PHYSIOLOGY AND NEUROANATOMY OF EMOTIONAL REACTIVITY IN FRONTOTEMPORAL DEMENTIA

A thesis submitted to University College London for the degree of Doctor of Philosophy

DR CHARLES R. MARSHALL

Dementia Research Centre

Institute of Neurology

University College London

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DECLARATION

I, Charles Marshall, confirm that the work presented here is my own. Where information has been derived from other sources, I confirm that this has been referenced accordingly.

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ABSTRACT AND SUMMARY OF EXPERIMENTAL FINDINGS

The frontotemporal dementias (FTD) are a heterogeneous group of neurodegenerative diseases that cause variable profiles of fronto-insulo-temporal network disintegration. Loss of empathy and dysfunctional social interaction are a leading features of FTD and major determinants of care burden, but remain poorly understood and difficult to measure with conventional neuropsychological instruments. Building on a large body of work in the healthy brain showing that embodied responses are important components of emotional responses and empathy, I performed a series of experiments to examine the extent to which the induction and decoding of somatic physiological responses to the emotions of others are degraded in FTD, and to define the underlying neuroanatomical changes responsible for these deficits. I systematically studied a range of modalities across the entire syndromic spectrum of FTD, including daily life emotional sensitivity, the cognitive categorisation of emotions, interoceptive accuracy, automatic facial mimicry, autonomic responses, and structural and functional neuroanatomy to deconstruct aberrant emotional reactivity in these diseases. My results provide proof of principle for the utility of physiological measures in deconstructing complex socioemotional symptoms and suggest that these warrant further investigation as clinical biomarkers in FTD.

Chapter 3:

Using a heartbeat counting task, I found that interoceptive accuracy is impaired in semantic variant primary progressive aphasia, but correlates with sensitivity to the emotions of others across FTD syndromes. Voxel based morphometry demonstrated that impaired interoceptive accuracy correlates with grey matter volume in anterior cingulate, insula and amygdala.

Chapter 4:

Using facial electromyography to index automatic imitation, I showed that mimicry of emotional facial expressions is impaired in the behavioural and right temporal variants of FTD.

Automatic imitation predicted correct identification of facial emotions in healthy controls and syndromes focussed on the frontal lobes and insula, but not in syndromes focussed on the temporal lobes, suggesting that automatic imitation aids emotion recognition only when social concepts and semantic stores are intact. Voxel based morphometry replicated previously identified neuroanatomical correlates of emotion identification ability, while automatic imitation was associated with grey matter volume in a visuomotor network including primary visual and motor cortices, visual motion area (MT/V5) and supplementary motor cortex.

Chapter 5:

By recording heart rate during viewing of facial emotions, I showed that the normal cardiac reactivity to emotion is impaired in FTD syndromes with fronto-insular atrophy (behavioural variant FTD and nonfluent variant primary progressive aphasia) but not in syndromes focussed on the temporal lobes (right temporal variant FTD and semantic variant primary progressive aphasia). Unlike automatic imitation, cardiac reactivity dissociated from emotion identification ability. Voxel based morphometry revealed grey matter correlates of cardiac reactivity in anterior cingulate, insula and orbitofrontal cortex.

Chapter 6:

Subjects viewed videos of facial emotions during fMRI scanning, with concomitant recording of heart rate and pupil size. I identified syndromic profiles of reduced activity in posterior face responsive regions including posterior superior temporal sulcus and fusiform face area. Emotion identification ability was predicted by activity in more anterior areas including anterior cingulate, insula, inferior frontal gyrus and temporal pole. Autonomic reactivity related to activity in both components of the central autonomic control network and regions responsible for processing the sensory properties of the stimuli.

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ABBREVIATIONS

ACC – anterior cingulate cortex
BPVS – British Picture Vocabulary Scale
bvFTD – behavioural variant frontotemporal dementia
C9orf72 – chromosome 9 open reading frame 72
CS – corrugator supercilii muscle
DARTEL – diffeomorphic anatomical registration through exponentiated lie algebra
ECG – electrocardiography
EMG – electromyography
EPI – echoplanar imaging
EX – sensitivity to the emotions of others component of RSMS
fMRI – functional magnetic resonance imaging
FTD – frontotemporal dementia
FTLD – frontotemporal lobar degeneration
FUS – fused in sarcoma
GDA – Graded Difficulty Arithmetic
GNT – Graded Naming Test
GRN - progranulin
HR – heart rate
IA – interoceptive accuracy
IFG – inferior frontal gyrus
LL – levator labii muscle
MAPT – microtubule associated protein tau
MMSE – Mini Mental State Examination
MRI – magnetic resonance imaging
MTG – middle temporal gyrus
MTL – medial temporal lobe
MT/V5 – middle temporal area/visual area 5 complex
M1 – primary motor cortex
nfvPPA – nonfluent variant primary progressive aphasia
OFC – orbitofrontal cortex
PAL – Paired Associate Learning test
PCC – posterior cingulate cortex
PHG – parahippocampal gyrus
RMT – Recognition Memory Test
RSMS – Revised Self-Monitoring Scale
rtvFTD – right temporal variant frontotemporal dementia
SMA – supplementary motor area
STS – superior temporal sulcus
svPPA – semantic variant primary progressive aphasia
TDP-43 – transactive response DNA binding protein 43
TIV – total intracranial volume
UPS – ubiquitin proteasome system
VBM – voxel based morphometry
VOSP – Visual Object and Spatial Perception battery
V1 – primary visual cortex
WAIS-R – Wechsler Adult Intelligence Scale – Revised
WASI – Wechsler Abbreviated Scale of Intelligence
WMS – Wechsler Memory Scale
ZM – zygomaticus major muscle

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EPIGRAPH

'In order to understand our neighbour, that is, in order to reproduce his sentiments in ourselves, we often, no doubt, plumb the cause of his feelings, as, for example, by asking ourselves, Why is he sad? in order that we may become sad ourselves for the same reason. But we much more frequently neglect to act thus, and we produce these feelings in ourselves in accordance with the effects which they exhibit in the person we are studying, —by imitating in our own body the expression of his eyes, his voice, his gait, his attitude, or we may at least endeavour to mimic the action of his muscles and nervous system. A like feeling will then spring up in us as the result of an old association of movements and sentiments which has been trained to run backwards and forwards.'

– Friedrich Nietzsche, Daybreak, 1880

1. INTRODUCTION

OVERVIEW OF THE FRONTOTEMPORAL DEMENTIAS

In 1892, while working at the University of Prague, Arnold Pick provided the first description of a neurodegenerative disease that for many years would bear his name (Pick *et al.*, 1994). August H was a 71 year-old man, who presented with two years of behavioural change including "raving and threatening his wife with a knife", and progressive loss of the ability to understand words. At post mortem, Pick found him to have focal left hemisphere atrophy predominantly affecting the temporal lobe, and argued for the first time that progressive cerebral atrophy could result in highly focal symptoms. For most of the twentieth century, dementias led by changes in behaviour and/or language were called Pick's disease, and in 1911 when Alois Alzheimer identified a pathological association with swollen neurons containing argyrophilic inclusions, he termed these Pick bodies (Alzheimer, 1911). Subsequent work led to a reclassification of Pick's disease into a heterogeneous group of neurodegenerative syndromes led by deficits in behaviour or language, caused by non-Alzheimer's pathology, and associated with variable profiles of frontal and temporal lobe atrophy: the frontotemporal dementias (FTD) (Warren *et al.*, 2013a). Aggregates of abnormal protein deposition are key findings at post mortem in these clinical syndromes, and multiple pathological bases have been recognised, of which Pick bodies are only one. These pathological entities are grouped under the umbrella term of frontotemporal lobar degeneration (FTLD, as distinct from the term FTD which refers to clinical syndromes) (Love and Spillantini, 2011). The two major pathological groups in the FTLD spectrum are tau and TDP-43, accounting for around 90% of cases, but these comprise numerous subtypes, and other distinct pathologies exist such as FTLD-FUS and FTLD-UPS (Mackenzie *et al.*, 2010).

FTD is a leading cause of young-onset dementia, typically presenting in the sixth decade (Johnson *et al.*, 2005; Rabinovici and Miller, 2010), with a prevalence in the United Kingdom of around 15/100,000 in the 45-64 age group (Ratnavalli *et al.*, 2002), a prevalence approaching that of Alzheimer's disease in this population. It is likely, however, that the true prevalence of FTD is higher due to under-diagnosis (Coyle-Gilchrist *et al.*, 2016). In an unselected cohort of 85 year-olds, FTD was shown to have a prevalence of 3% (Gislason *et al.*, 2003), and in post mortem studies, FTLD has been found to have a prevalence of 42% in young-onset dementia (Snowden *et al.*, 2011). Survival typically ranges from 3-14 years, although some slowly progressive forms may have an even longer duration (Onyike and Diehl-Schmid, 2013). A relatively high proportion of FTD cases (at least 20%) are familial, with autosomal dominant inheritance. Mutations in *MAPT*, *GRN*, and hexanucleotide repeat expansions in *C9orf72* account for the large majority of genetic FTD, and most of these cases present with behavioural alterations (Lashley *et al.*, 2015). Other rarer causative mutations have been described in genes including *TBK-1*, *CHMP2B*, *VCP* and *SQSTM1* (Lashley *et al*., 2015).

Current diagnostic criteria recognise three canonical clinical FTD syndromes defined according to their leading features (Warren *et al.*, 2013a); behavioural variant FTD (bvFTD) led by progressive decline in executive function, emotionality and interpersonal skills; semantic variant primary progressive aphasia (svPPA) led by erosion of language comprehension and semantic knowledge; and nonfluent variant primary progressive aphasia (nfvPPA) led by deficits in motor speech production and grammar. This syndromic classification admits considerable overlap and heterogeneity, both clinically and pathologically, and there is a tendency for syndromes to converge with time. There is also a significant overlap with other neurodegenerative diseases including motor neurone disease and the atypical parkinsonian syndromes of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), the underlying pathology of which is within the FTLD spectrum (McMonagle and Kertesz, 2015). There are significant difficulties with classification and early diagnosis of FTD, including

common diagnostic delays (Coyle-Gilchrist *et al.*, 2016; Draper *et al.*, 2016), a high rate of false positive diagnosis (Shinagawa *et al.*, 2016), and the existence of FTD phenocopies with alternative (usually psychiatric) diagnoses (Gossink *et al.*, 2015).

These diseases are remarkable for the highly selective patterns of network disintegration that they produce, predominantly involving frontotemporal intrinsic connectivity networks including emotional salience, semantic and sensorimotor networks (Seeley *et al.*, 2009). FTD is likely to be associated with selective vulnerability of particular types of neurone to the relevant molecular pathologies, particularly von Economo neurones (Seeley *et al.*, 2006). These are large projection neurones that have evolved convergently in the frontoinsular regions of animals that demonstrate self-awareness, and are hypothesised to represent a key step in the phylogeny of advanced social behaviour, with resultant implications for the characteristic changes in social cognition and self-awareness typically found in FTD (Seeley *et al.*, 2006; Seeley, 2008; Craig, 2009; Cauda *et al.*, 2013; Cauda *et al.*, 2014). FTDs are considered to be paradigmatic examples of 'molecular nexopathies': diseases where specific molecular pathologies induce selective patterns of neurodegeneration determined by regional translational and transcriptional profiles, and structural and functional network properties (including selective vulnerability of neuronal subtypes), and these patterns of large scale network degeneration produce particular constellations of clinical and symptomatic features (Warren *et al.*, 2013b).

Much of the linkage required for a comprehensive description of FTD in these terms from molecules to clinical syndromes remains undiscovered, but the special cases of genetic FTD where the pathological basis is known in life have revealed clear clinicoanatomical patterns related to individual molecular aetiologies (Rohrer and Warren, 2011; Downey *et al.*, 2014; Marshall *et al.*, 2016a). In sporadic FTD, post mortem studies have demonstrated imprecise mapping between molecular aetiologies and clinical syndromes (Rohrer *et al.*, 2011; Perry *et*

al., 2017), which may be due in large part to clinical and anatomical heterogeneity within canonical syndromic groupings. There is thus a strong imperative for more precise phenotyping of clinical features and anatomical patterns in FTD syndromes. A complete delineation of these diseases as molecular nexopathies would inform molecular and cellular neuroscience approaches, improve diagnosis (including allowing molecular stratification in life) and open the door to targeted molecular therapies. Physiological markers have the potential to signal alterations in network-level brain function, allowing changes in molecular physiology to be scaled up to a macroscopic level, and providing possible techniques to dynamically track the effects on neural function of both the diseases and future therapies.

CANONICAL SYNDROMES OF FTD

Despite the heterogeneity and nosological difficulty described above, a majority of clinical presentations of FTD can be readily assigned to one of the syndromic groupings in the current diagnostic criteria (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011). These have utility in the clinic and in research, despite not fully accounting for the clinicoanatomical diversity within each syndrome or the underlying molecular aetiologies, and are therefore used to group patients throughout the experimental work in this thesis. The following section is a synopsis of the clinical features and neuroanatomical profiles of these FTD syndromes, drawn from a synthesis of the existing literature and my experience of diagnosing and caring for these patients in the clinic, with an emphasis on the practical diagnosis of each syndrome.

BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA

Clinical presentation:

bvFTD is a disease of frontotemporal networks mediating self-awareness, social and emotional behaviour, motivation and executive function (Warren *et al.*, 2013a). Symptomatically, it is led by behavioural change, with the diagnostic criteria emphasising typical features including loss of empathy, apathy, disinhibition, stereotyped behaviours, hyperorality with altered eating

behaviour, and executive dysfunction (Rascovsky *et al.*, 2011). The history is typically insidious, with slowly progressive changes in behaviour often being dismissed completely, or ascribed to psychiatric diagnoses, marital disharmony or "midlife crises". As a result, there is usually a long diagnostic delay, with a median time to first consultation of over a year, and a subsequent period of over two years before receiving the diagnosis, meaning that a typical time from symptom onset to final diagnosis is almost four years (Coyle-Gilchrist *et al.*, 2016; Draper *et al.*, 2016).

It is common for bvFTD to be associated with a lack of insight, and patients may consider that they do not have any cognitive dysfunction, or may complain of memory difficulties (Warren *et al.*, 2013a). It is therefore important that a careful history is taken with an informant to uncover the key behavioural features. Changes in social circumstance, such as breakdowns in personal relationships and workplace discord may be relevant as early signs of degraded interpersonal behaviour. Because social dysfunction is often a leading symptom, it is generally helpful to ask the informant about whether they seem less warm or affectionate, and whether there have been any instances of social embarrassment. The latter may also reflect disinhibition, which can manifest as inappropriate jocularity or social faux pas, or as impulsive (but rarely malevolent) behaviours like excessive spending, violence or reckless driving. Disinhibition may lead to inappropriate sexual remarks, although true hypersexuality occurs in only a minority of bvFTD patients, with loss of libido being more characteristic (Miller *et al.*, 1995; Mendez and Shapira, 2013; Ahmed *et al.*, 2015b).

Attempts have been made to subclassify presentations of bvFTD according to the relative prominence of disinhibition or apathy (Snowden *et al.*, 2001). In practice, however, these frequently coexist, either simultaneously, or in series as the disease progresses, with apathy and inertia generally supervening later in the course of the illness, and a distinct anatomical basis for the two dimensions has not been reliably demonstrated (Peters *et al.*, 2006). The

distinction between disinhibition-predominant and apathy-predominant bvFTD is therefore seldom diagnostically useful. Apathy may be described in the history as reduced motivation, loss of previous interests, or reduced behavioural initiation (sometimes requiring vigorous prompting to perform daily activities). This may be associated with a decline in personal hygiene that can additionally reflect diminished self-awareness and disgust responses (Englund, 1993; Eckart *et al.*, 2012). Apathy is distinct from depression, but in practice frequently misdiagnosed as being a disorder of mood (Levy *et al.*, 1998). Symptoms of apathy overlap with those of executive dysfunction, particularly in the abandonment of premorbid interests and intellectual pursuits. Decline in executive dysfunction can manifest as cognitive inefficiency, difficulties with planning and sequencing complex tasks, or impaired attention and concentration with distractibility.

Compulsive and stereotyped behaviours can include wandering, repetitive movements or mannerisms (e.g. clapping, whistling, dancing), or more complex behaviours (e.g. rituals in activities of daily living, hoarding, playing solitaire). Patients may demonstrate marked behavioural rigidity, with assiduous adherence to routines (Perry *et al.*, 2012). Altered eating behaviours are common, and may include food compulsions, as well as carbohydrate craving ("sweet tooth") and gluttony with hyperphagia (Ahmed *et al.*, 2016a), with weight gain being a frequent feature (Miller *et al.*, 1995). The weight gain in bvFTD tends to be smaller than the increase in caloric intake would suggest, however, and a complex pattern of alterations in metabolic rate and neuroendocrine function have been proposed to account for this (Ahmed *et al.*, 2016b). Hyperorality, involving oral exploration of inedible objects is often seen, and is dissociable from changes in eating behaviour (Snowden *et al.*, 2001).

Various other distinctive neurobehavioural features have been described in the literature, but are not yet emphasised in the diagnostic criteria. These include changes in aesthetic preferences such as obsessive craving for music and colour ('musicophilia' and 'chromophilia'

respectively), which may be conversely accompanied by a dislike of environmental sounds and a failure to appreciate visual art (Fletcher *et al.*, 2013; Cohen *et al.*, 2015; Fletcher *et al.*, 2015b). Changes in sense of humour are near ubiquitous, and typically involve a shift in humour preference to less complex (e.g. slapstick), fatuous or even callous humour with Schadenfreude (Clark *et al.*, 2016; Santamaria-Garcia *et al.*, 2017). Neuropsychiatric features are found in a proportion of patients with bvFTD, and occasionally the syndrome can initially mimic diagnoses of schizophrenia, schizoaffective disorder or bipolar affective disorder (Velakoulis *et al.*, 2009; Lanata and Miller, 2016). Delusions and hallucinations in bvFTD tend to have a somatic focus, and are particularly common in carriers of *C9orf72* repeat expansions. These psychotic symptoms may be linked to changes in bodily awareness and body schema processing, including alterations in self/non-self differentiation, susceptibility to body ownership illusions, and pain and temperature sensitivity, all of which have been associated with cortico-thalamo-cerebellar network degeneration (Downey *et al.*, 2012; Snowden *et al.*, 2012; Downey *et al.*, 2014; Fletcher *et al.*, 2015a; Marshall *et al.*, 2016a).

Whilst the history from the patient with bvFTD may be uninformative, observation of their behaviour in the clinic can often assist in the diagnosis (Warren *et al.*, 2013a). A lack of empathic concern for the family members present may be readily apparent, especially as they describe the emotional toll of the patient's behavioural change. Other spontaneous behaviours may be evident, including stereotypies, disinhibition, inappropriate interaction with the clinician (e.g. inappropriate jocularity - 'moria'), or utilisation behaviour (a tendency to interact compulsively and automatically with objects in the environment). A lack of normal social reactivity may appear as hostility, impassivity, or even provoke a sense of unease in the observer (Edwards-Lee *et al.*, 1997; Perry *et al.*, 2001).

Neuropsychological assessment may corroborate the diagnosis, and frontal executive dysfunction as measured with psychological instruments is one of the optional diagnostic

criteria recognised by Rascovsky et al (Rascovsky *et al.*, 2011). However, in practice, neuropsychological deficits are often only detectable long after the onset of behavioural change, and normal neuropsychological assessment should therefore be interpreted with caution in the diagnostic phase (Gregory *et al.*, 1999). When abnormalities are detected, the pattern is usually one of impaired response inhibition on Stroop testing, reduced verbal fluency, concrete interpretation of proverbs, impaired cognitive estimates and difficulty with sequencing or set-shifting (Wittenberg *et al.*, 2008). Posterior cortical functions such as visuoperceptive function are typically preserved. Preserved episodic memory was previously used as a diagnostic criterion for bvFTD, although it is increasingly recognised that memory can be somewhat impaired, possibly due to attentional and executive inefficiencies (Hodges *et al.*, 1999; Wittenberg *et al.*, 2008). Mild language impairments on the spectrum of those found in svPPA may also be detected, and become more prominent as the disease progresses (Hardy *et al.*, 2016).

Late in the course of the illness, physical examination might reveal 'frontal release' signs such as grasp or pout reflexes, although these are seldom contributory to the diagnosis (Warren *et al.*, 2013a). Rather, physical examination is important to detect the frequent presence of other overlapping neurodegenerative syndromes. Evidence of amyotrophy may signal coexisting motor neurone disease, and atypical parkinsonian features (e.g. vertical gaze palsy, axial parkinsonism, hemineglect, apraxia, alien limb) can reveal incipient progressive supranuclear palsy or corticobasal syndrome (McMonagle and Kertesz, 2015).

bvFTD is the commonest FTD syndrome, representing 50-60% of cases with confirmed FTLD pathology (Rohrer *et al.*, 2011). It is also the most likely to have a genetic basis, with 30-50% of cases being familial (Onyike and Diehl-Schmid, 2013). At post mortem, the underlying pathology of most bvFTD is roughly evenly split between FTLD-tau and FTLD-TDP, with a small minority of cases due to alternative pathologies (FTLD-FUS, FTLD-UPS and occasionally

Alzheimer's disease) (Rohrer *et al.*, 2011; Perry *et al.*, 2017). In sporadic FTD, associations between clinicoanatomical features and underlying pathologies are weak, except where there are overlapping motor disorders, with the presence of motor neuron disease strongly predicting TDP-43 pathology, and the presence of features of progressive supranuclear palsy strongly suggesting tau pathology (corticobasal syndrome also suggests tau pathology, but can be due to TDP-43 in a minority of cases) (Rohrer *et al.*, 2011; Perry *et al.*, 2017). In general, therefore, it is not possible to molecularly stratify sporadic bvFTD during life, unlike the autosomal dominant genetic aetiologies, where the particular gene dictates a molecular class of FTLD pathology (tau in *MAPT* mutations, TDP-43 in *C9orf72* and *GRN* mutations) (Lashley *et al.*, 2015).

Neuroanatomy:

The anatomical manifestations of bvFTD are protean, involving variable patterns of atrophy in the frontal, insular and temporal cortices, as well as subcortical structures including basal ganglia, thalamus and cerebellum, with sparing of more posterior cortical regions (Rohrer, 2012). It has been conceptualised as being primarily a disease of an intrinsic connectivity 'salience' network comprising orbitofrontal cortex, anterior cingulate, anterior insula and presupplementary motor area (Seeley *et al.*, 2007). There is a consistent tendency for atrophy to be greater on the right, perhaps because those with left-predominant atrophy are more likely to present with a syndrome of svPPA or nfvPPA. Clinically, it is helpful to look at T1-weighted coronal images for evidence of widening of orbitofrontal and dorsolateral prefrontal sulci and the Sylvian fissure, and atrophy of the temporal poles and amygdalae, while sagittal sections may be helpful for visualising atrophy of medial frontal cortex, including the anterior cingulate, and may demonstrate a posterior to anterior volume gradient (see Figure 1.1). The presence of atrophy at first consultation is highly variable, and a normal scan does not exclude a diagnosis of bvFTD. Often serial imaging with registration of interval scans, or metabolic

imaging (e.g. with PET scan) are helpful in demonstrating subtle regional volume loss or hypometabolism that add support to the diagnosis when baseline volumetric imaging is equivocal (Gregory *et al.*, 1999).

The genetic bvFTD syndromes have been associated with specific anatomical hallmarks, *MAPT* mutations causing predominant bilateral medial temporal lobe atrophy, *GRN* mutations leading to asymmetrical hemispheric atrophy extending posteriorly into the parietal lobe, and *C9orf72* repeat expansions causing volume loss in distributed cortico-subcortical networks including the insula, thalamus and cerebellum (Rohrer and Warren, 2011; Rohrer *et al.*, 2015). Given the anatomical heterogeneity of bvFTD, and the suggestion from the genetic cases that there may be specific links between molecular pathologies and anatomical patterns, several attempts have been made to define anatomical clusters within sporadic bvFTD (Whitwell *et al.*, 2009; Ranasinghe *et al.*, 2016). Four principle subtypes have been proposed: frontal predominant, temporal predominant, frontotemporal, and subcortical. Practically, however, these subtypes do not predict particular symptoms or molecular aetiologies reliably enough to have real clinical utility, with the exception of the relatively distinct subtype with focal right temporal atrophy; the right temporal variant of FTD (rtvFTD) (Chan *et al.*, 2009; Rohrer *et al.*, 2011; Perry *et al.*, 2017).

RIGHT TEMPORAL VARIANT FRONTOTEMPORAL DEMENTIA

Clinical presentation:

rtvFTD is a behaviourally-led syndrome that meets current diagnostic criteria for bvFTD, but has long been recognised as a fairly well-defined syndrome of its own, with a hallmark atrophy pattern and symptom profile (Edwards-Lee *et al.*, 1997; Chan *et al.*, 2009; Kamminga *et al.*, 2015). As such, it is the most practically useful subtype within the heterogeny of bvFTD, and is frequently investigated as a separate group in the recent research literature, e.g. (Gola *et al.*, 2017; Pressman *et al.*, 2017).

The clinical syndrome is typically one of profound disturbance of social and emotional behaviour, but can occasionally be led by face recognition difficulty (prosopagnosia) (Evans *et al.*, 1995; Thompson *et al.*, 2003; Chan *et al.*, 2009). Relative to other presentations of FTD, rtvFTD has been particularly associated with severe interpersonal coldness (Rankin *et al.*, 2003). The unifying theme of these presentations is an erosion of person-specific semantics across all sensory modalities, including the affective person knowledge that is required for emotional comprehension (Rosen *et al.*, 2002b; Thompson *et al.*, 2004; Joubert *et al.*, 2006). This formulation is supported by work in the healthy brain, showing a key role for the right temporal lobe in social cognition and social concepts, as part of a network also incorporating amygdala and orbitofrontal cortex (Todorov *et al.*, 2007; Zahn *et al.*, 2007; Olson *et al.*, 2013).

Other prominent symptomatic changes in rtvFTD relative to other FTD syndromes include hyperreligiosity, hallucinations, cross-modal sensory experiences, obsessionality, topographical difficulties and (relative to other forms of bvFTD) language decline (Chan *et al.*, 2009; Josephs *et al.*, 2009; Kamminga *et al.*, 2015; Kumfor *et al.*, 2016). rtvFTD has also been associated with a particularly severe loss of insight, which may partly explain the relative paucity of rtvFTD in the clinic and in research, constituting the rarest subtype of FTD in most studies (Chan *et al.*, 2009). The deficits in rtvFTD may be subtle and not always recognisable to the non-specialist observer as obviously neurological in aetiology, and often the patient presents a well-preserved intellectual façade. In combination with the profound lack of insight, these difficulties may contribute to significant under-diagnosis and acquisition bias.

Neuroanatomy:

The key anatomical finding in rtvFTD is asymmetric temporal lobe atrophy, worse on the right (non-dominant) side (Chan *et al.*, 2009; Josephs *et al.*, 2009; Kamminga *et al.*, 2015; Kumfor *et al.*, 2016). This may be visualised on coronal T1-weighted MRI as marked 'knife blade' volume loss of the anterior temporal gyri, and profound atrophy of the amygdala giving the temporal

horn of the lateral ventricle a 'cored-out' appearance (see Figure 1.1). The imaging pattern is essentially a mirror image of svPPA (see below), having an anterior-posterior and inferior-superior gradient of atrophy within the temporal lobe, the temporal pole and fusiform gyrus typically being most severely affected (Josephs *et al.*, 2009). For this reason, the syndrome has sometimes been referred to as "right-sided semantic dementia" or "right-sided svPPA", although this nomenclature is problematic because the syndrome is rarely led by language features (Kamminga *et al.*, 2015; Kumfor *et al.*, 2016). Much like svPPA, volume loss in rtvFTD is normally clearly visualised at the time of first consultation. With time, atrophy progression is seen in the contralateral temporal lobe, such that the asymmetry eventually disappears, and there is a variable coexistence of frontal volume loss, especially of the orbitofrontal cortex (Josephs *et al.*, 2009; Kumfor *et al.*, 2016).

Even within rtvFTD, two distinct subtypes have been proposed: one with highly focal temporal atrophy, and another with coexisting frontal atrophy (Josephs *et al.*, 2009). These may to some extent predict the underlying molecular pathology, with the focal cases being highly predictive of TDP-43 pathology, and most of the cases with more distributed atrophy having *MAPT* mutations (and hence tau pathology).

SEMANTIC VARIANT PRIMARY PROGRESSIVE APHASIA

Clinical presentation:

svPPA typically begins as difficulty finding words (particularly nouns) - sometimes described as losing 'memory for names' - and an inability to express thoughts with precision. The patient's verbal messages become progressively more circumlocutory and empty, as fine-grained content (less frequently used vocabulary, such as 'dachshund' or 'ladybird') is replaced by increasingly generic ciphers ('animal', 'thing'). Blunting of verbal nuance in svPPA may predate diagnosis by many years (Heitkamp *et al.*, 2016). The true nature of the deficit is revealed in a history (almost pathognomonic for svPPA) of asking the meaning of previously familiar words

('What's broccoli?'): this is not merely a problem of accessing words in memory, but erosion of vocabulary itself. Indeed, svPPA is the paradigmatic disorder of semantic memory, the cognitive system that stores knowledge about objects and concepts (rather than the autobiographical events that populate 'episodic' memory) and allows us to attribute meaning to the world at large (Warrington, 1975; Hodges and Patterson, 2007). The language deficit in svPPA is fundamentally associated with loss of meaning about objects and people. While language impairment usually leads the presentation, deficits of nonverbal knowledge inevitably appear later in the course and ultimately blight all sensory channels (Hodges and Patterson, 2007; Goll *et al.*, 2010; Omar *et al.*, 2011; Omar *et al.*, 2013). Occasionally, patients may present with inability to recognise objects (visual agnosia) or familiar people (prosopagnosia) by sight.

Earlier in the course of the illness, the conversation of patients with svPPA is easily passed as normal by the casual listener, due to its well preserved surface structure and fluency, even garrulousness (Rohrer *et al.*, 2010b). However, closer attention generally reveals severe anomia. Impaired comprehension of single words in svPPA can be demonstrated by asking the patient to describe an item nominated by the examiner or to select it from an array or scene.

Assessment of other language channels corroborates the semantic deficit. When reading aloud or writing, patients with svPPA characteristically 'regularise' words according to superficial phonological 'rules' in place of learned vocabulary (e.g., sounding 'island' as 'izland' or 'sew' as 'soo'): so called 'surface' dyslexia or dysgraphia. Assessment of nonverbal semantic domains generally requires more detailed neuropsychological assessment, though in clinic visual knowledge might be conveniently sampled (within the limits of verbal comprehension and without requiring naming) by asking the patient to indicate the purpose of a familiar tool (such as a comb or stapler), to identify associations of a pictured item ('Which thing could be used in the garden?') or to supply biographical information from photographs of familiar people.

Across verbal and nonverbal semantic domains, loss of meaning in svPPA follows a stereotyped pattern. More specific knowledge about less familiar (low frequency) and atypical items is lost before knowledge of highly familiar and typical items; failures of recognition are accompanied by 'over-generalisation' errors that tend to regularise objects to a generic type (for example, the patient may draw a four-legged peacock or a rhino lacking its horn); and errors are highly consistent over time, so that the meanings of words and objects, once lost, are irretrievable (Lambon Ralph and Patterson, 2008).

A behavioural syndrome similar to that defining bvFTD characteristically develops in svPPA and indeed, these syndromes can sometimes be difficult to distinguish, even after a careful history. Initially, behavioural features in svPPA may be quite subtle but tend to manifest earlier and more floridly in patients with more marked right (non-dominant) temporal lobe involvement, and become universal as the march of disease involves the fronto-temporal networks that regulate social responsiveness (Hodges and Patterson, 2007; Ralph *et al.*, 2017). Symptoms found in bvFTD such as absent or misplaced empathy, social disinhibition and faux pas, a more fatuous sense of humour and pathological sweet tooth are common in svPPA (Snowden *et al.*, 2001; Rankin *et al.*, 2005; Rohrer and Warren, 2010; Hsieh *et al.*, 2013; Clark *et al.*, 2016; Clark and Warren, 2016). Within this spectrum, certain behavioural features, such as food faddism, exaggerated reactions to pain and ambient temperature, behavioural rigidity with clock-watching and obsessional interest in numbers, puzzles (especially Sudoku and jigsaws) and music ('musicophilia') seem particularly linked to svPPA (Snowden *et al.*, 2001; Fletcher *et al.*, 2015a; Fletcher *et al.*, 2015b; Harris *et al.*, 2016; Midorikawa *et al.*, 2017). A unifying theme here may be impaired understanding of emotional and somatic signals due to both deficient and over-generalised responses to sensory information (Rankin *et al.*, 2005; Omar *et al.*, 2011; Omar *et al.*, 2013; Clark and Warren, 2016), analogous to recognition failures and 'regularisation errors' in other cognitive domains. An impoverished concept of self may underlie increased rate of depression and suicidality in svPPA relative to other

neurodegenerative syndromes (Irish and Piolino, 2016). Insight and awareness of deficits often appear to be retained but may be superficial or incomplete. In contrast to bvFTD and nfvPPA, associated neurological signs are not typically found in svPPA, though atypical parkinsonian or motor neuron features may develop later in the course (Kremen *et al.*, 2011; Josephs *et al.*, 2013).

Completing the picture of a highly coherent clinical, anatomical and pathological syndrome, most cases of svPPA have TDP-43 (type C) pathology at post-mortem (Rohrer *et al.*, 2011; Chare *et al.*, 2014; Spinelli *et al.*, 2017). Primary tauopathies and Alzheimer's disease account for a small minority and may have certain distinguishing phenotypic markers (for example, prominent acalculia or extrapyramidal signs in association with Pick's disease pathology (Rohrer *et al.*, 2011; Spinelli *et al.*, 2017)). Most cases are sporadic though occasional pathogenic mutations are reported (Coyle-Gilchrist *et al.*, 2016) and may be relatively more likely if motor features are present (e.g., associated motor neuron disease with TBK1 mutations (Caroppo *et al.*, 2015)).

Neuroanatomy:

On neuroimaging, svPPA has a hallmark pattern of asymmetric, focal cerebral atrophy chiefly involving the dominant antero-inferior and mesial temporal lobe, including amygdala and anterior hippocampus (Chan *et al.*, 2001; Gorno-Tempini *et al.*, 2011). This is most easily visualised on a T1-weighted coronal MRI scan (see Figure 1.1). The profile of atrophy shows a clear gradient within the temporal lobe, with 'knife-blade' destruction of the pole and relative sparing of superior temporal gyrus and more posterior temporal cortices. This signature is consistently observed across patients and is unmistakeable. It is invariably present at diagnosis in typical svPPA and indeed (in contrast to nfvPPA) often 'the scan is worse than the patient'. Over time, atrophy spreads to involve more posterior temporal regions and homologous gyri in the contralateral temporal lobe as well as orbitofrontal cortex (Rohrer *et al.*, 2008b; Kumfor *et*

al., 2016): regions that together constitute the core of the brain's semantic memory network (Hodges and Patterson, 2007; Ralph *et al.*, 2017). This distinctive atrophy profile has provided an important neuroanatomical grounding for cognitive models of svPPA, according to which anterior temporal cross-modal 'hub' cortex interacts with more posterior, relatively modality-specific cortices across both left and right temporal lobes (Ralph *et al.*, 2017).

NONFLUENT VARIANT PRIMARY PROGRESSIVE APHASIA

Clinical presentation:

Patients with nfvPPA present with slow, effortful, hesitant and distorted speech. Speech sound errors are generally prominent and there is often a history of 'slurring' or mispronunciations. Words tend to be missed out and conversation is sometimes strikingly telegraphic; errors of grammar (mainly affecting syntax, function words such as articles and conjunctions, and verb usage) typically emerge and sometimes dominate the presentation (Rohrer *et al.*, 2010b; Wilson *et al.*, 2010). Inability to understand more complex conversations or instructions may signify impaired comprehension of sentences, which is generally integral to any grammatical deficit (Peelle *et al.*, 2008). Speech is usually more affected than written communication at the outset and patients tend to resort increasingly to nonverbal means of expression, manifestly frustrated by their inability to communicate.

On examination, there is usually marked difficulty producing polysyllabic words and sequences of syllables (e.g., 'puh-tuh-kuh') to command, due to impaired motor programming of speech and reduced articulatory agility. This can be brought out by asking the patient to repeat longer words or read aloud. The listener is left with an almost painful sense of the patient's struggle to speak (not experienced with other forms of PPA). In contrast to peripheral dysarthrias which tend to provoke stumbling consistently over particular sounds, the misshapen speech of patients with nfvPPA is protean, with characteristic 'groping' after the target sound: 'speech apraxia' (Josephs *et al.*, 2012). This is often accompanied by apraxia of posed orofacial

movements such as yawning or whistling, disproportionate to any limb apraxia (Rohrer *et al.*, 2010a); asked to perform an orofacial gesture, the patient may emphatically echo the command ('Cough!') while remaining quite unable to enact it. Speech sound errors can be classified according to whether syllables are wrongly selected ('phonemic' or 'phonological' errors) or misformed during execution ('phonetic' or articulatory errors). These arise at different stages during message production but often defy explicit categorisation in the clinic. It is useful to examine a specimen of the patient's writing: besides revealing spelling (phonological dysgraphic) errors, this is a more reliable index of associated agrammatism than the patient's speech, which may be constricted by the sheer effort involved.

The clinical spectrum of nfvPPA is diverse, with a number of variant sub-syndromes. The most important of these is 'pure' progressive speech apraxia associated with orofacial apraxia but without agrammatism or other aphasic features, which has been proposed to constitute a distinct entity (Josephs *et al.*, 2006; Josephs *et al.*, 2014). While apraxia of speech may indeed be relatively pure at presentation, most of these patients do in time develop aphasia, initially detected on detailed neuropsychological assessment(Rohrer *et al.*, 2010b).

General intellect is often remarkably well preserved, though a degree of executive dysfunction is usual and may be accompanied behaviourally by apathy or impulsivity (Rohrer and Warren, 2010; Harris *et al.*, 2016). Depression can be significant, particularly as insight is usually retained. Many patients with nfvPPA will develop Parkinsonism, often evolving into a progressive supranuclear palsy or corticobasal syndrome with associated supranuclear gaze palsy, postural instability, pseudobulbar dysfunction and limb apraxia, dystonia or 'alien limb' phenomena (Kremen *et al.*, 2011; Graff-Radford *et al.*, 2012).

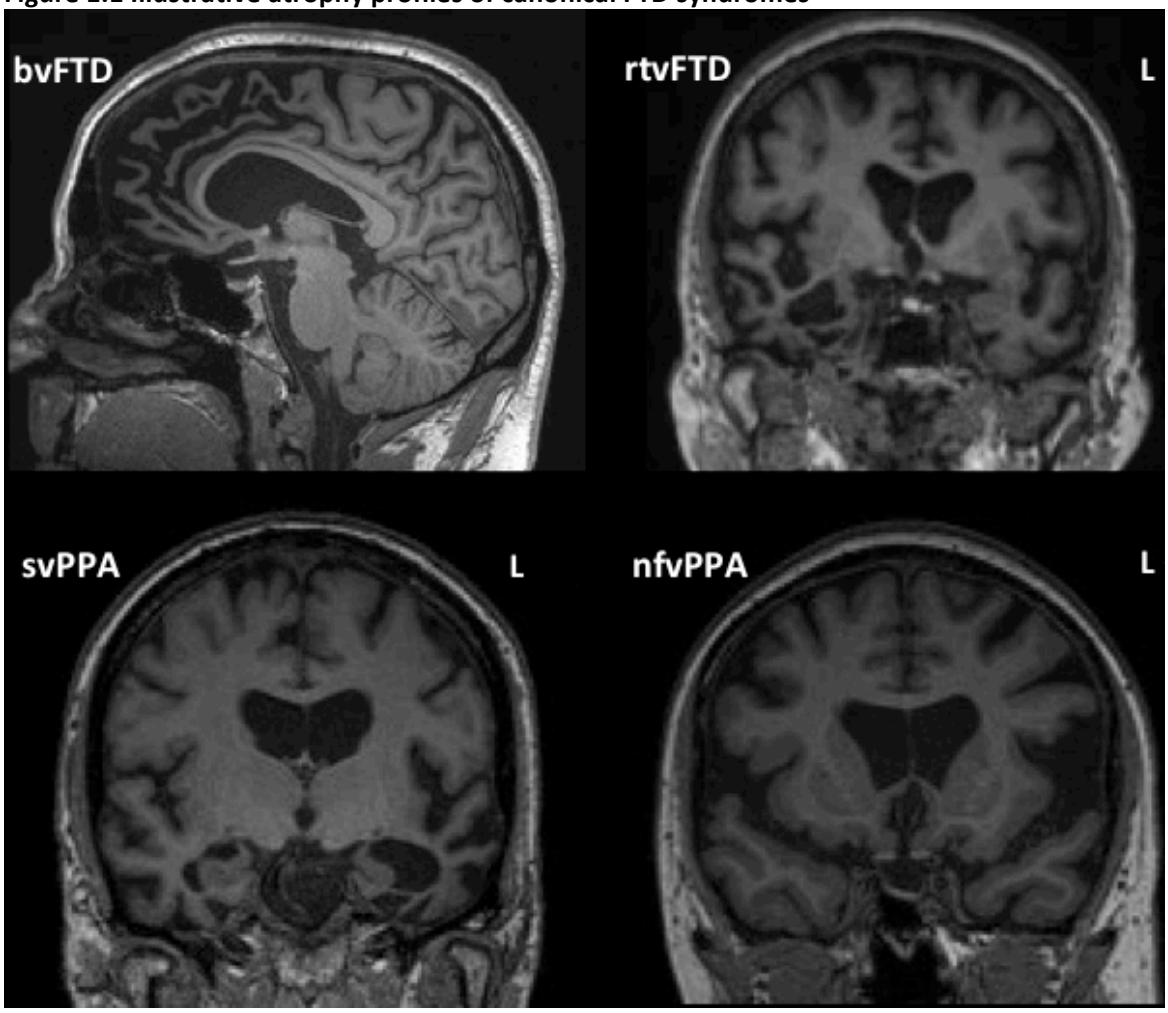
The pathological associations of nfvPPA are (in keeping with the clinical spectrum) more heterogeneous than svPPA. A majority of patients will have a tauopathy such as progressive supranuclear palsy or corticobasal degeneration at post mortem though a substantial (and still

uncertain) minority represent TDP-43 or Alzheimer pathology (Rohrer *et al.*, 2011; Chare *et al.*, 2014; Magnin *et al.*, 2016; Rogalski *et al.*, 2016; Spinelli *et al.*, 2017). While there are currently few reliable predictors of underlying pathology in individual patients (Xiong *et al.*, 2011), prominent apraxia of speech and parkinsonism are more closely associated with tauopathy (Rohrer *et al.*, 2011; Spinelli *et al.*, 2017). nfvPPA is less likely to be genetically mediated than bvFTD, although it is somewhat more heritable than svPPA, around 30% of patients having a relevant family history (Rohrer *et al.*, 2009). Causative mutations in all major (*GRN*, *MAPT*, *C9orf72*) genes causing frontotemporal dementia have been identified and at least some of these genetic forms may prove clinically distinct with more detailed phenotyping (Rohrer *et al.*, 2010b; Marshall *et al.*, 2015).

Neuroanatomy:

This syndrome is associated with atrophy of opercular inferior frontal gyrus ('Broca's area') and insula cortex in the dominant hemisphere (see Figure 1.1), with variable extension along and around the superior temporal gyrus. These brain regions play fundamental roles in language output, motor speech programming and sentence processing (Rohrer *et al.*, 2008a). Atrophy is generally best appreciated as widening of the left Sylvian fissure on a T1-weighted coronal MRI scan (Marshall *et al.*, 2016b). However, this may be subtle on cross-sectional imaging and is easily overlooked, even by experienced observers (Sajjadi *et al.*, 2017). A neuroradiological phenotype of homologous right-sided peri-Sylvian atrophy is recognised, though its clinical correlates remain ill-defined (Ghacibeh and Heilman, 2003; Vitali *et al.*, 2004).

Figure 1.1 Illustrative atrophy profiles of canonical FTD syndromes



T1-weighted volumetric MRI of selected patients that participated in the work presented in this thesis. Each panel demonstrates the typical focal atrophy pattern found in one of the canonical syndromes of frontotemporal dementia. Images are presented according to clinical convention with the left displayed to the observer's right. Top left: behavioural variant frontotemporal dementia (sagittal section showing "knife blade" atrophy of medial frontal and orbitofrontal cortex with a dramatic anterior-posterior atrophy gradient). Top right: right temporal variant frontotemporal dementia (coronal section showing focal right temporal lobe atrophy with marked loss of the amygdala). Bottom left: semantic variant primary progressive aphasia (coronal section showing a mirror image of rtvFTD with focal left temporal and amygdala atrophy. Note also the superior-inferior gradient within the temporal lobe, with the fusiform gyrus being particularly severely affected). Bottom right: nonfluent variant primary progressive aphasia (coronal section showing widening of the left Sylvian fissure due to atrophy of the insula and inferior frontal gyrus).

