Nonverbal processing in frontotemporal lobar degeneration

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SIGNED DECLARATION

I, Rohani Omar 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.

ABSTRACT

Frontotemporal lobar degeneration (FTLD) refers to a group of diseases characterised by focal frontal and temporal lobe atrophy that collectively constitute a substantial source of clinical and social disability. Patients exhibit clinical syndromes that are dominated by a variety of nonverbal cognitive and behavioural features such as agnosias, altered emotional and social responses, impaired regulation of physiological drives, altered chemical sense, somatosensory and interoceptive processing. Brain mechanisms for processing nonverbal information are currently attracting much interest in the basic neurosciences and deficits of nonverbal processing are a major cause of clinical symptoms and disability in FTLD, yet these clinical deficits remain poorly understood and accurate diagnosis is often difficult to achieve. Moreover, the cognitive and neuroanatomical correlates of behavioural and nonverbal cognitive syndromes in FTLD remain largely undefined. The experiments described in this thesis aim to address the issues of improving our understanding of the social and behavioural symptoms in FTLD through the integration of detailed neuro-behavioural, neuropsychological and neuroanatomical analyses of a range of nonverbal functions (including emotions, sounds, odours and flavours) with high-resolution structural magnetic resonance imaging (MRI).

A prospective study of emotion recognition in various domains including music, faces and voices shows that music is especially vulnerable to the effects of damage in FTLD. A profile of brain atrophy associated with impaired emotion recognition in music is identified, comprising a distributed bilateral cerebral network involving areas previously implicated in representing and evaluating the emotional content of stimuli including mesial temporal structures, insula and their connections in the mesolimbic system.

Prospective studies of face and chemosensory processing provide further insights into the neuroanatomical framework and structural neuroanatomy for face, odour and flavour processing deficits in FTLD. A profile of cognitive deficits in different components of face processing is shown which correlate with distinct but partly overlapping brain networks. Deficits in flavor and odour identification are shown in FTLD with neuroanatomical correlates involving temporal and limbic areas which include entorhinal cortex, hippocampus and parahipocampal gyrus.

A detailed systematic study of music knowledge in two expert musicians with different dementia diseases, sematic dementia (SemD) and dementia with Lewy bodies (DLB), involving a series of novel neuropsychological experiments probing various dimensions of music knowledge, yields new insights into the cognitive architecture of music knowledge and the brain organization of nonverbal knowledge systems.

This thesis therefore provides neuropsychological and imaging data in relation to various nonverbal cognitive processes in FTLD that can offer greater insights into our understanding of behavioural symptoms in this group of diseases as well as the cognitive architecture of hitherto relatively poorly understood nonverbal cognitive modalities such as music knowledge, emotion and chemosensory processing.

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ABBREVIATIONS

ACC	anterior cingulate gyrus
AD	Alzheimer's disease
AUC	area under the curve
BPVS	British Picture Vocabulary Scale
bvFTD	behavioural variant frontotemporal dementia
bvFTLD	behavioural-variant frontotemporal lobar degeneration
CBI	Cambridge Behavioural Inventory
DIY	do-it-yourself
DLB	dementia with Lewy bodies
DTI	diffusion tensor imaging
FDR	false discovery rate
FFA	fusiform face area
FG	fusiform gyrus
FrG	frontal gyrus
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
fvFTLD	frontal-variant frontotemporal lobar degeneration
FWE	family-wise error
GNT	Graded Naming Test
ITG	inferior temporal gyrus
LPA	logopenic progressive aphasia

MAPT	microtubule-associated protein tau
MBEA	Montreal Battery of Evaluation of Amusia
MMSE	Mini-Mental State Examination
MND	motor neuron disease
MNI	Montreal Neurological Institute stereotactic space
MP-RAGE	magnetization prepared rapid gradient echo
MRC	Medical Research Council
MRI	magnetic resonance imaging
NART	National Adult Reading Test
nfvPPA	non-fluent variant primary progressive aphasia
NPI	Neuropsychiatric Inventory
OFA	occipital face area
OFC	orbitofrontal cortex
PET	positron emission tomography
PFC	prefrontal cortex
PGRN	progranulin
PL	parietal lobe
PNFA	progressive non-fluent aphasia
PPA	primary progressive aphasia
REM	rapid eye movement
RFT	random field theory
RMT	Recognition Memory Tests
ROC	receiver operating characteristic

SAM	Self-Assessment Manikin
SemD	semantic dementia
SMA	supplementary motor area
SPM	statistical parametric mapping
STG	superior temporal gyrus
svPPA	semantic variant frontotemporal dementia
TIV	total intracranial colume
tvFTLD	temporal-variant frontotemporal lobar degeneration
UCL	University College London
UPSIT	University of Pennsylvania Smell Identification Test
VBM	voxel-based morphometry
VENs	von Economo neurons
VOSP	Visual Object and Space Perception Battery
WASI	Wechsler Abbreviated Scale of Intelligence

Chapter 1: GENERAL INTRODUCTION

Summary

Frontotemporal lobar degeneration (FTLD) refers to a group of diseases characterised by focal frontal and temporal lobe atrophy that collectively constitute a substantial source of clinical and social disability. Patients exhibit clinical syndromes that are dominated by a variety of nonverbal cognitive and behavioural features such as agnosias, altered emotional and social responses, impaired regulation of physiological drives, altered chemical sense, somatosensory and interoceptive processing. Brain mechanisms for processing nonverbal information are currently attracting much interest in the basic neurosciences and deficits of nonverbal processing are a major cause of clinical symptoms and disability in FTLD, yet these clinical deficits remain poorly understood and accurate diagnosis is often difficult to achieve. Moreover, the cognitive and neuroanatomical correlates of behavioural and nonverbal cognitive syndromes in FTLD remain largely undefined. The experiments described in this thesis aim to address the issues of improving our understanding of the social and behavioural symptoms in FTLD through the integration of detailed neuro-behavioural, neuropsychological and neuroanatomical analyses of a range of nonverbal functions (including emotions, sounds, odours and flavours) with high-resolution structural magnetic resonance imaging (MRI).

1.1 Frontotemporal lobar degeneration

In 1904, the Prague neuropsychiatrist Arnold Pick described the case of a 41-year old housewife with progressive personality change (Pick, 1904; Kertesz, 2004):

"(She) changed gradually…did not carry out her usual work, did not take care of her children, did not change her clothes or the bedding, and stopped combing her hair. She left work unfinished and laid about idly. She did not initiate conversation…tended to give stereotypical answers, and often perseverated…(she) was always asking for food. She had unusual fits of anger, verbally abused and hit her children…"

Thus was the first medical description of the dramatic, devastating consequences of the behavioural syndrome of frontotemporal dementia, also known as "Pick's disease". Pick was a pioneer of the concept of neurodegenerative dementias as focal brain diseases producing circumscribed cognitive and behavioural deficits related to a profile of cerebral atrophy, rather than a global loss of mental abilities. Nearly a century later, his clinical descriptions have lost none of their impact or accuracy in depicting the profound cognitive, personality and behavioural changes exhibited by patients with frontotemporal dementia. The immediate impression one has from reading these descriptions is a sense that patients have suffered a profound dislocation in their relations both with the social world and with the physical environment – a dislocation that is only partly dependent on the medium of language.

In recent decades, our understanding of the clinical syndromes subsumed under the umbrella term frontotemporal dementia or 'frontotemporal lobar degeneration' (FTLD) has greatly evolved, a result of a combination of advances in neuroimaging, molecular, histopathological,

genetic and neuropsychological techniques. The term FTLD is currently applied to a clinically and pathologically heterogeneous group of non-Alzheimer diseases associated with circumscribed atrophy of frontal and/or temporal lobes, which together constitute a common cause of dementia particularly in younger age groups. There are three canonical clinical syndromes of FTLD: behavioural-variant FTLD (bvFTLD) or frontotemporal dementia (FTD), and the two language-based, progressive aphasia syndromes semantic dementia (SemD) and progressive non-fluent aphasia (PNFA). In 1994, the Lund-Manchester clinical and pathological criteria for FTD was published, based on the largest study of the disease at the time with clinical evaluation of hundreds of patients and neuropathological analysis of over 60 brains, in an attempt to describe core diagnostic features of FTD distinguishing it from other disorders that may also affect frontotemporal structures including Alzheimer's disease (AD), Huntington's disease and schizoaffective disorders (Lund Manchester Group, 1994). The same collaborative group published further consensus criteria in 1998 describing the core diagnostic features of the three FTLD syndromes mainly for purposes of research (Neary et al., 1998). In 2001, a set of diagnostic guidelines were proposed by the Work Group on Frontotemporal Dementia and Pick's Disease to enable recognition of the FTLD syndromes in a clinical setting (McKhann et al., 2001). Although they share overlapping features, each syndrome is characterised by its predominant features: for bvFTLD, progressive change in personality and social behaviour associated with executive dysfunction; for SemD, multimodal loss of word and object knowledge resulting in verbal comprehension difficulties; and for PNFA, progressive impairment of speech and language output in the context of relatively preserved verbal comprehension.

FTLD is genetically and pathologically heterogenous (Lillo et al., 2010; Seelaar et al., 2011); it is commonly familial, with a autosomal dominant inheritance pattern in up to 40% of cases

(Chow et al 1999; Rohrer et al., 2009a). The 2 main genes known to cause familial FTLD are microtubule-associated protein tau (MAPT) and progranulin (PGRN), which are associated with tau-positive inclusions and TDP-43 pathology respectively. Mutations in other genes have been identified in a minority of cases, including valosin-containing protein (VCP), chromatin modifying protein 2B (CHMP2B), transactive DNA-binding protein (TARDP) and fused-in-sarcoma (FUS) (Rohrer & Warren, 2011). The degree of heritability varies between the different clinical syndromes, and there are predictable relationships between syndromes and underlying pathology. bvFTLD has greater heritability than the other language-based syndromes, the most common genetic mutations being in the MAPT gene (Rohrer et al., 2009a). More recently, an expanded hexanucleotide repeat in the C9ORF72 gene has been identified as another major cause of familial FTLD with or without motor neuron disease (Renton et al., 2011; Mahoney et al., 2012). Pathologically, bvFTLD is associated with frontal and anterior temporal atrophy with around half of cases exhibiting tau pathology (Snowden et al., 2007). SemD is typically considered a sporadic disease with little evidence of heritability, and is associated with bilateral though often asymmetrical trmporal lobe atrophy. PNFA is associated with striking asymmetric atrophy of the left hemisphere. There is greater histological concordance amongst the language based syndromes; both SemD and PNFA are associated with ubiquitin and TDP-43 pathology, SemD with type 1 FTLD-TDP and PNFA with type 3 FTLD-TDP (Rohrer et al., 2011). The clinical, neurobehavioural, neuropsychological and neuroimaging features characteristic to each FTLD syndrome will be discussed in detail further in this chapter.

1.1.1 The relevance of non-verbal deficits in FTLD

All three canonical FTLD syndromes exhibit clinically significant changes in nonverbal behaviour and cognition. These changes often lead to severe social handicap and patient and carer distress, and may result in misdiagnosis as a primary psychiatric disorder particularly in the absence of other more readily measurable cognitive deficits; indeed, disturbances of this kind are difficult to characterise and quantify using standard clinical and neuropsychological instruments. Common examples include altered eating behaviour, disinhibition, obsessionality, apathy, aggression, loss of empathy and sociopathy. There may also be deficits in processing particular kinds of nonverbal sensory information, such as faces (prosopagnosia) or voices (phonagnosia) (Hailstone et al., 2010). While such symptoms are most salient (and best recognised) in the case of bvFTLD, nonverbal cognitive and behavioural features are also increasingly recognised as integral to the progressive aphasias. Examples include deficits of prosody perception and environmental sound apperception in PNFA, multimodal semantic breakdown with development of associative agnosia for a range of sensory stimuli in SD, and complex behavioural alterations in both syndromes (Luzzi et al., 2007; Rohrer & Warren 2010; Rohrer et al., 2010b; Goll et al., 2010; Piwnica-Worms et al., 2010).

Taken together, these clinical observations underline the importance of nonverbal processes in the complex phenomenology of FTLD, and the close links between nonverbal cognitive operations and behavioural disturbance. Altered emotional understanding, for example, is integral to the loss of empathy, coldness and sociopathy that characterises bvFTLD; defective emotional understanding is itself likely to be underpinned by impaired mechanisms for encoding and experiencing emotional states in self and others (Lavenu et al., 1999; Cardinal et al., 2002;

Keane et al., 2002; Lough et al., 2005; Sturm et al., 2006), and so exemplifies a problem of nonverbal signal processing. Other kinds of social signals such as faces and voices are also critical to normal inter-personal functioning, and loss of the cognitive capacity to encode such signals would predictably lead to abnormal social behaviour (Damasio et al., 1990; Evans et al., 1995; Neuner & Schweinberger 2000; Perry et al., 2001; Snowden et al., 2004; Fernandez-Duque & Black 2005). A further example is abnormal eating behaviour, which might reflect changes in chemosensory function, impaired conceptual knowledge of food and flavours, altered appetitive drives or altered processing of endogenous feeding signals, in various combinations (Bathgate et al., 2001; Snowden et al., 2001; Liu et al., 2004; Rolls 2005; Luzzi et al., 2007; Woolley et al., 2007). To propose links between nonverbal cognitive processes and behaviour is not, or course, to deny the existence of more specific, higher level deficits of social cognition in FTLD (Gregory et al., 2002; Lough et al., 2005; Kipps et al., 2009): these mechanisms are likely to interact in the individual patient, however the nature of this interaction remains poorly understood.

From a clinical perspective, improved understanding of nonverbal deficits might assist differentiation of FTLD from other neuropsychiatric conditions and between FTLD syndromes. This understanding might also inform clinical management: designing rational management strategies for complex behavioural disturbances is particularly challenging when the underlying mechanism of the behaviour is not well understood or the means to assess (and ideally quantify) behavioural change are not available. More fundamentally the study of nonverbal cognitive processes may lead to improved understanding of a mechanism of complex behavioural disturbances. These processes could potentially offer important insights into the neurobiology of FTLD (Seeley et al., 2006; Seeley 2008a).

In order to understand nonverbal cognitive and behavioural deficits in FTLD, one approach is to correlate the presence and intensity of symptoms and neuropsychological performance with disease-associated anatomical changes. It is known, for example, that brain areas involving anterior cingulate and frontal insular cortices participate in a specific anatomical network involving limbic and subcortical systems that has been implicated in the pathogenesis of FTD (Rosen et al., 2002a; Broe et al., 2003; Boccardi et al., 2005; Schroeter et al., 2008). More recently a unique type of neuronal cell that populates these core areas of injury, referred to as von Economo neurons (VENs), has been implicated as an anatomical substrate for the behavioural syndrome, mediating a selective network vulnerability to the disease process in FTLD. VENs exemplify a candidate target for detailed studies addressing the linkage between brain and behaviour in FTLD (Viskontas et al., 2007; Seeley et al., 2006; Seeley 2008a).

The following sections of this Thesis review each of the canonical FTLD syndromes in turn, emphasising nonverbal cognitive and behavioural symptoms, and their neuroanatomical signatures.

1.1.2 Frontotemporal dementia

1.1.2.1 Clinical presentation

The FTD syndrome which, for the purposes in this Thesis, will be referred to as bvFTLD accounts for around 50% of all FTLD cases (Johnson et al., 2005). The clinical presentation of bvFTLD is characterised by prominent progressive personality and behavioural changes, as described in the clinical consensus criteria (Neary et al., 1998; McKhann et al., 2001). These can

be rather protean and often include changes in complex behaviours and social and emotional cognition that lead to significant patient and carer distress, severe social handicap, and unfortunately common misdiagnosis as a primary psychiatric disorder. The initial symptom may be difficulties with executive function such as the inability to plan and organise or to carry out complex tasks. Disinhibition, sociopathy, changes in eating behaviour, neglect of personal hygiene, obsessionality and rituals, apathy, aggression and loss of empathy are all cardinal symptoms within the bvFTLD spectrum (Bathgate et al., 2001; Diehl & Kurz 2002; Rosen et al., 2002b; Snowden et al., 2002; Kertesz 2008). Language impairment can be a feature in bvFTLD though this is often linked to behavioural change and often consists of either loss of verbal fluency with adynamia or conversely pressure of speech, and in more advanced disease echolalia, perseveration and mutism. Generally patients with bvFTLD show little by way of readily measurable focal cognitive deficits other than executive dysfunction when assessed using conventional neuropsychological instruments (Gregory & Hodges 1996; Lough et al., 2005). Neurologically there may be primitive reflexes and other frontal release signs, however these are commonly absent in early disease. Parkinsonian features such as akinesia, rigidity and tremor (Neary et al., 1998) may be present in more advanced disease, and the syndrome overlaps with "parkinson's-plus" disorders notably progressive supranuclear palsy and corticobasal degeneration. There is a recognised association between bvFTLD and motor neuron disease (MND) (Mitsuyama 1984), with 13% to 30% of bvFTLD patients eventually developing motor or bulbar symptoms (Lomen-Hoerth et al., 2002; Hodges et al., 2003; Kertesz et al., 2005; Snowden et al., 2007; Lillo et al., 2010), typically 6-12 months after onset of behavioural symptoms. FTD-MND patients demonstrate a more rapid disease progression and higher

occurrence of psychotic features, and generally have poorer prognosis with few surviving beyond three years of symptom onset (Hodges et al., 2003; Lillo et al., 2010).

As a clinical syndrome, bvFTLD demonstrates considerable clinical, pathological and genetic heterogeneity and the epidemiology of the disease has been somewhat more challenging to estimate partly as a result of diagnostic difficulty. The age of onset is typically between 45-65 years, although there is great variance with reported ages of onset ranging from 21 to 85 years. The duration of illness is even less clearly defined, and although a range of between 6-8 years has been suggested according to consensus clinical criteria (Neary et al., 1998; McKhann et al., 2001; Neary et al., 2005), the prognosis can range from several months in FTD-MND to over a period of decades (Kertesz et al., 2005; Kertesz et al., 2007; Le et al., 2006). One large epidemiological study reported a peak prevalence of 9.4 cases per 100,000 between the age range of 60-69 years, with a lower prevalence of 3.6 per 100,000 at ages 50-59 years and 3.8 per 100,000 at ages 70-79 years (Rosso et al., 2003). The mean age of onset has been cited to range from 55 - 60 years, with a positive family history, ie dementia in one or more first-degree relatives, in 18-43% of cases (Rosso et al., 2003; Johnson et al., 2005; Le et al., 2006), although a more recent study has shown only 10% with a clear autosomal-dominant history (Rohrer et al., 2009a). Primitive reflexes, parkinsonism and urinary incontinence occur as disease progresses in descending order of prevalence (Le et al., 2006). This diversity underlines the need for improved differentiation of clinical and pathological syndromes in FTD, both for diagnosis and for the purpose of future therapeutic trials.

1.1.2.2 *Neurobehavioural features*

Behavioural disturbances are a cardinal feature in bvFTLD, and can present in a variety of forms including disinhibition, apathy, aggression, loss of insight, poor social awareness and aberrant motor behaviours. Ritualistic and obsessive behaviours are common and may include hoarding, repetitive organisation of objects and compulsions. Loss of social awareness and disinhibition often manifests in behaviours violating social norms, such as making inappropriate sexual comments or gestures, urinating in public, to sociopathic acts such as stealing, physical violence, traffic violations and paedophilia. The loss of social judgement exhibited in some of these behaviours could be accounted for by different mechanisms including deficits in empathy, emotional responsiveness, insight, mentalizing, person recognition and control of immediate impulses. It has been suggested that this could be a form of "moral agnosia" or loss of semantic knowledge for moral rules (Mendez 2006). There can be shifts in ingrained personal attitudes or values, such as changes in religious beliefs or hyper-religiosity (Edwards-Lee et al., 1997; Miller et al., 2001; Chan et al., 2009). Disturbances of eating behaviour are often prominent: these may include craving sweet foods, unusual food fads, hyperphagia and compulsive food seeking (Bathgate et al., 2001; Snowden et al., 2001; Ikeda et al., 2002; Rosen et al., 2005; Woolley et al., 2007). There is alteration in pain and temperature responses, with reports of reduced pain and temperature awareness (Bathgate et al., 2001; Snowden et al., 2001) and increased pain thresholds (Carlino et al., 2010), as well as prominent sleep disturbance and disrupted sleep/wake cycles (Bathgate et al., 2001; Liu et al., 2004; Anderson et al., 2009). Not surprisingly, behavioural changes are often misinterpreted as a primary psychiatric disorder, particularly as there is little discernible cognitive impairment in early disease in contrast to these pronounced and disturbing neurobehavioural changes.

Given the heterogeneity of behavioural changes, attempts have been made to describe and classify different behavioural profiles amongst patients with bvFTLD, for example the suggestion that there are two subsyndromes, an apathetic form and disinhibited form of bvFTLD, the former associated with widespread frontal lobe atrophy and the latter with atrophy of the orbitofrontal lobes and temporal poles (Snowden et al., 2001). Several studies have attempted to examine the behavioural profiles which discriminate bvFTLD from primary psychiatric and other dementias such as AD, and delineate various behavioural phenotypes within the disease. Apathy has been found to be more common than disinhibition (Mourik et al., 2004; Le Ber et al., 2006). Loss of emotion and empathy, loss of insight, disinhibition, gluttony and altered eating behaviour, personal neglect, aberrant motor behaviour and indifference to pain differentiated bvFTLD from AD and vascular dementia (Bozeat et al., 2000; Bathgate et al., 2001; Snowden et al., 2001; Diehl & Kurz 2002; Liu et al., 2004). Whilst psychotic symptoms including hallucinations and delusions have been described as being much less common in bvFTLD compared to AD, dementia with Lewy bodies (DLB) and vascular dementia, the prevalence of psychosis in bvFTLD remains a source of debate, and there are studies suggesting that it may be more prevalent in bvFTLD than the traditional view (Bathgate et al., 2001; Mendez et al., 2008).

Several studies in recent years have examined emotion recognition abilities in bvFTLD, mostly through the recognition of facial expressions (Lavenu et al., 1999; Keane et al., 2002; Lavenu & Pasquier 2005; Lough et al., 2005; Rosen et al., 2006a; Diehl-Schmid et al., 2007), whilst few have assessed emotion recognition in other modalities such as vocal expressions (Keane et al., 2002). These studies have commonly shown profound emotion recognition deficits in FTD with disproportionate impairment for negative emotions (anger, disgust, fear and sadness), which is

separate from other aspects of face processing (Keane et al., 2002; Fernandez-Duque & Black 2005).

1.1.2.3 *Neuropsychological features*

The main cognitive deficit in bvFTLD is executive dysfunction, characterised by impairments in tasks associated with planning, organisation, problem solving, judgement, attention, mental flexibility and abstraction, whilst other cognitive domains including spatial skills, visual perception, memory and primary language abilities are well preserved (Neary et al., 1988; Snowden et al., 2001; Kramer et al., 2003). The language changes that occur are often related to executive dysfunction and include reduced verbal fluency, concreteness of thought, verbal stereotypies and, in later disease, echolalia and eventual mutism.

One of the reasons behind the diagnostic difficulty in early bvFTLD is that there is often no detectable abnormality using currently available standard neuropsychological assessment tools. The fact that standard neuropsychological batteries do not adequately probe cognitive functions such as emotion, empathy, social awareness and other non-verbal sensory processes such as those relating to person-specific knowledge such as faces and voices, chemosensory and somatic functions, processes which are relevant to the behavioural symptoms exhibited in bvFTLD, highlights the need to investigate these functions in a cognitive framework.

1.1.2.4 *Neuroimaging features*

An increasingly important aspect of the clinical diagnosis of bvFTLD relies on the use of neuroimaging techniques, particularly volumetric magnetic brain imaging (MRI) and more recently functional imaging techniques such as positron emission tomography (PET). bvFTLD is

frequently associated with bilateral frontal lobe atrophy (Rosen et al., 2002a), and this is often asymmetric (Fukui & Kertesz 2000; Seeley et al., 2008b). The association between the behavioural changes observed in bvFTLD and atrophy of the frontal lobes would be consistent with a priori knowledge of the role of the frontal lobes in mediating the many aspects of behaviour (Cummings 1993; Rosen et al., 2005; Williams et al., 2005; Peters et al., 2006). With the use of techniques including voxel-based morphometry (VBM) and quantitative volumetric MRI measures, frontal lobe regions have been studied in further detail to examine more specific associations to certain behavioural changes or abnormalities (Perry et al., 2006; Whitwell et al., 2009).

There is a growing body of work investigating the neural correlates of aberrant behaviours and the proposed mechanisms underlying these behaviours such as emotion, empathy, theory of mind and social judgement, with the presence of abnormal behaviours as a whole being found to correlate with grey matter volume loss in the dorso-medial frontal lobe and paracingulate region (Williams et al., 2005). The right temporoparietal cortex has been implicated in loss of insight or anosognosia (Zamboni et al., 2010). The orbitofrontal cortex (OFC), amygdala and right temporal structures have been implicated as possibly the earliest loci of atrophy before more widespread involvement as the disease progresses (Perry et al., 2006). It may be that one of the reasons standard tests assessing executive function fail to detect abnormalities in early bvFTLD is their lack of sensitivity towards dysfunction in these areas. Grey matter volume loss in the OFC has been implicated in a range of social cognitive impairments including deficits in empathy and theory of mind (mentalizing) (Gregory et al., 2002; Lough et al., 2005; Kipps et al., 2009), social reasoning (Eslinger et al., 2007), the ability to understand sarcasm (Kipps et al., 2009), the processing of emotion including fear conditioning (Lough et al., 2005; Werner et al.,

2007; Hoefer et al., 2008) and affective decision-making (Torralva et al., 2007), as well as abnormal eating behaviour (Whitwell et al., 2007; Woolley et al., 2007). The OFC and related structures including insula, amygdala, anterior cingulate cortex and right temporal pole appear to form a neural circuitry or network associated with these social cognitive processes, supporting the argument of FTD being a neural network disease (Adolphs et al., 1994; Boccardi et al., 2005; Rankin et al., 2006; Sturm et al., 2006; Schroeter et al., 2008; Kipps et al., 2009). That these regions correlating with loss of social cognition include the areas populated by von Economo neurons substantiates the idea of this being a selectively vulnerable neural circuit in early FTD (Viskontas et al., 2007; Seeley et al., 2006; Seeley 2008a).

More recent studies have shown, however, that rather than being confined to the frontal lobes, atrophy in bvFTLD is also associated with a network of other limbic areas that are likely to be involved in the modulation of human behaviour, including the insula, striatum, anterior cingulate and amygdala (Rosen et al., 2002a; Boccardi et al., 2005; Whitwell et al., 2005; Barnes et al., 2007). Temporal lobe structures such as the hippocampus and parahippocampal gyrus are also involved in bvFTLD (Galton et al., 2001; Grossman et al., 2004; Barnes et al., 2007; Whitwell et al., 2009). In keeping with the variability in behavioural presentations in bvFTLD, patients can show differing patterns of atrophy according to behavioural profile and pathology (Cummings, 1993; Snowden et al., 2001; Liu et al., 2004; Josephs et al., 2006; Le Ber et al., 2006; Whitwell et al., 2006; Massimo et al., 2009). For example, apathy has been associated with dorsolateral and medial frontal changes, and disinhibition with orbitofrontal and temporal lobe changes (Le Ber et al., 2006; Zamboni et al., 2008; Massimo et al., 2009). However, the association between distinct behavioural profiles and patterns of atrophy, such as the degree of temporal in relation to frontal atrophy as well as right versus left atrophy remains poorly understood.

1.1.3 Semantic dementia

1.1.3.1 Clinical presentation

The syndrome of semantic dementia (SemD) was first characterised in 1975 when Warrington reported three patients with a combination of anomia, visual associative agnosia and impaired comprehension of word meaning (Warrington 1975). It is the paradigmatic disorder of semantic memory. The classification of the SemD syndrome has not escaped the complex web of terminology associated with the FTLD spectrum of disorders. When considering the anatomical substrates involved in SemD, the syndrome has been described in the literature as synonymous with (or associated with) "temporal variant FTLD" due to the primarily bilateral but asymmetrical atrophy of anterior temporal lobes, in contrast to the term "frontal variant FTLD" which is generally associated with behavioural variant FTLD (Edwards-Lee et al., 1997; Mummery et al., 1999; Chan et al., 2001; Rosen et al., 2002a; Liu et al., 2004). SemD has also been subsumed under the label of primary progressive aphasia, which also includes progressive non-fluent aphasia (Mesulam 1987).

From the available epidemiological data, it has been reported that 20-45% of cases experienced symptom onset after 65 years of age, with survival ranging from 3-15 years (Gislason et al., 2003; Harvey et al., 2003; Hodges et al., 2003); a recent large study reported mean onset age of 64 years and median survival of around 13 years, a more benign course and older age of onset than suggested by earlier clinicopathological studies (Hodges et al., 2010). There is no clear evidence of a genetic factor in the majority of cases of SemD (Rohrer et al., 2009a).

Patients with SemD chiefly present with progressive loss of vocabulary and word knowledge, resulting in difficulties with naming and language comprehension. Patients are unable to produce the names of previously familiar places, people and objects, and fail to understand questions and follow conversations. Speech production is fluent, effortless and relatively grammatical with relative preservation of repetition, however the content of speech is impoverished and circumlocutory with increasing reliance on superordinate or vague designations, until many patients are left with only a few stereotypical phrases or expressions. SemD is not, however, purely a language disorder: as it evolves, there is impaired recognition of objects in multiple sensory domains (Warrington 1975; Hodges et al., 1992; Neary et al., 1998; Snowden 1999; Bozeat et al., 2000; Seeley et al., 2005; Jefferies & Lambon Ralph 2006) including faces and visual objects, environmental sounds (Bozeat et al., 2000; Goll et al., 2010), odours (Luzzi et al., 2007; Rami et al., 2007), flavours (Pwinica-Worms et al., 2010) and touch (Coccia et al., 2004). Clinically this manifests as an associative agnosia affecting one or more nonverbal domains, and this may be the leading clinical feature. Taken together, this evidence suggests that the neurodegenerative pathology in SemD targets a cognitive process that mediates the panmodal representation of knowledge about words and sensory objects.

1.1.3.2 Neurobehavioural features

Patients with SemD may exhibit various behavioural abnormalities. These overlap substantially with bvFTLD and may dominate the clinical picture, particularly in patients with nonverbal agnosias. Patients with SemD can develop degraded social skills similar to that in bvFTLD exhibiting a combination of apathy, depression, irritability and emotional withdrawal. Obsessiveness, rigidity and compulsions are particularly common, as is alteration of eating

behaviour in the form of bizarre food preferences more so than indiscriminate gluttony. SemD patients are more likely to exhibit food fads and have a tendency to eat inedible substances or unusual food combinations compared to those with bvFTLD (Snowden et al., 2001; Ikeda et al., 2002). Disruption of physiological drives such as sleep and libido can be an early feature (Seeley et al., 2005). Irritability, disinhibition and depression are also common in SemD. Loss of empathy and emotional responsiveness can also be observed particularly in the reaction to and expression of fear. Patients with SemD also tend to display unusual somatic and sensory behaviours, such as exaggerated responses to tactile stimuli, pain and temperature (Bozeat et al., 2000; Snowden et al., 2001; Hodges & Patterson 2007; Rohrer & Warren 2010).

The amygdala, anterior temporal and OFC are known to be involved in emotion processing (Adolphs et al., 1994; Anderson et al., 2000; Calder et al., 2001; Cardinal et al., 2002; Rolls, 2004; Menon and Levitin, 2005; Dolan, 2007), which are key regions damaged in SemD and are likely to form the basis of some of the social and behavioural abnormalities in this condition. Lack of empathy and emotional blunting are well recognised in SemD (Snowden et al., 2001), although very little is known about affective processing in SemD as few studies have been conducted specifically examining emotion recognition in these patients. It has been suggested that, in the domain of facial emotion recognition, patients with SemD have deficits in recognising specifically negative emotions (Rosen et al., 2002b; Rosen et al., 2004).

1.1.3.3 Neuropsychological features

In SemD, anomia and impaired word comprehension are the most striking neuropsychological features, with preservation of normal speech structure. Patients often demonstrate surface dyslexia and dysgraphia (difficulty reading and spelling irregular words), signifying a loss of

vocabulary-based processing with preserved ability to read and write regular words with standard grapheme – phoneme correspondence. Word and sentence repetition is generally intact.

More detailed testing reveals a breakdown both in verbal and non-verbal semantic knowledge. Deficits are shown on verbally based tasks that access semantic memory (Hodges et al., 1992; Hodges and Patterson 1996), such as picture naming, naming an item from a description, category fluency, synonym matching, and word–picture matching (Warrington et al., 1998). In naming tasks, there is sensitivity to frequency and familiarity effects (ie greater difficulty with infrequent or less familiar items), and a characteristic pattern of progression with errors restricted in early disease to the coordinate (ie semantically related items) then eventually to the superordinate (ie "animal" instead of "dog") and finally with no information at all on the item (Jefferies & Lambon Ralph 2006; Hodges & Patterson 2007). On non-verbal testing of semantic memory, patients show deficits in visual (ie. Picture and face recognition/identification) (Bozeat et al., 2000a; Snowden et al., 2004; Thompson et al., 2004), complex auditory (environmental sounds) (Bozeat et al., 2000a; Goll et al., 2010) and olfactory (Luzzi et al., 2007) domains. In contrast to the impairments seen on tests of semantic knowledge, patients perform well on tests of visuo-perceptual and spatial ability, non-verbal problem solving and working memory (Hodges et al., 1992; Graham et al., 1997; Hodges & Patterson 2007).

Impaired person knowledge is a feature of SemD, affecting not only the ability to name people but also to produce information from their faces (Snowden et al., 2004) and voices (Hailstone et al., 2010). Patients usually present first with difficulty naming people, followed by inability to identify a person from their face, name or voice, and finally are unable to establish familiarity (Snowden et al., 2004; Thompson et al., 2004; Hodges & Patterson 2007). There are, however,

patients who present with profound face recognition difficulties associated with greater right-sided antero-inferior temporal atrophy for whom the term "progressive prosopagnosia" has been applied, although deficits in person identification have been shown to extend to other modalities including names and voices (Joubert et al., 2006). In general, patients with predominant left temporal atrophy are better at person recognition from faces compared to names, and the reverse pattern is seen in those with predominant right temporal atrophy. It has been argued that predominant right temporal atrophy in SemD is associated with severe disruption of person-specific semantics with relative preservation of general semantic knowledge in other categories such as objects and animals, with the reverse being the case for those with predominant left temporal atrophy, suggesting partial cognitive and neural independence of person-specific knowledge from general semantic knowledge (Thompson et al 2004). On the basis of evidence from studies on prosopagnosic patients (De Renzi et al., 1994) and functional imaging (Kanwisher et al 1997) showing right hemispheric lateralisation in face processing, it is suggested that damage to anterior-inferior right temporal structures may interrupt the processing stream from more posterior temporal regions, thought to be involved in earlier stages of face processing, to anterior regions implicated in storage and retrieval of high level conceptual person-specific knowledge (Thompson et al., 2004). Nevertheless, the precise nature of the relationship between progressive prosopagnosia and general semantic memory in SemD remains poorly understood. This impairment of person knowledge affecting patients with right temporal atrophy may account for some of the more prominent behavioural symptoms in this group, such as disinhibition, aggression, depression, loss of insight, changes in affect and disordered social conduct (Thompson et al, 2003; Chan et al., 2009).

1.1.3.4 Neuroimaging features

The main neuroimaging signature in SemD is atrophy of the anterior and medial temporal lobes bilaterally, though typically asymmetrical, with one hemisphere more greatly affected than the other. As disease progresses the atrophy extends more posteriorly and/or rostrally into the postero-inferior frontal lobes patients. Studies using quantitative MRI method including manual segmentation and VBM have consistently shown severe atrophy of the temporal poles, perirhinal cortices and anterior fusiform gyri, the degree of which has been found to correlate with the severity of semantic memory deficit on cognitive testing (Mummery et al., 1999; Chan et al., 2001; Rosen et al., 2002a; Nestor et al., 2006). Functional imaging studies using FDG-PET have shown hypometabolism affecting these areas as well as medial temporal structures including the hippocampus.

Studies examining the cognitive and behavioural associations of hemispheric asymmetry in SemD have shown that patients with left-greater-than-right atrophy present with predominantly language-related deficits such as anomia and impaired comprehension, whilst those with greater right sided atrophy have a higher prevalence of person recognition difficulties, poor insight and behavioural abnormalities associated with a particular behavioural phenotype overlapping with the syndrome of bvFTLD. Patients with right temporal lobe atrophy exhibit greater social disinhibition, aggression and depression, in addition to particular behavioural symptoms specific to this group such as hyper-religiosity, somatic complaints, visual hallucinations, and unusual cross-modal sensory experiences, as well as a cognitive profile with prosopagnosia, topographical disorientation and episodic memory impairment (Miller et al., 1993; Evans et al., 1995; Edwards-Lee et al., 1997; Thompson et al., 2003; Zamboni et al., 2008; Chan et al., 2009).

Whilst both left and right temporal atrophy are associated with compulsive behaviours, the target of left temporal lobe atrophy compulsions are more often physical environmental objects, whilst right temporal lobe atrophy cases focused on abstract objects such as words, letters and symbols (Seeley et al., 2005).

1.1.4 Progressive non-fluent aphasia

1.1.4.1 Clinical presentation

Progressive non-fluent aphasia (PNFA) is the cardinal predominantly language-based syndrome within the FTLD spectrum (Neary et al., 1998; Rohrer et al., 2010a). The clinical picture is typically dominated by progressive impairment of speech production with characteristically hesitant and effortful or telegraphic speech, speech apraxia, and agrammatism. Patients are anomic due to difficulty finding words, with prolonged pauses and articulatory or speech sound errrors. Other common features include an oral apraxia, stuttering, impaired repetition and dysgraphia. Typically language comprehension and other cognitive domains are well preserved until later in the course, when various behavioural changes can occur (Neary et al., 1998; Mesulam 2001; Kertesz et al., 2003; Ogar et al., 2007; Rohrer & Warren 2010).

1.1.4.2 Neurobehavioural features

In comparison to the other FTLD syndromes, there have been relatively few studies examining the behavioural profile of PNFA per se. Many earlier studies have tended to look at PPA as a whole, including patients with SemD (Snowden et al 2001; Liu et al 2004; Marczinski et al 2004). One study found that patients with PNFA had significantly less socioemotional

behavioural dysfunction than SemD, at least in the first few years of illness (Rosen et al., 2006b), which lends support to the diagnostic criteria outlined by Neary et al in 1998. However, more recent evidence suggests that behavioural abnormalities including apathy, depression and agitation, develop in over half of PNFA cases during the course of the illness, with similar severity to other forms of primary progressive aphasia (PPA) including SemD (Rohrer & Warren 2010). The study also reported other neurobehavioural symptoms in PNFA, including altered eating behaviour, anxiety and emotional lability (occurring in 25-49% of the population). Disinhibition was seen in 14%, and a few patients (7%) suffered from delusions. Another recent study has shown that, in addition to demonstrating dysprosodic speech, PNFA patients also have receptive prosodic deficits which encompass acoustic, linguistic and also affective dimensions of prosodic analysis (Rohrer et al., 2010b). Prosody conveys multidimensional information about the speaker's intentions, meaning and affective state, and thus the ability to process prosodic information is an important aspect of decoding another person's emotional state from their speech.

