and cognitive characteristics of patients with C9ORF72-FTD in relation to healthy older individuals, patients with another genetically-mediated FTD syndrome (MAPT-FTD), and patients with sporadic FTD. Our primary objective in undertaking the study was to assess body schema processing and the nature and specificity of any disease-associated body schema deficits in C9ORF72-FTD. In this I was motivated by emerging clinical and neuroimaging evidence concerning the central role of cortico-subcortical dysfunction and impaired body schema processing in the pathogenesis of C9ORF72-FTD and other disorders with prominent neuropsychiatric features. I designed or adapted somatosensory tasks to assess different levels of body schema processing, comprising encoding and modulation of tactile and proprioceptive signals, body part representation and evaluation of the perceptual effects of self versus non-self tactile agency. I hypothesised, firstly, that patients with C9ORF72-FTD would manifest deficits on these tasks not attributable simply to general cognitive decline; and further, that these deficits would have specificity for C9ORF72-FTD versus other forms of FTD.

8.2. Methods

8.2.1. Participant characteristics

Seventeen patients with a diagnosis of bvFTD and 13 healthy older individuals were recruited according to methods outlined in Chapter 3 (see section 3.2). All participants underwent comprehensive clinical and general neuropsychological assessments as outlined in section 3.4. Due to the unique and unusual nature of the experimental tasks utilized in this Chapter, information on aspects deemed relevant to task performance, including psychiatric history, co-morbid peripheral neuropathy, and prescribed medication was also gathered from each patient's clinical notes and by using the Cambridge behavioural inventory (CBI; Wedderburn et al., 2008), which was completed by the patient's caregiver.

8.2.2. Genetic analyses

All patients were screened for pathogenic mutations in genes causing the FTD syndrome according to methods outlined in Chapter 3(3.2.3). Five patients were found to have pathogenic C9ORF72 expansions; of these, three had sufficient DNA for repeat size confirmation (3472, 3501 and 3600 base pairs respectively). A further seven patients had a pathogenic mutation in the MAPT gene (four exon10+16, two exon13 c.1212C>T; one novel presumptively pathogenic mutation c.1052A>G in exon12). All patients with C9ORF72-FTD were known to have had other family members affected with FTD or motor neuron disease, conforming to an autosomal dominant pattern of inheritance. Five patients in the present FTD cohort had no known pathogenic mutation identified, nor any

suggestion of a relevant family history, and were therefore classified as having sporadic FTD.

8.2.3. Clinical details

All patients had a typical clinical syndrome of FTD led by behavioural decline and inter-personal difficulties. All patients in the C9ORF72-FTD group exhibited early prominent anxiety, irritability or paranoia; three had somatically-focused preoccupations (obsessive exercising and body image concerns, unexplained somatosensory symptoms, compulsive scratching); and one presented with social phobia. None of the patients with C9ORF72-FTD gave a history to suggest frankly delusional ideation, however one reported auditory hallucinations of voices calling his name. Three patients in the sporadic-FTD group exhibited similar symptoms, including paranoia, anxiety, somatic preoccupations and agoraphobia; whereas only one patient in the MAPT-FTD group developed an early symptom of this kind (prominent anxiety). On the CBI (Wedderburn et al., 2008), the C9ORF72-FTD group showed a similar distribution of total scores to the other FTD group (see Table 25); although unusual beliefs were scored relatively prominently in the C9ORF72-FTD group, these were also reported by caregivers for individual patients in the other FTD groups.

Two patients with C9ORF72-FTD had features in keeping with early motor neuron disease (upper limb fasciculations) at the time of their participation; none had typical cerebellar signs or clinical features of peripheral neuropathy. No patients with C9ORF72-FTD had a past history or symptoms suggestive of peripheral neuropathy. Two patients in the sporadic-FTD group had a history of

incidental mild peripheral neuropathy (one diabetic and the other of undetermined cause); these patients did not subsequently participate in the tactile discrimination threshold experiment. Clinical electrophysiological studies undertaken in three patients with C9ORF72-FTD corroborated significant denervation in one case; no study showed evidence of peripheral neuropathy. At the time of assessment, two patients in the C9ORF72-FTD group and three patients in the MAPT-FTD group were prescribed acetylcholinesterase inhibitors; one patient in the C9ORF72-FTD group and one patient in the sporadic-FTD group were prescribed quetiapine.

Structural volumetric brain MRI in 16 of the 17 patients corroborated the clinical syndromic diagnosis of FTD (MRI was contraindicated in one patient with C9ORF72-FTD). Profiles of brain atrophy were in keeping with those previously described in each FTD syndrome (Rohrer and Warren, 2011; Mahoney et al., 2012a): whereas patients with MAPT-FTD showed a comparatively uniform profile of selective atrophy predominantly (and relatively symmetrically) affecting the anterior temporal lobes, atrophy profiles were highly variable in the other disease groups. In particular, regional atrophy profiles exhibited by individuals with C9ORF72-FTD included asymmetric selective frontal atrophy, mild fronto-subcortical atrophy, diffuse atrophy and relatively symmetric mesial temporal lobe atrophy (Figure 15); none of the patients showed definite cerebellar atrophy.

Figure 15. Representative T1-weighted MR brain sections for individual patients with C9ORF72-associated FTD
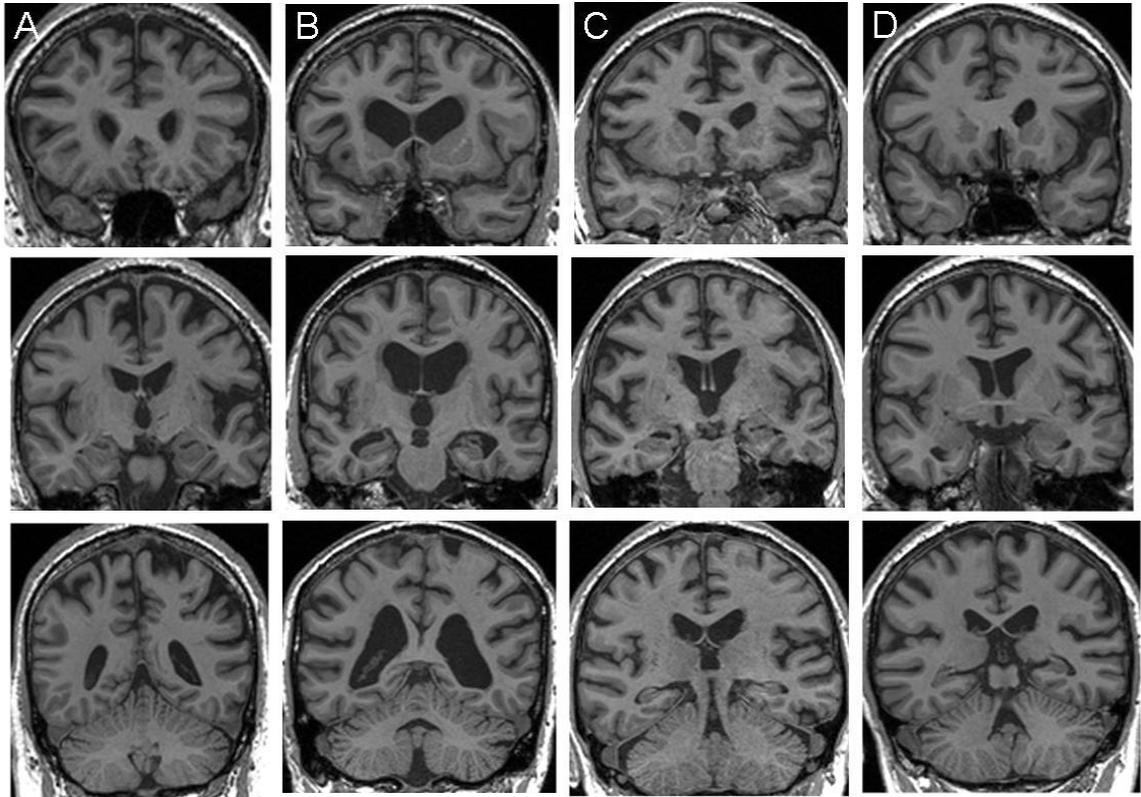
Representative coronal T1-weighted MR brain sections for individual patients (designated A to D) with C9ORF72-associated frontotemporal dementia (MRI was contraindicated in one case). Each column corresponds to a single patient; sections have been selected to capture the anterior frontal lobes and temporal poles (top row), anterior peri-Sylvian regions and medial temporal lobes (middle row), and posterior parietal lobes and cerebellum (bottom row). The left hemisphere is shown on the right in all sections.