SOCIOEMOTIONAL DYSFUNCTION IN FTD

At a basic level, emotion can be defined as an organism's behavioural and physiological response to environmental challenges (Panksepp, 1982). In humans, these responses are associated with particular subjective feeling states, and these subjective states are often referred to as affect, although there is significant semantic overlap between the terms 'emotion', 'feeling' and 'affect', and definitive definitions of each of these terms do not exist in psychology (Mulligan and Scherer, 2012). The literature on the nature, experience and expression of emotion is extensive, but for the purpose of this thesis, I will focus specifically on the social aspects of emotion, i.e. the processes by which we are able to identify and respond appropriately to the emotions of others, as this relates specifically to the symptoms that are of key clinical relevance in FTD.

Empathy (used here as a general term describing response to the emotions of others) is a complex construct with dissociable components, including emotion identification, affective empathy (the process of affect sharing or emotional contagion) and cognitive empathy (a more advanced system of cognitive perspective taking and mentalising – e.g. understanding what the other person feels and why - also referred to as emotional theory of mind) (Shamay-Tsoory *et al.*, 2009; Coll *et al.*, 2017). Collectively, these empathic processes are often referred to as interpersonal reactivity (Davis, 1983). In the following section, I will review how work to date has attempted to deconstruct these components in the study of degraded empathy in FTD syndromes.

Compared to other young-onset dementias, FTD is associated with disproportionately high economic costs and care burden (Kandiah *et al.*, 2016; Uflacker *et al.*, 2016; Galvin *et al.*, 2017) This discrepancy is due in large part to the prominence of socioemotional symptoms in FTD syndromes, and the devastating effect of loss of empathy on caregivers (Mourik *et al.*, 2004; Hsieh *et al.*, 2013; Mioshi *et al.*, 2013). Although social and empathic changes are among the

diagnostic criteria for bvFTD, and considered leading features in rtvFTD, all FTD syndromes are characterised by deficits in emotion processing (Kumfor and Piguet, 2012; Hazelton *et al.*, 2016). These changes occur early, and may predict subsequent FTD diagnoses in unselected population samples (Pardini *et al.*, 2013). They also effectively differentiate FTD from Alzheimer's disease, FTD phenocopies, and psychiatric mimics such as depression (Kipps *et al.*, 2009; Lee *et al.*, 2014; Goodkind *et al.*, 2015; Chiu *et al.*, 2018). There is therefore an impetus to improve understanding of the neurobiology of degraded interpersonal reactivity in FTD in order to define objective measures of social and emotional symptoms that might aid in diagnosis and monitoring of disease, and to clarify the brain bases for such symptoms, in the hope that this will aid in the stratification of molecular and anatomical syndromes.

Much of the work on emotion processing in FTD has centred on the ability to recognize and categorize emotional expressions. Visual recognition of emotional facial expressions is impaired across the FTD spectrum, and this extends to other modalities including vocal emotional expressions, music and prosody (Rosen *et al.*, 2002b; Rosen *et al.*, 2004; Snowden *et al.*, 2008; Kumfor *et al.*, 2011; Omar *et al.*, 2011; Kumfor and Piguet, 2012; Rohrer *et al.*, 2012b). These deficits have been correlated with atrophy in a distributed network of brain regions previously shown to support emotion processing in the healthy brain including amygdala, orbitofrontal cortex, insula, anterior cingulate, anteromedial temporal lobe, fusiform gyrus and frontal operculum (Rosen *et al.*, 2002b; Omar *et al.*, 2011; Rohrer *et al.*, 2012b; Couto *et al.*, 2013; Hazelton *et al.*, 2016). Two fMRI studies of facial emotion processing in bvFTD have revealed reduced activity in posterior face responsive regions outside canonical disease foci, and related this to disrupted top-down influences from frontal and limbic impairments (Virani *et al.*, 2013; De Winter *et al.*, 2016).

Beyond the cognitive categorisation of emotional states, attempts have been made to parse cognitive (e.g. affective mentalising and theory of mind) and affective (e.g. emotional

contagion) components of empathy in FTD syndromes. Theory of mind and social reasoning have both been shown to be impaired in bvFTD (Kipps and Hodges, 2006; Lough *et al.*, 2006), but measuring affective empathy is difficult, and most studies use emotion recognition in place of true measures of contagion, and hence fail to truly parse these two dimensions of emotional response (Rankin *et al.*, 2005; Baez *et al.*, 2014; Oliver *et al.*, 2015; Torralva *et al.*, 2015). Other approaches have demonstrated impairments of sensitivity to others' emotions and emotional responsiveness using caregiver ratings of empathy in questionnaires and interviews, which probably more closely reflect the importance of socioemotional deficits in daily life (Rankin *et al.*, 2003; Rankin *et al.*, 2005; Oliver *et al.*, 2015).

The ability to express emotion in FTD has been less intensively studied, but deficits have been shown in multiple modalities. Patients with bvFTD, and to an even greater extent rtvFTD, are impaired in the intentional formation of facial expressions, and this relates to grey matter loss in the frontal operculum, insula and orbitofrontal cortex (Gola *et al.*, 2017). Loss of the ability to depict emotion in art has also been demonstrated (Mendez and Perryman, 2003), as well as changes in affect that signal a restricted range of emotional expressivity such as a fatuous demeanour, a fixed false smile or a paucity of conversational laughter (Perry *et al.*, 2001; Mendez *et al.*, 2006; Pressman *et al.*, 2017).

Despite being a leading feature of FTD syndromes and a key determinant of social and economic disease burden, socioemotional dysfunction in FTD remains poorly understood and difficult to measure. Conventional neuropsychological instruments tend to emphasise the cognitive categorisation of emotion, which is confounded by other neuropsychological deficits such as semantic processing, and may not capture disturbances of affective empathy that are likely to be more important in guiding the non-verbal interpersonal reactivity upon which healthy social relationships depend (Carton *et al.*, 1999). Attempts to measure affective empathy using qualitative ratings by the patient are fraught with difficulties relating to

behavioural and linguistic impairments. Although carer questionnaires may capture this to some extent, their utility is limited by problems related to their inherent subjectivity. To find improved ways of detecting and measuring socioemotional dysfunction in FTD, clinical researchers will have to look to the study of these processes in the healthy brain in the hope of discovering new avenues of investigation grounded in established neurobiology.

SOCIAL AND EMOTIONAL PERCEPTION IN HEALTH

The ability to infer mental and emotional states in others is a key component of human cultural development (Heyes and Frith, 2014). Emotional states are commonly communicated using facial expressions or vocalisations. For the work contained in this thesis, I have largely addressed social and emotional perception at this most basic level, rather than addressing more complex social interactions or emotional constructs. In the 1960s, Ekman defined six fundamental human emotions: anger, disgust, fear, happiness, sadness and surprise. He showed that facial expressions communicating these core emotions are pan-cultural, and are recognisable across linguistic boundaries, even by members of previously uncontacted remote tribes (Ekman *et al.*, 1969). More recently, the same has been shown of emotional vocalisations representing the six basic emotions (Sauter *et al.*, 2010). Although much emotional nuance is culture-specific and communicated linguistically, the pan-cultural nature of the basic emotional expressions implies that they are evolutionarily ancient and may have played a key role in facilitating the social group formation that has underpinned the success of the species *(Frith and Frith, 2010)*. Not all theories of emotion allow for the existence of these basic emotional categories. For example Barrett believes that all emotions are complex constructs (Barrett, 2017), and many computational models of emotion have been developed (Marsella *et al.*, 2010). Nevertheless, healthy people are generally able to categorise displays of these crude emotions, whereas patients with FTD are impaired on such tasks, and therefore

despite perhaps being an oversimplification, this approach is a practical way to begin to address socioemotional deficits in the diseased brain.

The literature on the functional neuroanatomy of processing the emotional signals from others is extensive, but is perhaps best synopsised by a recent large meta-analysis of functional imaging studies (mostly of facial emotion perception), in which hierarchical clustering analysis defined four key levels of processing social and emotional stimuli, each of which comprises a distributed brain network (Alcalá-López *et al.*, 2017). At the lowest level, a "visual-sensory" network of face and biological motion responsive areas includes fusiform gyrus, MT/V5 and posterior superior temporal sulcus. Above this in the hierarchy, a "limbic" network (ventromedial prefrontal, anterior cingulate, amygdala, hippocampus and nucleus accumbens) and an "intermediate" network (anterior insula, midcingulate, inferior frontal gyrus, supramarginal gyrus, supplementary motor area, posterior superior temporal sulcus and cerebellum) were outlined, and then a "higher-level" network (frontal pole, temporal pole, dorsomedial prefrontal, posterior cingulate, temporoparietal junction, middle temporal gyrus and precuneus). These hierarchical levels are extensively interconnected, but individually map onto sensory processing, emotional responses, body state representations and the human 'mirror' system (brain regions showing activity during both performance and observation of an action), and theory of mind respectively. There is a risk of reverse inference in attributing these mental processes to the anatomical associations, although these anatomical regions have been extensively studied and their roles in emotional perception well established. For example, the sensory processing regions such as fusiform gyrus, MT/V5 and posterior superior temporal sulcus have been shown to respond preferentially to sensory properties of faces, and more so to dynamic emotional face stimuli (Haxby and Gobbini, 2011). The 'limbic' network including anterior cingulate and amygdala has a well defined role in emotional appraisal (Etkin *et al.*, 2011), while the intermediate network contains regions such as anterior insula that has a key role in integrating body state representations with affective representations

(Hennenlotter *et al.*, 2005; Jabbi *et al.*, 2007) and the inferior frontal gyrus and supplementary motor area that have a key role in motoric representations (Gazzola and Keysers, 2009; Braadbaart *et al.*, 2014). Theory of mind has been related to regions such as precuneus and temporoparietal junction that are important for self-other differentiation (Shamay-Tsoory, 2011) and social concept stores such as right temporal pole (Zahn *et al.*, 2007). Auditory stimuli such as emotional vocalisations have been less extensively studied, but are likely to induce similar interactions of sensory processing with embodied 'mirror system' representations (Warren *et al.*, 2006).

Thus, the functional neuroimaging literature suggests that body state and motoric representations are important components of the processing of socioemotional stimuli, and indeed social interaction has been suggested to function as an extension of the sensorimotor feedback that underpins motor behaviours (Wolpert *et al.*, 2003; Kilner *et al.*, 2007). In the following section I will explore direct evidence for the importance of these embodied representations in social cognition.

ANATOMY AND PHYSIOLOGY OF EMBODIED EMOTIONAL REACTIVITY

EMBODIED COGNITION OF EMOTION

Embodied emotional reactivity describes the physiological changes in the body that occur during emotion. The James-Lange theory of emotion developed from ideas proposed independently by William James in 1884 (James, 1884) and Carl Lange in 1885 (Lange, 1885). The central proposition of the theory is that affective stimuli induce physiological changes in the body of the observer, and that these changes underpin the subjective experience of emotion. James writes:

"Our natural way of thinking about these coarser emotions (e.g., grief, fear, rage, love) is that the mental perception of some fact excites the mental affection called the emotion, and that

this latter state of mind gives rise to the bodily expression. My theory on the contrary is that the bodily changes follow directly the perception of the exciting fact and that our feeling of the same changes as they occur IS the emotion." (James, 1884)

Ever since this time, the direction of causality between subjective feeling states and physiological reactions has been a vexed question among neuroscientists. Soon after James and Lange, Sherrington set about trying to disprove the James-Lange theory with a series of experiments involving vagotomy and spinal cord transection in dogs (Sherrington, 1899). Cannon and Bard then developed an inverse theory, suggesting that bodily physiological responses are too undifferentiated to support diverse emotions, and simply represent an epiphenomenon caused by arousal (Cannon, 1927).

More recent conceptions of embodied emotion including Barrett's "Constructed Emotions" (Barrett, 2017) and Seth and Friston's "Interoceptive Inference" (Seth and Friston, 2016) take a middle road between the extremes of James and Lange on the one hand, and Cannon and Bard on the other. They tend to emphasise that there is circular causality between peripheral physiology and subjective feeling states, and that complex emotions depend on the integration of sensory data from interoceptive, exteroceptive and proprioceptive modalities along with higher cognitive constructs such as context and affective mentalising (Ondobaka *et al.*, 2017). These theories reflect a spectrum of views on the necessity of embodiment for subjective emotion, i.e. whether bodily reactions are an epiphenomenon or an integral component of emotional feeling states. Even a relatively weak interpretation closer to the Cannon-Bard position has important implications for the study of aberrant emotionality in the diseased brain, however. Even as an epiphenomenon, peripheral physiology might serve as an objective marker of affective responses, including where these are altered by disease but self-reports are unreliable or a blunt instrument. Taking any stronger position than this on the role of embodied responses would go further in suggesting that aberrant physiological reactivity may

be a contributory mechanism to socioemotional changes in neurodegenerative disease. In the following section, I will review recent findings on physiological correlates of emotion processing, with specific emphases on the neuroanatomy of afferent and efferent processing of peripheral physiology; the evidence for a causal link between visceral and motor responses and subjective feeling states; and the evidence linking these findings specifically to empathy, emotional contagion and sensitivity to the emotions of others, with a view to addressing the key clinical issue of altered interpersonal behaviour in FTD.

INTEROCEPTION

Interoception describes the processing of sensory information arising from within the body, including from the heart, lungs, gut and chemosensory organs, although some definitions are more liberal, encompassing any information concerning the physiological condition of the organism (Craig, 2002; Critchley *et al.*, 2004). These internal signals convey vital information about an organism's physiological milieu, and hence have phylogenetically ancient homeostatic roles such as maintaining normoxia and normoglycaemia. Interoceptive afferents are predominantly composed of the afferent branches of the sympathetic and parasympathetic nervous systems, which are contained within lamina I of the spinothalamic tract, and the nucleus of the solitary tract respectively. These converge in the ventromedial thalamus, before projecting to the posterior insula, which is the seat of primary interoceptive cortex (Craig, 2002), and shows viscerotopic organisation (Cechetto, 1987). These pathways are the basis for sensations including hunger, thirst, vasomotor flush, air hunger, and body temperature. Exteroceptive sensory modalities that relate strongly to the condition of the body, such as pain, skin temperature and affective touch are also conveyed in the spinothalamic tracts, and then have a similar projection to posterior insula (as well as primary somatosensory cortex), and are hence often considered to be interoceptive modalities (Olausson *et al.*, 2002; Crucianelli *et al.*, 2017). Moving anteriorly in the insula, body state

representations become more complex and coherent, incorporating interoception with other modalities to generate feeling states that encompass emotional, social and motivational conditions (Craig, 2009). The anterior insula is thus implicated in a wide range of perceptual functions, and has been hypothesised to be the location of an embodied self model at the core of a global neuronal workspace (Allen and Friston, 2016).

Investigation of emotion processing has shown that overlapping regions of anterior insula are activated by both self-generated emotion and the recognition of emotion in others, and this is hypothesised to relate to the mapping of the feelings of others onto the bodily states of the observer (Hennenlotter *et al.*, 2005; Jabbi *et al.*, 2007). This convergence of body state representations, emotional experience and response to the emotions of others suggests a possible evolutionary basis for a James-Lange view of emotion, whereby ancient homeostatic imperatives relating to the condition of the body are exapted to support more complex feeling states and social cognition in higher organisms (Gallagher and Allen, 2016).

This perspective is readily encompassed by the theory of interoceptive inference, which proposes that subjective states are the result of actively inferred models of the causes of interoceptive sensations (Seth, 2013; Ainley *et al.*, 2016). The starting point for interoceptive inference is the free energy principle, which takes as axiomatic that organisms are ergodic, and keep an upper bound on their free energy by resisting the second law of thermodynamics and restricting their internal environment to a narrow range of physiological states (Ramstead *et al.*, 2017). From this, it follows that perturbations of the internal environment (i.e. increases in free energy) require the organism to infer the cause of the change, and then act on the environment to restore homeostasis. This would be most economically instantiated by a nervous system that created generative models of itself and the environment, and represented only the difference between expected and actual sensory states (prediction error or surprise) (Friston, 2010). The evidence for interoceptive predictive coding is in its infancy,

but as a general theory of brain function there is a growing body of evidence for predictive coding, especially in the domains of visual and auditory sensory processing (Rao and Ballard, 1999; Heilbron and Chait, 2017), and the theory is neurobiologically plausible because of the structure and arrangement of cortical microcircuits (Bastos *et al.*, 2012). Testing the predictive coding theory of interoceptive function is practically difficult because interoceptive channels are relatively inaccessible to experimental manipulation, but subliminally inducing unexpected interoceptive arousal impacts on metacognition, and this has been interpreted in a predictive coding framework (Allen *et al.*, 2016). Pain is often considered to be an interoceptive modality because it is a strong indicator of body state, and there is good evidence for predictive coding in pain processing, with expectations modulating both subjective and neural responses to noxious stimuli (Fardo *et al.*, 2017).

The implications of a predictive coding approach for interoceptive processing are as follows. Firstly, interoceptive prediction errors (where interoceptive afferent data differ from the generative model of the state of the body) are salient in that they represent a threat to homeostasis (or the effective maintenance of an upper bound on variational free energy). In response to interoceptive prediction error, the organism must minimise surprise in one of two ways: by revising the generative model (thus accepting a short term increase in free energy, but minimising surprise) or by performing an action to change the afferent sensory data. In interoceptive inference, this action could be a movement of the body, as in other forms of active inference, but the interoceptive inference framework also entails that autonomic reflexes are enslaved by the brain networks involved, and thus interoceptive prediction errors can induce autonomic efferent changes to maintain physiological homeostasis (Seth and Friston, 2016). This last element has important implications for the understanding of autonomic emotional reactivity, and introduces the circular causality between central and peripheral states that effectively encompasses both the James-Lange and Cannon-Bard views on the relationship between subjective states and autonomic responses. Finally, the

interoceptive inference theory points towards a parsimonious account of the phylogeny of social cognition and theory of mind, whereby subjective states that are rooted in bodily states are best understood and given salience through mapping them on to the bodily states of the observer (Ondobaka *et al.*, 2017). In other words, the simplest way to represent a signal concerning the condition of another individual's body is to simulate the bodily changes involved. Moreover, because interoceptive channels have such an important role in signalling the condition of the organism and the presence of salient challenges to homeostasis, they were well placed to be exapted for conferring salience upon social signals as these attained important survival value in higher organisms.

AUTONOMIC AFFERENT PROCESSING

The implications of these theories of interoception developed by Craig and Seth, among others, have generated intense interest in studying the links between interoception and a range of cognitive domains, especially emotional experience and empathy. Subjective interoceptive awareness can be measured using questionnaires that cover a range of interoceptive modalities, such as the Porges Body Perception Questionnaire (Porges, 1993). These instruments have psychometric limitations especially due to their subjectivity, however (Mehling *et al.*, 2009), and would be anticipated to be particularly problematic in the assessment of subjects with neurodegenerative disease and deficits in other cognitive domains, especially where language, behaviour and metacognition are affected. Objectively, interoception is most often measured as it relates to the heart. This is largely for practical reasons, as cardiac awareness can be measured in a fairly straightforward and noninvasive way, although there is some evidence for domain generality in interoception, as cardiac awareness correlates with awareness of other interoceptive channels (Herbert *et al.*, 2012). Cardiac interoception can be measured behaviourally using heartbeat counting (subjects are asked to sit quietly and count their heartbeats without taking their pulse) (Schandry, 1981),

heartbeat tracking (where a subject is asked to identify whether a series of auditory or visual stimuli are presented synchronously or asynchronously with their heartbeat), or using metacognitive awareness (where the second order construct of confidence in heartbeat judgements is used) (Garfinkel *et al.*, 2015). Using fMRI, interoceptive awareness has been associated with activity in the anterior insula, dorsal cingulate and somatomotor cortices (Critchley *et al.*, 2004). Of these loci, right anterior insula was most specifically associated with the ability to report heartbeats on the Schandry task, suggesting that it is the key region in allowing conscious access to interoceptive sensations. An important role has also been suggested for the amygdala in subconsciously incorporating interoceptive information into emotional judgements (Garfinkel *et al.*, 2014).

The Schandry task is problematic for several reasons. It is possible that Alternative approaches to studying cardiac interoception eliminate the need for self-reporting of heartbeats, and allow for the assessment of the role of interoceptive stimuli in emotional judgements without the subject being required to have conscious access to the interoceptive sensations. These approaches include determining the effect of stimulus timing in the cardiac cycle (Garfinkel *et al.*, 2014), or measuring heartbeat evoked brain potentials, which are a surrogate for heartbeat awareness and have principle neural sources in the insula and amygdala (Pollatos and Schandry, 2004; Park *et al.*, 2017). Other recent techniques have involved the manipulation of interoceptive afferent information using subliminal disgust stimuli (Allen *et al.*, 2016) or transcutaneous vagal nerve stimulation (Sellaro *et al.*, 2018).

Using approaches such as this, heartbeat awareness has been related to sensitivity to the emotions of others (Terasawa *et al.*, 2014), intensity of emotional experience (Wiens *et al.*, 2000) and emotional theory of mind (Shah *et al.*, 2017), but not to other, related tasks such as time perception or cognitive theory of mind, suggesting that interoception may play a specific role in affective judgements. However, other evidence has pointed to more general roles for

interoception in tasks including memory, perceptual decision-making and metacognition (Critchley *et al.*, 2013; Allen *et al.*, 2016). Using 'passive' interoceptive tasks, magnitude of heartbeat-evoked potentials has been correlated with measures of empathy (Fukushima *et al.*, 2011), and within the cardiac cycle, emotional facial stimuli are more easily detected and have greater valence during systole than diastole (Gray *et al.*, 2012; Garfinkel *et al.*, 2014). As might be anticipated, this effect relates to activity in the insula, but also in the amygdala, pointing to a key role for this region in the integration of interoceptive information during emotional judgements. Remarkably, this effect appears to extend to more complex constructs than simple emotional judgements, with subconscious racial bias also being modulated by stimulus timing within the cardiac cycle (Azevedo *et al.*, 2017). Experimental manipulation of interoceptive afferents by transcutaneous vagal nerve stimulation has been shown to improve emotion recognition from faces, but not from bodies, suggesting that interoception has an especially central role in the appraisal of more affectively salient social stimuli (Sellaro *et al.*, 2018).

AUTONOMIC EFFERENT REACTIVITY

This body of evidence makes a strong case for a contributory role for autonomic afferents in emotional judgements, but in parallel with this, the relationship between emotionality and efferent autonomic responses has also been extensively studied. The central autonomic control network was initially identified in animal studies, and comprises cortical and subcortical structures including the cingulate, insula, amygdala, hypothalamus, parabrachial complex, periaqueductal grey, ventrolateral medulla and the nucleus of the solitary tract (Cersosimo and Benarroch, 2013). Neuroimaging studies in humans have revealed an analogous network of structures involved in autonomic control, with additional roles suggested for regions including the cerebellar vermis, hippocampus, middle temporal and orbitofrontal cortex (Critchley *et al.*, 2000; Critchley *et al.*, 2003; Napadow *et al.*, 2008;

Macefield and Henderson, 2010; Critchley *et al.*, 2011; Beissner *et al.*, 2013). These structures control autonomic effectors via preganglionic sympathetic neurones found in the intermediolateral column of the spinal cord, and preganglionic parasympathetic neurones in the vagus nerve.

Heart rate is determined by the sinoatrial node under the influence of sympathetic and parasympathetic innervation (Thayer and Lane, 2009). The intrinsic rate of the sinoatrial node is around 120 beats per minute, and a normal resting heart rate of below 100 beats per minute is generated by tonic parasympathetic inhibition. Heart rate variability at rest is largely determined by normal fluctuations in the balance between sympathetic and parasympathetic tone that occur during the respiratory cycle (respiratory sinus arrhythmia). Increased sympathetic tone during inspiration causes an increase in heart rate, while increased parasympathetic tone during expiration causes a decrease in heart rate. Higher resting heart rate variability in neurologically normal subjects has been associated with various positive socioemotional traits, such as greater emotional positivity, emotion regulation ability, prosociality and social connectedness (Oveis *et al.*, 2009; Kok and Fredrickson, 2010; Kogan *et al.*, 2014). Conversely, reduced heart rate variability has been demonstrated in anxiety and posttraumatic stress disorder (Cohen *et al.*, 1998; Brosschot *et al.*, 2007). These findings suggest a key role for autonomic reactivity in healthy emotional function, including appropriate responses to the emotions of others.

As well as resting variability, transient heart rate responses to emotional stimuli have been widely studied. Although affective stimuli are consistently found to elicit heart rate changes, findings regarding the direction of heart rate change are inconsistent, and the picture is a complex one. Emotional arousal is associated with increased heart rate regardless of emotional valence (Brosschot and Thayer, 2003), and some studies have shown cardiac acceleration in response to affective images such as emotional facial expressions (Critchley *et*

al., 2005). However, stimulus onset is more typically accompanied by an initial parasympathetically mediated cardiac orienting deceleration, which is modulated by affective content, with emotional stimuli producing greater cardiac deceleration than neutral stimuli (Lang *et al.*, 1993; Bradley, 2009; Alpers *et al.*, 2011). The overall cardiac response to affective stimuli is in fact multiphasic, reflecting complex interactions of appetitive and defensive responses (Lang *et al.*, 1993; Bradley, 2009; Paulus *et al.*, 2016), and apparently inconsistent findings of initial acceleration or deceleration are likely related to idiosyncrasies to do with experimental set up, the type of stimulus used, or the specific cardiac analysis method.

As well as cardiac deceleration, affective stimuli induce sympathetically mediated pupil dilation and increased skin conductance, both of which vary as a function of the degree of arousal (Lang *et al.*, 1993; Bradley *et al.*, 2008; Bradley, 2009). These responses are mediated by components of the central autonomic control network, including anterior cingulate, amygdala and medial temporal lobe, as well as brainstem regions including the superior colliculus and locus coeruleus (for pupil dilation) and pons (for electrodermal activity) (Critchley, 2002; Joshi *et al.*, 2016). Multiple studies have attempted to define profiles of heart, pupil and skin conductance responses that are specific to stimulus valence or emotion type, but the prevailing consensus is that patterns of autonomic arousal reflect only stimulus intensity rather than valence or category (Wiens *et al.*, 2000; Bradley, 2009; Alpers *et al.*, 2011).

MOTOR REACTIVITY AND FACIAL IMITATION

Embodied emotional reactivity involves motoric as well as autonomic responses (Niedenthal, 2007). Motoric representations have been conceptualised within an active inference framework analogous to that for interoceptive inference (Kilner *et al.*, 2007). Within the hierarchical arrangement of the predictive coding architecture, prediction errors generated by kinematic and proprioceptive representations at lower levels of the hierarchy allow for more

complex inference of movement goals and affective states at higher levels of the hierarchy, where they are integrated with interoceptive processing (Ondobaka *et al.*, 2017).

Affective stimuli elicit changes in activity within facial muscles that can be measured with surface electromyography (EMG), and unlike autonomic responses, these show specificity for emotional category and valence (Lang *et al.*, 1993; Dimberg *et al.*, 2002). Positively valenced stimuli increase activity in the zygomaticus major muscle, which raises the corner of the mouth when smiling, whereas negatively valenced stimuli activate corrugator supercilii, which knits the brow when frowning. As distinct from autonomic responses, facial movements can be voluntarily controlled, although evidence suggests that these facial responses to affective stimuli are produced without conscious awareness and cannot be completely voluntarily suppressed (Dimberg *et al.*, 2002).

Rather than simply indexing affective valuation, facial muscle activation has been demonstrated to have a causal role in emotional judgements and subjective feeling states, analogous to the effects of interoceptive afferents in autonomic modalities. For example, during a task involving painful cold stimuli, covertly inducing participants to smile was shown to reduce both subjective ratings of stimulus negativity and autonomic arousal (Kraft and Pressman, 2012). Paralysing the corrugator muscle with botulinum toxin (thereby impairing frowning) improves symptoms of depression and reduces emotional responses to negative stimuli (Davis *et al.*, 2010; Finzi and Rosenthal, 2016). Conversely, impairments in the function of the zygomaticus major muscle (and hence the ability to smile) are predictive of greater depression and negative affect (VanSwearingen *et al.*, 1999).

While affective stimuli in general elicit facial muscle responses related to valence, facial expressions induce rapid, subconscious and involuntary imitation of the perceived expression in the face of the observer (Wood *et al.*, 2016b). This motor resonance is likely to facilitate social cohesion (Niedenthal and Brauer, 2012), but motoric representation and proprioceptive

feedback are also hypothesised to play a role in recognising and categorising the emotions of others. Automatic imitation predicts authenticity judgements on facial emotions, and disrupting mimicry with a constrictive gel facemask impairs recognition of emotion from faces, but not non-face stimuli (Korb *et al.*, 2014; Wood *et al.*, 2016a).

Facial mimicry has been linked to activity in primary and supplementary motor cortices, and inhibition of these areas by transcranial magnetic stimulation has been shown to disrupt emotion recognition from faces (Balconi and Bortolotti, 2013; Korb *et al.*, 2015). Functional imaging studies of automatic facial imitation have tended to use either analysis of overt facial movements or incorporated voluntary imitation into an in-scanner task, probably owing to the technical difficulties inherent in recording facial EMG during MRI scanning. These approaches have demonstrated anatomical correlates of facial emotion imitation including in precentral, inferior frontal, middle frontal, middle temporal and fusiform gyri, as well as supplementary motor cortex (Carr *et al.*, 2003; Lee *et al.*, 2006). One study using facial EMG during fMRI scanning found anatomical correlates of imitation in brain regions including inferior frontal gyrus, supplementary motor area, posterior middle temporal gyrus and superior temporal sulcus (Likowski *et al.*, 2012).

Taken together, the wealth of evidence for efferent and afferent processing of both autonomic and motor responses makes a strong case for Nietzsche's assertions regarding the mechanisms underlying emotional empathy (see Epigraph), and his conception of "an association of movements and sentiments, which has been trained to run backwards and forwards". Writing before James and Lange, he prefigured modern conceptions of the embodied processing of social stimuli, including the dissociability of emotional and cognitive empathy, and the bidirectional causality between central and peripheral states. Of course, science has developed far beyond these 19th century ideas, but the inspiration they have had on contemporary neuroscience is clear. Recent work has developed a complex picture of how witnessing the

emotions of others induces changes in the body, and how these changes in the body influence cognitive processes. If these phenomena are indeed an essential component of healthy social behaviour, then it would follow that they might be mechanistically linked to degraded interpersonal reactivity in diseases such as FTD.

RATIONALE AND HYPOTHESES

EVIDENCE FOR ABNORMAL CENTRAL CONTROL OF AUTONOMIC FUNCTION IN FTD

In the preceding section, I have described brain networks subserving both emotion processing and physiological reactivity that are largely encompassed by the distributed atrophy profiles of FTD syndromes described earlier in the chapter. On anatomical grounds, one might therefore expect to find abnormalities of physiological reactivity in addition to emotion processing deficits in these diseases, and given the extensive links between bodily reactivity and emotional experience in the healthy brain, the two are likely to be intimately linked in the genesis of socioemotional symptoms.

An emerging body of literature has begun to identify autonomic abnormalities in FTD, and some links between autonomic changes, emotionality and social behaviour have been suggested. Patients with bvFTD demonstrate autonomic dysfunction including orthostatic hypotension on clinical autonomic function tests (Struhal *et al.*, 2014). A variety of symptoms attributable to dysautonomia have also been identified in bvFTD relative both to healthy controls and patients with Alzheimer's disease. These include symptoms related to dysfunctional control of blood pressure, the gastrointestinal tract, thermoregulation, sweating and micturition (Ahmed *et al.*, 2015a).

Other studies have directly measured various modalities of autonomic reactivity in FTD. Reduced resting heart rate variability, reflecting impaired parasympathetic tone, has been found in bvFTD, and correlated both with BOLD signal in a predominantly left-lateralised

cingulo-insular network and with carer ratings of 'agreeableness' (Guo *et al.*, 2016). These findings largely echo the evidence regarding heart rate variability in the healthy brain, although are notable for the left lateralised correlates, when parasympathetic control is more usually shown to be right lateralised (Thayer and Lane, 2009). Two studies have previously shown impaired cardiac reactivity to affective pictures in bvFTD (Balconi *et al.*, 2015; Joshi *et al.*, 2017), although a third has associated increased cardiac reactivity to positive emotions in bvFTD with dysfunction of left frontal regulatory circuits, suggesting a complex stratification of abnormalities of emotional reactivity and emotion regulation (Sturm *et al.*, 2015).

Other autonomic modalities investigated so far include skin conductance, blood pressure responses and pupillometry. Low resting skin conductance (likely indicating reduced sympathetic tone) has been linked to emotional blunting and to volume of the putamen in bvFTD (Joshi *et al.*, 2014). In work showing a specific deficit of disgust reactivity in bvFTD, impaired blood pressure reactivity was found concomitantly with reduced subjective emotional ratings, and linked to atrophy of the insula (Eckart *et al.*, 2012). However, in another study, a mismatch between preserved subjective ratings of affective stimuli and impaired skin conductance has been shown, implying that cognitive and autonomic responses are at least partially dissociable (Balconi *et al.*, 2015).

Pupil reactions are the only modality to have previously been studied across the FTD spectrum, and similarly show abnormal coupling of autonomic and behavioural responses during the processing of auditory salience, semantics and emotions (Fletcher *et al.*, 2015c, d; Fletcher *et al.*, 2016). Diminished pupil responses were found to correlate with volume loss in the midbrain and temporal lobe, and showed differential patterns in FTD syndromes according to the type of stimulus used. Patients with svPPA had heightened autonomic reactivity to auditory semantics and salience, but reduced reactivity to emotion, whilst bvFTD and nfvPPA demonstrated reduced pupil reactivity in all experiments, and in bvFTD there was aberrant

coupling of physiological arousal and affective valuation. These findings suggest that while diseases predominantly affecting fronto-insular circuitry (bvFTD and nfvPPA) may have a general impairment of central autonomic control, diseases focussed on the temporal lobe may have retained capacity for central autonomic control, but deficient modulation of such signals by other cognitive processes.

To my knowledge, no studies of autonomic function have been performed in rtvFTD, although a single case report from 1984 raises tantalising questions about the psychophysiology of right temporal lobe dysfunction (Bauer, 1984). This was a case of traumatic injury to the right temporal lobe resulting in acquired prosopagnosia. The patient was unable to identify familiar faces spontaneously, although his electrodermal responses appeared to differentiate familiar and unfamiliar people better than he was able to declaratively. This raises the possibility that damage to the right temporal lobe may disconnect implicit physiological responses from cognitive personal semantics, and warrants further evaluation in the degenerative parallel of rtvFTD.

MOTIVATION FOR THE WORK IN THIS THESIS

These studies provide important proofs of concept to stimulate further work on the psychophysiology of FTD syndromes. They demonstrate that meaningful differences in physiological parameters can be detected in small groups with these rare diseases, and related to anatomical loci known to support embodied emotional reactivity in the healthy brain. There are several important directions in which further work might proceed in order to strengthen the case for the utility of studying physiological reactivity in FTD.

Nearly all of the studies to date have been restricted to bvFTD, and have not attempted to parse any of the heterogeneity within the bvFTD spectrum (for example by separating out the group with rtvFTD). If psychophysiology is to aid in disease monitoring and stratification, studying the full spectrum of FTD and demonstrating specificity for clinicoanatomical

syndromes will be key. To achieve this, a comprehensive delineation of the neuroanatomical basis for deficits in physiological reactivity will be necessary, including functional as well as structural neuroanatomy. This would allow a detailed understanding of the neurobiological bases for complex symptoms and physiological changes, and support the development of physiological biomarkers to aid in diagnosis, stratification and monitoring of FTD, in a way that conventional neuropsychological and imaging tests have failed to do. Physiological biomarkers might serve as proxies for specific patterns of network dysfunction and underlying pathogenic protein effects on brain circuitry. The roles of autonomic afferent processing (interoception) and motor reactivity have largely yet to be studied, and doing so will be vital in order to fully define the contribution of aberrant embodiment of emotion. Finally, although some of the studies to date have related physiological changes to socioemotional symptoms (e.g. agreeableness, emotional blunting), this linkage needs to be strengthened and focussed specifically upon the diminished empathic responses that are such key determinants of disease burden. This would enhance understanding of the pathophysiology of these devastating symptoms, and potentially yield important therapeutic implications.

AIMS AND HYPOTHESES

The overall rationale for this thesis is thus to further the nascent exploration of embodied emotional reactivity in FTD, with three prevailing aims across all chapters:

1. To investigate the entire disease spectrum of FTD (including separating rtvFTD from bvFTD when patient numbers allow), looking for evidence of clinicoanatomical stratification
2. To specifically relate physiological changes to the processing of others' emotions (rather than one's own emotional experience), with a view to defining the neurobiology of degraded social behaviour

3. To link both cognitive and physiological deficits to structural or functional neuroanatomy, with the aim of demonstrating specific relationships between psychophysiological profiles and underlying patterns of network degeneration

Specific aims and hypotheses for the individual experimental chapters are as follows. Further details regarding the rationale for hypotheses are contained within the relevant chapters.

Chapter 3. Interoceptive accuracy and sensitivity to the emotions of others:

Aims:

- To define impairments in interoceptive accuracy across the FTD spectrum
- To relate interoceptive deficits to impaired sensitivity to the emotions of others
- To define structural neuroanatomical correlates of interoceptive accuracy

Hypotheses:

- Interoceptive accuracy is impaired across the FTD spectrum but most severely in svPPA due to the specific clinicoanatomical features of this syndrome
- Interoceptive accuracy correlates with sensitivity to the emotions of others across the FTD spectrum
- Impaired interoceptive accuracy relates to grey matter loss in insula, cingulate and amygdala

Chapter 4. Recognition and automatic imitation of dynamic facial emotions:

Aims:

- To replicate findings of impaired recognition of facial emotion across the FTD spectrum

- To define impairments in automatic imitation of facial emotions in individual FTD syndromes
- To explore the relationship between identification and imitation of facial emotion
- To delineate structural neuroanatomical correlates of emotion recognition and imitation

Hypotheses:

- Emotion recognition is impaired in all FTD syndromes
- Automatic imitation is impaired in bvFTD and rtvFTD
- Automatic imitation predicts correct identification of facial emotions in syndromes targeting fronto-insular networks (bvFTD and nfvPPA), but not when temporal lobe semantic hubs are impaired (rtvFTD and svPPA)
- Facial emotion recognition correlates with grey matter volume in structures previously linked to emotion processing in FTD and the healthy brain
- Automatic imitation is associated with grey matter volume in visual and motor areas

Chapter 5. Cardiac reactivity to viewing facial emotion

Aims:

- To define impairments in cardiac reactivity to the emotions of others in FTD syndromes
- To explore the relationship between cardiac reactivity and the cognitive categorisation of facial emotions
- To delineate structural neuroanatomical correlates of impaired cardiac reactivity

Hypotheses:

- Cardiac reactivity is impaired in syndromes affecting fronto-insular networks (bvFTD and nfvPPA), but not in those focussed on the temporal lobes (rtvFTD and svPPA)
- Autonomic reactivity is at least partly dissociable from the cognitive categorisation of emotions
- Impaired cardiac reactivity relates to grey matter loss in the central autonomic control network

Chapter 6. Functional neuroanatomy and physiology of dynamic facial emotion processing

Aims:

- To replicate findings of impaired emotion recognition and physiological reactivity in FTD syndromes
- To define alterations in the functional neuroanatomy of the sensory processing of dynamic facial emotions
- To delineate the functional neuroanatomy of the ability to cognitively categorise emotional facial expressions
- To define the neuroanatomical basis for impaired heart rate and pupil responses

Hypotheses:

- In healthy subjects, viewing dynamic facial emotions is associated with neural activity in face and biological motion responsive regions
- Patterns of activation in these networks are differentially altered in FTD syndromes
- FTD syndromes show divergent functional neuroanatomical bases for impairments in emotion categorisation

- Aberrant autonomic reactivity is associated with altered neural responses in components of the central autonomic control network

2. OVERVIEW OF METHODS

RECRUITMENT AND ASSESSMENT OF PARTICIPANTS

RECRUITMENT AND CONSENT

Patients were recruited during a three-year period between 2014 and 2017, mostly from the Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery. A minority of patients were recruited via direct referral to the research programme from external clinicians. Control subjects without any significant neurological or psychiatric disease were recruited from a local database of volunteers aged between 50 and 80. Ethical approval for all studies in this thesis was obtained from the local Research Ethics Committee, and all participants gave informed consent in accordance with the Declaration of Helsinki. Some participants, having given informed consent at enrolment, subsequently lost capacity to decide on their continuing participation. These subjects were allowed to continue in the study provided that they continued to assent and that their caregivers believed that participation was in accordance with their previous wishes. A table showing the overlap of participants between chapters can be found in the appendix.

DIAGNOSTIC GROUPINGS

All subjects underwent clinical assessment and volumetric T1 MR imaging, allowing for application of the current diagnostic criteria for the canonical syndromes of FTD, as shown in Tables 2.1 and 2.2 (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011), and confirmation of the absence of neurological disease in the control group. Patients were included in the study if they met criteria for "Probable bvFTD" (see Table 2.1) or "Imaging-supported" PPA (see Table 2.2), i.e. in all cases the syndromic diagnosis was corroborated by brain imaging findings. Where patients exhibited features of more than one FTD syndrome they were assigned to one of three syndromic groupings of bvFTD, svPPA or nfvPPA after careful consideration of the

leading clinical features and regional atrophy profiles. Brain scans of patients with bvFTD were blindly rated to allow identification of those subjects meeting diagnostic criteria for bvFTD, but with an anatomical pattern consistent with the rtvFTD subtype (i.e. those with relatively focal right temporal lobe atrophy). Where there were a sufficient number of these rtvFTD cases in the sample for a given experiment (six or more), they were considered as a separate group.

Those presenting with behavioural features, but without evidence of cerebral atrophy were excluded as possible bvFTD phenocopies (i.e. a behavioural presentation due to a non-neurodegenerative aetiology). Patients with a syndrome of PPA that did not clearly conform to either svPPA or nfvPPA were also excluded, as the other PPA groups (logopenic variant PPA and unclassified PPA) are likely to have underlying Alzheimer's disease pathology. Thus, a large majority of included patients would be anticipated to have FTLD spectrum pathology at post mortem (Perry *et al.*, 2017; Spinelli *et al.*, 2017).

Clinical assessment

Clinical assessment was performed with an informant to provide reliable collateral information. Demographic information was obtained including age, gender, handedness and education history. Given the typical long delay between symptoms and diagnosis in FTD, estimated disease onset was calculated using caregiver recollection of the earliest symptoms. Subsequent clinical assessment included a detailed history of behavioural, neuropsychiatric, linguistic and cognitive symptoms, neurological examination for amyotrophic and Parkinsonian features, and bedside cognitive and linguistic assessment incorporating the Queen Square Screening Test for Cognitive Deficits and the Mini Mental State Examination (Folstein *et al.*, 1975). All participants gave blood to screen for a panel of 18 disease-causing genetic mutations (Beck *et al.*, 2014). A subset of patients also consented to having a lumbar puncture, and where this was available cerebrospinal fluid biomarkers were used to confirm the low likelihood of Alzheimer's disease pathology (Ewers *et al.*, 2015).

Table 2.1 Rascovsky diagnostic criteria for bvFTD

Level of diagnosis	Criteria
I.Neurodegenerative disease	Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).
II. Possible bvFTD	Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. A. Early behavioural disinhibition (one of the following must be present): A.1. Socially inappropriate behaviour A.2. Loss of manners or decorum A.3. Impulsive, rash or careless actions B. Early apathy or inertia (one of the following must be present): B.1. Apathy B.2. Inertia C. Early loss of sympathy or empathy (one of the following must be present): C.1. Diminished response to other people's needs and feelings C.2. Diminished social interest, interrelatedness or personal warmth D. Early perseverative, stereotyped or compulsive/ritualistic behaviour (one of the following must be present): D.1. Simple repetitive movements D.2. Complex, compulsive or ritualistic behaviours D.3. Stereotypy of speech E. Hyperorality and dietary changes (one of the following must be present): E.1. Altered food preferences E.2. Binge eating, increased consumption of alcohol or cigarettes E.3. Oral exploration or consumption of inedible objects F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following must be present): F.1. Deficits in executive tasks F.2. Relative sparing of episodic memory F.3. Relative sparing of visuospatial skills
III. Probable bvFTD	All of the following symptoms (A–C) must be present to meet criteria. A. Meets criteria for possible bvFTD B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores) C. Imaging results consistent with bvFTD (one of the following must be present): C.1. Frontal and/or anterior temporal atrophy on MRI or CT C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT
IV. Behavioural variant FTD with definite FTLD Pathology	Criterion A and either criterion B or C must be present to meet criteria. A. Meets criteria for possible or probable bvFTD B. Histopathological evidence of FTLD on biopsy or at post-mortem C. Presence of a known pathogenic mutation
V. Exclusionary criteria for bvFTD	Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD. A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders B. Behavioural disturbance is better accounted for by a psychiatric diagnosis C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

The table shows current consensus criteria for diagnosis of bvFTD (Rascovsky *et al.*, 2011). All patients included in the bvFTD and rtvFTD groups in subsequent experimental work in this thesis met criteria for "Probable bvFTD".