1.1.4.3 Neuropsychological features

The main neuropsychological findings in PNFA are impaired speech production in the absence of dysfunction in other cognitive domains including memory (eg normal scores on tests of visual memory), visuoperception and visuospatial function (Hodges & Patterson 1996; Neary et al., 1998). Recently the speech disorder in PNFA has been characterised as a speech apraxia, describing a motor speech impairment with hesitancy, effortfulness, "articulatory groping", phonetic errors and dysprosody, and some studies have stressed this as a cardinal feature of the condition (Ogar et al., 2007; Gorno-Tempini et al., 2004a, 2008). Orofacial apraxia and limb

apraxia have also been described in PNFA (Rohrer et al., 2010c). Agrammatism typically consists of omissions or incorrect use of grammatical terms. In contrast to SemD, single word comprehension is usually intact in PNFA, although sentence-level comprehension deficits are often present indicating a disorder of grammatical processing (Turner et al., 1996). Performance on tests of confrontational naming is often impaired although with intact recognition of the unnamed items. PNFA patients score poorly on tests of verbal fluency, particularly initial letter-based fluency, and produce phonological and syntactic errors in spontaneous speech, repetition and reading tasks, with reading errors distributed between regular and irregular words (Hodges & Patterson 1996; Gorno-Tempini et al., 2004a).

Within the PPA spectrum, a third syndrome known as logopenic or phonologic progressive aphasia (LPA) has been described more recently. These patients exhibit prolonged word-finding pauses, but do not have agrammatism nor motor speech impairment (Kertesz et al., 2003; Gorno-tempini et al., 2004a, 2008). This disorder is likely to be underpinned by Alzheimer pathology in most cases (Rohrer et al., 2012). Debate continues regarding the classification of other variants and phenotypes within the primary progressive aphasia spectrum, including progressive aphasia associated with the recently-discovered progranulin (PGRN) gene (Snowden et al., 2006; Pickering-Brown et al., 2008; Rohrer et al., 2010a), as well as findings of Alzheimer pathology in some cases of clinically diagnosed PNFA (Alladi et al., 2007).

1.1.4.4 Neuroradiological features

In the 1998 consensus criteria, the general brain imaging feature in PNFA is "asymmetric abnormality predominantly affecting the dominant hemisphere". Our understanding of the neuroimaging signatures of PNFA have advanced particularly with the application of VBM

methods to correlate clinical and behavioural measures with areas of focal atrophy on structural MRI or of abnormal hypoperfusion on functional MRI. The atrophy pattern in PNFA involves primarily the left perisylvian fissure, left inferior frontal and anterior insular cortices (Gorno-tempini et al., 2004a), as well as basal ganglia (Ogar et al., 2007; Schroeter et al., 2007) and temporal regions (Knibb et al., 2009; Rohrer et al., 2009b). Involvement of the left insula has been associated with apraxia of speech (Gorno-tempini et al., 2004a; Ogar et al., 2007; Rohrer et al., 2010c), the left inferior frontal lobe with agrammatism (Amici et al., 2007) and superior temporal regions with the analysis and short-term storage of speech signals (Scott & Johnsrude 2003).

1.2 From symptoms to brain processes

The above sections illustrate the range of nonverbal symptoms and neuroanatomical profiles in FTLD. Mapping FTLD symptoms to a cognitive and neuroanatomical framework is a key step toward understanding how such symptoms develop. However, this mapping is challenging, for several reasons. Foremost amongst these is our incomplete understanding of the cognitive architecture of complex behaviours in the healthy brain. Establishing neuroanatomical associations in FTLD is challenging, due both to the heterogeneity and individual variation encompassed by the FTLD spectrum. Finally, even robust neuroanatomical data do not reveal the mechanism of behavioural dysfunction.

The study of cognitive and behavioural dysfunction in FTLD has been advanced by a substantial body of work on the cognitive organisation of complex behaviours in the normal brain (Shallice et al., 1994; Fletcher et al., 1996; Nathaniel-James et al., 1997; Kelley et al., 2002; Ochsner et al., 2005; Amodio & Frith, 2006; Carrington & Bailey, 2009; Northoff et al., 2009; Fan et al., 2011).

Generation of complex behaviours is likely to require a "cognitive executive": a collection of regulatory and supervisory brain mechanisms that combine, coordinate and adapt behaviours to different contexts and direct behaviours to relevant goals (Warren and Warrington 2007; Shallice & Burgess 1996). According to Shallice and Burgess, the "default mode" of human behaviour is governed by an almost infinite repertoire of behavioural programs on the basis of automatic input-output associations. Executive operations such as problem-solving, sustained attention and monitoring rely on our capacity to modify, suppress or select the appropriate behavioural repertoire. This is likely to involve the construction of a cognitive model about internal, external and remembered events in relation to future goals, which would enable one to mentally test hypotheses and potential responses prior to generating an actual response. A supervisory system is thus required to manipulate information in parallel to input-output circuits. Patients with FTLD often display evidence of degradation of this supervisory system. Dinhibition, impulsivity, lack of insight, concreteness of thought, perseveration, rituals and obsessions may be explained by this inability to "gate" or modulate cognitive inputs according to overall sensory or cognitive context. Impaired modulation of executive output leads to loss of initiative and dependency on environmental cues to direct behaviour.

The putative central executive does not operate autonomously. Normal behaviour requires a continual interchange of information with the executive derived from incoming sensory traffic (including information about the consequences of one's own past behaviour) and stored knowledge and experience of the world at large. This implies that alterations in sensory information processing or memory functions could have profound effects on behavioural output, and this principle is well illustrated by patients with FTLD. Altered processing of external sensory objects and signals as well as interoceptive signals (physiological drives, pain and

temperature) are prominent features in the canonical FTLD phenotypes. Normal inter-personal functioning relies on the ability to encode social signals from faces. Deficits in mechanisms for processing and experiencing emotional states intrinsically and for representing the mental states of others (mentalizing), and to modulate social interactions appropriately by nonverbal and emotional cues, are likely to underpin problems with emotional understanding, loss of empathy and sociopathy. Abnormal eating behaviour may reflect alterations in chemosensory function and deficits in conceptual knowledge of food. From a neurobiological perspective, the core areas of vulnerability in FTLD have been linked to areas populated by VENs, a specific neuronal class restricted to the anterior cingulate and orbitofrontal insula cortices in humans and higher-order primates, which are thought to be implicated in social-emotional functioning. Recent neuropathological studies have revealed selective reduction in VEN counts in bvFTLD compared to AD (Seeley, 2008a).

The complex neural circuits linking frontal cortex with subcortical structures including basal ganglia and thalamus are clearly implicated in the pathogenesis of dysexecutive and behavioural syndromes (Cardinal et al., 2002; Rolls 2004; Brown et al., 2004; Menon and Levitin, 2005; Gosselin et al., 2006; Dolan, 2007; Schroeter et al., 2008; Seeley et al., 2006, 2009). Less well understood are the cortico-cortical and limbic circuits that feed into the fronto-subcortical executive. This distributed circuitry may be particularly relevant to the pathogenesis of FTLD: brain damage in the FTLD syndromes involves extensive but anatomically predictable brain networks including those implicated in the processing of faces, chemosensory stimuli, emotion and music (Schroeter *et al.*, 2008; Seeley et al., 2009; Zhou et al., 2010). The role of the OFC in complex behaviour may arise from it receiving inputs from a number of sensory systems including visual, chemosensory and somatosensory stimuli, acting as a decoder of the reward and

affective value of these stimuli and implementing learning mechanisms to enable stimulus-reinforcement associations with sensory objects (Rolls 2004). There is growing appreciation of the cognitive role of subcortical pathways and cortico-subcortical circuits in executive and behavioural processes. The brainstem, frontal-subcortical and limbic systems are extensively and reciprocally linked via neurotransmitter projection pathways. This complex network of connections may serve as a substrate to multiple parallel re-entrant circuits between brainstem structures and higher centres. A simplified scheme of this circuitry is presented in Figure 1.1. A "centrencephalic system" involving the upper brainstem and thalamus, as critical integrators of cerebral hemisphere function, was first proposed by Penfield (1954) and subsequently elaborated. Based on lesion studies in non-human species, regions including the caudate and putamen, globus pallidus, ventrolateral thalamus, substantia nigra, ventral tegmental area (VTA), superior colliculus, median raphe, and pontine reticular formation, have been proposed to constitute a distributed "general learning system" involved in problem-solving and other aspects of complex cognition and behaviour (Thompson, 1993). These circuits have the potential for global integration of interoceptive, sensory and cognitive information and could provide a substrate for the pervasive behavioural and personality changes that have been described in Parkinsonism (Foltynie et al., 2004), Huntington's disease (Caine and Shoulson, 1983), neuroacanthocytosis (Kartsounis and Hardie, 1996) and multiple sclerosis (Foong et al., 1997) as well as with focal brainstem lesions (Adair et al., 1996; Benke, 2006; Garrard et al., 2002; Lee et al., 2003; Meador et al., 1996; Minabe et al., 1990; Netsky & Strobos, 1952; Segarra, 1970; Trimble & Cummings, 1981). The striatal dopaminergic system, for example, has a role in mediating pleasure and reward, and is implicated in behaviours associated with reinforcement and motivation (Salimpoor et al., 2011).

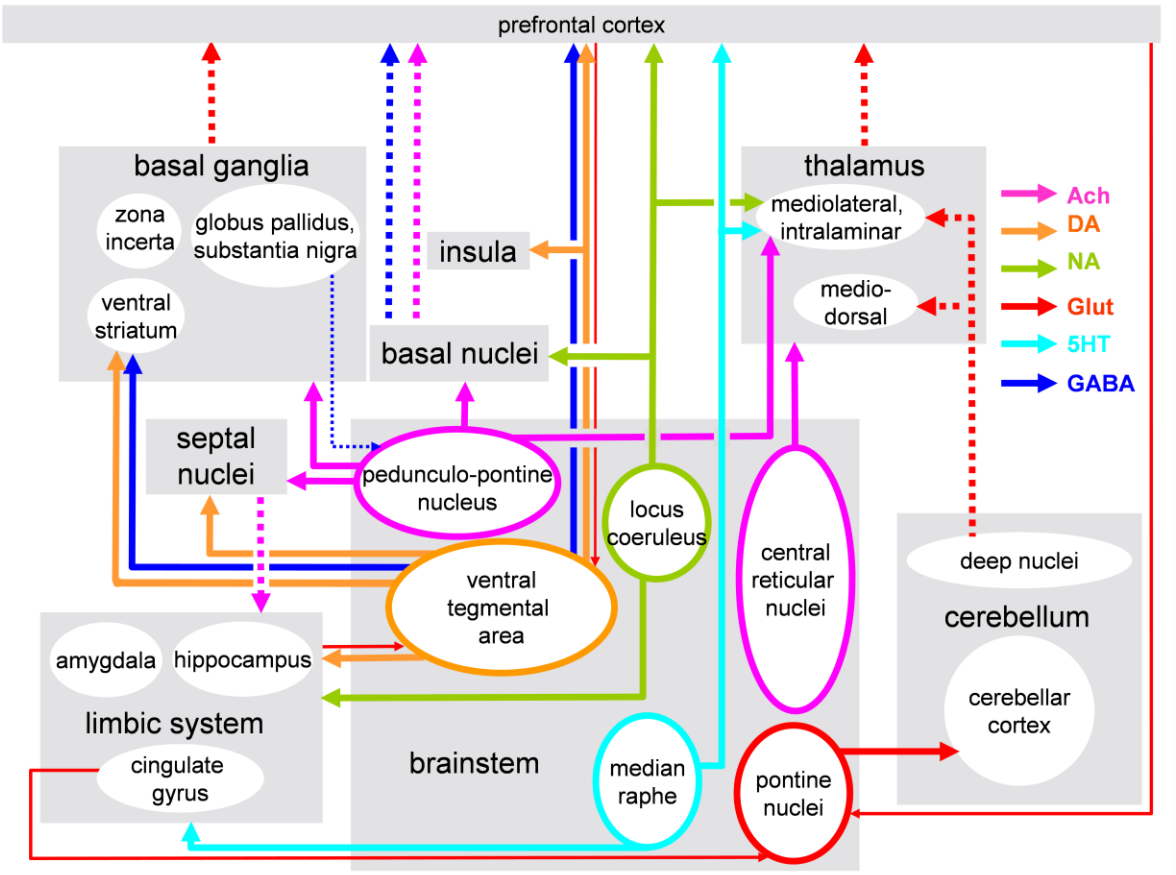


Figure 1.1 A schematic diagram of the major pathways linking the brainstem and limbic system with other cortical and subcortical regions. The schema is based on evidence derived from both humans and non-human species. Pathways are colour-coded according to their major neurotransmitters. Direct efferent pathways from the brainstem are represented using heavy solid lines; other efferent pathways are represented using heavy dotted lines; afferent projections to the brainstem are represented using fine lines. It is likely that most of these pathways are functionally bidirectional. The pedunculo-pontine nucleus, locus coeruleus, median raphe and central reticular nuclei can be loosely grouped on anatomical grounds as the 'reticular formation'. The extensive communications between brainstem nuclei are not shown. 5-HT, 5-hydroxytryptamine; ACh, acetylcholine; DA, dopamine; GABA, γ-aminobutyric acid; Glut, glutamate; NA, noradrenaline

From a neurobiological perspective, FTLD presents a unique 'experiment of nature' that offers certain advantages over other lesion-led paradigms in understanding the brain mechanisms that process nonverbal information. Furthermore, FTLD is a relatively common cause of dementia, enabling group-level neuroanatomical correlation. Understanding how FTLD symptoms map onto cognitive and brain mechanisms is not only of neurobiological interest, but also of

considerable clinical importance particularly in the differentiation of FTLD from other neuropsychiatric conditions and between FTLD syndromes. One example illustrating these diagnostic challenges concerns the uncertainty surrounding the prominence of positive psychotic symptoms (delusions and hallucinations) in FTLD.

1.2.1 Delusions in frontotemporal lobar degeneration

The traditional view is that psychotic symptoms are uncommon in FTLD, more associated with other neurodegenerative conditions such as DLB and AD (Gregory and Hodges, 1996; Levy et al., 1996; Engelborghs et al., 2005). The estimated prevalence of delusions in FTLD cohorts in previous studies has ranged from 0% to 23% (Mendez et al., 2008; Levy et al., 1996; Engelborghs et al., 2005; Hirono et al., 1999; Hodges et al., 2004). Within the FTLD spectrum, the bvFTLD syndrome and FTD-MND appear to be over-represented (Nitrini & Rosemberg, 1998; Hodges et al., 2004). Little information is available concerning the detailed phenomenology of delusions in FTLD; religious and paranoid delusions accompanied by auditory hallucinations have been described, as well as delusions of erotomania (Tartaglia et al., 2008; Waddington et al., 1995).

In a short study assessing the significance and nature of delusions in FTLD, a retrospective review of case notes of FTLD patients presenting to a tertiary level cognitive disorders clinic over a three year period was carried out. The DSM-IV definition of a delusion was used ("a false belief based on an incorrect inference about external reality that is firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary. The belief is not one ordinarily accepted by other members of the person's culture or subculture"). Delusions were assessed using a standard proforma based on the

clinical information, including the time of onset in relation to other symptoms, any previous psychiatric history, whether associated hallucinations were present (and their modality), and the phenomenological content of the delusions. The clinical subtype, neuropsychological and neuroimaging findings, and histopathological findings (where available) were also recorded in each case. Eight cases with delusions were ascertained from 56 patients with a clinical diagnosis of FTLD referred to the clinic during this period. All patients had detailed clinical and neuropsychological assessments and supportive brain magnetic resonance imaging (MRI) and/or pathological findings (reviewed with an experienced neuroradiologist and neuropathologist).

In this study, the estimated prevalence of delusions in FTLD patients was 14%, with eight out of 56 cases reporting a history of delusions. Two of the cases had pathological confirmation of FTLD: one with FTD-MND, the other with ubiquitin-positive, tau and α-synuclein-negative abnormal neuritis and intraneuronal cytoplasmic inclusions. In the eight cases reported, the delusions were an early and prominent feature of the disease, occurring as a leading symptom within a year of clinical onset in seven of the patients, and persisting in all eight patients through the course of the disease until time of recording. The delusions described were phenomenologically rich and diverse, including paranoid and persecutory delusions, delusions involving famous people, somatic delusions and delusions of parasitosis/infestation and body part distortion. bvFTLD was the most frequently associated clinical subtype and cerebral atrophy was bilateral or predominantly right-sided in most cases (Table 1.1).

Table 1.1 Clinical, neuropsychological, and brain imaging features of cases in this series

Case	Age	M/F	Syndrome	Brain MRI: regional atrophy	Neuropsychology										Delusions first year of illness?	Type of delusion(s)	Hallucinations	Other behavioural
					MMSE (/30)	VIQ	PIQ	Exec	Verb M	Vis M	Naming	SWC	FF	VS				
1*	65	F	bvFTLD-MND	Bilat FL	26	84	73	I[6, 17, 18]	I[9]	I[9]	N[11]	n/a	N	N[12, 13]	Yes	belief famous comedian resident in house	none	disinhibited, fatuous, echolalia distractible, hoarding, unempathic, hyperphagia
2*	59	F	bvFTLD	n/a	26	61	64	I[6]	I[9]	I[9]	I[11]	n/a	N	N[14]	Yes	paranoid; erotomania	visual	apathy
3**	56	M	bvFTLD	Bilat FL, R>L	15	91	n/a	I[3, 5]	N[9]	I[9]	I[11]	I[15]	N	N[12]	No	infestation (fleas and snakes)	tactile	impulsive, disinhibited, rituals, hyperphagia
4	52	F	bvFTLD	Bilat FL, aTL, peri-Sylvian	25	91	n/a	I[1]	I[8]	n/a	N[11]	n/a	n/a	n/a	Yes	religious	sinister visual and auditory	apathy, aggression, sweet tooth depression, stereotypies
5	60	M	bvFTLD	F-TL R>L	27	81	83	I[4, 6]	n/a	n/a	N[11]	N[15]	N	N[12]	Yes	persecutory; paranoid	none	depression, aggression, apathy, obsessionality, sweet tooth
6	53	M	bvFTLD	F-TL, R>L	26	95	87	I[2, 3, 4, 5]	N[9]	N[9]	N[11]	N[15]	N	N[12]	Yes	delusional memories of famous footballers	?visual	apathy, sweet tooth, religiosity, hoarding, rituals, mental rigidity
7	55	F	bvFTLD	Bilat aTL, R>L	22	73	70	I[4, 6]	N[10]	I[10]	I[11]	n/a	n/a	N[14]	Yes	body dysmorphic; contamination; grandiose belief of own celebrity	none	disinhibited, fatuous, rituals, mental rigidity, musicophilia
8	84	F	tvFTLD (SD)	Bilat aTL, L>R	26	n/a	125[22]	N[5, 20]	n/a	N[21]	I[11]	I[15]	N	N[12]	Yes	parasitosis, somatic	somatic, tactile	unempathic, mental rigidity

* pathologically confirmed; ** pathologically confirmed in parent (autosomal dominant dementia pedigree): all cases had ubiquitin positive, tau-negative neuronal inclusions

aTL anterior temporal lobe; *Bilat* bilateral; *bvFTLD* behavioural variant frontotemporal lobar degeneration; *Exec* executive function; *FF* famous faces recognition; *FL* frontal lobe; *I* impaired (< 5th percentile where normative data available); *L* left; *MMSE* Mini-Mental State Examination (Folstein) score; *MND* motor neuron disease; *N* normal (> 5th percentile where normative data available); *n/a* data not available; *PIQ* performance IQ; *R* right; *SD* semantic dementia; *SWC* single word comprehension; *tvFTLD* temporal variant FTLD; *Verb M* verbal memory; *VIQ* verbal IQ; *Vis M* visual memory; *VS* visuospatial/visuoperceptual function

Neuropsychological assessment: [1] CAMCOG-R; [2] Hayling Sentence Completion Test; [3] Modified Card Sorting Test; [4] Stroop Test; [5] Trail Making B Test; [6] Weigl Sorting Test; [7] Cognitive Estimates Test; [8] Wechsler Memory Scale-III: Logical Memory I and II; [9] Recognition Memory Test — Words and Faces; [10] Short Recognition Memory Test — Words and Faces; [11] Graded Naming Test; [12] VOSP Object Decision; [13] VOSP Cube Analysis; [14] VOSP Incomplete letters; [15] Synonyms Test; [16] Famous Faces; [17] Verbal fluency; [18] Proverb interpretation; [19] VOSP Position Discrimination; [20] Delis and Kaplan Design Fluency; [21] Camden Pictorial Memory Test; [22] Ravens Advanced Matrices

Aside from their implications for clinical diagnosis, delusions in FTLD are of considerable neurobiological interest due to the potential insights they hold into the brain mechanisms that link information about the external reality with internal representations of the world (Cummings, 1993; Arciniegas et al, 2001). Such mechanisms are likely to involve neural networks in the frontal and temporal lobes that are particularly vulnerable in FTLD (Arciniegas et al, 2001). However, the development of delusions is also likely to require altered affective mechanisms and perhaps also alterations in the processing of interoceptive signals (Mega et al., 2000; Shanks & Venneri, 2004; Bruen et al., 2008). Information on the brain processes by which elementary sensory percepts might be built into a complex internal 'model of the world' remain limited. This is particularly true of nonverbal processes, which in general have been much less rigorously studied than language. One important and promising exception to this generalisation is the special case of music, which is a major focus of this thesis for the potential insights it holds into the higher level organisation of nonverbal processing in FTLD.

1.3 Key examples of nonverbal processes in FTLD

The work described in this Thesis addresses three key examples of non-verbal cognitive processing in FTLD: sensory object analysis, focussing on faces and chemosensory stimuli; emotion recognition in different sensory modalities; and the processing of music, a specialised

abstract code which might be considered a nonverbal analogue of language with sensory, affective and cognitive dimensions. Here the evidence concerning brain mechanisms for each of these processes is briefly reviewed.

1.3.1 Face processing

Impaired processing of facial identity is an early and prominent feature in many patients with FTLD: impaired processing of facial identity (Evans et al., 1995; Seeley *et al.*, 2005; Chan et al., 2009), facial emotional expressions (Keane et al., 2002; Rosen et al., 2002b, 2004, 2006a; Lavenu and Pasquier, 2005) and perceptual analysis of faces (Keane et al., 2002; Joubert et al., 2003) have all been described. Progressive prosopagnosia has been associated particularly with right temporal lobe atrophy (Gainotti et al., 2003; Joubert et al., 2004; Josephs et al., 2008; Chan et al., 2009). The neuroanatomy of face processing has been studied extensively both in patients with focal brain lesions (for example, Meadows, 1974; De Renzi, 1986; Landis et al., 1986; Damasio et al., 1990; Barton et al., 2002; Fox et al., 2008; Steeves et al., 2009) and in functional imaging work in healthy subjects (for example, Kanwisher et al., 1997; Haxby et al., 2000; Rossion et al., 2003; Gobbini and Haxby, 2007; Vuilleumier and Pourtois, 2007; Ishai, 2008). It has been proposed that the cortical areas implicated in face recognition are distributed and hierarchically linked: early processing of facial features occurs in the 'occipital face area', dynamic processing of facial movements in the superior temporal sulcus, then abstraction of facial identity in the 'fusiform face area' (FFA) and subsequent higher order processing including biographical, semantic and hedonic associations of faces in more anterior temporal and extra-temporal areas (Gauthier et al., 2000; Haxby et al, 2000; Calder et al., 2007; Gobbini and Haxby, 2007; Ishai, 2008). Anatomically, the frontal and temporal cortical areas affected in

FTLD overlap brain regions implicated in face processing from focal lesion studies and functional imaging work, including the anterior temporal lobes and FFA (Damasio et al., 1990; Kanwisher et al., 1997).

1.3.2 Chemosensory stimuli

As mentioned previously, alterations in food preference, "food faddism" and unusual food combinations are common in SemD, whereas bvFTLD patients exhibit a tendency to eating excessively and indiscriminately. The brain basis for these behaviours is still poorly understood, due in part to the challenges of assessing cortical olfactory and gustatory processing in the laboratory. There is emerging evidence for a hierarchical organisation of flavour processing; projections from the primary olfactory cortex of the uncus pass to the association olfactory cortex of the parahippocampal gyrus and entorhinal area, collectively referred to as the pyriform cortex. The amygdala receives connections from the inferior association cortex (middle and inferior temporal gyri) and projects to the hypothalamus. The medial OFC, which receives input from the pyriform cortex, is implicated in olfactory functions, including olfactory discrimination (Luzzi et al., 2007; Van Hoesen et al., 2000). It would therefore be predicted on cognitive and neuroanatomical grounds that impairments in the processing of odours and flavours would occur in bvFTLD and SemD, with loss of conceptual knowledge of odours and flavours in SemD in the presence of intact detection and discrimination. Indeed, this pattern of impairment has been shown in SemD for both odour (Luzzi et al., 2007; Rami et al., 2007) and flavour identification (Piwnica-Worms et al., 2010). Such impairments in the semantic processing of chemosensory stimuli may well contribute to the development of some of the abnormal eating behaviours described above in patients with SemD; however, the association between semantic

flavour/odour processing and these altered eating behaviours has yet to be fully defined. bvFTLD patients may, in addition, exhibit perceptual deficits as a result of OFC atrophy.

1.3.3 Emotion

There is much evidence to suggest that the neuronal circuitry supporting emotion processing involves limbic structures such as the amygdala and hippocampus as well as paralimbic structures including orbitofrontal and insular cortices (Adolphs et al., 1994; Calder et al., 2001; Cardinal et al., 2002; Rolls 2004). The amygdala has been implicated in processing information about the emotional significance of the environment and in the expression of emotions, through robust pathways with prefrontal, anterior temporal areas, and central autonomic structures as revealed in animal studies (Ghashghaei & Barbas 2002; Barbas 2007), in studies on emotion recognition from lesions in humans (Adolphs et al., 1994; Anderson & Phelps 1998) and also in functional imaging work (Berthoz et al., 2002). There is evidence of laterality within this "emotion circuitry" with right-sided predominance (Anderson et al., 2000; Perry et al., 2001). These structures form part of the proposed neural network involved in the pathology of bvFTLD (Schroeter et al., 2008) thus providing further anatomical support for emotion processing deficits as a brain basis for some of the behavioural features of the disease. The most widely studied and best understood emotional stimulus remains facial expressions. Emotional facial expressions are likely to be processed at least partly in parallel with face identity information by a distinct but partly overlapping brain network including limbic structures in the medial temporal lobes (the amygdala and its connections), insula and orbitofrontal cortex (Phan et al 2002; Murphy et al., 2003; Vuilleumier et al., 2004; Vuilleumier & Pourtois, 2007; Ishai 2008).

1.3.4 Music as a complex multidimensional stimulus

Music is a complex sound, and is thus processed in the ascending auditory pathway to the primary auditory cortex in Heschl's gyrus and the auditory association area in the planum temporale. This involves analysis of its perceptual components including pitch, timbre and temporal structure. However, music is highly valued across human cultures chiefly for the powerful emotional responses it engenders: indeed, music activates brain circuitry associated with pleasure and reward (Blood and Zatorre 2001; Menon and Levitin 2005; Boso et al., 2006; Koelsch et al., 2006; Mitterschiffthaler et al., 2007) and musical emotion judgments are consistent amongst members of a musical culture (Peretz et al., 1998). This has been further supported by a recent PET imaging study showing endogenous dopamine release in the striatal system at peak emotional arousal in response to music listening (Salimpoor et al., 2011). Despite much recent interest in the neurobiology of music, the brain mechanisms that are critical for processing emotion in music remain poorly understood. The processing of musical emotion is likely to involve brain mechanisms that are partly shared with mechanisms that process other emotional stimuli, instantiated in limbic structures, orbitofrontal cortex (OFC) and insula (Adolphs et al 1994; Anderson et al., 2000; Calder et al., 2001; Cardinal et al., 2002; Griffiths et al., 2004; Rolls, 2004). However, it is also likely that understanding of the emotional content of music depends on brain mechanisms that abstract affective information from the analysis of inanimate signals that are qualitatively different from the signals that carry information in other emotional modalities (and in non-human species). Neural mechanisms of musical emotion therefore have potentially far-reaching implications for understanding how the brain codes affective value, and how affective signals acquire meaning. The brain basis of music emotion

processing has been studied using functional imaging techniques in healthy subjects (e.g., Blood and Zatorre 2001; Koelsch et al., 2006), but not in degenerative disease.

Music is an abstract, complex, rule-based non-verbal code, and is arguably a distinct domain of knowledge. The investigation of music knowledge provides an opportunity to elucidate brain processes that mediate nonverbal knowledge and a unique model for assessing the extent to which the cognitive organisation of nonverbal knowledge may mirror language. It may be that one aspect behind the alterations in interpersonal behaviour and impaired social skills in FTLD arise from difficulties in abstracting information from non-verbal social signals. Although preserved musical abilities in domains such as memory and recognition have been reported in patients with dementia, there has yet been a systematic study of the cognitive organisation of music knowledge in FTLD. Anatomically, the distributed brain networks affected in FTLD are likely to be critical for music processing (Platel et al, 2003; Satoh et al., 2006; Stewart et al., 2006; Warren, 2008).

1.4 Experimental objectives of the Thesis

The previous sections have set out the challenges faced by clinicians in the diagnosis of early FTLD and the distinct yet overlapping behavioural features in the FTLD syndromes. Many of these abnormal behaviours may be explained by alterations or impairments in the processing of non-verbal signals. Much of 20th-century neuropsychology has focused on understanding verbal deficits in focal neurodegenerative disease, including FTLD, however the cognitive organisation and brain basis for nonverbal functions are less well established. The key aims of this Thesis are

to highlight the importance of studying how the processing of signals from particular nonverbal sensory modalities is affected in FTLD, to further understand how these changes/deficits may account for some of the behavioural abnormalities which characterise the FTLD syndromes, and to identify key brain mechanisms underlying the cognitive processing of these nonverbal signals.

The general hypotheses of this Thesis are that:

1. FTLD patients are impaired in their ability to perform the various nonverbal cognitive tasks investigated in this Thesis compared to healthy age-matched controls.

2. Performance on tasks indexing different nonverbal cognitive functions would correlate with distinct neuroanatomical substrates, and that these substrates would comprise distributed cerebral networks.

1.4.1 Experiment 1: Face processing in FTLD

Are there distinct patterns of deficits in the cognitive operations underlying face processing in FTLD? Do these deficits associate with distinct areas of cortical atrophy?

Neurodegenerative diseases characteristically affect cerebral networks (Seeley et al., 2009), making precise anatomical correlation more difficult but also providing the opportunity to delineate distributed cortical systems that may be critical for certain cognitive operations (Rosen et al., 2006). This network perspective is likely to be particularly relevant to face processing (Landis *et al.* 1986; Evans *et al.* 1995; Haxby *et al.* 2000; Barton *et al.* 2002; Rossion *et al.* 2003; Fox *et al.* 2008). It is understood that the processing of faces involves various cognitive operations including perceptual analysis, semantic and affective processing, and that these operations are neuropsychologically dissociable in a modular neural framework (Bruce & Young

1986; De Renzi et al., 1991; Gobbini & Haxby 2007). There is a considerable body of work studying the neuroanatomy of face processing in patients with focal brain lesions as well as functional imaging work in healthy subjects. It has been proposed that the cortical areas implicated in face recognition are distributed and hierarchically linked (Gobbini & Haxby 2007). However, the effects on face processing in neurodegenerative disease are less well established. It is known that impaired face processing is an early and prominent feature in FTLD. The damage to cerebral networks in FTLD, as in other neurodegenerative conditions, provides an opportunity to delineate distributed cortical systems that may be critical for certain cognitive operations in face processing.

1.4.2 Experiment 2: Chemosensory processing in FTLD

How is chemosensory knowledge affected in FTLD? Are distinct brain mechanisms involved in the processing of information from odours and flavours?

The cognitive mechanisms underlying the processing of chemosensory information are not clearly understood. Defects of olfactory processing have been shown in FTLD (Rami et al., 2007; Luzzi et al., 2007), and it has been suggested recently that flavour knowledge is impaired in SemD (Piwnica-Worms et al., 2010), however there has yet to be a systematic group study examining the domains of odour and flavour knowledge in FTLD. Alterations in eating behaviour and food preference are common in the FTLD syndromes, yet the brain basis for these behaviours is not well defined, nor is it clear what contributions altered associative knowledge of odour and flavour processing may have.

1.4.3 Experiment 3: Music emotion processing in FTLD

How is the processing of emotion in music affected in FTLD compared to affective processing in other modalities? What does FTLD tell us about the neural correlates of emotion processing? Are distinct brain mechanisms involved in the processing of emotion in different sensory modalities?

Music engenders powerful emotional responses and activates brain circuitry associated with pleasure and reward (Blood and Zatorre 2001; Menon and Levitin 2005; Boso *et al.,* 2006; Koelsch *et al.,* 2006; Mitterschiffthaler et al., 2007). Despite much recent interest in the neurobiology of music, the brain mechanisms that are critical for processing emotion in music remain poorly understood. The processing of musical emotion is likely to involve brain mechanisms that are partly shared with mechanisms that process other emotional stimuli (Adolphs *et al* 1994; Anderson *et al.,* 2000; Calder *et al.,* 2001; Cardinal *et al.,* 2002; Griffiths et al., 2004; Rolls, 2004). FTLD is associated with dysfunction in distributed brain networks including those implicated in both music and emotion processing (Seeley et al., 2009; Schroeter *et al.,* 2008). It is hypothesised that emotion recognition in music, by virtue of its abstract nature, is neuropsychologically relatively more vulnerable in FTLD than other emotion modalities to the effects of damage involving distributed brain circuitry for representing and evaluating the affective content of stimuli. A further hypothesis is that this neuropsychological deficit of musical emotion recognition has a neuroanatomical substrate in the brain network previously implicated in the processing of affective stimuli, including limbic structures, insula and OFC.

1.4.4 Experiment 4: Music knowledge in dementias

How is an abstract non-verbal domain of knowledge, as indexed by music, affected in FTLD? Are distinct brain mechanisms involved in the encoding and processing of musical 'meaning'?

Assessment of musical semantic knowledge is especially challenging in patients with dementia. This reflects the intrinsic difficulty of assessing musical semantic memory compounded by the challenges of working with cognitively impaired subjects, particularly those with significant executive or aphasic deficits. In this chapter, the cognitive organization of music knowledge is studied systematically in expert musicians with SemD and DLB, in comparison with healthy expert musician controls. The extent of musical deficits or areas of retained musical competence is characterized using a series of novel neuropsychological tests investigating various components of associative musical knowledge that are specifically designed to minimise dependence on sustained attention, working memory, or verbal responses (e.g., naming).

CHAPTER 2 METHODS AND TECHNIQUES

Summary

The experiments described in this Thesis rest chiefly on two main techniques: the neuropsychological characterisation of behavioural deficits, and the morphometric characterisation of regional brain atrophy associated with these deficits. VBM is one of the most widely used automatic computational neuroanatomy techniques in studying patterns of brain atrophy in neurodegenerative disease and brain-behaviour correlates. This chapter firstly outlines the conduct of the group study including subject recruitment, clinical and standard neuropsychological assessment, followed by the principles and challenges of designing neuropsychological tests particularly in the assessment of FTLD patients with severe verbal impairments. The basic principles of VBM are outlined and the VBM methodology applied to these experiments described. The chapter concludes with a discussion of strategies adopted to facilitate brain morphometry in the presence of focal atrophy.

2.1 Structure and conduct of group study

The work in this thesis was supported by a cohort study of non-Alzheimer dementia, which began in November 2005 and is ongoing. This is a prospective longitudinal study of clinical, behavioural and neuropsychological assessments and volumetric imaging in the FTLD syndromes. Assessments for each subject were carried out at annual intervals. At each assessment timepoint, the same assessment procedures were administered including a clinical assessment with medical history and neurological examination, volumetric brain MR imaging and a standard battery of neuropsychological tests.

All studies in this thesis were carried out at the Dementia Research Centre, Institute of Neurology, University College London (UCL), and approved by the National Hospital for Neurology and Neurosurgery & Institute of Neurology Joint Research Ethics Committee. All human experiments were carried out in accordance with the declaration of Helsinki. All subjects gave informed, written consent to participate. In accordance with the Mental Capacity Act (2005) patients lacking capacity were not recruited. Study data were stored electronically on the Dementia Research Centre secure server. Personal information is protected in accordance with UCLH NHS Trust Information Governance policy and the handling, processing and storage of data were conducted in accordance with the Data Protection Act (1998).

2.2 Subject recruitment

Volunteers for the study were recruited from a tertiary cognitive disorders clinic at the National Hospital for Neurology and Neurosurgery. Individuals fulfilling the consensus criteria for a clinical diagnosis of FTLD (Neary et al., 1998) were recruited. The clinical diagnosis was correlated by volumetric T1 MR brain imaging in most cases. Healthy volunteers were also recruited as age- and gender-matched control subjects from an in-house database.

2.2.1 Disposition of subjects

A total of 63 FTLD subjects participated in the study. The patient cohort comprised three canonical FTLD subtypes: 31 patients had bvFTLD, characterised by profound personality and behavioural change with frontal and temporal lobe atrophy on brain MRI; 21 patients had SemD, characterised by breakdown of verbal and nonverbal knowledge systems with asymmetric, predominantly left-sided temporal lobe atrophy on MRI; and 11 patients had PNFA based on the

presence of speech apraxia and/or agrammatism and relatively intact single word comprehension. Of these patients, 32 participated in Experiment 1, 25 participated in Experiment 2, and 26 participated in Experiment 3. There was some degree of overlap between the patients who participated in these individual experiments, with 2 patients participating across the three experiments, 14 patients participating in both Experiments 1 and 3, and another 2 patients participating in both Experiments 2 and 3 (Table 2.1). In the case of Experiment 4, which was a study involving 2 expert musicians with neurodegenerative dementias, SemD and dementia with Lewy bodies (DLB) respectively, the same SemD case also participated in Experiment 3.

Table 2.1 Disposition of patients across experiments

	Number of patients
Experiment 1 only	16
Experiment 2 only	21
Experiment 3 only	8
Experiment 1 + 2 only	0
Experiment 2 + 3 only	2
Experiment 1 + 3 only	14
Experiment 1, 2 + 3	2
Total	63

2.3 Assessment procedures

All participants underwent the same assessment procedures. In order to allow sufficient time to complete all the behavioural and cognitive tests whilst avoiding stress or fatigue, subjects were offered the option of spreading each annual assessment over two visits if they wished. This allowed subjects to comfortably complete all required tests with allowances for adequate breaks, taking into account the cognitive and behavioural limitations expected in this cohort of patients.

Affected subjects were required to attend each visit with an informant, ie a person with close knowledge of the subject's symptoms, behaviour and personality. In most cases the informant was a spouse or first-degree relative who had known the subject well for at least ten years.

2.3.1 Neurological history and examination

Standard medical history and neurological examination were carried out in accordance with the MRC guidelines on dementia studies (MRC 1987). A collateral history of the subject's symptoms was also obtained from the informant. All subjects completed the Mini-Mental State Examination (Folstein et al., 1975), a screening general cognitive instrument, as an index of disease severity. In addition, an informant was required to complete questionnaires assessing the affected subject's behavioural and personality changes, using the Neuropsychiatric Inventory (NPI) and Cambridge Behavioural Inventory (CBI). The battery was designed to be completed within 2 hours and to minimise demands on concentration and attention. Both the NPI and CBI are designed to measure a wide range of behavioural and neuropsychiatric disturbances in dementia, including delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irratibility/lability, apathy, aberrant motor activity and changes in eating habits,

and have been shown to be reliable informant-based assessment tools of neuropsychiatric symptoms and everyday function particularly in frontal systems disruption (Malloy & Grace, 2005; Nagahama et al., 2006). In addition, a novel questionnaire of general nonverbal functions which aims to comprehensively assess any symptoms relating to visual (particularly face recognition), auditory, olfactory, gustatory, tactile (including pain and temperature) function (The non-verbal symptom questionnaire, see Appendix A1). However, whilst there is little doubt that behavioural rating scales are important tools in the measurement of complex behavioural syndromes and their application is now widespread in clinical trials, they do present fundamental measurement issues; it is difficult to include in one scale the measurement of discrete, episodic behaviour that is present on a daily basis (for example, lack of motivation) and some rare but highly salient disruptive behaviours may not lend themselves to easy measurement (such as Capgras delusions) (Malloy & Grace, 2005).