8.2.4. Experimental design

8.2.4.1. Structure of experimental test battery

In designing the experimental battery, I set out to sample processes relevant to the perception and cognitive evaluation of body schema and the sense of agency of self versus others acting on that schema. I selected four experimental tasks based on previous neuropsychological evidence demonstrating the utility of each task for assessing the relevant body schema process, where such evidence was available. In addition, I chose tasks suitable for use in cognitively-impaired patients, incorporating simple, uniform response procedures while minimising additional, task-irrelevant cognitive demands (for example, verbal mediation). I assessed perceptual encoding of spatial signals on the body surface using tactile two-point discrimination thresholds (previously identified as a marker for somatosensory dysfunction with schizotypy: (Lenzenweger, 2000), measured in a standard psychophysical procedure. Modulation of proprioceptive localisation of limb position was assessed using a tendon vibration paradigm, well documented in the classical neurophysiological literature as an index of proprioceptive acuity and body schema alteration in normal individuals (Goodwin et al., 1972; Lackner, 1988; Goble, 2010): this paradigm capitalises on the propensity of vibration to stimulate muscle spindle afferents and tendon organs (Naito et al., 1999), thereby producing an illusion of muscle stretch and limb motion at the joint. Body part representation and plasticity were assessed using a rubber hand paradigm: this has previously shown to modulate powerfully body schema boundaries and

content in normal individuals, with illusory incorporation of the rubber hand into the body schema (Ramachandran and Hirstein, 1998; Tsakiris et al., 2007). The rubber hand illusion is likely to arise at the interface between integration of (tactile and visual) sensory signals and top-down influences that interpret the origins of sensory signals and actions and attribute agency. Finally, I assessed the explicit attribution of agency in somatosensory signals to self versus others, using a modified version of a previously described tactile stimulation ('tickle') paradigm (Blakemore et al. 2003): in the healthy brain, this paradigm has been shown to engage a large-scale brain network including the cerebellum. No feedback was given to participants about their performance during the tests and no time limits were imposed on participant responses. All experiments were carried out by a single experimenter (L.E.D.), however due to the nature of administration of the tendon vibration task, an additional experimenter was required to mark each participant's response, while I administered the vibration to the participants secured arm.

8.2.4.2.   Tactile two-point discrimination

The experimental procedure used for this test was adapted from a previously-described procedure (Lenzenweger, 2000). Tactile two-point discrimination thresholds were determined using a standard clinical two-point aesthesiometer lightly applied along the transverse axis of each participant's dominant palm. Prior to commencing the test, it was established that each participant could easily detect the touch of the aesthesiometer. During the test, the participant was seated comfortably and blindfolded, and the task on each trial was to indicate whether

one or two points (applied simultaneously) had been detected. Both ascending and descending series were administered. In a descending series, the distance between the two points was incrementally reduced in 2 mm steps from an initial separation of 40 mm, until the participant indicated that 'one point' was detected on two consecutive trials; the first of these successive 'one point' responses was taken as the two point detection threshold for that descending series. In an ascending series, the distance between the two points was incrementally increased in 2 mm steps from an initial separation of 2 mm until the participant indicated that two points were detected on two consecutive trials; the first of the successive 'two points' responses was taken as the two-point detection threshold for that ascending series. Descending and ascending series were each repeated three times, yielding a total of six threshold estimates for each participant; a mean two-point discrimination threshold was calculated by averaging he threshold scores across all six series, and these individual participant mean two-point thresholds were incorporated in subsequent analyses of group tactile threshold differences.

8.2.4.3. 'Tickle task' - Self versus non-self attribution

The experimental set-up of the 'tickle task' is schematised in figure 20. A paintbrush (14.5 × 1 cm, 1"25 bristles) was suspended by using a cross-clamp from a rod positioned between two table-mounted retort stands, such that the rod (and the attached paintbrush) could be rotated freely by manipulating a handle attached to one end. The participant was positioned with the dominant hand resting palm-down on the table between the retort stands, and the

apparatus was adjusted so that the paintbrush lightly tracked across the skin of the hand when the handle was rotated by the participant, using the nondominant hand. During the experiment, the paintbrush was randomly moved along the suspending rod from trial to trial, such that the brush either would contact the participant's hand ("self" condition) or would not contact the participant's hand ("non-self" trials); on "other" trials, the experimenter delivered the tactile stimulus by using an identical paintbrush, either in time with the participant's own action (synchronous condition) or with a short delay (around 1 second; asynchronous condition). The retort-mounted paintbrush was shifted by the experimenter before every trial (whether self or non-self) to minimize any extraneous cues from sound or the absolute position of the brush. Participants were blindfolded and instructed to rotate the handle 3 times in every trial: the task on each trial was to decide whether the brush stimulus was generated by the participant's own action or by that of the experimenter. It was established before commencing the experiment that participants were able reliably to detect the sensory stimulus delivered by the brush. Thirty experimental trials were administered, comprising 10 self, 10 non-self synchronous, and 10 non-self asynchronous trials in randomized order. Participant responses were recorded and stored for offline analysis. No time limit was imposed, and no feedback about performance was given during the test.

Figure 16. Schematic diagram of the experimental set-up in the 'self' versus 'non-self' attribution task conditions.
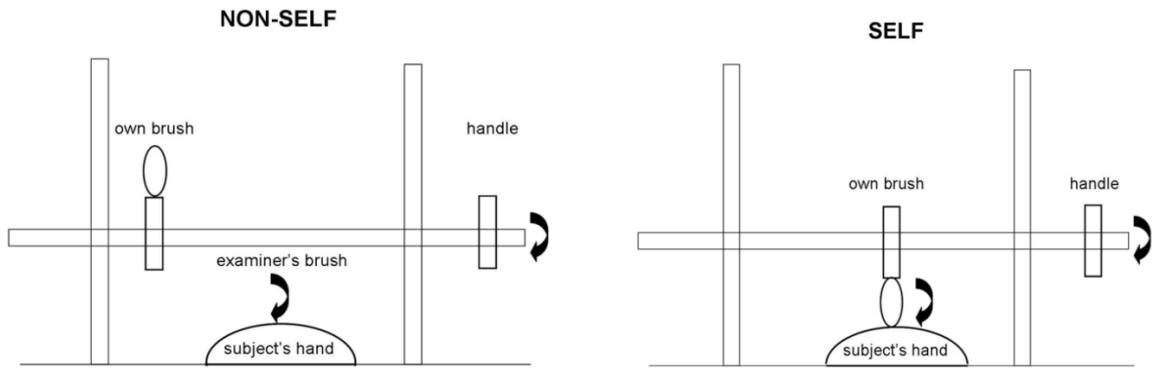
8.2.4.4. Proprioceptive localisation under tendon vibration

The experimental procedure for this test was adapted from a previously-described paradigm (Goodwin et al., 1972; Longo et al., 2009), and represented schematically in Figure 17. Participants were seated comfortably and blindfolded, with their arms flexed forward at the elbows and separated by a removable vertical cardboard partition. The participant's dominant arm was lightly secured to a hinged splint such that the angle of elbow flexion could be manipulated by the experimenter (the participant was instructed not to attempt actively to move the elbow). The participant touched the cardboard partition with their outstretched dominant index finger while flexion angles of 22.5 ° and -22.5° relative to the horizontal (determined using a protractor) were applied to the secured elbow, and the actual position of this reference finger was marked on the cardboard for each flexion angle, for offline analysis. The participant was then asked to make a pointing gesture with the dominant index finger (no longer in contact with the cardboard) while flexion angles of 22.5 ° and -22.5° were randomly applied at the secured elbow; at each flexion angle, the participant was asked to oppose the free (non-dominant) index finger as closely as possible to the estimated position of the pointing dominant index on the other side of the partition, in order to estimate the baseline accuracy of proprioceptive localisation matching in the absence of any tendon stimulation. Three baseline position-matching estimates were marked on the cardboard for each flexion angle, for offline analysis. In the subsequent stimulation trials, this procedure was repeated after biceps tendon stimulation at approximately 80Hz using a customised

mechanical vibrator: vibration was applied for 30 seconds to the biceps tendon of the secured arm and continued to be applied as the participant performed the localising task. A total of 20 stimulation trials were administered, comprising 10 trials at each flexion angle, randomly ordered. The position of the participant's proprioceptive matching estimate for each trial was marked on the cardboard for offline analysis.