Table 2.2 Gorno-Tempini diagnostic criteria for svPPA and nfvPPA

Level diagnosis	**svPPA**	**nfvPPA**
Clinical	*Both of:*	*At least one of:*
Core features	Impaired confrontation naming	Agrammatism in language production
	Impaired single-word comprehension	Effortful, halting speech with inconsistent speech sound errors and distortions (speech apraxia)
Other features	*At least three of:*	*At least two of:*
	Impaired object knowledge, particularly for low-frequency or low-familiarity items	Impaired comprehension of syntactically complex sentences
	Surface dyslexia or dysgraphia	Spared single-word comprehension
	Spared repetition	Spared object knowledge
	Spared speech production (grammar and motor speech)	
Imaging-supported	*At least one of:*	*At least one of:*
	Predominant anterior temporal lobe atrophy	Predominant left posterior fronto-insular atrophy on MRI
	Predominant anterior temporal hypoperfusion/metabolism on SPECT /PET	Predominant left posterior fronto-insular hypoperfusion/metabolism on SPECT /PET
Pathologically definite	*At least one of:*	*At least one of:*
	Histological evidence of specific neurodegenerative pathology	Histological evidence of specific neurodegenerative pathology
	Known pathogenic mutation	Known pathogenic mutation

The table shows current consensus criteria for diagnosis of svPPA and nfvPPA (Gorno-Tempini *et al.*, 2011). All patients included in the svPPA and nfvPPA groups in subsequent experimental work in this thesis met "Imaging-supported" criteria for the relevant syndrome.

NEUROPSYCHOLOGICAL ASSESSMENT

All participants underwent comprehensive neuropsychological assessment by a trained research psychologist. Standardized tests were administered to measure general intellect and performance in specific cognitive domains as shown in Table 2.3. Results of testing were used to corroborate syndromic diagnoses. In experiments where possible domain-specific cognitive confounds were anticipated, scores on specific tests were used as covariates in subsequent analyses (e.g. forward digit span as a proxy for working memory, British Picture Vocabulary Scale for semantic knowledge).

Table 2.3 General neuropsychological assessment

Cognitive domain	Test	Reference
General intellect	WASI verbal IQ	(Wechsler, 1997)
	WASI performance IQ	(Wechsler, 1997)
Episodic memory	Recognition Memory Test for words	(Warrington, 1984)
	Recognition Memory Test for faces	(Warrington, 1984)
	Camden Paired Associate Learning	(Warrington, 1996)
Executive skills	WASI Block Design	(Wechsler, 1997)
	WASI Matrices	(Wechsler, 1997)
	WMS-R digit span forward and backward	(Wechsler, 1987)
	D-KEFS Stroop	(Delis *et al.*, 2001)
	Letter (F) and category (animals) fluency	In-house test
	Trails-making task	(Lezak, 2004)
Language skills	WASI vocabulary	(Wechsler, 1997)
	BPVS	(Dunn and Whetton, 1982)
	Graded Naming Test	(McKenna and Warrington, 1980)
Posterior cortical skills	Graded Difficulty Arithmetic	(Jackson and Warrington, 1986)
	VOSP Object Decision	(Warrington and James, 1991)

The table shows the standard neuropsychological instruments administered to all participants to assess performance in the specified cognitive domains.
BPVS, British Picture Vocabulary Scale; D-KEFS, Delis Kaplan Executive System; VOSP, Visual Object and Spatial Perception Battery; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale

VIDEO STIMULUS PRESENTATION AND EXPERIMENTAL TESTING

VIDEO STIMULI

In chapters 4, 5 and 6 participants were presented with visual stimuli on a notebook computer. In chapter 6 participants were additionally presented with in-scanner stimuli – these are discussed separately within the chapter. Stimuli were selected from the FG-Net Facial Emotions and Expressions Database (Wallhoff, 2006-2015). These are dynamic naturalistic videos of subjects displaying facial emotions. They were generated by playing the participants emotional stimuli and filming their responses. They are therefore not acted or posed, and are

hence likely to be more ecological than similar stimuli in frequent use. Such dynamic stimuli are likely to induce more robust physiological responses in the observer than static images or morphs (Rymarczyk *et al.*, 2016). Each video begins with a neutral expression that then develops into an emotional expression over a period of several seconds. I selected ten videos each to represent the canonical emotions of anger, disgust, fear, happiness and surprise, balancing for sex within each emotion (see Table 2.4 for further details). I omitted the emotion of sadness because it has a more diffuse time course, and the representative videos were significantly longer in duration than the other five emotions, making it less suitable for analysis of event-related physiology and inappropriate for comparison with the other emotions. I did not use a neutral facial stimulus as a control, as there is no adequate analogue of a dynamic emotional facial expression that does not carry any affective value.

For each video stimulus, the FG-Net database specifies the frame in which the emotion first starts to develop from the neutral baseline. The display times of these frames were used to align the data traces between trials, rather than the start of the video, in order to better capture the effect of the developing emotion rather than the initial presentation of a neutral face.

Table 2.4. Summary of video stimuli characteristics for each emotion

Emotion	Male:Female faces	Mean duration (range) (s)
Anger	4:6	4.0 (4-4)
Disgust	5:5	6.0 (6-6)
Fear	5:5	6.2 (6-8)
Happiness	6:4	4.4 (4-6)
Surprise	6:4	4.1 (4-5)
Overall	26:24	4.9 (4-8)

The table shows data for duration and sex balance for the video stimuli conveying each of the universal emotional facial expressions, derived from the FG-Net Facial Expressions and Emotions Database (Wallhoff, 2006-2015)

STIMULUS PRESENTATION AND RESPONSES

Stimuli were presented in pseudorandomised order (to ensure the same emotion did not appear more than twice in succession) using Matlab R2014b (chapters 4 and 5) or Eyelink Experiment Builder (chapter 6). Following the presentation of each stimulus, subjects were asked to choose an emotion identification response from a list of the five canonical emotions. They could do this verbally, by pressing a number key on the computer keyboard, or by pointing to their preferred response. Thus, it was ensured that speech output difficulty and apraxia did not overly influence the response procedure. The experiment was continually supervised by me to ensure adequate attention to the task. All participants were first familiarised with the experiment to ensure that they understood the procedure and were able to provide answers. No time limits were imposed on responses, and hence the interstimulus interval varied, but was subject to a minimum interval of eight seconds.

STRUCTURAL BRAIN IMAGING AND VOXEL BASED MORPHOMETRY

STRUCTURAL IMAGE ACQUISITION

At each visit, each patient had a volumetric T1 MR brain image acquired on a 3T scanner. The scanner was upgraded prior to the work performed in chapter 6, and the relevant imaging parameters are described separately within that chapter, including the functional imaging acquisition protocol. For chapters 3, 4 and 5, each subject had a sagittal 3-D magnetization-prepared rapid-gradient-echo T1-weighted volumetric brain MR sequence (echo time/repetition time/inversion time 2.9/2200/900 ms, dimensions 256 256 208, voxel size 1.1 1.1 1.1 mm), acquired on a Siemens Trio 3T MRI scanner using a 32-channel phased-array head-coil.

STRUCTURAL IMAGE PREPROCESSING

Pre-processing of patients' brain images was performed using the New Segment (Weiskopf *et al.*, 2011) and DARTEL (Ashburner, 2007) toolboxes of SPM12 (www.fil.ion.ucl.ac.uk/spm), following an optimised protocol (Ridgway *et al.*, 2008). Normalisation, segmentation and modulation of grey and white matter images were performed using default parameter settings and grey matter images were smoothed using a 6 mm full width-at-half-maximum Gaussian kernel. A study-specific template mean brain image was created by warping all bias-corrected native space brain images to the final DARTEL template and calculating the average of the warped brain images. Total intracranial volume was calculated for each patient by summing grey matter, white matter and cerebrospinal fluid volumes after segmentation of the three tissue classes.

VOXEL BASED MORPHOMETRIC ANALYSIS

Preprocessed brain MR images were entered into VBM analyses of the patient cohorts. Healthy control subjects were not included in the VBM analyses, as factors other than regional brain volume are likely to mediate much of the variance in experimental parameters in the absence of neurodegenerative disease, and there would be a risk of identifying spurious anatomical associations where patients have significant grey matter atrophy relative to healthy controls in regions not necessarily associated with the parameter of interest.

Full factorial models were used to assess associations of regional grey matter volume (indexed as voxel intensity) with the parameter of interest, for each syndromic group. The use of a full factorial model (with results reported for within-group associations between grey matter volume and the parameter of interest) was chosen to minimise the effect of anatomical heterogeneity between groups. Evaluating diagnostic groups together when impairment was found in one specific group would risk identifying the syndromic atrophy pattern of that group in the VBM analysis, rather than grey matter volumes truly associated with the parameter of interest.

Age, total intracranial volume and WASI Matrices score (a measure of nonverbal executive function used here as an index of disease severity) were incorporated as covariates of no interest in all models. Whilst there is no ideal measure of disease severity across the heterogeneous groupings of FTD, the WASI Matrices score is a reasonable measure of nonverbal executive and general intellectual function. The inclusion of this covariate aimed to increase the specificity of the anatomical findings by removing the variance attributable to advancing disease with widespread grey matter atrophy. Statistical parametric maps of regional grey matter associations were assessed at threshold $p<0.05$ after family-wise error (FWE) correction for multiple voxel-wise comparisons over the whole brain and within pre-specified regional volumes of interest. The regions of interest were defined individually for each analysis according to previous neuroanatomical evidence in FTD and in the healthy brain, and were delineated using the Harvard-Oxford Brain Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

Presentation of VBM results

Anatomical associations derived from VBM at the specified threshold of $p<0.05$ after FWE correction are presented in tables within each chapter, indicating which loci were significant over the whole brain, and which were within prespecified regions of interest (ROIs). For display purposes, the statistical parametric maps that are presented in each chapter are superimposed on the study-specific template mean brain image at an uncorrected threshold of $p<0.001$. The uncorrected threshold aids visualization, provides an indication of the overall distribution of change, and avoids suggesting a higher level of anatomical precision than is actually possible with smoothed VBM data.

Statistical analyses

For experimental data, assumptions of homoscedasticity and normality were tested using Levene's test and visualisation of a Q-Q plot of residuals respectively. Where these

assumptions were violated, I used non-parametric statistical tests where possible (e.g. Kruskal-Wallis or Welch's F in place of ANOVA, Spearman rank rather than Pearson correlation etc.). In all my experimental chapters sample sizes were unequal, and this is likely to affect the outcome of parametric tests due to increasing the likelihood of heteroscedasticity (Keppel and Wickens, 2004). I therefore used homoscedasticity testing to ensure appropriate tests were used when this was likely to be an issue. For data requiring more complex models with interactions (e.g. EMG data in chapter 4), analysis could not be performed using non-parametric approaches, and therefore parametric tests were used. This could potentially increase the risk of Type II error, as according to the Neyman-Pearson lemma, parametric tests are less sensitive when the underlying assumptions are violated, but would be unlikely to increase the risk of Type I error for the same reason. I used correction for multiple comparisons when multiple between-group tests were performed, using post hoc tests appropriate to the original omnibus test (e.g. Bonferroni after ANOVA, Games Howell after Welch's F test). Neuropsychological data were analysed using parametric tests, as these standardised tests are designed to have normally distributed scores in the population. Categorical demographic data (e.g. sex, handedness) were analysed using the chi-squared distribution.

3. INTEROCEPTIVE ACCURACY AND SENSITIVITY TO THE EMOTIONS OF OTHERS: BEHAVIOUR AND STRUCTURAL NEUROANATOMY

CHAPTER SUMMARY

As discussed in chapter 1, interoception is strongly linked to emotional experience and sensitivity to the emotions of others in healthy subjects. Interoceptive impairment may contribute to the profound socio-emotional symptoms that characterize FTD syndromes, but remains poorly defined. In this experiment, patients representing all major frontotemporal dementia syndromes and healthy age-matched controls performed a heartbeat counting task as a measure of interoceptive accuracy. Additionally, patients had volumetric MRI for voxel based morphometric analysis, and their caregivers completed a questionnaire assessing patients' daily-life sensitivity to the emotions of others. Interoceptive accuracy was impaired in patients with svPPA relative to healthy age-matched individuals, but not in bvFTD and nfvPPA. Impaired interoceptive accuracy correlated with reduced daily-life emotional sensitivity across the patient cohort, and with atrophy of right insula, cingulate and amygdala on voxel-based morphometry in the impaired svPPA group, delineating a network previously shown to support interoceptive processing in the healthy brain. Interoception is a promising novel paradigm for defining mechanisms of reduced emotional reactivity, empathy and self-awareness in neurodegenerative syndromes, and may yield objective measures for these complex symptoms.

INTRODUCTION

Interoception (the ability to sense one's internal physiological states) is closely linked to emotional experience (Critchley and Harrison, 2013) and can be measured using awareness of one's heartbeat as a surrogate for interoceptive sensitivity (Schandry, 1981; Garfinkel *et al.*, 2015). According to recent interoceptive inference formulations, hierarchically organized brain networks compare afferent interoceptive information with predictions about bodily states, with prediction errors activating autonomic reflexes or motivating actions to maintain homeostasis (Seth and Friston, 2016). At lower hierarchical levels, these relate to direct physiological homeostasis, such as maintaining blood oxygen and glucose levels. Coherent representations of the physiological state of one's body are important determinants of subjective feeling states (Craig, 2009), and those with weaker interoception are less able to identify and describe their own emotions (Brewer *et al.*, 2016). At higher hierarchical levels, inferences about more complex causes of physiological perturbations can be made, such as the autonomic changes induced by the emotions of others. Interoception is therefore hypothesized to play a key role in empathy and theory of mind (Ondobaka *et al.*, 2017). This is borne out by evidence showing that interoceptive ability predicts both sensitivity to the emotions of others and performance on emotional theory of mind tasks (Terasawa *et al.*, 2014; Shah *et al.*, 2017). Empathy has been correlated with the magnitude of heartbeat-evoked potentials, and both cognitive and neural responses to the emotions of others are influenced by stimulus timing within the cardiac cycle (Fukushima *et al.*, 2011; Gray *et al.*, 2012; Garfinkel *et al.*, 2014).

Interoceptive signals and exteroceptive information from the environment are integrated in a reciprocal manner, with diminished interoception tending to promote greater environmental dependency, and vice versa. Those with less interoceptive ability are more susceptible to exteroceptive signals that alter perception of body ownership (Tsakiris *et al.*, 2011), while

inducing the illusion of decreased body ownership reduces both the amplitude of heartbeat evoked potentials (Park *et al.*, 2016) and the ability to cognitively detect signals arising from the heart (Filippetti and Tsakiris, 2016). Interoception is therefore likely to play a key role in generating a coherent sense of the bodily self. The reciprocal relationship between interoception and exteroception has also been demonstrated in perceptual decision-making, with interoceptive arousal limiting the influence of exteroceptive sensory noise on confidence (Allen *et al.*, 2016). Interoception entails dissociable cognitive dimensions. The term interoceptive accuracy is used to describe the objective reporting of interoceptive sensations, while interoceptive awareness is used to describe metacognitive accuracy in interoceptive judgements, assessed by measuring both interoceptive accuracy and confidence in perceptual judgments (Garfinkel *et al.*, 2015). Interoceptive sensibility is used to describe subjective sensitivity to interoceptive sensations, and is most often measured with a body perception questionnaire (Porges, 1993). Cardiac awareness is mediated principally by cingulate and insula (Critchley *et al.*, 2004) under the influence of amygdala (Garfinkel and Critchley, 2016). Together these structures, constitute a network engaged in both interoception and emotion processing (Craig, 2009).

Interoception has been hypothesized to be a factor mediating changes in emotional sensitivity in normal ageing (Mather, 2012). Different dimensions of interoception - accuracy and awareness - might be separably targeted by brain disease. FTD syndromes profoundly disrupt emotional and physiological reactivity (Rankin *et al.*, 2005; Fletcher *et al.*, 2015d; Guo *et al.*, 2016), producing complex neuropsychiatric symptoms such as loss of empathy and altered bodily awareness (Downey *et al.*, 2014; Fletcher *et al.*, 2015a). These symptoms are of key clinical relevance but remain difficult to measure and poorly understood (Hsieh *et al.*, 2013). Impaired interoception is a plausible mechanism that may link neurodegeneration to socioemotional phenotypes in FTD (García-Cordero *et al.*, 2016). However, interoceptive processing has not been studied systematically across the FTD syndromic spectrum, nor

specifically related to reduced emotional awareness or to underlying neuroanatomical substrates (García-Cordero *et al.*, 2016).

Here I used heartbeat counting to assess interoceptive accuracy in canonical FTD syndromes (bvFTD, svPPA and nfvPPA) versus healthy older individuals. I related patients' interoceptive accuracy both to a clinical index of emotional sensitivity and to regional grey matter on voxel-based morphometry (VBM). As all syndromes within the FTD spectrum are associated with socioemotional deficits and insular atrophy, some degree of impaired interoception leading to abnormal emotional awareness might be anticipated across the FTD spectrum. However, among FTD syndromes, svPPA in particular has been linked to abnormally heightened responsiveness to exteroceptive stimuli (Fletcher *et al.*, 2015a), altered bodily awareness and an impoverished concept of self (Irish and Piolino, 2016). The associations between interoception, exteroception, body ownership and sense of self identified in the healthy brain (Tsakiris *et al.*, 2011; Allen *et al.*, 2016; Filippetti and Tsakiris, 2016; Park *et al.*, 2016) suggest that reduced interoceptive accuracy may be a core feature of svPPA and disproportionately severe in this syndrome relative to other FTD syndromes. Moreover, incorporation of interoceptive information into emotional judgements has been shown to depend on the amygdala, which is particularly severely affected in svPPA (Rosen *et al.*, 2002a; Garfinkel and Critchley, 2016). This further suggests a brain mechanism that could link reduced interoceptive accuracy to emotional sensitivity in this syndrome. I therefore hypothesized that all FTD syndromes would be associated with a degree of impaired interoception leading to reduced emotional sensitivity, but that svPPA would be associated with a particularly severe deficit of interoceptive accuracy, based on the specific psychophysiological profile of this syndrome.

METHODS

PARTICIPANTS

Thirty-two FTD patients (16 bvFTD, seven svPPA, nine nfvPPA) and 19 age-matched healthy individuals (overall 51 participants, mean age 67.6 years (range 51 – 84), 22 female) participated. There were too few rtvFTD patients to constitute a separate disease group within this experiment. No participant had a history of cardiac arrhythmia, clinical depression or anxiety disorder. Clinical, demographic and neuropsychological characteristics of all participants are summarized in Table 1. Participant groups did not differ significantly in age or gender, symptom duration or use of antihypertensive medication. No participant was taking cardiac rate-limiting medication.

HEARTBEAT COUNTING TASK

I adapted a previously described heartbeat counting task as a measure of interoceptive accuracy (Schandry, 1981; Garfinkel *et al.*, 2015). Participants were asked to try to identify their heartbeats by 'listening to their body' (rather than feeling their pulse) and were first familiarized with the paradigm to ensure they understood the task. ECG was recorded continuously from electrodes placed over the right clavicle and left iliac crest. During the experiment, the number of sensed beats was reported for four epochs of variable duration (25, 35, 45, 100 seconds) signalled by start and stop tones and presented in randomized order, to preclude anticipation or guessing based on previous epochs. For each participant, an interoceptive accuracy index (IA) was calculated based on an established method as follows (Garfinkel *et al.*, 2015):

1 - |actual beats - reported beats|/((actual beats + reported beats)/2)

This method for deriving the IA index, with reported beats in the denominator, differs from the original Schandry method, and was designed specifically to mitigate the potential overestimation of IA in those who report more heartbeats than actually occurred.

Emotional sensitivity rating

Patients' caregivers completed the Sensitivity to Socio-emotional Expressiveness Score (EX) component of the Revised Self-Monitoring Scale (Lennox and Wolfe, 1984), a daily-life index of sensitivity to the emotions of others. As this was a caregiver questionnaire, it was unlikely to be directly comparable to self-administered ratings and was therefore not performed for the healthy control group.

Data analysis

Between-group differences were assessed using ANOVAs, except where the homogeneity of variance assumption was violated, when Welch's F test and Games Howell post hoc tests (a multiple comparison procedure without the assumption of homoscedasticity) were used. In addition, I assessed correlations of IA with EX (sensitivity to others' emotions), auditory reverse digit span (a standard index of nonverbal sensory working memory), British Picture Vocabulary score (a standard measure of semantic comprehension), Trails-making task performance (a standard measure of executive function) and mean heart rate (a peripheral interoceptive signal characteristic). A threshold $p<0.05$ was accepted as the significance criterion for all tests.

Brain image acquisition and analysis

Each patient had a structural T1 MR brain image acquired then preprocessed and entered into a VBM analysis as per the protocol specified in chapter 2. A full factorial model was used to assess associations between IA and regional grey matter volume within each syndromic group. Statistical parametric maps of regional grey matter associations were assessed at threshold

$p<0.05$ after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-determined regions of interest. These were chosen as regions known to support heartbeat awareness and incorporation of interoceptive information into emotional judgements in the healthy brain (cingulate, insula and amygdala (Critchley *et al.*, 2004; Garfinkel and Critchley, 2016) defined from the Harvard-Oxford Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

Table 3.1. Clinical and neuropsychological characteristics of participant groups

Characteristic	Controls	bvFTD	svPPA	nfvPPA
Demographic and clinical				
No (m:f)	8:11	13:3	5:2	4:5
Age (yrs)	68.8(5.5)	65.8(7.3)	65.9(7.4)	69.6(6.5)
Handedness (R:L:A)	17:1:1	15:1:0	7:0:0	7:2:0
MMSE (/30)	29.6(0.6)	24.6(4.5)[a]	22.6(5.8)[a]	23.7(6.0)[a]
Duration (yrs)	N/A	7.6(4.7)	4.4(2.0)	4.6(2.2)
IA	-0.19(0.77)	-0.51(0.63)	-0.82(0.25)[a]	-0.40(0.53)
EX	N/A	5.4(4.7)[d]	9.5(2.3)[d]	20.0(7.6)
Mean heart rate	69.5(10.2)[d]	72.5(12.9)	69.7(5.2)[d]	85.5(17.1)
Neuropsychological				
General intellect				
WASI verbal IQ	125.4(7.0)	86.4(22.4)[a]	78.6(20.4)[a]	80.0(17.3)[a]
WASI performance IQ	125.1(9.7)	102.44(21.4)[a]	112.3(20.1)	98.8(21.5)[a]
Episodic memory				
RMT words (/50)	49.3(0.9)	36.2(8.0)[a]	30.3(6.9)[a,d]	41.4(9.5)[a]
RMT faces (/50)	44.7(3.7)	34.0(7.6)[a]	32.7(6.4)[a]	39.5(6.6)
Camden PAL (/24)	20.3(3.5)	10.5(7.5)[a]	2.7(4.2)[a,b,d]	16.3(7.8)
Executive skills				
WASI Block Design (/71)	46.0(10.1)	32.6(19.2)	41.6(19.0)	25.1(19.7)[a]
WASI Matrices (/32)	26.6(4.1)	17.8(9.4)[a]	21.7(8.5)	17.4(9.0)[a]
WMS-R digit span forward (max)	7.1(1.2)	6.6(1.2)	7.0(1.2)	4.8(0.8)[a,b,c]
WMS-R digit span reverse (max)	5.6(1.3)	4.4(1.4)	5.1(2.0)	3.0(0.7)[a]
D-KEFS Stroop colour naming (s)	32.4(6.4)[b,d]	49.5(20.8)[d]	50.3(27.9)[d]	87.0(6.7)
D-KEFS Stroop word reading (s)	23.5(5.7)[d]	35.9(22.2)[d]	30.9(19.2)[d]	85.4(10.3)
D-KEFS Stroop interference (s)	56.2(16.9)[b,d]	103.3(47.3)[d]	82.7(50.5)[d]	165.0(30.8)
Letter fluency (F: total)	18.1(5.7)	7.6(4.4)[a]	9.7(7.2)[a]	3.5(1.7)[a]
Category fluency (animals: total)	24.7(5.9)	11.6(6.2)[a]	6.7(5.4)[a]	8.8(3.5)[a]
Trails A (s)	32.2(5.6)[b,d]	59.5(33.5)	47.0(21.0)	81.7(48.4)
Trails B (s)	66.1(20.5)[b,d]	184.1(89.0)	133.6(110.1)	211.1(94.6)
Language skills				
WASI vocabulary	72.2(3.4)	42.6(21.8)[a]	34.7(22.7)[a]	31.7(13.9)[a]
BPVS	148.5(1.1)	123.8(35.3)[a]	94.4(49.4)[a,d]	142.6(10.1)
GNT	26.3(2.4)	10.6(9.8)[a]	2.0(5.3)[a,b,d]	15.5(6.6)[a]
Posterior cortical skills				
GDA (/24)	15.8(5.4)	7.8(5.7)[a]	11.3(8.3)	5.4(1.9)[a]
VOSP Object Decision (/20)	19.1(1.6)	15.6(3.0)[a]	15.7(5.1)	15.3(4.7)[a]

Mean (standard deviation) scores are shown unless otherwise indicated; maximum scores are shown after tests (in parentheses). [a]significantly less than controls, [b]significantly less than bvFTD, [c]significantly less than svPPA, [d]significantly less than nfvPPA, (all $p<0.05$). See Table 2.3 for details of neuropsychological tests and references.

RESULTS

Clinical and neuropsychological data are shown in Table 3.1. Interoceptive accuracy data are presented in Figure 3.1 and neuroanatomical correlates in Table 3.2 and Figure 3.2.

The homogeneity of variance assumption was violated for IA data (Levene's test p=0.001). Welch's F test revealed a main effect of participant group on IA (p=0.021). Games Howell post hoc tests showed that IA was significantly lower in the svPPA group than healthy controls (p=0.022). No other significant group differences were identified for IA. Mean EX was significantly higher in the nfvPPA group than the other patient groups (p<0.001) but did not differ between the bvFTD and svPPA groups (p=0.29). Across the patient cohort, there was a significant positive correlation between IA and EX (rho=0.516, p=0.004); there was no significant association between IA and reverse digit span (rho = 0.133, p=0.372), British Picture Vocabulary Score (rho=0.242, p=0.09), trails-making task (rho=-0.08, p=0.592), mean heart rate (rho=0.038, p=0.8), age (rho=-0.062, p=0.67), disease duration (rho=-0.1, p=0.59) or antihypertensive use (p=0.5). Mean heart rate during the period of recording showed a main effect of participant group (p=0.017), with increased heart rate in the nfvPPA group relative to controls (p=0.001).

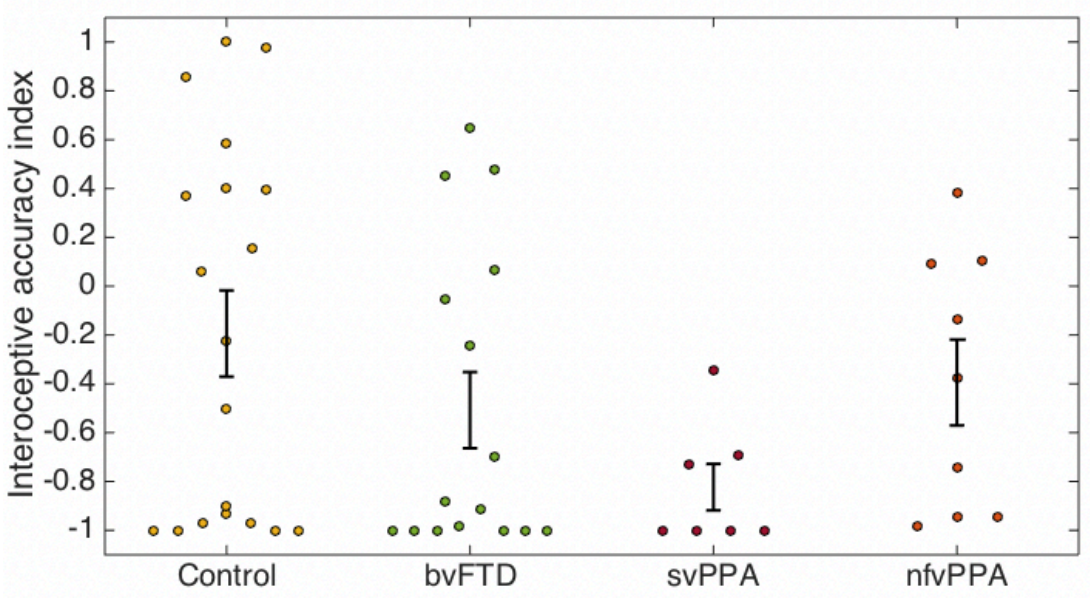
In the svPPA group, IA was significantly positively associated with grey matter volume in right amygdala, right anterior and posterior cingulate cortex and right insula (all $p<0.05_{FWE}$ over the whole brain (amygdala locus) or within pre-specified regions of interest). No significant grey matter associations were identified at the prescribed threshold in the other patient groups.

Table 3.2 VBM associations of interoceptive accuracy in svPPA

Region	Side	Cluster (voxels)	X	Y	Z	T	P_{FWE}
Amygdala/MTL	R	1336	18	-15	-21	6.26	0.041*
PCC	R	122	2	-30	28	4.41	0.022
ACC	R	101	4	0	34	4.36	0.027
Insula	R	147	44	-4	-8	4.32	0.029

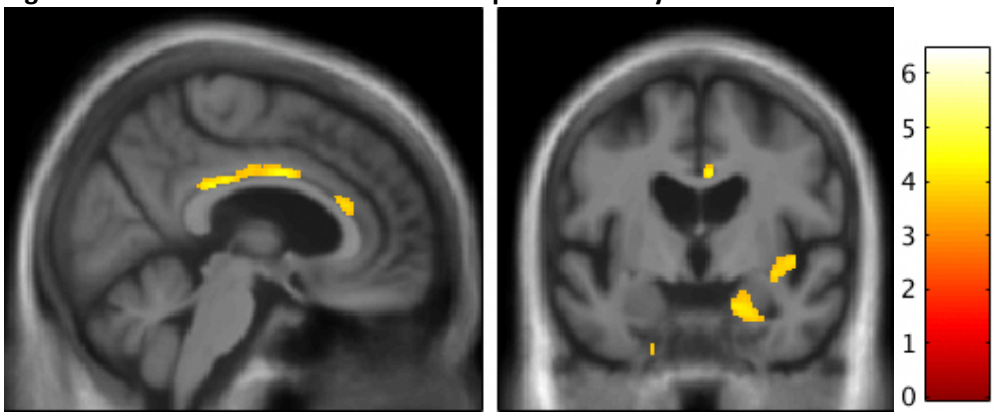
The table presents regional grey matter correlates of IA in the impaired svPPA group, based on VBM. Coordinates of local maxima are in standard MNI space. P values are all significant after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-specified anatomical regions of interest except * at whole brain.

Figure 3.1. Interoceptive accuracy in participant groups: behavioural data



The plots (above) show individual raw data for accuracy on the heartbeat counting task expressed as an interoceptive accuracy index (see text) in each participant group. Error bars represent standard error of the mean.

Figure 3.2. VBM associations of interoceptive accuracy in svPPA



The statistical parametric map of regional grey matter volume associated with interoceptive accuracy in the impaired svPPA group has been overlaid on representative sections of the normalised study-specific T1-weighted group mean brain MR image; the MNI coordinate (mm) of the plane of each section is indicated. The colour bar codes T values; the SPM is thresholded here at $p<0.001$ uncorrected over the whole brain for display purpose. Regional local maxima were significant at $p<0.05_{FWE}$ corrected for multiple comparisons over the whole brain (right amygdala, MNI coordinates {18 -15 -21}) or within pre-specified anatomical regions of interest (anterior cingulate cortex, {4 0 34}; posterior cingulate cortex, {2 -30 28}; right insula, {44 -4 -3})

DISCUSSION

My findings demonstrate that interoceptive accuracy is impaired in svPPA relative to healthy older individuals. There was a wide range of IA scores in the control group, as typically found in studies of healthy individuals (Tsakiris *et al.*, 2011; Garfinkel *et al.*, 2015). Overall performance in the control group was lower than typically found in studies of younger subjects, with several being unable to detect heartbeats, but this is consistent with evidence that interoception declines with age (Khalsa *et al.*, 2009b; Murphy *et al.*, 2017a; Murphy *et al.*, 2017b). Over the patient cohort, impaired IA did not correlate with any reduction in generic sensory monitoring, semantic capacity or peripheral interoceptive signal. In line with current models of interoception (Critchley *et al.*, 2004; Garfinkel *et al.*, 2015; Garfinkel and Critchley, 2016) and evidence for abnormal processing of homeostatic and affective signals in FTD syndromes (Fletcher *et al.*, 2015d), the findings suggest that svPPA affects the initial cognitive decoding of interoceptive signals. Interoceptive accuracy in the patient cohort was correlated with sensitivity to others' emotions: coupled with evidence in the healthy brain (Critchley *et al.*, 2004; Fukushima *et al.*, 2011; Terasawa *et al.*, 2014; Garfinkel *et al.*, 2015; Garfinkel and Critchley, 2016; Shah *et al.*, 2017), this suggests that degraded inference of others' emotions from one's own embodied responses might serve as a generic mechanism for the blunted emotional reactivity and empathy loss that characterizes FTD and may be particularly pervasive in svPPA (Rankin *et al.*, 2005). Moreover, interoceptive impairment is a plausible mechanism for the severe impoverishment of self-projection described in svPPA, and for the increased dependency on exteroceptive signals found in these patients (Fletcher *et al.*, 2015a; Irish and Piolino, 2016).

Emotional sensitivity was comparably reduced in both the svPPA and bvFTD groups (relative to the nfvPPA group) here, while bvFTD has been associated with impaired interoceptive awareness in previous work (García-Cordero *et al.*, 2016). Taken together with the present

findings, the emerging picture suggests a complex stratification of autonomic abnormalities across FTD syndromes: autonomic reactivity in these syndromes may be differentially altered under particular conditions (such as detection of salient changes in self or environment versus monitoring of bodily states) (Fletcher *et al.*, 2015d; García-Cordero *et al.*, 2016). FTD syndromes may target separable levels of interoceptive processing, svPPA producing a more fundamental deficit of interoceptive signal analysis and decoding of autonomic responses to emotion, while bvFTD impairs autonomic reactivity and the metacognitive analysis of body state representations in self and others (Joshi *et al.*, 2014; Balconi *et al.*, 2015; Guo *et al.*, 2016).

The neuroanatomical substrate for impaired interoceptive accuracy in the present svPPA group comprised a rightward-asymmetric cingulo-insulo-amygdalar network: this network is encompassed by the distributed atrophy profile of svPPA (Rosen *et al.*, 2002a), has been previously implicated in interoception both in the healthy brain and disease states (Critchley *et al.*, 2004; García-Cordero *et al.*, 2016; Garfinkel and Critchley, 2016), and is well-placed anatomically to integrate homeostatic and external socio-emotional signals in building representations of self and others (Craig, 2009). The anterior insula and anterior cingulate are key components of the salience network, while the posterior cingulate locus identified here is part of the default mode network, and the amygdala contains nuclei that contribute to both (Damoiseaux *et al.*, 2006; Seeley *et al.*, 2007). Building on previous work showing a causal influence of salience network dysfunction on the ability to recruit the default mode network for a task requiring reasoning and cognitive control in FTD (Chiong *et al.*, 2013), these results suggest that performance on the heartbeat counting task might reflect both the salient processing of interoceptive stimuli by more anterior areas, and the requirement for introspective cognitive control by the default mode network, with the amygdala providing the linkage between the two.

There are several important limitations to this work. Chief among these are the small sample sizes and high degree of variability in interoceptive accuracy among the healthy controls. The small sample size in the impaired svPPA group is particularly problematic, and raises the possibility that the results may have been simply Type I error due to random sampling. The results should therefore be interpreted with caution. Considering the patients as a single group may have improved power to detect a true effect across patient groups and might have been more appropriate, although on clinical and anatomical grounds there would be a strong expectation for differential patterns of deficits across the patient groups. Another approach that might have mitigated the effect of small sample size would have been to include a larger sample of control subjects and then use a single case study approach. The reason for only having 19 controls in this experiment was that only those who had been intensively phenotyped with clinical, neuropsychological and imaging assessment were included, and some of these were excluded due to the presence of cardiac arrhythmias. In future work, deriving age-adjusted norms for performance on the interoceptive accuracy task could allow for a more accurate assessment of deficits in small patient groups.

The Schandry task used here, although widely utilised, has several important limitations that should encourage caution during the interpretation of these results. It has been suggested that exteroceptive information may be used to detect and count heartbeats during the task, and it may not therefore be a pure interoceptive measure (Khalsa *et al.*, 2009a). Moreover, performance on the task is influenced by prior expectations of heart rate (Brener and Ring, 2016), and this could be a significant confound in these patient groups with semantic deficits, despite the lack of association between task performance and semantic ability as measured with the BPVS in this study. Another potential confound here is the known influence of body mass index (BMI) on interoceptive accuracy (Rouse *et al.*, 1988). Data concerning the BMI of the participants here were not obtained, and I am therefore unable to exclude the possibility that variation in BMI significantly influenced the results. Other potential influences on task

performance include heart rate variability. The incorporation of a baseline period of heart rate recording would have allowed for assessment of the effect of resting heart rate variability on interoceptive accuracy.

This small experiment provides proof-of-principle for further systematic investigation of interoception as an attractive, novel paradigm for deconstructing complex deficits of emotional reactivity, empathy and self-awareness in neurodegenerative syndromes. At present, we lack quantifiable metrics for cardinal socio-emotional symptoms of dementia. Interoception may plausibly underpin such symptoms and can be assessed using simple, objectively verifiable procedures. Clearly, the variation in intrinsic interoceptive sensitivity among healthy people will need to be taken into account in applying interoceptive measures in clinical settings. However, acknowledging this caveat, interoceptive sensitivity warrants further evaluation, both as a potential biomarker in individuals with retained baseline capacity to perform the task, and to identify neuroanatomical and physiological correlates, which might yield outcome measures in clinical trials. Future work should assess different interoceptive dimensions longitudinally, in larger cohorts sampling representatively across syndromes and with molecular correlation, to determine the reliability, sensitivity and specificity of potential interoceptive biomarkers. Larger studies with greater power may additionally reveal less profound interoceptive deficits within the heterogeneous bvFTD population. Control conditions involving exteroceptive counting tasks of comparable difficulty might help to further disambiguate interoceptive deficits from other cognitive difficulties impairing task performance. The use of passive interoception tasks such as those based on stimulus timing in the cardiac cycle and measurement of heartbeat evoked potentials would also be of value to provide further confirmation that deficits in interoceptive reporting are not confounded by other neuropsychological impairments (Garfinkel *et al.*, 2014; Maister *et al.*, 2017).

4. RECOGNITION AND AUTOMATIC IMITATION OF DYNAMIC FACIAL EMOTIONS: BEHAVIOUR, EMG REACTIVITY AND STRUCTURAL NEUROANATOMY

CHAPTER SUMMARY

Automatic motor mimicry is essential to the normal processing of perceived emotion, and disrupted automatic imitation might underpin socio-emotional deficits in neurodegenerative diseases, particularly FTD. However, the pathophysiology of emotional reactivity in these diseases has not been elucidated. In this experiment, I studied facial electromyographic responses during emotion identification on videos of dynamic facial expressions in 37 FTD patients versus 21 healthy older individuals. Neuroanatomical associations of emotional expression identification accuracy and facial muscle reactivity were assessed using voxel-based morphometry. Controls showed characteristic profiles of automatic imitation, and this response predicted correct emotion identification. Automatic imitation was reduced in the bvFTD and rtvFTD groups, while the normal coupling between imitation and correct identification was lost in the rtvFTD and svPPA groups. Grey matter correlates of emotion identification and imitation were delineated within a distributed network including primary visual and motor, prefrontal, insular, anterior temporal and temporo-occipital junctional areas, with common involvement of supplementary motor cortex across syndromes. Impaired emotional mimesis may be a core mechanism of disordered emotional signal understanding and reactivity in frontotemporal dementia, with implications for the development of novel physiological biomarkers of socio-emotional dysfunction in these diseases.

INTRODUCTION

As discussed in Chapter 1, motor mimicry supports the decoding of perceived emotions by the healthy brain (Niedenthal, 2007; Wood *et al.*, 2016b). Viewing emotional facial expressions rapidly and involuntarily engages the facial muscles of neurologically normal observers (Dimberg and Thunberg, 1998; Dimberg *et al.*, 2002). Emotional mimesis may have evolved as a specialized 'exaptation' of action observation, and by promoting emotional contagion and affective valuation may have facilitated the development of advanced human social behaviour and theory of mind (Neumann *et al.*, 2014; Tramacere and Ferrari, 2016; Wood *et al.*, 2016b). In line with this interpretation, motor recoding of observed emotion correlates with empathy and emotion identification ability (Kunecke *et al.*, 2014) and predicts authenticity judgments on facial expressions (Korb *et al.*, 2014); while conversely, facial paralysis induced by botulinum toxin attenuates emotional reactivity (Kim *et al.*, 2014). The linkage between emotion observation, recognition and mimesis is precise: viewing of universal facial emotional expressions (Ekman *et al.*, 1969) produces signature profiles of electromyographic (EMG) activity in the facial muscles conveying each expression (Vrana, 1993; Dimberg and Thunberg, 1998). This phenomenon is mediated by distributed, cortico-subcortical brain regions that may together instantiate a hierarchically organised neural substrate for inferring the intentions and subjective states of others (Leslie *et al.*, 2004; Kilner *et al.*, 2007; Schilbach *et al.*, 2008; Foley *et al.*, 2012): primary visual representations of emotions would comprise the lowest level of the hierarchy, ascending through sensorimotor representations of emotional movement kinematics, prediction of movement goals and affective states, and encoding of intentions, including affective mentalising.

On clinical, pathophysiological and neuroanatomical grounds, altered motor recoding might be anticipated to underlie impaired emotional and social signal processing in FTD. Deficits in emotion recognition, empathy and social understanding and behaviour are defining features of

bvFTD and rtvFTD but integral to all FTD syndromes (Rosen *et al.*, 2004; Omar *et al.*, 2011; Kumfor and Piguet, 2012; Rohrer *et al.*, 2012b; Couto *et al.*, 2013; Hazelton *et al.*, 2016) and collectively engender substantial distress and care burden (Hsieh *et al.*, 2013). Impaired facial emotion recognition in bvFTD, svPPA and nfvPPA has been linked to atrophy of an overlapping network of cerebral regions including orbitofrontal cortex, posterior insula and antero-medial temporal lobe (Hsieh *et al.*, 2012; Couto *et al.*, 2013), implicated in evaluation of facial emotional expressions and integration with bodily signals (Gobbini and Haxby, 2007; Hale and Hamilton, 2016; Kraaijenvanger *et al.*, 2017).

Patients with bvFTD have been noted to have reduced facial expressivity (Edwards-Lee *et al.*, 1997) and indeed, deficient volitional imitation of emotional faces (Gola *et al.*, 2017). However, whereas impaired facial EMG reactivity to facial expressions has been linked to emotion processing deficits in Parkinson's disease (Argaud *et al.*, 2016; Balconi *et al.*, 2016), Huntington's disease (Trinkler *et al.*, 2017) and schizophrenia (Peterman *et al.*, 2015), the motor physiology of emotional reactivity has not been addressed in the FTD spectrum.

In this experiment, I investigated facial motor responses to viewing facial emotional expressions in a cohort of patients representing all major phenotypes of FTD (bvFTD, svPPA and nfvPPA) relative to healthy older individuals. There were six rtvFTD subjects identified within the wider bvFTD group here, and these were therefore considered as a separate group. Patients with rtvFTD have been shown to have particularly severe disturbances of facial empathy (Mendez and Perryman, 2003; Ranasinghe *et al.*, 2016; Gola *et al.*, 2017). I compared facial EMG response profiles with emotion identification accuracy on the FG-Net Facial Emotions and Expressions Database (as described in chapter 2). These stimuli are more faithful exemplars of the emotions actually encountered in daily life and are anticipated to engage mechanisms of motor imitation more potently than the static images conventionally used in neuropsychological studies (Trautmann *et al.*, 2009; Rymarczyk *et al.*, 2016). Neuroanatomical associations of facial expression identification and EMG reactivity in the patient cohort were

assessed using VBM. Based on previous clinical and physiological evidence (Edwards-Lee *et al.*, 1997; Dimberg and Thunberg, 1998; Dimberg *et al.*, 2002; Mendez and Perryman, 2003; Eckart *et al.*, 2012; Rohrer *et al.*, 2012a; Joshi *et al.*, 2014; Fletcher *et al.*, 2015a; Fletcher *et al.*, 2015c; Guo *et al.*, 2016), I hypothesised that healthy older individuals would show rapid and characteristic patterns of facial muscle responses to perceived emotional expressions coupled with efficient emotion identification. In contrast, I hypothesised that all FTD syndromes would be associated with impaired emotion identification but would exhibit separable profiles of facial muscle reactivity. In particular, I predicted that bvFTD and rtvFTD would be associated with reduced EMG responses while svPPA would be associated with aberrant coupling of muscle reactivity to emotion identification and nfvPPA with a more selective, emotion-specific reactivity profile. Based on previous neuroimaging studies both in the healthy brain and in FTD (Warren *et al.*, 2006; Schilbach *et al.*, 2008; Trautmann *et al.*, 2009; Hsieh *et al.*, 2012; Likowski *et al.*, 2012; Couto *et al.*, 2013; Vrticka *et al.*, 2013), I further hypothesised that facial emotion identification and EMG reactivity would have partly overlapping neuroanatomical correlates within distributed cortical circuitry previously implicated in the decoding of visual emotional signals, supplementary motor and insular cortices mediating the integration of somatic representations and antero-medial temporal and prefrontal circuitry involved in the evaluation of emotion.