2.3.2 Standard neuropsychology battery

A standardised neuropsychology battery was used as a comprehensive screening tool evaluating the main cognitive domains of general intellectual function, word retrieval and comprehension, visual and verbal memory, reading, writing, calculation, visuoperceptual function, face processing, frontal lobe functions including executive skills, as well as theory of mind (Table 2.2). This standard neuropsychological battery was utilised throughout the experiments described in Chapters 3, 5 and 6. A modified battery was adopted for the experiment in Chapter 4, which will be detailed within the chapter.

Table 2.2 Standard neuropsychological tests.

General intellectual function	Ravens advanced matrices [a]
Memory	Camden pictorial memory test [b]
	Recognition Memory words [b]
	Recognition Memory faces [b]
	Verbal paired associate learning [b]
Language	Word repetition
	Picture naming
	Word-picture matching
	Irregular word reading
	Synonyms test (concrete) [c]
Executive function	Trail making test A [d]
	Trail making test B [d]
Visuospatial and visuoperceptual skills	VOSP object decision [e]
	Dot counting
Face processing	Famous faces naming [f]
	Benton Facial Recognition [g]
	Ekman facial emotion recognition test [h]
Theory of Mind	Reading the Mind in the Eyes [i]
Other skills	Digit span [j]
	Graded difficulty arithmetic test [k]

[a]Raven et al., 2003; [b]Warrington 1996; [c]Warrington et al., 1998; [d]Reitan, 1959; [e]Warrington & James, 1991; [f]Warrington & James, 1967; [g] Benton AL et al., Oxford University Press, 1983; [h] Ekman & Friesen, 1976; [i] Baron-Cohen et al., J Child Psychiatry 2001; [j]WAIS-R; [k]Jackson & Warrington, 1986;

2.4 Novel neuropsychology tests

One of the main aims of the thesis is to address the lack of available neuropsychological tests specifically assessing nonverbal sensory functions. The poverty of assessment tools may partly be due to the challenges in designing tests which adequately probe nonverbal abilities with minimal demand on verbal and other cognitive skills (in order that the test is a purer measure of the nonverbal modality of interest). Given the cognitive and behavioural impairments in our population of subjects, one consideration in designing these novel tests is to reduce the load placed on executive control by the need to coordinate cross-modality tasks and to minimise interference from 'goal-irrelevant' distractors in other modalities (Brand-D'Abrescia & Lavie, 2008). This problem is particularly relevant to tasks which require objects with a temporal pattern of delivery such as complex sounds and music, where the test stimuli need to be maintained in working memory. Another challenge is to formulate tests which can be administered meaningfully to patients with severe language difficulties (eg. with speech production in the case of PNFA and with language comprehension in the case of SemD) so as to limit the potentially confounding effects of verbal labelling. Previous studies examining nonverbal cognition have either tended to rely upon tasks that require verbal input (eg. word-to-picture matching) or output (eg. overt picture naming tasks), whilst attempts to produce nonverbal assessment tasks often required other cross-modality matching abilities, such as matching a sound to a picture of the target item or concept (Bozeat et al., 2000a).

Many of the experiments in this thesis utilise a combination of nonverbal within-modality matching tasks and cross-modality matching tasks. To minimise confounds from impairments in other cognitive domains including working memory and attention, simple response criteria were

utilised such as a two-choice "same/different/" or "yes/no" answer, and forced choice procedures for multiple choice cross-modality tasks. For the novel tests described in Chapters 4, 5 and 6 (which examined chemosensory identification, emotion recognition and music knowledge respectively) stimuli were presented and subject responses were recorded using MATLAB 7.0® (http://www.mathworks.com) on a notebook computer. Auditory stimuli were presented as digital wavefiles on a notebook computer in free field at a comfortable listening level (typically at least SPL 70dB) in a quiet room. Visual stimuli were presented and subject responses were collected for off-line analysis in Cogent 2000 (www.vislab.ucl.ac.uk/Cogent2000) running under MATLAB 7.0®. In general, experimental subtests were presented in block design, with a fixed number of trials presented in a fixed randomised order within each subtest (chapters 3 – 6). Responses on each trial generally were made according to a forced choice procedure with between 2 and 4 alternatives (for example, which of four target emotions was best represented by the music stimulus in chapter 5). The words and/or pictures corresponding to the choices were simultaneously displayed on the computer monitor and the choices were also read aloud by the examiner to the subject on each trial. Subjects were given practice trials before the start of each subtest to ensure the task was understood; no feedback about performance was given during a test. No time limit was imposed, and after the initial experience of the stimulus (eg listening to sound/music in chapter 5, sniffing an odour and tasting a flavour in chapter 4) subjects were given the opportunity to repeat the stimulus experience once more if required before providing a response. Subject responses were stored for off-line analysis. Further details of individual tests will be described in the experiment chapters 3 - 6.

2.5 Statistical analysis of behavioural data

Statistical analyses were performed using Stata© software version 9. The general statistical approach was to analyse the following:

1. Group differences in the mean scores on individual behavioural and neuropsychological tests of interest between disease and control, and between disease subgroups.
2. Associations between particular neuropsychological test scores and group membership, taking into consideration potential nuisance covariates such as age, gender and level of education.
3. Associations between one neuropsychological test score and another behavioural or psychological score.

In chapters 3 and 4, linear regression models (incorporating age and gender as nuisance covariates) were used to assess group differences and within-group correlations in performance between psychology tests. To assess the extent to which psychology test scores were independently useful in differentiating between patient subgroups and controls, these variables were each related in turn to group status while adjusting for the nuisance covariates. Robust standard errors were used in these models to allow for differential heterogeneity between groups. For chapter 5, logistic regression models were fitted containing main effects and group interactions in order to assess emotion recognition scores across different modalities. Logistic regression is of particular value in the prediction of a discrete outcome, such as group membership, from a set of variables that may be continuous, discrete, dichotomous, or a mix of any of these. The logistic function is useful because it can take an input of any value from

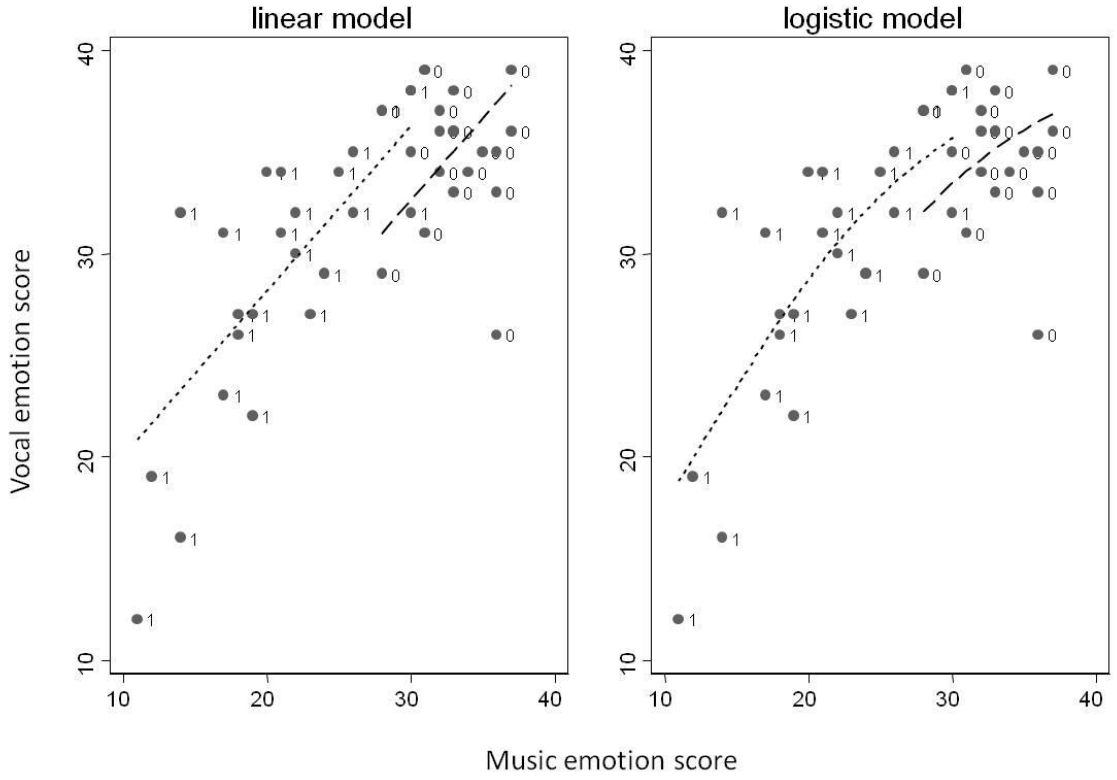
negative infinity to positive infinity, and confine the output to values between 0 and 1. The relationship between the predictor and response variables is not a linear function unlike in linear regression, but the logit transformation of a probability of success. The formula of a logistic curve relating the independent variable *X* to the rolling mean of the dependent variable *P* can be represented as:

$$P = \frac{e^{a+bX}}{1 + e^{a+bX}}$$

where *P* is the probability of a value 1, *e* the base of the natural logarithm, and *a* and *b* the parameters of the model. The value of *a* yields *P* when *X* is zero, and *b* adjusts the rate by which the probability changes with a single unit change in *X*. The logistic formula thus produces a sigmoidal curve rather than a linear one.

This is useful when relating scores on a particular psychology test to group membership whilst adjusting for multiple other test scores as it makes no assumption about the distribution of the independent variables, ie the independent or predictor variables can take any form and do not have to be normally distributed, linearly related or of equal variance within each group. In the case of the experiment in chapter 5, the interest was in emotion recognition scores across three different modalities and the extent to which they were each independently useful in predicting group membership whilst adjusting for the other test scores. The logistic regression model is appropriate in this situation as it does not assume a linear relationship between emotion recognition scores for the different modalities (Figure 2.1).

Figure 2.1 Comparison of logistic and linear regression models relating vocal emotion recognition scores to group adjusting for music emotion recognition score, illustrating how the logistic model is more representative of the data than the linear model. In the logistic model, which does not allow scores to exceed the maximum of 40, the fitted lines are more closely approximated than in the linear model.



2.6 Brain image acquisition

For the experiments described in Chapters 3, 5 and 6, MR brain imaging was performed on a 1.5T GE Signa scanner (General Electric, Milwaukee, WI). The scanning protocol involved volumetric imaging using an inversion recovery-prepared fast Spoiled Gradient Echo acquisition (echo time = 5ms, repetition time = 12ms, inversion time = 650ms). T1-weighted volumetric

images were obtained with a 24cm field of view and 256 x 256 matrix to yield 124 contiguous 1.5mm-thick slices in the coronal plane.

For the experiment described in Chapter 4, MR images were acquired on a Siemens Trio TIM 3T scanner (Siemens Medical Systems). T_1-weighted volumetric magnetic resonance images were acquired using a 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence producing 208 contiguous 1.1 mm thick sagittal slices with 28 cm field of view and a 256 × 256 acquisition matrix, giving approximately isotropic 1.1 mm cubic voxels.

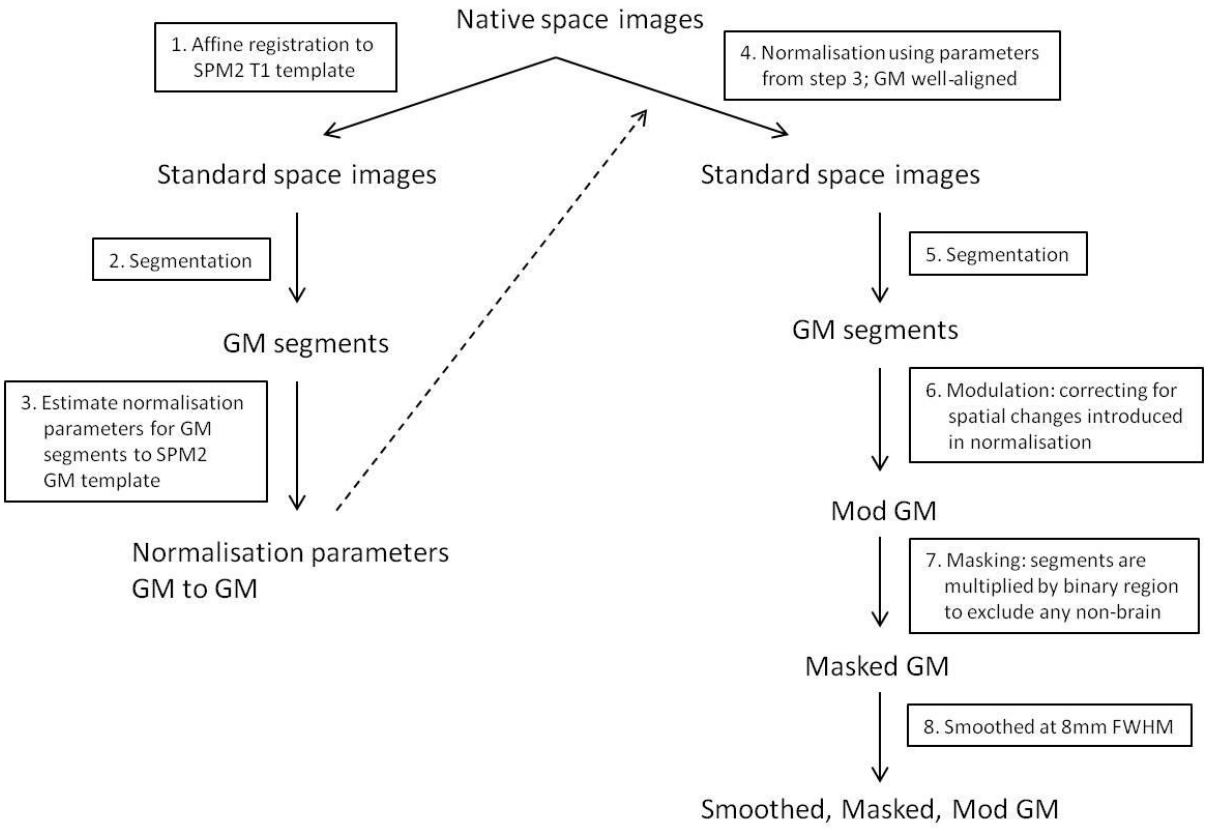
2.7 Voxel-based morphometry

Over the past two decades, VBM (Ashburner & Friston, 2000) has become an increasingly widely used tool in assessing neuroanatomical correlates of cognitive and behavioural, and is now widely used in the study of neurodegenerative disease. VBM is a computational neuroimaging technique which allows analysis of structural MRI scans to investigate differences in morphology (tissue density) between groups, for example, focal loss of grey matter density in a disease population compared to controls. In this Thesis the key objective of VBM is to analyse every voxel within the MR image to determine significant correlations between grey matter and neuropsychological score, using t-tests with appropriate corrections for multiple comparisons. In general, VBM requires extensive pre-processing of raw MR brain images prior to analysis. The key steps are spatial normalisation of images to the same stereotactic space, segmentation of grey matter from the normalised images and spatial smoothing of the grey matter segments. Voxel-wise statistical tests (mass-univariate parametric general linear model analyses) are performed on the smoothed grey matter images.

2.7.1 Image pre-processing

For the work in this Thesis, brain images are processed using MATLAB 7.0® (www.mathworks.co.uk) and SPM2 (Wellcome Department of Cognitive Neurology, ION, London). Image pre-processing was carried out using a modified in-house algorithm (Henley et al., 2008; Gaser, http://dbm.neuro.uni-jena.de/vbm/) as summarised in Figure 2.2.

Figure 2.2 VBM pre-processing algorithm



2.7.1.1 Spatial normalisation

Spatial normalisation involves transforming all raw MR image data to the same stereotactic space by registering each image to the same template image. The native space study images were affine-registered using the standard SPM2 T1 template, and initial grey matter segmentation was performed. Normalisation parameters were estimated for warping these grey matter segments onto the SPM2 grey matter template, and these normalisation parameters were then used to warp the original native space images.

2.7.1.2 Grey matter segmentation and modulation

Following normalisation, the study images underwent segmentation into grey matter, white matter and CSF. Grey matter segmentations were modulated with volume changes from the normalisation procedure. Modulation corrects for any changes in volume that occur as a result of the normalisation procedure, such as smaller brains being stretched to match larger brains thus minimising disease effect. Intensities within the segmented images are multiplied by the Jacobian values (a measure of volume change from normalisation), so that the intensities represent relative volume. As the primary interest was in grey matter changes, the white matter and CSF segments were not used in any further analyses in the experiments detailed in this Thesis.

2.7.1.3 Masking

Each grey matter segment then underwent masking, which essentially removes non-brain voxels by multiplying by a binary brain mask. Each brain mask was derived from the corresponding

original image using a semi-automated segmentation software, MIDAS (Freeborough et al., 1997).

2.7.1.4 Smoothing

Smoothing the images allows data to be more normally distributed, which is required for the VBM assumptions to be valid and also reduces the effect of misregistration. The images in this work were smoothed using an 8mm full-width-at-half-maximum Gaussian kernel.

2.7.2 Statistical analysis

Statistical parametric mapping (SPM) analysis was performed in each experiment using linear regression models to examine correlations between psychological scores and grey matter intensity. Voxel intensity, V, was modelled as a function of score in each test with, as a minimum, subject age and total intracranial volume (TIV) included as nuisance covariates in each experiment. The particular model used in each of the experiments described in this Thesis is shown in the relevant chapter. Whole brain volumetric measurement was performed using a rapid, semi-automated technique of brain segmentation was performed for each scan using the MIDAS software package (Freeborough et al., 1997). This involved interactive selection of thresholds, followed by a series of erosions and dilations, and yielded a brain region which was separated from the surrounding cerebrospinal fluid, skull and dura. This provided a whole brain volume measurement in millilitres.

2.7.3 Issues in applying voxel-based-morphometry to the study of frontotemporal lobar degeneration

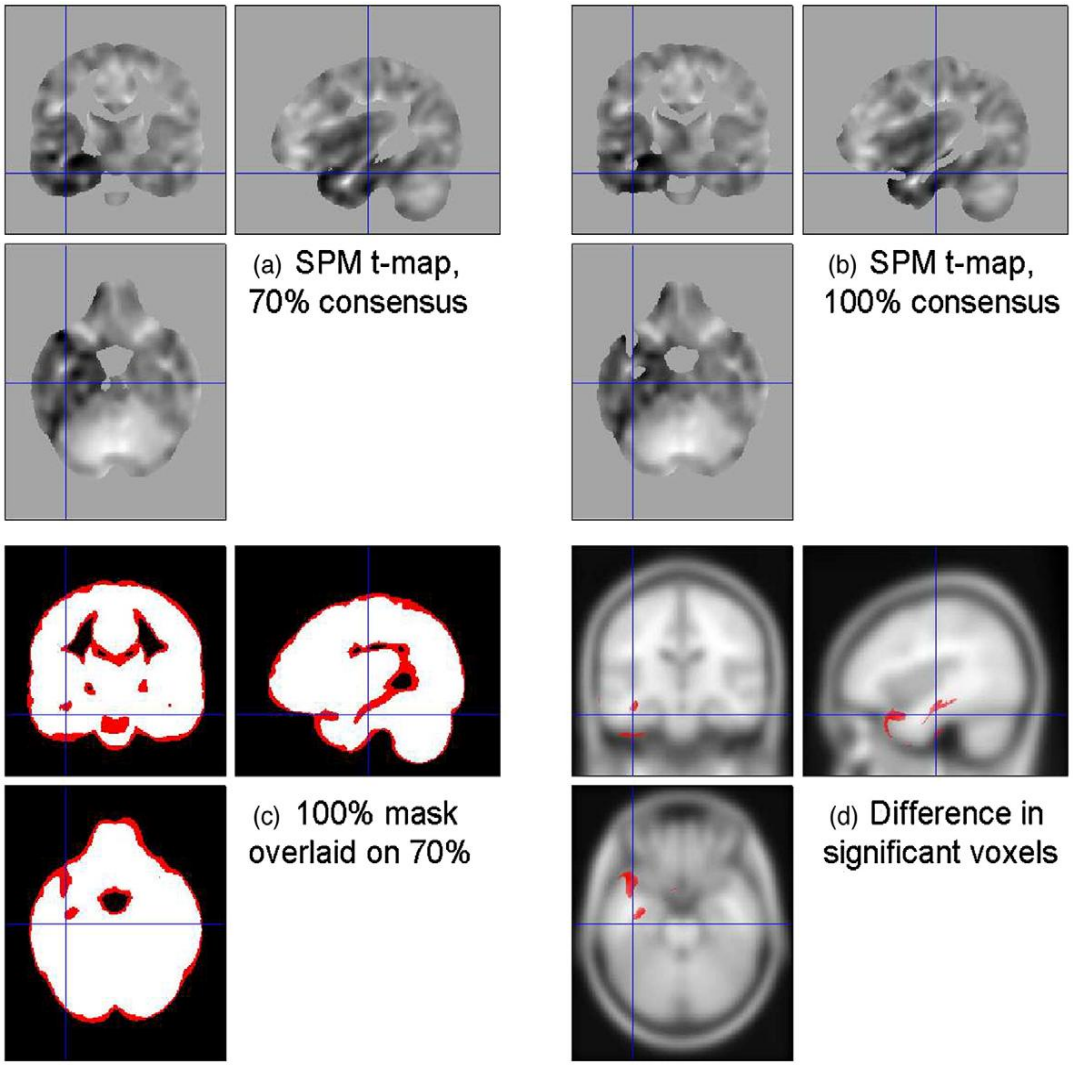
One of the key issues encountered during the VBM analysis concerned threshold masking. Masking is necessary for several reasons, one of which is that whole-brain family-wise error (FWE) correction using random field theory (RFT) is more powerful for smaller regions of analysis. For false-discovery rate (FDR) correction, masking removes non-brain voxels from the analysis which may otherwise result in skewed p-value distribution as well as implausible false positives outside the brain (Genovese et al., 2002). Negotiating the fine balance between an overly inclusive mask which may compromise statistical power and sensitivity, and an overly restrictive mask which carries a greater risk of false negatives, can be a particular problem when analysing pathological brains with areas of sometimes marked focal atrophy, as is the case with FTLD (Ridgway et al., 2009). Hence the potential problem of using a commonly employed standard approach with mask generation which appears reasonable a priori, for example the one used as a default by SPM.

In order to address the issue of overly restrictive masks excluding potentially relevant findings in the most atrophied structures, an analysis was carried out comparing two masking strategies on patients with FTLD. A group of 14 FTD patients (M:F 7:7, mean age 63.5) with pronounced, focal temporal lobe atrophy was compared to an age- and gender-matched control group (M:F 10:12, mean age 65.8), using both the standard SPM masking strategy which employed an absolute threshold of 0.05 (ie requiring 100% of subject images to exceed a threshold of 0.05), and a new consensus masking strategy whereby any voxels >30% of subjects' images had intensity value <0.05 (ie consensus 70%, threshold 0.05).

The VBM comparison of FTD patients with healthy controls reveals a pattern of tissue loss with focal left temporal lobe atrophy. Unthresholded SPM t-maps are shown in Figures 2.3 (a) and (b). It was found that the 100% consensus mask excluded tissue in the temporal lobes, particularly on the left, as shown in Figure 2.3 (c) where the two masks used for these analyses are overlaid. The difference in volume of these two masks was over 300 ml. Most importantly, (d) showed that some of the statistically significant voxels (pFWE<0.05) found when using the less stringent mask would have been ignored in the analysis using the standard 100% consensus mask. This lost significant volume amounts to 8.19 ml, or over 1000 2 mm isotropic voxels, in exactly the areas that these FTLD brains were most atrophied.

These findings show that SPM2® default threshold masking may exclude the most severely affected regions from statistical analysis in subjects with marked focal atrophy. As a result, the novel consensus masking strategy is employed in the experiments in this thesis. After model estimation an explicit mask is applied using a masking strategy that excluded any voxels for which >30% of images has intensity value <0.05 (i.e., consensus 70%, threshold 0.05).

Figure 2.3 Masks and regions of significance (pFWE<0.05) for the comparison of FTLD subjects with controls.



(a) and (b) show t-values for masking requiring either 70% (a) or 100% (b) of images to exceed a threshold of 0.05 (the latter corresponding to SPM's default strategy). (c) overlays the 100% mask on the 70% one. (d) overlaid on the group average segmentation is the region of significance present when using the 70% mask which is excluded from the analysis with the default SPM masking strategy.

Chapter 3: FACE PROCESSING IN FRONTOTEMPORAL LOBAR DEGENERATION

Summary

Face processing is a complex multi-component cognitive task that is vulnerable in FTLD. This chapter describes a systematic prospective study of the structural neuroanatomy of face processing in FTLD. Neuropsychological measures of face perception identification and emotion recognition were correlated with grey matter on brain MRI using VBM in a cohort of 32 FTLD patients. The cognitive components of face processing correlated with distinct but partly overlapping brain networks. Performance on a test of perceptual analysis (face matching) correlated with grey matter in an extensive fronto-parietal network. Face identification performance correlated with grey matter in bilateral inferior temporal cortices, including the fusiform face area and more anterior areas. Facial emotion recognition correlated with grey matter in widespread parietal, temporal, inferior frontal and limbic areas, and recognition of individual negative emotions had partially separable grey matter signatures, including most saliently the insula for recognition of anger. This study provides a neuroanatomical framework for understanding face processing deficits in neurodegenerative disease (specifically, FTLD) that is in accord with the modular neural architecture of face processing proposed in contemporary cognitive models. The breakdown of distributed neural networks in FTLD provides a neuroanatomical perspective that is complementary to normal functional imaging and focal lesion work, with implications for our understanding of face processing in health as well as disease.

3.1 Background

The brain mechanisms that analyse and identify human faces are of great clinical and neurobiological interest. Processing of faces involves a number of cognitive operations including perceptual analysis (encoding of facial features and configurations), semantic and mnestic processing (identifying or recollecting the individual) and affective processing (recognition of emotional expression). Selective deficits of processing facial perceptual features, facial identity (prosopagnosia) and facial expressions have been described, indicating that these operations are neuropsychologically dissociable and influencing cognitive organisational models of face processing (Bruce & Young, 1986, De Renzi et al., 1991; Haxby et al., 2000; Gobbini & Haxby, 2007; Ishai, 2008; Steeves et al., 2009). The neuroanatomy of face processing has been studied extensively both in patients with focal brain lesions (for example, Meadows, 1974; De Renzi, 1986; Landis et al., 1986; Damasio et al., 1990; Barton et al., 2002; Fox et al., 2008; Steeves et al., 2009) and in a large body of functional imaging work in healthy subjects (for example, Kanwisher et al., 1997; Haxby et al., 2000; Rossion et al., 2003; Gobbini & Haxby, 2007; Vuilleumier & Pourtois, 2007; Ishai, 2008). However, the effects on face processing of neurodegenerative disease are less well established.

It has been proposed that the cortical areas implicated in face recognition are distributed and hierarchically linked: early processing of facial features occurs in the 'occipital face area' (OFA) and dynamic processing of facial movements in the superior temporal sulcus followed by abstraction of facial identity in the 'fusiform face area' (FFA) and subsequent higher order processing including biographical, semantic and hedonic associations of faces in more anterior temporal and extra-temporal areas (Gauthier et al. 2000; Haxby et al, 2000; Calder et al., 2007;

Gobbini & Haxby, 2007; Ishai, 2008). Emotional facial expressions are likely to be processed at least partly in parallel with identity information by a distinct but partly overlapping brain network including limbic structures in the medial temporal lobes (the amygdala and its connections), insula and orbitofrontal cortex (Phan et al 2002; Murphy et al., 2003; Vuilleumier et al., 2004; Vuilleumier & Pourtois, 2007; Ishai 2008); there may be specific substrates for processing particular facial emotions. Neurodegenerative diseases can potentially provide a perspective on the neuroanatomy of face processing that is complementary to focal lesion and normal functional imaging studies: whereas focal lesions illustrate the effects of damage at a critical node of the face processing network, and functional imaging studies identify areas recruited by face processing tasks that may or may not be integral to the network, neurodegenerative diseases illustrate the effects of distributed network-level brain damage.

Impaired face processing is a prominent feature in many patients with FTLD: impaired processing of facial identity (Evans et al., 1995; Seeley et al. 2005; Chan et al., 2009), facial emotional expressions (Keane et al. 2002; Rosen et al., 2002b, 2004, 2006; Lavenu & Pasquier 2005) and perceptual analysis of faces (Keane et al 2002; Joubert et al. 2003) have all been described. Anatomically, the frontal and temporal cortical areas affected in FTLD overlap brain regions implicated in face processing from focal lesion studies and functional imaging work, including the anterior temporal lobes and FFA (Damasio et al. 1990; Kanwisher et al. 1997). Progressive prosopagnosia has been associated particularly with right temporal lobe atrophy (Gainotti et al. 2003; Joubert et al. 2004; Josephs et al., 2008; Chan et al. 2009). Patients with FTLD commonly have difficulty interpreting social and emotional signals from faces, particularly where the disease involves antero-mesial temporal, inferior frontal and insular cortices previously implicated in the analysis of facial emotion in healthy subjects (Keane et al.

2002; Rosen et al., 2002b, 2004, 2006; Lavenu & Pasquier, 2005; Lough et al., 2006). Taken together, this evidence suggests FTLD as a promising disease model for investigating cerebral correlates of deficits affecting the range of cognitive operations that support face analysis.

3.2 Experimental hypotheses

In this experiment the structural neuroanatomical correlates of facial perceptual analysis, face identification and recognition of facial emotions were investigated using voxel based morphometry (VBM) in a cohort of patients with FTLD. Based on previous work in cases of prosopagnosia and healthy subjects, it was hypothesised that performance on tasks indexing these different aspects of face processing would correlate with distinct neuroanatomical substrates, and that these substrates would comprise distributed cerebral networks. More specifically, the hypothesis was that identification and perceptual analysis of faces would correlate with grey matter in inferior temporal regions (Meadows, 1974; De Renzi, 1986; Damasio et al. 1990; Kanwisher et al. 1997; Gobbini & Haxby, 2007), and processing of facial emotions with grey matter in temporal, inferior frontal and insula cortices (Phan et al 2002; Murphy et al., 2003; Vuilleumier et al., 2004; Vuilleumier & Pourtois, 2007; Ishai 2008).

3.3 Methods

3.3.1 Subjects

32 patients fulfilling consensus clinical criteria for FTLD (Neary et al., 1998; McKhann et al 2001) were studied. All subjects underwent volumetric brain MR imaging. 19 subjects were classified as having frontal-variant FTLD (fv-FTLD) based on the presence of predominant frontal atrophy on visual inspection of the MRI and 13 as having temporal-variant FTLD (tv-

FTLD) based on the presence of predominantly (left or right) temporal lobe atrophy on visual inspection of the MRI. This anatomical classification was used because, whereas behavioural abnormalities are frequently a leading clinical feature in association with right temporal or frontal lobe atrophy, prosopagnosia more commonly accompanies temporal lobe atrophy, especially right-sided (Josephs et al., 2008), while emotion deficits are more prominent in association with frontal atrophy (Rosen et al., 2004). In this study, subjects with fv-FTLD had a clinical syndrome of behavioural disturbance (Neary et al., 1998), while subjects with tv-FTD had a clinical syndrome of semantic dementia with impaired single word comprehension if atrophy was predominantly left-sided or behavioural disturbance if atrophy was predominantly right-sided (Seeley et al., 2005). Only one patient (with predominantly right-sided temporal lobe atrophy) had prosopagnosia as a clinical symptom. Subject characteristics are summarised in Table 3.1. 23 healthy age-matched control subjects also participated.

Table 3.1. Summary of subject characteristics and behavioural data.

		fv-FTLD n = 19	tv-FTLD n = 13	Controls n = 23
Demographic data				
Gender M:F		15:4	6:7	11:12
Handedness R:L		17:2	12:1	n/a
Age		66.7 (8.7)	63.5 (8.8)	66.2 (8.1)
Behavioural data				
MMSE		27.3 (3.0)	24.1 (3.7)	n/a
Benton face perception (/56)		44.9 (7.0)[a]	46.1 (4.4)	48.5 (2.5)
Famous Faces recognition (/12)		11.1 (1.5)	7.9 (4.5)* [b]	n/a
Ekman emotion recognition (/24)		17.7 (4.8)[a]	18.1 (3.4)[a]	21.4 (1.9)
Individual emotions: (% correct)	Anger	60.5 (29.2)	62.5 (23.5)	88.8 (12.8)
	Disgust	73.7 (30.6)	66.1 (31.9)	95.0 (13.1)
	Fear	44.7 (34.9)	62.5 (27.3)	68.8 (26.8)
	Happiness	94.7 (13.4)	91.1 (12.4)	100.0 (0.0)
	Sadness	78.9 (28.0)	83.9 (23.2)	86.3 (20.6)
	Surprise	89.5 (24.0)	85.7 (25.4)	96.3 (9.2)

Mean (standard deviation) values are shown.

Key: fv-FTLD, frontal variant frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination; n/a, not available; tv-FTLD, temporal variant frontotemporal lobar degeneration;

*3 patients in this group fell below the 5th percentile score (6) based on normative data from an historical group of 100 healthy controls aged 55 – 70; a, significantly worse ($p < 0.05$) than controls; b, significantly worse ($p < 0.05$) than the fv-FTLD group

3.3.2 Neuropsychological assessment

All subjects were assessed on tests of perceptual analysis, identification and affective processing of faces. Perceptual analysis of faces was assessed using the Benton Facial Recognition Test (Benton et al. 1983), in which the subject was required to match the identity of a photograph of

an unfamiliar target face to one (or three) of six other photographs in an array including the target plus distractor faces, presented under different viewing conditions (e.g., angle of view, illumination). Identification of faces was assessed using a Famous Faces recognition test (Warrington & James, 1967, see Appendix Table A1) which requires recognition of black and white photographs of 12 national and international public figures widely familiar to UK residents (comprising six prominent British politicians, two prominent American politicians, two high profile entertainers and two members of the British Royal family) (EK Warrington, personal communication); evidence of recognition other than naming can also be used to score performance on this test, enabling it to be used in individuals with severe naming impairment (e.g., in semantic dementia). Facial emotion recognition was assessed using 24 faces from the Ekman and Friesen battery (Ekman & Friesen, 1976); this set was the same as that used in previous studies of emotion recognition in Huntington's disease (Gray et al., 1997; Henley et al., 2008) and is suitable for use in cognitively impaired subjects. On each trial of this test, an unfamiliar face was displayed representing one of six canonical facial emotions "happiness", "sadness", "surprise", "disgust", "anger" or "fear", and the subject was required to match the facial expression to the label best describing that emotion in a six-alternative forced choice procedure. Behavioural data were analysed statistically under Stata® using linear regression models (incorporating age and gender as nuisance covariates) (see Chapter 2) to assess group differences and within-group correlations in performance between face processing tests. For the Famous Faces test, performance of FTLD patients was compared with normative data from an historical cohort of 100 healthy normal older controls aged 55 - 70 (EK Warrington, personal communication).

3.3.3 Brain image acquisition and analysis

All FTLD subjects had volumetric brain MR imaging at the time of the neuropsychological assessment. T1-weighted volumetric MR images were acquired on a 1.5 T Signa unit scanner (GE, Milwaukee, USA) as described in Chapter 2. Scores on the face processing tests for the entire FTLD group were entered into linear regression models to investigate associations between test score and grey matter signal. For each test score, voxel intensity, V, was modelled as a function of score, adjusting for age, gender, total intracranial volume (TIV) and MMSE by including them in the model as covariates. TIV was measured outside SPM2 according to a previously described protocol (Whitwell et al., 2001). Performance on the Benton test, the famous faces identification test and recognition of individual facial emotions in the Ekman test were analysed in separate models. Because face identity and emotion processing both also involve structural perceptual analysis of faces (Bruce & Young, 1986), scores on the Benton test were also included as a covariate in the design matrices assessing correlates of face identification and emotion recognition, in order to separate specific correlates of these functions from correlates of the perceptual analysis of faces.

Statistical parametric maps (SPMs) for each behavioural contrast were assessed at a voxel-level significance threshold of $p < 0.001$ uncorrected over the whole brain volume and after correction for false discovery rate (FDR) at threshold $p<0.05$ (Genovese et al., 2002). In order to reduce the possibility of spurious anatomical correlations, analyses were restricted to those brain voxels that showed significant atrophy relative to healthy controls (thresholded at $p < 0.1$ uncorrected) and clusters exceeding 50 voxels in size. In addition, the effects of small volume correction using anatomical regions based on the a priori hypotheses were also assessed at threshold $p<0.05$ and

$p<0.1$. Anatomical regions were derived by manual tracing from the customised template brain image using MRIcro® (http://www.sph.sc.edu/comd/rorden/mricro.html) and comprised bilateral orbitofrontal cortices (including the orbital surface of both frontal lobes and the lateral orbital gyri below the inferior frontal sulcus bilaterally); right and left insula; and right and left inferior and mesial temporal lobes (including the cortex of the entire ventral surface extending anteriorly to the pole and posteriorly to the occipito-temporal junction, parahippocampal gyrus, hippocampus and amygdala).

3.4 Results

3.4.1 Behavioural data

Behavioural scores for patients with FTLD and control subjects are shown in Table 3.1. On the Benton face perception task, the combined FTLD group and the fv-FTLD subgroup but not the tv-FTLD subgroup performed significantly worse ($p<0.05$) than the healthy control group; the tv-FTLD subgroup showed a trend ($p =0.059$) to worse performance than healthy controls, and both FTLD subgroups showed greater variance in scores than controls. There was no significant difference in performance between the two FTLD subgroups on the Benton test. On the famous face identification task 3 / 13 patients in the tvFTLD subgroup (and no patients in the fv-FTLD subgroup) performed < 5^{th} percentile for healthy control norms, and the tv-FTLD subgroup performed significantly worse ($p < 0.05$) than the fv-FTLD subgroup. On the Ekman facial emotion recognition task both FTLD subgroups performed significantly worse ($p<0.05$) than the healthy control group: the most severe deficits for both subgroups occurred for recognition of anger and fear (healthy controls also performed relatively poorly on recognition of fear). There was no significant difference in performance between the two FTLD subgroups on the Ekman

test. Scores on the face perception task correlated significantly with scores for emotion recognition ($p<0.05$, r^2 0.286) but not for face identification (though the last may have been partly confounded by a number of ceiling scores on the face identification task).

3.4.2 Neuroanatomical correlates of perceptual analysis of faces

Performance on perceptual analysis of faces (a face matching task) correlated with grey matter signal in a distributed fronto-parietal cortical network (Table 3.2, Figure 3.1) including superior and inferior parietal areas, precuneus, dorsal prefrontal cortex, supplementary motor area, anterior cingulate and frontal pole (all $p < 0.001$ uncorrected).