Figure 17. Schematic diagram of the experimental set-up in the proprioceptive localization task
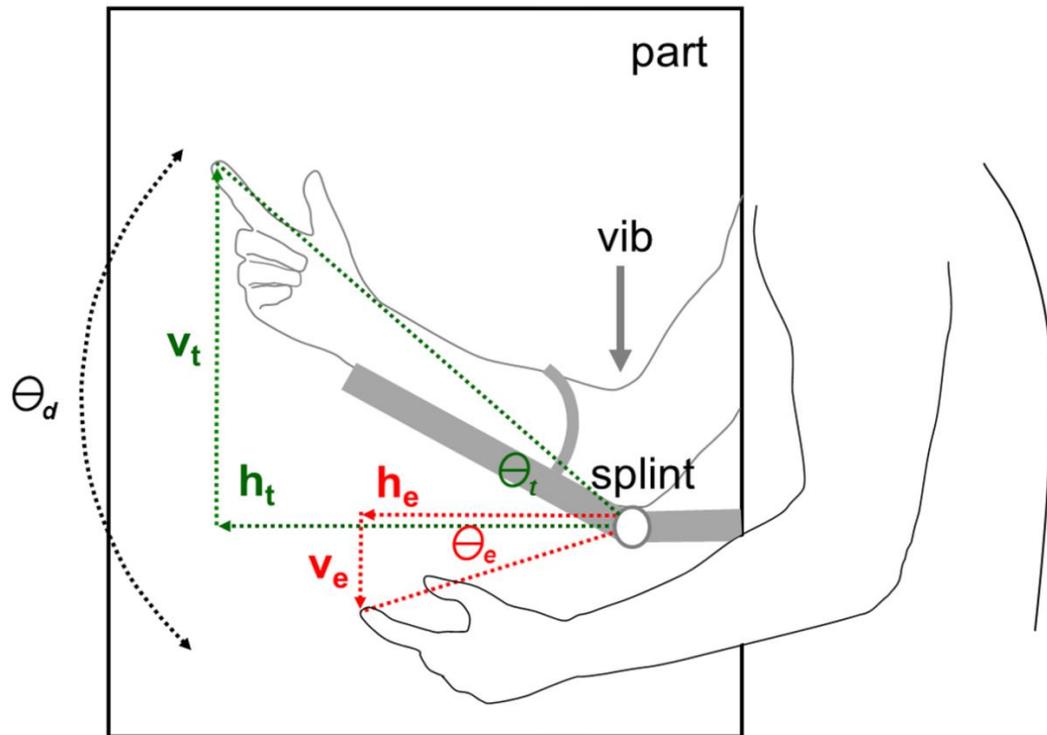

For clarity, angles have been exaggerated and the fixed (reference, stimulated) arm is shown 'transparently' behind the plane of the central partition, part on which participant position matching estimates were marked and above the participant's free (localising) arm. The participant's fixed arm was supported by the adjustable splint hinged at the elbow; the angle of the splint was varied randomly (either +22.5° or -22.5° relative to horizontal) from trial to trial, and during stimulation trials the vibrator, vib was applied to the biceps tendon of this arm. The horizontal (h_t) and vertical (v_t) coordinates of the true position of the target index finger of the fixed arm and the horizontal (h_e) and vertical (v_e) coordinates of the estimated position of the target finger are shown. From these measurements relative to the elbow the true angle of the target finger Θ_t and the position estimation angles Θ_e on each trial were calculated trigonometrically. Angles of deviation from the target angle Θ_d were calculated as the difference between Θ_t and Θ_e., both for baseline (no stimulation) trials and stimulation (tendon vibration) trials; the absolute value of each participant's mean Θ_d in each condition was entered into the group analysis.

8.2.4.5.   Rubber Hand illusion task

The experimental procedure for this test was adapted from a previously-described paradigm (Botvinick and Cohen, 1998), represented schematically in Figure 25. Participants were seated comfortably at a table wearing rubber gloves with both hands facing forward palms-down on the table. A vertical partition completely obscured the participant's view of their own dominant hand, while a rubber hand was placed visibly on the table alongside the participant's obscured dominant hand. The rubber hand closely resembled the participant's own gloved hand (to reduce potentially confounding visual or auditory cues during the stimulation procedure) and the origins of the participant's own hands and the rubber hand were obscured by a sheet in order further to enhance the illusion that the rubber hand was the participant's own dominant hand. Light tactile stimulation was delivered using a paintbrush (14.5 × 1 cm, 1"25 bristles) on the index finger of the participant's dominant hand and synchronously simulated in identical fashion on the rubber hand for three minutes. The participant's task during stimulation was to watch the brush stroking the hand in front of them. On cessation of stimulation, the participant completed a questionnaire (administered verbally by the experimenter) to assess the presence and extent of any somatosensory illusory experience during stimulation. This questionnaire (adapted from Botvinick and Cohen, 1998) comprised three target items (for example, 'Did you feel as if the rubber hand was your own hand?') interspersed with foil items (for example, 'Did you feel your real hand turning rubbery?') and

responses were graded using a 7-point Likert scale, a score of 1 signifying a strong percept and a score of 7 signifying no percept. Each participant's scores on the Likert scale were summed for the three target items, such that a higher score indicated a stronger illusory percept (highest possible sore = 21). These summed scores were entered for each participant in subsequent group analyses.

Figure 18. Schematic diagram of the experimental set-up in the rubber hand illusion task
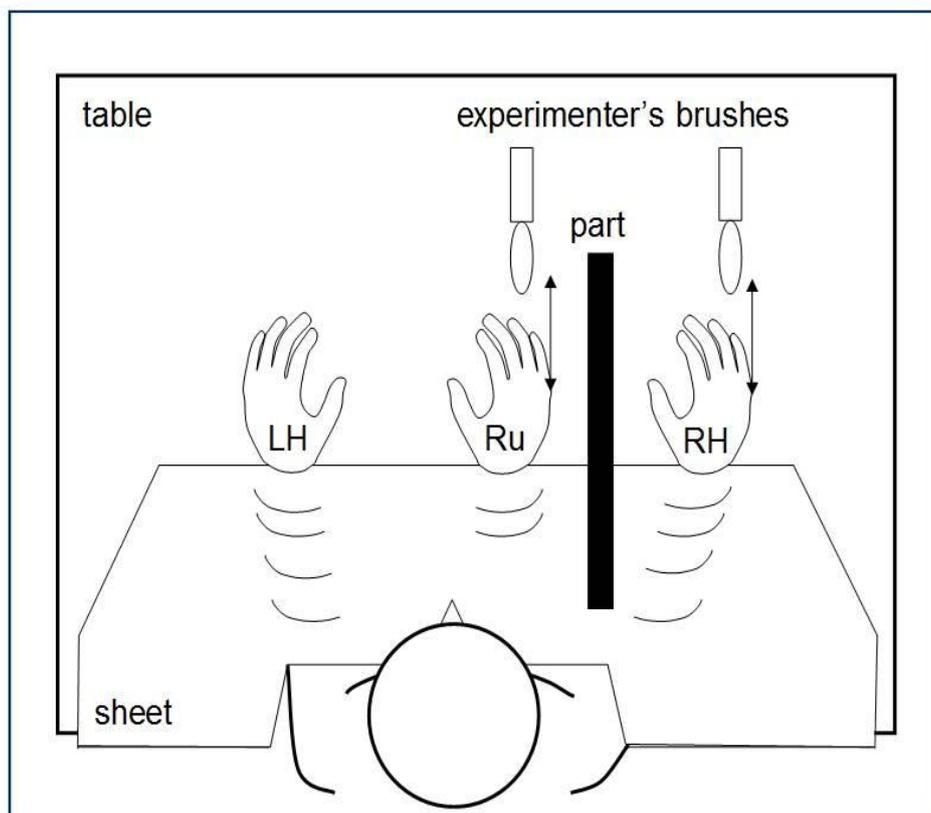
LH, left hand; part, partition; Ru, rubber hand; RH, right hand. See text for further explanation

8.2.5. Analysis of neuropsychological performance

Neuropsychological data were assessed according to methods outlined in chapter 3 (section 3.8.4.2).

8.2.6. Analysis of behavioural data

Data on all behavioural subtests were firstly assessed to ascertain whether the distribution of scores on that subtest was normal. Where parametric normality assumptions were met, patient groups were compared with the healthy control group, and to each other, using analysis of variance models implementing F tests and two-tailed t tests. Where normality assumptions were not met, Kruskal-Wallis and Mann-Whitney U exact tests were used. A statistical threshold $p < 0.05$ was taken as the criterion of significance for all tests. As the observations here were made on non-independent behavioural data, corrections for multiple comparisons were not employed, in line with standard statistical practice.

For the two-point discrimination task, an average score was analysed by summing the threshold score obtained across both ascending and descending step-wise estimates across the three trials and dividing by the number of trials. This mean score was used for analysing group threshold differences.

For the tickle paradigm, scores were summed for each condition, (highest possible score for each trial =10), and mean accuracy score for each of the three

conditions for each participant was used in regression analyses as the covariate of interest.

For the rubber hand task, scores obtained on the likert scale (1-7) were summed for the three questions of interest, whereby a higher score indicated a stronger illusory percept (highest possible sore = 21).