MATERIALS AND METHODS

PARTICIPANTS

37 FTD patients (13 with bvFTD, six with rtvFTD nine with svPPA, nine with nfvPPA) and 21 healthy control subjects participated. General characteristics of the participant groups are summarised in Table 4.1. No participant had a history of facial palsy or clinically significant visual loss after appropriate correction. There was clinical evidence of orofacial apraxia in seven patients in the nfvPPA group, but none in any of the other participant groups. Between-

group differences in demographic and neuropsychological variables were analysed using ANOVAs with post hoc T-tests when main effects were found, except for categorical variables, for which a chi-squared test was used.

FACIAL EXPRESSION STIMULI

Stimuli from the FG-Net Facial Emotions and Expressions Database (Wallhoff, 2006-2015) representing the canonical emotions of anger, fear, disgust, happiness and surprise were presented in pseudorandomised order via the monitor of a notebook computer running the Cogent toolbox of Matlab R2014b as described in chapter 2. The participant's task on each trial was to identify from among the five alternatives (verbally or by pointing to the appropriate written name) which emotion was displayed; participant responses were recorded for offline analysis. Participants were first familiarised with the stimuli and task to ensure they understood and were able to comply with the protocol. During the test, no feedback was given and no time limits were imposed on responses. Emotion identification scores were compared among groups using ANOVAs, with Bonferroni-corrected post hoc T-tests when main effects were found.

EMG ACQUISITION AND ANALYSIS

While participants viewed the video stimuli, facial EMG was recorded continuously from left corrugator supercilii, levator labii and zygomaticus major muscles with bipolar surface electrodes, according to published guidelines for the use of EMG in research (Fridlund and Cacioppo, 1986). These facial muscles were selected as the key drivers of the canonical expressions represented by the video stimuli (Vrana, 1993; Dimberg and Thunberg, 1998). Expressions of anger and fear engage corrugator supercilii (which knits the brow) and inhibit zygomaticus major (which raises the corner of the mouth); expressions of happiness and surprise are associated with the reverse muscle activity profile, while disgust engages both corrugator supercilii and levator labii (which curls the top lip). EMG data were sampled at

2048Hz with a 0.16-100Hz band-pass filter and the EMG signal was rectified, high-pass filtered to correct for baseline shifts and smoothed with a 100 data point sliding filter using MATLAB R2014b; trials with signal amplitude >3 standard deviations from the mean (attributable to large artefacts, e.g., blinks) were removed prior to analysis. For each trial, the mean change in EMG activity from baseline (mean activity during a 500ms period prior to trial onset) was analysed for each muscle in 500ms epochs, starting 1s before the onset of expression change in the video stimuli; the EMG response for each muscle was calculated as the area under the curve of EMG signal change from baseline.

I first assessed the presence of automatic imitation (any EMG change from baseline) and emotion-specific muscle activation (any interaction of muscle EMG response with emotion) for the healthy control group, using a repeated measures ANOVA (mean EMG activity for five emotions in eight 500ms time bins for the three muscles). To determine if there was an overall effect of participant group on the degree of emotion-specific muscle activation, EMG responses were compared across all participants using a restricted maximum likelihood mixed effects model incorporating interactions between emotion, muscle and participant group, with participant identity as a level variable and time bin as a covariate of no interest. After assessing the overall effect of participant group in the omnibus test, I proceeded to establish the basis for any group differences by examining particular emotion-specific muscle contrasts. Emotion-specific EMG response profiles were quantified for each trial by combining individual muscle responses pairwise as follows: for anger and fear, (corrugator response minus zygomaticus response); for happiness and surprise, (zygomaticus response minus corrugator response); for disgust, (corrugator response plus levator response). These pairwise muscle contrasts have been shown to improve reliability and internal consistency of facial EMG analysis (Hess *et al.*, 2017). Muscle contrast EMG reactivity for each trial was then analysed as a dependent variable in an ANOVA incorporating participant group and emotion as fixed factors. Significant main

effects in the ANOVA were explored with post hoc T-tests, using Bonferroni correction for multiple comparisons.

To test the hypothesis that emotional imitation supports identification, I assessed any relationship between average EMG reactivity and emotion identification score using Spearman's rank correlation across the participant cohort. In addition, I compared EMG responses on trials with correct versus incorrect emotion identification and assessed any interaction with participant group membership using an ANOVA.

To generate an overall measure of reactivity for each participant for use in the voxel based morphometry analysis, EMG reactivity was averaged over all trials for that participant and then normalised as the square root of the absolute value of the change in muscle activity from baseline (subzero values corresponding to muscle activity changes in the reverse direction to that expected were restored).

For all tests, the criterion for statistical significance was thresholded at $p<0.05$.

BRAIN IMAGE ACQUISITION AND ANALYSIS

Each patient had a structural T1 MR brain image acquired and preprocessed as described in chapter 2. Preprocessed brain MR images were entered into a VBM analysis of the patient cohort. Separate full factorial models were used to assess associations of regional grey matter volume with mean overall emotion identification score and EMG reactivity. Statistical parametric maps of regional grey matter associations were assessed at threshold $p<0.05$ after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-specified regional volumes of interest. For the emotion identification contrast, these regions were informed by previous studies of emotion processing in FTD and in the healthy brain, comprising insula, anteromedial temporal lobe (including amygdala, fusiform gyrus and temporal pole), inferior frontal cortex, anterior cingulate and supplementary motor cortices

(Warren *et al.*, 2006; Hsieh *et al.*, 2012; Couto *et al.*, 2013). For the EMG reactivity analysis, regions of interest were based on previous functional imaging studies of facial mimicry and dynamic facial stimuli in the healthy brain (Schilbach *et al.*, 2008; Trautmann *et al.*, 2009; Likowski *et al.*, 2012; Vrticka *et al.*, 2013), comprising visual (V1, MT/V5, parahippocampal and fusiform gyri) and primary and supplementary motor cortices.

RESULTS

GENERAL CHARACTERISTICS OF PARTICIPANT GROUPS

General clinical characteristics of the participant groups are presented in Table 4.1. There was a significant gender difference between participant groups (chi^2_4=10.31, p=0.036), but no significant age difference. The patient groups did not differ in mean disease duration or level of overall cognitive impairment (as indexed using MMSE score) (ANOVAs and post hoc T-tests all p>0.4).

Table 4.1. Demographic, clinical and neuropsychological characteristics of participant group

Characteristic	Controls	bvFTD	rtvFTD	svPPA	nfvPPA
Demographic / clinical					
No. (male:female)	9:12	10:3	6:0[a]	7:2	4:5
Age (years)	69.1 (5.3)	66.2 (6.3)	63.8 (6.4)	66.1 (6.5)	69.6 (6.5)
Handedness (R:L)	20:1	12:1	6:0	8:1	7:2
Education (years)	15.7 (3.5)	13.2[c] (2.5)	18.0 (3.1)	14.9 (2.8)	15.0 (2.1)
MMSE (/30)	29.6 (0.6)	24.5[a] (4.6)	25.3[a] (4.3)	21.8[a] (6.9)	23.7[a] (6.0)
Symptom duration (years)	N/A	7.7 (6.0)	6.5 (3.5)	5.6 (3.0)	4.7 (2.2)
Neuropsychological					
General intellect					
WASI verbal IQ	125 (6.7)	89[a] (21.9)	87[a] (22.2)	77[a] (19.7)	80[a] (17.3)
WASI performance IQ	125 (10.2)	104[a] (20.3)	107 (24.6)	108 (23.5)	99[a] (21.5)
Episodic memory					
RMT words (/50)	49.0 (1.4)	37.4[a] (7.9)	37.2[a] (9.3)	30.0[a,c] (6.3)	41.4[a] (9.5)
RMT faces (/50)	44.7 (3.5)	33.5[a] (6.9)	34.8[a] (7.9)	32.8[a] (6.9)	39.5 (6.6)
Camden PAL (/24)	20.4 (3.3)	10.8[a] (8.1)	12.5[a] (6.2)	2.2[a,b,c,e] (3.7)	16.3 (7.8)
Executive skills					
WASI Block Design (/71)	44.8 (10.5)	32.5 (16.7)	37.2 (22.1)	39.1 (21.7)	25.1[a] (19.7)
WASI Matrices (/32)	26.6 (3.9)	19.3[a] (9.4)	19.0[a] (9.8)	19.8[a] (10.6)	17.4[a] (9.0)
WMS-R DS forward (max)	7.1 (1.1)	6.6 (1.2)	6.8 (1.2)	6.7 (1.2)	4.8[a,b,c,d] (0.8)
WMS-R DS reverse (max)	5.6 (1.2)	4.0[a] (1.5)	4.7 (1.4)	5.3 (1.8)	3.0[a, d] (0.7)
D-KEFS Stroop:					
colour (s)	33.4 (7.2)	48.0 (20.5)	48.8 (21.4)	53.2[a] (28.2)	87.0[a,b,c,d] (6.7)
word (s)	23.9 (5.6)	32.5 (19.0)	38.7 (26.1)	36.0 (24.0)	85.4[a,b,c,d] (10.3)
interference (s)	57.6 (16.7)	99.6[a] (47.5)	98.3 (45.1)	90.1 (56.1)	165[a,b,c,d] (30.8)
Fluency:					
letter (F total)	18.1 (5.6)	7.8[a] (4.6)	9.0[a] (4.7)	8.9[a] (7.1)	3.5[a] (1.7)
category (animals total)	24.4 (6.0)	13.8[a] (7.5)	10.3[a] (2.3)	5.7[a,b] (5.1)	8.8[a] (3.5)
Trails A (s)	33.7 (7.3)	56.5 (32.3)	59.8 (32.9)	49.7 (20.1)	81.7[a] (48.4)
Trails B (s)	67.3 (21.5)	171.7[a] (88.2)	186.7[a] (100.4)	134.9 (101.7)	211.1[a] (94.6)
Language skills					
WASI vocabulary	72.3 (3.2)	42.4[a] (21.5)	47.0[a] (19.1)	33.6[a] (22.0)	31.7[a] (13.9)
BPVS	148.6 (1.1)	120.8 (38.7)	141.8 (7.2)	85.8[a,b,c,e] (53.8)	142.6 (10.1)
GNT	26.1[a] (2.7)	12.2[a] (10.2)	12.5 (10.1)	1.6[a,b,c,e] (4.7)	15.5[a] (6.6)
Other skills					
GDA (/24)	15.8 (5.3)	7.8[a] (6.6)	7.5[a] (6.3)	11.9 (8.6)	5.4[a] (1.9)
VOSP (/20)	19.0 (1.5)	15.9[a] (3.4)	16.7 (2.3)	15.8 (4.5)	15.3[a] (4.7)

Mean (standard deviation) scores are shown unless otherwise indicated; maximum scores are shown after tests (in parentheses). [a]significantly different from healthy controls, [b]significantly different from bvFTD, [c]significantly different from rtvFTD, [d]significantly different from svPPA, [e]significantly different from nfvPPA (all $p<0.05$). See chapter 2 for details of neuropsychological tests and references.

EMOTION IDENTIFICATION

Group data for facial emotion identification are summarised in Table 4.2.

Overall accuracy of facial emotion identification showed a main effect of participant group (F_4=10.89, p<0.001), and was reduced in all syndromic groups relative to controls (all p_{bonf}<0.012) (Table 2). Considering particular emotions, identification accuracy was preserved for happiness (p=0.13) but reduced for all other emotions (all p<0.001) in each patient group relative to healthy controls. There was no significant relationship between emotion identification accuracy and age but a significant effect of gender (p=0.04), with higher identification scores overall in female participants. The main effect of participant group persisted after covarying for gender (F_4=13.852, p<0.001). Emotion identification accuracy in the patient cohort correlated with a measure of nonverbal executive function and disease severity (WASI matrices score; rho=0.547, p<0.001).

Table 4.2. Summary of emotion identification and EMG reactivity findings for participant groups

Response parameter	Controls	bvFTD	rtvFTD	svPPA	nfvPPA
Emotion identification					
Anger	4.6 (2.2)	1.8 (1.4)[a]	2.5 (1.6)	1.1 (0.9)[a]	3.4 (1.7)
Disgust	8.1 (1.0)	5.3 (3.3)[a]	3.5 (3.9)[a]	3.8 (3.3)[a]	5.4 (3.3)
Fear	5.4 (2.1)	2.6 (2.0)[a]	2.0 (1.7)[a]	3.9 (2.0)	4.4 (2.4)
Happiness	9.2 (0.8)	8.0 (3.2)	8.3 (1.9)	7.0 (3.2)	7.8 (1.6)
Surprise	8.4 (1.0)	4.9 (2.8)[a]	3.7 (2.8)[a]	4.1 (3.2)[a]	5.8 (3.0)
Overall (/50)	35.7 (4.6)	22.7 (9.5)[a]	20.0 (9.7)[a]	20.2 (7.9)[a]	26.9 (9.3)[a]
Facial EMG reactivity					
Anger	1.3 (3.3)	0.5 (1.5)	0.2 (1.0)	1.2 (5.1)	0.3 (4.0)
Disgust	2.6 (8.9)	-0.9 (9.0)[a]	0.5 (1.7)	1.4 (6.2)	0.9 (3.7)
Fear	0.7 (2.9)	0.3 (1.3)	-0.1 (1.9)	0.8 (4.4)	-0.9 (3.5)[a,b,d]
Happiness	1.3 (2.3)	0.5 (1.3)[e]	0.2 (1.6)[e]	1.8 (8.2)	2.3 (4.9)
Surprise	1.0 (2.5)	0.01 (3.1)[d,e]	0.3 (1.8)	1.7 (5.3)	1.7 (3.8)
Overall	1.4 (4.7)	0.09 (4.4)[a,d,e]	0.2 (1.6)[a,d]	1.4 (6.0)	0.9 (4.2)

Mean (standard deviation) scores on the emotion identification task and mean facial EMG reactivity (as defined in Figure 1) to viewed emotional expressions are shown for each emotion, in each participant group. [a]significantly less than healthy controls, [b]significantly less than bvFTD, [c]significantly less than rtvFTD, [d]significantly less than svPPA, [e]significantly less than nfvPPA (all p_{bonf}<0.05).

FACIAL EMG REACTIVITY

Mean time courses of EMG responses for each facial muscle and emotion are shown for all participant groups in Figure 4.1. Group data for EMG reactivity are summarised in Table 4.2 and Figure 4.2.

Healthy older participants showed the anticipated profiles of facial muscle activity in response to viewing facial expressions (Figure 4.1): corrugator supercilii was activated by anger, fear and disgust, and inhibited by happiness and surprise; zygomaticus major was activated by happiness and surprise, and inhibited by anger and fear; and levator labii activity was maximal for disgust. Due to the proximity of levator labii and zygomaticus major, and the limited spatial specificity of surface electrodes (Fridlund and Cacioppo, 1986), there was substantial electrical leakage between these two muscles. However, zygomaticus major was maximally activated by happiness and surprise, and levator labii by disgust; moreover, these muscles were not combined in any of the pairwise muscle contrasts. Automatic imitation was evident in the EMG signal before unambiguous emotional expression onset as rated by examining the videos frame-by-frame (Figure 4.1): this early onset of emotion-specific muscle response was confirmed on a repeated measures ANOVA within the healthy control group examining the first second before clearly detectable expression change (interaction of emotion and muscle $F_{(2.43,48.58)}$=4.25, p=0.014), arguing against volitional imitation of the viewed expressions.

EMG reactivity to viewed facial expressions was modulated in an emotion- and muscle-specific manner in healthy controls ($F_{(2.20,43.94)}$=5.03, p=0.009) and the participant cohort as a whole ($chi^2_{(8)}$= 80.05, p<0.001). There was further evidence that this interaction between emotion and muscle reactivity varied between participant groups (interaction of group, emotion and muscle: ($chi^2_{(32)}$=143.91, p<0.001). After the generation of a muscle contrast reactivity measure for each trial, ANOVA revealed significant main effects of participant group ($F_{(4)}$=10.84, p<0.001), emotion ($F_{(4)}$=3.40, p=0.009) and the interaction of group and emotion ($F_{(16)}$=2.79,

p<0.001; Table 4.2). In post hoc T-tests comparing participant groups (with Bonferroni correction), overall EMG reactivity across the five emotions was significantly reduced in the bvFTD group relative to the healthy control group (p_{bonf} <0.001), the svPPA group (p_{bonf}<0.001) and the nfvPPA group (p_{bonf}=0.042); and significantly reduced in the rtvFTD group relative to the healthy control group (p_{bonf}=0.001) and the svPPA group (p_{bonf}=0.005). Comparing EMG responses to particular emotions between patients and healthy controls revealed significantly reduced reactivity to disgust in the bvFTD group and reduced reactivity to fear in the nfvPPA group (both p_{bonf}<0.001; see also Table 4.2).

There was no significant relationship between EMG reactivity and age (p=0.1), gender (p=0.42), digit span (used here as a measure of attention and working memory; p=0.8), trails-making task performance (used here as a measure of executive function; p=0.41) or score on WASI matrices (used here as a measure of disease severity; p=0.63) in the patient cohort.

Relationship between emotion identification and facial EMG reactivity

Across the participant cohort, overall EMG reactivity was significantly correlated with emotion identification accuracy (rho=0.331, p=0.011) and mean overall EMG reactivity was significantly higher for trials on which the emotion was correctly identified (n=1586) than on error trials (n=1314; p=0.002). This differential effect of correct versus incorrect trials showed a significant interaction with participant group ($F_{(4)}$=4.18, p=0.002; see Figure 4.2). Among healthy controls, there was a strong trend towards greater reactivity predicting correct identification (p=0.087). Comparing trial types within patient groups, EMG reactivity was significantly higher on correct identification trials than error trials in the bvFTD group (p=0.009) and the nfvPPA group (p=0.01) but not the rtvFTD group (p=0.76) or the svPPA group (p=0.06, here signifying a trend towards greater EMG reactivity on incorrect trials). Exploring the relationship between EMG reactivity and correct identification for individual emotions across the participant cohort (Figure 4.3) revealed that this effect was driven almost exclusively by responses to disgust

(p=0.002) and fear (p=0.008) rather than anger (p=0.88), surprise (p=0.81) or happiness (p=0.016, with greater EMG reactivity in incorrect trials).

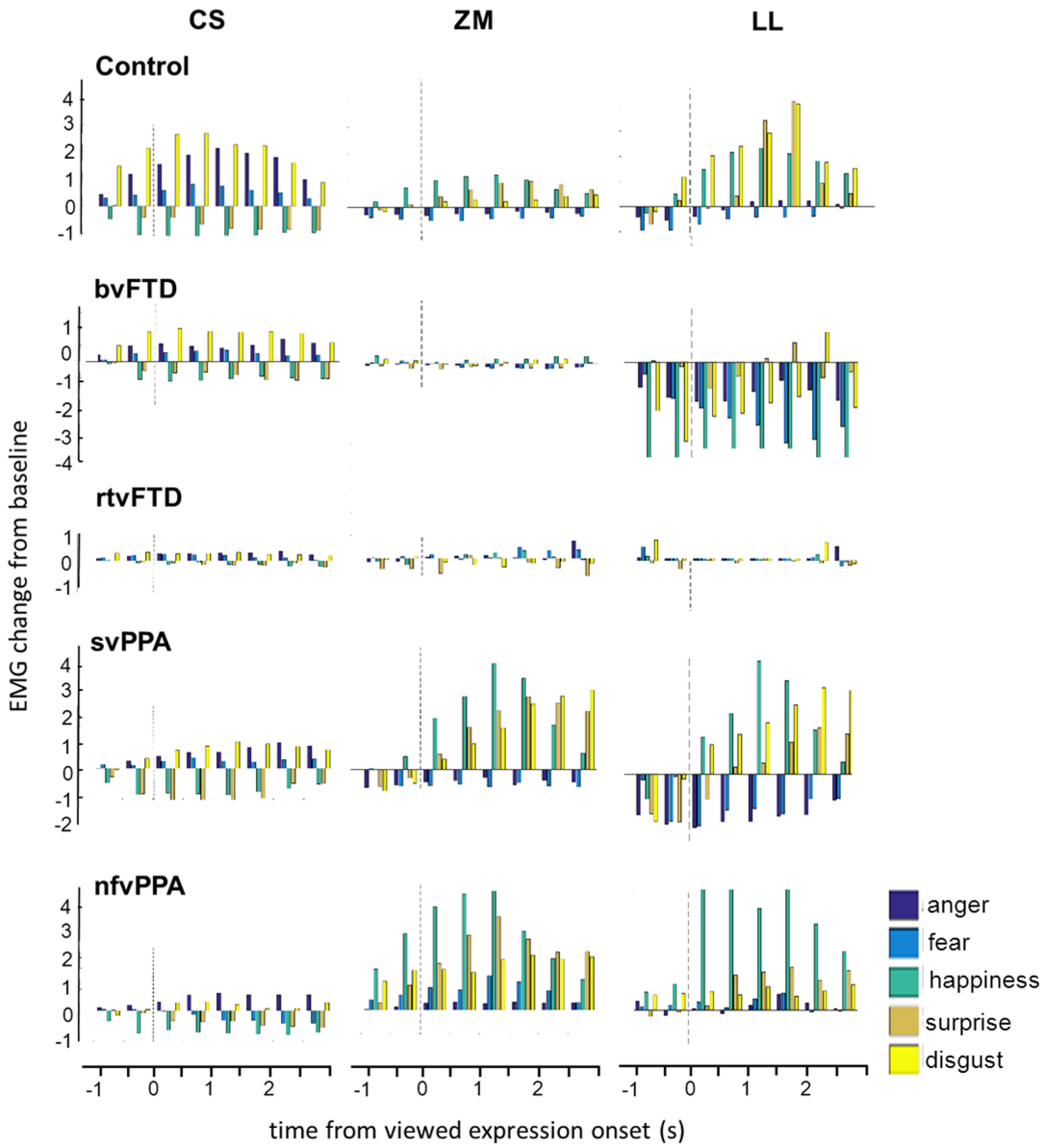
NEUROANATOMICAL ASSOCIATIONS

Significant grey matter associations of emotion identification and EMG reactivity for the patient cohort are summarised in Table 4.3 (all thresholded at $p_{FWE}<0.05$ within pre-specified anatomical regions of interest); statistical parametric maps are presented in Figure 4.4 and.

Accuracy identifying dynamic emotional expressions was correlated with regional grey matter volume in left supplementary motor cortex in all syndromic groups. Additional regional grey matter correlates of emotion identification were delineated for particular syndromic groups. The bvFTD, svPPA and nfvPPA groups showed syndromic grey matter correlates within a bi-hemispheric (predominantly left-lateralised) frontotemporal network including opercular inferior frontal gyrus, anterior cingulate, anterior insula and antero-inferior temporal lobe; while the svPPA group showed a further correlate in left posterior superior temporal cortex and the rtvFTD group showed a correlate in right temporo-occipital junctional cortex in the vicinity of MT/V5 complex (Dumoulin *et al.*, 2000).

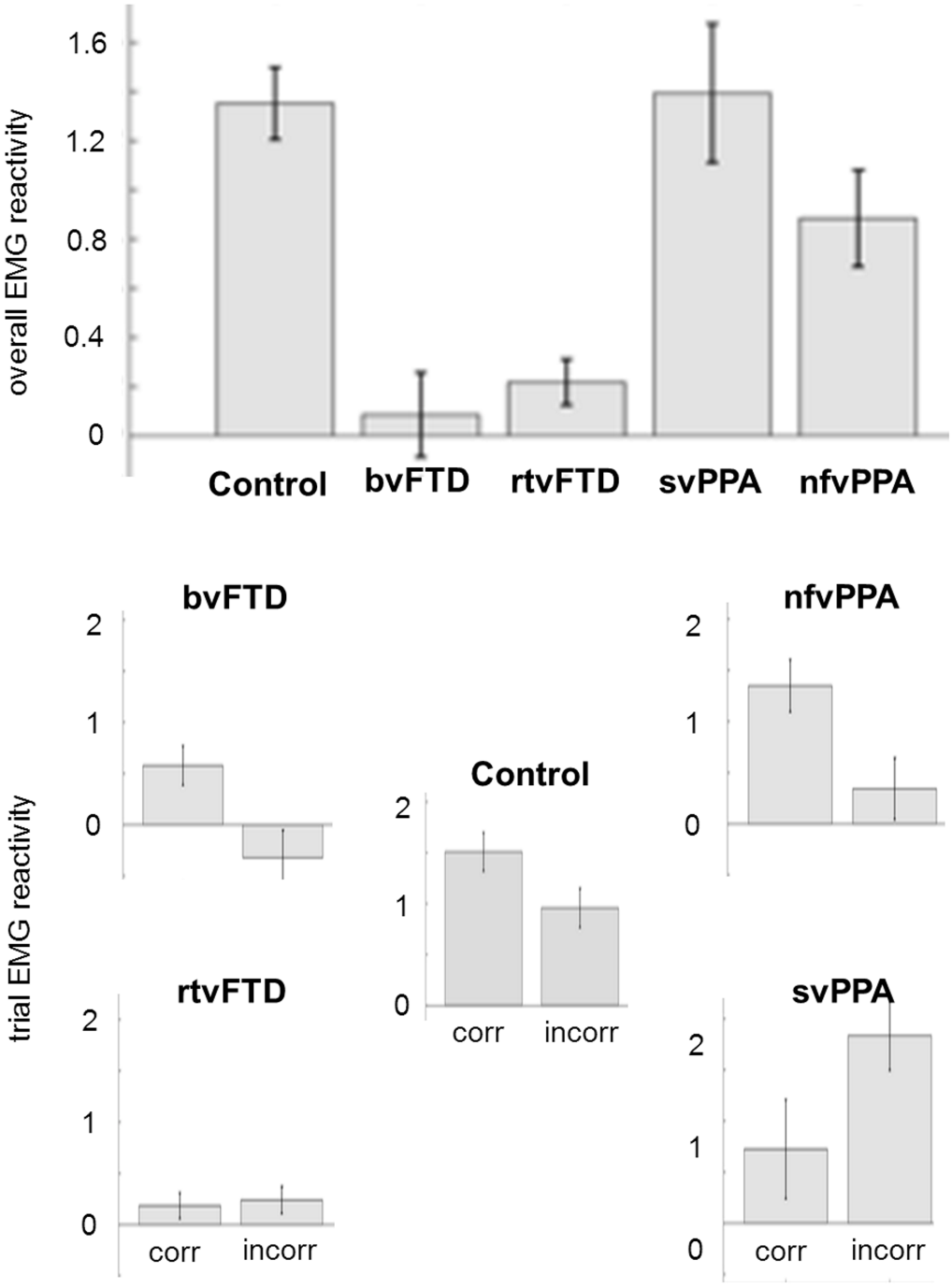
Across the patient cohort, overall mean EMG reactivity was correlated with regional grey matter in an overlapping but more posteriorly directed and right-lateralised network, with variable emphasis in particular syndromic groups. The bvFTD and nfvPPA groups showed grey matter correlates of EMG reactivity in supplementary and primary motor cortices, while all syndromic groups showed grey matter associations in cortical areas implicated in the analysis of visual signals, comprising primary visual cortex in the nfvPPA group; temporo-occipital. junction (MT/V5 complex) in the bvFTD and rtvFTD groups; and parahippocampal gyrus in the svPPA group.

Figure 4.1. Patterns of EMG reactivity for each muscle in each participant group



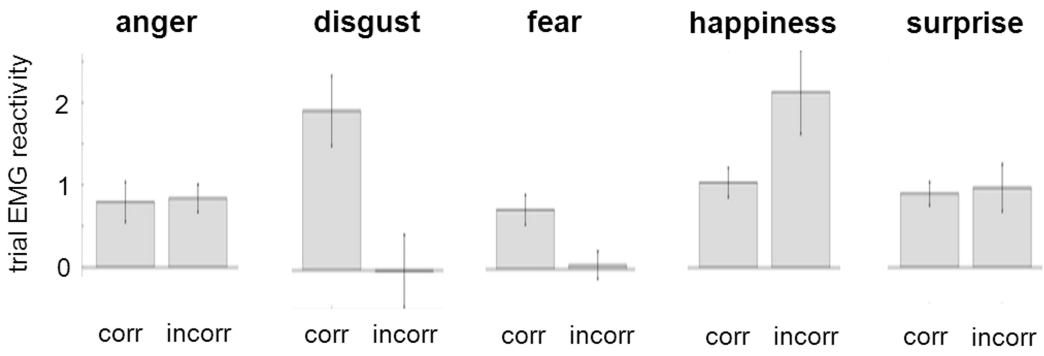
For each participant group, the plots show the time course of average EMG reactivity in microvolts for key facial muscles while participants watched videos of emotional facial expressions (coded on the right). EMG reactivity, here indexed in arbitrary units as mean EMG change from baseline, is shown on the y-axis (after rectifying, high-pass filtering and removing artefacts as described in Methods). Onset of the viewed facial expression (as determined in a prior independent analysis of the video stimuli) is at time 0 (dotted line) in each panel. In healthy controls, corrugator supercilii (CS) was activated during viewing of anger, fear and disgust, but inhibited during viewing of happiness and surprise; zygomaticus major (ZM) was activated during viewing of happiness and surprise, but inhibited during viewing of anger and fear; and levator labii (LL) was inhibited during viewing of anger and fear, and maximally activated during viewing of disgust. Note that in healthy controls muscle responses consistently preceded the unambiguous onset of viewed emotional expressions.

Figure 4.2. EMG reactivity in each participant group, and the relationship with emotion identification accuracy



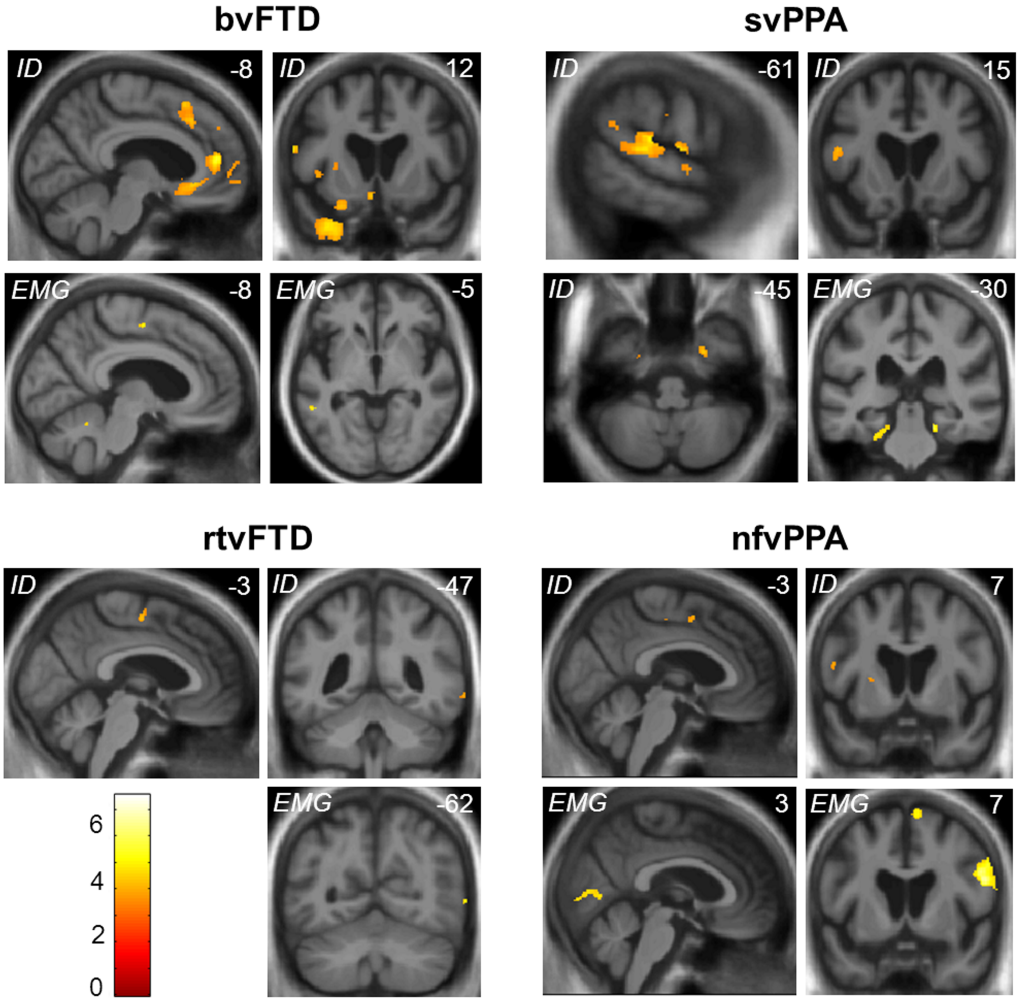
For each participant group, the histograms show mean overall facial muscle EMG reactivity (top) and EMG reactivity separately (below) for those trials on which viewed emotional expressions were identified correctly (corr) versus incorrectly (incorr); error bars indicate standard error of the mean (see also Table 4.2).

Figure 4.3 Relationship between EMG reactivity and correct identification for individual emotions



The histograms show mean overall facial muscle EMG reactivity for those trials on which viewed emotional expressions were identified correctly (corr) versus incorrectly (incorr), for each emotion in the combined participant group; error bars indicate standard error of the mean.

Figure 4.4. Neuroanatomical correlates of emotion identification and EMG reactivity



Statistical parametric maps (SPMs) show regional grey matter volume positively associated with overall emotion identification accuracy and facial EMG reactivity during viewing of emotional facial expressions, based on voxel-based morphometry of patients' brain MR images (see also Table 4.3); T-scores are coded on the colour bar. SPMs are overlaid on sections of the normalised study-specific T1-weighted mean brain MR image; the MNI coordinate (mm) of the plane of each section is indicated (coronal and axial sections show the left hemisphere on the left). Panels code syndromic profiles of emotion identification (*ID*) or EMG reactivity (*EMG*). SPMs are thresholded for display purposes at $p<0.001$ uncorrected over the whole brain, however local maxima of areas shown were each significant at $p<0.05$ after family-wise error correction for multiple voxel-wise comparisons within pre-specified anatomical regions of interest (see Table 4.3).

Table 4.3. Neuroanatomical correlates of emotion identification and reactivity in patient groups

Group	Region	Side	Cluster	Peak (mm)			T score	P_{FWE}
			(voxels)	x	y	z		
Emotion identification								
bvFTD	Anterior cingulate	L	196	-8	44	12	5.59	0.003
	Anterior insula	L	123	-30	27	0	4.07	0.047
	Supplementary motor area	L	5	-10	4	50	3.81	0.044
	Opercular IFG	L	32	-57	12	18	5.14	0.003
	Anteromedial temporal:							
	Temporal pole	L	2133	-32	8	-38	5.11	0.010
	Amygdala			-24	2	-38	4.94	0.015
	Fusiform gyrus			-30	-9	-38	4.82	0.019
rtvFTD	Supplementary motor area	L	34	-3	-10	57	4.15	0.022
	Temporo-occipital junction	R	18	66	-50	-8	4.06	0.038
svPPA	STG / STS	L	536	-58	-30	14	7.21	0.005
	Supplementary motor area	L	19	-4	-2	50	4.23	0.019
	Opercular IFG	L	25	-57	12	18	5.05	0.003
	Anterior cingulate	L	24	-2	44	3	4.11	0.042
	Fusiform gyrus	R	44	22	-4	-44	4.43	0.042
nfvPPA	Supplementary motor area	L	37	-4	-2	50	4.14	0.023
	Opercular IFG	L	9	-52	8	18	3.96	0.033
Facial EMG reactivity								
bvFTD	Supplementary motor area	L	12	-8	-9	56	3.99	0.030
	Temporo-occipital junction	L	25	-54	-45	-4	4.29	0.064
rtvFTD	Temporo-occipital junction	R	8	52	-62	2	3.96	0.046
svPPA	Parahippocampal gyrus	L	59	-20	-28	-24	4.25	0.028
	Parahippocampal gyrus	R	72	18	-33	-18	5.25	0.003
nfvPPA	Primary visual cortex	R	291	12	-80	3	5.92	0.001
	Primary motor cortex	R	521	56	8	27	5.43	0.007
	Supplementary motor area	R	18	8	8	58	4.42	0.012

The table presents regional grey matter correlates of mean overall emotion identification score and facial EMG reactivity (as defined in Figure 4.1) during viewing of facial expressions in the four patient groups, based on voxel-based morphometry. Coordinates of local maxima are in standard MNI space. P values are all significant after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-specified anatomical regions of interest (see text). bvFTD, patient group with behavioural variant frontotemporal dementia (excluding right temporal cases); IFG, inferior frontal gyrus; nfvPPA, patient group with nonfluent variant primary progressive aphasia; rtvFTD, patient subgroup with right temporal variant frontotemporal dementia; STG/S, superior temporal gyrus/sulcus; svPPA, patient group with semantic variant primary progressive aphasia.

DISCUSSION

Here I have demonstrated facial motor signatures of emotional reactivity in the FTD spectrum. As anticipated, healthy older individuals showed characteristic profiles of facial muscle engagement by observed facial emotions; moreover, facial muscle reactivity developed rapidly (preceding reliable overt detection of the stimulus expressions by independent normal observers) and predicted correct trial-by-trial identification of facial emotions. Together these findings provide further evidence that (in the healthy brain) facial mimesis is an automatic, involuntary mechanism supporting stimulus decoding and evaluation, rather than simply an accompaniment of conscious emotion recognition. In contrast, overall facial muscle reactivity and the normal coupling of muscle reactivity to facial emotion identification were altered differentially in the patient groups representing major FTD syndromes. As predicted, identification of facial expressions was impaired across the patient cohort: however, whereas the bvFTD group showed globally reduced facial muscle reactivity to observed emotional expressions, the svPPA group had preserved overall muscle reactivity but loss of the linkage between muscle response and correct expression identification, while the nfvPPA group showed a specific loss of reactivity to fearful expressions. Among those patients with syndromes dominated by behavioural decline, the profile of facial muscle reactivity stratified cases with rtvFTD from other cases of bvFTD: the subgroup with rtvFTD had a particularly severe phenotype, exhibiting both globally reduced facial reactivity and also aberrant coupling of muscle reactivity to facial expression identification.

Considered collectively, the motor signatures of emotional reactivity identified in this patient cohort amplify previous clinical, neuropsychological and physiological evidence in particular FTD syndromes. The generalised impairment of emotional mimesis in the bvFTD and rtvFTD groups is consistent with the clinical impression of facial impassivity (Edwards-Lee *et al.*, 1997; Lee *et al.*, 2014), impaired intentional imitation (Gola *et al.*, 2017) and blunting of autonomic

responsiveness (Eckart *et al.*, 2012; Joshi *et al.*, 2014; Fletcher *et al.*, 2015c, d; Guo *et al.*, 2016) in these patients. Abnormal coupling of facial mimesis to facial expression identification in my svPPA group is in line with the disordered autonomic signalling of affective valuation previously documented in this syndrome (Fletcher *et al.*, 2015c, d), and could be considered analogous to the loss of interoceptive sensitivity shown in this group in the previous chapter. The more severe impairments of disgust reactivity in the bvFTD group and fear reactivity in the nfvPPA group here further corroborate previous findings of reduced cognitive and autonomic responses to these emotions in the respective syndromes (Eckart *et al.*, 2012; Rohrer *et al.*, 2012b). The present findings go further in suggesting that aberrant motor recoding of perceived expressions may constitute a core physiological mechanism for impaired emotion processing in FTD.

This mimetic mechanism may be particularly pertinent to the dynamically shifting and subtle emotions of everyday interpersonal encounters. Our own emotional expressions are normally subject to continual modulation by the expressed emotions of others, including tracking of transient 'micro-expressions' (Shen *et al.*, 2016); this modulation occurs over short timescales (a few hundred milliseconds) and contributes importantly to the regulation of social interactions, prosociality and empathy (van Baaren *et al.*, 2009; Kuhn *et al.*, 2011; Chartrand and Lakin, 2013; Hale and Hamilton, 2016). If facial mimesis plays a key role in tuning such responses, loss of this modulatory mechanism (most notably in bvFTD and rtvFTD) might underpin not only impaired socio-emotional awareness in FTD but also the 'poker-faced' sense of unease these patients commonly provoke in others (Edwards-Lee *et al.*, 1997). I do not wish to over-interpret any specificity of mechanisms for processing particular emotions. To establish such specificity would require an examination of nonvisual sensory channels (to disambiguate modality- from emotion-related effects); moreover, the key behavioural relevance of emotional mimesis may lie in maintaining affective congruence, fluidity and rapid contextual responsiveness in social interactions, rather than in simulating discrete emotions

(van Baaren *et al.*, 2009; Kuhn *et al.*, 2011; Hess and Fischer, 2013). Nevertheless, the disproportionate syndromic deficits of disgust and fear reactivity exhibited by the bvFTD and nfvPPA groups here, and the particular importance of automatic imitation in the identification of these emotions are neurobiologically plausible (Stark *et al.*, 2003; Peelen *et al.*, 2010). Disgust and fear are arguably the emotions of highest intrinsic biological survival value and therefore have the greatest imperative for rapid recognition and contagion. Whereas the perception of disgust entails an appraisal of interoceptive signals (to assess any immediate breach of bodily integrity, for example by common exposure to a noxious substance), the perception of fear entails an appraisal of external threat (and in general, perspective-taking, in order to determine why the other is afraid). For responses to happiness, the reverse profile was seen, with greater EMG reactivity predicting incorrect identification: this apparently paradoxical pattern would follow if mimesis were particularly engaged in the processing of ambiguous emotional expressions (since in comparison to negative emotional expressions, happiness is intrinsically less likely to be confused with other emotions).

The neuroanatomical correlates I have identified speak to the coherent nature of dynamic emotion mimesis and identification. In line with previous evidence (Gola *et al.*, 2017), these processes mapped onto a distributed cerebral network within which FTD syndromes showed separable profiles of grey matter atrophy. Involvement of supplementary motor cortex was a feature across syndromes and associated both with emotion identification and motor reactivity, though joint correlation was observed in the bvFTD and nfvPPA groups but not the rtvFTD and svPPA groups (see Table 3). Supplementary motor cortex is a candidate hub for the computation of sensorimotor representations unfolding over time, an integral function of the mirror neuron system: this region generates both facial sensory-evoked potentials and complex facial movements (Allison *et al.*, 1996) and it is activated during facial imitation and empathy (Braadbaart *et al.*, 2014) as well as by dynamic auditory emotional signals (Warren *et al.*, 2006). Furthermore, transcranial magnetic stimulation of the supplementary motor region

disrupts facial emotion recognition (Rochas *et al.*, 2013). The uncoupling of motor reactivity from emotion identification in the rtvFTD and svPPA groups may reflect disconnection of this key hub from linked mechanisms for affective semantic appraisal (Leslie *et al.*, 2004), perhaps accounting for lack of an EMG reactivity correlate in supplementary motor cortex in these syndromic groups. Two further cortical hubs correlating both with emotion identification and mimesis were delineated in our patient cohort. In the svPPA and rtvFTD groups, a joint correlate was identified in the temporo-occipital junction zone, overlapping posterior superior temporal sulcus and MT/V5 visual motion cortices (Tootell *et al.*, 1995; Dumoulin *et al.*, 2000): this region has been implicated in the imitation and decoding of dynamic facial expressions (Kilts *et al.*, 2003; Pelphrey *et al.*, 2007; Foley *et al.*, 2012; Likowski *et al.*, 2012), integration of dynamic social percepts, action observation and theory of mind (Allison *et al.*, 2000; Yang *et al.*, 2015). In the svPPA group, infero-medial temporal cortex was linked both to emotion identification and mimesis: this region has previously been shown to respond to dynamic facial stimuli (Trautmann *et al.*, 2009).

Additional grey matter associations of facial expression identification accuracy were delineated in cingulo-insular, antero-medial temporal and inferior frontal areas previously implicated both in the detection and evaluation of salient affective stimuli and in canonical FTD syndromes (Critchley, 2005; Omar *et al.*, 2011; Foley *et al.*, 2012; Hsieh *et al.*, 2012; Kumfor and Piguet, 2012; Couto *et al.*, 2013; De Winter *et al.*, 2016). Additional grey matter associations of facial motor reactivity were identified (for the nfvPPA group) in primary visual and motor cortices: enhanced responses to emotional facial expressions have previously been demonstrated in visual cortex (Vuilleumier *et al.*, 2004), while motoric responses to social stimuli have been located in precentral gyrus (Schilbach *et al.*, 2008). However, it is noteworthy that certain grey matter associations emerging from this analysis - in particular, the 'hub regions' of supplementary motor cortex and temporo-occipital junction and (in the nfvPPA group) primary visual and motor cortices - lie beyond the brain regions canonically targeted in particular FTD

syndromes or indeed, in previous studies of emotion processing in FTD (Kumfor and Piguet, 2012). It is likely that the dynamic expression stimuli employed here allowed a more complete picture of the cerebral mechanisms engaged in processing naturalistic emotions. Moreover, involvement of brain regions remote from zones of maximal atrophy may reflect distributed functional network effects (for example, visual cortical activity has been shown to be modulated by amygdala (Vuilleumier *et al.*, 2004). These effects could operate in conjunction with disease-related network connectivity changes, which are known to extend beyond the atrophy maps that conventionally define particular FTD syndromes (Goll *et al.*, 2012). Taken together, the present neuroanatomical findings are compatible with the previously proposed, hierarchical organisation of embodied representations supporting emotional decoding and empathy (Warren *et al.*, 2006; Kilner *et al.*, 2007; Ondobaka *et al.*, 2017; Simon and Mukamel, 2017): whereas early visual and motor areas may support automatic imitation via low-level visual and kinematic representations, higher levels of the processing hierarchy engage the human 'mirror' system and substrates for semantic, evaluative and mentalising processes that drive explicit emotion identification.