3.4.3 Neuroanatomical correlates of face identification

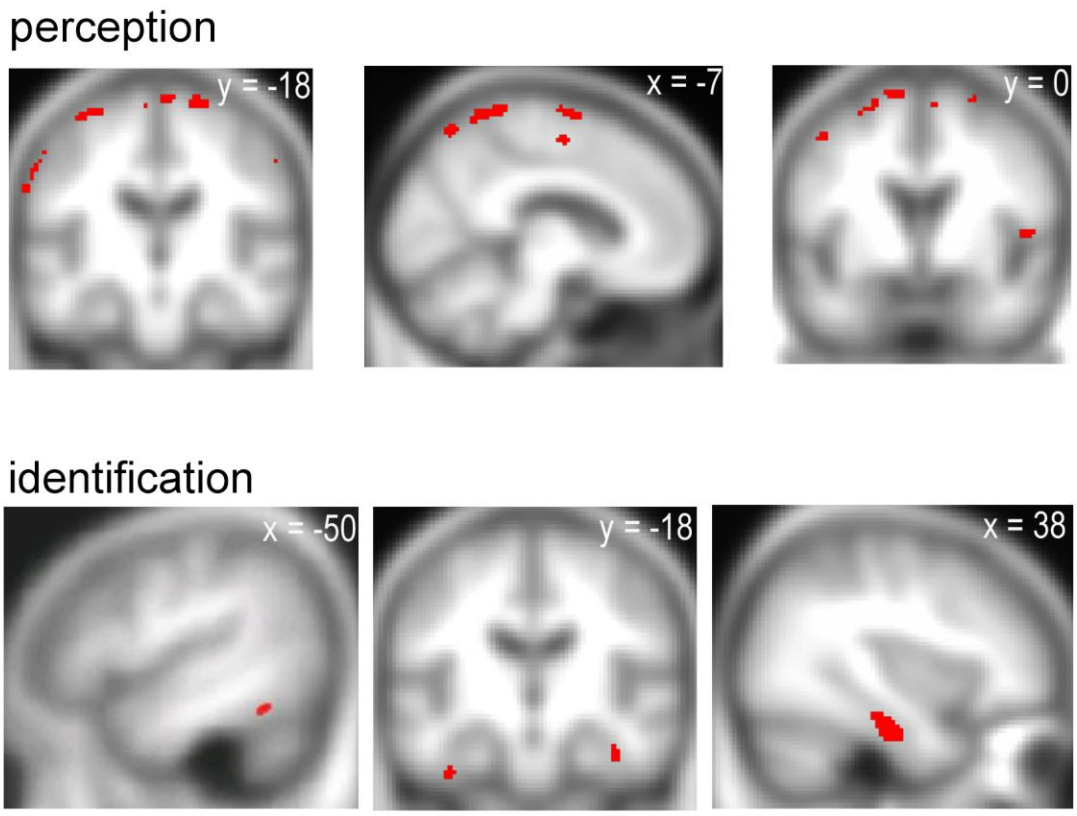
As face identification performance differed significantly between the tv-FTLD and fv-FTLD subgroups, anatomical correlates of face identification performance were initially assessed within each FTLD subgroup separately: neither subgroup showed a correlate at whole brain level or following small volume correction. In the combined FTLD group analysis, performance on face identification correlated with grey matter signal in areas within fusiform gyrus bilaterally, including bilateral anterior fusiform areas, more prominent on the right ($p<0.05$ after small volume correction) and a left posterior fusiform area ($p < 0.1$ after small volume correction) (Table 3.2, Figure 3.1).

Table 3.2 Local maxima of grey matter correlations with face processing performance in patients with FTLD.

Face processing function		Brain region R	Brain region L	MNI Coordinates x, y, z (mm)	Z score
Perceptual analysis			precuneus	-13, -65, 63	4.51
		SMA		3, -12, 73	4.49
			superior PL	-9, -52, 69	4.44
		superior PL		6, -32, 72	4.41
			dorsal PFC	-12, -2, 71	4.34
		inferior FrG		51 0 5	3.95
			inferior PL	-62 -15 40	3.73
			ACC	-7, -7, 55	3.47
			frontal pole	-38, 57,2	3.44
Identification			posterior FG*	-50, -52, -19	3.84
		anterior FG**		38 -21 -22	3.74
			anterior FG*	-36,-6,-38	3.41
Emotion recognition	All negative		parieto-occipital cortex	-47 -79 26	4.15
			dorsal PFC	-39 50 16	3.82
			ACC	-2 40 0	3.71
		superior PL		39 -33 44	3.48
	Anger	insula**		29, -23, 12	4.17
		dorsal PFC		41, -9, 44	4.02
		parieto-occipital cortex		41, -89, 11	3.99
			parieto-occipital cortex	-53, -78, 24	3.87
		inferior FrG		52, 7, 20	3.83
			inferior FrG	-47, 0, 6	3.79
			insula**	-41, -19, 1	3.72
		posterior STG		47 -23 6	3.71
			dorsal PFC	-56, -8, 35	3.37
	Fear	dorsal PFC		49, 14, 40	4.36
			dorsal PFC	-28, 31 45	4.12
		superior PL		27, -12, 55	4.02
		inferior PL		58, -54, 21	3.88
			superior PL	-27, -76, 51	3.70
		ACC		1, 39, 29	3.48
			inferior PL	-53, -63, 30	3.40
	Sadness	posterior STG		68, -39, 20	3.70
	Surprise	ITG		59, -7, -37	3.99
			temporal pole	-55, 15, -21	3.61
			medial OFC*	-8, 41, -28	3.50
		medial OFC*		9, 40, -26	3.45
			dorsal PFC	-44, -11, 60	3.16

All maxima exceeding threshold $p < 0.001$ (uncorrected for whole brain volume) and cluster extent of 50 voxels are shown. **areas surviving small volume correction ($p < 0.05$); *areas surviving small volume correction ($p < 0.1$); Key: ACC, anterior cingulate gyrus; FG, fusiform gyrus; FrG, frontal gyrus; ITG, inferior temporal gyrus; MNI, Montreal Neurological Institute stereotactic space; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PL, parietal lobe; SMA, supplementary motor area; STG, superior temporal gyrus

Figure 3.1 VBM correlates of face perception (Benton face matching, above) and famous face identification (below) in patients with FTLD. Statistical parametric maps show areas of grey matter correlating with behavioural performance, displayed on the customised template MR brain image in Montreal Neurological Institute standard stereotactic space at threshold p<0.001 uncorrected. The plane of each section is shown (coordinates in mm); for coronal sections, the left hemisphere is displayed on the left.

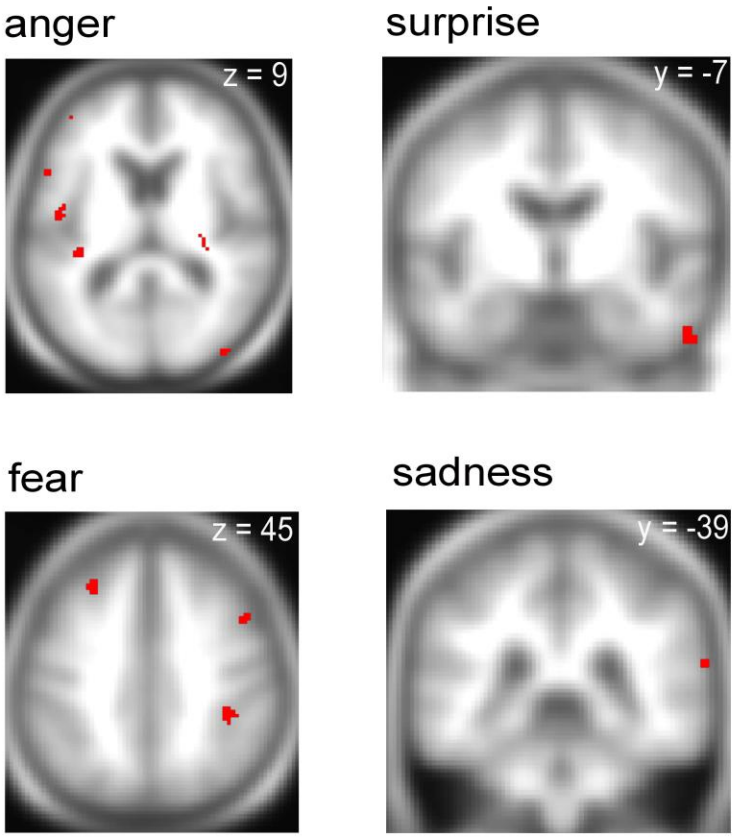


3.4.4 Neuroanatomical correlates of facial emotion recognition

Performance on recognition of individual facial emotions showed separable but overlapping anatomical correlates (Table 3.2, Figure 3.2). The most extensive anatomical correlates were found for recognition of anger, fear and surprise. Recognition of anger correlated with grey

matter signal in a distributed bilateral network including insula ($p < 0.05$ after small volume correction), parieto-occipital cortex, dorsal PFC, inferior frontal gyrus, and posterior superior temporal gyrus ($p<0.001$ uncorrected). Recognition of fear correlated with grey matter signal in a bilateral predominantly fronto-parietal network including dorsal prefrontal cortex, anterior cingulate, superior and inferior parietal lobe areas (all $p < 0.001$ uncorrected). Recognition of surprise correlated with grey matter signal in a network including bilateral medial orbitofrontal cortex ($p < 0.1$ after small volume correction), right inferior temporal gyrus, left temporal pole, and dorsal prefrontal cortex ($p < 0.001$ uncorrected). Recognition of sadness had a discrete grey matter correlate in right posterior superior temporal gyrus. No grey matter correlates of disgust or happiness recognition were detected at the specified voxel-wise significance and cluster extent thresholds. The combined score for recognition of negative valence emotions (anger, disgust, fear, sadness, surprise) correlated with a bilateral cerebral network subsuming cortical correlates identified for recognition of the individual emotions: this common network included dorsal prefrontal cortex, parietal and parieto-occipital junction zones and anterior cingulate gyrus (Table 3.2).

Figure 3.2 VBM correlates of facial emotion recognition in patients with FTLD. Statistical parametric maps (SPMs) show areas of grey matter correlating with behavioural performance for recognition of each of the negative emotions anger, fear, sadness and surprise. SPMs are displayed on the customised template MR brain image at threshold p<0.001 uncorrected. The plane of each section is shown (coordinates in mm) in Montreal Neurological Institute standard stereotactic space; for all sections, the left hemisphere is displayed on the left.



3.5 Discussion

The findings in this experiment corroborate previous evidence for deficient face analysis in patients with FTLD, and show that different components of face processing depend on distinct but partly overlapping brain networks in FTLD. Performance on a test of perceptual analysis (face matching) was linked to grey matter in an extensive fronto-parietal network. Independently of this cortical correlate of perceptual performance, face identification performance correlated with grey matter in bilateral inferior temporal areas, while facial emotion recognition correlated with grey matter in widespread parietal, temporal, inferior frontal and limbic (insular) areas and specific emotion recognition deficits had partially separable grey matter signatures. This study provides a neuroanatomical framework for understanding face processing deficits in neurodegenerative disease (specifically, FTLD) that is in accord with the modular neural architecture of face processing proposed in contemporary cognitive models (Bruce & Young, 1986). The findings extend and complement previous work in delineating distributed brain networks that are required for particular cognitive components of face processing.

The cortical correlates of performance on the Benton face matching task, based on uncorrected data at $p<0.001$, were extensive but located in fronto-parietal areas remote from occipito-temporal cortex classically associated with face processing (Haxby et al. 2000; Rossion et al. 2003; Gobbini & Haxby, 2007; Vuilleumier & Pourtois, 2007; Ishai, 2008). Although these were weak effects, the areas implicated in face matching here are in proximity both to anterior areas implicated in visual scanning of faces (Pollmann & Yves von Cramon 2000; Barton et al., 2006) and parietal areas previously identified as mediating perceptual analysis of unusual or 'non-canonical views' of visual objects and associated with the clinical syndrome of apperceptive

agnosia for visual objects including faces (Warrington & James, 1988; Young et al., 1993; Cavanna & Trimble, 2006). Perceptual matching of alternative views of faces in the Benton task may therefore be mediated by a cortical network that plays a more generic role in visual object analysis under perceptually demanding viewing conditions. It is possible that the FTLD patients here performed the Benton task using a feature matching strategy that did not depend on the integrity of face-specific mechanisms in FFA, an interpretation forecast previously on neuropsychological grounds (Duchaine & Weidenfeld, 2003). This suggests that inefficient 'social search' processes may contribute to the inter-personal difficulties experienced by many patients with fv-FTLD, just as an altered visual search strategy may contribute to abnormal face processing in individuals with autism (Teunisse & de Gelder, 2003).

The cortical areas implicated in face identification in this study are broadly in keeping with the a priori anatomical hypotheses, and support the findings of previous functional imaging and focal lesion studies. The correlation between face identification performance and focal damage in left posterior fusiform gyrus overlapped with the cortical region previously identified as the site of the FFA (Kanwisher et al 1997; Spiridon et al., 2006), reaffirming a critical role of the FFA in processing of facial identity. However, additional correlates of face identification within fusiform gyrus but anterior to the previously identified boundaries of FFA, and more prominent in the right temporal lobe, were also demonstrated here. These correlates are likely to reflect components of semantic and episodic memory for faces indexed by the famous faces identification task, and would be consistent both with previous studies of associative prosopagnosia in FTLD (Snowden et al., 2004; Josephs et al., 2008) and with functional imaging studies of familiar face processing in normal individuals (Gobbini & Haxby 2007). Although the present study does not speak directly to the issue of the face specificity of these fusiform regions,

the cortical correlates of face identification here did not overlap with the network correlating with performance on the perceptual matching task. Previous functional imaging evidence suggests that the FFA is specifically activated by faces, but not by low-level stimulus features present in faces (Kanwisher et al 1998; Spiridon & Kanwisher, 2002), as may have driven performance of the Benton task here.

Recognition of emotions with 'negative' valence (anger, fear, sadness and surprise) here correlated with grey matter signal in a common cerebral network including dorsal prefrontal, parietal and parieto-occipito-temporal junctional areas (Table 3.2). Activation of this network has been demonstrated in functional imaging studies of facial emotion processing, particularly if there is a requirement for categorisation, evaluation or behavioural responses (Vuilleumier & Pourtois 2007), and a similar network has previously been linked to controlled or 'reflective' perception of social signals (Satpute & Lieberman, 2006). This network may be functionally separable from an alternative (but interacting) network including the amygdala which mediates automatic or 'reflexive' processing of facial emotions and other salient social signals (Satpute & Lieberman, 2006; Dolan, 2007): it is noteworthy that the amygdala was not identified as a correlate of emotion recognition in this study nor in a previous VBM study (Rosen et al., 2006), which may reflect the relatively low behavioural value and limited arousal potential of the face stimuli for these FTLD patients. The network implicated here in facial emotion recognition did not overlap with the network correlating with performance on the face identification task but did partly overlap with the fronto-parietal network correlating with performance on the perceptual matching task. This suggests a structural anatomical basis for neuropsychological models of face processing that posit cognitive modules for face identification and expression that are

functionally in parallel, and modules for face perception and emotion recognition that interact partly in series (Bruce & Young, 1986).

Involvement of the putative emotion recognition network was not uniform between individual negative emotions, and additional specific correlates for recognition of individual negative facial emotions were identified: these findings corroborate a substantial body of functional imaging evidence for emotion-specific cerebral networks (Phan et al 2002; Murphy et al., 2003; Vuilleumier et al., 2004; Vuilleumier & Pourtois, 2007). The most robust and specific grey matter correlates were in bilateral insula for recognition of anger (Table 3.2). The insula has been implicated previously in the processing of anger in facial expressions (Phan et al 2002; Murphy et al., 2003), voices (Ethofer et al., 2009) and subjective feeling states (Denson et al. 2009), and may contribute to the neural regulation of approach-avoidance behaviours that pertain particularly to anger (Carver & Harmon-Jones, 2009). Additional specific correlates of anger recognition were identified in inferior frontal gyrus, a region previously associated with processing of anger and possibly linked to mirror responses to this 'social' emotion (Kimbrell et al., 1999; Kilts et al., 2003; Lee et al., 2006). Limited information is available concerning the neuroanatomy of perceiving surprise; previous studies have identified correlates of surprise and novelty processing in inferior temporal cortex (Schroeder et al., 2004; Wright et al., 2006), though not overlapping with the more anteriorly sited area here. For recognition of surprise, additional grey matter correlates were identified in medial orbitofrontal and anterior temporal cortices: these regions have been implicated in evaluation of the behavioural relevance of emotional stimuli (Vuilleumier & Pourtois, 2007; Ishai, 2008), and may be particularly relevant for processing intrinsically 'ambiguous' emotional signals such as surprise (which may carry either positive or negative valence depending on context). The neural correlates of sadness and

fear recognition identified here were less robust but nevertheless in line with previous evidence in both healthy and brain damaged populations. Processing of fearful faces has been shown to engage a distributed network of frontal and parietal regions extending beyond the temporal lobes (Vuilleumier & Pourtois, 2007): these areas may mediate alerting, social and somatic as well as cognitive responses to perceived fear. Processing of sadness from social cues including facial expressions has been shown to activate a brain network including superior temporal gyrus: this region is likely to be involved in the detailed perceptual analysis of faces as well as more general processing of social signals and inferences concerning others' mental states (Britton et al., 2006). It is of interest that a similar anatomical correlate of impaired processing of sad expressions was found in a previous VBM study of a mixed population of patients with neurodegenerative disease (Rosen et al., 2006).

The lack of a grey matter correlate of disgust recognition here (Table 3.2) is somewhat surprising in light of the present and previous behavioural findings in FTLD (Lough et al., 2006). However, it has been proposed that the conceptual and linguistic complexity of disgust may account for variations in performance on tests of disgust recognition in FTLD and other neurodegenerative diseases (notably Huntington's disease) (Snowden et al., 2008): if this neuropsychological complexity is underpinned by wide variation in the distribution of brain damage sufficient to produce impairments of disgust recognition and labelling, this might militate against the detection of localised VBM correlates. Similar considerations may apply to recognition of happiness (a compound of poorly differentiated positive affects: amusement, satisfaction, triumph, etc); however, the lack of a VBM correlate of happiness is also likely to reflect the high level of recognition (with low variance in scores: Table 3.1) achieved by patients with FTLD, consistent with previous observations in FTLD (Rosen et al., 2006).

This study has therefore provided further insight into the neuroanatomical framework for understanding face processing deficits in FTLD that corroborates the modular neural architecture of face processing proposed in current cognitive models. The study shows that the breakdown of distributed neural networks provides a complementary neuroanatomical window on complex multi-component cognitive functions such as face processing, with implications for our understanding of those functions in health as well as disease.

Chapter 4: CHEMOSENSORY PROCESSING IN FRONTOTEMPORAL LOBAR DEGENERATION

Summary

Deficits of flavour processing may be clinically important in FTLD and other dementias. However, little information is currently available concerning flavour processing in neurodegenerative disease. In this chapter, an experiment investigating flavour identification in FTLD is described. 25 patients with FTLD (12 behavioural variant frontotemporal dementia (bvFTLD), eight semantic variant primary progressive aphasia (svPPA), five non-fluent variant primary progressive aphasia (nfvPPA)) and 17 healthy control subjects were studied using a novel test based on cross-modal matching of flavours to words and pictures. All subjects completed a general neuropsychological assessment, and odour identification was assessed using a modified University of Pennsylvania Smell Identification Test. Brain MRI volumes from the patient cohort were analysed using VBM to identify regional grey matter associations of flavour identification. Relative to the healthy control group, the bvFTLD and svPPA subgroups showed significant deficits of flavour identification and all three FTLD subgroups showed deficits of odour identification. Flavour identification performance did not differ significantly between the FTLD syndromic subgroups. Flavour identification performance in the combined FTLD cohort was significantly associated with grey matter volume in left entorhinal cortex, hippocampus, parahippocampal gyrus and temporal pole. This study shows that certain FTLD syndromes are associated with impaired identification of flavours and this is underpinned by grey matter atrophy in an antero-medial temporal lobe network. These findings have implications for our understanding of abnormal eating behaviour in these diseases.

4.1 Background

The brain mechanisms that analyse and identify flavours are of considerable clinical and neurobiological interest, yet remain poorly understood. The characteristic flavours of food and drink represent a complex convergence of gustatory, olfactory, and other sensory inputs (Royet et al., 1999; Rolls, 2005; Gottfried et al., 2010). The processing of chemosensory stimuli involves a hierarchy of cognitive operations including perceptual analysis (encoding of elementary smell and taste qualities), mnestic and semantic processing (identifying specific flavours and odours) and affective processing including evaluation of pleasantness and satiety in directing behaviour. The primary gustatory and olfactory cortices are located in the anterior insula and pyriform cortex, whilst higher-order gustatory and olfactory association cortices are contained in OFC; structures in the anterior and medial temporal lobes are engaged during the recognition and evaluation of flavours, including amygdala, hippocampus and other limbic structures that modulate emotional and arousal states (Royet et al., 1999; Savic, 2002; Kareken et al., 2003; Small et al., 1997, 2001a, 2001b, 2004, 2005; Small, 2006; Haase et al., 2009).

Relatively little information is available concerning flavour processing in human disease. Focal damage of the anterior temporal lobes has been associated with gustatory agnosia (Small et al., 1997, 2001a, 2005). In the neurodegenerative disease spectrum, altered eating behaviour is a cardinal feature of FTLD. As recognised in recently revised consensus criteria (Rascovsky et al., 2011), abnormalities of eating behaviour are particularly early and prominent in bvFTLD. These abnormalities include hyperphagia, compulsive food seeking behaviour, pathological sweet tooth, alterations in food preference, food fads and eating unusual food combinations (Snowden et al.,

2001; Ikeda et al., 2002; Thompson et al., 2003; Gorno-Tempini et al., 2004b; Rosen et al., 2005). Such abnormalities could be at least partly underpinned by deficits of flavour processing. This interpretation would fit with the distribution of regional atrophy in FTLD, overlapping cortical areas implicated in flavour processing: abnormal eating behaviours in FTLD have been linked to cortical atrophy in a distributed network including OFC, anterior insula and striatum (Whitwell et al., 2007; Woolley et al., 2007). Furthermore, flavour and odour agnosia have been associated with focal anterior temporal lobe damage and in patients with bvFTLD and PPA, especially as part of a "pan-modal" disintegration of semantic knowledge in svPPA (Luzzi et al., 2007; McLaughlin et al., 2008; Rami et al., 2007; Piwnica-Worms et al., 2010; Gorno-Tempini et al., 2011; Pardini et al., 2009). However, the neuropsychology and neuroanatomy of flavour processing have not been systematically assessed in these FTLD syndromes.

4.2 Experimental hypotheses

In this study flavour identification and its brain basis were assessed prospectively in a cohort of patients clinically diagnosed with each of the major clinical syndromes of FTLD: bvFTLD, svPPA and nfvPPA. Flavour identification was assessed using a novel battery, in relation to odour identification and general neuropsychological functions. The structural neuroanatomical associations of flavour and odour identification were assessed using VBM. It was hypothesised that each of the FTLD syndromic groups would show deficits of flavour identification, and that these deficits would be linked to grey matter loss involving higher-order gustatory and olfactory association cortices and cortical areas engaged in multi-modal semantic processing in the anterior temporal lobes and inferior frontal lobes.

4.3 Methods

4.3.1 Subjects

Twenty-five consecutive patients (17 male, 20 right-handed, mean (standard deviation) age 65.2 (7.3) years) fulfilling consensus criteria for a diagnosis of FTLD (Neary et al., 1998) were recruited from a tertiary cognitive disorders clinic (demographic and clinical data for all subjects are summarized in Table 4.1). The patient cohort comprised each of the three canonical FTLD syndromic subtypes: 12 patients had bvFTLD, characterized by profound personality and behavioural change with frontal and temporal lobe atrophy on brain magnetic resonance imaging (MRI); eight patients had svPPA, characterized by breakdown of verbal and nonverbal knowledge systems with asymmetric, predominantly left-sided temporal lobe atrophy on MRI; and five patients had nfvPPA, based on the presence of speech apraxia and/or agrammatism and relatively intact single word comprehension (Rohrer et al., 2010; Gorno-Tempini et al., 2011). All cases included in this series had typical clinical and MRI profiles of bvFTLD, svPPA or nfvPPA, as previously described and would have fulfilled recent revised consensus criteria for probable bvFTLD or PPA (Rascovsky et al., 2011; Gorno-Tempini et al., 2011). All patients had an assessment of general neuropsychological functions (see Table 4.1) which supported the clinical syndromic classification. 17 healthy control subjects matched with the patient group for age and educational background were also assessed. The presence of any significant difference between performances on the neuropsychological assessments in the patient subgroups and controls was examined using standard t-tests.

Prior to recruitment, questionnaire data were gathered for all subjects to screen for any prior history of chronic olfactory or gustatory dysfunction (no patients were excluded from the study

on this basis). In addition, patients' carers completed the Cambridge Behavioural Inventory (CBI) to provide a rating of the presence and severity of any abnormal eating behaviours exhibited by the patient. Any symptoms of altered flavour or olfactory processing previously reported by the patient or inferred by their carer since the onset of the illness (flavours or odours more or less intense, more or less pleasant, or otherwise altered in quality) were also recorded.

Informed consent to participate in the study was obtained for all subjects and the study was approved by the local institutional research ethics committee in accord with Declaration of Helsinki guidelines.

4.3.2 Experimental assessment of flavour and odour identification

Identification of flavours was assessed using a novel battery. Flavour stimuli were commercially available jelly bean candies ((JellyBelly®). Jelly beans have been used previously to assess flavor processing in patients with FTLD and other dementias (Piwnica-Worms et al., 2010; Gorno-Tempini et al., 2004b), and offer the advantages of wide sampling from the flavor 'space' with relatively uniform stimulus quantity and presentation and minimal extraneous cues to flavor identity. Twenty flavours with high familiarity and identifiability for healthy older British residents (as previously determined using these stimuli (Piwnica-Worms et al., 2010)) were presented sequentially. On each trial, three word-picture combinations representing the target flavour, a semantically related foil item and a semantically more distant foil item (e.g., target, orange; related foil, lemon; distant foil, popcorn) were shown on a computer monitor and also read aloud to the subject (all flavours and foils are listed in Table A2). The flavour battery was constructed such that target flavours were either fruits or non-fruit items with equal probability; on each trial, the semantically related foil was derived from the same broad food category as the

target flavour (i.e., 'fruit' or 'non-fruit') and the semantically distant foil was derived from the other category. The task on each trial was to select the word-picture combination matching the target flavour in a three-alternative forced choice procedure. Presentation of word-picture combinations was designed to reduce dependency on a single cross-modal response modality (words), as verbal labelling is likely to be disproportionately impaired in patients with svPPA. Flavours were presented in randomized order. Jelly beans were placed in the subject's hand out of vision by the examiner, and the subject was instructed to lift them directly to the mouth, to minimize any use of color cues. Subjects were instructed to rinse their mouth between flavour trials. Visual word-picture trials were presented and subject responses were collected for off-line analysis on a notebook computer running Matlab7.0® (see Chapter 2).

To provide an index of odour identification performance for comparison with flavour identification, all subjects completed the British version of the University of Pennsylvania Smell Identification Test (UPSIT). This is a widely validated 40 item four-alternative-forced-choice odour to word matching procedure (Doty et al., 1984). For this study, the standard UPSIT procedure was modified as previously described (Rami et al., 2007; Piwnica-Worms et al., 2010), such that word – picture combinations corresponding to the target and each of the three foil items were presented on each trial. As in the flavour identification test, this modified procedure was designed to reduce dependency on a single response modality.

Behavioural data were analysed under Stata® using an ANOVA linear regression model. The model incorporated scores on the flavour and odour identification tests and group membership (bvFTLD, svPPA, nfvPPA, healthy control), together with a measure of executive performance (the Stroop test ink color naming task), verbal semantic knowledge (British Picture Vocabulary

Scale (BPVS)), subject age and gender as covariates of no interest which might have influenced performance on the experimental tests. For each subject, error trials on the flavour identification task were classified according to whether these selected the semantically related foil or the semantically more distant foil, and a 'flavour categorization' score ((no. of trials correct + no. of semantically related errors) / total no. of trials) was derived. Correlations between flavour and odour identification scores were examined in both the patient and control groups. Correlations between flavour and odour identification scores and the presence/severity of abnormal eating behaviours (as indexed using the CBI) were also assessed.

4.3.3 Brain image acquisition and analysis

Brain MR images were acquired for all patients on a Siemens Trio TIM 3T scanner as described in Chapter 2. Linear regression was used to examine voxel-wise associations between regional grey matter volume and performance on flavour and odour identification tasks, modelling voxel intensity as a function of identification score and incorporating age, TIV and the Stroop test ink color naming task as covariates. A separate model incorporating additional covariates of FTLD subgroup membership (bvFTLD, svPPA or nfvPPA) was also analysed in order to assess neuroanatomical associations of flavour identification performance after taking clinical syndrome into account.

Statistical parametric maps were assessed both at a voxel-wise significance threshold $p < 0.001$ uncorrected over the whole brain volume and at a threshold $p < 0.05$ after false discovery rate (FDR) correction for multiple comparisons over the whole brain volume and over the anatomical small volumes of interest specified in our prior anatomical hyopotheses. These anatomical small volumes (as described in Chapter 3) comprised bilateral OFC (including the orbital surface of

both frontal lobes and the lateral orbital gyri below the inferior frontal sulcus bilaterally), right and left insula cortex and right and left temporal lobes anterior to Heschl's gyrus.

4.4 Results

4.4.1 Behavioural data

Behavioural data for patients and control subjects are summarized in Table 4.1 and Figure 4.1. Abnormal eating behaviours (predominantly, hyperphagia and pathological sweet tooth) were exhibited by 50% of bvFTLD, 63% of svPPA, and 40% of nfvPPA patients. Olfactory symptoms were reported by 33% of bvFTLD patients but not by patients in the other syndromic subgroups; whilst 8% of bvFTLD and 13% of svPPA patients but no nfvPPA patients reported symptoms of altered flavour processing. On the flavour identification task, the bvFTLD subgroup and the svPPA subgroup performed significantly worse ($p<0.05$) than the healthy control group; there was no significant performance difference ($p=0.46$) between the nfvPPA subgroup and healthy controls (perhaps reflecting wide individual performance variation within the nfvPPA group) nor between the three FTLD subgroups. On the odour identification task, each of the three FTLD subgroups performed significantly worse than the healthy control group, however there were no significant performance differences between the FTLD subgroups. Eight patients in the bvFTLD group, four in the svPPA group and one in the nfvPPA group scored less than the 5^{th} centile based on published normative data for the UPSIT (Doty et al., 1984). Examining the types of errors made on the flavour identification task, patients and healthy control subjects were more likely to select semantically related than semantically unrelated foils, both for fruit and for non-fruit items (see Table 4.1): for each group, identification within general flavour categories (i.e.,

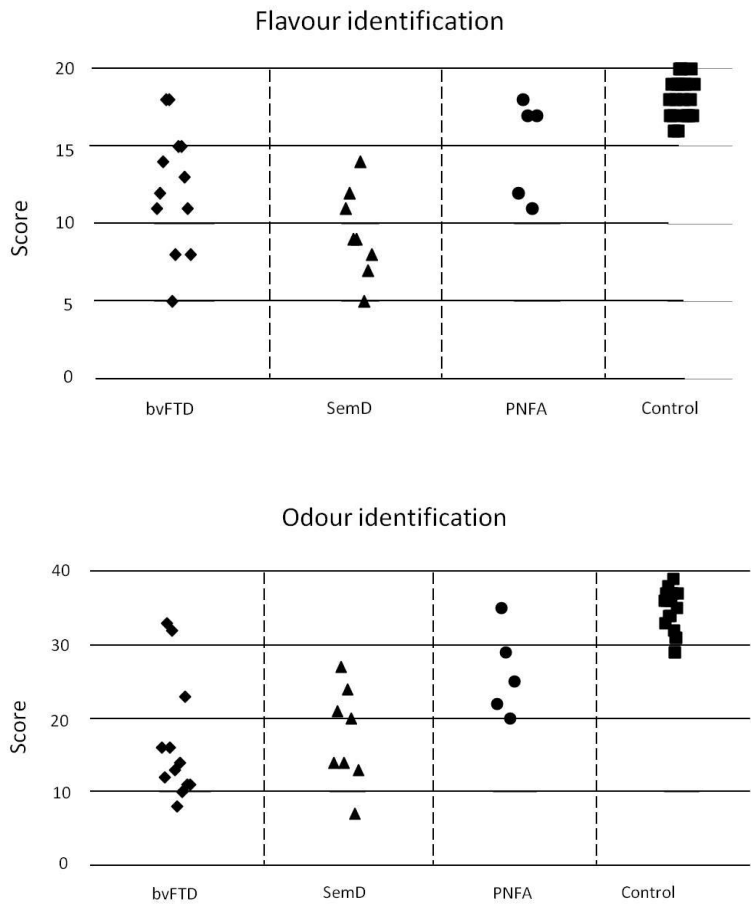
'fruit – non-fruit' flavour categorization, or superordinate flavour knowledge) was better preserved than identification of particular flavours. All three patient groups showed a deficit of flavour categorization relative to the healthy control group, however the syndromic subgroups did not differ in their ability to categorize the target flavour. Flavour and odour identification scores were significantly correlated in the patient group ($p<0.05$, r^2 0.324); there was no significant correlation between flavour and odour identification scores in the control population, however this may reflect controls' near-ceiling performance on the flavour task. There was no evidence of correlation between flavour or odour identification performance and the presence or severity of abnormal eating behaviours (see Table 4.1).

Table 4.1 Summary of subject characteristics and behavioural data.

		bvFTLD n = 12	**svPPA** n = 8	**nfvPPA** n = 5	**Controls** n = 17
Demographic data					
Gender M:F		12:0	5:3	1:4	8:9
Handedness R:L		8:4	7:1	5:0	15:2
Age		66.1 (7.6)	66.1 (6.9)	62.7 (8.2)	66.2 (8.1)
MMSE (/30)		23.5 (6.0)†	22.8 (5.6)†	19.2 (10.8)	29.9 (0.3)
General cognitive functions					
NART (/50)		26.5 (16.1)†	18.7 (11.9)†	17.0 (15.3)†	42.7
RMT	Words (/50)	32.1 (11.5)†¶	32.6 (7.3)†¶	42.5 (4.8)	48.2 (2.3)
	Faces (/50)	32.4 (5.7)†	31.1 (8.3)†	33.3 (7.1)	42.4 (4.3)
Digit Span	Forward (/12)	7.4 (2.6)	7.1 (2.9)	4.8 (2.2)	9.0 (1.7)
	Reverse (/12)	5.2 (2.8)	6.0 (2.9)	3.5 (3.0)	6.6 (1.7)
BPVS (/150)		119.5 (42.3)†≠	68.1 (54.6)†	117.2 (50.8)	148.4 (1.1)
GNT (/30)		9.1 (6.7)†≠	1.1 (2.8)†	9.2 (12.2)†	25.9 (3.1)
Arithmetic (/24)		13.3 (7.3) ¶	10.8 (9.9)	3.0 (0.0)†	14.6 (4.6)
VOSP object decision (/20)		15.7 (3.1)†	14.3 (4.3)†	15.6 (3.2)	19.4 (0.7)
WASI	Vocabulary (/80)	41.5 (22.6)†	21.8 (20.8)†	19.4 (19.1)†	70.5 (4.3)
	Block design (/71)	19.6 (15.1)†	31.6 (17.9)	23.6 (20.2)	46.2 (11.2)
	Similarities (/48)	19.6 (14.0)†	10.3 (11.9)†	12.4 (15.9)†	39.1 (5.1)
	Matrices (/32)	13.0 (8.3)†	18.8 (8.4)	15.8 (11.2)	24.7 (2.8)
Stroop ink color naming (secs)		72.2 (19.1)†	111.8 (44.6)†	124.0 (48.5)†	57.3 (9.6)
Stroop word naming (secs)		25.9 (10.8)	34.9 (11.7)†	58.4 (28.2)†	20.4 (3.2)
Experimental assessments					
Flavour identification (/20)		12.3 (4.0)†	9.4 (2.9) †	15.0 (3.2)	18.1 (1.3)
Flavour categorization (/20)††		17.0 (2.4)†	16.4 (1.7)†	18.8 (0.8)†	19.7 (0.6)
UPSIT (/40)		16.6 (8.4)†	17.5 (6.6) †	26.2 (6.0)†	34.7 (3.0)
Abnormal eating behaviours*(n)		6	5	2	n/a
Flavour symptoms (n)		1	1	0	n/a
Odour symptoms (n)		4	0	0	n/a

Mean (standard deviation) values are shown. Key: †Significantly worse than controls ($p<0.05$); ≠significantly different to svPPA ($p<0.05$); ¶significantly different to nfvPPA ($p<0.05$). BPVS, British Picture Vocabulary Scale (McCarthy and Warrington, 1992); bvFTLD, behavioural variant frontotemporal dementia; GNT, Graded Naming Test (Warrington, 1997); NART, National Adult Reading Test (Nelson, 1982); nfvPPA, non-fluent variant primary progressive aphasia; RMT, Recognition Memory Tests (Warrington, 1984); svPPA, semantic variant primary progressive aphasia; Stroop, Delis-Kaplan Executive Function System Stroop test (Delis *et al*, 2001); UPSIT, University of Pennsylvania Smell Identification Test (British version); VOSP, Visual Object and Space Perception Battery (Warrington and James, 1991); WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); ††see text for details; *most patients with abnormal eating behaviour exhibited hyperphagia and pathological sweet tooth; one patient with bvFTLD exhibited a preference for eating unusual items.

Figure 4.1 Raw scores for flavour identification of individual subjects by subgroup



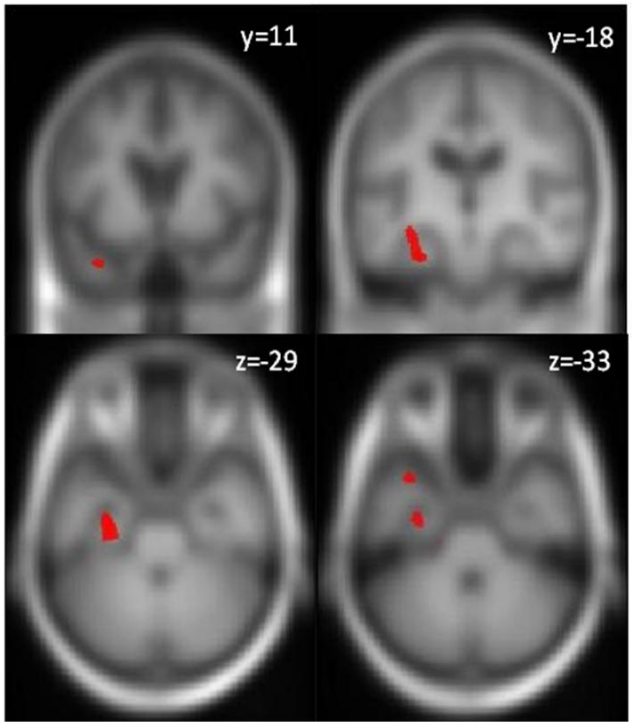
4.4.2 Neuroanatomical data

Performance on the flavour identification task across the FTLD cohort was positively associated with grey matter volume in a network of areas in the left anterior temporal lobe, including entorhinal cortex, hippocampus and parahippocampal gyrus (peak MNI coordinates = -29 -18 -29; z-score = 3.77) and temporal pole (peak MNI coordinates = -35 11 -33; z-score = 3.43) ($p<0.05$ after FDR correction within the anatomical small volume of interest). Statistical parametric maps of grey matter regions associated with flavour identification performance are

shown in Figure 4.2. These same regions remained associated with flavour identification performance after incorporation of covariates of FTLD subgroup membership and in an additional subgroup analysis restricted to the bvFTLD subgroup (each at a less stringent threshold $p<0.01$ uncorrected).

No significant grey matter associations were identified for flavour or odour identification performance at threshold $p<0.05$ after correction across the whole brain volume, nor for odour identification at $p<0.05$ after FDR correction within the anatomical small volumes of interest.

Figure 4.2 Grey matter associations of flavour identification in patients with FTLD. Statistical parametric maps (SPMs) show areas in which grey matter volume was associated with behavioural performance in a voxel-based morphometric analysis. SPMs are displayed on the template MR brain image in Montreal Neurological Institute (MNI) standard stereotactic space, at threshold $p<0.001$ uncorrected; the grey matter associations shown were significant ($p<0.05$) after correction for multiple comparisons within the pre-specified anatomical small volume (see text). The plane of each section is shown (MNI coordinates in mm); for coronal sections, the left hemisphere is displayed on the left.