For the arm position-matching task, each position estimate was measured and recorded according to vertical and horizontal position using a tape-measure. These estimates were then subtracted from the real position obtained pre-stimulation by recording the position of the index finger of the secured arm at each angle position, to give an accuracy estimate for both vertical and horizontal planes. Approximate angle estimate was then obtained using the formula:

Angle=1/tan (vertical accuracy estimate/horizontal accuracy estimate)

The degrees of the angle were then obtained using the formula:

Degrees (radians) = arc tan (vertical accuracy estimate/horizontal accuracy estimate)

The true vertical and horizontal position estimates were then obtained using the formulas:

Real vertical estimate= (true vertical position – vertical accuracy estimate)

Real horizontal estimate= (true horizontal position – horizontal accuracy estimate)

whereby true vertical and horizontal positions were obtained from the original positional recordings of the secured index finger at each of the three angles. Pythagoras' theorem was then applied using the real vertical and horizontal estimates in order to obtain a final measure of the overall accuracy of the estimated index finger position at each trial. This was obtained using the formula:

Position accuracy estimate = square root [(vertical accuracy estimate) ^{2} + (horizontal accuracy estimate) ^{2}]

Mean estimation accuracy scores for each participant were generated and used in regression analyses as the covariate of interest.

8.3. Results

8.3.1. Demographic characteristics

Demographic and clinical characteristics for each of the patient groups and the healthy control group are summarised in Table 25. All groups were well matched for age (p>0.05), gender (p>0.05), handedness (p>0.05), and clinical symptom duration (p>0.05)

8.3.2. Neuropsychological performance

General neuropsychological findings for each of the patient groups and the healthy control group are summarised in Table 25. The findings corroborated the syndromic diagnosis of FTD in the patient groups: all three groups performed inferiorly to the healthy control group on standard neuropsychological tests of general intellectual, executive, social cognition, episodic and semantic memory functions, with sparing of short-term memory and posterior cortical functions. Graded naming performance was reduced in both the MAPT-FTD group ($p<0.002$) and the sporadic-FTD group ($p<0.02$) compared with the C9ORF72-FTD group. Patient groups did not differ significantly on any other standard neuropsychological measures: in particular, there were no group differences on IQ, executive, or social-cognition measures. As patient groups were well-matched for potentially relevant clinical and neuropsychological characteristics, and as general neuropsychological characteristics were not anticipated *a priori* to be correlated with performance on any of the experimental tasks, these were not included as covariates in analyses of the experimental test data.

Table 25. Demographic, clinical, and general neuropsychological characteristics of patient and healthy control groups

	C9ORF72	MAPT	Sporadic FTD	Healthy controls
Number	5	7	5	13
Age (y)	65(8)	62(4)	66(11)	62(5)
Sex (M:F)	5:0	5:2	5:0	10:3
Disease duration (y)	7(3.9)	5(2.4)	9.3(6.3)	NA
Handedness (R:L)	5:0	6:0	5:1	13:0
CBI total score (range)	119 (62 – 168)	128 (57 – 200)*	104 (30 – 214)	NA
CBI beliefs score (range)	3.8 (0 – 12)	2.8 (0 – 6)*	3.2 (0 – 7)	NA
IQ				
WASI Vocab	**35 (24)**	**41 (23)**	**41 (26)**	71 (9.2)
WASI Blocks	**18 (22)**	**27 (14)**	**28 (13)**	54 (8.1)
WASI Similarities	**26 (6.7)**	**20 (14)**	**22 (14)**	42 (2.7)
WASI Matrices	**15 (12)**	**16 (5.7)**	**17 (10)**	25 (8)
NART (/50)	**26 (13)**	**27 (16)**	**28 (19)**	41 (8.2)
Episodic memory				
RMT Words (/50)	**37 (6.1)**	**32 (5.8)**	**35 (2.5)**	47 (3)
RMT Faces (/50)	36 (7.5)	**27 (2.8)**	**34 (9.0)**	42 (5.9)
Semantic memory				
BPVS (/150)	**132 (17)**	**123 (17)**	**131 (17)**	148 (1.7)
Executive function				
D-KEFS Stroop (s)	**127 (47)**	**87 (43)**	**92 (33)**	52 (11)
Social cognition				
TASIT emotion (/14)	**8.4 (1.6)**	**8.7 (1.6)**	**8.1 (0.6)****	11(1.3)†
TASIT sarcasm (/24)	**15 (4.8)**	**15 (7.7)**	**14 (5.2)****	22(2.3)†
Other skills				
GNT (/30)	20 (3.9)††	**3.8 (4.0)**	**10 (11)**	27 (3)
Forward DS (/12)	6.5 (3.1)	8.5 (2.1)	8.4 (3.2)	8.9 (1.8)
Reverse DS (/12)	4.2 (0.9)	7.7 (1.7)	6.0 (3.4)	6.4 (2.1)
GDA	9.5 (10)	12 (5.8)	11 (7.7)	15 (3.2)
VOSP	17 (2.5)	**16 (2.4)**	17 (1.3)	18 (2)

Mean (standard deviation) values are shown unless otherwise indicated. Scores statistically different from control group performance at p<0.05 are in bold. *completed by 6 participants; **completed by 4 participants; †data in a separate group of 37 age-matched healthy individuals; ††significantly superior to both other patient groups; BPVS, British picture vocabulary scale; C9ORF72, pathogenic expansions associated with C9ORF72; CBI, Cambridge Behavioural Inventory; D-KEFS Stroop (word and response inhibition), Delis-Kaplan Executive Function System; DS, digit span; FTD, frontotemporal dementia; GNT, Graded Naming Test; GDA, Graded difficulty arithmetic; NA, not available; MAPT, pathogenic mutations in the microtubule-associated protein tau gene; NART, National Adult Reading Test; RMT, Recognition Memory Test; TASIT, The Affective and Social Inference Task;

VOSP, Visual Object and Space Perception; WASI, Wechsler Abbreviated Scale of Intelligence; y, years.

8.3.3. Experimental task performance

Performance profiles for each of the patient groups and the healthy control group on the experimental tasks are summarised in Table 26. The C9ORF72-FTD group performed on average significantly worse than both the healthy control group and the other FTD groups on all the experimental measures. Individual data for each test are plotted in Figure 19.

Figure 19. Scatter plots of individual data from experimental tests
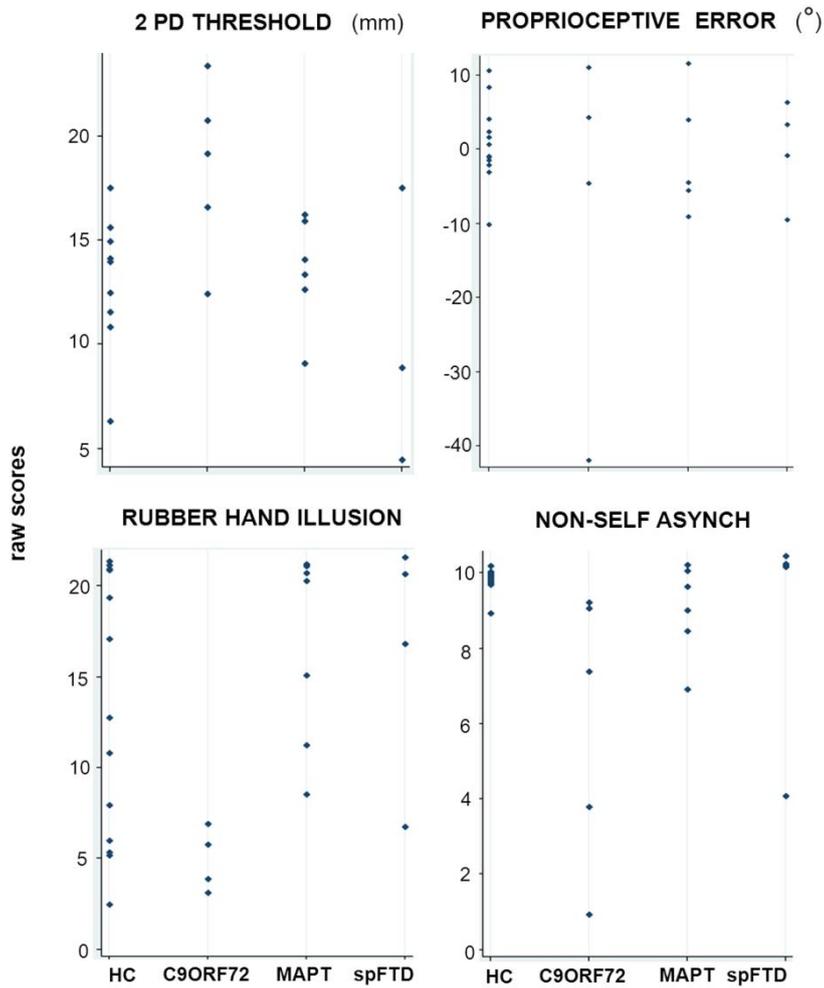
Note change of vertical scale between plots. 2PD, two-point tactile discrimination threshold (millimetres); Asynch, asynchronous stimulation condition in "tickle task" (see text); C9ORF72, pathogenic expansions associated with C9ORF72; HC, healthy control individuals; MAPT, pathogenic mutations in the microtubule-associated protein tau gene; Proprioceptive error, raw mean angle (degrees) of deviation of matching estimate from target under biceps tendon stimulation, where negative values correspond to perceived increasing elbow extension (see text); Rubber hand illusion, rating of intensity of percept on questionnaire (Botvinick and Cohen, 1998); spFTD, sporadic frontotemporal dementia.