From a clinical perspective, this work suggests a pathophysiological framework for deconstructing the complex social and emotional symptoms that characterise FTD syndromes. Such symptoms are difficult to measure using conventional neuropsychological tests, and may only be elicited by naturalistic social interactions. Dynamic motor physiological surrogates might index both the affective dysfunction of patients' daily lives and the underlying disintegration of culprit neural networks (Gola *et al.*, 2017). These physiological metrics might facilitate early disease detection and tracking over a wider spectrum of severity than is currently possible and enable socio-emotional assessment in challenging clinical settings (such as aphasia). My findings further suggest that such metrics are not simply ciphers of reduced cognitive capacity but may help stratify broad disease groupings (such as the heterogeneous bvFTD syndrome) and at the same time, may capture mechanisms that transcend traditional

syndromic boundaries. I therefore propose that the paradigm of emotional sensorimotor reactivity may yield a fresh perspective on FTD nosology and candidate novel biomarkers of FTD syndromes. Looking forward, this paradigm suggests a potential strategy for biofeedback-based retraining of emotional responsiveness, perhaps in conjunction with disease-modifying therapies (Kempnich *et al.*, 2017).

This work has several important limitations. Chief among these is the small sample sizes of the individual patient groups, especially with respect to the VBM analysis, which is likely to have been significantly underpowered. Considering the patients collectively would have resulted in a larger group size, but would have made it impossible to demonstrate the specificity of particular findings for clinicoanatomical syndromes. Another limitation is that automatic imitation is likely to be highly sensitive to attention, which is known to be particularly impaired in the patient groups, especially the bvFTD group. Although no relationship between automatic imitation and neuropsychological measures of attention and executive function was found, caution is warranted in interpreting the results as there was no measure of attention during the task itself.

This study suggests a number of directions for future work. Larger patient cohorts encompassing a wider range of pathologies will be needed in order to determine the general applicability of the paradigm and the specificity of syndromic motor profiles; it would be of interest, for example, to assess the heightened emotional contagion previously documented in Alzheimer's disease (Sturm *et al.*, 2013b) in this context. Longitudinal cohorts including presymptomatic mutation carriers will be required in order to assess the diagnostic sensitivity of mimetic indices and their utility as biomarkers; ultimately, histopathological correlation will be necessary to establish any molecular correlates of the syndromic stratification suggested here. It will be relevant to explore the cognitive milieu of emotional motor responses in greater detail: for example, the effects of other sensory modalities (in particular, audition: (Warren *et al.*, 2006), micro-expressions (Shen *et al.*, 2016), sincere versus social emotions

(Slessor *et al.*, 2014) and emotional 'caricatures' in FTD (Clark and Warren, 2016)) and the correlation of mimetic markers with measures of social cognition and daily life empathy (Gola *et al.*, 2017). Emotional reciprocity might be modeled using virtual reality techniques to generate model social interactions (van Baaren *et al.*, 2009). Beyond mimesis, integration of somatic and cognitive mechanisms during social emotional exchanges demands the joint processing of autonomic and neuroendocrine signals under executive control (Hess and Fischer, 2013; Kret, 2015; Kraaijenvanger *et al.*, 2017): future work should assess other physiological markers alongside EMG. Functional MRI would amplify the present structural neuroanatomical correlates by capturing disease-related changes in underlying brain network connectivity and dynamics. Multimodal studies of this kind may set motor mimicry in the context of a comprehensive physiology of socio-emotional reactivity in neurodegenerative disease.

5. CARDIAC RESPONSES TO VIEWING FACIAL EMOTION: HEART RATE REACTIVITY AND STRUCTURAL NEUROANATOMY

CHAPTER SUMMARY

Heart rate responses to the emotions of others are a key component of social responses in health, but have not yet been explored as an objective biomarker of degraded interpersonal reactivity across the frontotemporal dementia spectrum. In this chapter 32 patients representing all major frontotemporal dementia syndromes and 19 healthy older controls performed an emotion recognition task, viewing dynamic, naturalistic videos of facial emotions while ECG was recorded. Cardiac reactivity was indexed as the increase in interbeat interval at the onset of facial emotions. Grey matter associations of emotional reactivity were assessed using voxel-based morphometry of patients' brain MR images. Relative to healthy controls, all patient groups had impaired emotion identification, whereas cardiac reactivity was attenuated in nonfluent primary progressive aphasia, preserved in semantic variant primary progressive aphasia, and differentiated subtypes of behavioural variant frontotemporal dementia, with preserved cardiac responses in the subgroup with focal right temporal lobe atrophy. Impaired cardiac reactivity correlated with grey matter atrophy in a fronto-cingulo-insular network that overlapped correlates of cognitive emotion processing. Autonomic indices of emotional reactivity stratify frontotemporal dementia syndromes and show promise as novel biomarkers. Attenuated cardiac responses to the emotions of others suggest a core pathophysiological mechanism for emotional blunting and degraded interpersonal reactivity found in these diseases.

INTRODUCTION

Deficits in emotion processing and empathy are prominent in all FTD syndromes (Rosen *et al.*, 2004; Couto *et al.*, 2013), but remain poorly characterised and difficult to quantify. In health, emotional stimuli produce autonomic effects including modulation of heart rate. Stimulus onset induces a cardiac orienting deceleration, which is modulated by affective content, with more arousing stimuli tending to promote greater cardiac slowing (Lang *et al.*, 1993; Vrana and Gross, 2004; Bradley, 2009). These visceral autonomic responses support emotional contagion and empathy (Seth and Friston, 2016), and are mediated by anterior cingulate cortex (ACC), insula and orbitofrontal cortex (OFC) (Critchley, 2005; Beissner *et al.*, 2013). bvFTD has been associated with abnormal autonomic reactivity to affective stimuli (Eckart *et al.*, 2012; Sturm *et al.*, 2013a; Fletcher *et al.*, 2015d; Joshi *et al.*, 2017) and alterations of resting skin conductance and heart rate variability (Joshi *et al.*, 2014; Guo *et al.*, 2016), while nfvPPA has been associated with reduced pupil responses to arousing stimuli (Fletcher *et al.*, 2015c, d). These findings are consistent with the targeting of fronto-cingulo-insular circuitry in bvFTD and nfvPPA (Seeley *et al.*, 2009) and form part of a wider repertoire of autonomic dysfunction in FTD (Struhal *et al.*, 2014; Ahmed *et al.*, 2015a; Fletcher *et al.*, 2015a).

Here I explored the potential for cardiac responses to stratify FTD syndromes in response to viewing naturalistic emotional expressions. I hypothesized that cardiac modulation would be attenuated in bvFTD and nfvPPA, but relatively preserved in syndromes targeting the anterior temporal lobes (svPPA and rtvFTD), and that cardiac reactivity would correlate with atrophy in components of the autonomic regulatory network (ACC, insula and OFC) (Critchley, 2005; Beissner *et al.*, 2013; Guo *et al.*, 2016).

METHODS

PARTICIPANTS

Fifty-one participants were included in the experiment (mean age 67.6 years (range 51 – 84), 22 female), comprising 32 patients with FTD (ten bvFTD, six rtvFTD, seven svPPA, nine nfvPPA) and 19 age-matched healthy controls. No participant had a history of cardiac arrhythmia, and none was taking cardiac rate-limiting medication. Clinical, demographic and neuropsychological characteristics of all participant groups are summarised in Table 5.1.

STIMULI

Videos of emotional facial expressions were taken from the Face and Gesture Recognition Research Network database as described in Chapter 2 (Wallhoff, 2006-2015). These dynamic, naturalistic facial expressions are similar to those encountered in the unregulated social milieu of daily life; I anticipated that such stimuli should induce greater physiological responses than less ecological, static stimuli (Rymarczyk *et al.*, 2016).

Stimuli were presented in randomised order via a notebook computer using Cogent presentation software in MatlabR2012b. On each trial, the participant was asked to identify the emotion by selecting one of the five alternative emotion names using a response procedure as described in Chapter 2. The minimum inter-stimulus interval was eight seconds.

ECG RECORDING AND ANALYSIS

ECG was recorded continuously from electrodes over the right clavicle and left iliac crest. ECG data were high-pass filtered at 0.01 Hz to remove linear drift and establish a baseline from which the time point of each R wave local maximum was determined. Mean heart rate and heart rate variability (variance of RR intervals) during the period of recording were calculated for each participant. To visualize the phases of the cardiac response in the participant groups, each data point was converted into the heart rate corresponding to the RR interval in which it

lay, before smoothing with a 1 second sliding average. Continuous heart rate response data were then averaged across trials and subjects for each group. A simplified index of cardiac reactivity to viewing facial emotion was derived for each trial as the percentage change in RR interval for three heart beats before and after the onset of each facial expression, to capture both initial orienting responses and subsequent potentiation by affective content, using the formula:

((mean of 3 RR intervals after onset) minus (mean of 3 RR intervals before onset))

* 100 / mean RR interval

Cardiac reactivity was calculated for each participant for each emotion separately and averaged across all five emotions to provide a measure of overall emotional autonomic reactivity.

The cardiac reactivity index (as defined above) was assessed for each emotion using one-sample Mann-Whitney U tests versus zero (no heart rate response) and in a parametric model incorporating both cardiac reactivity and mean heart rate. Between-group differences were initially assessed using ANOVAs and post hoc t-tests were used to compare groups if a significant overall group effect was shown. For non-normally distributed data, equivalent non-parametric tests were used (Kruskal-Wallis rank and post hoc Mann-Whitney U). Between-group differences in categorical variables (i.e. sex and handedness) were assessed using chi-square contingency tests. A threshold $p<0.05$ was accepted as the criterion of statistical significance for all group comparisons.

BRAIN IMAGE ACQUISITION AND ANALYSIS

For each patient, volumetric T1 MR imaging was acquired and preprocessed for entry into a VBM analysis as described in Chapter 2. In the VBM analysis, associations between regional grey matter volume and both heart rate reactivity and emotion identification performance

were assessed separately for those syndromic groups showing altered heart rate reactivity relative to healthy controls, incorporating age and total intracranial volume as covariates of no interest. Statistical parametric maps were evaluated at peak voxel threshold $p<0.05$, after family-wise error (FWE) correction for multiple voxel-wise comparisons at whole brain level and separately within pre-specified anatomical regions of interest. These regions of interest were chosen *a* priori based on previous functional neuroimaging studies of central autonomic control and affective integration in the healthy brain (Critchley, 2005; Beissner *et al.*, 2013), and comprised ACC, insula and OFC as defined using the Harvard-Oxford Brain Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

RESULTS

CLINICAL, BEHAVIOURAL AND HEART RATE REACTIVITY DATA

Clinical, behavioural and heart rate reactivity data for the participant groups are summarized in Table 5.1. The participant groups did not differ in age, sex or handedness; patients and healthy controls did not differ in premorbid educational attainment and the patient groups had similar overall symptom duration (all $p>0.05$).

Emotion identification was impaired in all syndromic groups relative to the healthy control group (overall group effect $F_{(4)}=9.7$, $p<0.001$; bvFTD, rtvFTD, svPPA all $p<0.001$, nfvPPA $p=0.01$). No differences were found between patient groups.

Mean heart rate over the entire recording was higher in the nfvPPA group than in healthy controls ($p=0.002$). No other differences between groups were identified for mean heart rate. Overall heart rate variability during the recording did not differ between participant groups ($p=0.33$).

Mean continuous heart rate time courses for participant groups are shown in Figure 5.1. These demonstrate a biphasic cardiac deceleration with an initial orienting response followed by a

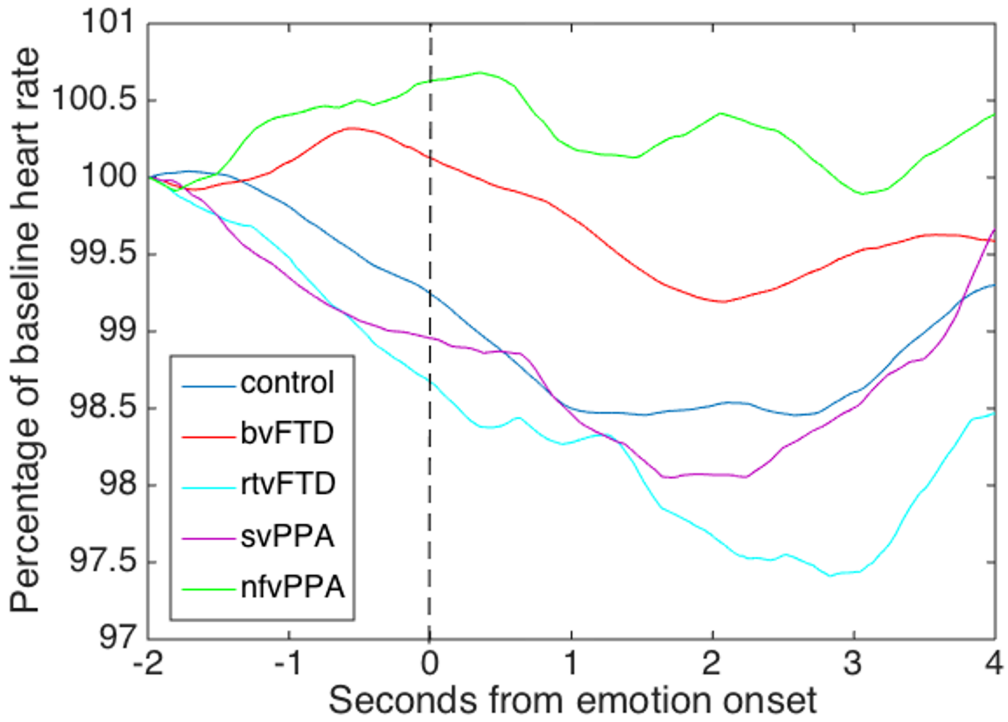
second phase of deceleration related to viewed emotional expression onset in the healthy control, rtvFTD and svPPA groups; both cardiac response phases appear attenuated in the bvFTD and nfvPPA groups relative to controls.

Table 5.1. Demographic, clinical and neuropsychological characteristics of participant groups

Characteristic	Healthy controls	bvFTD	rtvFTD	svPPA	nfvPPA
Demographic and clinical					
No. (m:f)	19(8:11)	10(7:3)	6(6:0)	7(5:2)	9(4:5)
Age (yrs)	68.8(5.5)	67(6.3)	63.8(9.1)	65.9(7.5)	69.6(6.5)
Handedness (R:L)	18:1	9:1:0	6:0:0	7:0:0	7:2:0
Education (yrs)	15.5(2.9)	12.8(2.5)[c]	18(3.1)	15.3(2.8)	15(2.7)
MMSE (/30)	29.6(0.6)	24.1(4.9)[a]	25.3(4.3)	22.6(5.8)[a]	23.7(6.0)[a]
Duration (yrs)	-	8.2(5.3)	6.5(3.5)	4.4(2.1)	4.6(2.2)
Mean heart rate	69.5(10.2)	72.9 (14.2)	71.8(11.8)	69.7(5.2)	85.5(17.1)[a]
Heart rate variance	0.23(0.7)	0.21(0.6)	0.05(0.07)	0.08(0.08)	0.03(0.04)
Cardiac reactivity index	1.67(1.5)	0.54(0.4)[a,c]	2.42(1.4)	1.61(1.6)	0.12(1.1)[a,c]
Emotion recognition (%)	70.5(9.2)	41.4(18.9)[a]	40.0(19.4)[a]	40.2(16.1)[a]	53.8(18.5)[a]
Neuropsychological					
General intellect					
WASI verbal IQ	125.4(7.0)	86.2(23.7)[a]	86.7(22.2)[a]	78.6(20.4)[a]	79.6(17.3)[a]
WASI performance IQ	125.1(9.7)	99.8(20.2)[a]	106.8(24.6)	112.3(10.1)	98.8(21.5)[a]
Episodic memory					
RMT words (/50)	44.7(3.7)	33.5(7.9)[a]	34.8(7.9)[a]	32.7(6.4)[a]	39.5(6.6)
RMT faces (/50)	49.3(0.9)	35.6(7.5)[a]	37.2(9.3)[a]	30.3(6.9)[a,e]	41.4(9.5)[a]
Camden PAL (/24)	20.3(3.5)	9.3(8.2)[a]	12.5(6.2)	2.7(4.2)[a,c,e]	16.3(7.8)
Executive skills					
WASI Block Design (/71)	46.0(10.1)	29.9(17.9)	37.2(22.1)	41.6(19.0)	25.1(19.7)[a]
WASI Matrices (/32)	26.6(4.1)	17.1(9.6)[a]	19.0(9.8)	21.7(8.5)	17.4(9.0)[a]
WMS-R digit span forward	7.1(1.2)	6.4(1.3)	6.8(1.2)	7.0(1.2)	4.8(0.8)[a,c,d]
WMS-R digit span reverse	5.6(1.3)	4.2(1.5)	4.7(1.4)	5.1(2.0)	3.0(0.7)[a]
D-KEFS Stroop color naming (s)	32.4(6.4)[e]	49.9(21.7)[e]	48.8(21.4)[e]	50.3(27.9)[e]	87.0(6.7)
D-KEFS Stroop word reading (s)	23.5(5.7)[e]	34.3(20.9)[e]	38.7(26.1)[e]	30.9(19.2)[e]	85.4(10.3)
D-KEFS Stroop interference (s)	56.2(16.9)[b,e]	106.2(50.7)[e]	98.3(45.1)[e]	82.7(50.5)[e]	165.0(30.1)
Letter fluency (F: total)	18.1(5.7)	6.8(4.3)[a]	9.0(4.7)[a]	9.7(7.2)[a]	3.5(1.7)[a]
Category fluency (animals: total)	24.7(5.9)	12.4(7.7)[a]	10.3(2.3)[a]	6.7(5.4)[a]	8.8(3.5)[a]
Trails A (s)	32.2(5.6)[e]	59.3(35.5)	59.8(32.9)	47.0(21.0)	81.7(48.4)
Trails B (s)	66.1(20.5)[b,c,e]	182.5(87.2)	186.7(100.4)	133.6(110.1)	211.1(94.6)
Language skills					
WASI vocabulary (/80)	72.2(3.4)	39.9(23.8)[a]	47.0(19.1)[a]	34.7(22.7)[a]	31.7(13.9)[a]
BPVS (/150)	148.5(1.1)	112.9(41.3)[a]	141.8(7.2)	94.4(49.4)[a,c,e]	142.6(10.1)
GNT (/30)	26.3(2.4)	9.4(9.9)[a]	12.5(10.1)[a]	2.0(5.3)[a,c,e]	15.5(6.6)[a]
Other skills					
GDA (/24)	15.8(5.4)	7.9(5.7)[a]	7.5(6.3)[a]	11.3(8.3)	5.4(1.9)[a]
VOSP Object Decision (/20)	19.1(1.6)	15.0(3.3)[a]	16.7(2.3)	15.7(5.1)	15.3(4.7)

Mean (standard deviation) scores are shown unless otherwise indicated; maximum scores are shown after tests (in parentheses). [a]different from controls, [b]different from bvFTD, [c]different from rtvFTD, [d]different from svPPA, [e]different from nfvPPA (all at significance threshold $p<0.05$). See Table 2.3 for details of neuropsychological tests and references.

Figure 5.1. Mean continuous heart rate response profiles of participant groups.

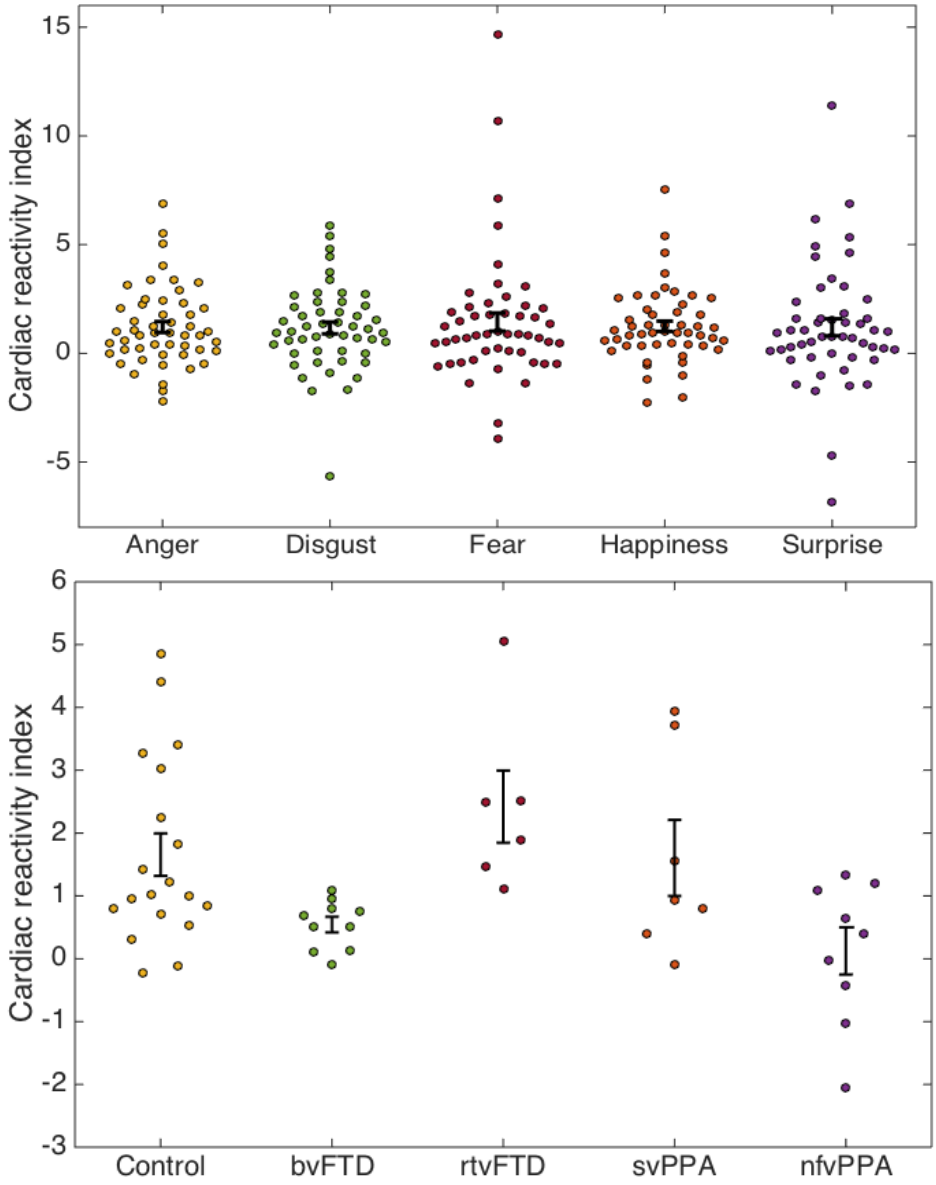


Time courses of change in heart rate from baseline are here shown averaged across all trials and participants for each participant group (see text for details of procedure). The vertical dotted line (time 0) indicates onset of the emotional expression within the stimulus.

Cardiac reactivity indices for all participants are shown for each emotion and the average over all emotions for each participant group in Figure 5.2. For the combined participant cohort, an increase in RR interval (cardiac deceleration) was found in response to viewing every emotion (all $p<0.001$). An ANOVA of cardiac reactivity incorporating all emotions showed a main effect of participant group ($p<0.001$) but not emotion type ($p=0.78$), nor any interaction of participant group and emotion type ($p=0.58$). When considering the control participants alone, there was no effect of emotion type on cardiac reactivity ($p=0.93$). There was a main effect of participant group on cardiac reactivity averaged over all emotions (Kruskal-Wallis rank test $chi^2_{(4)}=15.4$, $p=0.004$). Post hoc tests revealed attenuated heart rate responses relative to healthy controls in the bvFTD group ($p=0.018$) and nfvPPA group ($p=0.027$) but not the rtvFTD group ($p=0.21$) or svPPA group ($p=0.93$). Comparing patient groups, heart rate reactivity was reduced in the bvFTD group ($p<0.001$) and nfvPPA group ($p=0.002$) relative to the rtvFTD

group; no other differences were identified between patient groups for overall emotion reactivity or reactivity to particular emotions. There was no effect of mean heart rate on cardiac reactivity (R^2=0.02, p=0.317) and the main effect of participant group on cardiac reactivity persisted after covarying for mean heart rate (F_4=3.9, p=0.008). There were no correlations between emotion identification performance and heart rate reactivity in any participant group (all p>0.05). Considering the FTD syndromes as a single patient group, cardiac reactivity was significantly less for the patients than for healthy controls (p=0.028). There was no relationship between cardiac reactivity and measures of intelligence (WASI matrices score; p=0.34), executive function (trails-making test performance; p=0.34) or attention and working memory (digit span; p=0.43).

Figure 5.2. Cardiac reactivity indices by emotion and participant group.



Plots show individual participants' mean cardiac reactivity index (mean percentage change in RR interval, see text) to viewing each of the assessed universal facial emotions (left) and mean overall cardiac reactivity index across viewed emotions, separately for each participant group (right; note change of scale on y-axis). Error bars represent standard error of the mean.

VOXEL-BASED MORPHOMETRIC DATA

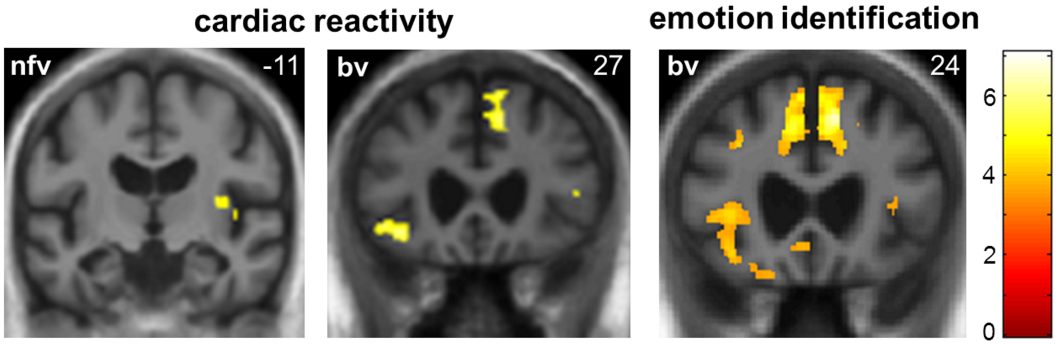
Neuroanatomical associations of heart rate reactivity and emotion identification are summarised in Table 5.2 and statistical parametric maps of the relevant contrasts are presented in Figure 5.3. In the bvFTD group, both reduced heart rate reactivity to viewing facial emotion and reduced emotion identification score were associated with grey matter loss in right dorsal anterior cingulate cortex and left orbitofrontal cortex. Emotion identification in the bvFTD group was additionally associated with grey matter loss in left anterior cingulate cortex and bilateral anterior insula. In the nfvPPA group, reduced heart rate reactivity was associated with grey matter loss in posterior right insula. No grey matter associations of emotion identification were identified in the nfvPPA group at the prescribed threshold. All local maxima were significant at $p<0.05_{FWE}$ after correction for multiple voxel-wise comparisons over the whole brain or within the prespecified anatomical region of interest.

Table 5.2. Neuroanatomical associations of emotion reactivity and identification in patients

Parameter	Group	Region	Side	Cluster (voxels)	Peak (mm) x	y	z	P_{FWE}
Cardiac reactivity	bvFTD	Dorsal ACC	R	1040	8	33	33	0.007
		OFC	L	247	-36	27	-12	0.021
	nfvPPA	Posterior insula	R	38	36	-10	9	0.044
Emotion identification	bvFTD	Dorsal ACC	R	2208	8	28	45	0.019*
		OFC	L	875	-33	28	0	0.021
		ACC	L	2428	-6	45	14	0.016*
		Anterior insula	L	44	-36	-4	15	0.006
		Anterior insula	R	32	40	15	0	0.043

The Table presents grey matter correlates of mean overall cardiac reactivity index (mean percentage change in RR interval, see text) in the bvFTD and nfvPPA groups and emotion identification score in the bvFTD group. Peak coordinates given are in mm in standard MNI space. are all corrected; *indicates P value significant after family-wise error (FWE) correction for multiple voxel-wise comparisons over whole brain; other P values significant after FWE correction for multiple comparisons within prespecified anatomical regions of interest.

Figure 5.3. Neuroanatomical correlates of heart rate response to viewing facial emotion and emotion identification in patients.



Statistical parametric maps of regional grey matter volume associated with change in RR interval and performance on a facial emotion identification task (derived from a voxel-based morphometric analysis) are shown for patients with behavioural variant frontotemporal dementia (bv) and nonfluent variant primary progressive aphasia (nfv; these syndromic groups showed an attenuated heart rate response relative to healthy controls). Maps have been overlaid on representative coronal sections of the normalised study-specific T1-weighted group mean brain MR image, thresholded at $p<0.001$ uncorrected over the whole brain for the purpose of display; regional local maxima (see text) were significant at $p<0.05_{FWE}$ corrected for multiple comparisons within pre-specified anatomical regions of interest. The MNI coordinate (mm) of the plane of each section is indicated (the right hemisphere is on the right in each case) and the colour bar codes T values.

DISCUSSION

Here I have shown differential impairment of cardiac reactivity to facial emotion across the FTD syndromic spectrum. Cardiac responses to emotional facial expressions, incorporating both orienting and affective components, were attenuated in patients with bvFTD and nfvPPA relative both to healthy older individuals and to patients with rtvFTD. Patients with svPPA and rtvFTD showed preserved heart rate responses when viewing facial emotions. Across the participant cohort, the degree of heart rate modulation did not correlate with accuracy identifying facial emotions, which was impaired in all syndromic groups. In line with current models of visceral responses to emotion, this work has identified a physiological correlate of reduced emotional responsiveness in bvFTD and nfvPPA, which dissociates from the more widely studied ability to cognitively categorise emotions. My findings further suggest that FTD

syndromes are stratified according to the profile of altered autonomic reactivity they exhibit. The findings are consistent with previous work showing reduced autonomic reactivity in bvFTD and nfvPPA (Eckart *et al.*, 2012; Fletcher *et al.*, 2015c) and preserved autonomic reactivity in svPPA (Fletcher *et al.*, 2016). The present work goes further in demonstrating a physiological basis for differentiating sub-syndromes within the canonical diagnostic grouping of bvFTD: although a distinct syndrome of rtvFTD has been proposed on neuroanatomical and clinical grounds (Chan *et al.*, 2009; Ranasinghe *et al.*, 2016), these are to a degree arbitrary given the extensive clinico-anatomical overlap between patients and without mechanistic grounding. Although classification can be attempted on structural imaging, as I have done here, structural MRI does not readily allow for precise categorisation of bvFTD subtypes on a single subject basis, and reliable clinical and neuropsychological markers of subsyndromes do not exist. Autonomic profiling might establish a principled neurobiological rationale for subclassifying bvFTD, which has long presented nosological difficulties on account of its marked phenotypic and pathological heterogeneity.

Profiles of cardiac reactivity were homogeneous across emotions and did not correlate with explicit emotion identification in the FTD cohort, consistent with the idea that autonomic mechanisms govern emotional arousal and intensity (rather than the cognitive categorisation of emotions). This interpretation is supported by work in the healthy brain (Wiens *et al.*, 2000; Alpers *et al.*, 2011). The subjective experience of emotion is likely to be integral to the internalisation of observed emotional states in others during emotional contagion. My findings therefore provide a candidate neurobiological mechanism for the blunted emotional reactions and loss of empathy that characterise FTD syndromes (Rosen *et al.*, 2004; Rankin *et al.*, 2005; Kumfor and Piguet, 2012; Couto *et al.*, 2013) and amplify previous work linking altered cardiac vagal tone to reduced agreeableness in bvFTD (Guo *et al.*, 2016). Impaired awareness of heartbeat in FTD has also previously been shown, including in chapter 3 here (García-Cordero *et al.*, 2016): taken together with the present findings, this suggests that both induction and

decoding of embodied emotional responses contribute to emotional contagion and may be separably targeted in FTD syndromes.

This work additionally delineates a neuroanatomical substrate for the differentiated profiles of physiological reactivity and explicit emotion identification in these syndromes. Grey matter associations of heart rate modulation in the bvFTD and nfvPPA groups comprised a predominantly right-lateralised fronto-cingulo-insular 'salience' network previously implicated in autonomic regulation in functional neuroimaging studies of healthy individuals (Critchley, 2005; Thayer and Lane, 2009) and patients with bvFTD (Guo *et al.*, 2016). The components of this network are likely to play hierarchically organised roles in autonomic control, based on predictive integration of internal homeostatic and external affective signals (Seth and Friston, 2016): according to this interoceptive inference formulation, the regulatory network compares incoming afferent information with predicted autonomic states and engages subcortical, modulatory autonomic reflexes in response to prediction errors (unexpected events) (Seth and Friston, 2016). Posterior insula is the seat of primary interoceptive cortex (Craig, 2009): noisy processing of cardiac along with other visceral afferent information in this region (as in the nfvPPA group here) would tend to reduce interoceptive sensory precision and therefore lead to reduced prediction errors in response to salient stimuli, and hence a failure to engage autonomic modulatory networks during emotion processing. This attenuation of autonomic arousal is likely to result in impaired empathy as a consequence of reduced motivational responses to the emotions of others. Higher stages of the processing hierarchy in ACC and OFC are likely to mediate top-down control of visceral states by integrating autonomic and cognitive state representations (Critchley *et al.*, 2011; Seth and Friston, 2016); shared neuroanatomical resources for cardiac reactivity and emotion identification in ACC and OFC (as illustrated by the bvFTD group here) would support such integration, as proposed in previous studies of the healthy brain and bvFTD (Critchley, 2009; Gray *et al.*, 2012; Sturm *et al.*, 2013a). It is also noteworthy that additional grey matter correlates of emotion identification were

demonstrated in the bvFTD group (Table 5.2), suggesting a neuroanatomical substrate for dissociation of autonomic and cognitive processing over the FTD cohort.

These findings open a window on the pathophysiology of a complex neurodegenerative phenotype. It is of interest that this study employed dynamic emotional stimuli: whether in the domain of vision or sound (Fletcher *et al.*, 2015d; Fletcher *et al.*, 2016), stimuli that unfold in time more closely reflect the natural socio-emotional milieu and may be more adequate for eliciting autonomic responses than the static stimuli that are currently widely used in clinical behavioural experiments. From a clinical perspective, the autonomic profiles reported here constitute simple, quantitative and readily translatable indices of a behavioural hallmark of FTD (altered emotional responsiveness) that is largely inaccessible to conventional neuropsychological instruments. Indeed, in this study autonomic metrics proved superior to an emotion identification task in differentiating FTD syndromes. Autonomic indices of this kind warrant further evaluation as disease biomarkers in FTD, particularly with a view to stratifying heterogeneous and poorly demarcated syndromes such as bvFTD and the eventual creation of physiologically informed diagnostic criteria. This will be of considerable practical importance if we are to track disease evolution and the effect of disease modifying therapies dynamically. More immediately, the impaired emotional awareness of patients with FTD is a major determinant of caregiver distress (Hsieh *et al.*, 2013): improved understanding of this symptom would assist counselling and the design of nonpharmacological as well as pharmacological interventions.

This experiment has several important limitations. The small sample sizes, especially in the rtvFTD group mean that the results should be interpreted with caution. The absence of an affectively neutral control condition makes it impossible to specifically associate the findings with a response to emotion, and it is possible that the cardiac reactivity findings are simply indexing a more general orienting response to salience. Whilst I have highlighted the potential for cardiac reactivity to stratify clinicoanatomical syndromes, this assertion is obviously limited

by the fact that the groups were determined *a priori* based on clinico-anatomical features. Further work with larger sample size might allow a transdiagnostic analysis and cluster analysis of the patient group based on autonomic, anatomical and neuropsychological features.

6: DISSOCIATING COMPONENTS OF DYNAMIC FACIAL EMOTION PROCESSING: BEHAVIOUR, HEART RATE, PUPILLOMETRY AND FUNCTIONAL NEUROANATOMY

CHAPTER SUMMARY

Impairments in the recognition of and response to social signals are key features of FTD syndromes, and major determinants of care burden and morbidity. However, the functional neuroanatomy of emotion processing across the FTD spectrum has not been elucidated, and neither have the separable components of sensory processing, emotional evaluation and affective autonomic responses. In this experiment, I performed activation fMRI in 38 patients with FTD and 22 healthy older controls, with concurrent cardiac monitoring and pupillometry while the participants viewed videos of dynamic naturalistic facial emotions. Primary visual cortex responses to stimuli were consistent across the participant groups, but activity in regions selective for faces and biological motion (fusiform gyrus, MT/V5, posterior STS and TPJ) was attenuated differentially across the FTD spectrum. Impaired categorisation of facial emotions was associated with syndrome-specific patterns of reduced activity in regions associated with motoric representations (frontal operculum), emotional evaluation (ACC and anterior insula) and social concepts (anteromedial right temporal lobe). Heart rate responses were found to be attenuated in all FTD syndromes, while pupil responses were impaired in svPPA and nfvPPA. Functional anatomical associations of these autonomic responses delineated separate sympathetic and parasympathetic central autonomic control networks, as well as associations with the processing of the sensory properties of the stimuli. These findings open a new window onto the cerebral mechanisms underpinning complex socioemotional

symptoms in FTD, and point towards possible future disease biomarkers based on central and peripheral physiology.

INTRODUCTION

In health, the processing of emotion from social signals is performed by distributed hierarchical networks for sensory processing, motoric representations, affective autonomic arousal, and higher evaluative responses (Kilner *et al.*, 2007; Alcalá-López *et al.*, 2017; Ondobaka *et al.*, 2017). Previous work in FTD, and my results from experiments in Chapters 4 and 5 suggest that these dimensions of social emotion processing may be differentially affected by the focal patterns of network degeneration in the syndromes of FTD. However, the functional neuroanatomy of these changes has not yet been defined.

Using VBM, facial emotion recognition deficits in FTD have been correlated with atrophy of amygdala, orbitofrontal cortex, insula, anterior cingulate, anteromedial temporal lobe, fusiform gyrus and frontal operculum (Rosen *et al.*, 2002b; Omar *et al.*, 2011; Rohrer *et al.*, 2012b; Couto *et al.*, 2013; Hazelton *et al.*, 2016). In the previous work in this thesis, the dynamic stimuli employed revealed additional correlates related to sensory processing (MT/V5), motoric representation (SMA) and the posterior STS 'hub' region, as well as showing overlapping correlates of autonomic arousal and emotion evaluation. Taken together, these findings in FTD largely delineate the four levels of network associated with social emotion processing in health: 1) a "visual-sensory" network of face and biological motion responsive areas (fusiform gyrus, MT/V5 and posterior STS); 2) a "limbic" network (ventromedial prefrontal, ACC, amygdala, hippocampus); 3) an "intermediate" network (anterior insula, midcingulate, operculum, SMA, posterior STS); and 4) a "higher-level" network (frontal pole, temporal pole, dorsomedial prefrontal, posterior cingulate, TPJ and MTG) (Alcalá-López *et al.*, 2017). Autonomic reactivity during the viewing of facial emotions in health has been related to activity both in areas associated with the sensory processing of stimulus properties (including

fusiform, lingual gyrus and superior temporal cortex), and in components of the central autonomic control network (including ACC and insula) (Critchley *et al.*, 2005).

Whilst structural anatomical findings in FTD are largely concordant with previous functional anatomical work in the healthy brain, VBM is a relatively blunt instrument. It remains difficult to disentangle true anatomical associations from syndromic atrophy profiles with VBM, and it is not possible to define altered activity or connectivity in regions without grey matter volume change. Functional neuroimaging is therefore necessary to truly detect functional and network level changes in brain activity, to separate the various components of emotion processing, and to detect alterations in activity outside regional atrophy profiles that might contribute to complex socioemotional changes in FTD.

Two previous fMRI studies of facial emotion processing in bvFTD have revealed reduced activity in posterior face responsive regions outside canonical disease foci, and hypothesised that this is due to disrupted top-down influences from frontal and limbic regions (Virani *et al.*, 2013; De Winter *et al.*, 2016). However, the relative contributions of dysfunction within the four networks described earlier have not been effectively parsed, and the divergent patterns of altered brain function responsible for convergent socioemotional symptoms across the FTD spectrum have not yet been elucidated. Moreover, despite mounting evidence for abnormalities in autonomic responses to emotion, the functional neuroanatomy of altered autonomic responses to affective stimuli has not previously been studied in any of the FTD syndromes.

The aim of this experiment was therefore to study the functional neuroanatomy of emotion processing from facial expressions across the FTD spectrum, with the additional inclusion of emotion recognition performance and autonomic reactivity to allow the delineation of the neural responses associated with changes in sensory processing, cognitive categorisation of emotion and affective autonomic arousal. I performed activation fMRI with concurrent cardiac

monitoring and pupillometry in age-matched healthy controls and subjects with all canonical FTD syndromes during the viewing of dynamic naturalistic emotional facial expressions. I hypothesised that sensory processing of dynamic facial emotions would be associated with activity in face and biological motion responsive areas including fusiform gyrus, MT/V5 and posterior STS, and that activity in these areas outside the core atrophy profiles of FTD syndromes would be attenuated due to aberrant top-down influences, despite normal activation of primary visual cortex. I further hypothesised that all FTD syndromes would be associated with impaired emotion identification in association with syndrome-specific functional neural correlates in brain regions previously associated with emotion evaluation and categorisation, while impairments in pupil response in all FTD syndromes and cardiac responses in bvFTD and nfvPPA would be associated both with activity in regions responsible for sensory processing of stimulus properties and components of the central autonomic control network, as has previously been shown in the healthy brain (Critchley *et al.*, 2005).

METHODS

PARTICIPANTS

60 participants were included in this experiment, including 17 with bvFTD, 12 with svPPA, 9 with nfvPPA and 22 healthy controls. There were too few subjects with focal right temporal lobe atrophy to constitute a separate rtvFTD group. Participant groups did not differ significantly in terms of age or gender, and patient groups had similar symptom durations.

Detailed demographic and neuropsychological characteristics of the participant groups are shown in Table 6.1.

Table 6.1. Clinical and neuropsychological characteristics of participant groups

Characteristic	Controls	bvFTD	svPPA	nfvPPA
Demographic and clinical				
No (m:f)	10:12	13:4	8:4	4:5
Age (yrs)	68.6(6.8)	64.8(6.8)	66.9(7.0)	67.4(8.1)
Handedness (R:L:A)	22:0	15:1	12:0	8:0
MMSE (/30)	29.8(0.4)	23.7(4.8)[a]	23.8(7.4)[a]	16.9(10.9)[a,b,c]
Duration (yrs)	N/A	7.2(6.3)	6.0(2.6)	3.8(1.7)
Neuropsychological				
General intellect				
WASI verbal IQ	122(8.6)	92(31.5)[a]	74(20.1)[a]	69(17.7)[a]
WASI performance IQ	124(12.9)	96(18.3)[a,c]	119(15.4)	94(20.8)[a,c]
Episodic memory				
RMT words (/50)	48.9(1.4)	37.6(10.2)[a]	33.8(7.3)[a]	39.2(10.8)[a]
RMT faces (/50)	44.8(4.7)	37.3(7.0)[a]	32.1(5.0)[a]	39.0(7.9)
Camden PAL (/24)	20.6(2.8)	13.7(6.1)[a]	6.5(8.0)[a,b,d]	16.5(2.1)
Executive skills				
WASI Block Design (/71)	46.8(11.0)	26.9(15.1)[a]	38.5(15.6)	20.5(20.5)[a]
WASI Matrices (/32)	25.5(4.4)	16.7(8.7)[a,c]	26.6(3.5)	15.4(10.2)[a,c]
WMS-R digit span forward (max)	7.1(1.1)	5.7(1.1)[a]	6.6(0.9)	4.3(1.4)[a,c]
WMS-R digit span reverse (max)	5.4(1.3)	4.6(1.4)	5.3(1.3)	3.2(0.8)[a,c]
D-KEFS Stroop colour naming (s)	29.6(4.8)	45.3(19.5)[a]	37.8(8.9)	70.0(18.7)[a,b,c]
D-KEFS Stroop word reading (s)	22.3(3.4)	28.2(7.5)	25.6(10.7)	61.4(16.2)[a,b,c]
D-KEFS Stroop interference (s)	55.9(16.7)	101.1(52.6)[a]	67.3(19.0)	123.3(44.3)[a,c]
Letter fluency (F: total)	17.4(5.0)	9.0(5.6)[a]	9.6(3.8)[a]	5.8(3.3)[a]
Category fluency (animals: total)	23.7(4.2)	13.0(8.0)[a]	6.5(4.5)[a,b]	12.6(4.7)[a]
Trails A (s)	31.9(9.3)	58.1(36.3)[a]	46.7(16.1)	65.3(45.4)[a]
Trails B (s)	66.3(28.6)	143.7(81.6)[a]	130.5(18.8)[a]	160.1(89.7)[a]
Language skills				
WASI vocabulary	70.3(3.4)	40.9(24.8)[a]	30.6(18.9)[a]	21.8(21.3)[a]
BPVS	148.0(1.4)	126.2(30.6)[a]	74.8(37.1)[a,b]	106.4(52.8)[a]
GNT	26.9(2.3)	16.7(10.2)[a]	2.0(5.6)[a,b]	9.0(7.3)[a]
Posterior cortical skills				
GDA (/24)	14.1(5.4)	9.3(6.1)	12.8(5.0)	4.8(5.1)[a]
VOSP Object Decision (/20)	18.9(1.1)	15.7(3.4)[a]	15.9(2.0)[a]	15.5(3.9)[a]

Mean (standard deviation) scores are shown unless otherwise indicated; maximum scores are shown after tests (in parentheses). [a]significantly less than controls, [b]significantly less than bvFTD, [c]significantly less than svPPA, [d]significantly less than nfvPPA, (all $p<0.05$). See Table 2.3 for details of neuropsychological tests and references.