4.5 Discussion

These findings demonstrate deficits of flavour identification in two major clinical syndromes of FTLD, bvFTLD and svPPA, relative to healthy control subjects. The lack of significant group effects for the nfvPPA subgroup may partly reflect the small size of the cohort. The profile of odour identification performance essentially paralleled flavour identification across subgroups, and there was a significant correlation between flavour and odour identification scores in the patient population. An error analysis showed that identification of general flavour categories was better preserved than identification of particular flavours: this pattern would be difficult to explain were impaired flavour identification simply the result of impaired cross-modal labelling, and suggests that FTLD is accompanied by a true semantic deficit of flavour processing. Relatively greater vulnerability of specific compared with superordinate flavour knowledge would be consistent with the cognitive organization demonstrated for other knowledge modalities in neurodegenerative disease (see Chapter 6). This is further supported by the present neuroanatomical evidence. Flavour identification deficits were associated with a profile of regional grey matter atrophy in the left antero-medial temporal lobe, overlapping brain regions previously associated with stimulus identification in other modalities in neurodegenerative disease such as faces (Chapter 3) and voices (Hailstone et al., 2011). It is noteworthy that these neuroanatomical associations were not driven simply by inclusion of a particular disease group (such as svPPA, itself associated with focal left temporal lobe atrophy): very similar associations were identified even after taking syndromic subgroup into account, suggesting that this antero-medial temporal lobe network indexes flavour knowledge across the FTLD syndromic spectrum.

The grey matter correlates of flavour identification here included entorhinal cortex, hippocampus, parahippocampal gyrus and temporal pole. In line with our prior anatomical hypotheses, this neuroanatomical profile comprises brain substrates in the antero-medial temporal lobe previously implicated in the associative processing of chemosensory stimuli (Small et al., 1997, 2001a, 2001b, 2004, 2005; Small, 2006; Gorno-Tempini et al., 2004b; Rolls, 2005; Luzzi et al., 2007; Rami et al., 2007; Gottfried, 2010; Piwnica-Worms et al., 2010). The precise role of each of these structures in flavour analysis remains unclear. However, the hippocampus and parahippocampal region link incoming sensory stimuli with behavioural context (Brown & Aggleton, 2001; De la Cruz et al., 2008; Haase et al., 2009) while the temporal pole integrates semantic processing in different sensory modalities (Lambon-Ralph et al., 2010a), functions that are likely to be integral to flavour processing. The present data in this neurodegenerative disease cohort amplify previous work in patients with dementia (Gorno-Tempini et al., 2004b; Luzzi et al., 2007; Rami et al., 2007; Piwnica-Worms et al., 2010) and with focal brain damage (Small et al., 2001b, 2005): the evidence collectively suggests that the antero-medial temporal lobe is critical for the semantic analysis of flavours. One does not wish to over-emphasize the laterality of the present effects: previous evidence suggests that both the right and the left temporal lobes are involved in flavour processing (Small et al., 1997, 2001b, 2005), and it is likely that both anterior temporal lobes cooperate in a bihemispheric semantic processing network (Lambon-Ralph et al., 2010b). There was no correlate of flavour identification performance identified in OFC in the present FTLD cohort: this is perhaps somewhat surprising in light of previous evidence implicating OFC in processes relevant to flavour identification (Rolls, 2005; Small, 2006). It is speculated that this may reflect the essentially ‘cognitive’ nature of our task here, with minimal requirement for subjects to process the flavour stimuli for behavioural value or

reward potential (flavour dimensions which might be particularly likely to engage OFC (Rolls, 2005)).

From a clinical perspective, these findings have implications for our understanding of abnormal eating behaviour in dementia syndromes. It is plausible a priori that altered flavour processing might lead to altered eating behaviour; in particular, loss of understanding of food items could lead to unusual or inappropriate food preferences or faddism. Current standard behavioural rating scales are not equipped to characterize such altered eating behaviours in detail. Although there was no clear evidence of a simple correlation between eating behaviour and flavour identification here, this may reflect both the relatively small numbers of patients studied and the relatively crude metrics used to assess eating behaviour; it was found that abnormal eating behaviours commonly developed alongside deficits of flavour identification in the bvFTLD and svPPA subgroups (Table 4.1).

The present study has several limitations and suggests directions for future work. As in the study described in Chapter 3, these findings are based on data from a relatively small cohort of subjects representing a particular disease cluster (ie FTLD) at a single time point and using a single neuroimaging technique; here, a single measure of flavour processing was employed with standard behavioural indices. The deficits of flavour processing and neuroanatomical associations identified here suggest that impaired flavour processing is an important feature in this degenerative disease population with predictable anatomical substrates and the potential for clinical consequences. As discussed in Chapter 2, this work should motivate further studies in other neurodegenerative diseases and assessing the longitudinal evolution of flavour deficits in relation to other cognitive and behavioural features, using customized behavioural batteries. The

close linkage between flavour processing, food ingestion and emotional value could constitute an informative model system for assessing disease-related changes in complex behaviour, using multimodal structural and functional imaging approaches.

Chapter 5: MUSIC EMOTION PROCESSING IN FRONTOTEMPORAL LOBAR DEGENERATION

Summary

Despite growing clinical and neurobiological interest in the brain mechanisms that process emotion in music, these mechanisms remain poorly understood. Patients with FTLD frequently exhibit clinical syndromes that illustrate the effects of breakdown in affective and social functioning. This chapter describes an experiment whereby recognition of emotion in music, facial expressions and voices is assessed in a cohort of 26 patients with FTLD (16 with bvFTLD, 10 with SemD) compared with age-matched healthy control subjects. Neuroanatomical associations of emotion recognition performance were assessed using VBM. A deficit in recognition of canonical emotions (happiness, sadness, anger and fear) in music was demonstrated in patients with FTLD. Music emotion performance was a sensitive and specific predictor of disease, comparable to recognition of emotions from facial expressions and a significantly better predictor of disease than emotion recognition from voices. The performance profiles of patients with the bvFTLD and SemD subgroups of FTLD were similar. Analysing each emotion separately, recognition of negative emotions was impaired in all three modalities in FTLD, and this effect was most marked for fear and anger. Impaired recognition of emotions in music was specifically associated with grey matter loss in a distributed cerebral network including amygdala, anterior temporal lobe, insula and orbitofrontal and medial prefrontal cortex. This network constitutes an essential brain substrate for recognition of emotion in music that overlaps with brain regions previously implicated in coding affective value, behavioural context, semantic knowledge and memories. It is proposed that musical emotion recognition probes the

interface of these processes, and delineates a profile of brain damage that is both core to FTLD and essential for the abstraction of complex social emotions.

5.1 Introduction

Despite much recent interest in the neurobiology of music, the brain mechanisms that are critical for processing emotion in music remain poorly understood. Music is universal and highly valued for the powerful emotional responses it engenders: indeed, music activates brain circuitry associated with pleasure and reward (Blood & Zatorre 2001; Menon & Levitin 2005; Boso et al., 2006; Koelsch et al., 2006; Mitterschiffthaler et al., 2007) and musical emotion judgments are consistent amongst members of a musical culture (Peretz et al., 1998; Menon & Levitin 2005). Music has the ability to specifically induce an intense arousal response in normal listeners (Blood and Zatorre, 2001), a response which is mediated by structures such as amygdala and insula that have been implicated in encoding key dimensions of many other kinds of salient emotional stimuli (Adolphs et al., 1994; Anderson et al., 2000; Calder et al., 2001; Cardinal et al., 2002; Dolan, 2007). Deficits of musical emotion comprehension have been reported following focal damage of these same structures (Griffiths et al., 2004 ; Gosselin et al., 2007). This is surprising considering the biological relevance of music is less clear than for other kinds of emotional stimuli (Blood & Zatorre, 2001): unlike emotion-laden animate stimuli such as human faces and voices, music is an abstract entity without obvious survival value. Nevertheless, music serves a clear social role in all human cultures, raising the possibility that the processing of musical signals may have certain similarities with the processing of other kinds of complex social and emotional signals. Music engages brain areas involved in the formation of learned

associations and representation of value in stimuli, including orbitofrontal cortex (OFC) (Rolls, 2004; Menon & Levitin, 2005; Dolan, 2007), as well as dopaminergic reward circuitry (Salimpoor et al., 2011). This conjunction may be the basis for a biologically relevant role for music that is more or less specific for our species.

The processing of musical emotion is likely to involve brain mechanisms that are partly shared with mechanisms that process other emotional stimuli; however, it is also likely that understanding of the emotional content of music depends on additional brain mechanisms that abstract affective information from the analysis of inanimate signals that are qualitatively different from the animate emotional signals that are carried by other modalities such as facial and vocal expressions. One candidate brain mechanism of this kind might be engaged in 'theory of mind' processing: the attribution of mental states to other individuals using emotional and other social cues (Gallagher & Frith, 2003) and based on learned social 'rules' and concepts (Ross & Olson, 2010), including those embodied in music (Steinbeis & Koeslch, 2009). Brain areas that mediate such processes include medial prefrontal and anterior temporal lobe cortices (Saxe et al., 2004; Gallagher & Frith, 2003; Carrington & Bailey, 2009). Neural mechanisms of musical emotion therefore have potentially far-reaching implications for understanding how the brain codes emotional value, and how emotional signals acquire meaning.

While the brain basis of music emotion processing has been studied using functional imaging techniques in healthy subjects (e.g., Blood & Zatorre 2001; Koelsch et al., 2006), to establish critical neural substrates requires alternative approaches that address the effect of strategic brain damage (Griffiths et al., 2004; Stewart et al., 2006). However, naturally-occurring brain lesions are often focal, generally non-uniform and infrequently directed to anatomical locations critical

for emotion processing. The study of populations with neurodegenerative diseases potentially offers a complementary perspective, as such diseases strike distributed but functionally connected brain networks (Seeley et al., 2009). Furthermore there is currently considerable clinical interest in the processing and potential therapeutic uses of music in patients with dementia (Drapeau et al., 2009; Raglio & Gianelli, 2009) with accumulating evidence that the ability to process emotion in music may be differentially affected by different dementia diseases. This is likely to be particularly relevant in FTLD; many patients present with derangements of complex social and emotional behaviour. Impaired emotion processing in FTLD has been documented for facial expressions (Snowden et al., 2001; Rosen et al., 2002b, 2004; Fernandez-Duque & Black 2005; Kessels et al., 2007), voices (Keane et al., 2002; Snowden et al., 2008), and music (Matthews et al., 2009). From a neurobiological perspective, brain damage in FTLD involves distributed brain networks including those implicated in music and emotion processing (Seeley et al., 2009; Schroeter et al., 2008; Zhou et al., 2010).

5.2 Experimental hypotheses

The key objective of this study was to investigate critical neuroanatomical associations of emotion recognition from music in FTLD. The processing of emotion in music is likely to be a hierarchical and multi-component process (Juslin & Laukka, 2003; Juslin & Vastjfall, 2008; Zentner et al., 2008; Koelsch, 2010) and in this study the interest was chiefly in overt recognition of musical emotions, as indexed by patients' ability to categorise the dominant emotional characteristics expressed by a particular musical piece. A novel neuropsychological battery (see Chapter 2) was designed comparable to that used previously to assess emotion recognition in other modalities (fixed-alternative, forced-choice verbal labelling of the expressed emotion) in

order to compare performance on recognition of canonical emotions as represented in music with the same emotions in human facial expressions and nonverbal vocal sounds. Anatomical associations of emotion recognition performance were assessed using VBM. Because music requires the abstraction of emotional content from inanimate cues, it was hypothesised that emotion recognition from music in FTLD is vulnerable to the effects of damage involving distributed brain circuitry for representing and evaluating the emotional content of stimuli; specifically, areas previously implicated in processing valence, salience and subjective states associated with other kinds of emotion-laden stimuli, including mesial temporal structures, insula and their connections in the mesolimbic system. In addition, it was hypothesised that recognition of emotion in music would place particular demands on brain mechanisms involved in analysis and evaluation of the emotional content of complex social signals, including OFC, medial prefrontal and anterior temporal cortex.

5.3 Methods

5.3.1 Subjects

Twenty-six consecutive patients (18 male, 24 right-handed, mean age 63.8 (8.4) years) fulfilling consensus criteria for a diagnosis of FTLD (Neary et al., 1998) were recruited from a tertiary cognitive disorders clinic. The patient cohort comprised two canonical FTLD subtypes: behavioural variant frontotemporal dementia (bvFTLD; n = 16; mean (sd) disease duration 6.9 (4.1) years), characterised by profound personality and behavioural change with frontal and temporal lobe atrophy on brain MRI; and semantic dementia (SemD; n = 10; mean (sd) disease duration 4.6 (1.6) years), characterised by breakdown of verbal and nonverbal knowledge

systems with asymmetric, predominantly left-sided temporal lobe atrophy on MRI. The cases included in this series had typical clinical and radiological profiles of bvFTLD or SemD, as previously described (Edwards-Lee et al., 1997; Chan et al., 2001; Liu et al., 2004). No patients had a history of deafness. In order to characterise the clinical syndrome and to provide background data for the experimental tests, all patients had an assessment of general neuropsychological functions as described in Chapter 2; patients with bvFTLD were also assessed on a test of theory of mind (Mind in the Eyes: Baron-Cohen et al., 2001). Twenty-one healthy control subjects with no history of neurological, psychiatric or otological illness and matched with the patient group for age and educational background also participated. Subject demographic characteristics and background neuropsychological results are summarised in Table 5.1. Most subjects had fewer than two years formal music training, corresponding to the 'least trained' (novice, non-musician) category of musical experience described by Halpern et al., (1995): one of the patients was a professional musician, and two control subjects had had five years of piano lessons in childhood.

Table 5.1 Subject demographics and background psychological scores

	FTLD cases		Controls
	bvFTLD	**SemD**	**(n = 21)**
	(n = 16)	**(n = 10)**	
Age	64.7 (8.0)	62.4 (8.8)	67.0 (8.8)
M:F	15:1	3:7	10:11
Years of education	14.1 (3.5)	12.5 (2.4)	13.4 (3.6)
Years of disease duration	6.9 (4.1)	4.6 (1.6)	n/a
Mini-Mental State Examination score[1]	**26.9 (3.9)**	**24.2 (3.5)**	29.5 (0.7)*
Ravens Advanced Matrices[2**]	**9.2 (3.6)**	12.9 (3.6)	13.8 (1.7)
Camden Pictorial Memory[3] (/30)	**26.7 (4.7)**	26.8 (5.3)	29.5 (0.7)*
Benton Facial Recognition[4] (/54)	45.4 (3.8)	46.5 (4.2)	47.2 (3.1)*
Famous Faces[5] (/12)	**10.7 (1.9)**	**7.3 (4.5)**	11.9 (0.3)*
Synonyms Comprehension[6] (/25)	**20.2 (3.4)**	**16.4 (5.8)**	23.6 (1.4)*
Reading the Mind in the Eyes[7] (/36)	**17.8 (6.7)**	n/a	24.4 (4.9)*
Trail-making test B[8] (scaled score)	**7.4 (4.7)**	**8.0 (3.3)**	12.0 (2.4)*

Mean (s.d.) values are shown. *available for n=10 control subjects; **scaled scores; **bold**, significantly inferior to controls ($p<0.05$); n/a, not available;

1 Folstein MF et al., J Psychiatr Res 1975; 12:189-198; 2 Raven J San Antonio, TX: Harcourt Assessment, 2003; 3 Warrington EK, Psychology Press, 1996; 4 Benton AL *et al.*, Oxford University Press, 1983; 5 Warrington EK, James M. 1967. Cortex 1967; 3: 317-326; 6 Warrington EK *et al.*, Neuropsychol Rehab 1998; 8: 143-154; 7 Baron-Cohen *et al.*, J Child Psychiatry 2001 - this test was not administered to patients with SemD, in order to avoid potentially confounding effects from verbal comprehension impairment; 8 Reitan RM, Indiana University Press, 1958.

5.3.2 Assessment of emotion recognition

A novel battery was designed to assess recognition of four emotions (happiness, sadness, anger, fear) as represented in music, for comparison with recognition of these emotions from facial expression and nonverbal vocal sounds. The target emotions chosen represent four of the six canonical emotions in the original set of emotional faces created by Ekman & Friesen (1976); surprise and disgust were excluded due to the difficulty of creating musical equivalents for these.

Stimuli: music

The stimuli for recognition of emotion in music were excerpts drawn from the Western classical canon and film scores (mean duration (range) as follows: anger 11.6 sec (9.8 – 13.3); fear, 12.2 sec (10.3 – 16.4); happiness, 10.5 sec (8 – 13.3); sadness, 11.6 sec (10.1 – 16)). Stimuli were selected for inclusion in the battery based on an initial pilot study (described in Appendix A2) in 16 healthy subjects who did not participate in the subsequent experiment. Most pieces were orchestral works; some chamber pieces were also included. No vocal musical excerpts were included. Stimuli are listed in Appendix Table A3.

Stimuli: facial expressions

The facial emotion stimuli comprised black and white photographs of posed facial expressions derived from the set produced by Ekman & Friesen (1976); the most reliably recognised exemplars from the original set for each target emotion were selected.

Stimuli: nonverbal vocal sounds

The vocal emotion stimuli were brief nonverbal vocalisations recorded by male and female actors to express each of the same target canonical emotions (Sauter, 2006). The most reliably recognised exemplars from the original set for each target emotion were selected.

General testing procedure

The auditory and visual stimuli of the test were presented on a notebook computer as described in Chapter 2. For each modality, 40 trials were presented, comprising 10 stimuli representing each of the four target canonical emotions. Modalities were presented in a block design, in the order: faces, vocal sounds, music. Within each modality (block), the 40 trials were presented in pseudo-randomised order (i.e., for a particular subject the order of stimulus presentation was random but this same order was used for all subjects). On each trial, the subject was asked to choose which one of the four target emotions was best represented by the stimulus. The words corresponding to the choices on each trial were simultaneously displayed on the computer monitor and spoken by the examiner. Before the start of each modality block, four practice trials were administered to ensure the subject understood the task.

Additional procedures in control subjects

In order to estimate any effect from prior familiarity with the music stimuli on music emotion recognition, healthy control subjects undertaking the experimental battery were asked to decide whether each music stimulus was familiar or unfamiliar.

Arousal may contribute to variance in emotion judgments *(Lang et al.,* 1997). In order to assess the relative arousal potential of stimuli in different modalities, three healthy control subjects

undertaking the test battery were also asked to rate all stimuli using a scoring system based on the Self-Assessment Manikin (SAM) (Bradley & Lang, 1994), a graphic figure depicting values on a scale ranging from 1 (sleepy) to 5 (wide-eyed excitement) (see Appendix A3). Subjects were asked to rate how calm or excited a particular stimulus made them feel using this rating scale.

5.3.3 Assessment of music perception

Music perceptual functions were assessed in a subset of six FTLD patients (3 bvFTLD, 3 SemD) using the Montreal Battery of Evaluation of Amusia (MBEA). The MBEA battery is based on a two alternative (same/different) forced choice comparison of pairs of short unfamiliar musical sequences. Four subtests of the MBEA were used: scale (key), pitch contour (melody), pitch interval, and rhythm. Age-matched normative data for performance on the MBEA are available for musically untrained subjects (Peretz et al., 2003); a subset of 58 normal controls aged 45 years and older derived from this published dataset was used as the comparison group for the patient group here. The patients completing the MBEA were similar in age (mean (sd) 62 (9.8) years), gender (M:F 5:1) and disease severity (mean (sd) 6.5 (3.6) years) to the FTLD cohort as a whole.

5.3.4 Statistical analysis of behavioural data

Statistical analyses were performed using Stata©. For each emotion recognition score by modality (/ 40), by emotion (/ 30), and by modality:emotion combination (/ 10)), the mean (SD) and a 95% bias-corrected bootstrap confidence interval (100,000 bootstrap samples) for the mean was found.

In order to compare emotion recognition in different modalities, the ability of modalities and emotion:modality combinations to discriminate FTLD patients from healthy controls were assessed. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was used to quantify discriminatory ability. The AUC is the probability that, in a randomly selected patient/control pair, the patient has a lower emotion recognition score than the control (Hanley, 1982); perfect discrimination between patient and control groups would correspond to an AUC of 1, while the same distribution of scores in patients and controls would correspond to an AUC of 0.5. Since the AUC generally depends upon the characteristics of the population in which it is calculated, covariate-adjusted AUCs were calculated (Janes & Pepe, 2008; Janes et al, 2009) using the linear adjustment method with covariates of age, gender, and years of education. Covariate-adjusted AUCs for discriminating between the bvFTLD subgroup and controls, between the SemD subgroup and controls, and between FTLD patients (ignoring subgroup) and controls were reported. Similarly, the utility of emotion recognition scores in discriminating between bvFTLD and SemD subgroups was assessed using adjusted AUCs with covariates of age, gender and years of education. Differences between AUCs for different modalities were assessed using a z-test with the bootstrap-estimated standard error.

In order to assess any associations between emotion recognition and theory of mind (Mind in the Eyes test, data from 11 bvFTLD patients), executive function (Trail Making test, data from all FTLD patients) or nonverbal fluid intelligence (Raven's Advanced Matrices, data from 23 FTLD patients), mixed effects logistic regression models were fitted. Separately for each modality, a logistic regression for the individual item response (emotion correctly recognised = 1) was fitted, with random subject and item effects, and the neuropsychological factor and emotion as fixed

effects. Further logistic regressions were fitted using data from control subjects to estimate the effect of music familiarity and years of musical training on the odds of correct emotion recognition in music; the intended (correct) emotion for each musical item and its familiarity (i.e., whether or not it was familiar to the subject) were fixed effects, with random subject and item effects.

Arousal scores from control subjects were analysed using a linear mixed model for mean score in each modality as dependent variable and modality as a fixed effect with subject as a random effect. Mean differences in music perception (MBEA) performance between FTLD patients and the external healthy control sample were compared using t-tests, allowing for unequal standard deviations.

5.3.5 Brain image acquisition and analysis

Image acquisition

MR brain images were acquired in all FTLD patients at the time of behavioural testing, on the same 1.5T GE Signa scanner using the protocol described in Chapter 2.

Image analysis

Brain images were processed using MATLAB 7.0® and SPM2® (http://www.fil.ion.ucl.ac.uk/spm/). Voxel-based morphometry (VBM) was performed using a modified version of an optimised method (Good *et al.*, 2001; Henley *et al.*, 2008; Ridgway et al., 2009) as described in Chapter 2.

Linear regression was used to examine voxel-wise associations between grey matter volume and emotion recognition performance, modelling voxel intensity as a function of emotion recognition score. Neuroanatomical associations of emotion recognition in the three modalities were assessed in separate design matrices for each modality (separate-modality analysis) and in a combined regression matrix including all three modalities (combined-modalities analysis); the latter analysis was designed to assess associations of emotion recognition in a particular modality after adjusting for any association with other modalities and to directly compare modalities. In the combined-modalities analysis, direct pair-wise contrasts between emotion recognition regressors were assessed for music with respect to each of the other modalities; in addition, in order to identify grey matter associations common to different modalities, a conjunction analysis was run for music with respect to each of the other modalities. Age, gender, total intracranial volume (calculated using a previously described procedure: Whitwell et al., 2001) and disease duration were incorporated as covariates. In addition, in order to assess whether grey matter associations of music emotion recognition were modulated by general executive performance, Trails score was also incorporated as a covariate of music emotion recognition score in a separate design matrix.

For each model, statistical parametric maps were examined at two voxel-level statistical thresholds: at $p < 0.05$ after FDR correction over the whole brain (Genovese et al., 2002), and at $p < 0.05$ after small volume correction using anatomical regions based on the *a priori* hypotheses. These anatomical volumes comprised bilateral OFC (including the orbital surface of both frontal lobes and the lateral orbital gyri below the inferior frontal sulcus bilaterally), right and left insula, and right and left temporal lobes anterior to Heschl's gyrus. SPMs were also assessed at an

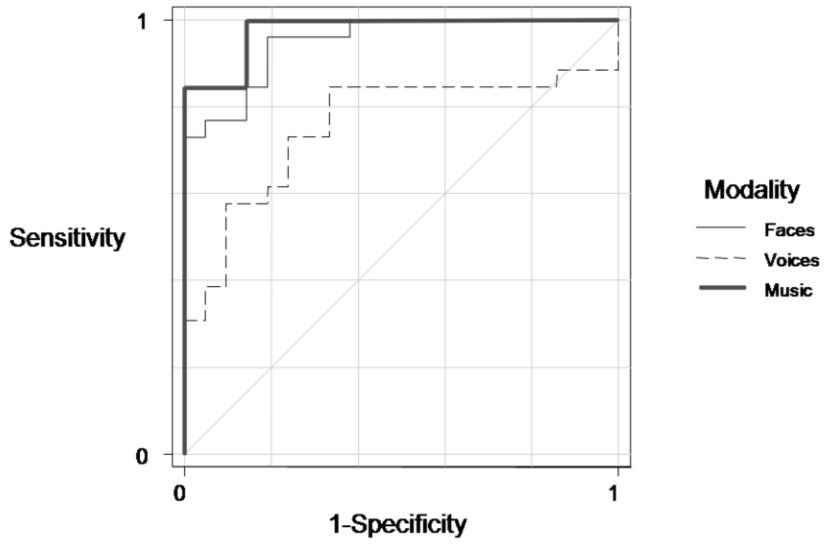
uncorrected significance level $p < 0.001$. In the conjunction analysis, non-orthogonality between the regressors was assumed and a conjoint conjunction threshold was applied ($p < 0.001$ for each of the component regressors).

5.4 Results

5.4.1 Modality and disease effects

The performance of the FTLD subgroups and the healthy control group on emotion recognition tests within and between modalities is summarised in Table 5.2. Overall, both patients and healthy control subjects scored highest for emotion recognition from faces, followed by voices, and music. Table 5.3 shows AUCs for the various combinations of modality and emotion comparing each FTLD subgroup and the combined FTLD group with the healthy control group, and comparing the two FTLD subgroups with one another. Figure 5.1 shows covariate (age, gender, years of education) adjusted ROC curves using emotion recognition performance in each modality to discriminate between FTLD patients (ignoring subtype) and controls.

Figure 5.1 Prediction of disease by emotion recognition modality. Covariate (age, gender, years of education) adjusted ROC curves, using total emotion recognition scores (/40) in each modality to discriminate between FTLD patients (ignoring subtype) and controls.



Comparing total music emotion recognition scores between the combined FTLD group and controls, the AUC was 0.98 (95% CI 0.86, 1.00, $p<0.05$) (Table 5.3 and Figure 5.1): i.e., an estimated 98% probability that a randomly selected patient scores lower than a healthy control subject matched for age, gender and education. The AUC for total facial emotion recognition score was similar to music (0.95, 95% CI 0.84, 0.99). There was no evidence that the music and face emotion modalities differ in their discriminatory ability ($p=0.45$). The AUC for total vocal emotion recognition score (0.76, 95% CI 0.58, 0.91) was statistically significantly greater than 0.5, indicating that vocal emotion recognition performance also discriminates FTLD patients from controls. However, there was evidence that the discriminatory power of vocal emotion recognition is significantly lower than discrimination from emotion recognition in music ($p=0.009$) and faces ($p=0.02$). The separate analyses comparing the bvFTLD and SemD

subgroups with healthy controls showed very similar results to those for the combined FTLD group. When the disease subgroups were directly compared none of the estimated AUCs differed significantly from 0.5: i.e., there was no evidence that emotion recognition performance discriminates between bvFTLD and SemD.

Within the control group, estimated mean scores were lowest for anger and fear particularly in music. This effect was further exaggerated in the FTLD groups, whose performance was worst for anger and fear in all modalities but much more so in music (Table 5.3).

5.4.2 Relations with general neuropsychological and other factors

There was a significant association between performance on tests of theory of mind and emotion recognition in each modality (see Appendix Table A4). There was a significant association between executive performance and emotion recognition in music and voices, and a significant association between a non-verbal fluid intelligence measure and emotion recognition in music and faces (and a borderline statistically significant association with emotion recognition in voices). In the healthy control group, there was evidence of an association between familiarity of musical pieces and emotion recognition performance in music: the odds of correctly identifying the target emotion on a given trial were almost doubled if the music was familiar (see Appendix Table A4). There was no evidence of any association between musical emotion recognition and previous musical training. Based on data from three control subjects, there was strong evidence ($p<0.005$) that arousal scores differed between modalities: the mean arousal score for music was 1.08 (95% CI 0.76, 1.39) higher than for faces and 1.00 (95% CI 0.69, 1.31) higher than for voices.

Table 5.2 Mean scores for healthy control, bvFTLD and SemD groups in tests of emotion recognition in different modalities and for individual emotions combining modalities.

Modality	Emotion	Mean score (SD) (95% CI for mean)		
		Controls	bvFTLD	SemD
Faces	Total† / 40	37.6 (1.40) (37.1, 38.2)	32.3 (4.29) (30.2, 34.3)	32.5 (5.87) (28.6, 35.5)
	Happiness /10	10 (0)*	9.75 (0.58) (9.50, 10.0)	9.90 (0.32) (9.80, 10.0)
	Sadness /10	9.62 (0.81) (9.33, 10.00)	8.50 (1.46) (7.81, 9.19)	8.20 (1.93) (7.00, 9.20)
	Anger /10	8.14 (1.15) (7.71, 8.67)	6.56 (2.10) (5.63, 7.56)	6.90 (2.03) (5.70, 8.10)
	Fear /10	9.86 (0.48) (9.67, 10.00)	7.50 (2.00) (6.56, 8.44)	7.50 (2.22) (6.20, 8.70)
Voices	Total† /40	35.0 (3.26) (33.5, 36.2)	29.7 (5.85) (26.7, 32.3)	29.0 (8.21) (23.7, 33.4)
	Happiness /10	8.24 (1.61) (7.57, 8.90)	8.25 (1.77) (7.44, 9.06)	7.70 (2.26) (6.30, 9.00)
	Sadness /10	9.43 (0.87) (9.05, 9.76)	8.13 (2.19) (7.00, 9.06)	7.30 (2.00) (6.20, 8.50)
	Anger /10	8.24 (1.51) (7.62, 8.86)	6.75 (1.91) (5.94, 7.75)	6.90 (2.51) (5.40, 8.30)
	Fear /10	9.05 (1.32) (8.48, 9.57)	6.56 (2.63) (5.38, 7.88)	7.10 (3.07) (5.20, 8.80)
Music	Total† /40	32.9 (2.63) (31.9, 34.1)	21.8 (5.55) (19.2, 24.4)	21.2 (6.03) (17.8, 24.9)
	Happiness /10	8.86 (1.24) (8.38, 9.38)	7.81 (1.94) (6.44, 8.63)	7.10 (1.73) (6.20, 8.20)
	Sadness /10	9.29 (1.01) (8.86, 9.67)	6.81 (2.48) (5.63, 7.94)	6.40 (1.96) (5.30, 7.60)
	Anger /10	7.38 (1.60) (6.76, 8.10)	3.13 (1.75) (2.31, 4.00)	3.20 (1.93) (2.10, 4.30)
	Fear /10	7.38 (1.16) (6.95, 7.90)	4.06 (1.95) (3.19, 5.06)	4.50 (2.51) (3.10, 6.00)
Total††	Happiness /30	27.1 (1.97) (26.3, 27.9)	25.8 (3.41) (24.0, 27.3)	24.7 (3.20) (22.9, 26.6)
	Sadness /30	28.3 (1.80) (27.6, 29.1)	23.4 (5.19) (20.6, 25.6)	21.9 (5.38) (18.7, 25.0)
	Anger /30	23.8 (2.97) (22.6, 25.1)	16.4 (4.47) (14.5, 18.8)	17.0 (5.54) (13.4, 19.9)
	Fear /30	26.3 (1.88) (25.5, 27.1)	18.1 (5.28) (15.6, 20.6)	19.1 (7.16) (14.6, 23.0)

CI, confidence interval; SD, standard deviation; * CI not reported: since all controls scored 10/10 for recognition of happy faces, bootstrapping cannot provide a valid CI. † total score for modality over all emotions. †† total score for emotion over all modalities.

Table 5.3 Estimated area under the covariate (age, gender, years of education) adjusted ROC curves (95% bootstrap CI)

Modality	Emotion	Adjusted AUC (95% CI)			
		FTLD vs controls	bvFTLD vs controls	SemD vs controls	SemD vs bvFTLD
Faces	Total† / 40	**0.95 (0.84, 0.99)**	**0.98 (0.87, 1)**	**0.90 (0.69, 1)**	0.61 (0.36, 0.87)
	Happiness /10	**0.58 (0.54, 0.67)***	**0.59 (0.53, 0.75)***	**0.55 (0.50, 0.75)***	0.55 (0.41, 0.69)*
	Sadness /10	**0.78 (0.62, 0.91)**	**0.79 (0.54, 0.95)**	0.76 (0.47, 0.97)	0.52 (0.26, 0.83)
	Anger /10	**0.73 (0.56, 0.86)**	**0.77 (0.56, 0.93)**	0.67 (0.39, 0.88)	0.56 (0.31, 0.81)
	Fear /10	**0.93 (0.84, 0.99)**	**0.96 (0.88, 1)**	**0.89 (0.66, 1)**	0.54 (0.31, 0.80)
Voices	Total† /40	**0.76 (0.58, 0.91)**	0.71 (0.46, 0.90)	**0.84 (0.60, 0.99)**	0.35 (0.14, 0.62)
	Happiness /10	0.45 (0.27, 0.64)	0.35 (0.15, 0.60)	0.61 (0.35, 0.86)	0.27 (0.08, 0.51)
	Sadness /10	**0.74 (0.54, 0.90)**	0.68 (0.41, 0.89)	**0.83 (0.58, 0.99)**	0.33 (0.13, 0.60)
	Anger /10	**0.68 (0.51, 0.84)**	0.63 (0.41, 0.85)	0.75 (0.49, 0.95)	0.43 (0.21, 0.72)
	Fear /10	**0.76 (0.60, 0.88)**	**0.76 (0.55, 0.91)**	0.75 (0.48, 0.95)	0.51 (0.27, 0.78)
Music	Total† /40	**0.98 (0.86, 1)**	**0.98 (0.78, 1)**	**0.97 (0.83, 1)**	0.47 (0.22, 0.73)
	Happiness /10	0.70 (0.49, 0.85)	0.63 (0.37, 0.84)	**0.81 (0.56, 0.94)**	0.30 (0.10, 0.56)
	Sadness /10	**0.88 (0.76, 0.97)**	**0.87 (0.71, 0.98)**	**0.90 (0.68, 1)**	0.45 (0.21, 0.72)
	Anger /10	**0.97 (0.90, 1)**	**0.98 (0.89, 1)**	**0.97 (0.83, 1)**	0.53 (0.24, 0.83)
	Fear /10	**0.92 (0.81, 0.99)**	**0.98 (0.89, 1)**	**0.83 (0.57, 1)**	0.64 (0.39, 0.87)
Total††	Happiness /30	0.62 (0.44, 0.80)	0.52 (0.30, 0.76)	**0.78 (0.52, 0.95)**	0.31 (0.14, 0.57)
	Sadness /30	**0.88 (0.73, 0.96)**	**0.89 (0.71, 0.98)**	**0.85 (0.60, 0.99)**	0.41 (0.18, 0.69)
	Anger /30	**0.89 (0.75, 0.97)**	**0.88 (0.68, 0.99)**	**0.91 (0.70, 0.99)**	0.52 (0.26, 0.79)
	Fear /30	**0.95 (0.86, 0.99)**	**0.98 (0.93, 1)**	**0.89 (0.66, 1)**	0.58 (0.33, 0.81)

* area under the unadjusted ROC curve (AUC) shown, since covariate effects in controls could not be estimated due to all controls scoring 10/10 for happy faces. † total score for modality over all emotions. †† total score for emotion over all modalities. Confidence intervals excluding 0.5 (bold) indicate that the corresponding measure has discriminatory power.

In the subset of FTLD patients assessed on the MBEA, there was no evidence of a difference in performance between FTLD patients and controls (differences in means (95% CI)) for scale (2.22 (-0.14, 4.57)), contour (0.99 (-0.96, 2.95)) or rhythm (0.16 (-2.44, 2.76)) subtests. Patients with FTLD had evidence of a lower mean performance than controls on the interval subtest (difference in means 2.91 (1.47, 4.35)), however all performed within the normative range for age-matched controls.

5.4.3 Neuroanatomical associations

As the behavioural profiles of the bvFTLD and SemD subgroups were very similar these subgroups were combined in the VBM analysis. For the combined FTLD group, emotion recognition performance (total score across emotions) was associated with grey matter density in overlapping but distinct cerebral networks in each modality. Statistical parametric maps of grey matter loss associated with impaired emotion recognition in music, faces and voices are shown in Figure 5.2; local maxima of grey matter loss are summarised in Table 5.4.

Considering first the separate-modality analyses, recognition of emotion from music was positively associated with grey matter in an extensive bilateral cerebral network including insula, anterior cingulate, OFC and medial prefrontal (anterior paracingulate) cortex, dorsal prefrontal, inferior frontal, anterior and superior temporal cortices, fusiform and parahippocampal gyri, more posterior parietal cortices, limbic areas including amygdala and hippocampus, and other subcortical structures including nucleus accumbens and ventral tegmentum (all at significance threshold $p<0.05$ corrected for multiple comparisons over the whole brain). Covarying for a general executive measure (Trails score) produced a very similar profile of grey matter associations (Appendix Figure A1). Impaired recognition of emotion in facial expressions was

associated with grey matter loss in left lateral OFC and bilateral insula ($p<0.05$ FDR corrected for anatomical small volumes of interest), bilateral superior temporal sulcus, bilateral prefrontal cortices, anterior and posterior cingulate and left anterior temporal cortex ($p<0.001$ uncorrected). Impaired recognition of emotion in voices was associated with grey matter loss in a left-sided cerebral network including parahippocampal gyrus, temporal pole, lateral OFC, anterior cingulate and insula (all $p<0.001$ uncorrected). When emotion modalities were compared in a common regression analysis, grey matter substrates for recognition performance for emotion in music ($p<0.05$ FDR corrected for anatomical small volumes of interest), faces and voices (both $p<0.001$ uncorrected) were similar to those revealed by the separate modality-specific regression analyses shown in Figure 5.2.

Although certain grey matter regions were similarly associated with emotion recognition from music and faces (Table 5.4), no voxels were found to be common to two or more modalities in a conjunction analysis (conjoint conjunction threshold $p<0.001$ uncorrected). In a direct contrast between music and vocal emotion regressors in the combined-modalities analysis, a significantly stronger association with emotion recognition from music versus voices was identified in a bilateral cortical network including lateral OFC, medial prefrontal cortex and insula (all $p < 0.05$ corrected for anatomical small volumes of interest; local maxima in Appendix Table A5). No grey matter areas showed evidence of a significantly stronger (or weaker) association with emotion recognition from music contrasted with faces.

Figure 5.2 Statistical parametric maps (SPMs) of grey matter loss associated with impaired emotion recognition in music and faces. Maps are based on separate modality-specific regression analyses (see Methods). SPMs are presented on sections of the normalised structural template brain image in MNI stereotactic space; the left hemisphere is on the left and slice coordinates in mm are shown. For music, SPMs are thresholded at p<0.05 FDR corrected for multiple comparisons over the whole brain volume; for other emotion modalities, SPMs are thresholded at p<0.001 uncorrected.