Table 26. Experimental task performance of patient and healthy control participants

	C9ORF72	MAPT	Sporadic-FTD	Healthy Controls
Tactile discrimination				
Number completing test	5	6	3	9
Mean (SD) threshold (mm)	**18.5(4.1)**	13.4(2.6)	10.3(6.5)	13.1(3.2)
Range thresholds (mm)	12 - 23	9 - 16	4 - 18	6 - 18
Tendon vibration				
Number completing test	4	5	4	12
Baseline accuracy				
Mean (SD) angle† score (degrees)	4.8(3.4)	5.8(5.4)	6.7(4.2)	2.4(2.0)
Range angle scores (degrees)	0.8 - 9.2	0.3 - 13.5	3.1 – 12.6	0.6 - 6.3
Stimulation accuracy				
Mean (SD) angle score (degrees)	**15.5(18)**	7.01(3.2)	4.84(3.8)	3.8(3.7)
Range angle scores (degrees)	4 - 43	4 - 11	1 - 9	0 - 10
Rubber hand illusion				
Number completing test	4	7	4	13
Mean questionnaire score	**5(1.8)***	17.3(5.2)	16.5.4(6.8)	13.1(7.1)
Range questionnaire scores	3 - 7	9 - 21	7 - 21	3 - 21
Tickle task				
Number completing test	5	6	5	13
Tickle self				
Mean (SD) score (/10)	**7.2(2.2)***	9.8(.4)	10 (0)	9.8(.3)
Range scores	5 - 10	9 - 10	10	9 - 10
Tickle non-self synchronous				
Mean (SD) score (/10)	4(0.7)	5.5(1.5)	5.4(3.4)	4.6(3.2)
Range scores	3 - 5	3 - 7	1 - 10	0 - 9
Tickle non-self aysnchronous				
Mean (SD) score (/10)	**6.2(3.5)****	9.1(1.2)	8.8(2.7)	9.9(0.2)
Range scores	1 - 9	7 - 10	10	9 - 10

Mean (standard deviation) values shown for experimental task performance. Scores statistically different from control group performance at p<0.05 are in bold. †all angle values are based on individual absolute mean values; *also significantly different from both other patient groups; **also significantly different from the sporadic FTD group; C9ORF72, pathogenic expansions associated with C9ORF72; FTD, frontotemporal dementia; MAPT, pathogenic mutations in the microtubule-associated protein tau gene.

8.3.3.1.   Tactile discrimination

Mean tactile two-point discrimination threshold for the C9ORF72-FTD group was significantly higher than the healthy control group ($p < 0.02$). In contrast, mean thresholds for both the MAPT-FTD group and the sporadic-FTD group did not differ significantly from healthy control participants (MAPT-FTD, $p > 0.05$; sporadic-FTD, $p > 0.05$). Comparing patient groups, Mann-Whitney rank estimates revealed a strong trend for the C9ORF72-FTD group to have a higher mean tactile discrimination threshold than both the MAPT-FTD group ($p = 0.05$) and the sporadic-FTD group ($p = 0.1$), however these estimates did not reach statistical significance. Individual tactile thresholds fell above the healthy control range (and indeed, above the MAPT-FTD and sporadic-FTD ranges) for most patients with C9ORF72-FTD (Figure 19).

8.3.3.2.   Proprioceptive localisation

Proprioceptive localization position accuracy in the absence of tendon stimulation did not differ between the healthy control group and either of the genetically-defined patient groups (C9ORF72-FTD, $p > 0.05$; MAPT-FTD, $p > 0.05$), though the sporadic-FTD group performed marginally poorer than healthy controls in this condition ($p = 0.048$). Under tendon vibration, however, proprioceptive localisation in the C9ORF72-FTD group was significantly less accurate than for healthy participants ($p < 0.015$). In contrast, neither the MAPT-

FTD group nor the sporadic-FTD group showed a deficit relative to the healthy control group on this task (MAPT-FTD, p>0.05; sporadic-FTD, p>0.05). Mann-Whitney rank estimates did not reveal significant differences between the C9ORF72-FTD group and other patient groups. The magnitude of individual proprioceptive errors under tendon vibration varied widely among individual patients with C9ORF72-FTD (Figure 19). Indeed, the group difference relative to healthy controls on this test was attributable to one patient with C9ORF72-FTD who experienced a very strong illusion of elbow extension. This patient had a history of unexplained somatosensory symptoms, anxiety and paranoia but showed normal baseline proprioceptive acuity relative to the healthy control group.

8.3.3.3. Rubber hand illusion

The mean score relating to the rubber hand illusion questionnaire was significantly different between groups (Kruskal-Wallis χ^2=8.27, p=0.04). A Mann-Whitney U exact test revealed that the rubber hand illusory percept was stronger in the C9ORF72-FTD group compared to healthy control participants (p=0.05), while scores for the MAPT-FTD group and the sporadic-FTD group did not differ significantly from healthy participants (both p>0.05). Comparing patient groups, Mann-Whitney exact rank estimates revealed a significantly greater illusory perceptual effect of the rubber hand in the C9ORF72-FTD group compared both to the MAPT-FTD group (p<0.006) and the sporadic-FTD group (p=0.05; see Figure 19).

8.3.3.4. Tickle task

A Mann-Whitney U exact test revealed that differentiation of self-generated from externally-generated actions was significantly impaired in the C9ORF72-FTD group relative to the healthy control group in both the self-generated (p=0.005) and asynchronous non-self (p=0.0004) tickle conditions. In contrast, neither the MAPT-FTD group nor the sporadic-FTD group showed a deficit for either of these conditions (both p>0.05); nor were there any significant group differences for the synchronous non-self 'control' condition (p>0.05). When patient groups were compared, a Mann-Whitney U exact test further indicated a performance deficit in determining self-generated actions in the C9ORF72-FTD group compared to the other groups (MAPT-FTD, p=0.04; sporadic-FTD, p=0.02); and trends toward inferior performance in the asynchronous non-self tickle condition for the C9ORF72-FTD group compared to the other groups (MAPT-FTD, p=0.07; sporadic-FTD, p=0.06; see Figure 19).

8.4. Discussion

Here I have shown that C9ORF72-FTD is associated with deficits of body schema relative to healthy older individuals. These deficits span levels of body schema processing from tactile encoding and modulation of proprioceptive signals, through representation of body parts, to the cognitive attribution of the agency of somatosensory signals to self versus others (essential for maintaining a stable self-image: (Frith et al., 2000; Schmahmann et al., 2007). Our findings further suggest a qualified specificity of these body schema alterations for C9ORF72-FTD

versus MAPT-FTD and sporadic FTD. The findings are unlikely to have been attributable to nonspecific or confounding effects from general cognitive capacity or disease severity as the FTD groups were well matched for these other characteristics; furthermore, the somatosensory processes implicated are unlikely to have imposed substantial, extraneous task-related cognitive demands.

I propose altered body schema processing as a plausible, generic pathophysiological mechanism that could potentially underpin various clinical features identified as hallmarks of C9ORF72-FTD in previous work (Mahoney et al., 2012a; Galimberti et al., 2013; Larner, 2013; Arighi et al., 2012; Snowden et al., 2012). While more florid neuropsychiatric features (delusions and hallucinations) have been emphasised in case reports of C9ORF72-FTD, the mechanism I propose here is potentially of much wider relevance. It might, for example, account for the prominent (though non-delusional), otherwise unexplained somatosensory symptoms, social phobias, anxiety, paranoia and other specific inter-personal difficulties these patients often experience, in the present cohort as in earlier series (Priebe and Röhricht, 2001; Miles et al., 2011; Aybek et al., 2013).