STIMULI

Visual stimuli for this experiment comprised 50 silent videos from the FG-NET database, as described in previous chapters (Wallhoff, 2006-2015). In addition, I created 20 dynamic mosaics from these videos by dividing each video frame into 400 rectangles, and then randomizing the position of the rectangles within each video (the positions then remained consistent across all frames for a given stimulus). These dynamic mosaics were thus matched with the original videos in terms of luminance, contrast, motion, and duration, but without discernible face or emotional content, i.e. the same physical information was present, but the global configuration was radically altered.

STIMULUS PRESENTATION

During fMRI scanning, stimuli were presented in a pseudorandomised block design via a notebook computer using the Eyelink Experiment Builder software package. Each stimulus trial was triggered by the MR scanner at the onset of an EPI volume acquisition in a continuous acquisition protocol. Visual stimuli were presented on a screen placed outside the bore of the MRI scanner, visible to participants in a mirror affixed to the head coil. 90 total trials were used, comprising 50 dynamic facial stimuli, 20 dynamic scrambled visual mosaics and 20 fixation cross trials. Participants were instructed to lie still and concentrate on the stimuli with their eyes open. No responses from the participant were obtained during scanning, as response procedures in the scanner are highly unreliable in patients with behavioural and linguistic impairments.

PULSE OXIMETRY RECORDING AND ANALYSIS

Pulse oximetry was recorded continuously from the left index finger during scanning using a Siemens Physiological Monitoring Unit MRI-compatible Bluetooth pulse oximeter. Raw oximetry data were then analysed in MATLAB using a custom script to identify local maxima corresponding to pulse peaks in the waveform. All data were then manually inspected to

ensure consistency and accuracy of pulse detection. Subjects with arrhythmias or insufficient data quality were excluded from subsequent heart rate analyses (3 controls, 4 bvFTD, 2 svPPA and 1 nfvPPA).

For each subject, a continuous smoothed heart rate trace was generated by converting each data point to the heart rate corresponding to the interbeat interval in which it lay, and then smoothing with a 1 second sliding filter. A heart rate reactivity trace was then generated for each trial by normalising to the baseline heart rate for that trial, so that all values represented percentage heart rate change from trial baseline. Visualisation of the mean trial heart rate trace for controls showed that there was a consistent cardiac deceleration, with a nadir at around 3s from stimulus onset (see Figure 6.2). The cardiac reactivity measure for each trial was therefore defined as the percentage heart rate change from baseline at 3 seconds (due to the smoothing this was equivalent to the mean heart rate change from baseline during the period 2.5s-3.5s from stimulus onset). This heart rate reactivity measure was analysed as the dependent variable in an ANOVA, incorporating stimulus type and diagnostic group as fixed factors. Post hoc tests were performed when main effects were found.

PUPILLOMETRY RECORDING AND ANALYSIS

Pupil size from the right eye was recorded throughout the scanning session using an MRI compatible Eyelink 1000 Plus eyetracker (http://www.sr-research.com/eyelink1000plus.html). A long-range mount positioned within the bore of the scanner captured the eye in the head coil mounted mirror. Pupillometry was then analysed offline using the SR Research Data Viewer software.

Pupil reactivity was calculated for each trial as follows:

max pupil during 5s post stimulus onset/mean pupil during 1s prior to stimulus

Trials with pupil reactivity values more than two standard deviations above the mean for the experiment were excluded to remove large artefacts. Trials with insufficient pupil capture for analysis were also excluded.

Pupil reactivity was then analysed for facial emotions and scrambled videos, but not for fixation cross trials, as the large difference in luminance between the video conditions and fixation cross conditions made them unsuitable for direct comparison. I performed ANOVAs to assess main effects on pupil size change of participant group, stimulus type and the interaction between the two. Post hoc tests were performed when significant main effects were found.

POST-SCAN BEHAVIOURAL TESTING

Following the scanning session, each subject was again shown the 50 facial emotions, presented in the Eyelink Experiment Builder software package on a notebook computer. After each video, they were asked to identify the emotion from a list of the five canonical emotions used in the experiment, using the response procedures outlined in Chapter 2. Responses were recorded for offline analysis. No time limits were imposed on responses, and no feedback was given during the task.

FUNCTIONAL MRI ACQUISITION

Functional MRI was acquired on a Siemens Prisma 3T MRI scanner with a 12-channel RF head coil. A continuous acquisition EPI sequence was used comprising 48 oblique axial slices. The angle of acquisition was set at -30° from the intercomissural plane to minimise T2* signal dropout in orbitofrontal cortex and anterior temporal lobe due to the proximity of these regions to the skull base. Interleaved slices of 2mm thickness were obtained in descending order with voxel size 2mm X 2mm X 2mm, FOV, 192mm, TR/TE 2930ms/30ms. An initial volume was obtained to allow equilibration of longitudinal T1 magnetisation, and discarded from subsequent analysis. 550 EPI volumes were obtained for analysis, with a total scanning

time of 27 minutes. Following acquisition of the EPI sequence, a B0 field map was acquired to allow for geometric correction of EPI data for field inhomogeneity distortions (FOV 192mm, slice thickness 3mm interleaved, voxel size 2.4mm X 2.4mm X 3mm, TR 688ms, TE1 4.92ms, TE2 76.38ms).

To enable structural co-registration, volumetric brain MR images were acquired for all patients in the same 3T Siemens Magnetom Prisma MRI scanner, using a 64-channel head-and-neck receiver array coil and a T1-weighted sagittal 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (TE = 2.93ms, TI = 850ms, TR = 2000ms), with matrix size 256x256x208 and voxel dimensions 1.1x1.1x1.1mm. Parallel imaging was used (GRAPPA with acceleration factor 2), resulting in an overall scan time of 5min 6s.

Functional MRI preprocessing and analysis

Functional MRI data were processed using SPM12 software (www.fil.ion.ucl.ac.uk/spm) in Matlab R2014b. The EPI series for each participant was realigned to the first image, and then unwarped with the incorporation of B0 field map distortion information to correct for field inhomogeneity. The T1 volumetric image for each subject was then registered to their EPI images before segmenting the T1 image into grey matter, white matter and CSF using the New Segment toolbox of SPM. The forward deformations from the segmentation step were then used to normalize the EPI images into MNI space before smoothing the normalized unwarped EPI images with a 6mm full width at half maximum Gaussian kernel. Each registration and normalization step was manually visualized for quality control, and in those subjects with inadequate registration and normalization, preprocessing was repeated with an additional skull-stripping step prior to registration.

Preprocessed EPI images were then entered into a first-level analysis for each subject incorporating the experimental conditions as separate covariates, as well as six head motion covariates (X, Y, Z translation, pitch, roll and yaw). Threshold masking at first level was changed

from the default parameter to 0.1, to ensure that regions showing atrophy in some subjects were not entirely excluded in the second-level analyses, where a majority threshold mask was applied. T contrasts were then generated for the first level analyses for facial emotion> fixation cross and for facial emotion> scrambled video.

At second-level, T contrasts from the first-level analysis were entered into a full factorial model incorporating all subjects, with diagnostic group as a covariate. Masking was performed with a study-specific majority threshold mask. The effects of experimental conditions were modelled by assessing T contrasts for effect of condition across all subjects, and F contrasts to detect group differences. Where main effects of participant group were found in the F contrast, I assessed group differences by generating beta plots incorporating all voxels in the relevant cluster. Beta plots for primary visual cortex were also generated to examine whether there were any between-group differences in primary afferent processing.

To establish the neural basis for differences in emotion identification ability and autonomic responses, I added emotion recognition score or mean physiological response parameter for each subject as a covariate at second-level, assessing T contrasts within each diagnostic group separately to establish haemodynamic responses that explained variance in these parameters within each disease group. For cardiac responses, I assessed both negative (parasympathetic) and positive (sympathetic) correlations.

For all fMRI analyses, results are reported at cluster-level $p_{FWE}<0.05$ over the whole brain with a cluster-defining threshold of $p<0.005$ uncorrected, or at peak-level $p_{FWE}>0.05$ within prespecified regions of interest. The cluster defining threshold was selected according to evidence that it provides the optimal balance between the risks of Type I and Type II errors (Lieberman and Cunningham, 2009). The regions of interest were defined separately for each analysis based on previous evidence in FTD and the healthy brain: fusiform face area, MT/V5 and posterior STS for the sensory processing of dynamic facial expressions; fusiform gyrus,

ACC, insula, operculum and anteromedial temporal lobe for the identification of facial emotions; fusiform gyrus, anteromedial temporal lobe, ACC and insula for autonomic responses (Critchley *et al.*, 2005; Fletcher *et al.*, 2016; Alcalá-López *et al.*, 2017).

A study-specific mean brain image was generated from the 60 participants' normalised T1 MR images, and this was used to display SPM results.

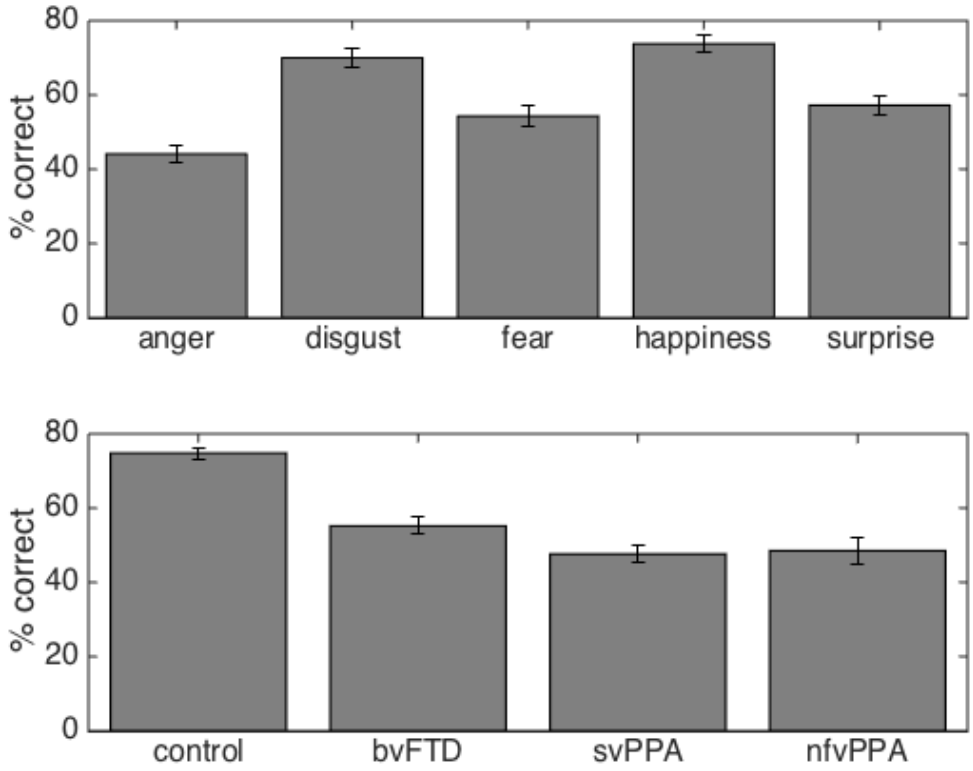
RESULTS

EMOTION RECOGNITION FROM FACES

Data for scores in the out of scanner emotion identification task are presented in Figure 6.1 by emotion type and participant group.

ANOVA of emotion recognition scores revealed main effects of participant group (F_3=49.9, p<0.001) and emotion type (F_4=26.0, p<0.001), but no interaction between the two (F_{12}=1.55, p=0.10). Post hoc tests with Bonferroni correction demonstrated impaired emotion recognition in all disease groups relative to controls (all p<0.001) and in svPPA relative to bvFTD (p=0.038). Across all participants, recognition scores were higher for disgust and happiness than for the other three emotions (all Bonferroni corrected pairwise comparisons p<0.001). Additionally, scores for anger recognition were lower than those for fear (p=0.046) and surprise (p=0.012). As there was no interaction of emotion and group membership, I did not explore further for emotion-specific deficits within participant groups. Overall emotion identification ability correlated significantly with attention and working memory (digit span; p=0.002), executive function (trails-making; p<0.001), intelligence (WASI matrices; p=0.001) and semantic performance (BPVS;p<0.001).

Figure 6.1 Emotion identification scores



The figure shows percentage of emotional stimuli correctly identified by emotion (top) and subject group (bottom). Error bars represent the standard error of the mean.

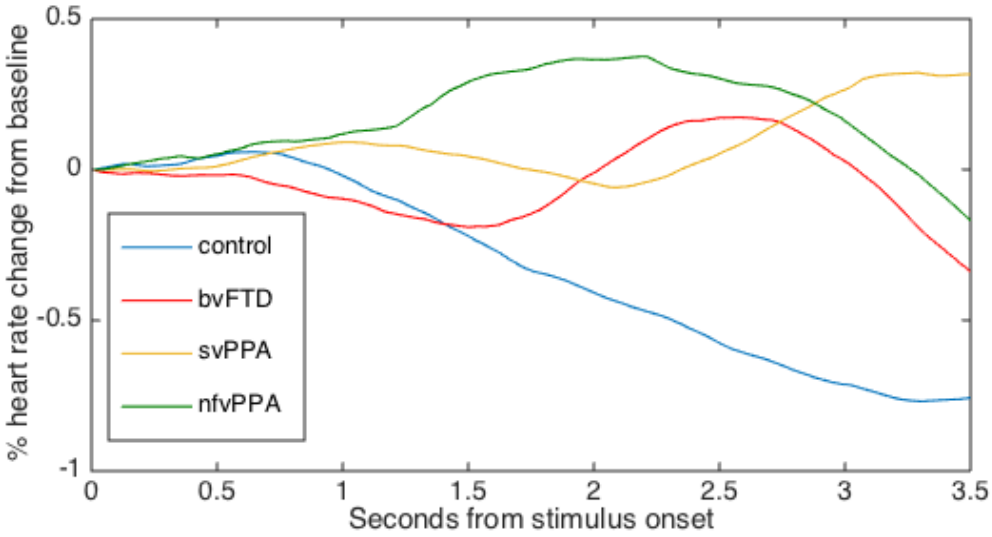
CARDIAC REACTIVITY

Continuous mean heart rate reactivity to stimulus onset for each group is shown in Figure 6.2 and group means for the 3-second cardiac reactivity index are shown in Figure 6.3.

In the control group, a consistent cardiac deceleration was shown for all visual stimuli (one-sample T-test vs 0, $p<0.001$), but an ANOVA showed no effect of stimulus type (videos vs. scrambled videos vs. fixation cross, $p=0.572$). There was a main effect of participant group on cardiac reactivity ($p=0.029$), but no effect of stimulus type ($p=0.08$), and no interaction of the two ($p=0.83$). Post hoc deviation contrasts showed that cardiac deceleration was greater in controls than all patient groups ($p=0.003$). No other significant between group differences

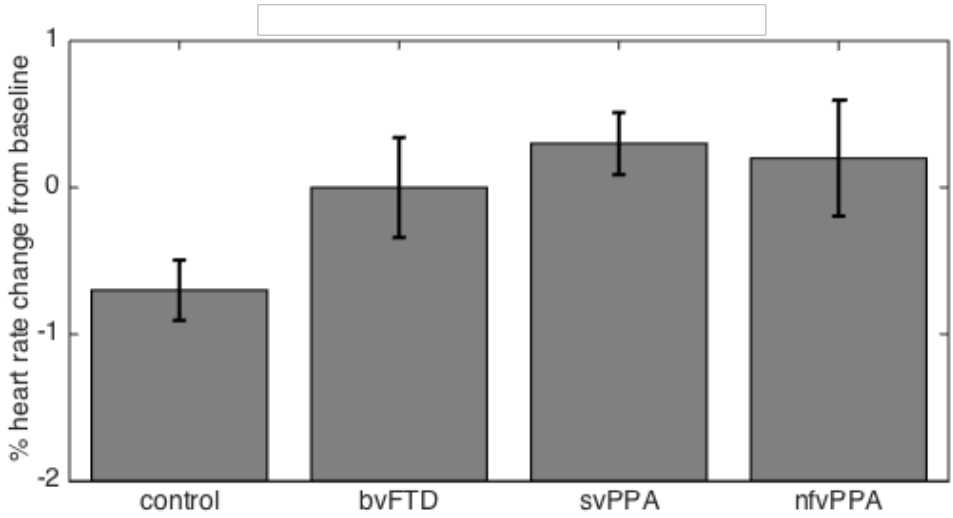
were identified. There was no correlation between heart reactivity and executive function, intelligence, attention and working memory, or semantic performance (all p>0.3).

Figure 6.2 Continuous heart rate responses to visual stimuli



Time courses of change in heart rate from baseline are here shown averaged across all trials and participants for each participant group (see text for details of procedure).

Figure 6.3 Heart rate reactivity by group



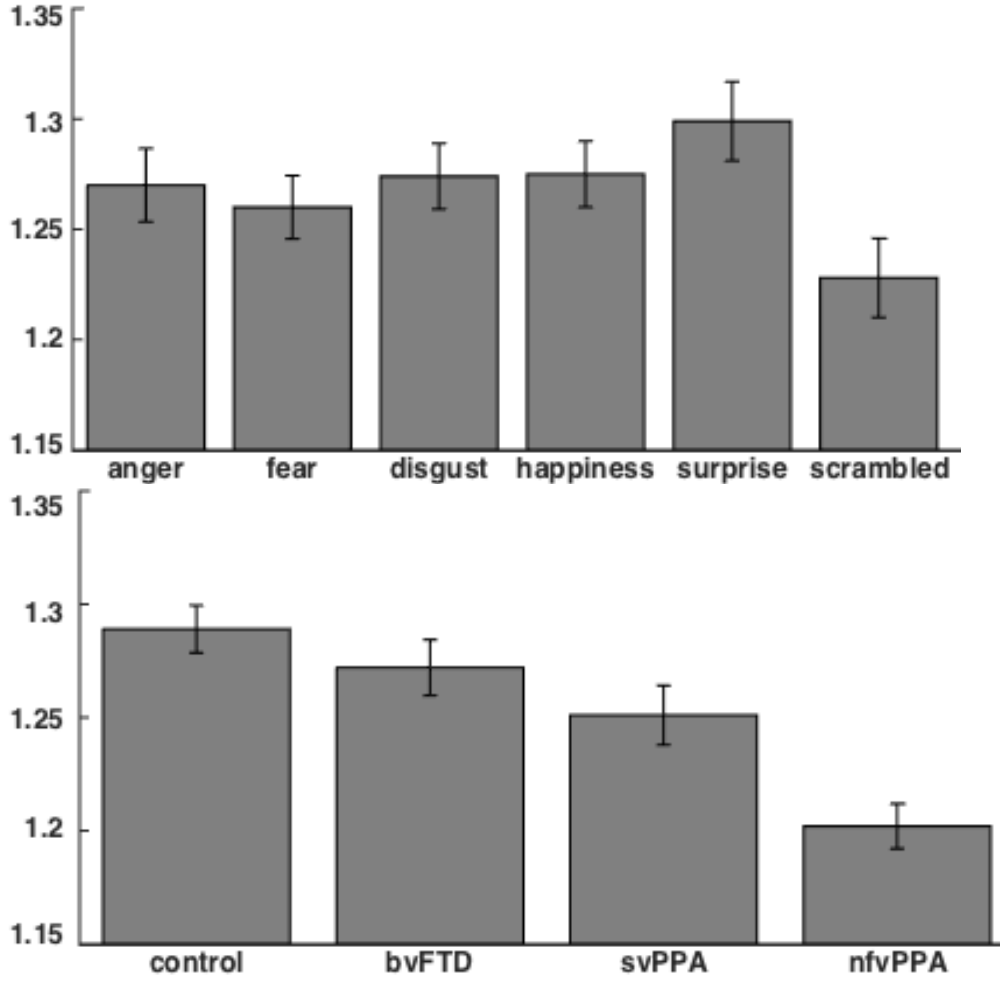
The graph shows mean % change in heart rate at 3 seconds post stimulus onset for each diagnostic group (see text for details). Error bars represent the standard error of the mean.

PUPIL REACTIVITY

Pupil responses by stimulus type and participant group are displayed in Figure 6.4. ANOVA of pupil responses to video stimuli revealed main effects of both participant group (F_3=8.714, p<0.001) and stimulus type (F_5=3.149, p=0.008), but no interaction of the two (F_{15}=0.91, p=0.55). Post hoc deviation contrasts revealed that pupil reactivity was significantly less for scrambled videos than for facial emotions (p<0.001), but did not differ among the emotion categories (all p>0.08). Relative to controls, pupil responses to visual stimuli were significantly reduced in the nfvPPA group (p<0.001) and svPPA group (p=0.026), but not in the bvFTD group (p=0.51).

As no interactions between participant group and stimulus type were found in the omnibus tests, I did not explore for syndrome-specific changes in the relationship between stimulus type and pupil reactivity. There was no correlation between pupil response and neuropsychological measures of executive function, intelligence, attention and working memory or semantic function (all p>0.12).

Figure 6.4 Pupil responses according to stimulus type and participant group



The figure shows mean proportional pupil change from baseline according to stimulus type for all subjects (top) and participant group for all stimuli (bottom). Error bars represent the standard error of the mean

FUNCTIONAL NEUROANATOMY

Neuroanatomical correlates of viewing and identifying facial emotions are shown in Table 6.2 and Figures 6.5-7, and correlates of autonomic reactivity are shown in Table 6.3 and Figures 6.8-10.

Across all subjects, viewing facial emotions was associated with activity in bilateral V1, fusiform face area, and a cluster of temporoparietal junction regions including MT/V5, angular gyrus and posterior STS. Both fusiform face area and temporoparietal junction were shown to have a main effect of diagnostic group in the F contrast, and beta plots revealed reduced TPJ

activation relative to controls in bvFTD and nfvPPA, and reduced fusiform activation in all syndromes, whilst activation in bilateral V1 was consistent across diagnostic groups.

Activity predicting identification score for the facial emotions was found in syndrome-specific loci; left ACC and anterior insula in bvFTD, right anteromedial temporal lobe in svPPA, and right operculum in nfvPPA.

Within the svPPA group, associations with cardiac deceleration were found in bilateral fusiform gyri, left MTG and SFG, whilst pupil dilation was associated with responses in bilateral superior parietal lobules, bilateral fusiform gyri and left anteromedial temporal lobe. In the nfvPPA group, associations were found for both cardiac deceleration (reflecting parasympathetic activity) and cardiac acceleration (reflecting sympathetic activity). Parasympathetic associations included bilateral medial prefrontal cortex, right insula, ACC and STS, and left operculum. For sympathetic activity these included right OFC and TPJ, left insula, central pons (in the regions of the locus coeruleus and parabrachial complex) and bilateral ventrolateral medulla. Correlation with pupil dilation in nfvPPA was found in the right dorsal ACC. No correlates of autonomic reactivity were identified in the control or bvFTD groups at the prescribed threshold.

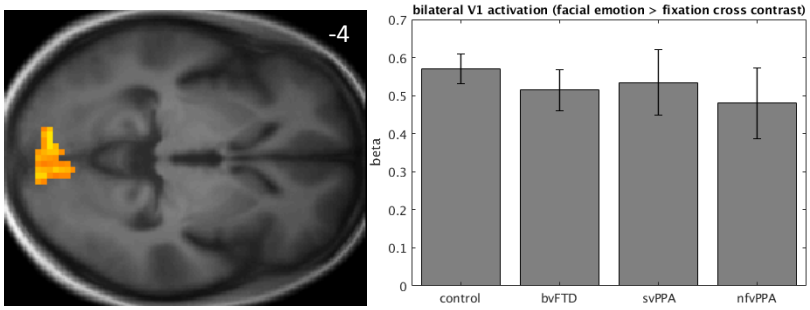
Table 6.2 fMRI correlates of viewing dynamic facial emotions

Group	Region	Side	Cluster (voxels)	Peak (mm) X	Y	Z	P_{FWE}
Facial Emotion > Fixation Cross – T contrast (effect of condition)							
All	Occipital poles including:		279				<0.001
	V1	R		15	-94	14	
	V1	L		-12	91	2	
Facial Emotion > Scrambled Video – T contrast (effect of condition)							
All	Temporoparietal junction including:	R	345				<0.001
	MT/V5	R		51	-70	2	
	STS	R		57	-34	2	
	Angular gyrus	R		63	-58	14	
	Fusiform gyrus	R	71	42	-46	-16	0.001*
	Fusiform gyrus	L	62	-42	-52	-19	0.021*
	MT/V5	L	87	-45	-58	11	0.010*
Facial Emotion > Scrambled Video – F contrast (main effect of group)							
All	Temporoparietal junction including:	R	145				0.001
	MT/V5	R		54	-67	-4	
	STS	R		60	-55	11	
	Fusiform gyrus	R	32	42	-46	-16	0.020*
Facial Emotion > Scrambled Video – T contrast with emotion ID score predictor							
bvFTD	Medial frontal including:	L	189				0.004
	ACC	L		-24	29	11	
	Anterior insula	L		-27	27	10	
	Caudate	L		-12	15	7	
svPPA	Fusiform gyrus	R	5	36	2	-37	0.010*
nfvPPA	Frontal operculum	R	72	42	2	17	0.045*

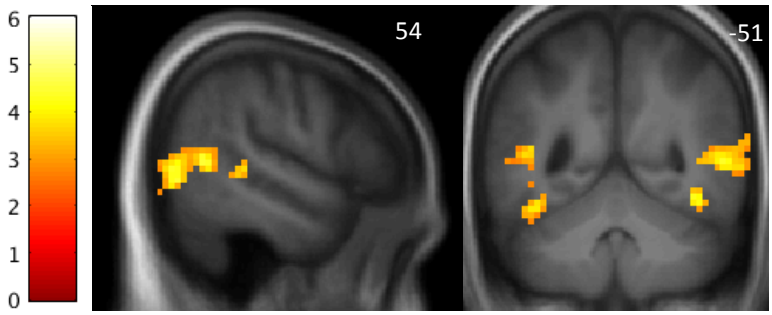
The table presents fMRI correlates for the individual specified contrasts. P-values represent cluster-level FWE-corrected values over the whole brain, except * peak level FWE-corrected within pre-specified regions of interest.

Figure 6.5 Anatomical correlates of viewing facial emotions (T contrasts for effect of condition)

Emotional faces > fixation cross



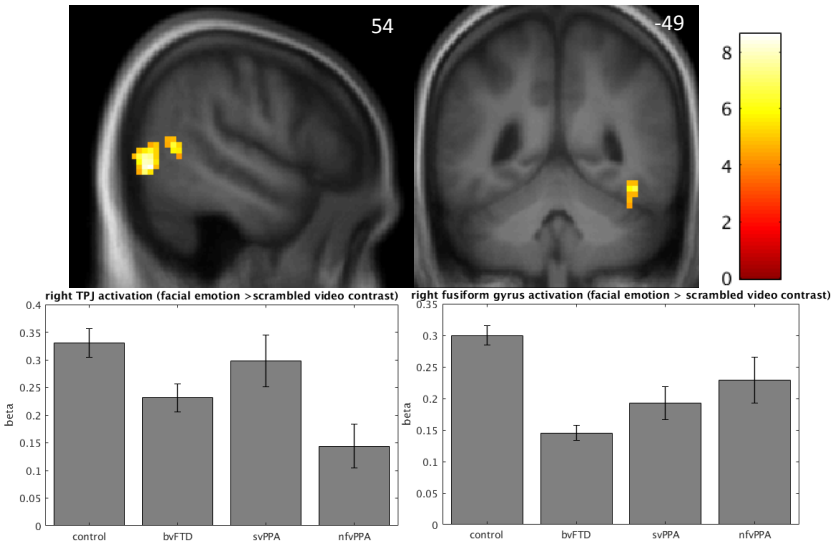
Emotional faces >scrambled videos



Statistical parametric maps showing fMRI associations of the stimulus conditions across all participants (T-contrasts for effect of condition) for the contrasts specified, together with a beta plot demonstrating consistent activation of bilateral V1 across groups. SPMs are thresholded at the cluster-defining threshold of p<0.005 uncorrected. The plane of each section (in mm in MNI space) is shown in the top right of each image. The coronal section displays the right hemisphere on the right. The colour bar codes T-values.

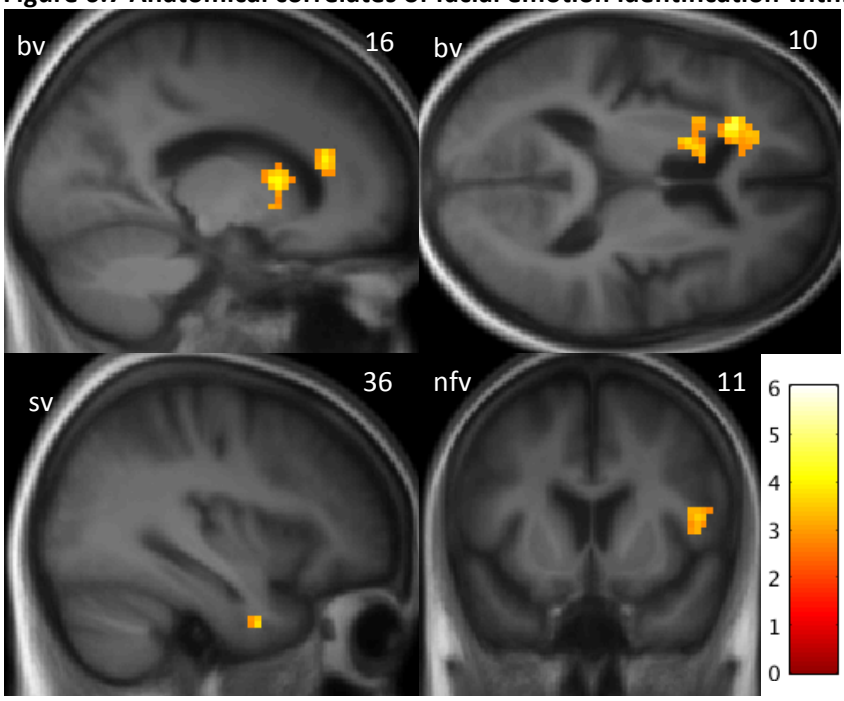
Figure 6.6 Anatomical correlates of viewing facial emotions (F contrast for effect of group)

Emotional faces >scrambled videos



SPMs showing fMRI associations for the F-contrast (main effect of group), together with beta plots demonstrating differential patterns of attenuated BOLD response in the two significant clusters. SPMs are thresholded at the cluster-defining threshold of p<0.005. The plane of each section (in mm in MNI space) is shown in the top right of each image. The coronal section displays the right hemisphere on the right. The colour bar codes F-values.

Figure 6.7 Anatomical correlates of facial emotion identification within syndromic groups



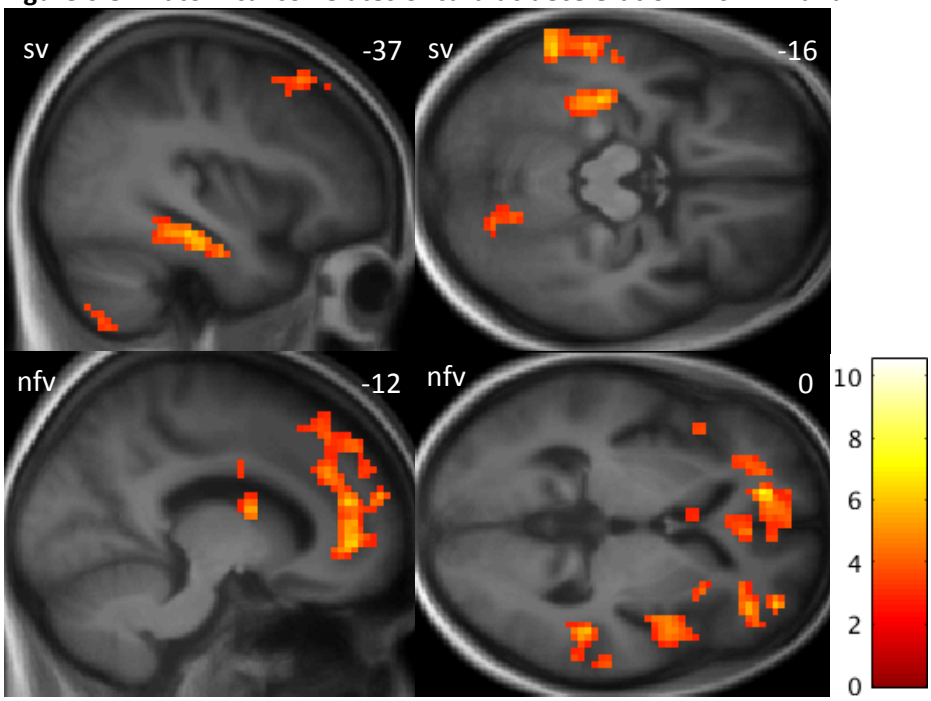
SPMs showing fMRI associations within each disease group of subsequent performance on the out of scanner emotion recognition task (bv – bvFTD, sv – svPPA, nfv – nfvPPA). SPMs are thresholded at the cluster-defining threshold of $p<0.005$. The plane of each section (in mm in MNI space) is shown in the top right of each image. The coronal section displays the right hemisphere on the right. The colour bar codes T-values.

Table 6.3 fMRI correlates of autonomic reactivity

Group	Region	Side	Cluster (voxels)	Peak (mm) X	Y	Z	P_{FWE}
Negative association with heart rate (parasympathetic)							
svPPA	Fusiform gyrus	L	166	-36	-28	-16	0.008
	Middle temporal gyrus	L	142	-57	-49	-16	0.019
	Superior frontal gyrus	L	131	-18	-1	-68	0.028
	Fusiform gyrus	R	49	18	-76	-16	0.033*
nfvPPA	Bilateral frontal including:		3023				<0.001
	DLPFC	R		36	38	17	
	Medial prefrontal	R		18	22	49	
	ACC	R		10	45	11	
	Insula	R		43	2	-2	
	Medial prefrontal	L		-6	42	33	
	ACC	L		-10	48	16	
	Operculum	L	343	-42	20	8	<0.001
	STS	R	122	48	-34	1	0.040
Positive association with heart rate (sympathetic)							
nfvPPA	Orbitofrontal and entorhinal cortex	R	346	15	5	-19	<0.001
	Temporoparietal junction	R	160	45	-34	29	0.010
	Brainstem including:		119				0.045
	Pons			1	-25	-32	
	Lateral medulla	L		-7	-27	-44	
	Lateral medulla	R		14	-29	-44	
	Insula	L	76	-36	-1	-13	<0.001*
Positive association with pupil dilation							
svPPA	Superior parietal lobule	L	186	-42	-64	59	0.004
	Superior parietal lobule	R	122	45	-40	41	0.039
	Fusiform and lingual gyri	L	129	-18	-52	-7	0.030
	Anteromedial temporal lobe	L	68	-27	14	-31	0.001*
	Fusiform gyrus	R	37	42	-67	-16	0.017*
nfvPPA	Dorsal ACC	R	62	12	17	23	0.045*

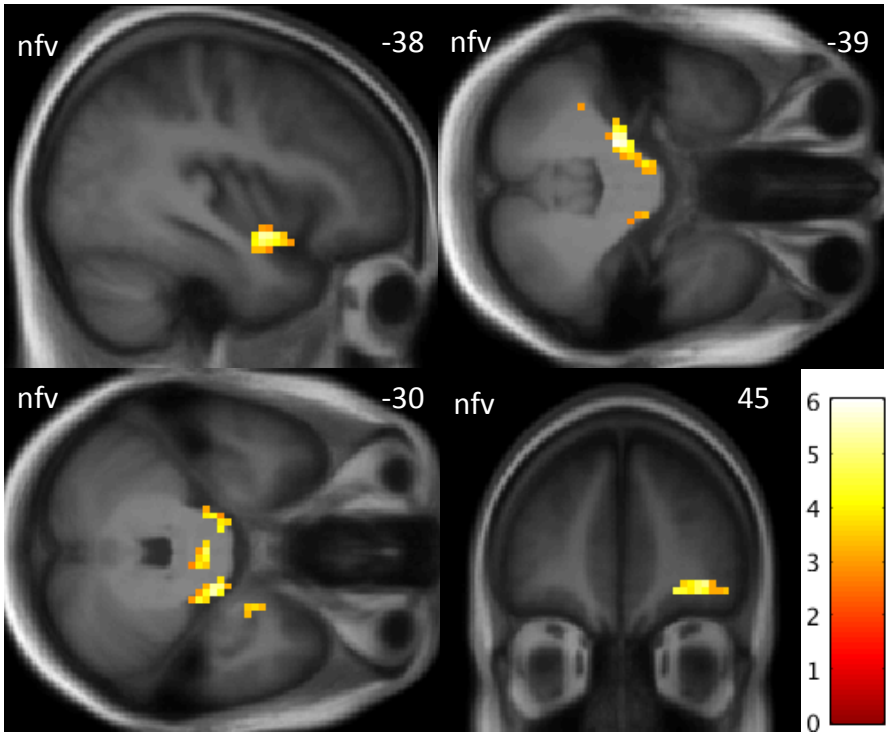
The table presents fMRI correlates for the specified physiological response measures within the svPPA and nfvPPA groups. P-values represent cluster-level FWE-corrected values over the whole brain, except * peak-level FWE-corrected within pre-specified regions of interest.

Figure 6.8 Anatomical correlates of cardiac deceleration in svPPA and nfvPPA



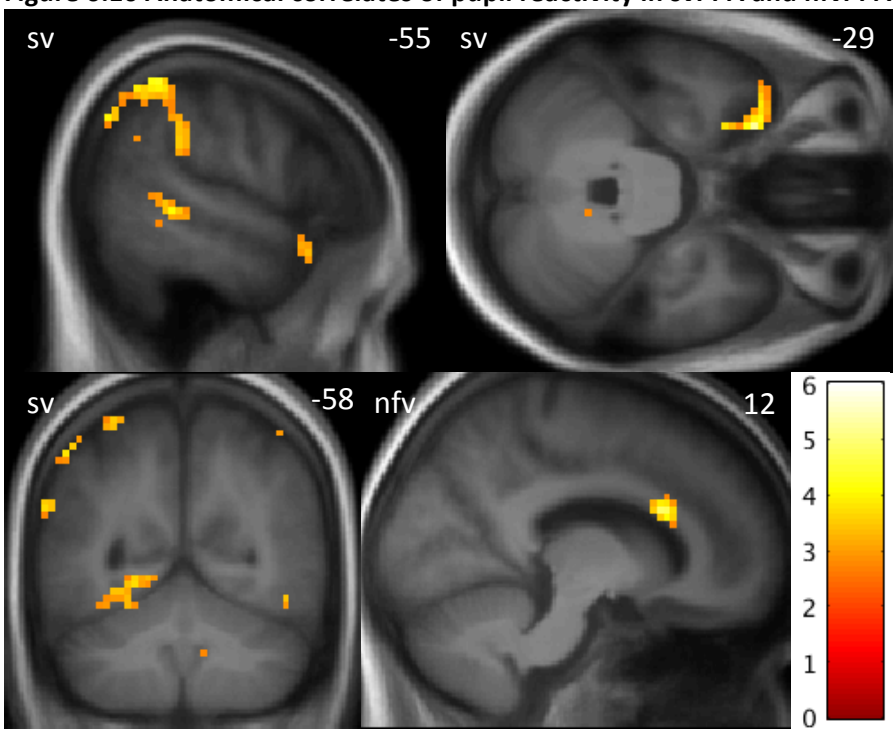
SPMs showing fMRI associations of cardiac deceleration within the svPPA and nfvPPA disease groups (sv – svPPA, nfv – nfvPPA). SPMs are thresholded at the cluster-defining threshold of $p<0.005$. The plane of each section (in mm in MNI space) is shown in the top right of each image. The colour bar codes T-values.

Figure 6.9 Anatomical correlates of cardiac acceleration in nfvPPA



SPMs showing fMRI associations of cardiac acceleration within the nfvPPA disease group (nfv – nfvPPA). SPMs are thresholded at the cluster-defining threshold of $p<0.005$. The plane of each section (in mm in MNI space) is shown in the top right of each image. The coronal section displays the right hemisphere on the right. The colour bar codes T-values.

Figure 6.10 Anatomical correlates of pupil reactivity in svPPA and nfvPPA



SPMs showing fMRI associations of pupil response within the svPPA and nfvPPA disease groups (sv – svPPA, nfv – nfvPPA). SPMs are thresholded at the cluster-defining threshold of $p<0.005$. The plane of each section (in mm in MNI space) is shown in the top right of each image. The coronal section displays the right hemisphere on the right. The colour bar codes T-values.

DISCUSSION

Here, I have defined the functional neuroanatomical signatures of three dimensions of response to social emotions in FTD: sensory processing, emotion evaluation and autonomic arousal. Despite consistent activation of primary visual cortex, activity in areas that are specific to the processing of faces and biological motion was differentially attenuated across the FTD spectrum. The delineation of these predominantly right-lateralised intermediate sensory areas replicates precisely the established anatomical correlates of perceiving dynamic emotional facial expressions (Haxby and Gobbini, 2011). The fusiform face area responds selectively to faces, with greater responses to emotional facial expressions (Vuilleumier *et al.*, 2001), which here were attenuated in all syndromes of FTD. Both MT/V5 and posterior STS show preferential responses to dynamic facial stimuli (Kilts *et al.*, 2003; Pelphrey *et al.*, 2007; Foley

et al., 2012). MT/V5 activation primarily reflects biological motion detection, while the posterior STS shows greater representation of specific expression characteristics (Said *et al.*, 2010). The posterior STS is hypothesised to be a key hub for the perception of social stimuli across modalities, linking early sensory processing to higher associative areas such as the adjacent right TPJ that plays a key role in theory of mind (Deen *et al.*, 2015; Schuwerk *et al.*, 2017). The large temporoparietal junction cluster identified here incorporated MT/V5, posterior STS and TPJ, and showed attenuated activation in bvFTD and nfvPPA, but preserved responses in svPPA. It is noteworthy that both the fusiform face area and TPJ cluster are remote from canonical regions of grey matter loss in these diseases, and it is likely therefore that the use of functional imaging has revealed the effects of large scale network dysfunction that could not be adequately captured with structural imaging.

These findings of altered neural responses at relatively early sensory processing stages largely echo two previous studies showing similar results in bvFTD (Virani *et al.*, 2013; De Winter *et al.*, 2016). This work goes further, however, in demonstrating variable patterns of change across the FTD spectrum, and in showing that these impaired sensory responses are not the key drivers of impairments in the ability to cognitively categorise emotional expressions. Rather, this ability was linked to activity in more anterior regions in a syndrome-specific manner: left ACC, anterior insula and caudate in bvFTD, right anteromedial temporal lobe in svPPA, and right frontal operculum in nfvPPA. While the emotion recognition scores here replicate previous findings of impairments across the FTD spectrum, the known functional associations of these anatomical correlates suggest distinct mechanisms for impairments of categorization in each syndrome based on the hierarchical organisation of these structures in emotion processing networks. The frontal operculum is a component of the human mirror system and is hypothesised to represent motoric features of dynamic emotional faces, to which it responds preferentially (Montgomery *et al.*, 2009; Said *et al.*, 2010). Activity here triggers responses in the anterior insula, where coactivation with the ACC is linked to the

integration of body state representations and motivational conditions on which affective judgements depend (Jabbi and Keysers, 2008; Craig, 2009). The right anterior temporal lobe is known to represent social concepts and person-specific semantics, suggesting that the emotion identification failure in svPPA is at this higher level of the hierarchy (Zahn *et al.*, 2007; Olson *et al.*, 2013). The anterior temporal lobe and frontal operculum are contained within the canonical atrophy profiles of svPPA and nfvPPA respectively, but in both cases the left hemisphere is typically more affected, whereas the correlates here are right sided (Rohrer, 2012). In both syndromes, homologous atrophy is eventually seen in the contralateral hemisphere as the disease progresses, and these results suggest that it is this disease spread that is primarily responsible for the development of emotion recognition failures in these syndromes. This could account for the fact that despite being well recognised in svPPA and nfvPPA, socioemotional symptoms are not usually leading features at presentation.