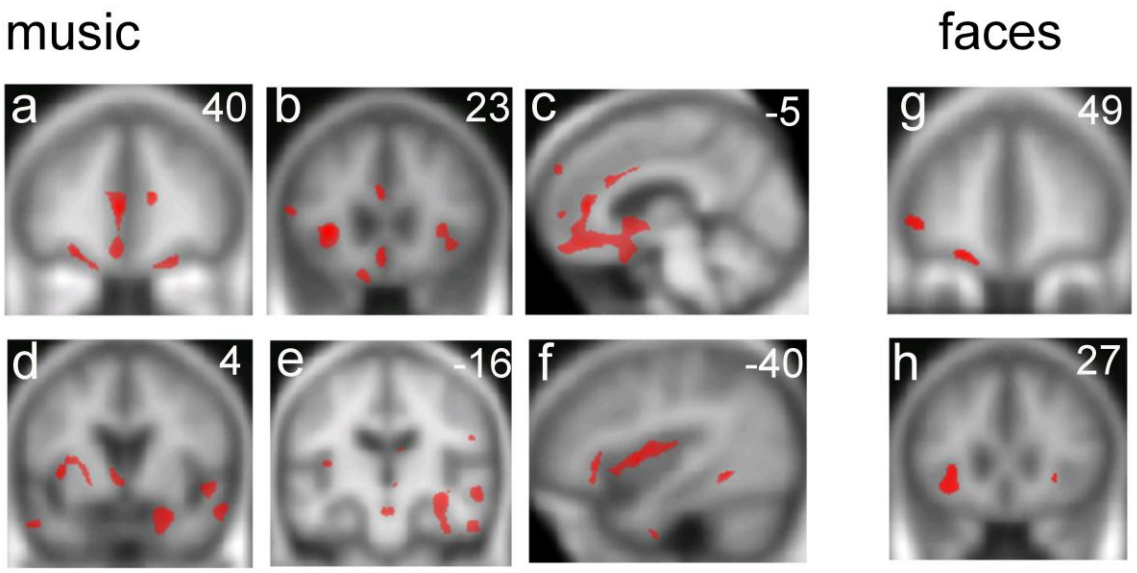


Table 5.4 Local maxima of grey matter loss associated with impaired emotion recognition in FTLD

Emotion modality	Brain region R	Brain region L	MNI coordinates x, y, z (mm)	Z score
Music*		anterior insula	-33 23 3	5.10
		ACC	-4 39 10	4.81
		lateral OFC	-17 15 -23	4.32
	amygdala		25 6 -25	4.27
		FG	-40 -50 -7	4.18
		temporal pole	-55 7 -30	4.18
	ACC		13 40 16	4.13
		medial OFC	-2 25 -12	4.05
	inferior parietal		55 -18 26	4.03
		caudate / basal ganglia	-8 9 -4	4.00
	anterior insula		31 30 0	3.92
	hippocampus		37 -16 -13	3.90
	fusiform		50 -27 -19	3.80
		parieto-occipital cortex	-24 -85 11	3.79
	anterior STS/STG		60 3 -21	3.79
		middle STG	-54 -23 -2	3.74
		IFG	-45 50 -3	3.64
	dorsal PFC		22 12 53	3.64
	medial PFC		2 54 20	3.62
	lateral OFC		24 40 -21	3.58
		medial PFC	-4 59 36	3.48
	MTG		67 -28 -15	3.47
		MTG	-65 -9 -22	3.42
	PHG		19 -14 -38	3.36
	frontal pole		29 62 1	3.30
	fornix		8 -17 18	3.23
Faces		posterior STS/MTG	-54 -37 -7	4.37
		IFG**	-50 40 -4	4.08
		anterior insula**	-36 15 4	3.96
	anterior insula**		29 26 -4	3.85
		lateral OFC**	-22 49 -16	3.83
		dorsal PFC	-39 7 54	3.83
		frontal operculum**	-37 28 -9	3.81
		ACC	-4 40 8	3.74
		temporal pole	-40 16 -41	3.72
	posterior STS		48 -43 14	3.62
	PCC / precuneus		18 -38 47	3.62
		anterior MTG	-65 -5 -25	3.52
	dorsal PFC		6 71 18	3.44
Voices		parahippocampal gyrus	-38 -50 -6	4.70
		temporal pole	-43 11 -39	3.79
		IFG/lateral OFC	-45 53 0	3.70
		ACC	-9 -1 41	3.65
		anterior insula	-33 29 0	3.28
		lateral OFC	-25 44 -17	3.27

The Table shows maxima exceeding threshold $p < 0.001$ (uncorrected for whole brain volume) and cluster extent of 50 voxels, derived from separate modality-specific regression analyses. *Whole-brain correction using FDR $p<0.05$. **Areas surviving small volume correction ($p < 0.05$); Key: ACC, anterior cingulate gyrus; FG, fusiform gyrus; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; MNI, Montreal Neurological Institute stereotactic space; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PCC, posterior cingulated gyrus; PFC, prefrontal cortex; PHG, parahippocampal gyrus; PL, parietal lobe; SMA, supplementary motor area; STG, superior temporal gyrus; STS, superior temporal sulcus

5.5 Discussion

This experiment provides evidence for impaired recognition of emotion in music in patients with FTLD relative to healthy individuals, and a profile of brain atrophy associated with this deficiency of musical emotion processing has been demonstrated. Music emotion recognition performance was a sensitive and specific marker of brain damage in this patient group, comparable as a predictor of disease (ROC analysis) to emotion recognition from facial expressions and significantly superior to emotion recognition from voices. Deficient emotion recognition in music had a critical brain substrate comprising a distributed bilateral cerebral network including insula, OFC, medial prefrontal cortex, amygdala and other limbic structures, anterior temporal and more posterior parietal cortices and striatum.

Music is a complex stimulus and music processing is potentially affected by a range of cognitive and experiential factors: it is legitimate firstly to ask how such factors might have influenced the behavioural and anatomical profiles observed. The findings were not attributable simply to age, gender, musical or educational background, or clinical duration of disease. Emotion recognition performance was influenced by executive function for music and voices, but not facial expressions: this executive effect did not mirror the overall profile of emotion recognition across modalities (as assessed using AUC discriminability from healthy controls). There was evidence

of a relative musical perceptual deficit affecting pitch interval discrimination in the subset of FTLD patients in which this was assessed. However, patients all performed within the normative control range for pitch interval processing; in any case, affective information carried by pitch intervals is in general less salient than other factors such as tempo and melody (Maher, 1980; Juslin & Laukka, 2003; Juslin & Vastjfall, 2008) which patients here processed normally. Music was rated as more highly arousing than faces or voices by healthy control subjects, making it unlikely that the deficit of music emotion recognition shown by patients was due to intrinsically lower affective salience of music. It remains possible that the deficit exhibited by patients was at least partly underpinned by a disease-associated failure of subjective arousal. However, previous work incorporating autonomic reactivity measures did not produce evidence that emotion recognition deficits in FTLD are underpinned by a failure of reactivity (Werner et al., 2007); moreover, autonomic response has been shown to dissociate from other emotional responses to music in brain-damaged populations (Johnsen et al., 2009). Taking these various factors into account, the clinical and neurobiological implications of these findings are now considered.

From a clinical perspective, the present findings corroborate an extensive clinical literature demonstrating that patients with FTLD have deficits processing emotion in various modalities. It has previously been observed that processing of emotion in music may be relatively resistant to brain damage (Peretz et al., 1998): in conjunction with the findings which will be discussed in Chapter 6, the present findings suggest a qualification of this conclusion. Processing of musical emotions has been shown to be spared in Alzheimer's disease (Drapeau et al., 2009; Gagnon et al., 2009), suggesting that the deficit identified here is not a universal accompaniment of neurodegenerative disease but may be relatively specific to certain degenerative pathologies:

notably, those in the FTLD spectrum. Behavioural interventions such as music therapy in patients with dementia have attracted much recent interest (Drapeau et a., 2009; Raglio & Gianelli, 2009; Choi et al., 2009): the present findings suggest a need for selectivity both in targeting particular disease populations and potentially also in the form of the intervention, and should motivate future work in this area. More fundamentally, our findings suggest a truly 'panmodal' deficit of emotional understanding in FTLD. This deficit implicates not only animate emotional modalities such as facial and vocal expressions, but 'inanimate' abstract emotional stimuli such as music.

From a neurobiological perspective, the cerebral associations of music emotion recognition included, as anticipated, areas previously implicated in processing certain dimensions of emotion across a range of emotional stimuli. These included areas involved in processing emotional valence and intensity (amygdala, striatum: Adolphs et al., 1994; Anderson et al., 2000; Calder et al., 2001; Blood & Zatorre, 2001; Cardinal et al., 2002; Dolan, 2007; Gosselin et al., 2007; Mitterschiffthaler et al., 2007), 'reward' (ventral striatum: Blood & Zatorre, 2001; Cardinal et al., 2002; Brown et al., 2004; Menon & Levitin, 2005; Koelsch et al., 2006; Mitterschiffthaler et al., 2007; Suzuki et al., 2008), coupling of subjective feeling states and autonomic responses (insula: Calder et al., 2001; Blood & Zatorre, 2001; Molnar-Szakacs & Overy, 2006; Critchley, 2009) and representation of stimulus value (OFC: Rolls, 2004; Menon & Levitin, 2005; Dolan, 2007) from music as well as facial expressions and other sensory stimuli. In the present study, anterior insula and lateral OFC damage was associated with impaired emotion recognition from both music and faces, consistent with a generic role for these areas in the analysis, representation and contextual evaluation of emotional signals. Amygdala damage was associated with impaired emotion recognition only from music: it is possible that this might reflect greater dependence on

subjective arousal responses for coding musical emotion compared with the other stimuli used in this study (Dolan, 2007). This factor may also account for anterior cingulate gyrus involvement in the music condition (Mitterschiffthaler et al., 2007).

Music emotion recognition performance was associated with a number of other brain areas not identified with facial or vocal emotion recognition. The behavioural data here suggest that patients with FTLD had comparable deficits of music and face emotion recognition, based on the comparable power of a deficit in either modality to detect the presence of disease in relation to the performance of healthy subjects (Figure 5.1), and similar variance of music and facial expression recognition scores across the FTLD group. It could therefore be argued that the more extensive neuroanatomical associations of musical emotion recognition here reflect additional processes that are particularly associated with processing emotions from music (and perhaps less strongly associated with emotion recognition via other modalities). These music-associated brain areas included medial prefrontal (anterior paracingulate) cortex and antero-mesial temporal lobes and the superior temporal sulcus, previously implicated in evaluating diverse emotional stimuli and others' mental states based on conceptual and autobiographical learning and theory of mind processes (Saxe et al., 2004; Gallagher & Frith, 2003; Carrington & Bailey, 2009; Steinbeis & Koeslch, 2009; Ross & Olson, 2010). These neuroanatomical findings corroborate previous evidence in healthy individuals indicating that music is potentially both highly engaging for the human limbic system (Blood & Zatorre, 2001) and a rich source of semantic and autobiographical associations that interact with emotion judgments (Eldar et al., 2007; Eschrich et al., 2008). While the concept of meaning in music is problematic, there is an important sense in which the 'meaning' of a piece of music is the emotional message it conveys, which must be actively decoded by the brain based partly on associations learned by exposure to a musical

culture (Peretz et al., 1998; Juslin & Vastfjall, 2008) and past experience of the particular musical piece (Eschrich et al., 2008), as well as transcultural factors (Fritz et al., 2009). It is noteworthy that the bvFTLD subgroup in this study exhibited a deficit of theory of mind (Table 1) as indexed by the Reading the Mind in the Eyes test (Baron Cohen et al., 2001; this test is not suitable for patients with SemD as it requires relatively sophisticated verbal comprehension). The neuroanatomical findings in this patient population provide circumstantial evidence for involvement of theory of mind processing in the interpretation of musical emotions. Since the musical pieces used here were all nonvocal ensemble (mainly orchestral) excerpts, it is unlikely the stimuli conveyed a strong sense of individual human agency. Rather, the findings suggest that recognition of emotion in music may entail attribution of a 'mental state' to an abstract stimulus. This is consistent with fMRI evidence for mental state attribution to musical pieces by healthy individuals (Steinbeis & Koelsch, 2009).

Previous anatomical and functional evidence in both healthy and disease populations suggests that the disparate brain areas identified here as associated with musical emotion recognition are linked via a distributed brain network or networks. Anatomically, the key structures (amygdala, antero-mesial temporal lobes, insula, striatum, anterior cingulate, OFC and prefrontal cortex) are densely and reciprocally interconnected (Cardinal et al., 2002; Rolls 2004; Brown et al., 2004; Menon & Levitin, 2005; Gosselin et al., 2006; Dolan, 2007; Schroeter et al., 2008; Seeley et al., 2006, 2009). Integrity of this network may be maintained in part by VENs concentrated at anatomical hubs including anterior cingulate, insula and prefrontal cortex (Seeley et al., 2006, 2009). Functionally, the components of this putative network have frequently been observed to be coactivated during the processing of emotions in music and other stimuli (Blood & Zatorre, 2001; Menon & Levitin, 2005; Baumgartner et al., 2006; Eldar et al., 2007; Mitterschiffthaler et

al., 2007; Carrington & Bailey, 2009; Steinbeis & Koelsch, 2009), and enhanced effective connectivity between mesolimbic and cortical components of the network during music listening has been demonstrated (Menon & Levitin, 2005). As mentioned in Chapter 1, the modulation of interactions between frontostriatal and limbic circuit systems involve dopaminergic mechanisms including structures such as the ventral tegmental area (VTA), which projects direct dopaminergic innervations to prefrontal, OFC and cingulate cortices (Le Moal & Simon, 1991; Oades & Halliday, 1987) and forms part of the "general learning system" proposed by Thompson (1993). These dopaminergic pathways have recently been shown to be directly activated during pleasurable response to music (Salimpoor et al., 2011). All key components of the mesolimbic (ventral tegmental area, nucleus accumbens, amygdala, hippocampus) and mesocortical (OFC, medial prefrontal cortex) dopaminergic systems were identified in the present study.

This network could potentially have a generic role in linking brain mechanisms for assigning emotional value (in music and other stimuli) with mechanisms that assess the behavioural context and relevance of the stimulus in relation to conceptual knowledge, memories and other sensory signals. This interpretation fits with involvement of the anterior structures previously implicated in processing emotionally salient stimuli (Seeley et al., 2006, 2009). The present results underscore the involvement of the phylogenetically ancient dopaminergic mesolimbic brain reward system during music processing (Salimpoor et al., 2011), and further suggest that this involvement is not merely epiphenomenal but required for comprehension of the emotional content of music, as previously forecast (Menon & Levitin, 2005). The cortical components of the network may be loaded particularly where cognitive processing demands are high (for example when labelling specific musical emotions, as in the present study). Moreover, the

present results show that whilst FTLD patients have greater difficulty recognising fear and anger in faces and voices compared to other emotions, this effect was markedly exaggerated for recognition of emotion in music. This suggests that music emotion recognition may require a greater degree of abstraction, whereas biologically, fear and anger in faces and voices are more likely to induce primal responses to threatening stimuli. This abstract representation of emotion in music may require the interaction of frontal and temporal mechanisms, hence areas which are particularly vulnerable in FTLD. Dependence on this interaction would also be consistent with the similar behavioural performance of the bvFTLD (frontotemporal atrophy) and SemD (temporal atrophy) groups here. The profile of network damage identified subsumes previous lesion studies demonstrating that defects of emotion recognition in music may result from focal insults involving anterior and mesial temporal lobes, prefrontal cortex, insula and parieto-temporal cortices (Griffiths et al., 2004; Gosselin et al., 2005, 2006, 2007; Stewart et al., 2006; Johnsen et al., 2009).

It is not the intention of this study to suggest that the network mediating music emotion recognition as delineated here necessarily or indeed usually operates en bloc. Indeed, the areas identified here could constitute at least two functionally distinct networks, a mesolimbic network involved in assigning behavioural value to music and a cortical network involved in processing this information in the context of past experience, intimately linked by hub structures including the anterior cingulate and insula. This issue of network differentiation is importantly informed by recent evidence concerning the network basis for neurodegenerative disease (Seeley et al., 2009; Zhou et al., 2010). The neuroanatomical associations of music emotion recognition here overlap with both the anterior peri-allocortical salience network previously linked with bvFTLD and the temporal pole-subgenual-ventral striatum-amygdala network previously linked with SemD (Zhou

et al., 2010). While the intrinsic connectivity profiles and syndromic associations of these networks have previously been shown clearly to be dissociable, the interactions of the networks during cognitive processing remain to be fully explored. Correlation with behavioural performance as in the present study offers a potential avenue to assess network interactions. The extent and nature of network differentiation and modulation by behavioural tasks are key issues for future work.

There are several potential caveats to this study. Previous studies have assessed different kinds of musical emotion judgment, and it is likely that musical emotion is processed hierarchically, more 'primitive' attributes (such as dissonance / consonance, unpleasant / pleasant) and generic emotional responses to highly familiar music (e.g., Matthews et al., 2009) being potentially more resistant to the effects of brain damage than specific emotion labels, such as those required here. Related to this, there is no objective measure of emotional arousal in this patient group. At a more basic level, however, it remains unclear to what extent music can instantiate simple emotion categories such as those represented in canonical facial expressions and how far musical emotions can be categorised verbally (Zentner et al., 2008). An important rationale for this study was to compare processing of emotions in music with analogous emotions in other modalities. However, while there is evidence that the taxonomy of emotions in music partly converges with other modalities, the repertoire of music-specific emotions appears to be wide (Zentner et al., 2008): this discrepancy should be explored in future studies. A further factor that may have confounded comparisons between music and other emotion modalities in this and much previous work is the use of more or less familiar musical examples alongside novel stimuli in other sensory channels. Ideally, musical emotion recognition should be assessed using novel musical pieces, in order to assess the extent to which the involvement of brain memory systems in the

antero-mesial temporal lobes and beyond (as demonstrated here) reflects the processing of familiarity rather than musical emotion per se. Finally, the chief interest in this study was modality-specific anatomical associations of emotion processing; however, in future work it will be important to address brain substrates for processing particular emotions independently of modality, and interactions between emotion and modality, which the present study was under-powered to detect.

Taking these caveats into account, the present neuropsychological and neuroanatomical findings suggest that the processing of emotion in music may tap a core pathophysiological lesion of FTLD, namely, the breakdown of a vulnerable frontotemporal network (Seeley et al., 2009). It has previously been proposed that FTLD may be a paradigmatic disorder of social cognition to which humans are particularly susceptible (Seeley et al., 2006), and core deficits in emotion processing may contribute to alterations of more complex social behaviours in FTLD (Lavenu et al., 1999; Bathgate et al., 2001). It has been argued elsewhere that music provides a substrate for integrating emotional states with complex social behaviours (Molnar-Szakacs & Overy, 2006). The present study suggests a convergent formulation: the processing of emotion in music may act as a model system for the abstraction of emotions in complex real-life social situations and for the breakdown of emotional understanding in particular disease states. This interpretation would be consistent with the observation that (in contrast to FTLD) comprehension of both social signals and music is often retained in Alzheimer's disease (Drapeau et al., 2009). A capacity to capitalise on past emotional experience encapsulated in music would require interactions between musical affective and mnestic processing: such interactions would be influenced in turn by musical familiarity, consistent with present and previous evidence (Juslin & Laukka, 2003; Eldar et al., 2007; Juslin & Vastjfall, 2008; Eschrich et al., 2008). Recent insights

into the organisation of large-scale brain networks provide a framework for addressing these issues (Seeley et al., 2007,2009; Zhou et al., 2010), while the distinct network profiles of different dementia diseases (for example, sparing of the salience network in Alzheimer's disease) predicts differential patterns of performance in the analysis of musical emotion. Future work should address these issues using the complementary perspectives provided by functional imaging of the healthy brain and the analysis of music processing in other neurodegenerative diseases (for example, Huntington's disease) with defective emotion encoding.

Chapter 6: MUSIC KNOWLEDGE IN DEMENTIAS

Summary

Despite much recent interest in the clinical neuroscience of music processing, the cognitive organisation of music as a domain of nonverbal knowledge has been little studied. The present study addresses this issue systematically in two expert musicians with clinical diagnoses of semantic dementia (SemD) and dementia with Lewy bodies (DLB) in comparison with a control group of healthy musicians. In a series of neuropsychological experiments, recognition of musical compositions (musical objects), musical emotions, musical instruments (musical sources) and music notation (musical symbols) was investigated. These aspects of music knowledge were assessed in relation to musical perceptual abilities and extra-musical neuropsychological functions. The patient with SemD showed relatively preserved recognition of musical compositions and musical symbols despite severely impaired recognition of musical emotions and musical instruments from sound. In contrast, the patient with DLB demonstrated relatively intact recognition of popular compositions, but impaired recognition of large-scale classical music with somewhat better recognition of composer and musical era, and normal recognition of musical instruments from sound, despite deficits in music perception and musical emotion recognition. The findings suggest that associative knowledge of music is separable from processes of verbal mediation and music perception. The various dimensions of music knowledge are multiply fractionated, and superordinate musical knowledge is relatively more robust than knowledge of particular music. Based on these findings, it is proposed that music constitutes a distinct domain of nonverbal knowledge but shares certain cognitive organisational features with other brain knowledge systems. Within the domain of music knowledge,

dissociable cognitive mechanisms process knowledge derived from physical sources and knowledge of abstract musical entities.

6.1 Introduction

Understanding of the cognitive and neurological bases for music processing has advanced greatly in recent decades (Peretz & Coltheart 2003; Peretz & Zatorre 2005; Koelsch & Siebel 2005; Stewart et al. 2006). However, while the perceptual and affective dimensions of music have received much attention, the cognitive organisation of music knowledge has been less widely studied. Knowledge of music is multidimensional, involving abstract objects (compositions, notes), emotions as represented in music, physical sources (instruments), and symbols (musical notation). Each of these dimensions of music could be considered to convey 'meaning' beyond the purely perceptual features of the sounds or notations that compose them. The nature of meaning in music is a difficult problem and the subject of much philosophical and neuroscientific debate (Meyer, 1956; Huron, 2006). However, the terms 'meaning' and 'knowledge' are generally used by neuropsychologists to refer to learned facts and concepts about the world at large. Here 'music knowledge' is used in this neuropsychological sense to refer to the association of music with meaning based on learned attributes (such as recognising a familiar tune or identifying the instrument on which it is played): i.e., associative knowledge of music. Musical emotions can also be considered in this framework, and warrant attention as the aspect of music that is most immediately meaningful for many listeners: while emotional responses themselves are not learned, the attributes and conventions that convey emotions in music are at least partly leaned to the extent that they are products of a particular musical culture (Meyer, 1956).

The brain processes that mediate associative knowledge of music have a wider extra-musical significance. The organisation of brain knowledge systems is an important neurobiological and clinical issue (Wilson et al., 1995; Jefferies & Lambon Ralph, 2006; Warrington 1975; Hodges & Patterson, 2007). Neuropsychological accounts of brain knowledge systems have been heavily influenced by the study of patients with verbal deficits. However, the extent to which verbally-derived models apply to the processing of complex nonverbal objects and concepts remains unresolved. Among the domains of nonverbal knowledge, music is comparable to language in complexity, in its extensive use of both sensory objects and abstract symbols and in the richness of its semantic associations (Peretz & Coltheart 2003; Peretz & Zatorre 2005). While individual variation in musical experience and expertise is wide, music (like language) is universal in human societies. The investigation of music knowledge therefore provides both an opportunity to elucidate brain processes that mediate nonverbal knowledge and a unique model system for assessing the extent to which the cognitive organisation of nonverbal knowledge may mirror language.

The brain mechanisms that process meaning in music have been addressed in functional imaging and electrophysiological studies of healthy subjects (Halpern & Zatorre 1999; Platel et al., 2003; Koelsch 2005; Satoh *et al.* 2006; Steinbeis & Koelsch 2008a,b) and clinical studies of individuals with focal brain damage (Eustache *et al.* 1990; Schuppert *et al.* 2000; Mendez 2001; Ayotte *et al.* 2000; Stewart et al., 2006). However, there are few systematic studies of music processing and particularly associative knowledge of music in neurodegenerative disease (Table 6.1). Although the study of cognitively impaired patients is challenging, the study of music knowledge in dementia offers valuable neurobiological and clinical perspectives. Certain

neuropsychological functions relevant to the processing of music are characteristically affected in dementia: examples include semantic memory in SemD and episodic memory in AD. The nature of the neuropsychological deficits in degenerative disorders offers a perspective on the breakdown of brain knowledge stores that is complementary to the study of acute focal lesions: whereas lesions such as stroke typically disrupt access to stored information, degenerative disorders such as SemD and AD affect knowledge stores proper (Jefferies & Lambon Ralph, 2006). Disorders in the frontotemporal degeneration spectrum (including SemD) have characteristic deficits in the processing of emotion (Rosen et al., 2002b; Werner et al, 2007), which may be particularly pertinent to music. Anatomically, the common dementia diseases affect regions of the frontal, temporal and parietal lobes that are likely to be critical for music processing (Platel et al, 2003; Satoh et al., 2006; Stewart et al., 2006; Warren, 2008). Finally, improved understanding of music processing and more specifically musical memory would provide a rationale for music-based therapies that have been used empirically in dementia populations (Raglio et al., 2008). Consistent with evidence from cases of focal brain damage (Wilson et al., 1995), selectively preserved memory for music despite episodic memory impairment has been described in patients with dementia, including AD (Polk & Kertesz, 1993; Beatty *et al.,* 1994; Cowles *et al.*, 2003). However, this effect has been attributed to retained procedural memory for musical motor programmes rather than explicit memory for familiar music (Baird & Samson, 2009) and more detailed analysis of music recognition may demonstrate deficits (Barlett et al., 1995).

Several recent studies have addressed music knowledge in non-AD diseases and in particular SemD. Deficits of familiar song identification have been reported in association with impaired

familiar face identification in SemD with prominent right temporal lobe atrophy (Gentileschi et al., 2001). SemD patients have been reported to show deficits in melody identification based on impaired matching to song titles, as well as impaired familiarity and impaired detection of pitch errors in famous tunes relative both to healthy controls and AD patients (Hsieh et al., 2011; Johnson et al., 2011). As mentioned in Chapter 2, interpretation of cross-modal procedures in SemD is problematic given the significant aphasia and nonverbal agnosias typically exhibited by these patients. It is of interest that relatively preserved musical knowledge, in particular the ability to identify melodies and musical symbols, despite evidence of widespread impairment in other semantic domains has been found in a significant proportion of patients with SemD (Hailstone et al., 2009; Hsieh et al., 2011; Weinstein et al., 2011). It therefore appears that musical knowledge is rather variable amongst SemD patients in contrast to the more or less uniform deficits of other knowledge modalities exhibited by this disease group.

Table 6.1 Summary of previous studies of semantic memory for music in dementia

Study	N	Age M (SD) (yrs)	Music training (yrs)	Diag	MMSE /30 M (SD)	Comment	Anatomy
Crystal et al, 1989	1	82	>12	AD	n/a (PIQ 129)	Able to play piano pieces (13/15) from piano intro, unable to identify tune or composer	CT normal
Polk & Kertesz, 1993	1	58	?†	PPA	3	Able to whistle continuations of familiar melodies from piano intro (11/15); impaired music reading	MRI: L>R diffuse cerebral atrophy
	1	53	?†	PCA	n/a	Able to name familiar melodies (15/15); impaired music reading	MRI: R>L.PL / OL atrophy
Beaty et al., 1994/1997	1	71	?†	AD	20	Retained ability to play trombone Identified 18/20 Christmas songs	Path: AD changes in TL (esp hippocampi), PL
Beaty et al., 1999	1	79	Competent piano and organ	AD	13**	Initially preserved identification of Christmas tunes, notes, octaves, meters; subsequent deterioration over 2 years	MRI: diffuse cerebral atrophy with marked hippocampal atrophy
Bartlett et al., 1995	15	74 (7.2)	No professional musicians	AD	20 (3.0)	Identification of familiar tunes (semantic memory) near normal in contrast to impaired identification of	n/a

						recently presented tunes (impaired episodic memory)	
Gentileschi et al., 2001	1	60	0	SemD	27	Subjective familiarity reported for 14/33 ?previously familiar songs; unable to name songs (in context of more generalized anomia)	MRI: R > L antero-inferior TL atrophy
Cowles et al., 2003	1	80	>5?	AD	16	Identified 17/20 Christmas songs; played songs (38/45) to verbal cue	n/a
Warren et al., 2003	1	76	Competent classical piano	PPA	21	Able to sing a variety of well-known tunes (but not accompanying lyrics) to command or from intro; able to generate novel continuations for musical phrases, but not for spoken sentences (dynamic aphasia); preserved music reading	MRI: bilateral FL atrophy
Cuddy & Duffin, 2005	1	84	8	AD	8	Identified familiar tunes (based on behavioral cues); able to produce familiar melodies to verbal cue or sing along	n/a
Drapeau et al., 2009	7	74 (9)	n/a	AD	23 (4)	Preserved identification of emotions from music (4 alternative forced choice labelling) and voices, impaired emotion identification from faces	n/a
Gagnon et al., 2009	12	74 (range 56 - 85)	<5	AD	23 (range 16 – 27)	Able to use mode and tempo cues to classify musical emotions (happy – sad)	n/a
Hailstone et al., 2009	1	58	0	SemD	Untestable due to aphasia	Able to sing popular tunes (12/20) from piano intro (cf 5/20 lyrics)	MRI: focal L > R anterior TL atrophy
Matthews et al., 2009	1	30	n/a	?√	29	Retained enjoyment of familiar music Able to reproduce lyrics of popular songs correctly, but melodies unrecognizable	MRI: bilateral peri-Sylvian, medial TL atrophy
Samson et al., 2009	13	n/a	Non-musicians	AD	Range 7 – 15	Able to judge emotional valence (happy – sad) of musical excerpts	n/a
Hailstone et al., 2010	1	61	0	bvFTLD	28	Impaired musical instrument identification (naming and cross-modal matching)	MRI: R > L TL, FL atrophy
	1	72	2	PP	25	Impaired musical instrument naming, preserved cross-modal identification	MRI: R > L anterior TL atrophy
Vanstone et al., 2009	2	85 83	8 lessons	AD	8 17	Able to identify tunes and lyrics as familiar, sing tunes from spoken lyrics	Path: AD changes esp medial TL, FL CT: R > L TL, FL atrophy
Vanstone & Cuddy, 2010	12	81 (range 77 -86)	Variable	AD	Moderate – severe	Overall AD group deficits on familiar tune identification and detection of pitch distortions in novel tunes; 5 patients performed in control range for most tasks	n/a
Weinstein et al., 2011	1	64	Lessons on piano, organ; 26 years performing harpsichord	SemD	Severe aphasia, object agnosia	Able to sight read, embellish and ornament Baroque pieces appropriately according to rules of musical structure	MRI: focal L > R anterior TL atrophy
Johnson et al., 2011	12	65.3 (9.4)	5.1 (5.2)	AD	22.1 (5.1)	SemD showed deficits in song title matching and detection of pitch errors in familiar melodies compared with other groups	VBM: R anterior TL grey matter associated with performance on
	20	66.2 (9.5)	4.6 (5.8)	SemD	23.2 (5.7)		

	11	59.8 (6.5)	3.7 (5.3)	bvFTLD	26.3 (3.4)		distorted melody detection test
Hsieh et al., 2011	14	64.1 (7.7)	1 musician	AD	24.4 (4.2)	SemD (but not AD) showed a group deficit on familiarity decision for famous vs novel melodies; 3 patients with SemD performed normally on the tune familiarity test despite evidence of widespread semantic deficits	VBM: R anterior TL, insula, amygdala, orbitofrontal grey matter associated with performance on famous tune familiarity
	13	64.4 (5.7)	No professional musicians; 6 had played an instrument	SemD	23.3 (4.3)		

Key: AD, Alzheimer's disease; bvFTLD, behavioral variant frontotemporal dementia; CT, brain computed tomography; Diag, clinical diagnosis; FL, frontal lobe; FTD, frontotemporal dementia; L, left; n/a, not available; M, mean; MMSE, Mini-Mental State Examination score; MRI, brain magnetic resonance imaging; N, number of patients; n/a, not available; OL, occipital lobe; path, pathology; PCA, posterior cortical atrophy; PL, parietal lobe; PIQ, performance IQ; PP, progressive prosopagnosia; PPA, primary progressive aphasia; R, right; SD, standard deviation; SemD, semantic dementia; TL, temporal lobe; VBM, voxel-based morphometry; * index of general cognitive performance; † performed regularly on instrument to high standard; √ diagnosis unclear - possible mitochondrial encephalopathy; **at first visit.

In this experiment the cognitive organisation of music knowledge is addressed systematically in two expert musicians with characteristic dementia syndromes of SemD and DLB, in comparison with a control group of healthy expert musicians. In a series of neuropsychological experiments, associative knowledge of musical objects (at levels ranging from whole compositions to single notes), musical emotions (recognition of emotions represented in music), musical sources (musical instruments) and musical symbols (music notation) is examined. These dimensions of music knowledge were assessed in relation to musical perceptual abilities and extra-musical neuropsychological functions, in particular verbal skills.

6.2 Experimental hypotheses

It is hypothesised that music is a distinct domain of knowledge, with a modular cognitive organisation comparable to other non-musical knowledge modalities including language. It is

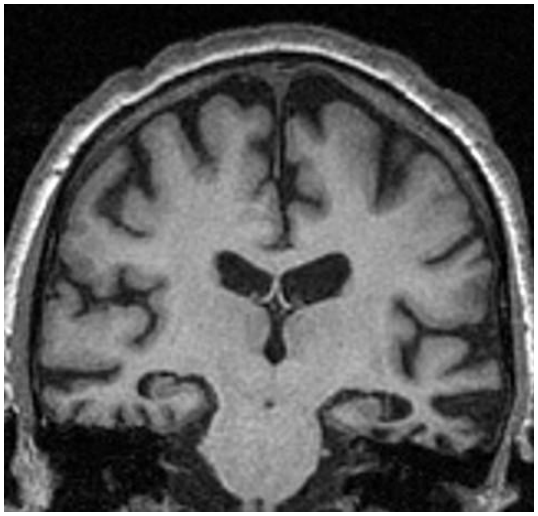
also hypothesised that associative knowledge of music is at least partly dissociable from other neuropsychological functions and also from musical perceptual ability.

6.3 Methods

6.3.1 Subject details

Case 1 is a 56 year old right-handed male professional trumpet player and music teacher with 16 years music training and a career performing in professional orchestras. He possessed absolute pitch. He presented with a two year history of progressive word-finding and naming difficulty, circumlocutory speech and later difficulty recognising faces and voices of friends. Three months prior to assessment he had relinquished his professional musical commitments, but he continued to play the trumpet for several hours a day and to perform at social events; he reportedly remained highly competent in both playing and sight-reading. He continued to derive pleasure from music with no change in musical preferences. On cognitive examination, Mini-Mental State Examination (MMSE) score was 20/30, Frontal Assessment Battery score was 13/18, and there was evidence of anomia and surface dyslexia. The general neurological examination revealed a positive pout reflex but was otherwise unremarkable. A clinical diagnosis of SemD was made. Brain MRI (Figure 6.1) showed selective, predominantly left-sided anterior and inferior temporal lobe atrophy typical of SemD.

Figure 6.1 Representative T1-weighted coronal MR brain section from Case 1 showing asymmetric (predominantly left-sided), selective anterior and inferior temporal lobe atrophy, typical of semantic dementia. The left hemisphere is shown on the right.



Case 2 is a 63 year old right-handed professional singer and music teacher with 16 years music training and a career performing with professional opera companies. He presented with a three year history of progressive forgetfulness, difficulty learning new musical material, word- and route-finding problems and difficulty performing do-it-yourself (DIY) tasks. He later developed visual hallucinations, REM sleep disorder, fluctuations in his cognitive state and parkinsonism. Six months prior to assessment he had relinquished his professional musical commitments and his ability to read music and learn new musical material was deteriorating although he was still highly competent in singing familiar repertoire. He continued to derive pleasure from music with no change in musical preferences. On examination MMSE score was 14/30, he had anomia, impaired recall, executive and visuoperceptual dysfunction and ideomotor apraxia. General neurological examination revealed extrapyramidal signs with marked akinesia and rigidity,

camptocormia and myoclonus. A clinical diagnosis of DLB was made. Brain MRI showed generalised cortical atrophy with disproportionate bilateral hippocampal atrophy.

Control subjects. Six healthy professional musicians (age range 49 – 78 years) with similar musical backgrounds to the patients participated as normal control subjects for the assessment of music cognition. Between two and six controls completed each of the tests in the experimental battery. Details of control subjects are shown in Appendix Table A6.

6.3.2 Background assessment: general neuropsychology, audiometry and music perception

In view of the potential influence on the experimental assessment of music knowledge by cognitive skills in non-musical domains and by perceptual encoding of musical information, both patients had an assessment of general neuropsychological functions, peripheral hearing and musical perceptual abilities.

General neuropsychological assessment (Table 6.2) was consistent with the clinical diagnosis in each case. Case 1 had profound impairment of semantic memory for both verbal and nonverbal material and severe dyslexia particularly affecting irregular word reading (surface dyslexia), with preserved general intellect, patchy impairment on executive tests, and intact arithmetical and visuoperceptual abilities. Case 2 had evidence of widespread cognitive impairment with relative preservation of word comprehension, reading and visual perceptual skills.

Audiometric assessment showed mildly impaired peripheral hearing in both patients relative to age-matched healthy controls, possibly occupational (noise-related) in origin, although neither patient gave a clinical history of altered hearing.

Musical perceptual abilities were assessed in the patients and musician controls using the Montreal Battery of Evaluation of Amusia (MBEA), a widely used and normed test of music perception in musically untrained subjects (Peretz et al., 2003) based on a two alternative (same/different) forced choice comparison of two short unfamiliar musical sequences. Scale (key), pitch contour (melody), pitch interval, and rhythm discrimination subtests of the MBEA were administered. In addition, subjects were administered a novel timbre discrimination test (previously described in Garrido et al., 2009) in which the subject was presented with two different melodic excerpts each played by a single instrument, and the task was to decide whether the excerpts were played by the same instrument or by different instruments. Results are summarised in Table 6.3. On the MBEA, Case 1 exhibited deficits on the contour and interval discrimination subtests and Case 2 exhibited a deficit on the interval discrimination subtest relative to healthy control musicians; on the interval subtest, Case 2 (but not Case 1) had a perceptual deficit ($p<0.05$) relative to published norms for healthy non-musician controls. Case 2 also had significantly inferior ($p<0.05$) performance on the scale, contour and rhythm subtests compared to published norms for healthy non-musician controls. On the timbre discrimination task, Case 1 exhibited a moderate deficit; this test was not administered to Case 2 as the patient was too tired and agitated to complete the test.

Table 6.2 General neuropsychological assessment of patients

Test	Case 1		Case 2	
	Score	**%ile**	**Score**	**%ile**
General intellectual function				
Ravens advanced matrices (/12)	11	95th	abandoned	<5th
Memory				
Camden pictorial memory test (/30)	30	>50th	21	<5%
Language				
Word repetition (/30)	30	>5th b	29	>5th b
Picture naming (/20)	1	<5th b	9	<5th b
Word-picture matching (/30)	7	<5th b	10	<5th b
Synonyms test (concrete) (/25)	13	<5th*	22	10-25th*
Irregular word reading (/30)	16	<5th b	20	25-50thb
Executive function				
Trail making test A	62s	<5th a	out of time	<5th a
Trail making test B	109s	10-25th a	out of time	<5tha
Number cancellation (no. in 45 seconds)	21	20-40th b	out of time	<5th b
Other skills				
Famous faces naming (/12) recognition (/12)	1 3†	<5th <5th	- 11	- >75th
Digit span (forwards, backwards)	-	-	3,2	<5th a
Graded difficulty arithmetic test: addition items (/12)	6	25-50th c	-	-
VOSP object decision (/20)	16	20-40th	14	5-10th

Key: - not attempted; †scored <5th percentile on a recognition test of famous buildings, 50th percentile on Benton test of face perception; *test administered with both visual and auditory presentation of words whereas the standardised percentiles are calculated for auditory presentation only. Percentiles calculated from standardised tests, except where marked: a, approximated from standardised scores; b, calculated from previous healthy control sample (n=41-72); c, calculated from previous healthy control sample (n=100-143)

Comment. While deficits in certain aspects of musical perception have been described with neurodegenerative disease (Polk & Kertesz, 1993; Beatty et al., 1994; Cowles et al., 2003), the basis for these deficits remains uncertain. The perceptual tasks here involved serial comparisons between unfamiliar musical items, and therefore required musical material to be maintained in

working memory: working memory impairment may therefore have contributed to any deficit, and indeed the most severe deficits were exhibited by Case 2, with impaired working memory (Table 6.2). However, it is unlikely this is the entire explanation for the pattern of deficits observed: Case 2's performance on another task involving serial comparison between melodies (Experiment 1, melody matching task: Table 6.3) was normal. The severity of musical perceptual impairment exhibited by our patients was, in any case, not marked: for Case 1, musical perceptual functions were in general not impaired relative to healthy nonmusicians.