The most consistent and robust differences between the C9ORF72-FTD and other groups were recorded for the rubber hand illusion and somatosensory self / non-self-differentiation. These aspects of body schema processing are likely to depend on the integration of multimodal sensory signals and integration of sensory with internal motor efference signals, respectively (Blakemore et al., 2000; Frith et al., 2000; Moseley et al., 2012; Jakobs et al., 2012). Further, both

aspects may entail comparison of incoming sensory signals with a stored

representation and calibration of a prediction error within a feed-forward-model

in which predictions about the sensory consequences of actions are compared

with incoming perceptual information. In this model, parietal cortex and

posterior insula play a crucial role in integrating multisensory and sensori-motor

representations and cerebellum acts as a comparator between incoming afferent

signals and outgoing motor commands (Blakemore et al., 2003; Blakemore et al.,

2000; Tsakiris et al., 2007; Tsakiris and Haggard, 2005; Synofzik et al., 2009;

Jeannerod, 2009). The interpretation of agency has been shown to recruit a

distributed network including thalamus and posterior parietal cortex for

transmission and updating of the sensory consequences of actions and prefrontal

and cingulate cortex for cognitive appraisal of integrated percepts (Jeannerod,

2009). The impaired ability to distinguish the sensory consequences of own from

others' actions and enhanced bodily illusions shown by our C9ORF72-FTD group

might therefore be attributable to impaired prediction coding in the cerebellum

or defective integration of sensory percepts by the thalamus or the parietal or

prefrontal cortex (Blakemore et al., 2003; Schmahmann and Caplan, 2006), either

by direct involvement of these regions or impaired connectivity across the

network (Schmahmann and Pandya, 2008). Although neuroanatomical

correlation was not possible here due an insufficient number of participants, the

elements of this distributed network are those previously implicated in

neuroimaging (Mahoney et al., 2012a; Mahoney et al., 2012b; Whitwell et al.,

2012) and neuropathological (Al-Sarraj et al., 2011; Mahoney et al., 2012a;

Mahoney et al., 2012b; Arighi et al., 2012) studies of patients with C9ORF72

expansions. It is noteworthy that the rubber hand illusion was abnormally

enhanced in the C9ORF72-FTD group here: this suggests increased plasticity of body-part representations, which in turn would be consistent with the finding of impaired self / non-self-differentiation on the action attribution task. If, as has been proposed (Apps and Tsakiris, 2013b, a), the representation of self requires a hierarchical interaction between incoming integrated sensory (visuo-tactile) traffic and error minimisation according to a top-down predictive model, then enhanced incorporation of non-self stimuli into the self-schema would follow if the model itself, the error minimisation process or both were deficient. From a clinical perspective, the finding of an 'enhanced' perceptual process in C9ORF72-FTD aligns this neurodegenerative disease pathophysiologically with schizophrenia, phantom limb phenomena, thalamic strokes and other entities accompanied by abnormal enhancement of body schema plasticity or a breakdown in the normal boundaries of the schema (Head and Holmes, 1911; Ramachandran and Hirstein, 1998; Jeannerod, 2009; Moseley et al., 2012).

Body schema alterations in our C9ORF72-FTD group also extended to the more elementary processing required to encode somatic spatial relations or postural change, in the two-point discrimination and proprioceptive localisation tasks. Deficits of tactile discrimination have been identified in paradigmatic disorders of body schema, including schizotypy (liability to schizophrenia: Lenzenweger, 2000) and anorexia nervosa (Keizer et al., 2012) and are likely to index a fundamental abnormality of low-level somatic coding. As in those other disorders, the question arises whether abnormalities of peripheral sensory pathways might account for increased tactile threshold in patients with C9ORF72-FTD. This is unlikely: no patients included in the present C9ORF72-FTD cohort had clinical or

electrophysiological evidence of peripheral sensory dysfunction, nor is it likely that this finding is related simply to abnormal efferent influences on sensory traffic associated with motor neuron disease, as only two of the patients had mild clinical signs of amyotrophy. Some caution is required in interpreting the specificity of the tactile discrimination deficit as the disease group comparisons did not reach the statistical criterion for a significant inter-group difference, likely due to the small case numbers. A similar caveat applies to the findings on the proprioceptive localisation task, as only one patient with C9ORF72-FTD demonstrated substantially reduced proprioceptive accuracy under tendon vibration, albeit in the direction predicted with an enhanced illusion of limb stretch. This effect was a true index of illusory modulation of a specific postural cue contributing to body schema, since baseline proprioceptive accuracy was normal. Although I only assessed the relevant functions using single tasks, the conjunction of impaired tactile spatial acuity and normal baseline proprioceptive acuity in C9ORF72-FTD would be consistent with the existence of multiple neural representations for these functions within the multimodal body matrix (Head and Holmes, 1911; Moseley et al., 2012). On the other hand, neither the healthy control group nor the patient groups showed a consistent direction of perceptual modulation on the proprioceptive matching task: the basis for this is uncertain, though it has been shown previously that healthy older individuals are less efficient and less accurate in explicit proprioceptive localisation tasks and under perceptual illusions than their younger counterparts (Goble, 2010; Boisgontier and Nougier, 2013). Again, conclusions must be tentative in view of the small case numbers here. Taking these caveats into account, the alterations of body schema processing shown by patients with C9ORF72-FTD on these tasks implicate

pathways linking thalamus and somatosensory cortex (Head and Holmes, 2011; Naito et al., 1999; Moseley et al., 2012), again consistent with previous neuroanatomical evidence (Whitwell et al., 2012; Mahoney et al., 2012a).

Taken together, our findings suggest that C9ORF72-FTD is associated with loss of body schema definition and abnormally enhanced modulation of body schema boundaries. Involvement of multiple levels of body schema processing is consistent with dysfunction of the common distributed cortico-subcortical network previously identified in this disease. The present findings leave unresolved the primary locus of dysfunction within the body schema processing hierarchy: this might itself be distributed across multiple components, or might target the anatomical or functional interactions among those components. Emerging functional neuroanatomical evidence suggests that the body schema processing hierarchy behaves as a unit with transformation of information and reciprocal interactions among network elements in health and under the impact of disease states (Creem-Regehr et al., 2007; Klostermann et al., 2009; Freudenmann et al., 2010; Jakobs et al., 2012; Woodward et al., 2012; Aybek et al., 2013; Vazquez et al., 2013). From the broader perspective of neurodegenerative disease, there is currently considerable interest in understanding how phenotypes map onto brain networks and a specific distributed fronto-insular brain network responsible for processing and evaluating the salience and behavioural relevance of environmental stimuli has been implicated in the pathogenesis of the FTD syndrome (Seeley et al., 2006; Seeley et al., 2009). However, the FTD syndrome subsumes a number of distinct molecular pathologies, and predicting the phenotypic consequences of particular

proteinopathies is arguably an even more pressing issue in the quest for rational therapeutic intervention and monitoring (Warren et al., 2013). Particular molecular pathologies might, for example, be defined in terms of additional protein-specific network interactions with the core fronto-insular network: here, I have identified a candidate pathophysiological marker (aberrant body schema processing) that may arise from such a specific network interaction (the insula could plausibly act as a hub region linking body schema and salience processing: Tsakiris et al., 2007; Moseley et al., 2012). From a more clinical perspective, body schema alterations associated with C9ORF72-FTD would in principle be relatively straightforward to detect and track in individual patients or in the context of clinical trials.

This study has several limitations that suggest directions for future work. Case numbers here were small, limiting power to detect effects and precluding direct neuroanatomical correlation. It must be noted that patients with C9ORF72 exhibited poorer performance on the Stroop inhibition task than their bvFTD counterparts. While I have no a-priori reason to suspect that behavioural inhibition is in any way related to the integration of proprioceptive integration required in the tasks examined here, I cannot discount that this may have played some role in the deficit in experimental performance uniquely associated with the C9ORF72 patients in this chapter.

Future work should engage larger patient cohorts, including conditions such as motor neuron disease, GRN-FTD and the spinocerebellar ataxias that might also be predicted to show deficits of body schema processing on neuroanatomical and neurophysiological grounds. Other dimensions of body schema processing

besides those investigated here and the relations between those dimensions should be explored. Longitudinal studies will be required to establish whether altered body schema processing is an early hallmark of C9ORF72 mutation carrier status (Lenzenweger, 2000; Hauser et al., 2011). Structural and functional neuroanatomical techniques that can capture distributed alterations in network connectivity would allow evaluation of specific hypotheses about the pathophysiology of body schema processing. The generic pathophysiological mechanism I propose is potentially relevant for improved understanding of a wide range of neuropsychiatric and behavioural symptoms in C9ORF72-FTD and indeed, the FTD syndrome more broadly; one example is the loss of empathy shown by many of these patients (Rascovsky et al., 2011; Moseley et al., 2012). Body schema processing is a novel candidate pathophysiological bridge linking more basic autonomic and homeostatic processes with higher cognition in the neurodegenerative proteinopathies: I hope that this work will stimulate interest in the physiological phenotyping of these diseases.