The autonomic findings here suggest that pupil responses are more specific to affective content than heart rate, with greater responses to emotional faces than the affectively neutral scrambled videos. This reactivity was impaired in svPPA and nfvPPA, but not in bvFTD. Cardiac responses were not greater for affective stimuli, and may in fact be indexing a more general stimulus orienting response. This cardiac response was impaired here in all FTD syndromes. The neuroanatomical correlates of autonomic responsiveness identified in svPPA and nfvPPA suggest two distinct mechanisms for reductions in physiological reactivity. In svPPA, the associations for both cardiac deceleration and pupil dilatation are indicative of altered responses to the sensory properties of the stimulus. Fusiform face area activation has previously been linked to cardiac reactivity to facial emotions in the healthy brain (Critchley *et al.*, 2005). In the svPPA group here it predicted both parasympathetically mediated cardiac deceleration and sympathetically mediated pupil dilatation. Pupil dilatation in svPPA was also associated with activity in bilateral superior parietal lobules, which are higher visual sensory regions that mediate the link between visuomotor cognitive load and pupil dilatation, and

have been previously associated with central control of sympathetic function (Beissner *et al.*, 2013; Hosseini *et al.*, 2017). This linkage between stimulus properties and heart rate response in svPPA might explain the finding of impaired heart rate reactivity here, which is at odds with my findings in Chapter 5. The key difference here is the absence of a task, which may have provided the necessary context to generate an orienting response to stimuli in svPPA, which was then not seen in response to the sensory features of the stimulus alone. By contrast, in nfvPPA this experiment replicates the finding of impaired cardiac reactivity, and the bidirectional fMRI associations with cardiac reactivity delineated parasympathetic and sympathetic components of the central autonomic network, suggesting that nfvPPA is associated with primary failures of autonomic control and alterations in the balance between sympathetic and parasympathetic activity. The parasympathetic network identified here comprised bilateral medial prefrontal cortex and ACC, right insula and superior temporal gyrus, all of which have been defined as components of central parasympathetic control in a meta-analysis of functional neuroimaging studies (Beissner *et al.*, 2013). The sympathetic associations here are similarly convergent with this meta-analysis, including left insula, right orbitofrontal cortex and right dorsal ACC. The finding of bilateral correlates for both parasympathetic and sympathetic activity would seem to support the view that there is no distinct lateralisation of emotional autonomic control in the cerebral hemispheres (Hagemann *et al.*, 2003; Beissner *et al.*, 2013). Here, I additionally identified brainstem sympathetic components in the regions of locus coeruleus, parabrachial complex and ventrolateral medulla. These brainstem structures link forebrain control of autonomic function to sympathetic outflow and are known to be affected by neurodegenerative diseases, but are not typically identified in functional neuroimaging studies in humans, as the technique is relatively insensitive to the small and rapid fluctuations in tonic activity of these regions that mediate peripheral autonomic changes (Cersosimo and Benarroch, 2013; Macey *et al.*, 2015). It is likely

that the presence of pathologically altered network function in subjects with nfvPPA increased the power to detect associations with activity in these brainstem nuclei.

Taken together, these findings outline a complex stratification of aberrant responses to social emotion in FTD syndromes, which goes beyond previous behavioural and anatomical findings. In bvFTD, sensory responses are attenuated in fusiform gyrus and temporoparietal junction, activations in left ACC and anterior insula determine emotion categorisation ability, and parasympathetic heart rate responses are impaired, while sympathetic pupil responses are preserved. In svPPA, fusiform gyrus responses are impaired but TPJ responses are preserved, and the ability to label emotions relates to the retrieval of social concepts from the right anterior temporal lobe. Both cardiac and pupil responses are impaired in this syndrome, but chiefly as a function of the processing of sensory properties of the stimulus. In nfvPPA, both fusiform gyrus and TPJ show attenuated responses to emotional faces, and emotion identification is compromised by reduced motoric representation in frontal operculum. Autonomic impairments in this syndrome are due to primary failures of central autonomic control in both sympathetic and parasympathetic networks.

This work has several limitations. Despite impaired cardiac responses in bvFTD, no fMRI associations of autonomic control were identified in this syndrome. It is likely that the more homogeneous syndromes of svPPA and nfvPPA had relatively greater power to detect functional anatomical associations. On anatomical grounds it is likely that in the heterogeneous bvFTD group impaired autonomic responses are due to a combination of stimulus processing deficits due to temporal lobe involvement (as in svPPA) and primary autonomic control deficits due to frontoinsular involvement (as in nfvPPA). Larger studies with the capability to separate sub-syndromes of bvFTD, for example with a distinct rtvFTD group, might increase the power to detect these associations. Additionally, the incorporation of trial-

by-trial physiological reactivity at first level in the fMRI analysis might help to detect associations with autonomic control both in bvFTD and the healthy control group.

Both BOLD responses and pupil responses were greater to the emotional faces used here than to the scrambled mosaics, which were matched for low-level information content. It is therefore unlikely that these effects were due to lower-level salience rather than being specific to the emotional content of the stimuli. However, this was not true of the heart rate response, which was the same for all visual stimuli. It is therefore possible that the heart rate reactivity is indexing a more general orienting response to salience. Heart rate responses may also be more susceptible to other concomitant mental processes such as mind wandering or extraneous thoughts. It is therefore possible that the posterior cortical activation and pupil reactivity are less noisy indices of altered brain function in the patients.

There are some inherent limitations in the use of fMRI in subjects with neurodegenerative diseases. These patient groups are known to have impairments in attention and concentration, and this experiment did not include any means of measuring attention to the stimuli in the scanner, other than confirming with the eyetracker that their eyes remained open. However, although emotion identification ability was related to attention, working memory and executive function, there was no association between these measures and cardiac or pupil reactivity. Behavioural alterations lead to increased movement in the scanner, which might not be adequately controlled for, even with the incorporation of movement parameters in the first-level design for each subject. Furthermore, the effect of cerebral atrophy on regional BOLD signal is difficult to take into account fully. Whilst many of the loci here were outside canonical disease foci, those that were within atrophy zones may be indexing loss of grey matter rather than reduced haemodynamic response per se. Conversely, in regions where atrophy is particularly severe, it may not be possible to detect functional alterations at all. For example, one might have expected to find associations with amygdala function in the

emotional responses studied here, but this region is often almost entirely 'cored-out' in FTD syndromes focussed on the anterior temporal lobes, and this may have made it impossible to detect an effect.

Beyond the effect of neurodegeneration on BOLD signal, the direct influence of physiological parameters like the cardiac and respiratory cycles on BOLD and the haemodynamic response function is a potential confound. I modelled heart rate reactivity at second level here, and it is unlikely that the cardioballistic effects of the cardiac cycle would explain a significant proportion of the between subject variance in heart rate response at second level, although incorporating a heart beat time series at first level would have ensured that any variance attributable to this was removed. There is also a small proportion of variance in BOLD response (about 1%) attributable to phasic changes in heart rate, and not accounting for this may have influenced the results (Chang *et al.*, 2009). It is also possible, however, that including a heart rate differential as a nuisance covariate would have taken out much of the variance of interest when assessing the correlates of the between subjects differences in heart rate responses. Much of the artefact related to respiration is accounted for by head movement parameters, but this may not be totally adequate, and the inclusion of respiratory monitoring would have allowed direct incorporation of the respiratory cycle as a nuisance covariate.

Based on my anatomical findings and evidence for network configurations in the healthy brain, I have made inferences here about altered network function in these diseases. However, the mass univariate approach to the analysis that I have used does not allow direct conclusions about connectivity and network function to be drawn. Further work could include the use of techniques for assessing connectivity to more clearly define changes in network function in FTD. For example, the loci identified in the mass univariate analyses could be analysed with dynamic causal modelling to assess how they are likely to be interconnected (or disconnected) in the participant groups. Alternatively a psychophysiological interaction approach could

demonstrate how activity in sensory processing areas (e.g. fusiform face area) relates to activity in higher limbic, motoric and associative regions.

7. GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

SUMMARY OF FINDINGS

The central aim of this thesis was to define physiological markers of impaired responses to the emotions of others across the syndromic spectrum of FTD, and to relate these to underlying neuroanatomical changes. The key findings are summarised in Table 7.1.

In Chapter 3 I used a heartbeat counting task to define deficits in interoceptive accuracy in FTD syndromes. Interoception was particularly impaired in svPPA, but correlated with a daily life measure of emotional sensitivity across the patient cohort, and may be less markedly impaired in the syndromes of bvFTD and nfvPPA. This lends further support to recent theories that propose a key role for awareness of one's own bodily states in empathic responses. In the svPPA group interoceptive deficits were correlated with grey matter volume in right ACC, insula and amygdala; structures known to support heartbeat awareness and the incorporation of interoceptive information into affective judgements in the healthy brain.

In Chapter 4 I performed facial EMG recording during an emotion identification task on videos of dynamic facial emotions to define motor signatures of emotional reactivity across the FTD spectrum. Facial emotion recognition was impaired in all FTD syndromes, and related to syndrome-specific patterns of grey matter loss in fronto-insulo-temporal regions previously implicated in emotion recognition in FTD and in the healthy brain, with additional associations found in SMA and MT/V5, likely due to the use of dynamic naturalistic stimuli. Unlike emotion recognition, automatic imitation of facial expressions was differentially impaired in the patient groups. Facial mimicry was markedly impaired in bvFTD and rtvFTD, preserved in svPPA and showed a selective loss of fear reactivity in nfvPPA. In healthy controls and fronto-insular syndromes (bvFTD and nfvPPA) greater imitation predicted correct identification, supporting

the concept of automatic imitation as a key evaluative component of social signals, but this effect was abolished in syndromes focussed on the temporal lobes (rtvFTD and svPPA), suggesting that temporal lobe degeneration disconnects motoric representations from emotion appraisal based on semantic social concepts. Anatomical correlates of facial mimicry were identified in visual and motor areas including V1, PHG, MT/V5, M1 and SMA.

In Chapter 5 I recorded ECG during an emotion identification task on videos of dynamic facial emotions. A consistent cardiac deceleration response was seen in controls, which was impaired in bvFTD and nfvPPA, but preserved in syndromes focussed on the temporal lobes (rtvFTD and svPPA). In contrast to the motor responses in Chapter 4, there was no relationship identified between cardiac reactivity and the ability to cognitively categorise emotions, and no emotion-specificity of the reactions. This provides support for the idea that autonomic responses relate to emotional intensity and arousal rather than demonstrating category-specificity. Impaired cardiac reactivity related to grey matter loss in components of the central autonomic control network including ACC, insula and orbitofrontal cortex.

In Chapter 6 subjects underwent activation fMRI with concurrent pulse oximetry and pupillometry while they viewed videos of dynamic facial emotions. Emotion recognition deficits and impaired cardiac deceleration responses were found in all FTD syndromes, and impaired pupil responses in svPPA and nfvPPA. I delineated the functional neuroanatomy of three dimensions of emotion processing: sensory analysis of the stimuli, cognitive categorisation of emotions and autonomic arousal. Primary visual cortex was activated consistently across syndromes, while fusiform face area responses were reduced in all patient groups, and activity in temporoparietal junction areas including MT/V5 and posterior STS was attenuated in bvFTD and nfvPPA. Correlates of the ability to identify emotions were found in regions associated with emotional appraisal in bvFTD (ACC and anterior insula), with social concepts in svPPA (right anterior temporal lobe), and with motoric simulation in nfvPPA

(frontal operculum). Autonomic arousal in svPPA was associated with activity in regions responsible for visual sensory processing (including fusiform face area and superior parietal lobule). In nfvPPA, both parasympathetic and sympathetic autonomic control networks were identified, including medial frontal regions, insulae and key brainstem nuclei.

Table 7.1 Summary of emotional reactivity findings in FTD syndromes

	bvFTD	**rtvFTD**	**svPPA**	**nfvPPA**
Behavioural metrics:				
Emotion categorisation	↓↓	↓↓	↓↓	↓↓
Daily life emotional sensitivity	↓↓	↓↓	↓	↓
Interoceptive accuracy	(↓)	?	↓↓	(↓)
Motor reactivity:				
Automatic imitation	↓	↓↓	Normal	Lost for fear
Imitation-ID linkage	Normal	↓	↓	Normal
Autonomic responses:				
Cardiac reactivity	↓	Normal	Task-specific (↓)	↓↓
Pupil reactivity	Normal	?	↓	↓
Neuroanatomy:				
FFA response	↓	?	↓	↓
TPJ response	↓	?	Normal	↓
Proposed basis for recognition deficits	Appraisal (ACC/insula)	Social concepts (right ATL)	Social concepts (right ATL)	Motoric (operculum)
Proposed basis for autonomic deficits	Autonomic control	N/A	Sensory processing	Autonomic control

RELEVANCE AND CLINICAL IMPLICATIONS

These findings build on previous studies showing emotional and autonomic deficits in FTD. Deficits in the categorisation of emotional facial expressions have been studied extensively in all FTD syndromes. Pupil responses to auditory stimuli have previously been studied across the FTD spectrum, but autonomic deficits have mainly been shown in bvFTD, including in heart rate variability, cardiac orienting responses and skin conductance (Kumfor *et al.*, 2011; Couto *et al.*, 2013; Joshi *et al.*, 2014; Guo *et al.*, 2016; Joshi *et al.*, 2017). This work goes further in several important ways. Throughout, I have specifically linked interoceptive, motoric and

autonomic changes to social emotion processing, addressing symptoms that are of paramount importance in these diseases. Unlike most other studies, I have systematically studied patients from across the FTD spectrum, allowing specific links to be drawn between physiological changes and patterns of large-scale network degeneration. Finally, the wide range of modalities I have used here (behaviour, caregiver ratings, interoception, cardiac reactivity, pupil reactivity, facial EMG, structural and functional MRI) has provided an unprecedented opportunity to begin to disentangle the various dimensions of degraded emotional reactivity in these diseases.

Taken together, the results provide a novel neurobiological account of the mechanisms underlying socioemotional deficits in the FTD spectrum. They suggest a model firmly rooted in modern neuroscientific concepts of the embodied nature of emotional reactivity, which (as extensions of the ideas originally proposed by James, Lange and Nietzsche) propose that bodily responses both signal and inform affective valuation. From a clinical perspective, this has several important implications. By deconstructing the complex entity of emotional reactivity, it sheds new light on the diverse socioemotional changes described by patients and their carers in the clinic. While conventional neuropsychological instruments emphasise the cognitive categorisation of emotions, this ability does not really capture the multiple dimensions upon which quotidian interpersonal interactions depend.

Normal social behaviour requires sensory detection of social signals, appropriate inference of emotional states based on these signals, arousal and motivational responses, affective mentalising, and selection of appropriate behavioural strategies (Adolphs, 2003). Both the work in this thesis and the symptoms encountered in FTD suggest that these components are at least partially dissociable. For example, families frequently describe emotional blunting and callousness, reporting that the patient knows how others are feeling but appears unmoved and uncaring. The relationship between interoceptive accuracy and subjective caregiver

ratings of emotional sensitivity, and the dissociation between cardiac reactivity and emotional identification that I have identified in chapters 3 and 5 make it likely that the induction and decoding of autonomic changes are key mediators of these deficits in emotional motivation. This view is in keeping with the interoceptive inference framework, and such changes have been hypothesised to mediate a wide range of psychopathological symptoms (Seth and Friston, 2016; Murphy *et al.*, 2017a). Conversely, another frequent description in the clinic is of the patient who does not appear to pick up on how others are feeling, but responds appropriately or even excessively when explicitly told about another's emotional state, suggesting a deficit at the level of social signal processing. Abnormalities at the level of visual sensory processing and motoric representation including facial mimicry (as defined in chapters 4 and 6) would be leading candidates to mediate this symptom, as well as the 'poker face' and lack of social resonance often seen in FTD (Wood *et al.*, 2016b). Impairments in the storage and retrieval of social concepts are suggested by the anatomical findings and the loss of the linkage between mimicry and identification in chapter 4, especially in the syndromic groups with predominant temporal lobe atrophy. This is likely to lead to the inability to declaratively categorise emotions, but may also contribute to an inability to understand the social context of someone else's affective state and hence lead to deficient or over-generalised social responses. This is perhaps best exemplified by a patient with svPPA who was devastated when his wife died. He was concerned that their children were very sad, but could not understand why and repeatedly asked what was upsetting them.

Apart from clinical implications, my results have potential implications for the neurocognitive mechanisms of interoception, emotion and social cognition, and indeed it has been suggested that FTD is a useful disease model for studying the interactions between these processes (Van den Stock and Kumfor, 2017). These syndromes are network based degenerative disorders, and therefore may be better placed to shed light on complex processes requiring interaction of multiple brain regions than conventional focal lesion studies (Kennedy and Adolphs, 2012).

Very generally, my results support the integration of interoception, emotion and social cognition by demonstrating that degeneration of fronto-insulo-temporal networks causes deficits in all three, but there are also some more specific points concerning these mechanisms. For example, my findings demonstrate that effective emotion recognition requires contributions from distributed brain networks for visuomotor representation, emotional appraisal and emotional semantics, and that dysfunction in any one of these can lead to the common endpoint of impaired categorisation of facial expressions. The findings concerning cardiac reactivity support the view that autonomic arousal does not support emotional categorisation, but the findings in chapter 3 suggest that interoception may nevertheless be important for motivating healthy social behaviour. Moreover, my fMRI findings echo previous work showing that autonomic reactivity depends not just on the function of the central autonomic control network, but also on the effective processing of sensory properties of the stimulus (Critchley *et al.*, 2005).

Deficits in interoception and autonomic reactivity might be hypothesised to mediate symptoms in domains other than emotionality, and indeed many potentially relevant symptoms are prominent in FTD syndromes. The relationship between interoception and embodied selfhood could account for symptoms such as an impoverished sense of self, altered bodily awareness, changes in sense of agency and somatically focussed delusions (Tsakiris *et al.*, 2011; Downey *et al.*, 2012; Seth, 2013; Downey *et al.*, 2014; Filippetti and Tsakiris, 2016; Irish and Piolino, 2016; Mitra *et al.*, 2017). Other cognitive processes that have been shown to have a relationship with interoception in health include exteroception and metacognition, both of which are frequently pathologically altered in FTD (Eslinger *et al.*, 2005; Fletcher *et al.*, 2015a; Allen *et al.*, 2016). As well as supporting emotional feeling states, autonomic arousal has a broader role in attentional, appetitive and motivational responses (Bradley, 2009). It would therefore be valuable to explore the potential linkage between autonomic responses and behavioural changes in FTD including apathy, distractibility and altered reward-seeking

behaviours (Stopford *et al.*, 2012; Perry *et al.*, 2014; Ducharme *et al.*, 2018). Insula lesions due to ischaemia have been associated with cerebrogenic sudden death due to aberrant central autonomic control (Cheung and Hachinski, 2000). There is some epidemiological evidence for sudden death in FTD, and it will be important to define whether this is a more sinister manifestation of the degeneration of core cerebral autonomic control networks (Nunnemann *et al.*, 2011).

Beyond a mechanistic account of complex symptoms, more practical clinical implications of my work include the biomarker potential of these modalities. Physiological metrics constitute a non-invasive method to objectively quantify affective responses, and as such may prove to be a method of measuring and tracking change in a cognitive domain that has largely proved elusive to measurement in clinical neuropsychology. In all the experimental chapters in this thesis, markers of embodied responses differentiated patients from controls, raising the possibility of diagnostic physiological biomarkers, while large differences between groups for some of the responses (e.g. in chapters 4 and 5) and specific correlations with underlying neuroanatomy suggest that there may be an additional role for physiological biomarkers in clinico-anatomical stratification. If the linkage between clinico-anatomical syndromes and molecular aetiologies were more clearly delineated, such metrics could also help to define molecular pathology dynamically and *in vivo.*

LIMITATIONS

The work in this thesis has several important limitations beyond those specific to the individual studies, which I have discussed in each chapter. Chief among these is the small sample size of the individual patient groups studied here, which was as low as six for the rtvFTD groups in chapters 4 and 5. Whilst this is generally accepted to inflate Type II error rate, there is also likely to be an increased risk of Type I error, and hence the results should be interpreted with a degree of caution (Button *et al.*, 2013). This could have been mitigated to some extent by

considering all the FTD syndromes as a single patient group, with a sample of more than thirty patients in all chapters. However, this approach would have greatly limited the power to detect specific anatomical associations due to the heterogeneity between groups, and it would not have been possible to explore the potential to stratify clinico-anatomical syndromes. Other approaches could have included building a complex model including symptom severity, leading symptom and neuropsychological scores, and then assessing which features best predicted the experimental findings. Alternatively, in those subjects who performed multiple experiments in the thesis, it might have been useful to perform a clustering analysis to assess how combinations of parameters of interest defined subcategories of patients within the wider FTD group. Both of these approaches may well have been underpowered with the numbers of subjects here, however. A third approach, perhaps more appropriate to the small sample sizes and more statistically conservative would have been to adopt a case series methodology (Crawford *et al.*, 2010).

Small sample size is to some extent an inevitable consequence of studying a rare disease in a single centre, and the patient numbers here are in line with those in work from other centres around the world in the recent literature. Based on a point prevalence of 15/100,000 in the 45-64 age group, and the fact that this age group represents around 25% of the UK population (as per 2011 UK census) the 62 FTD patients in these experiments would be expected to be drawn from a catchment population of around 1.5 million people. In my experience, around half of all FTD patients at our centre are willing and/or able to take part in research, and therefore an estimated catchment population of 3 million people would be required for these numbers. Significantly increasing these numbers in a single centre would therefore be unrealistic even in a regional referral centre. Hopefully this work provides proof of principle to encourage larger studies with multi-centre collaboration. This type of approach is already proving invaluable in the study of genetic FTD through the international GENFI project (Rohrer *et al.*, 2015).

The patients here were exclusively FTD patients, and this represents a limitation in interpreting the findings. Including a disease control group, for example a group of patients with Alzheimer's disease would have been valuable to show that the findings were specific to FTD and not to neurodegenerative disease more broadly. The FTD patients were also grouped by canonical FTD syndrome from the outset, and this casts doubt on the utility of the metrics here to assist in the stratification of syndromes that were defined *a priori*. The hope is that the work at least provides proof of principle for the potential specificity of physiological metrics for clinicoanatomical syndromes that will stimulate future work employing a transdiagnostic approach in larger cohorts to evaluate this more rigorously. There was also significant overlap between the participants in each chapter here, and although each chapter had a different focus, it should be noted that any sampling bias present will likely have persisted through all the work.

Another potential limitation is that all the data presented here are cross-sectional. Physiological markers would have great clinical utility if they were to track disease severity and evolution. Longitudinal work will be necessary to establish whether this is the case. Moreover, by virtue of incorporating a cross section of patients with a range of disease severities, the group analyses included some subjects with quite early disease, who may not yet have been very different to controls. This may have reduced power to detect differences between patient groups and controls (e.g. for interoceptive accuracy in chapter 3).

Throughout the thesis I have related the findings to the symptoms reported by patients and their carers. Although I attempted to reflect the social milieu of daily life as far as possible (using a daily life measure of emotional sensitivity in chapter 3 and relatively ecological stimuli in chapters 4, 5 and 6), it is important to recognise that the necessarily reductionist nature of my experimental paradigms cannot fully capture the complexity of real world social interactions. Whether this could ever be fully achieved in an experimental set up is moot, but

future work could focus on trying to capture this better, for example with the use of wearable technology or virtual reality environments.

FUTURE DIRECTIONS

In addition to the requirement for longitudinal work in larger cohorts to replicate and amplify the findings of this thesis, there are several key directions in which future work could proceed to further disentangle the complexities of dysfunctional emotional reactivity in FTD, to generate novel biomarkers with practical clinical utility, and potentially to yield both pharmacological and non-pharmacological interventions.

This thesis has largely studied the processing of social signals from faces, but this is just one of several important modalities. Building a comprehensive picture of social signal processing in FTD will require the study of other domains including body language, auditory (both verbal and non-verbal), and tactile, all of which are key channels for interpersonal communication of affect in daily life (de Gelder, 2006; Sauter *et al.*, 2010; Kirsch *et al.*, 2017). Affective touch would perhaps be the most interesting of these in FTD, as it specifically reflects insula function and embodied selfhood, and is closely related to interoceptive processing (Gentsch *et al.*, 2016). The PPA syndromes have been associated with specific auditory signal processing deficits, and might therefore be hypothesised to show distinct patterns of dysfunction in the decoding of auditory social signals (Rohrer *et al.*, 2012b; Hardy *et al.*, 2017a; Hardy *et al.*, 2017b). In real-world scenarios, these modalities are frequently encountered simultaneously, and should therefore ideally be studied both separately and in combination. Much of the work on emotion processing in disease, including in this thesis, focuses on the canonical emotions as popularised by Ekman (Ekman *et al.*, 1969), but this approach eschews much of the nuance of social interaction in ecological settings. More complex emotions (e.g. pride, moral disgust), and subtler facets of communication (e.g. sincerity, sarcasm, humour) may be more sensitive to FTD than coarser emotion categories, particularly in early disease, and might therefore

prove a valuable direction for future studies. Enhanced ecological validity may also be achieved through the use of wearable physiological monitoring devices and new developments in magnetoencephalography (MEG) that allow for movement and genuine social interaction during studies of this kind (Jo *et al.*, 2016; Boto *et al.*, 2018). The incorporation of MEG imaging would have additional benefits in terms of temporal resolution, and would allow more precise delineation of alterations in functional connectivity in FTD (Stam, 2010; Hughes *et al.*, 2013).

While efforts to develop the first effective disease-modifying therapy for FTD are ongoing, even symptomatic therapeutic strategies remain scarce. A non-pharmacological approach to the optimisation of verbal communication is used in the PPA syndromes, but is largely based on work in post-stroke aphasias without a strong evidence base in neurodegenerative disease (Carthery-Goulart *et al.*, 2013). Nevertheless, it is possible that similar types of strategy (e.g. assistive augmentative communication and communication skills training) might be useful in optimising non-verbal emotional communication in FTD, and this would merit further exploration. In parallel with this, the education of carers and practical tips to help manage in daily life might alleviate some of the burden of these symptoms. At the very least, carers would hopefully be empowered by a fuller understanding of the complexities of socioemotional dysfunction.

The nature of the deficits identified in this thesis suggests several potential avenues for symptomatic pharmacotherapy. One possible strategy would be the use of neuropeptides such as oxytocin, which has previously been shown to have some benefit on neuropsychiatric symptoms in FTD (Jesso *et al.*, 2011). In health, oxytocin has been found to increase resting heart rate variability, so it is possible that this kind of approach would act via influences on peripheral physiology as well as direct effects on neural function (Kemp *et al.*, 2012). Drugs that modulate central neurotransmitter function may also be of benefit. Deficiencies in most major neurotransmitters are found in the FTD spectrum, including in dopamine, noradrenaline,

serotonin, and acetylcholine (Murley and Rowe, 2018). Although cholinesterase inhibitors are of benefit in Alzheimer's disease, they are associated with worsening of behavioural symptoms in FTD and are therefore unlikely to prove useful (Mendez *et al.*, 2007). However there is some evidence that selective serotonin reuptake inhibitors improve response inhibition in FTD, and therefore have a beneficial effect on behaviour (Hughes *et al.*, 2015). Noradrenaline is associated with generating arousal and enhancing attention to salient stimuli, as well as having a role in autonomic modulation (De Martino *et al.*, 2008; Samuels and Szabadi, 2008). Dopamine also has autonomic control functions, as well as being important for signalling motivation, reward and emotional salience (Gibbs *et al.*, 2007). All of these neurotransmitter systems should therefore be considered candidates for modulation of autonomic arousal, motivation and emotional salience where it is pathologically altered in FTD, and should be explored in future.

Some of the results here raise exciting possibilities for the development of physiological biomarkers in FTD, but a great deal of further work would be required to bring these to fruition. There are four key ways in which such a metric might have clinical utility. Firstly, it might be possible to detect early change, and therefore both hasten and improve the accuracy of diagnosis. To establish this it will be necessary to study patients with very early or even presymptomatic disease (such as those with pathogenic mutations), and to compare them not just to asymptomatic controls but also to those with FTD phenocopies, as in practice it is this distinction that poses the greatest challenge in the clinic. Secondly, a physiological biomarker might dynamically assay neural function, tracking disease progression, and therefore representing a means of measuring the efficacy of a therapeutic intervention. Longitudinal work will be required to further explore this possibility. Thirdly, physiological reactivity could provide a means to validate animal models of FTD where at present there is no reliable assay for capturing the kind of changes in social response that characterise the disease in humans, and indeed this kind of approach is already gaining some traction (Ahmed *et al.*, 2018).

Fourthly, patterns of physiological change that show specificity for underlying anatomical patterns of neurodegeneration might improve the clinico-anatomical stratification of FTD syndromes, and by extension potentially help to define and dynamically track molecular aetiologies in life. Future work in genetic FTD cohorts where the molecular pathology is known will be crucial for defining this potential, and in this way physiology might provide the key missing link in relating molecular changes to complex human behaviours, and fully realising the 'molecular nexopathy' paradigm of neurodegenerative diseases (Warren *et al.*, 2013b).

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APPENDIX

PARTICIPANT INVOLVEMENT BY CHAPTER

Number	Diagnosis	Chapter 3	Chapter 4	Chapter 5	Chapter 6
1	control	✗	✓	✗	✗
2	control	✗	✗	✗	✓
3	control	✓	✓	✓	✓
4	control	✓	✓	✓	✗
5	control	✓	✓	✓	✓
6	control	✗	✓	✗	✓
7	control	✓	✓	✓	✓
8	control	✓	✓	✓	✓
9	control	✓	✓	✓	✓
10	control	✓	✓	✓	✓
11	control	✓	✓	✓	✗
12	control	✓	✓	✓	✓
13	control	✓	✓	✓	✓
14	control	✓	✓	✓	✓
15	control	✓	✓	✓	✗
16	control	✗	✗	✗	✓
17	control	✓	✓	✓	✓
18	control	✓	✓	✓	✓
19	control	✓	✓	✓	✓
20	control	✗	✗	✗	✓
21	control	✓	✓	✓	✗
22	control	✗	✗	✗	✓
23	control	✓	✓	✓	✓
24	control	✗	✗	✗	✓
25	control	✗	✗	✗	✓
26	control	✗	✗	✗	✓
27	control	✓	✓	✓	✗
28	control	✓	✓	✓	✓
29	bvFTD	✗	✗	✗	✓
30	bvFTD	✓	✓	✓	✓
31	bvFTD	✓	✓	✓	✓
32	bvFTD	✗	✗	✗	✓
33	bvFTD	✗	✗	✗	✓
34	bvFTD	✗	✗	✗	✓
35	bvFTD	✗	✓	✗	✓
36	bvFTD	✓	✓	✓	✗
37	bvFTD	✓	✓	✓	✗
38	bvFTD	✓	✓	✓	✓
39	bvFTD	✓	✓	✓	✓

40	bvFTD	✓	✓	✓	✗
41	bvFTD	✓	✓	✓	✓
42	bvFTD	✗	✗	✗	✓
43	bvFTD	✓	✓	✓	✓
44	bvFTD	✓	✓	✓	✗
45	bvFTD	✗	✗	✗	✓
46	bvFTD	✗	✗	✗	✓
47	bvFTD	✗	✗	✗	✓
48	bvFTD	✓	✓	✗	✗
49	bvFTD	✓	✓	✗	✗
50	rtvFTD	✗	✗	✗	✓
51	rtvFTD	✓	✓	✓	✗
52	rtvFTD	✓	✓	✓	✓
53	rtvFTD	✓	✓	✓	✗
54	rtvFTD	✓	✓	✓	✗
55	rtvFTD	✗	✓	✓	✗
56	rtvFTD	✗	✓	✓	✗
57	svPPA	✓	✓	✓	✗
58	svPPA	✗	✗	✗	✓
59	svPPA	✗	✗	✗	✓
60	svPPA	✗	✗	✗	✓
61	svPPA	✗	✓	✗	✓
62	svPPA	✗	✗	✗	✓
63	svPPA	✗	✗	✗	✓
64	svPPA	✓	✓	✓	✓
65	svPPA	✓	✓	✓	✓
66	svPPA	✓	✓	✓	✓
67	svPPA	✗	✗	✗	✓
68	svPPA	✓	✓	✓	✗
69	svPPA	✗	✗	✗	✓
70	svPPA	✓	✓	✓	✗
71	svPPA	✗	✓	✗	✗
72	svPPA	✓	✓	✓	✗
73	svPPA	✗	✗	✗	✓
74	nfvPPA	✗	✗	✗	✓
75	nfvPPA	✓	✓	✓	✗
76	nfvPPA	✓	✓	✓	✗
77	nfvPPA	✓	✓	✓	✗
78	nfvPPA	✗	✗	✗	✓
79	nfvPPA	✓	✓	✓	✗
80	nfvPPA	✓	✓	✓	✗
81	nfvPPA	✗	✗	✗	✓
82	nfvPPA	✗	✗	✗	✓
83	nfvPPA	✗	✗	✗	✓
84	nfvPPA	✗	✗	✗	✓
85	nfvPPA	✓	✓	✓	✗

86	nfvPPA	✓	✓	✓	✓
87	nfvPPA	✓	✓	✓	✗
88	nfvPPA	✓	✓	✓	✗
89	nfvPPA	✗	✗	✗	✓
90	nfvPPA	✗	✗	✗	✓

The table shows participants ordered by diagnostic group, and the chapters in which they participated

PUBLICATIONS ARISING FROM EXPERIMENTAL WORK IN THIS THESIS

Marshall CR, Hardy CJD, Russell LL, Clark CN, Dick KM, Brotherhood EV, et al. Impaired Interoceptive Accuracy in Semantic Variant Primary Progressive Aphasia. Front Neurol. 2017;8:610.

Marshall CR, Hardy CJD, Russell LL, Clark CN, Bond RL, Dick KM, et al. Motor signatures of emotional reactivity in frontotemporal dementia. Scientific Reports. 2018;8(1):1030.

Marshall CR, Hardy CJD, Allen M, Russell LL, Clark CN, Bond RL, et al. Cardiac responses to viewing facial emotion differentiate frontotemporal dementias. Annals of Clinical and Translational Neurology. 2018;0(0).

OTHER RELEVANT FIRST AUTHOR PUBLICATIONS DURING THE TIME PERIOD OF THE THESIS

Marshall CR, Guerreiro R, Thust S, Fletcher P, Rohrer JD, Fox NC. A Novel MAPT Mutation Causing Corticobasal Syndrome Led by Progressive Apraxia of Speech. Journal of Alzheimer's disease : JAD. 2015;48(4):923-6.

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Marshall CR, Hardy CJD, Volkmer A, Russell LL, Bond RL, Fletcher PD, et al. Primary progressive aphasia: a clinical approach. Journal of neurology. 2018.

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Impaired Interoceptive Accuracy in Semantic Variant Primary Progressive Aphasia

Charles R. Marshall[1,2], Chris J. D. Hardy[1], Lucy L. Russell[1], Camilla N. Clark[1], Katrina M. Dick[1], Emilie V. Brotherhood[1], Rebecca L. Bond[1], Catherine J. Mummery[1], Jonathan M. Schott[1], Jonathan D. Rohrer[1], James M. Kilner[2†] and Jason D. Warren[1†]*

[1] Dementia Research Centre, Department of Neurodegenerative Disease, London, United Kingdom, [2] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, United Kingdom

Background: Interoception (the perception of internal bodily sensations) is strongly linked to emotional experience and sensitivity to the emotions of others in healthy subjects. Interoceptive impairment may contribute to the profound socioemotional symptoms that characterize frontotemporal dementia (FTD) syndromes, but remains poorly defined.

Methods: Patients representing all major FTD syndromes and healthy age-matched controls performed a heartbeat counting task as a measure of interoceptive accuracy. In addition, patients had volumetric MRI for voxel-based morphometric analysis, and their caregivers completed a questionnaire assessing patients' daily-life sensitivity to the emotions of others.

Results: Interoceptive accuracy was impaired in patients with semantic variant primary progressive aphasia relative to healthy age-matched individuals, but not in behavioral variant frontotemporal dementia and nonfluent variant primary progressive aphasia. Impaired interoceptive accuracy correlated with reduced daily-life emotional sensitivity across the patient cohort, and with atrophy of right insula, cingulate, and amygdala on voxel-based morphometry in the impaired semantic variant group, delineating a network previously shown to support interoceptive processing in the healthy brain.

Conclusion: Interoception is a promising novel paradigm for defining mechanisms of reduced emotional reactivity, empathy, and self-awareness in neurodegenerative syndromes and may yield objective measures for these complex symptoms.

Keywords: interoception, autonomic, cardiac, empathy, primary progressive aphasia, frontotemporal dementia

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***Correspondence:**
Jason D. Warren
jason.warren@ucl.ac.uk

†*Joint senior authors.*

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INTRODUCTION

Interoception (the ability to sense one's internal physiological states) is closely linked to emotional experience (1) and can be measured using awareness of one's heartbeat as a surrogate for interoceptive sensitivity (2, 3). According to recent interoceptive inference formulations, hierarchically organized brain networks compare afferent interoceptive information with predictions about bodily states, with prediction errors activating autonomic reflexes or motivating actions to maintain homeostasis (4). At lower hierarchical levels, these relate to direct physiological homeostasis, such as maintaining blood oxygen and glucose levels. Coherent representations of the physiological

state of one's body are important determinants of subjective feeling states (5), and those with weaker interoception are less able to identify and describe their own emotions (6). At higher hierarchical levels, inferences about more complex causes of physiological perturbations can be made, such as the autonomic changes induced by the emotions of others. Interoception is therefore hypothesized to play a key role in empathy and theory of mind (7). This is borne out by evidence showing that interoceptive ability predicts both sensitivity to the emotions of others and performance on emotional theory of mind tasks (8, 9). Empathy has been correlated with the magnitude of heartbeat-evoked potentials, and both cognitive and neural responses to the emotions of others are influenced by stimulus timing within the cardiac cycle (10–12).

Interoceptive signals and exteroceptive information from the environment are integrated in a reciprocal manner, with diminished interoception tending to promote greater environmental dependency, and *vice versa*. Those with less interoceptive ability are more susceptible to exteroceptive signals that alter perception of body ownership (13), while inducing the illusion of decreased body ownership reduces both the amplitude of heartbeat-evoked potentials (14) and the ability to cognitively detect signals arising from the heart (15). Interoception is therefore likely to play a key role in generating a coherent sense of the bodily self. The reciprocal relationship between interoception and exteroception has also been demonstrated in perceptual decision-making, with interoceptive arousal limiting the influence of exteroceptive sensory noise on confidence (16). Interoception entails dissociable cognitive dimensions, interoceptive accuracy (objective reporting) supporting awareness (confidence in interoceptive judgments) (3). Interoceptive sensitivity is mediated principally by cingulate and insula (17) under the influence of amygdala (18). Together, these structures constitute a network engaged in both interoception and emotion processing (5).

Interoception has been hypothesized to be a factor mediating changes in emotional sensitivity in normal aging (19). Different dimensions of interoception—accuracy and awareness—might be separately targeted by brain disease. One leading candidate, on clinical and neuroanatomical grounds, is the group of neurodegenerative diseases comprising frontotemporal dementia (FTD). This heterogeneous entity comprises three major clinicoanatomical syndromes: behavioral variant frontotemporal dementia (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent variant primary progressive aphasia (nfvPPA). All three syndromes profoundly disrupt emotional and physiological reactivity (20–22), producing complex neuropsychiatric symptoms such as loss of empathy and altered bodily awareness (23, 24). These symptoms are of key clinical relevance but remain difficult to measure and poorly understood (25). Impaired interoception is a plausible mechanism that may link neurodegeneration to socioemotional phenotypes in FTD (26). However, interoceptive processing has not been studied systematically in the FTD syndromic spectrum nor specifically related to reduced emotional awareness in particular FTD syndromes and to underlying neuroanatomical substrates (26).

Here, we used heartbeat counting to assess interoceptive accuracy in canonical FTD syndromes (svPPA, bvFTD, and nfvPPA) versus healthy older individuals. We related patients' interoceptive accuracy both to a clinical index of emotional sensitivity and to regional gray matter on voxel-based morphometry (VBM). As all syndromes within the FTD spectrum are associated with socioemotional deficits and insular atrophy, some degree of impaired interoception leading to abnormal emotional awareness is anticipated across the FTD spectrum. However, among FTD syndromes, svPPA in particular has been linked to abnormally heightened responsiveness to exteroceptive stimuli (24), altered bodily awareness, and an impoverished concept of self (27). The associations between interoception, exteroception, body ownership, and sense of self identified in the healthy brain (13–16) suggest that reduced interoceptive accuracy may be a core feature of svPPA and disproportionately severe in this syndrome relative to other FTD syndromes. Moreover, incorporation of interoceptive information into emotional judgments has been shown to depend on the amygdala, which is particularly severely affected in svPPA (18, 28). This further suggests a brain mechanism that could link reduced interoceptive accuracy to loss of emotional sensitivity in this syndrome. We therefore hypothesized that all FTD syndromes would be associated with a degree of impaired interoception leading to reduced emotional sensitivity, but that svPPA would be associated with a particularly severe deficit of interoceptive accuracy, based on the specific psychophysiological profile of this syndrome and linked to grey matter loss in a frontotemporal network including amygdala.

MATERIALS AND METHODS

Participants

Thirty-two consecutive patients fulfilling consensus criteria for a syndrome of FTD (29, 30) (16 bvFTD, 7 svPPA, and 9 nfvPPA) and 19 age-matched healthy individuals [overall 51 participants, mean age 67.6 years (range 51–84), 22 females] participated. No participant had a history of cardiac arrhythmia, clinical depression, or anxiety disorder. Neuropsychological assessment and MR brain imaging corroborated the syndromic diagnosis in all patients. Clinical, demographic, and neuropsychological characteristics of all participants are summarized in **Table 1**. Participant groups did not differ significantly in age or gender, symptom duration, or use of antihypertensive medication; no participant was taking cardiac rate-limiting medication. The study was approved by the local ethics committee and all participants gave informed consent.

Heartbeat Counting Task

We adapted a previously described heartbeat counting task as a measure of interoceptive accuracy (2, 3). Participants were asked to try to identify their heartbeats by "listening to their body" (rather than feeling their pulse) and were first familiarized with the paradigm to ensure they understood the task. ECG was recorded continuously from electrodes placed over the right clavicle and left iliac crest. During the experiment, the number of sensed beats was reported for four epochs of variable duration (25, 35, 45, and 100 s) signaled by start and stop tones and presented in

TABLE 1 | Clinical and neuropsychological characteristics of participant groups.

Characteristic	Controls	bvFTD	svPPA	nfvPPA
Demographic and clinical				
No (m:f)	8:11	13:3	5:2	4:5
Age (years)	68.8 (5.5)	65.8 (7.3)	65.9 (7.4)	69.6 (6.5)
Handedness (R:L:A)	17:1:1	15:1:0	7:0:0	7:2:0
MMSE (/30)	29.6 (0.6)	24.6 (4.5)[a]	22.6 (5.8)[a]	23.7 (6.0)[a]
Duration (years)	N/A	7.6 (4.7)	4.4 (2.0)	4.6 (2.2)
EX	N/A	5.4 (4.7)[d]	9.5 (2.3)[d]	20.0 (7.6)
Mean heart rate	69.5 (10.2)[d]	72.5 (12.9)	69.7 (5.2)[d]	85.5 (17.1)
Neuropsychological				
General intellect				
WASI verbal IQ	125.4 (7.0)	86.4 (22.4)[a]	78.6 (20.4)[a]	80.0 (17.3)[a]
WASI performance IQ	125.1 (9.7)	102.44 (21.4)[a]	112.3 (20.1)	98.8 (21.5)[a]
Episodic memory				
RMT words (/50)	49.3 (0.9)	36.2 (8.0)[a]	30.3 (6.9)[a,d]	41.4 (9.5)[a]
RMT faces (/50)	44.7 (3.7)	34.0 (7.6)[a]	32.7 (6.4)[a]	39.5 (6.6)
Camden PAL (/24)	20.3 (3.5)	10.5 (7.5)[a]	2.7 (4.2)[a,b,d]	16.3 (7.8)
Executive skills				
WASI block design (/71)	46.0 (10.1)	32.6 (19.2)	41.6 (19.0)	25.1 (19.7)[a]
WASI matrices (/32)	26.6 (4.1)	17.8 (9.4)[a]	21.7 (8.5)	17.4 (9.0)[a]
WMS-R digit span forward (max)	7.1 (1.2)	6.6 (1.2)	7.0 (1.2)	4.8 (0.8)[a,b,c]
WMS-R digit span reverse (max)	5.6 (1.3)	4.4 (1.4)	5.1 (2.0)	3.0 (0.7)[a]
D-KEFS Stroop color naming (s)	32.4 (6.4)[b,d]	49.5 (20.8)[d]	50.3 (27.9)[d]	87.0 (6.7)
D-KEFS Stroop word reading (s)	23.5 (5.7)[d]	35.9 (22.2)[d]	30.9 (19.2)[d]	85.4 (10.3)
D-KEFS Stroop interference (s)	56.2 (16.9)[b,d]	103.3 (47.3)[d]	82.7 (50.5)[d]	165.0 (30.8)
Letter fluency (F: total)	18.1 (5.7)	7.6 (4.4)[a]	9.7 (7.2)[a]	3.5 (1.7)[a]
Category fluency (animals: total)	24.7 (5.9)	11.6 (6.2)[a]	6.7 (5.4)[a]	8.8 (3.5)[a]
Trails A (s)	32.2 (5.6)[b,d]	59.5 (33.5)	47.0 (21.0)	81.7 (48.4)
Trails B (s)	66.1 (20.5)[b,d]	184.1 (89.0)	133.6 (110.1)	211.1 (94.6)
Language skills				
WASI vocabulary	72.2 (3.4)	42.6 (21.8)[a]	34.7 (22.7)[a]	31.7 (13.9)[a]
BPVS	148.5 (1.1)	123.8 (35.3)[a]	94.4 (49.4)[a,d]	142.6 (10.1)
GNT	26.3 (2.4)	10.6 (9.8)[a]	2.0 (5.3)[a,b,d]	15.5 (6.6)[a]
Posterior cortical skills				
GDA (/24)	15.8 (5.4)	7.8 (5.7)[a]	11.3 (8.3)	5.4 (1.9)[a]
VOSP Object Decision (/20)	19.1 (1.6)	15.6 (3.0)[a]	15.7 (5.1)	15.3 (4.7)[a]

Mean (SD) scores are shown unless otherwise indicated; maximum scores are shown after tests (in parentheses).