6.3.3 Experimental assessment of music cognition: general procedure

Novel experiments designed to probe various dimensions of music knowledge were administered to subjects over several sessions. Auditory stimuli were presented from digital wavefiles on a notebook computer in free field at a comfortable listening level in a quiet room. Visual stimuli were presented and subject responses were collected for off-line analysis as described in Chapter 2. Where the test required matching between an auditory stimulus and a verbal label, the words corresponding to the verbal choices were simultaneously displayed on the computer monitor and read out to the subject on each trial. Before the start of each test, several practice trials were administered to ensure the subject understood the task. Musical excerpts used are summarised in Appendix Table A3. The structure of the experimental tests is summarised in Appendix Table A7.

Patient performance was assessed statistically ($p < 0.05$) in relation to healthy musician controls using the modified t test procedure described by Crawford and Howell (1998) for comparing

individual test scores against norms derived from small samples. Patient and control results for the experimental battery are summarised in Table 6.3.

Table 6.3 Assessment of music cognition

Experiment	Musical domain	Test	Scores			
			Case 1	Case 2	Controls	
					mean (sd)	no.
Background	Music perception	MBEA Scale (/30; 15)	28	**23***	28.8 (0.4)	4
		MBEAContour (/30; 15)	**25**	**23***	29 (1.1)	4
		MBEA Interval (/30; 15)	**23**	**18***	27.8 (1.8)	4
		MBEA Rhythm (/30; 15)	30	**26***	29.5 (0.5)	4
		Timbre discrimination test (/20; 10)	**16**	-	20 (0)	4
Exp 1	Knowledge of musical objects: composition-specific	Famous melody naming (/20)	**0**	**12**	16.5 (2.1)	4
		Famous melody matching (/20; 10)	**17**	19	19.2 (0.7)	6
		Pieces played from memory from name only (/15)	2	-	-	
		Pieces played from memory from music cueing (/15)	13	-	-	
Exp 2	Knowledge of musical objects: categorical	Solo test: era (/20; 7)	-	**15**	18.8 (1.1)	6
		Solo test: composer (/20; 7)	-	**12**	17.2 (1.3)	6
		Solo test: instrument (/20; 7)	-	**8**	18.3 (1.5)	6
Exp 3	Knowledge of musical emotions	Emotion recognition in music (/40; 10)	**17**	24	33.3 (4.1)	3
Exp 4	Knowledge of musical sources: instruments	Instrument picture naming (/20)	**4**	**19**	20 (0)	5
		Instrument picture recognition (/20)	**19**	20	20 (0)	5
		Instrument sound naming (/20)	**2**	**17**	19.8 (0.4)	5
		Instrument sound recognition (/20)	**8**	19	19.8 (0.4)	5
		Instrument sound-picture matching (/20; 5)	**18**	-	20 (0)	5
Exp 5	Knowledge of musical symbols	Musical symbol naming (/10)	**6**	-	10 (0)	4
		Musical symbol identification (/10)	10	-	10 (0)	4
		Music theory: keys and pitches identification (/18)	-	-	17 (1.4)	2
		Music theory: 'musical synonyms' (/20; 10)	20	-	19.3 (1.3)	4

For each test (total score; chance score) is indicated in parentheses. Key: scores significantly different from control mean ($p < 0.05$; modified t test, Crawford & Howell, 1998) in **bold**; **-,** not attempted; MBEA, Montreal Battery for Evaluation of Amusia. *also abnormal in relation to published norms for healthy non-musicians. See text for details of experimental tests

6.3.4 Experiment 1. Knowledge of musical objects: composition-specific

Musical compositions can be considered as 'musical objects' about which associative knowledge can be acquired. Whereas objects in other modalities (for example, vision) can be defined more or less unambiguously, defining a musical object is problematic. Musical works can be altered substantially or present in only fragmentary form, yet still retain essential aspects of their musical identity: we can recognise musical melodies and motifs under widely varying acoustic conditions (for example, when presented on different instruments or in different keys). In studies in non-musician controls, 'musical objects' are often defined by well-known melodies (such as *Happy Birthday*), and only a few notes (and particularly, the initial notes) of the melody are needed for normal controls to recognise the piece (Schulkind et al., 2004). In this experiment associative knowledge about musical compositions was probed using a series of tests in which the requirement for verbal processing was minimal.

In the first test, patients and healthy musician controls performed a melody matching task in which they were required to determine whether two melodic fragments were derived from a single musical composition. Twenty famous tunes derived from the Western classical canon, folk and pop music (Appendix Table A3) were transcribed and recorded on a piano (by the author) using a single melody line, in the same key (G major), at fixed tempo; 19/20 melodies were in a different key to the original key of the composition. Tunes were selected such that two readily

recognisable but distinct melodic fragments could be extracted for each tune (e.g., *God Save the Queen*). These fragments were presented in pairs such that a given pair contained fragments from the same or different tunes: the task was to decide whether the two fragments belonged to the same tune or to different tunes. Melodic fragments from the "same" tune could not be matched simply by matching pitch at the end of first clip to the beginning of the second clip. This test comprised 20 trials (10 same, 10 different pairs), presented in randomised order. Subjects were subsequently presented with the same excerpts and asked to name the tune.

Additional procedures to assess knowledge of particular musical compositions were tailored to Case 1's particular musical abilities and cognitive profiles, capitalising on his retained skills in performance. Fifteen pieces of music in his trumpet repertoire (see Appendix Table A3) were nominated by his wife. In the first part of the test, he was presented with a musical introduction to each piece (not containing a trumpet part), and in the second part of the test with the name of each piece in turn: the task on each trial was to play the piece from memory based on the introduction (part 1) or the name (part 2). His performances were recorded, and played back to a blinded assessor (JH) who was asked to identify each piece from the recording. Only pieces that were identifiable to the assessor were counted as successfully played.

6.3.5 Experiment 2. Knowledge of musical objects: superordinate

The complexity of large-scale classical musical works makes it unlikely *a priori* that they are processed as unitary objects. Knowledge about such musical objects can be acquired at different levels of analysis. Non-musicians are able to categorise musical pieces according to genre (jazz,

folk, classical, etc) and other associative attributes (e.g., Christmas music, nursery songs) (Halpern, 1984). The categorisations available to trained musicians are more elaborate and may range from single notes or pitch intervals to generic stylistic features linked to knowledge of composers or musical eras. Whereas a particular composition can be assigned to a musical era based on a number of rather broad timbral and melodic characteristics, the association with a particular composer (compositional style) is more specific, but does not rely on knowledge of the particular composition. By analogy with other kinds of sensory objects, these different levels of musical knowledge might equate to superordinate knowledge about compositions versus fine-grained knowledge specific to particular compositions. However, it has not been established whether distinctions between levels of musical knowledge and between musical categories are reflected in the brain organisation of knowledge about music. In this experiment these issues were addressed using further procedures tailored to Case 2's retained verbal abilities.

A novel test, the 'solo test', was therefore designed to probe different kinds of knowledge about musical pieces. Thirty excerpts of orchestral music covering Baroque, Classical, Romantic and 20th Century eras were selected: pieces were chosen because each was written for a prominent solo instrument, however this solo instrument was not present in the orchestral excerpt presented. On hearing each excerpt, the subject was asked to match the piece with its era, its composer and the solo instrument for which it had been written. On each trial era, composer and solo instrument choices were presented sequentially as randomised three-item written word arrays; within the composer arrays, choices were selected such that all derived from a single musical era so that era could not be used as a cue to composer identification (for example, on hearing the introduction to Schumann's Piano Concerto, the subject was presented with the arrays: 'Baroque

– Romantic – 20th Century'; followed by: 'Bruch – Grieg - Schumann'; followed by: 'piano – cello – viola'). It is reasoned that determination of an (unheard) solo instrument would depend on specific knowledge of the composition in question. This part of the experiment was not administered to Case 1.

6.3.6 Experiment 3. Knowledge of emotions in music

The relations between emotion recognition in music and other aspects of music cognition have not been fully defined. It is clear that dissociations between emotion processing and other musical perceptual and associative functions can occur (Peretz et al., 1998; Griffiths et al., 2004; Peretz & Zatorre, 2005). Furthermore, music emotion judgments have been found to be relatively resistant to brain damage (Peretz et al., 1998). Recognition of emotion in music is likely to be influenced by the internalisation of 'rules' or conventions for conveying particular emotions in the listener's particular musical culture (Juslin & Vastfjall, 2008) as well as by transcultural factors (Fritz et al., 2009). The objective here was to assess emotion recognition in music alongside other forms of musical associative knowledge. This was done using the multimodal emotion recognition battery described in Chapter 5, which assessed recognition of four emotions (happiness, sadness, anger, fear) as represented in music. In order to rule out any confound from the use of verbal labels in this test, Case 1's ability to identify emotions from facial expressions was also assessed using an identical procedure with corresponding stimuli (Ekman & Friesen, 1976).

6.3.7 Experiment 4. Knowledge of musical sources: instruments

If musical compositions are the objects around which knowledge of music is built, to convey music in general requires an acoustic source. These sources, musical instruments, may constitute a specialised category of semantic knowledge (Dixon et al., 2000; Mahon & Caramazza, 2009). The distinction drawn here between musical compositions as 'objects' and instruments as 'sources' is largely pragmatic, since instrument timbres are 'auditory objects' in a broader sense (Griffiths & Warren, 2004). However, much previous work has addressed recognition of musical instruments from their pictures (i.e., instruments as visual artefacts) whereas it could be argued that the essential character of a musical instrument is auditory (the sound of a violin can be synthesised and still fulfil the musical functions of a real violin, whereas a visually accurate model of a violin does not). In this experiment identification, naming and cross-modal matching of musical instruments in the visual and auditory modalities were assessed. Pictures of 20 musical instruments were presented sequentially in randomised order, and audio clips of the same instruments were presented in an alternative randomised order. Subjects were asked to name or otherwise identify the instrument. Apart from naming, instrument recognition could be demonstrated by providing a piece of information about the instrument (e.g. "not a clarinet, it begins with 's'" to indicate recognition of a saxophone) or by miming how the instrument would be played; as it is difficult to indicate specific identification of some instruments without naming, recognition was also credited if the instrument family was identified correctly (e.g., percussion, woodwind). A recognition deficit in either modality was further probed using a cross-modal procedure in which instrument audio clips were presented in randomised order together with

arrays of four written instrument names and pictures, and the subject was asked to match each instrument sound with the correct name-picture combination.

6.3.8 Experiment 5. Knowledge of musical symbols.

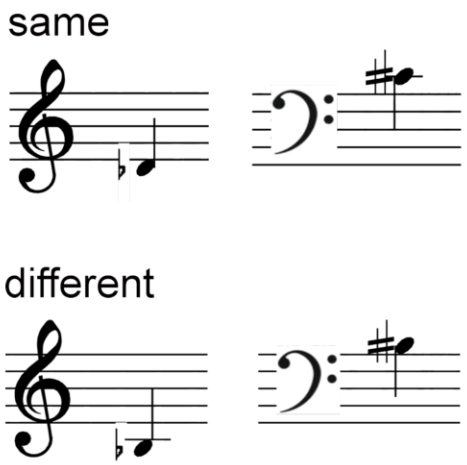
Like many languages, music has a complex system of symbolic written notation with agreed 'rules' for how these symbols should be understood and translated into musical output. A series of tests were designed to probe knowledge of these rules based on written musical symbols of different kinds. The particular interest was to compare measures of musical symbol comprehension with measures of text reading and word comprehension such as the Synonyms Test (see Table 6.2). While there is no precise equivalent to a 'synonym' in musical notation, there are often alternative ways of writing the same musical instruction which differ substantially in surface structure. Experiment 5 was not administered to Case 2 as he was too tired and agitated to perform the test.

In the first part of the experiment 10 common musical symbols were presented sequentially and the task was to identify each symbol. If the subject was unable to name but was able to indicate unambiguously that they recognised the symbol (e.g., describing a crotchet as 'like a minim but just one not two'), this was recorded.

The second part of the experiment was designed as a musical analogue of the 'Synonyms Test' on word pairs which has been widely used to assess single word comprehension (Warrington et al., 1998); in order to compare written symbols in both modalities, here the verbal Synonyms

Test was presented in written as well as spoken form (Table 6.2). Whereas a particular musical symbol might be named or otherwise identified on the basis of its surface characteristics, to determine whether two musical notations are equivalent requires understanding of the musical meaning of each instruction. Twenty pairs of musical notes or rests were presented sequentially in randomised order. The two items in each pair were always notated differently, however 10 pairs represented the same note (or rest duration) if played ('musical synonyms'), while the remaining 10 pairs represented notes with different pitch or duration (or rests of different duration) if played (examples shown in Figure 6.2). On each trial the subject was asked to determine whether the two notes or rests were equivalent (i.e., the same if played/observed).

Figure 6.2 Examples of stimuli from the 'Musical Synonyms' test: the notations above signify the 'same' note when played; the notations below signify 'different' notes when played. See text for details



6.4 Results

6.4.1 Experiment 1. Knowledge of musical objects: composition-specific

The performance of Case 2 on the within-modality famous melody matching task was not significantly inferior to healthy controls (scoring 19/20), although he was impaired in overt melody naming (9/20). In contrast, Case 1 showed deficits on the famous melody matching task (17/20), and was unable to name any tunes (Table 6.3).

Case 1 was able to play only 2/15 pieces from name but played 13/15 pieces from a musical introduction (Table 6.3), indicating that he was able to access knowledge of particular musical compositions successfully from musical but not from verbal cues.

Comment. Taken together, these findings suggest that knowledge of particular musical objects (compositions) is at least partly dissociable from the ability to label music verbally. Retained item-specific knowledge of music can be demonstrated even in the face of profound verbal impairment (as in Case 1), thus supporting previous evidence for a relatively preserved knowledge of familiar tunes in SD (Hailstone et al., 2009).

An important issue in the psychology of music concerns the existence and role of procedural versus episodic and semantic memory systems for music. The use of tasks based on stimuli that were altered from their canonical form (piano versions transposed to a key different from the original) or presented as fragments requiring familiarity with a larger whole (the musical introductions played to Case 1) is likely to have reduced dependence on musical episodic memory here. While the melody matching task may have involved musical imagery, this is likely

to be mediated by brain networks that are at least partially distinct from those mediating episodic memory (Halpern & Zatorre, 1999; Schurmann et al., 2002; Platel et al., 2003). Furthermore, while it is possible to perform music competently as a learned motor programme (i.e., based on musical procedural memory), it is unlikely that retained procedural memory for music accounts entirely for the pattern of Case 1's results on the performance test. Such a mechanism would not predict Case 1's successful performance of pieces cued from an initial fragment or in a form other than the trumpet arrangement in which he had learned them. In order to access the motor programme required to execute a piece, it was first necessary for Case 1 to match the musical introduction with stored information about the composition as a whole: it is postulated that this matching process accesses stored knowledge about the musical (rather than motor) characteristics of the piece.

6.4.2 Experiment 2. Knowledge of musical objects: superordinate

On the solo test, Case 2 performed best for recognition or era, followed by composer, followed by solo instrument. Case 2's performance on solo instrument recognition was almost at chance (8/20), whilst his ability to recognise musical era (15/20) and composer (12/20) was better but still inferior to healthy control musicians (Table 6.3).

Comment. These findings suggest that memory for music is hierarchically organised. Whereas a particular piece of music can be assigned to a musical era based on a number of rather broad timbral and melodic characteristics, the association with a particular composer (compositional style) is more specific and the knowledge that the piece was written for a particular solo instrument is more specific still. The pattern of results on the solo test suggests that superordinate

generic knowledge about musical style (era and composer) may be more robust to the effects of brain damage than item-specific knowledge about particular compositions (such as the specific instrument for which a piece is written). Such a scheme would parallel the hierarchical organisation of semantic memory in other domains. Furthermore the use of tasks based on stimuli that were altered from their canonical form (as in the piano transcriptions in Experiment 1) or presented as fragments requiring familiarity with a larger whole (the excerpts in the 'solo test') is likely to have reduced dependence on procedural or episodic memory.

6.4.3 Experiment 3. Knowledge of emotions in music

Case 1 showed very impaired performance (score 17/40) while Case 2 showed a better level of performance (score 24/40) that was not significantly inferior to controls (control mean 33.3) (Table 6.3). Case 1's poor performance was not attributable to the verbal response procedure, since his recognition of facial emotions was significantly better (score 30/40; $X^2(1)$ 7.42, $p<0.01$). Case 1 had relatively greater difficulty recognising negative than positive musical emotions (individual scores: anger, 1/10; fear 4/10; happiness, 7/10; sadness, 5/10). Case 2's scores on the same stimuli (anger 5/10; fear 4/10; happiness, 8/10; sadness, 7/10) showed a lesser degree of difference in performance between positive and negative emotions, arguing that Case 1's performance profile was not attributable simply to stimulus factors. The healthy control performance as discussed in Chapter 5 lends further support to this; emotion recognition performance on the same music stimuli was highest for sadness (93%), followed by happiness (89%), then anger and fear equally (74%).

Comment. Together with the results of Experiments 1 and 2, these findings indicate a partial dissociation of emotion recognition from other aspects of musical object knowledge. Such an interpretation would be consonant with findings in previous case studies of patients with focal brain damage (Peretz et al., 1998; Griffiths et al., 2004; Peretz & Zatorre, 2005). The present findings further suggest that some focal degenerative pathologies (like SemD) may degrade emotion recognition in music, whereas this may be relatively resistant to other forms of neurodegeneration. This corroborates previous evidence for impaired emotion recognition in other modalities in SemD (Rosen et al., 2002b; Werner et al., 2007) and the results of the multimodal emotion study reported in Chapter 5, suggesting a generic deficit in processing affective information. Case 1 exhibited a more severe deficit for recognition of negative compared with positive musical emotions: this would also be consistent with previous data in other affective modalities, but requires care in interpretation since 'happiness' in music (like other modalities) requires less fine-grained differentiation than do individual negative emotions. Case 1's deficit of musical emotion recognition was more severe than the deficits he exhibited for recognition of musical compositions, yet recognition of emotions from music does not require any specialised musical training (Peretz et al., 1998). The more abstract nature of musical emotion compared with animate emotion channels, such as facial expressions, may render this dimension of music knowledge particularly vulnerable to diseases that disrupt frontotemporal mechanisms involved in interpreting more complex affective and social signals (Werner et al., 2007).

6.4.4 Experiment 4. Knowledge of musical sources: instruments

Case 1 was able to name only 4/20 instruments from pictures and only 2/20 instruments from sound (Table 6.3): he was able to identify 19/20 instruments from pictures but only 9/20 instruments from sound. On the cross-modal instrument sound to picture 4-alternative-forced-choice matching task, his score improved to 18/20, which was still inferior to the flawless performance of healthy musicians on this task. Cases 2 made errors on naming instruments both from sounds and pictures, however his ability to identify instruments in each modality did not differ from healthy musician controls (Table 6.3).

Comment. Together with the results of Experiments 1 and 2, these findings support a dissociation between knowledge of musical objects (compositions) and knowledge of musical sources (instruments): Case 1 showed very impaired auditory instrument recognition despite relatively preserved composition-specific knowledge. Furthermore, within the category of musical instruments, Case 1's markedly impaired identification of instruments within the auditory modality contrasted with his largely intact ability to recognise instruments visually. His auditory identification performance improved (though not to a normal level of performance) if cross-modal visual information was available. His performance contrasted with that of Case 2 who, despite impaired naming ability, was able to identify instruments normally in both the auditory and visual modalities. While it is tempting to ascribe the pattern of deficits exhibited by Case 1 to an auditory associative agnosia, the findings on the musical perceptual tasks (Experiment 1, Table 6.3) suggest a need for some caution with this interpretation. Case 1 did have evidence of a perceptual deficit affecting, in particular, timbre discrimination: it is therefore possible that the effects of degraded timbral representations interacted with auditory semantic

memory for particular instruments. This interpretation would be consistent with previous neuropsychological evidence for 'basic object level' processing in the initial recognition of musical instruments (Palmer et al., 1989; Kohlmetz et al., 2003) and with the known extension of pathology to posterior temporal lobe areas in established SD (Rohrer et al., 2009). On the other hand, a purely perceptual deficit would not easily account for the clear improvement shown by Case 1 on the auditory-visual matching task; nor does the explanation sit easily with the perceptual deficits exhibited by Case 2, who despite these deficits was able to identify instruments normally. It is therefore proposed that Case 1 retained sufficient general categorical information about instrument sounds (for example, knowledge about the general characteristics of particular instrument families) to enable identification to be achieved once more specific visual information was available (Palmer et al., 1989).

6.4.5 Experiment 5. Knowledge of musical symbols.

Although Case 1 was impaired in his naming ability to name musical notes (score 6/10), he performed flawlessly on tests of symbol comprehension, similar to healthy control musicians. This was in contrast to his severe dyslexia for verbal material (irregular words: Table 6.2), suggesting a dissociation between verbal and musical comprehension: while one would not wish to suggest these tasks are precisely analogous, they probe an analogous capacity (comprehension of the meaning that inheres in a symbol beyond its surface structure) in each domain.

6.5 Discussion

This study presents neuropsychological profiles from two expert musicians with different dementia syndromes that together suggest a cognitive organisation for music knowledge. The findings suggest associative knowledge of music is at least partly dissociable from other neuropsychological (in particular, verbal) functions and from musical perceptual skills. This is illustrated by Case 1's creditable performance on tests of knowledge of musical objects (compositions) and symbols (notation) despite profoundly impaired verbal skills, and Case 2's normal performance on tests of knowledge of musical objects (compositions) and musical sources (instruments) despite a perceptual deficit. Within the domain of music knowledge, the findings support a modular organisation with some degree of dissociation (summarised in Table 6.4) between knowledge of musical objects (compositions) and symbols (notation) versus knowledge of musical sources (instruments) and emotions. With respect to knowledge of musical objects, superordinate knowledge about musical style (eras, composers) is less vulnerable than fine-grained, item-specific knowledge about particular compositions. The findings further suggest the potential for fractionation of knowledge within the domain of music according to modality (Case 1's ability to recognise musical instruments was clearly superior in the visual compared with the auditory modality).

Table 6.4 Neuropsychological dissociations within the domain of music knowledge

Musical domain	Case 1 (SemD)	Case 2 (DLB)
Musical objects	↓	↓*
Musical emotions	↓↓	**N**
Musical sources	↓↓	**N**
Musical symbols	**N**	n/a

N normal performance, ↓ impaired performance relative to controls, ↓↓ impaired performance relative to both controls and other case; *solo test impaired, music matching test normal; DLB, dementia with Lewy bodies; SemD, semantic dementia

Based on these findings, it is proposed that music constitutes a distinct domain of nonverbal associative knowledge. The tasks here were designed to be relatively independent of episodic and procedural memory systems, and to employ musical analogues to tasks that are widely accepted to index semantic memory in other cognitive domains (such as the 'Musical Synonyms' test). The present findings could therefore be interpreted as evidence of a relatively independent associative knowledge system for music that is neuropsychologically equivalent to semantic memory systems in other cognitive domains. Findings such as the (partial) dissociation of musical semantic information from perceptual and affective information and the relative preservation of superordinate versus item-specific musical knowledge suggest certain cognitive parallels between music and other domains of knowledge (Murre et al., 2001). If it is indeed the

case that these experiments illustrate the operation of a musical semantic memory system, this system is likely to be fractionated, anatomically as well as cognitively. It is clear that at least some aspects of music knowledge may remain intact even in the face of extensive brain damage of some severity (Case 2). Case 1 demonstrates that impaired knowledge of music sources but preserved knowledge of musical objects and symbols may be associated with focal degeneration of the anterior left temporal lobe, a brain region often considered to be critical for semantic memory in domains other than music. The relatively selective sparing of knowledge of musical compositions shown by BR is consistent with previous evidence in SemD (Hailstone et al., 2009).

The separation of musical object and symbol knowledge from other kinds of musical and extra-musical associative knowledge might reflect a fundamental neuropsychological distinction between these different kinds of associative knowledge. Musical instrument sounds and musical emotions are closely associated respectively with physical objects and affective states in the extra-musical world: musical instruments exist as artefacts, and musical instrument timbres share many features with animate voices (Belizaire et al., 2007), while musical emotions align with similar emotions expressed by voices and faces (Eldar et al., 2007). It is therefore plausible that the processing of these aspects of musical knowledge should have neuropsychological similarities with the processing of other kinds of sensory object knowledge, and perhaps also with language, which derives meaning exclusively from its external referents. In contrast, musical compositions and symbols may constitute a relatively self-contained knowledge system that is more dependent on abstract characteristics that are intrinsic to the musical stimulus and less grounded in the non-musical world (Huron, 2006; Steinbeis & Koelsch, 2008a). Though any parallel must be made with a degree of caution, it may be speculated that knowledge of abstract

musical entities (such as compositions) may align with knowledge of another abstract nonverbal system, mathematics, some aspects of which may also be relatively spared in SemD (Crutch & Warrington, 2002; Jefferies et al., 2005; Zamarian et al., 2006).

While anatomical correlation is necessarily limited in degenerative pathologies such as the present cases, the pattern of findings would be consistent with a substrate for musical semantic memory that is at least partly separable from other domains of semantic memory. In particular, knowledge of musical objects (compositions) and symbols may have a substrate distinct both from non-musical knowledge domains and from knowledge of musical sources and emotions. Anatomically, this could reflect a greater dependence of musical semantic memory on brain areas beyond the anterior temporal lobe, in proximity to higher order sensory cortices: this interpretation would be consistent with anatomical data from normal functional imaging (Platel et al., 2003; Satoh et al., 2006) and focal lesion (Stewart et al., 2006) studies implicating a distributed network of peri-Sylvian areas in processes such as familiar melody recognition. Functional imaging studies in healthy subjects have shown engagement of widespread bilateral anterior and mesial temporal, frontal and parietal lobe areas with preponderant involvement of the superior temporal gyrus and sulcus (Baird & Sampson, 2009; Peretz et al., 2009; Groussard et al., 2010). Together this evidence suggests that the neuroanatomical substrates for semantic processing of melodies may lie relatively posterior and dorsal to the anterior (temporo-polar) and inferior temporal substrates implicated in the semantic processing of many non-musical objects (Lambon-Ralph et al., 2009). Such an anatomical formulation would predict relative sparing of semantic memory for melodies in SemD. In contrast, knowledge of musical instruments and emotions may depend on inferior frontal and anterior temporal areas previously implicated in

processing analogous kinds of information in voices and other domains (Griffiths et al., 2004; Khalfa et al., 2005; Eldar et al., 2007; Belizaire et al., 2007, Schirmer & Kotz, 2006).

There is as yet limited VBM evidence in the dementias to corroborate this formulation. Melody identification and detection of melodic distortions have been linked to grey matter in the left anterior and right anterior temporal lobes respectively (Johnson et al., 2011), and familiarity judgement on melodies has been linked to grey matter in the right temporal pole, insula, amygdala and OFC, in regions overlapping those linked to face identification (Hsieh et al., 2011). However, it is important to note that these studies employed either cross-modal procedures requiring verbal labelling (which is problematic given the significant aphasia and nonverbal agnosias typically exhibited by these patients) or detection of melodic distortions or familiarity decisions on melodies which are difficult to compare with other non-musical modalities or semantic memory. This present study has the benefit of employing within-modality music matching procedures, thus circumventing the potential confounds that arise from cross-modal tasks. On the other hand, within-modality matching tests are potentially vulnerable to working memory effects and executive dysfunction, at least in the auditory domain.

From a clinical perspective, the findings of this study provide a rationale for the use of music-based therapies in patients with dementia. While the efficacy and clinical utility of such therapies remain open empirical questions, the demonstration of dissociated preservation of some forms of musical memory suggests that music has the potential to access certain kinds of stored knowledge that might otherwise inaccessible. Our findings also affirm previous (largely anecdotal) evidence that emotional responses to music can be relatively preserved even in the context of widespread cognitive impairment (e.g. Case 2). As yet, no studies have been done

examining emotion recognition in DLB, although patients with AD have been shown to have retained ability to rate happiness and sadness in music (Gagnon et al., 2009; Samson et al., 2009) and to identify (using forced choice procedures) happiness, sadness, fear, peacefulness and anger in music (Drapeau et al., 2009). This is perhaps somewhat surprising in light of documented impairments in emotional prosody processing in AD (Taler et al., 2008), though few studies have assessed music and prosody together. Identification of musical emotions in AD appears not to correlate closely with overall dementia severity (Gagnon et al., 2009) and may dissociate from emotion identification in other modalities (eg facial expressions: Drapeau et al., 2009). In contrast to these observations in AD, the results of the experiment described in Chapter 5 are in line with emerging evidence suggesting that identification of musical emotion is impaired in the FTLD spectrum of disorders (Matthews et al., 2009) even though enjoyment of music frequently appears to be retained in these patients (Gentileschi et al., 2001; Hailstone et al., 2009). The finding that musical emotion identification can be impaired despite near-normal identification of melodies in SemD in this study implies that melody identification is not simply an idiosyncrasy of special expertise, rather, that knowledge of musical emotions and melodies are dissociable components on musical semantic memory.

There are several caveats on this study. The conclusions are necessarily based on a small number of individuals with highly specialised skills and disparate forms of brain pathology. The group of healthy musicians here performed near to ceiling on a number of tests, reducing the potential to detect differences between patients and control subjects. Furthermore it was not possible to assess all musical functions uniformly in all subjects. However, studies of this kind capitalise on the interaction of strategic forms of brain damage with premorbid specialised knowledge

(McNeil & Warrington, 1993; Crutch & Warrington, 2002, 2003; Jefferies et al., 2005); indeed, the unique skills possessed by expert musicians here were an essential prerequisite in order to undertake a detailed analysis of multiple dimensions of music knowledge. Furthermore, music offers certain advantages over other domains of specialist knowledge in that musical expertise is not rare in the wider population and there is a widely accepted 'canon' of musical skills and compositions, enabling the uniform assessment of music knowledge in a population of healthy individuals with similar musical backgrounds. The experience of music is universal, and musical knowledge in some form is possessed by all normal listeners. Taking these considerations into account, the present findings raise fundamental issues concerning the brain organisation of nonverbal knowledge systems, the nature of musical knowledge, and particularly, the neuropsychological relations between music and language. On the one hand, the existence of separable brain knowledge systems for music and language reduces the likelihood that these two modes of human communication shared a common evolutionary pathway. On the other hand, evidence for a multidimensional neuropsychological organisation with analogous features in music and language argues for important similarities in the cognitive architecture of these different brain knowledge systems.

Chapter 7: GENERAL CONCLUSIONS

This Thesis provides new insights into various nonverbal cognitive processes that are affected in the FTLD syndromes from a clinical, neuropsychological and anatomical standpoint. One of the aims of this Thesis was to improve our understanding of the behavioural symptoms exhibited by patients with FTLD, through investigation of the nonverbal cognitive and neuroanatomical mechanisms that may underpin these abnormal behaviours. The Thesis incorporated the use of standard neuropsychological assessment tools alongside novel experimental tests designed to systematically investigate different nonverbal modalities. From the standpoint of behavioural analyses, FTLD patients were shown to be significantly impaired compared to healthy controls in the recognition of emotion in faces, voices and music, as well as in the recognition of odours and flavours. The findings suggest that impaired processing of these nonverbal modalities could contribute to alterations in behaviour in FTLD such as abnormal social and emotional responses, agnosias, abnormal eating behaviours and deficient regulation of physiological drives. As set out in the Introduction chapter, the key aims of this Thesis are to highlight the importance of investigating how the ability to process signals from particular nonverbal sensory modalities is affected in FTLD, so that we may further understand how these alterations or deficits may account for some of the behavioural abnormalities characterising the FTLD syndromes, as well as identifying key brain mechanisms underpinning these cognitive processes. The results of this Thesis have shown that patients with FTLD are deficient in the ability to process emotion in a variety of modalities, which corroborate the existing clinical literature.

The employment of different terminology to describe the FTLD subtypes amongst the individual experiments was a result of newly emergent research which has lead to alterations to the

terminology, definition and classification of these clinical syndromes during the period of experimental work for this Thesis. Recently revised consensus criteria examining the behavioural variant of FTLD (Rascovsky et al., 2011) and primary progressive aphasias (PPA) (Gorno-Tempini et al., 2011) have led to reclassification of the FTLD syndromes to improve diagnostic accuracy and improve uniformity of case reporting. The description of 'probable' versus 'possible' behavioural variant FTD in recent consensus criteria includes the presence of functional disability and characteristic neuroimaging features in addition to behavioural and cognitive changes. The PPA are now classified into three main variants - nonfluent, semantic and logopenic – based on distinct speech and language features, with the support of specific patterns of atrophy from neuroimaging, with semantic-variant PPA (svPPA) being associated with atrophy in ventrolateral anterior temporal lobes bilaterally but usually greater on the left. The grouping of FTLD patients in this Thesis into bvFTD and SemD (Chapter 5) was essentially compatible with this recent classification in terms of clinical and neuroimaging features. In Chapter 3, in which face processing was studied, patients were grouped into frontal-variant FTLD and temporal-variant FTLD based on anatomical criteria, ie the presence of predominant frontal or temporal (left or right) atrophy on MRI, because whilst behavioural abnormalities are associated with both right temporal and frontal lobe atrophy, prosopagnosia is more common with right-sided temporal lobe atrophy and emotion deficits more prominent in frontal atrophy (Josephs et al., 2008; Rosen et al., 2004). Although efforts have been made to delineate the right-temporal variant FTLD group in terms of distinct behavioural, cognitive and anatomical profiles compared to other FTLD syndromes (Chan et al., 2009), the debate is still ongoing with regards to specific classification for this group of patients.

Figures 7.1 and 7.2 provide a summary of the neural correlates of the various nonverbal cognitive deficits in this Thesis. The following sections recapitulate the main findings from each experiment and how these findings address the initial objectives and hypotheses.

Figure 7.1 Statistical parametric maps (SPMs) of grey matter loss associated with impaired identification of faces (red), flavour (green) and recognition of emotion from music (yellow) in FTLD. SPMs are presented on sections of the mean normalised T1-weighted structural brain image in MNI stereotactic space (for illustrative purposes, the T1-weighted structural brain image from Chapter 5 is used); the left hemisphere is on the left and slice coordinates in mm are shown. For recognition of emotion in music, SPMs are thresholded at p<0.05 FDR corrected for multiple comparisons over the whole brain volume. For face identification and flavour identification, SPMs are displayed at p<0.001 uncorrected.

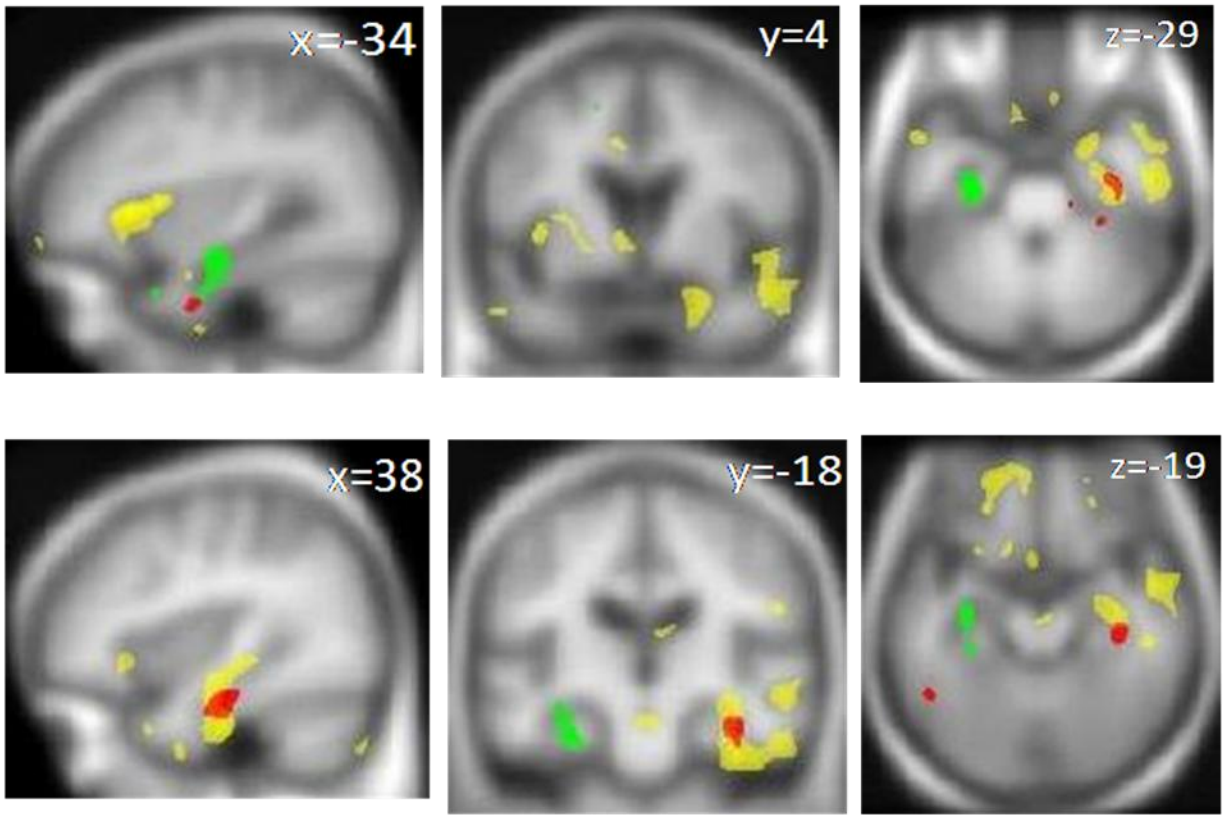
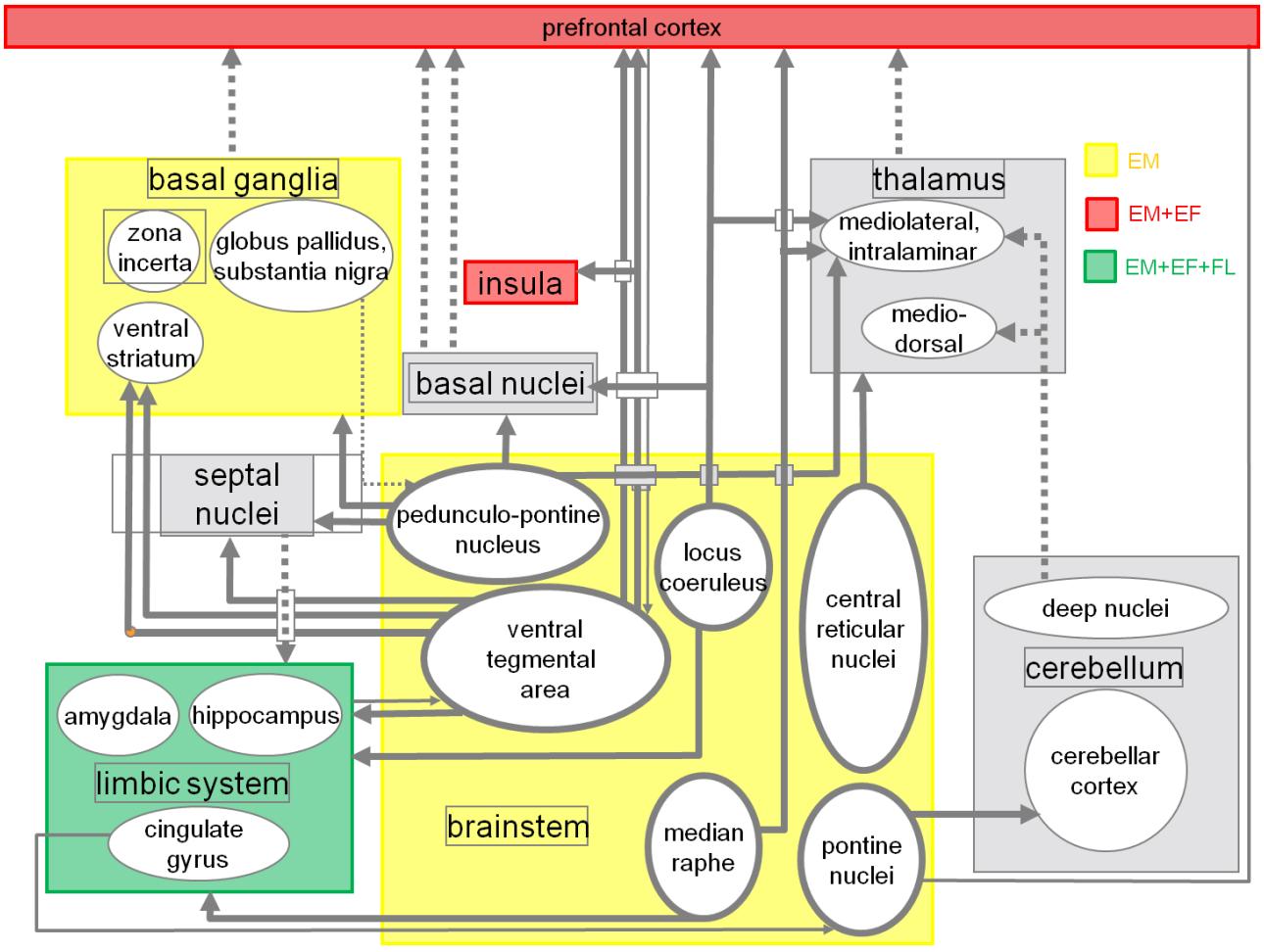


Figure 7.2 A schematic diagram of the major pathways linking the brainstem and limbic system with other cortical and subcortical regions, showing distinct and overlapping brain regions correlating to performance on recognition of emotion in music (EM), recognition of facial emotion (EF) and flavour identification (FL) summarised from the VBM findings in this Thesis. Brain regions associated with EM only are represented in yellow; brain regions associated with both EM and EF are represented in red; brain regions associated with EM, EF and FL are represented in green. Direct efferent pathways from the brainstem are represented using heavy solid lines; other efferent pathways are represented using heavy dotted lines; afferent projections to the brainstem are represented using fine lines.