8.5. CHAPTER CONCLUSIONS

I propose that impaired ability to disentangle and interpret somatosensory proprioceptive information in C9ORF72 mutations may index a generic mechanism of defective own-action modelling and representation that may be somewhat analogous to the deficit proposed previously in patients with schizophrenia (Franck et al., 2001). Such a pathophysiologic mechanism could potentially be expressed in a range of clinical neuropsychiatric phenomena. This suggests a generic pathophysiological mechanism that may link the distributed cortico-subcortical network previously implicated in C9ORF72-FTD with a wide

range of neuropsychiatric and behavioural symptoms, which may constitute a physiological marker of this neurodegenerative proteinopathy.

9. THESIS CONCLUSIONS

9.1. Chapter Introduction

The findings described in this thesis confirm and extend the observations regarding multiple behavioural, cognitive and social-emotional deficits in behavioural variant frontotemporal dementia (bvFTD), which can be correlated with discrete neural areas within the brain and their connecting pathways. Within this thesis, I have attempted to explore the behavioural and neuroimaging profile of behavioural variant frontotemporal dementia. In doing this, I have utilised both standardised and novel behavioural tasks in order to specifically examine the psychological phenomena of social cognition, executive function, and psychosis within the context of frontotemporal dementia. I have also employed the structural imaging analytical methods of voxel-based morphology and diffusion tensor imaging in an attempt to derive both the grey and white matter correlates of behavioural metrics. In reviewing this thesis in its entirety, I have come to a number of conclusions, which I believe have important theoretical and clinical implications.

9.2. Distinct neurobiological signatures for social cognition impairments in FTD

In Chapters 4 and 5 I have explored the capacity to engage in social cognition in patients with frontotemporal dementia. In Chapter 4, I utilised common

assessment tools for social cognition to discern that the ability to identify emotion and understand sarcasm was degraded in bvFTD and in semantic dementia (SD) in comparison to healthy controls. Furthermore, using the techniques of VBM and DTI, I was able to show that this dysfunction mapped onto a network of cortical and subcortical areas and their connecting white matter pathways that has previously been implicated in the literature. This study provided a novel insight into the relationship between grey matter atrophy and the integrity of white matter fibers in the domain of social cognition, as the DTI appeared to be more sensitive to dysfunction than the VBM, which has not been shown before.

Furthermore, in order to devise a more ecologically-valid test of social cognition, I developed an auditory task in which participants were required to assign either an emotive or non-emotive label to a musical piece. bvFTD participants were dysfunctional in the assignment of an emotive label, indicating a social cognitive deficit independent of any general lack of ability to complete the task accurately. Again, this mapped onto a discrete neural area that has previously been implicated in self-awareness and social cognitive processing as part of a larger social cognition network.

These findings delineate a brain network for the social impairment that characterises FTLD syndromes. The findings further suggest that DTI can generate sensitive and functionally-relevant indices of white matter damage in FTLD, with potential to transcend conventional syndrome boundaries. Taken together, these findings further define neurobiological signatures for the social

impairment that characterises FTLD syndromes, grounded in the emerging neural network paradigm of neurodegenerative disease.

9.3. Executive dysfunction varies in both nature and extent across the FTD spectrum

In Chapters 6 and 7, I explored executive function in patients with frontotemporal dementia using a number of higher-order cognitive tasks, including task switching, simple and choice reaction time, and paced and self-paced tapping tasks. Furthermore, in light of recent evidence which reports the executive dysfunction reported in frontally-damaged patients to be mediated entirely by a reduction in intelligence, I explored the relationship between executive capacity and intelligence in both imaging and behavioural datasets. These results provided interesting and novel insights into the relationship between intelligence and executive function.

Results indicated several dissociable executive capacities, which mapped onto discrete neural areas as part of a larger executive function network, which has been previously implicated in the literature. Executive capacities appeared to be selectively damaged in the bvFTD patient population above that observed in the other FTD and AD groups, and in healthy controls, independent of level of general intelligence.

I interpret these data as evidence that structures implicated in executive functioning, specifically neural timing and task switching, can be targeted by this neurodegenerative brain disease, and that disregulated neural timing and

inability to accurately and swiftly switch between transient task requirements underpins aspects of the bvFTD phenotype.

9.4. C9ORF72-defined frontotemporal dementia may have a unique physiological signature

In the final experimental chapter of this thesis, Chapter 8, I sought to examine the novel phenotype of psychosis in patients with a mutation in the expansion C9ORF72. To date, no other study has examined the bases to this phenotype. I devised a novel battery of tests to examine the bases of these psychotic symptoms and administered this battery in affected patients with the C9ORF72 mutation, sporadic bvFTD patients, patients with a MAPT mutation, and healthy controls. The battery was based on literature within the schizophrenia population, and examined somatosensory proprioception, differentiation between self and other-generated actions, and illusory somatosensory percepts.

Results of this study indicated a specific and unique impairment in the ability to interpret somatosensory proprioceptive information in the C9ORF72 patients alone, which I attribute to dysfunction in a striatal-thalamo-cerebellar network. This network has been previously implicated in the proprioceptive literature, and is also selectively targeted by C9ORF72-specific pathology.

This work represents the first experimental study into the phenotype of psychosis in C9ORF72 mutation carriers, and provides an exciting and novel insight into the neurological and physiological bases to this phenotype. This has important clinical and theoretical implications and suggests that dysfunction in

somatosensory proprioception may be a clinically relevant phenotypic marker of C9ORF72-defined frontotemporal dementia.

9.5. Clinical implications

Improved understanding of the brain mechanisms of particular aspects of cognitive dysfunction in FTD could potentially facilitate earlier and more accurate diagnosis and symptom management and ultimately, evaluation of therapies in clinical trials. The present findings suggest that certain DTI metrics provide sensitive and functionally relevant indices of white matter damage in FTD and support the further assessment of sarcasm as a useful model for probing social and other cognitive functions that depend on large-scale brain networks. These results also suggest that white matter metrics of complex behavioural deficits can yield robust signatures of brain network disintegration in FTD, such as presented here in relation to social cognition and executive function, that may transcend conventional clinical and imaging markers.

Such disintegration of functionally- and anatomically-connected brain networks further suggests that dysfunction in one area of cognition may be interlinked with integrity of other cognitive capacities. For example, the same network that has been implicated in the present study as important for executive functions comprises structures that have also been implicated in the present study of social cognition. Recent evidence supports the existence of a reciprocal relationship between social cognition and executive processes such as cognitive control, whereby one must engage in cognitive control in order to flexibly adapt behavior toward social goals (Dumontheil et al., 2012). This combination of processes has

been shown to be deficient in FTD patients (Snowden et al., 2003), including those in the early stages of the disease (Torralva et al., 2009). Frontotemporal dementia may thus provide a clinically-relevant paradigm in which to gain valuable insight into the reciprocal nature of social and executive processes and their common biological bases.

The present results also have wider ecological validity outside the domain of neurodegenerative disease. Variation in or damage to any of the areas highlighted as key to normal social and executive cognitive function or their connections could produce important individual differences. For example, developmental or traumatic alterations to the key nodes highlighted in cortical control and executive function circuitry could give rise to psychiatric symptoms such as impulsivity or inattention (Alexander et al., 2011; Ridderhinkof et al., 2004).

The generic pathophysiological mechanism I propose to be uniquely affected in C9ORF72-FTD is potentially relevant for improved understanding of a wide range of neuropsychiatric and behavioural symptoms in C9ORF72-FTD and indeed, the FTD syndrome more broadly, such as the loss of empathy shown by many of these patients (Rascovsky et al., 2011; Moseley et al., 2012). Body schema processing is a novel candidate pathophysiological bridge linking more basic autonomic and homeostatic processes with higher cognition in the neurodegenerative proteinopathies. Further physiological phenotyping of these diseases may shed greater light on such mechanisms contributing to disease phenotypes.

9.6. Limitations and future directions

The findings from this thesis have several limitations that suggest directions for future work.

Firstly, the study of human populations is inherently open to bias in terms of generalizability and representativeness. Unbiased, consecutive selection of participants is often difficult. For example, patients who live closer to the research facility, or are more mobile, may be more likely to participate than those who do not. The anosognosic and disinhibited behavioural profile that characterises FTD adds a further level of selection bias, such that the less insightful patients may be more reluctant to participate in research, or the more disinhibited patients may have an inability to sit through the testing. Each of these factors impacts the generalisability of the participants presented here to the wider community of those affected with FTD. Future research may benefit by addressing these patient selection issues through means such as conducting home visits to more patients who are less able to travel, or encouraging both patients and their spouses to participate in research together to encourage the less insightful affected patients to engage in the research process.

There also exists an important bias in the research population towards patients that do and do not agree to participate in research, due to a variety of personal and social circumstances, which is an important factor in the present thesis. In particular, there exists a bias in the patient population in the present thesis towards more male than female participants. This could be for any number of

reasons, however I feel that it is most likely that it is carer support that drives whether a patient participates in research or not. Anecdotally, female carers are more likely to seek medical help at an earlier stage of the disease manifestation than are male carers for their partners. Female carers in our research cohort are also more likely to engage with the research process in organizing research visits, and escorting their male patient partners to and from research appointments. This is most likely the reason behind a greater proportion of male patients that compose our patient cohorts. This is an important consideration when interpreting the data about the generalizability of the present findings to the wider patient population affected by FTD.

The present findings should also be corroborated in larger cohort studies comparing other neurodegenerative diseases and mimic syndromes such as primary psychiatric disorders for which differentiating biomarkers are particularly required. This may also increase the generalisability of the current findings to the wider population.

Where DTI analysis is possible, targeting specific candidate white matter pathways for more detailed tractographic analysis would allow for more specific correlations between behavioural phenotypes and the corrosion of white matter fibers. With particular relevance to the erosion of executive capacities in FTD, the present results warrant further analysis into the white matter microstructure of pathways connecting the implicated cortical areas using methods such as DTI in order to investigate the relationship between key cortical nodes and their connections within a larger 'executive function network'.

Furthermore, longitudinal studies will be essential to establish the sequence of alterations in candidate behavioural and neuroimaging biomarkers, ideally including pre-symptomatic individuals with genetic forms of FTLD, in order to capture very early disease effects. Subsequent histopathological correlation will be required to assess the molecular specificity of biomarker signatures. In the case of C9ORF72-FTD, correlation between expansion length and disease penetrance may also shed light on important biological mechanisms of disease.

Case numbers presented here were small, limiting power to detect effects, and with respect to the analyses in Chapter 8, precluding direct neuroanatomical correlation. Future work should engage larger patient cohorts, including other neurodegenerative and primary psychiatric conditions. Structural and functional neuroanatomical techniques that can capture distributed alterations in network connectivity would allow evaluation of specific hypotheses about the pathophysiology of the cognitive processes examined here.

9.7. Chapter conclusion

The studies described in this thesis contribute to the growing interest in characterising and understanding the behavioural phenotypes of FTD. The nature and extent of social cognition and executive function impairment within bvFTD is strikingly different from that observed in the PPA syndromes and in AD patients. The degradation of an interconnected network of both cortical and sub-cortical components and their connecting white matter pathways appears to be responsible for this cognitive phenotype. Pathogenic expansions of C9ORF72

contribute uniquely to the presence of psychosis in FTD, and a dysfunction in proprioceptive somatosensory integration may provide a candidate mechanism for this neuropsychiatric feature.

CONTRIBUTIONS TO WORK

I would like to acknowledge the work of a number of people who have directly contributed to this thesis. Development and support of experimental ideas and paradigms for each of the Chapters was provided by Dr. Sebastian Crutch, Dr. Jason Warren, and Dr. Susie Henley. Dr Jennifer Nicolas conducted all of the statistical analyses for the neural timing and executive function data modelling in Chapters 6 and 7, and provided consultation for the statistical analyses presented in Chapters 4, 5, and 8. Dr Gerard Ridgeway provided consultation on the design and analysis of VBM imaging data and Dr Colin Mahoney and Dr Kirsi Kinnunen provided consultation on the analysis and design of DTI data presented in Chapters 4 and 6. Neuropsychological evaluation of participants was carried out by Hannah Golden in the event of my absence, which occurred up to five times in total. Clinical evaluation of the vast majority of participants was provided by Dr Colin Mahoney and Dr. Phillip Fletcher. All other neuropsychology, experimental testing, and imaging analysis were conducted by me.

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PUBLICATIONS DIRECTLY RESULTING FROM THIS THESIS

The following publications have been derived directly from work presented in this thesis:

<u>CHAPTER FIVE</u>

Downey LE, Blezat A, Nicholas J, Omar R, Golden HL, Mahoney CJ, Crutch SJ, and Warren JD. Mentalising music in frontotemporal dementia. Cortex, 49(7): 1844-1855, 2013.

LED conducted all neuropsychological and experimental testing, conducted statistical analyses of results, conducted neuroimaging analysis, and wrote manuscript. AB and RO collected pilot data for the project as part of a masters project. JN provided statistical consultation on the analyses of results. HLG conducted neuropsychological assessment of participants in LED's absence. JDW designed experimental set-up and edited manuscript.

CHAPTER EIGHT

Downey LE, Fletcher PD, Golden HL, Mahoney CJ, Augustus JL, Schott JM, Rohrer JD, Beck J, Mead S, Rossor MN, Crutch SJ, Warren JD. Altered body schema processing in frontotemporal dementia with c9ORF72 mutations. JNNP, in press, 2014

LED conducted all neuropsychological and experimental testing, conducted statistical analyses of results, and wrote manuscript. PDF aided in marking experimental test

responses on-line while LED conducted testing. HLG conducted neuropsychological assessment of participants in LED's absence. CJM, JMS, JDR, and MNR referred participants from cognitive clinic into research program. SM and JB provided data on genetics of participants. SJC and JDW edited manuscript.

Downey LE, Mahoney CJ, Rossor MN, Crutch SJ, and Warren JD. Impaired self-other differentiation in frontotemporal dementia due to the C9ORF72 expansion. Alzheimers Res Ther, 4(5): 42, 2012.

LED conducted all neuropsychological and experimental testing, conducted statistical analyses of results, and wrote manuscript. CJM and MNR referred patients from cognitive clinic into research programme. SJC edited manuscript and built one of experimental apparatus. JDW contributed to designing of experimental set-up, recording on-line results while LED conducted experiment, and edited manuscript

Mahoney CJ, **Downey LE**, Ridgway GR, Beck J, Clegg S, Blair M, Finnegan S, Leung KK, Yeatman T, Golden H, Mead S, Rohrer JD, Fox NC, and Warren JD. Longitudinal neuroimaging and neuropsychological profiles of frontotemporal dementia with C9ORF72 expansions. Alzheimers Res Ther, 4(5): 41, 2012.

LED conducted all neuropsychological assessments for this study and contributed to the writing and editing of the manuscript. CJM conducted all analysis for imaging data and lead on writing and editing of the manuscript. GRR provided statistical guidamce for imaging analysis. JB and SM provided genetic details on all patients. SC, MB, TY, and HG assisted with collation and segmentation of neuroimaging data. NCF and JDW contributed to the design of the study and the editing of the manuscript.

OTHER RELATED PUBLICATIONS

Fletcher PD, **Downey LE**, Agustus JL, Hailstone JC, Tyndall MH, Cifelli A, Schott JM, Warrington EK, and Warren JD. Agnosia for accents in primary progressive aphasia. Neuropsychologia, 51(9): 1709-1715, 2013a.

Fletcher PD, **Downey LE,** Witoonpanich P, and Warren JD. The brain basis of musicophilia: evidence from frontotemporal lobar degeneration. Front Psychol, 4: 347, 2013b.

Mahoney CJ, **Downey LE,** Beck J, Liang Y, Mead S, Perry RJ, and Warren JD. The presenilin 1 P264L mutation presenting as non-fluent/agrammatic primary progressive aphasia. J Alzheimers Dis, 36(2): 239-243, 2013a.

Clark CN, **Downey LE**, Golden HL, Fletcher PD, de Silva R, Cifelli A, and Warren JD. `The mind is its own place': Amelioration of claustrophobia in semantic dementia. Behav Neurol, 2013.

Mahoney CJ, Malone IB, Ridgway GR, Buckley AH, **Downey LE**, Golden HL, Ryan NS, Ourselin S, Schott JM, Rossor MN, Fox NC, and Warren JD. White matter tract signatures of the progressive aphasias. Neurobiol Aging, 34(6): 1687-1699, 2013b.

Clark, C., **Downey, LE.,** Warren, JD. Music biology: All this useful beauty. Current Biology. *In press*

Clark, C., **Downey, LE.,** Warren, JD. All this useless beauty'? Brain disorders and the biological role of music. Social Cognitive and Affective Neuroscience. *In revision*

Downey, LE., Nicholas, JM., Kinnunen, KM., Golden, HL., Buckley, A., Henley, SM., Mahoney, CJ., Crutch, SJ. Degradation of cognitive timing mechanisms in behavioural variant frontotemporal dementia. Neuropsychologia. *Under review*

Golden, HG., **Downey, LE.,** Fletcher, PD., Mahoney, CJ., Schott, JM., Mummery, CJ., Crutch, SJ., Warren, JD. Identification of environmental sounds and melodies in syndromes of anterior temporal lobe degeneration. Cortex. *Under review*

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