7.1 Chapter 3: Experiment 1. Face processing in FTLD

Are there distinct patterns of deficits in the cognitive operations underlying face processing in FTLD? Do these deficits associate with distinct areas of cortical atrophy?

The results showed distinct patterns of deficits in the cognitive operations underlying the processing of faces in two groups of patients with FTLD, tv-FTLD and fv-FTLD. The FTLD patients performed worse than controls in all face processing tasks. Although no significant difference was shown between the two FTLD groups in performance on face perception and face emotion recognition tasks, the tv-FTLD group was significantly worse at face identification than the fv-FTLD group. The most severe deficits within both FTLD subgroups in the facial emotion recognition task were for recognition of anger and fear. In terms of neuroanatomical correlates of face processing within the combined FTLD group, performance on face perception was associated with grey matter signal in a distributed fronto-parietal cortical network, whilst face identification correlated with grey matter signal within the fusiform gyrus bilaterally, more prominently on the right anterior fusiform (Figure 2). Performance on recognition of individual facial emotions showed separable but overlapping anatomical correlates, with the most extensive correlates shown for negative emotions anger, fear and surprise comprising bilateral distributed networks involving fronto-parietal regions, temporal and limbic areas.

These findings provide a neuroanatomical framework for understanding face processing deficits in neurodegenerative disease and corroborate the existing body of work based on studies of focal brain lesions and functional imaging work on healthy subjects, showing these cognitive operations to be in accord with the modular neural architecture proposed in contemporary

cognitive models of face processing (Bruce & Young, 1986; De Renzi et al., 1991; Gobbini & Hazby, 2007). The network implicated in facial emotion recognition did not substantially share brain regions with the network correlating with face identification, but did overlap with the fronto-parietal network correlating with face perception, thus suggesting that cognitive modules for face identification and expression are functionally in parallel whilst modules for face perception and emotion recognition interact partly in series. The finding of non-uniform involvement of the putative emotion recognition network between individual negative emotions with specific correlates for each negative emotion is in keeping with previous evidence from functional imaging studies for emotion-specific cerebral networks, and also ties in with the findings from Chapter 5. From a clinical perspective, the findings support current evidence for deficient face analysis in FTLD and shows that within the FTLD population there are subgroup differences in specific face processing operations.

7.2 Chapter 4: Experiment 2. Chemosensory processing in FTLD

How is chemosensory knowledge affected in FTLD? Are distinct brain mechanisms involved in the processing of information from odours and flavours?

This Thesis provides new insights into odour and flavour knowledge in FTLD and posits a structural anatomical basis for flavour identification. It is the first study of its kind to systematically examine associative knowledge of odours and flavours in the different FTLD syndromes at group level, and addressing how changes in flavour and odour knowledge may be related to alterations in eating behaviour. It was found that abnormal eating behaviours commonly developed alongside deficits of flavour identification in bvFTD and svPPA subgroups,

and the lack of a simple correlation between flavour or odour identification and presence of abnormal behaviour may reflect the relatively small numbers of patients studied and the relatively crude metrics available in assessing eating behaviour. Deficits of flavour identification were demonstrated in bvFTD and svPPA, with a significant correlation between flavour and odour identification scores. A 'superordinate effect' was also shown in flavour knowledge, with relative preservation of general categories (fruit or non-fruit) compared with more specific knowledge of particular flavours, which would be consistent with the cognitive organisation found in other knowledge modalities. To further support this, flavour identification across the FTLD syndromes correlated with grey matter signal in a left antero-medial temporal lobe network (Figure 2), including entorhinal cortex, hippocampus, parahippocampal gyrus and temporal. This neuroanatomical profile comprises brain regions previously shown in focal lesion and functional imaging studies to be implicated in associative processing of flavours (Small et al, 1997; Small et al., 2001; Haase et al., 2009) as well as stimuli identification in other modalities (see Chapter 3; also Hailstone et al., 2011). These findings provide evidence of the critical role for the antero-medial temporal lobe in the semantic processing of flavour stimuli, consistent with the "panmodal" role of the anterior temporal lobe in semantic knowledge (Lambon Ralph et al., 2010a).

7.3 Chapter 5: Experiment 3. Music emotion processing in FTLD

How is the processing of emotion in music affected in FTLD compared to affective processing in other modalities? What does FTLD tell us about the neural correlates of emotion processing? Are distinct brain mechanisms involved in the processing of emotion in different sensory modalities?

This Thesis provides a systematic investigation of music emotion processing as a means of accessing emotion in an abstract or inanimate form, to complement the body of work on emotion recognition in faces and voices. The finding of a 'panmodal' deficit of emotional understanding in FTLD is consistent with a common representation of emotion concepts. Performance was worst for anger and fear in all modalities but much more so in music. The profile of brain atrophy associated with emotion recognition across modalities showed grey matter loss in areas previously implicated in representing and evaluating the emotional content of stimuli, including mesial temporal structures, insula and their connections in the mesolimbic system. More specifically, emotion recognition from music which was shown on behavioural analysis to be especially vulnerable to the effects of damage in FTLD was associated with a critical brain substrate comprising a distributed bilateral cerebral network including insula, OFC, medial PFC, limbic structures, anterior temporal as well as parietal cortices and striatum (Figure 1); areas that, in line with the hypotheses, are involved in the processing of emotional valence, salience, the coupling of subjective states and autonomic responses, and in evaluation of the emotional content of complex social signals. These findings demonstrate that the brain substrates critical for recognition of emotions in faces, voices and music in FTLD are separable, and more extensive for music than for other channels of emotional expression. Music may be a sensitive probe of emotional deficits in FTLD and other brain diseases, perhaps because it requires a more distributed and abstract representation of emotion than do animate stimuli (faces and voices). ROC evidence that processing of emotion in music was better able to distinguish FTLD patients from controls than processing of emotion in faces or voices is consistent with the idea that the more abstract representation of musical emotion requires the interaction of frontal and temporal areas, thus making it more vulnerable to damage in FTLD. The findings further suggest that the

processing of emotion in music may tap a core pathophysiological lesion of FTLD, namely, the breakdown of a vulnerable frontotemporal salience network (Seeley et al., 2009). The processing of emotion in music may constitute a model system for the abstraction of emotions in complex real-life social situations and for the breakdown of emotional understanding in particular disease states.

7.4 Chapter 6: Experiment 4. Music knowledge in dementias

How is an abstract non-verbal domain of knowledge, as indexed by music, affected in FTLD? Are distinct brain mechanisms involved in the encoding and processing of musical 'meaning'?

While music (unlike emotion-laden animate stimuli, such as human faces and voices) is an abstract entity without obvious survival value, music serves a clear and important social role across human cultures. This Thesis incorporated a detailed systematic analysis of the cognitive processing of music through a series of novel neuropsychological experiments designed to probe various dimensions of music knowledge, including knowledge of musical compositions, musical emotions, musical instruments and music notation, in dementia patients with premorbid musical expertise. These aspects of music knowledge were assessed in relation to musical perceptual and extra-musical neuropsychological functions. The patient with SemD showed relatively preserved recognition of musical compositions and musical symbols despite severely impaired recognition of musical emotions and musical instruments from sound. In contrast, the patient with DLB demonstrated relatively intact recognition of popular compositions, but impaired recognition of large-scale classical music with somewhat better recognition of composer and musical era, and normal recognition of musical instruments from sound, despite deficits in music perception and

musical emotion recognition. The distinct patterns of deficits between the two diseases, SemD and DLB, suggest a modular organisation of music knowledge with dissociable cognitive mechanisms processing knowledge of abstract musical entities (musical compositions and symbols) and knowledge derived from physical sources (instruments) and emotions. Anatomically, this could reflect a greater dependence of musical semantic memory on brain areas beyond the anterior temporal lobe, in proximity to higher order sensory cortices. In contrast, knowledge of musical instruments and emotions may depend on inferior frontal and anterior temporal areas previously implicated in processing similar information in voices and other domains (Griffiths et al., 2004; Eldar et al., 2007; Belizaire et al., 2007, Schirmer & Kotz, 2006). Superordinate musical knowledge is relatively more robust than knowledge of particular music, in line with evidence for the organisation of knowledge in other modalities [references]. The findings raise fundamental issues concerning not only the cognitive architecture of musical knowledge, but also the brain organisation of nonverbal knowledge systems, suggesting that music is a distinct domain of nonverbal associative knowledge separable from other neuropsychological processes including verbal function and music perceptual ability.

7.5 Clinical implications

From a clinical perspective, the present findings corroborate an extensive clinical literature demonstrating that patients with FTLD have deficits in the cognitive processing of nonverbal signals in various modalities, including faces, chemosensory stimuli and emotions. Statistical parametric maps of grey matter regions associated with performance on specific nonverbal cognitive tasks, in particular face identification, flavour identification and emotion recognition in music, are shown in Figure 1 The experimental results show distinct regions for associative

knowledge of faces and flavours, overlapping with areas within a wider frontotemporal network as indexed by the cognitive processing of emotion particularly in music. The anatomical findings of correlating brain areas to specific nonverbal cognitive operations could potentially suggest new anatomical biomarkers in FTLD.

The identification of specific anatomical associations with deficits in face identification in FTLD corroborate previous findings from focal lesion studies and normal functional imaging work of associative prosopagnosia being associated with right temporal atrophy (Evans et al., 1995; Seeley et al., 2005), and show that impaired identification of faces and facial expressions are separable components of face processing associated with distinct brain areas. With regards to chemosensory processing, the present findings have implications for our understanding of abnormal eating behaviour in FTLD. The deficits of flavour processing and anatomical associations identified in this Thesis suggest that impairment of flavour processing is an important feature in FTLD with predictable anatomical substrates and may potentially explain the evolution of altered eating behaviour. These findings could provide an informative model system for assessing disease-related changes in complex behaviour including person knowledge, eating behaviour and social judgements. Previous evidence has suggested that processing of emotion in music may be relatively resistant to brain damage (Peretz et al., 1998), and has been shown to be spared in AD (Drapeau et al., 2009; Gagnon et al., 2009). The present findings provide further qualification of this conclusion, suggesting that the music emotion recognition deficits identified in this Thesis may be relatively specific to certain degenerative pathologies: notably, those in the FTLD spectrum. Clinically, these findings may be of value in informing behavioural interventions such as music therapy in patients with dementia (Drapeau et a., 2009;

Raglio & Gianelli, 2009; Choi et al., 2009), suggesting a need for selectivity in targeting particular disease populations and potentially also in the form of the intervention.

This information, aside from improving our understanding of the symptoms in FTLD, may also have clinical utility in the design of targeted screening tools to improve diagnosis of FTLD especially in early disease. Accurate diagnosis of the FTLD syndromes is often difficult to achieve with standard available tests. Recent revised guidelines for improving diagnostic accuracy and sensitivity for bvFTD highlight the importance of developing new tools for capturing behavioural change (Rascovsky et al., 2011), and points at a trend in the field of dementia research towards operationalization of behavioural assessments. For example, chemosensory deficits may be a potential marker for altered eating behaviour, and impaired emotion recognition a marker for loss of empathy. The findings in this Thesis add towards achieving this goal by identifying certain nonverbal cognitive deficits that may reflect the presence of behavioural symptoms in FTLD.

7.6 Neurobiological implications

The work in this Thesis provide further insights into the cognitive architecture of hitherto relatively poorly understood nonverbal cognitive modalities including music knowledge, emotion and chemosensory processing. The present findings support modular cognitive models for these individual knowledge domains, and suggest dissociable modules for different cognitive operations within these domains. The findings also posit certain parallels between these and other more well-studied modalities such as language. Both music and flavour knowledge exhibit similarities with the cognitive organisation previously demonstrated for other knowledge

modalities, such as the relatively greater vulnerability of object-specific compared with superordinate knowledge, thus lending further support to the notion that musical and flavour categories (such as composer, or fruit/non-fruit) have neuropsychological validity. Our findings also suggest a truly 'panmodal' deficit of emotional understanding in FTLD implicating not only 'animate' emotional modalities such as facial and vocal expressions, but 'inanimate' abstract emotional stimuli such as music.

The behavioural findings are further supported by neuroanatomical data from VBM work (Figure 1), showing distinct brain regions associated with individual cognitive operations for face and flavour identification, overlapping with a wider frontotemporal salience network associated with music emotion recognition. The finding of an association between both face and flavour identification and an antero-medial temporal lobe network supports previous work implicating these areas in the integration of semantic processing in different modalities and in linking incoming sensory stimuli with behavioural context. This provides further evidence towards the role of the antero-medial temporal lobe in multimodal semantic analysis. In addition, however, the findings across the experiments presented in this Thesis suggest anatomical substrates for linking cognitive operations with subcortical and limbic pathways that mediate basic biological drives (summarised in Figure 2). This was most clearly shown in the case of music emotion processing, which engaged a distributed network of mesiolimbic, striatal and mesial temporal lobe structures. Broadly interpreted, these neuroimaging data suggest mechanisms whereby cognitive, emotional and homeostatic pathways might cooperate in generating integrated behaviour, and more pertinently, how these mechanisms may break down in particular neurodegenerative brian diseases.

This work has implications towards understanding the clinicopathological processes underpinning FTLD. The extensive bilateral areas of cortical damage correlating to impaired music emotion recognition are similar to brain areas found to be populated by unique von Economo neurons (VENs), which have been implicated as an anatomical substrate for the selective network vulnerability of FTLD (Seeley et al., 2009). One of the caveats in the work covered by this Thesis is the lack of post-mortem pathological information supporting the neuropsychological and neuroanatomical data. Behavioural correlations amongst the different FTLD syndromes were investigated in this Thesis, in an attempt to further our understanding of the varied and distinct clinical presentations of the FTLD syndromes. Of interest is the finding of different degrees of deficit in nonverbal cognitive functions between different FTLD subtypes. For example, it has been demonstrated that tvFTLD patients are worse than fvFTLD and controls in face identification, which contributes to the body of knowledge on prosopagnosia in SemD. However, there was an apparent lack of distinction on certain novel tests (eg emotion recognition in music and faces, and odour and flavour identification) between presumably different pathological entities, such as SemD and bvFTD. Recent studies have succeeded in uncovering specific associations between individual FTLD syndromes and neuropathological features, such as the association of the SemD phenotype and TDP-43 type C, and bvFTD with TDP-43 types A and B (Rohrer et al., 2011). The association of the newly identified C9ORF72 gene mutation with particular features in the bvFTD population including prominent neuropsychiatric symptoms and involvement of subcortical grey matter atrophy (Mahoney et al., 2012) highlights the relevance of applying the novel emotion recognition tests in patients with this mutation. Moreover, the fragmentation of cognitive operations does not appear to be clearly along the lines

of syndromic classification. These findings raise the important issue of studying these cognitive processes by stratification according to molecular specificity.

The experiments described in Chapters 3-5 also share certain general limitations of VBM as a technique: VBM can demonstrate anatomical associations with behavioural functions but can only infer any causal relationship between those anatomical changes and the behaviour, and the strength of any correlation is ultimately dependent on the variance in behavioural performance. The VBM technique cannot resolve the relations between the various components of the putative face processing network, an area of active controversy (Steeves et al., 2009). Moreover, there are certain anatomical biases inherent in studying neurodegenerative populations: VBM can only 'see' anatomical changes in those brain regions affected by the disease, i.e., in FTLD, predominantly in the frontal, parietal and anterior temporal cortices.

7.7 Issues for future work

Future work on improving diagnosis as well as syndrome stratification could therefore be built on a deeper understanding of the underlying cognitive and neuroanatomical correlates of behavioural and nonverbal cognitive deficits in the FTLD syndromes and other dementias. The issues concerning future work arising from the individual experiments in this Thesis have been addressed in the relevant chapters. One avenue could involve extending these experiments towards a wider range of neurodegenerative diseases such as Alzheimer's disease and Huntington's disease, to provide further insights into the distinct network profiles of these diseases. The gold standard would be to correlate the behavioural and imaging findings with pathological and genetic data in future studies. It would also be important to study the evolution

of these nonverbal cognitive deficits in relation to disease progression and whether convergence of syndromes occurs over time. These issues may be addressed through the analysis of longitudinal data in FTLD.The issue of diagnostic accuracy and sensitivity is one that needs much work in FTLD, which should direct future work in identifying early markers of change in disease both clinically and radiologically. The suggestion that complex behavioural function could be indexed by "network-based" cognitive processes could inform future studies looking into brain-behaviour correlations by utilising connectivity measures, which could be structural such as diffusion tensor imaging (DTI), or functional using fMRI. The collective knowledge of how these cognitive deficits arise from specific brain damage and the pathological basis of such damage should be utilised in the development of robust biomarkers of early disease and disease progression.

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9. DIVISION OF LABOUR FOR EXPERIMENTAL WORK

Chapter 3

The author was involved in study planning, design and coordination, and in designing, running and performing the VBM analysis and in the statistical analysis of behavioural data. Data from face processing tests was acquired by the author with additional support from Dr Julia Hailstone. Dr Julia Hailstone was involved in the acquisition of general neuropsychological data. Dr Gerard Ridgway provided statistical support for the VBM analysis. Brain segmentations were performed mostly by Elizabeth Gordon and Shona Clegg.

Chapter 4

The author was involved in study planning, design and coordination, acquisition and analysis of experimental behavioural and neuroimaging data. Dr Colin Mahoney provided additional support in acquisition of behavioural and neuroimaging data. Acquisition of general neuropsychological data was performed by Aisling Buckley. Dr Jason Warren was involved in the design of the MATLAB script for running the experimental test battery and in providing advice on study design. Brain segmentations were performed mostly by Elizabeth Gordon.

Chapter 5

The author was involved in study planning, design and coordination, acquisition and analysis of experimental behavioural and neuroimaging data. Dr Susie Henley and Dr Julia Hailstone were involved in the design and data acquisition for the initial pilot study from which the final set of music stimuli for the experimental battery was selected. Dr Jason Warren was involved in the

design of the MATLAB script for running the emotion recognition battery and providing advice on study design. Prof Chris Frost and Dr Jonathan Bartlett provided additional statistical support in the analysis of behavioural data. Dr Susie Henley provided additional support in the statistical analysis of neuroimaging data. Brain segmentations were performed mostly by Elizabeth Gordon.

Chapter 6

The author was involved in study planning, design and coordination, acquisition and analysis of experimental behavioural data. The author was involved in the design and creation of the novel music knowledge tests with additional support and advice from Dr Jason Warren. The author transcribed, played and recorded the tunes for the within-modality melody matching test. Dr Jason Warren, Dr Sebastian Crutch, Dr Jane Warren and Prof Elizabeth Warrington provided additional support and advice on overall study design. Dr Doris-Eva Bamiou performed the audiometric assessments. Dr Julia Hailstone provided support as a blind assessor for the analysis of Case 1's music performance.

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11: PUBLICATIONS ARISING FROM THIS THESIS

Chapter 1: Introduction

- Omar R, Warren JD, Ron MA, Lees AJ, Rossor MN, Kartsounis LD. The neuro-behavioural syndrome of brainstem disease. Neurocase. 2007 Oct;13(5):452-65.
- Omar R, Sampson EL, Loy CT, Mummery CJ, Fox NC, Rossor MN, Warren JD. Delusions in frontotemporal lobar degeneration. J Neurol. 2009 Apr;256(4):600-7.

Chapter 3: Face processing in FTLD

- Omar R, Rohrer JD, Hailstone JC, Warren JD. Structural neuroanatomy of face processing in frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry. 2011 Dec;82(12):1341-3.

Chapter 5: Music emotion processing in FTLD

- Omar R, Henley SM, Bartlett JW, Hailstone JC, Gordon E, Sauter DA, Frost C, Scott SK, Warren JD. The structural neuroanatomy of music emotion recognition: evidence from frontotemporal lobar degeneration. Neuroimage. 2011 Jun 1;56(3):1814-21.

Chapter 6: Music knowledge in dementias

- Omar R, Hailstone JC, Warren JE, Crutch SJ, Warren JD. The cognitive organization of music knowledge: a clinical analysis. Brain. 2010 Apr;133(Pt 4):1200-13.
- Omar R, Hailstone JC, Warren JD. Semantic memory for music in dementia. Music Perception: An Interdisciplinary Journal. 2012 June;29(5):467-77.

12: APPENDIX

Appendix A1. Non-verbal symptom questionnaire

Nonverbal symptoms

To be completed by the person accompanying the patient to the clinic or research visit

With regard to [**subject's name**] …… :

1. Topographical orientation

Have you noticed any of the following:

Difficulties finding his/her way around a place or building they should know well?	Y / N
Difficulties following directions or maps?	Y / N
Difficulties identifying familiar landmarks?	Y / N

2. Face recognition

Does he/she have any difficulty recognising the faces of people they should know well?	Y / N
Does the person still seem familiar even if their name cannot be recalled?	Y / N

3. Voice recognition

Does he/she have any difficulty recognising the voices of people they should know well? Y / N

(e.g., on the telephone)

Does the person still seem familiar even if their name cannot be recalled? Y / N

4. Emotion

Have you or anyone else noticed any of the following:

He/she is less aware of others' feelings? Y / N

He/she is less able to read/understand other people's emotions? Y / N

He/she is less able to express emotions? Y / N

Please give brief details:

If so, are any of the following emotions particularly difficult (please circle)?

happiness, sadness, anger, fear, disgust, surprise

5. Auditory symptoms

Does his/her hearing seem to have altered? Y / N

If yes, please give brief details:

Has he/she experienced tinnitus (ringing in the ears)? Y / N

Has he/she more sensitive to sound? Y / N

If yes, please give brief details:

Do some sounds seem more pleasant or less pleasant than before the illness? Y / N

If yes, please give brief details:

Has their appreciation of music altered compare with before the illness? Y / N

If yes, please give brief details:

6. Smell and taste

Has he /she noticed a change in their sense of smell? Y / N

If yes, please give details:

Has he/she noticed a change in their sense of taste? Y / N

If yes, please give details:

7. Somatic symptoms

Has he /she complained of any unusual bodily sensations? Y / N

If yes, please give details:

Has he /she complained of persistent unexplained physical symptoms? Y / N

If yes, please give details:

Does their experience of pain seem different compared with before the illness? Y / N

If yes, please give brief details:

Has their tolerance of hot or cold weather or hot or cold environments altered? Y / N

If yes, please give details:

Appendix A2. Creation of the music emotion battery

Stimuli used to represent canonical emotions in music:

Anger
Egmont Overture (Beethoven)
Enigma Variation No. 4: Allegro di molto (Elgar)
Mars, from The Planets (Holst)
New World Symphony: Allegro (Dvorak)
New World Symphony: Scherzo (Dvorak)
Organ Symphony: Scherzo (Saint Saens)
Summer, from The Four Seasons (Vivaldi)
Symphony No. 5: Moderato (Shostakovich)
Symphony No. 5: Allegro non troppo (Shostakovich)
Symphony No. 6: Storm (Beethoven)

Fear
Aliens Theme
Alien 3 Theme
Bluebeard's Castle: The Lake of Tears (Bartok)
Concerto Grosso No 3 for Two Violins and Harpsichord: Pesante (Schnittke)
Jaws Theme
Music for Strings, Percussion and Celesta: Adagio (Bartok)
Night on a Bare Mountain (Mussorgsky)
Pictures at an Exhibition: Cum Mortuis (Mussorgsky)
Psycho Theme
Saturn, from The Planets (Holst)

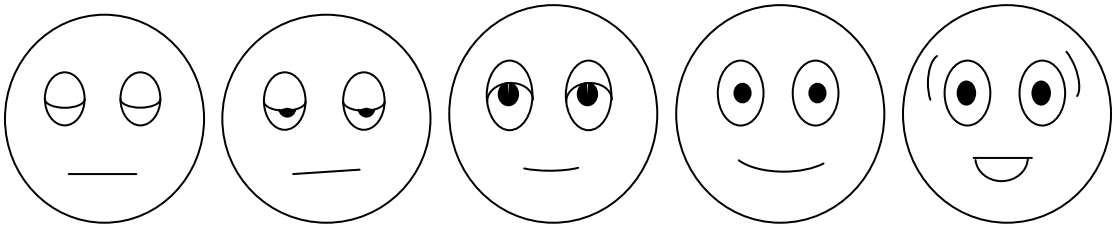
Happiness
Autumn, from The Four Seasons (Vivaldi)
Big Country Theme
La Boheme Overture (Puccini)
Canon in D (Pachelbel)
Capriccio Espagnol: Alborada (Rimsky-Korsakov)
Capriccio Espagnol: Fandango (Rimsky-Korsakov)
Jurassic Park Theme
Marriage of Figaro Overture (Mozart)
Ma Vlast: Vltava (Smetana)
Romanze in F (Brahms)

Sadness
Adagio for Strings (Barber)
La Boheme Finale (Puccini)
Fantasia on a Theme by Thomas Tallis (Vaughan Williams)
Intermezzo in A major, Opus 118 (Brahms)

Pathetique Sonata: Grave (Beethoven)
Russian Easter Festival Overture (Rimsky-Korsakov)
Scheherazade (Rimsky-Korsakov)
Schindler's List Theme
Symphony No 3: Poco Allegretto (Brahms)
Symphony No. 5: Largo (Shostakovich)

Selection of stimuli was based on an intial pilot study in 16 healthy subjects who did not participate in the subsequent experiment. Pilot subjects were presented with a larger set of 104 musical excerpts and asked to rate each excerpt for how strongly it represented each of the four target emotions using a paper scale ranging from 0 (not at all) to 4 (very strongly). Ratings for each excerpt for each emotion were averaged across the control group. An excerpt for which one and only one emotion achieved a mean rating ≥ 2 was considered to portray that emotion (other excerpts were considered insufficiently salient, or ambiguous). Excerpts fulfilling this criterion were ordered based on rating, and the 10 highest-ranking excerpts for each emotion were used in the test battery. Mean (range) ratings for each emotion were as follows: anger, 3.0 (2.8 – 3.8); fear, 3.1 (2.5 – 3.8); happiness, 3.2 (2.6 – 3.9); sadness, 2.8 (2.1 – 3.5).

Appendix A3. Arousal scoring system based on the Self-Assessment Manikin (SAM) (Bradley and Lang, 1994). Graphic faces depicting arousal ratings for musical stimuli, ranging from score 1 (far left: not arousing) to 5 (far right: very arousing).



Appendix Table A1. Names of public figures in the Famous Faces recognition test

TRIAL	NAME
1	Bruce Forsyth
2	George W Bush
3	Bill Clinton
4	Tony Blair
5	Prince Andrew
6	Princess Anne
7	Jack Straw
8	Gordon Brown
9	Terry Wogan
10	David Blunkett
11	Ian Duncan Smith
12	Charles Kennedy

Appendix Table A2. Stimuli used in the experimental assessment of flavour identification

TRIAL	TARGET	RELATED FOIL	DISTANT FOIL	TARGET FRUIT/NON-FRUIT
1	Strawberry	Blackberry	Popcorn	F
2	Vanilla	Licorice	Strawberry	NF
3	Cherry	Raspberry	Cinnamon	F
4	Blackberry	Strawberry	Peanut	F
5	Coffee	Chocolate	Lemon	NF
6	Banana	Pear	Coffee	F
7	Chocolate	Peanut	Orange	NF
8	Pear	Banana	Peanut	F
9	Raspberry	Cherry	Caramel	F
10	Cinnamon	Licorice	Pear	NF
11	Lemon	Orange	Peanut	F
12	Licorice	Cinnamon	Banana	NF
13	Orange	Lemon	Popcorn	F
14	Peanut	Chocolate	Cherry	NF
15	Popcorn	Vanilla	Lemon	NF
16	Caramel	Chocolate	Blackberry	NF
17	Ginger Ale	Licorice	Banana	NF
18	Pineapple	Orange	Chocolate	F
19	Blueberry	Cherry	Ginger Ale	F
20	Bubblegum	Caramel	Pear	NF

Appendix Table A3. Musical excerpts used in composition and emotion recognition experiments

Excerpts are listed alphabetically for convenience; stimuli were presented in randomised order

Experiment 1. Famous melody matching

Auld Lang Syne
Edelweiss
Eine Kleine Nachtmusik (Allegro)
God Save the Queen
Greensleeves
Hark! The Herald Angels Sing
Hey Jude
I Vow to Thee, My Country
Jerusalem
Jingle Bells
Joy to the World
Land of Hope and Glory
Brahms' Lullaby
Waltzing Matilda
Ode to Joy
Que Sera Sera
Silent Night
Spring, from The Four Seasons
Star Wars Theme
Swan Lake (Scene: Allegro giusto)
Yesterday

Experiment 1. Pieces played by BR following introduction

A Trumpeter's Lullaby (Anderson)
Carnival of Venice (Arban)
Coronation Street Theme
La Cucaracha (folk song)
Eastenders Theme
Last of the Summer Wine Theme
Match of the Day Theme
Memory from Cats
Mexican Hat Dance (folk song)
Michelle
Oklahoma! from Oklahoma
Trumpet Tune (Purcell)
Trumpet Voluntary (Clarke)
When I'm 64
Yesterday

Experiment 2. Solo test

Bach: Violin Concerto in A
Bach: Oboe Concerto in D minor
Beethoven: Piano Concerto No. 3 in C minor
Beethoven: Violin Concerto in D
Brahms: Piano Concerto No. 1 in D minor
Dvorak: Cello Concerto in B minor
Dvorak: New World Symphony (Adagio)
Gershwin: Rhapsody in Blue

Grieg: Piano Concerto in A minor
Handel: Organ Concerto No. 13 in F
Handel: Let the Bright Seraphim
Haydn: Trumpet Concerto in E-flat
Mozart: Clarinet Concerto in A
Mozart: Flute Concerto in G major
Rodrigo: Concierto de Aranjuez
Saint Saens: Organ Symphony
Shostakovich: Violin Concerto No. 1 in A minor
Tchaikovsky: Violin Concerto in D major
Vaughan Williams: The Lark Ascending
Vaughan Williams: Oboe Concerto in A minor

Experiment 3. Emotion recognition in music

Anger
Egmont Overture (Beethoven)
Enigma Variation No. 4 (Elgar)
Mars, from The Planets (Holst)
New World Symphony: Allegro (Dvorak)
New World Symphony: Scherzo (Dvorak)
Organ Symphony: Scherzo (Saint Saens)
Summer, from The Four Seasons (Vivaldi)
Symphony No. 5 clip 1 (Shostakovich)
Symphony No. 5 clip 2 (Shostakovich)
Symphony No. 6: Storm (Beethoven)

Fear
Aliens Theme
Alien 3 Theme
Concerto Grosso for Two Violins and Harpsichord (Schnittke)
Jaws Theme
Music for Strings, Percussion and Celesta clip 1 (Bartok)
Music for Strings, Percussion and Celesta clip 2 (Bartok)
Night on a Bare Mountain (Mussorgsky)
Pictures at an Exhibition: Gnomus (Mussorgsky)
Psycho Theme
Saturn, from The Planets (Holst)

Happiness
Autumn, from The Four Seasons (Vivaldi)
Big Country Theme
La Boheme Overture (Puccini)
Canon in D (Pachelbel)
Capriccio Espagnol clip 1 (Rimsky-Korsakov)
Capriccio Espagnol clip 2 (Rimsky-Korsakov)
Jurassic Park Theme
Marriage of Figaro Overture (Mozart)
Ma Vlast: (Smetana)
Romanze in F (Brahms)

Sadness
Adagio for Strings (Barber)
La Boheme Finale (Puccini)

Easter Festival Overture (Rimsky-Korsakov)
Fantasia on a Theme by Thomas Tallis (Vaughan Williams)
Intermezzo in A major, Opus 118 (Brahms)
Pathetique Sonata: Grave (Beethoven)
Scheherezade (Rimsky-Korsakov)
Schindler's List Theme
Symphony No 3: Poco Allegretto (Brahms)
Symphony No. 5 clip 3 (Shostakovich)

Appendix Table A4. Associations between correct emotion recognition and other factors: odds ratios (95% CI) for 1 unit increase in factor

Modality	**Factor**				
	Theory of mind (Mind in the Eyes)*	**Executive function (Trail-making)****	**Fluid intelligence (Raven's Matrices)*****	**Music familiarity rating********	**Years of music training*********
Faces	1.105 (1.061, 1.152)	1.047 (0.957, 1.145)	1.103 (1.010, 1.205)	-	-
Voices	1.128 (1.076, 1.183)	1.121 (1.036, 1.212)	1.096 (0.999, 1.203)	-	-
Music	1.091 (1.053, 1.130)	1.090 (1.032, 1.151)	1.072 (1.007, 1.141)	1.81 (1.16, 2.81)	1.001 (0.887, 1.131)

* data from 11 patients; ** data from 26 patients; *** data from 23 patients;
**** data from 20 controls; ***** data from 16 controls

Appendix Table A5. Local maxima of grey matter loss associated with impaired emotion recognition in FTLD: modality comparisons

Emotion modality	Brain region R	Brain region L	MNI coordinates x, y, z (mm)	Z score
Music > voices		lateral OFC**	-31 22 -22	4.55
		medial PFC**	-6 58 -5	4.29
		anterior insula**	-33 22 5	4.06
	medial PFC**		3 52 -13	4.04
		medial OFC**	0 16 -16	3.94
		frontal pole	-17 71 13	3.77
	superior PL		27 -29 66	3.71
	frontal pole		13 71 7	3.64
		parieto-occipital cortex	-26 -87 13	3.58
	lateral OFC		38 49 2	3.55
	ACC		13 41 10	3.54
		occipital	-31 -87 -10	3.50
	PHG		24 -7 -40	3.35
	temporal pole		31 7 -47	3.33
	amygdala		29 5 -29	3.32
		posterior insula	-37 -17 9	3.31
		ACC	-11 47 11	3.23
Voices > music		primary motor	-27 -25 50	4.46

The Table shows maxima exceeding threshold $p < 0.001$ (uncorrected for whole brain volume) and cluster extent of 50 voxels, derived from contrasts between the emotion modalities indicated. **Areas surviving small volume correction ($p < 0.05$); Key: ACC, anterior cingulate gyrus; MNI, Montreal Neurological Institute stereotactic space; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PHG, parahippocampal gyrus; PL, parietal lobe

Appendix Table A6. Details of healthy musician controls

	Control 1	Control 2	Control 3	Control 4	Control 5	Control 6
Age / gender	53M	78M	75F	49M	49F	72M
Musical background	Professional conductor, vocalist. 12 years music training, performs with professional orchestra	Professional oboist (retired), music teacher. 17 years music training, performs in professional orchestra	Professional violinist (retired) and music teacher. 21 years music training, violinist in professional orchestras	Professional trumpet player and music teacher. 22 years music training, performs in professional orchestras	Professional cellist and music teacher. 21 years music training, performs in professional orchestra	Professional flautist. 11 years music training, performs in professional orchestras

Appendix Table A7. Examples of stimuli used in the experimental assessment of music cognition

Examples of the musical stimuli available from the authors

Experiment no.	Experiment name	Stimulus name	Task	Target name/answer	Foil names
Exp 1	Famous melody matching	1. Jingle Bells 1 2. Jingle Bells 2	"Do the 2 excerpts belong to the same song?"	Yes	
		1. Waltzing Matilda 2. I Vow to Thee, My Country	"Do the 2 excerpts belong to the same song?"	No	
	Pieces played from memory (Case 1)	Clarke's "Trumpet Voluntary"			
		Anderson's "A Trumpeter's Lullaby"			
Exp 2	Solo test	Mozart's Flute Concerto in G major	Era	Classical	• Baroque • 20th century
			Solo instrument	Flute	• Violin • Horn
			Composer	Mozart	• Haydn • Beethoven
		Vaughan Williams' "The Lark Ascending"	Era	20th century	• Romantic • Classical
			Solo instrument	Violin	• Viola • Piano
			Composer	Vaughan Williams	• Walton • Finzi

Exp 3	Emotion recognition in music	Holst's "Mars" from "the Planets"	Which emotion is represented in this music?	Anger	• Happiness • Sadness • Fear
		Mussorgsky's "Cum Mortuis in Lingua Mortua" from "Pictures at an Exhibition"		Fear	• Sadness • Happiness • Anger
		Mozart's Overture from "the Marriage of Figaro"		Happiness	• Anger • Fear • Sadness
		Barber's Adagio for Strings		Sadness	• Fear • Happiness • Anger
Exp 4	Instrument sound recognition	Piano			
		Oboe			

Appendix Figure A1. Statistical parametric map (SPM) of grey matter loss associated with impaired emotion recognition from music in FTLD: effect of covarying for general executive performance (Trails score). The SPM is thresholded at p<0.05 FDR corrected for multiple comparisons over the whole brain volume and presented on sections of the mean normalised T1-weighted structural brain image in MNI stereotactic space; the left hemisphere is on the left and slice coordinates in mm are shown. Letter codes are as for Figure 2.