[a]Significantly less than controls, [b]significantly less than bvFTD, [c]significantly less than SD, [d]significantly less than PNFA (all $p < 0.05$).

BPVS, British Picture Vocabulary Scale (31); category fluency for animal category and letter fluency for the letter F in 1 min (32); EX, sensitivity to the emotions of others component of the Revised Self-Monitoring Scale (33); GDA, Graded Difficulty Arithmetic (34); GNT, Graded Naming Test (35); MMSE, Mini-Mental State Examination score (36); N/A, not assessed; PAL, Paired Associate Learning test (37); RMT, Recognition Memory Test (38); Stroop D-KEFS, Delis Kaplan Executive System (39); Trails-making task based on maximum time achievable 2.5 min on task A, 5 min on task B (40); VOSP, Visual Object and Spatial Perception Battery (41); WAIS-R, Wechsler Adult Intelligence Scale – Revised (42); WASI, Wechsler Abbreviated Scale of Intelligence (43); WMS, Wechsler Memory Scale (44).

randomized order, to preclude anticipation or guessing based on previous epochs. For each participant, an interoceptive accuracy index (IA) was calculated based on an established method as follows (3):

$$1 - \left|\text{actual beats} - \text{reported beats}\right| / ((\text{actual beats} + \text{reported beats}) / 2).$$

Emotional Sensitivity Rating

Patients' caregivers completed the Sensitivity to Socioemotional Expressiveness Score (EX) component of the Revised Self-Monitoring Scale (33), a daily-life index of sensitivity to the emotions of others.

Data Analysis

Between-group differences were assessed using ANOVAs, except where the homogeneity of variance assumption was violated, when Welch's *F* test and Games Howell *post hoc* tests (a multiple comparison procedure without the assumption of homoscedasticity) were used. In addition, we assessed correlations of IA with EX (sensitivity to others' emotions), auditory reverse digit span (a standard index of nonverbal sensory working memory), British Picture Vocabulary score (a standard measure of semantic comprehension), and mean heart rate (a peripheral interoceptive signal characteristic). A threshold $p < 0.05$ was accepted as the significance criterion for all tests.

Brain Image Acquisition and Analysis

Each patient had a sagittal 3-D magnetization-prepared rapid-gradient-echo T1-weighted volumetric brain MR sequence (TE/TR/TI 2.9/2,200/900 ms, dimensions 256 256 208, voxel size 1.1 mm^3), acquired on a Siemens Trio 3 T MRI scanner using a 32-channel phased-array head-coil. Normalization, segmentation, and modulation of gray and white matter images were

performed using SPM12[1] with default parameter settings and gray matter images were smoothed using a 6 mm full width-at-half-maximum Gaussian kernel. A study-specific template mean brain image was created by warping all bias-corrected native space brain images to the final DARTEL template and calculating the average of the warped brain images. Total intracranial volume (TIV) was calculated for each patient by summing gray matter, white matter, and cerebrospinal fluid volumes following segmentation of all three tissue classes.

A full factorial model was used to assess associations between IA and regional gray matter volume (voxel intensity) within each syndromic group, incorporating age and TIV as covariates of no interest. Statistical parametric maps of regional gray matter associations were assessed at threshold $p < 0.05$ after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-determined regions of interest [cingulate cortex, insula, and amygdala (17, 18) defined from the Harvard-Oxford Brain Atlas].[2]

RESULTS

Interoceptive accuracy data and neuroanatomical correlates are presented in **Figure 1**.

The homogeneity of variance assumption was violated for IA data (Levene's test $p = 0.001$). Welch's F test revealed a main effect of participant group on IA ($p = 0.021$). Games Howell *post hoc* tests showed that IA was significantly lower in the svPPA group than healthy controls ($p = 0.022$). No other significant group differences were identified for IA. Mean EX was significantly higher in the nfvPPA group than the other patient groups ($p < 0.001$) but did not differ between the bvFTD and svPPA groups ($p = 0.29$). Across the patient cohort, there was a significant positive correlation between IA and EX (rho = 0.516, $p = 0.004$); there was no significant association between IA and reverse digit span (rho = 0.133, $p = 0.372$), British Picture Vocabulary Score (rho = 0.242, $p = 0.09$), mean heart rate (rho = 0.038, $p = 0.8$), age (rho = −0.062, $p = 0.67$), disease duration (rho = −0.1, $p = 0.59$), or antihypertensive use ($p = 0.5$).

In the svPPA group, IA was significantly positively associated with gray matter volume in right amygdala, right anterior, and posterior cingulate cortex and right insula (all $p < 0.05_{FWE}$ within pre-specified regions of interest). No significant gray matter associations were identified at the prescribed threshold in the other patient groups.

DISCUSSION

Our findings demonstrate that interoceptive accuracy is impaired in svPPA relative to healthy older individuals. There was a wide range of IA scores in the control group, as typically found in studies of healthy individuals (3, 13). Overall performance in the control group was lower than typically found in studies of younger subjects, with several being unable to detect heartbeats, but this is consistent with evidence that interoception declines with age (45–47). Over the patient cohort, impaired IA did not correlate with any reduction in generic sensory monitoring, semantic capacity, or peripheral interoceptive signal. In line with current models of interoception (3, 17, 18) and evidence for abnormal processing of homeostatic and affective signals in FTD syndromes (21), the findings suggest that svPPA affects the initial cognitive decoding of interoceptive signals. Interoceptive accuracy in the patient cohort was correlated with sensitivity to others' emotions: coupled with evidence in the healthy brain (3, 8–10, 17, 18), this suggests that degraded inference of others' emotions from one's own embodied responses might serve as a generic mechanism for the blunted emotional reactivity and empathy loss that characterizes FTD and may be particularly pervasive in svPPA (20). Moreover, interoceptive impairment is a plausible mechanism for the severe impoverishment of self-projection described in svPPA, and for the increased dependency on exteroceptive signals found in these patients (24, 27).

Emotional sensitivity was comparably reduced in both the svPPA and bvFTD groups (relative to the nfvPPA group) here,

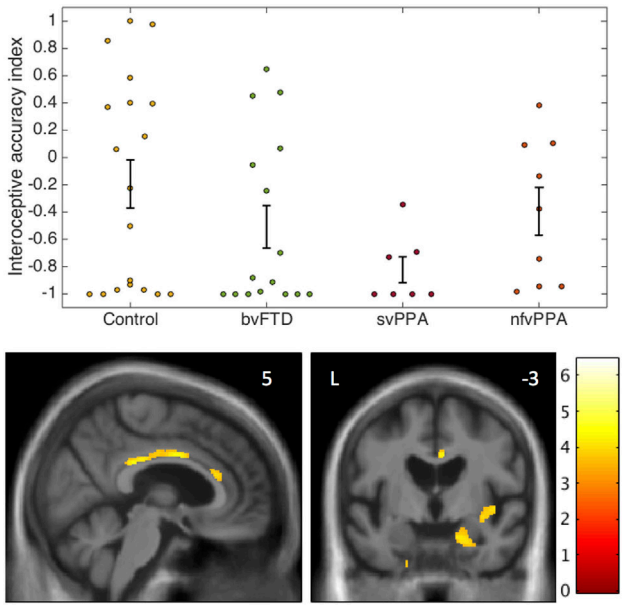

FIGURE 1 | Interoceptive accuracy in participant groups: behavioral and voxel-based morphometry data. The plots (above) show individual raw data for accuracy on the heartbeat counting task expressed as an interoceptive accuracy index (see text) in each participant group. Error bars represent SEM. The statistical parametric map of regional gray matter volume associated with interoceptive accuracy in the impaired svPPA group (below) has been overlaid on representative sections of the normalized study-specific T1-weighted group mean brain MR image; the MNI coordinate (millimeters) of the plane of each section is indicated. The color barcodes T values; the SPM is thresholded here at $p < 0.001$ uncorrected over the whole brain for display purpose. Regional local maxima were significant at $p < 0.05_{FWE}$ corrected for multiple comparisons over the whole brain (right amygdala, MNI coordinates [18 −15 −21]) or within pre-specified anatomical regions of interest (anterior cingulate cortex [4 0 34]; posterior cingulate cortex [2 −30 28]; right insula [44 −4 −3]). bvFTD, patients with behavioral variant frontotemporal dementia; Control, healthy control group; L, left; nfvPPA, patients with nonfluent variant primary progressive aphasia; svPPA, patients with semantic variant primary progressive aphasia.

[1] www.fil.ion.ucl.ac.uk/spm.

[2] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases.

while bvFTD has been associated with impaired interoceptive awareness in previous work (26). Taken together with the present findings, the emerging picture suggests a complex stratification of autonomic abnormalities across FTD syndromes: autonomic reactivity in these syndromes may be differentially altered under particular conditions (such as detection of salient changes in self or environment versus monitoring of bodily states) (21, 26). FTD syndromes may target separable levels of interoceptive processing, svPPA producing a more fundamental deficit of interoceptive signal analysis and decoding of autonomic responses to emotion, while bvFTD impairs autonomic reactivity and the metacognitive analysis of body state representations in self and others (22, 48, 49). The neuroanatomical substrate for impaired interoceptive accuracy in the present svPPA group comprised a rightward-asymmetric cingulo-insulo-amygdalar network: this network is encompassed by the distributed atrophy profile of svPPA (28), has been previously implicated in interoception both in the healthy brain and disease states (17, 18, 26), and is well-placed anatomically to integrate homeostatic and external socioemotional signals in building representations of self and others (5).

This small study provides proof of principle for further systematic investigation of interoception as an attractive, novel paradigm for deconstructing complex deficits of emotional reactivity, empathy, and self-awareness in neurodegenerative syndromes. At present, we lack quantifiable metrics for cardinal socioemotional symptoms of dementia. Interoception may plausibly underpin such symptoms and can be assessed using simple, objectively verifiable procedures. Clearly, the variation in intrinsic interoceptive sensitivity among healthy people will need to be taken into account in applying interoceptive measures in clinical settings. However, acknowledging this caveat, interoceptive sensitivity warrants further evaluation, both as a potential biomarker in individuals with retained baseline capacity to perform the task and to identify neuroanatomical and physiological correlates, which might yield outcome measures in clinical trials. Future work should assess different interoceptive dimensions longitudinally, in larger cohorts sampling representatively across syndromes and with molecular correlation, to determine the reliability, sensitivity, and specificity of potential interoceptive biomarkers. Larger studies with greater power may additionally reveal less profound interoceptive deficits within the heterogeneous bvFTD population. Control conditions involving exteroceptive counting tasks of comparable difficulty might help to further disambiguate interoceptive deficits from other cognitive difficulties impairing task performance. The use of passive interoception tasks such as those based on stimulus timing in the cardiac cycle and measurement of heartbeat-evoked potentials would also be of value to provide further confirmation that deficits in interoceptive reporting are not confounded by other neuropsychological impairments (12, 50).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of The National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by The National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee.

AUTHOR CONTRIBUTIONS

Conception and design of the study: CM, JK, and JW. Acquisition and analysis of data: CM, CH, LR, CC, KD, EB, CM, JS, JR, JK, and JW. Drafting of manuscript: CM, CH, RB, JS, JK, and JW.

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Motor signatures of emotional reactivity in frontotemporal dementia

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Charles R. Marshall[1,2], Chris J. D. Hardy[1], Lucy L. Russell[1], Camilla N. Clark[1], Rebecca L. Bond[1], Katrina M. Dick[1], Emilie V. Brotherhood[1], Cath J. Mummery[1], Jonathan M. Schott[1], Jonathan D. Rohrer[1], James M. Kilner[2] & Jason D. Warren[1]

Automatic motor mimicry is essential to the normal processing of perceived emotion, and disrupted automatic imitation might underpin socio-emotional deficits in neurodegenerative diseases, particularly the frontotemporal dementias. However, the pathophysiology of emotional reactivity in these diseases has not been elucidated. We studied facial electromyographic responses during emotion identification on viewing videos of dynamic facial expressions in 37 patients representing canonical frontotemporal dementia syndromes versus 21 healthy older individuals. Neuroanatomical associations of emotional expression identification accuracy and facial muscle reactivity were assessed using voxel-based morphometry. Controls showed characteristic profiles of automatic imitation, and this response predicted correct emotion identification. Automatic imitation was reduced in the behavioural and right temporal variant groups, while the normal coupling between imitation and correct identification was lost in the right temporal and semantic variant groups. Grey matter correlates of emotion identification and imitation were delineated within a distributed network including primary visual and motor, prefrontal, insular, anterior temporal and temporo-occipital junctional areas, with common involvement of supplementary motor cortex across syndromes. Impaired emotional mimesis may be a core mechanism of disordered emotional signal understanding and reactivity in frontotemporal dementia, with implications for the development of novel physiological biomarkers of socio-emotional dysfunction in these diseases.

Motor mimicry supports the decoding of perceived emotions by the healthy brain[1,2]. Viewing emotional facial expressions rapidly and involuntarily engages the facial muscles of neurologically normal observers[3,4]. Emotional mimesis may have evolved as a specialized 'exaptation' of action observation, and by promoting emotional contagion and affective valuation may have facilitated the development of advanced human social behaviour and theory of mind[2,5,6]. In line with this interpretation, motor recoding of observed emotion correlates with empathy and emotion identification ability[7] and predicts authenticity judgments on facial expressions[8]; while conversely, facial paralysis induced by botulinum toxin attenuates emotional reactivity[9]. The linkage between emotion observation, recognition and mimesis is precise: viewing of universal facial emotional expressions[10] produces signature profiles of electromyographic (EMG) activity in the facial muscles conveying each expression[3,11]. This phenomenon is mediated by distributed, cortico-subcortical brain regions that may together instantiate a hierarchically organised neural substrate for inferring the intentions and subjective states of others[12–15]: primary visual representations of emotions would comprise the lowest level of the hierarchy, ascending through sensorimotor representations of emotional movement kinematics, prediction of movement goals and affective states, and encoding of intentions, including affective mentalising.

On clinical, pathophysiological and neuroanatomical grounds, altered motor recoding might be anticipated to underlie impaired emotional and social signal processing in the frontotemporal dementias (FTD). This diverse group of neurodegenerative diseases manifests as three canonical clinico-anatomical syndromes[16]; behavioural

[1]Dementia Research Centre, Department of Neurodegenerative Disease, Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK. [2]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK. James M. Kilner and Jason D. Warren jointly supervised this work. Correspondence and requests for materials should be addressed to C.R.M. (email: charles.marshall@ucl.ac.uk)

variant (bvFTD), semantic variant primary progressive aphasia (svPPA) and nonfluent variant primary progressive aphasia (nfvPPA). These broad syndromic groupings encompass various sub-syndromes: in particular, within the heterogeneous bvFTD syndrome at least two major variants can be defined, based on the relative selectivity of right temporal lobe atrophy[17,18]. Deficits in emotion recognition, empathy and social understanding and behaviour are defining features of bvFTD but integral to all FTD syndromes[19–24] and collectively engender substantial distress and care burden[25]. Impaired facial emotion recognition in bvFTD, svPPA and nfvPPA has been linked to atrophy of an overlapping network of cerebral regions including orbitofrontal cortex, posterior insula and antero-medial temporal lobe[23,26], implicated in evaluation of facial emotional expressions and integration with bodily signals[27–29]. Moreover, various abnormalities of physiological reactivity have been documented in FTD, including changes in resting skin conductance and heart rate variability in bvFTD and altered homeostatic and affective autonomic responses in bvFTD, svPPA and nfvPPA[30–36]. Patients with bvFTD have been noted to have reduced facial expressivity[37] and indeed, deficient volitional imitation of emotional faces[38]. However, whereas impaired facial EMG reactivity to facial expressions has been linked to emotion processing deficits in Parkinson's disease[39,40], Huntington's disease[41] and schizophrenia[42], the motor physiology of emotional reactivity has not been addressed in the FTD spectrum.

In this study, we investigated facial motor responses to viewing facial emotional expressions in a cohort of patients representing all major phenotypes of FTD (bvFTD, svPPA and nfvPPA) relative to healthy older individuals. In addition to the canonical syndromic FTD variants, we identified a subset of patients presenting with behavioural decline and selective right temporal lobe atrophy (right temporal variant, rtvFTD): this entity has been proposed previously to account for much of the heterogeneity of the broader bvFTD syndromic spectrum and is associated with particularly severe disturbances of facial empathy[18,38,43,44]. We compared facial EMG response profiles with emotion identification accuracy on a stimulus set comprising video recordings of dynamic, natural facial expressions: such expressions are more faithful exemplars of the emotions actually encountered in daily life and are anticipated to engage mechanisms of motor imitation more potently than the static images conventionally used in neuropsychological studies[45,46]. Neuroanatomical associations of facial expression identification and EMG reactivity in the patient cohort were assessed using voxel-based morphometry (VBM). Based on previous clinical and physiological evidence[3,4,30,31,33,34,36,37,43,47], we hypothesised that healthy older individuals would show rapid and characteristic patterns of facial muscle responses to perceived emotional expressions coupled with efficient emotion identification. In contrast, we hypothesised that all FTD syndromes would be associated with impaired emotion identification but would exhibit separable profiles of facial muscle reactivity. In particular, we predicted that bvFTD and rtvFTD would be associated with reduced EMG responses while svPPA would be associated with aberrant coupling of muscle reactivity to emotion identification and nfvPPA with a more selective, emotion-specific reactivity profile. Based on previous neuroimaging studies both in the healthy brain and in FTD[14,23,26,45,48–50], we further hypothesised that facial emotion identification and EMG reactivity would have partly overlapping neuroanatomical correlates within the extensive cortical circuitry previously implicated in the decoding of visual emotional signals, supplementary motor and insular cortices mediating the integration of somatic representations and antero-medial temporal and prefrontal circuitry involved in the evaluation of emotion. Within these distributed networks (given the known neuroanatomical heterogeneity of the target syndromes) we predicted a differential emphasis of grey matter correlates, with more marked involvement of inferior frontal, anterior cingulate and insular cortices in bvFTD and nfvPPA and more extensive, lateralised temporal lobe involvement in svPPA and rtvFTD[16–18].

Materials and Methods

Participants. Thirty-seven consecutive patients fulfilling consensus criteria for a syndrome of FTD[51,52] (19 with bvFTD, nine with svPPA, nine with nfvPPA) and 21 healthy older individuals with no history of neurological or psychiatric illness participated. General characteristics of the participant groups are summarised in Table 1. No participant had a history of facial palsy or clinically significant visual loss after appropriate correction. There was clinical evidence of orofacial apraxia in seven patients in the nfvPPA group, but none in any of the other participant groups. General neuropsychological assessment (see Table 1) and brain MRI corroborated the syndromic diagnosis in all patients; no participant had radiological evidence of significant cerebrovascular damage. Based on visual inspection of individual brain MR images, six patients with a behavioural syndrome and relatively selective right temporal lobe atrophy were re-categorised as a rtvFTD subgroup (throughout this paper, we use 'bvFTD' to refer to those patients with a behavioural presentation not re-classified as rtvFTD). Between group differences in demographic and neuropsychological variables were analysed using ANOVAs with post hoc T-tests when main effects were found, except for categorical variables, for which a chi-squared test was used.

This study was approved by the University College London institutional ethics committee and all methods were performed in accordance with the relevant guidelines and regulations. All participants gave informed consent in accordance with the Declaration of Helsinki.

Facial expression stimuli. Videos of emotional facial expressions were obtained from the Face and Gesture Recognition Research Network (FG-NET) database[53]. This database comprises silent recordings of healthy young adults viewing emotional scenarios: the scenarios were designed to elicit spontaneous, canonical facial expressions, but were presented without any instruction to pose or inhibit particular expressions (further details in Supplementary Material). In order to sample the spectrum of facial expressions, for each of the canonical emotions of anger, fear, happiness, surprise and disgust[10] we selected 10 videos (50 stimuli in total; see Table S1) that clearly conveyed the relevant expression (the canonical emotion of sadness was omitted because its more diffuse time course sets it apart from other emotional expressions). Each video stimulus lasted between four and eight seconds (mean 4.9 seconds), commencing as a neutral facial expression and evolving into an emotional expression (further information in Supplementary Material). The video frame in which an emotional expression first

Characteristic	Controls	bvFTD	rtvFTD	svPPA	nfvPPA
Demographic/clinical					
No. (male:female)	9:12	10:3	6:0[a]	7:2	4:5
Age (years)	69.1 (5.3)	66.2 (6.3)	63.8 (6.4)	66.1 (6.5)	69.6 (6.5)
Handedness (R:L)	20:1	12:1	6:0	8:1	7:2
Education (years)	15.7 (3.5)	13.2[c] (2.5)	18.0 (3.1)	14.9 (2.8)	15.0 (2.1)
MMSE (/30)	29.6 (0.6)	24.5[a] (4.6)	25.3[a] (4.3)	21.8[a] (6.9)	23.7[a] (6.0)
Symptom duration (years)	N/A	7.7 (6.0)	6.5 (3.5)	5.6 (3.0)	4.7 (2.2)
Neuropsychological					
General intellect					
WASI Verbal IQ	125 (6.7)	89[a] (21.9)	87[a] (22.2)	77[a] (19.7)	80[a] (17.3)
WASI Performance IQ	125 (10.2)	104[a] (20.3)	107 (24.6)	108 (23.5)	99[a] (21.5)
Episodic memory					
RMT words (/50)	49.0 (1.4)	37.4[a] (7.9)	37.2[a] (9.3)	30.0[a,c] (6.3)	41.4[a] (9.5)
RMT faces (/50)	44.7 (3.5)	33.5[a] (6.9)	34.8[a] (7.9)	32.8[a] (6.9)	39.5 (6.6)
Camden PAL (/24)	20.4 (3.3)	10.8[a] (8.1)	12.5[a] (6.2)	2.2[a,b,c,e] (3.7)	16.3 (7.8)
Executive skills					
WASI Block Design (/71)	44.8 (10.5)	32.5 (16.7)	37.2 (22.1)	39.1 (21.7)	25.1[a] (19.7)
WASI Matrices (/32)	26.6 (3.9)	19.3[a] (9.4)	19.0[a] (9.8)	19.8[a] (10.6)	17.4[a] (9.0)
WMS-R DS forward (max)	7.1 (1.1)	6.6 (1.2)	6.8 (1.2)	6.7 (1.2)	4.8[a,b,c,d] (0.8)
WMS-R DS reverse (max)	5.6 (1.2)	4.0[a] (1.5)	4.7 (1.4)	5.3 (1.8)	3.0[a, d] (0.7)
D-KEFS Stroop:					
color (s)	33.4 (7.2)	48.0 (20.5)	48.8 (21.4)	53.2[a] (28.2)	87.0[a,b,c,d] (6.7)
word (s)	23.9 (5.6)	32.5 (19.0)	38.7 (26.1)	36.0 (24.0)	85.4[a,b,c,d] (10.3)
interference (s)	57.6 (16.7)	99.6[a] (47.5)	98.3 (45.1)	90.1 (56.1)	165[a,b,c,d] (30.8)
Fluency:					
letter (F total)	18.1 (5.6)	7.8[a] (4.6)	9.0[a] (4.7)	8.9[a] (7.1)	3.5[a] (1.7)
category (animals total)	24.4 (6.0)	13.8[a] (7.5)	10.3[a] (2.3)	5.7[a,b] (5.1)	8.8[a] (3.5)
Trails A (s)	33.7 (7.3)	56.5 (32.3)	59.8 (32.9)	49.7 (20.1)	81.7[a] (48.4)
Trails B (s)	67.3 (21.5)	171.7[a] (88.2)	186.7[a] (100.4)	134.9 (101.7)	211.1[a] (94.6)
Language skills					
WASI Vocabulary	72.3 (3.2)	42.4[a] (21.5)	47.0[a] (19.1)	33.6[a] (22.0)	31.7[a] (13.9)
BPVS	148.6 (1.1)	120.8 (38.7)	141.8 (7.2)	85.8[a,b,c,e] (53.8)	142.6 (10.1)
GNT	26.1[a] (2.7)	12.2[a] (10.2)	12.5 (10.1)	1.6[a,b,c,e] (4.7)	15.5[a] (6.6)
Other skills					
GDA (/24)	15.8 (5.3)	7.8[a] (6.6)	7.5[a] (6.3)	11.9 (8.6)	5.4[a] (1.9)
VOSP (/20)	19.0 (1.5)	15.9[a] (3.4)	16.7 (2.3)	15.8 (4.5)	15.3[a] (4.7)

Table 1. Demographic, clinical and neuropsychological characteristics of participant groups. Mean (standard deviation) scores are shown unless otherwise indicated; maximum scores are shown after tests (in parentheses). [a]significantly different from healthy controls, [b]significantly different from bvFTD, [c]significantly different from rtvFTD, [d]significantly different from svPPA, [e]significantly different from nfvPPA (all $p < 0.05$). BPVS, British Picture Vocabulary Scale (Dunn LM *et al*., 1982); bvFTD, patient group with behavioural variant frontotemporal dementia (excluding right temporal cases); Category fluency totals for animal category and letter fluency for the letter F in one minute (Gladsjo *et al*., 1999); Controls, healthy control group; D-KEFS, Delis Kaplan Executive System (Delis *et al*., 2001); DS, digit span; GDA, Graded Difficulty Arithmetic (Jackson M and Warrington, 1986); GNT, Graded Naming Test (McKenna and Warrington, 1983); MMSE, Mini-Mental State Examination score (Folstein *et al*., 1975); N/A, not assessed; NART, National Adult Reading Test (Nelson, 1982); nfvPPA, patient group with nonfluent variant primary progressive aphasia; PAL, Paired Associate Learning test (Warrington, 1996); RMT, Recognition Memory Test (Warrington, 1984); rtvFTD, patient subgroup with right temporal variant frontotemporal dementia; svPPA, patient group with semantic variant primary progressive aphasia; Synonyms, Single Word Comprehension: A Concrete and Abstract Word Synonyms Test (Warrington *et al*., 1998); Trails-making task based on maximum time achievable 2.5 minutes on task A, 5 minutes on task B (Lezak *et al*., 2004); VOSP, Visual Object and Spatial Perception Battery – Object Decision test (Warrington and James, 1991); WAIS-R, Wechsler Adult Intelligence Scale--Revised (Wechsler, 1981); WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1997); WMS, Wechsler Memory Scale (Wechsler, 1987).

began to develop unambiguously from the neutral baseline (previously determined by independent normal raters and provided with the FG-NET database) was used to align data traces across trials.

Stimuli were presented in randomised order via the monitor of a notebook computer running the Cogent toolbox of Matlab R2012b. The participant's task on each trial was to identify from among the five alternatives

(verbally or by pointing to the appropriate written name) which emotion was displayed; participant responses were recorded for offline analysis. Participants were first familiarised with the stimuli and task to ensure they understood and were able to comply with the protocol. During the test, no feedback was given and no time limits were imposed on responses. Emotion identification scores were compared among groups using ANOVAs, with Bonferroni-corrected post hoc T-tests when main effects were found.

EMG acquisition and analysis. While participants viewed the video stimuli, facial EMG was recorded continuously from left corrugator supercilii, levator labii and zygomaticus major muscles with bipolar surface electrodes, according to published guidelines for the use of EMG in research[54]. These facial muscles were selected as the key drivers of the canonical expressions represented by the video stimuli[3,11]. Expressions of anger and fear engage corrugator supercilii (which knits the brow) and inhibit zygomaticus major (which raises the corner of the mouth); expressions of happiness and surprise are associated with the reverse muscle activity profile, while disgust engages both corrugator supercilii and levator labii (which curls the top lip). EMG data were sampled at 2048Hz with a 0.16–100Hz band-pass filter and the EMG signal was rectified, high-pass filtered to correct for baseline shifts and smoothed with a 100 data point sliding filter using MATLAB R2012b; trials with signal amplitude >3 standard deviations from the mean (attributable to large artifacts, e.g., blinks) were removed prior to analysis. For each trial, the mean change in EMG activity from baseline (mean activity during a 500 ms period prior to trial onset) was analysed for each muscle in 500 ms epochs, starting 1s before the onset of expression change in the video stimuli; the EMG response for each muscle was calculated as the area under the curve of EMG signal change from baseline.

We first assessed the presence of automatic imitation (any EMG change from baseline) and emotion-specific muscle activation (any interaction of muscle EMG response with emotion) for the healthy control group, using a repeated measures ANOVA (mean EMG activity for five emotions in eight 500 ms time bins for the three muscles). To determine if there was an overall effect of participant group on the degree of emotion-specific muscle activation, EMG responses were compared across all participants using a restricted maximum likelihood mixed effects model incorporating interactions between emotion, muscle and participant group, with participant identity as a level variable and time bin as a covariate of no interest. After assessing the overall effect of participant group in the omnibus test, we proceeded to establish the basis for any group differences by examining particular emotion-specific muscle contrasts. Emotion-specific EMG response profiles were quantified for each trial by combining individual muscle responses pairwise as follows: for anger and fear, (corrugator response minus zygomaticus response); for happiness and surprise, (zygomaticus response minus corrugator response); for disgust, (corrugator response plus levator response). These pairwise muscle contrasts have been shown to improve reliability and internal consistency of facial EMG analysis[55]. Muscle contrast EMG reactivity for each trial was then analysed as a dependent variable in an ANOVA incorporating participant group and emotion as fixed factors. Significant main effects in the ANOVA were explored with post hoc T-tests, using Bonferroni correction for multiple comparisons.

To test the hypothesis that emotional imitation supports identification, we assessed any relationship between overall EMG reactivity and emotion identification score using Spearman's rank correlation across the participant cohort. In addition, we compared EMG responses on trials with correct versus incorrect emotion identification and assessed any interaction with participant group membership using an ANOVA.

To generate an overall measure of reactivity for each participant for use in the voxel based morphometry analysis, EMG reactivity was averaged over all trials for that participant and then normalised as the square root of the absolute value of the change in muscle activity from baseline (subzero values corresponding to muscle activity changes in the reverse direction to that expected were restored).

For both emotion recognition and EMG reactivity, we assessed correlations with neuropsychological instruments indexing general nonverbal intellectual ability (nonverbal executive performance on the WASI Matrices task) and semantic knowledge (performance on the British Picture Vocabulary Scale), to examine the extent to which the experimental parameters of interest were influenced by disease severity and background semantic deficits.

For all tests, the criterion for statistical significance was thresholded at $p < 0.05$.

Brain image acquisition and analysis. Each patient had a sagittal 3-D magnetization-prepared rapid-gradient-echo T1-weighted volumetric brain MR sequence (echo time/repetition time/inversion time 2.9/2200/900 msec, dimensions 256 256 208, voxel size 1.1 1.1 1.1 mm), acquired on a Siemens Trio 3T MRI scanner using a 32-channel phased-array head-coil. Pre-processing of brain images was performed using the New Segment[56] and DARTEL[57] toolboxes of SPM8 (www.fil.ion.ucl.ac.uk/spm), following an optimised protocol[58]. Normalisation, segmentation and modulation of grey and white matter images were performed using default parameter settings and grey matter images were smoothed using a 6 mm full width-at-half-maximum Gaussian kernel. A study-specific template mean brain image was created by warping all bias-corrected native space brain images to the final DARTEL template and calculating the average of the warped brain images. Total intracranial volume was calculated for each patient by summing grey matter, white matter and cerebrospinal fluid volumes after segmentation of tissue classes.

Processed brain MR images were entered into a VBM analysis of the patient cohort. Separate regression models were used to assess associations of regional grey matter volume (indexed as voxel intensity) with mean overall emotion identification score and EMG reactivity, for each syndromic group. Age, total intracranial volume and WASI Matrices score (a measure of nonverbal executive function and index of disease severity) were incorporated as covariates of no interest in all models. Statistical parametric maps of regional grey matter associations were assessed at threshold $p < 0.05$ after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-specified regional volumes of interest. For the emotion identification contrast, these regions were

Response parameter	Controls	bvFTD	rtvFTD	svPPA	nfvPPA
Emotion identification					
Anger	4.6 (2.2)	1.8 (1.4)[a]	2.5 (1.6)	1.1 (0.9)[a]	3.4 (1.7)
Disgust	8.1 (1.0)	5.3 (3.3)[a]	3.5 (3.9)[a]	3.8 (3.3)[a]	5.4 (3.3)
Fear	5.4 (2.1)	2.6 (2.0)[a]	2.0 (1.7)[a]	3.9 (2.0)	4.4 (2.4)
Happiness	9.2 (0.8)	8.0 (3.2)	8.3 (1.9)	7.0 (3.2)	7.8 (1.6)
Surprise	8.4 (1.0)	4.9 (2.8)[a]	3.7 (2.8)[a]	4.1 (3.2)[a]	5.8 (3.0)
Overall (/50)	35.7 (4.6)	22.7 (9.5)[a]	20.0 (9.7)[a]	20.2 (7.9)[a]	26.9 (9.3)[a]
Facial EMG reactivity					
Anger	1.3 (3.3)	0.5 (1.5)	0.2 (1.0)	1.2 (5.1)	0.3 (4.0)
Disgust	2.6 (8.9)	−0.9 (9.0)[a]	0.5 (1.7)	1.4 (6.2)	0.9 (3.7)
Fear	0.7 (2.9)	0.3 (1.3)	−0.1 (1.9)	0.8 (4.4)	−0.9 (3.5)[a,b,c]
Happiness	1.3 (2.3)	0.5 (1.3)[d]	0.2 (1.6)[d]	1.8 (8.2)	2.3 (4.9)
Surprise	1.0 (2.5)	0.01 (3.1)[c,d]	0.3 (1.8)	1.7 (5.3)	1.7 (3.8)
Overall	1.4 (4.7)	0.09 (4.4)[a,c,d]	0.2 (1.6)[a,c]	1.4 (6.0)	0.9 (4.2)

Table 2. Summary of emotion identification and EMG reactivity findings for participant groups Mean (standard deviation) scores on the emotion identification task and mean facial EMG reactivity (as defined in Fig. 1) to viewed emotional expressions are shown for each emotion, in each participant group. [a]significantly less than healthy controls, [b]significantly less than bvFTD, [c]significantly less than svPPA, [d]significantly less than nfvPPA (all $p_{bonf} < 0.05$). bvFTD, patient group with behavioural variant frontotemporal dementia (excluding right temporal cases); Controls, healthy control group; nfvPPA, patient group with nonfluent variant primary progressive aphasia; rtvFTD, patient subgroup with right temporal variant frontotemporal dementia; svPPA, patient group with semantic variant primary progressive aphasia.

informed by previous studies of emotion processing in FTD and in the healthy brain, comprising insula, anteromedial temporal lobe (including amygdala, fusiform gyrus and temporal pole), inferior frontal cortex, anterior cingulate and supplementary motor cortices[23,26,48]. For the EMG reactivity contrast, regions of interest were based on previous functional imaging studies of facial mimicry and dynamic facial stimuli[14,45,49,50], comprising visual (V1, MT/V5, parahippocampal and fusiform gyri) and primary and supplementary motor cortices.

Results

General characteristics of participant groups. General clinical characteristics of the participant groups are presented in Table 1. There was a significant gender difference between participant groups ($chi^2_4 = 10.31$, $p = 0.036$), but no significant age difference. The patient groups did not differ in mean symptom duration or level of overall cognitive impairment (as indexed using WASI Matrices score; ANOVAs and post hoc T-tests all $p > 0.4$).

Emotion identification. Group data for facial emotion identification are summarised in Table 2.

Overall accuracy of facial emotion identification showed a main effect of participant group ($F_4 = 10.89$, $p < 0.001$), and was reduced in all syndromic groups relative to controls (all $p_{bonf} < 0.012$) (Table 2). There was no significant relationship between emotion identification accuracy and age but a significant effect of gender ($p = 0.04$), with higher identification scores overall in female participants. The main effect of participant group persisted after covarying for gender ($F_4 = 13.852$, $p < 0.001$). Emotion identification accuracy in the patient cohort correlated with standard measures of nonverbal executive function (WASI Matrices score, an index of disease severity; $rho = 0.547$, $p < 0.001$) and semantic competence (British Picture Vocabulary Scale; $rho = 0.676$, $p < 0.001$).

Facial EMG reactivity. Mean time courses of EMG responses for each facial muscle and emotion are shown for all participant groups in Fig. 1. Group data for EMG reactivity are summarised in Table 2 and Fig. 2.

Healthy older participants showed the anticipated profiles of facial muscle activity in response to viewing facial expressions (Fig. 1): corrugator supercilii was activated by anger, fear and disgust, and inhibited by happiness and surprise; zygomaticus major was activated by happiness and surprise, and inhibited by anger and fear; and levator labii activity was maximal for disgust. Due to the proximity of levator labii and zygomaticus major, and the limited spatial specificity of surface electrodes[54], there was substantial electrical leakage between these two muscles. However, zygomaticus major was maximally activated by happiness and surprise, and levator labii by disgust; moreover, these muscles were not combined in any of the pairwise muscle contrasts.

EMG reactivity to viewed facial expressions was modulated in an emotion- and muscle-specific manner in healthy controls ($F_{(2.20,43.94)} = 5.03$, $p = 0.009$) and the participant cohort as a whole ($chi^2_{(8)} = 80.05$, $p < 0.001$). There was further evidence that this interaction between emotion and muscle reactivity varied between participant groups (interaction of group, emotion and muscle: ($chi^2_{(32)} = 143.91$, $p < 0.001$). After the generation of a muscle contrast reactivity measure for each trial, ANOVA revealed significant main effects of participant group ($F_{(4)} = 10.84$, $p < 0.001$), emotion ($F_{(4)} = 3.40$, $p = 0.009$) and the interaction of group and emotion ($F_{(16)} = 2.79$, $p < 0.001$; Table 2). In post hoc T-tests comparing participant groups (with Bonferroni correction), overall EMG reactivity across the five emotions was significantly reduced in the bvFTD group relative to the healthy

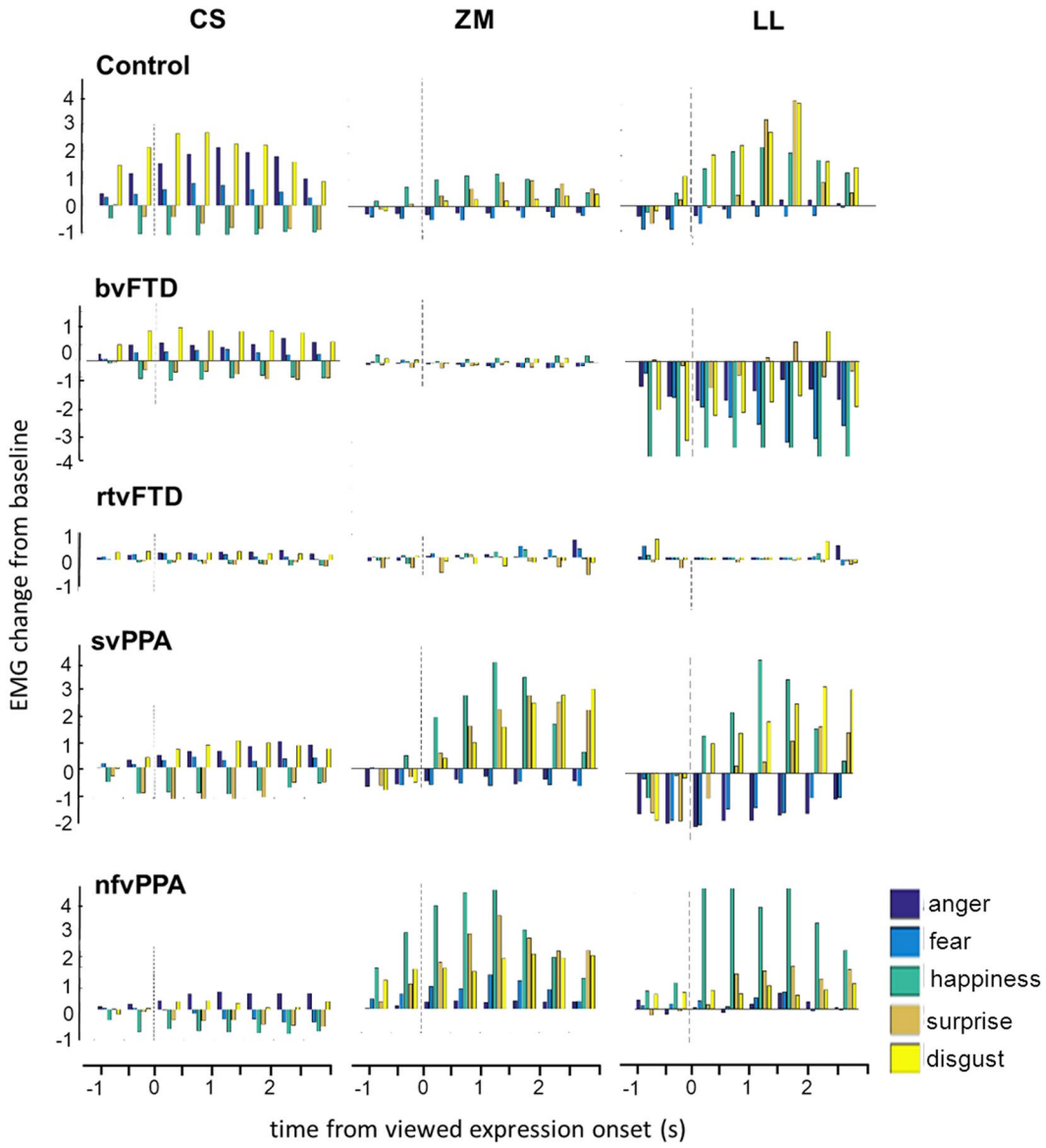

Figure 1. Patterns of EMG reactivity for each muscle in each participant group. For each participant group, the plots show the time course of average EMG reactivity (in microvolts) for key facial muscles while participants watched videos of emotional facial expressions. EMG reactivity, here indexed in arbitrary units as mean EMG change from baseline, is shown on the y-axis (after rectifying, high-pass filtering and removing artefacts as described in Methods). Onset of the viewed facial expression (as determined in a prior independent analysis of the video stimuli) is at time 0 (dotted line) in each panel. In healthy controls, corrugator supercilii (CS) was activated during viewing of anger, fear and disgust, but inhibited during viewing of happiness and surprise; zygomaticus major (ZM) was activated during viewing of happiness and surprise, but inhibited during viewing of anger and fear; and levator labii (LL) was inhibited during viewing of anger and fear, and maximally activated during viewing of disgust. Note that in healthy controls muscle responses consistently preceded the unambiguous onset of viewed emotional expressions. bvFTD, patient group with behavioural variant frontotemporal dementia (excluding right temporal cases); Control, healthy control group; nfvPPA, patient group with nonfluent variant primary progressive aphasia; rtvFTD, patient subgroup with right temporal variant frontotemporal dementia; svPPA, patient group with semantic variant primary progressive aphasia.

control group ($p_{bonf} < 0.001$), the svPPA group ($p_{bonf} < 0.001$) and the nfvPPA group ($p_{bonf} = 0.042$); and significantly reduced in the rtvFTD group relative to the healthy control group ($p_{bonf} = 0.001$) and the svPPA group ($p_{bonf} = 0.005$).

There was no significant relationship between EMG reactivity and age ($p = 0.1$), gender ($p = 0.42$), or WASI Matrices score (used here as a measure of disease severity; $p = 0.63$) in the patient cohort, nor with a standard measure of semantic knowledge (British Picture Vocabulary Scale; $p = 0.5$).

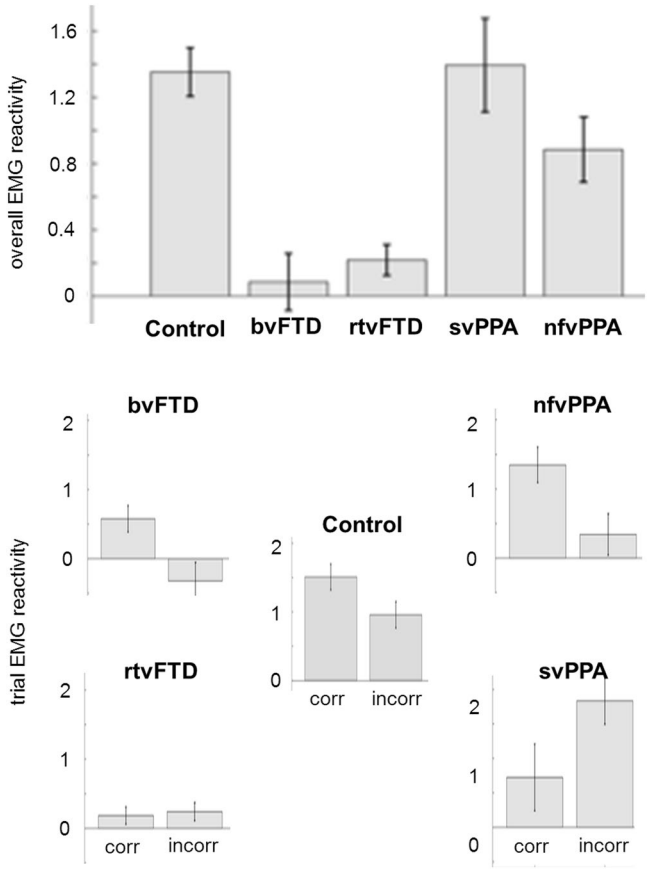

Figure 2. EMG reactivity in each participant group, and the relationship with identification accuracy. For each participant group, the histograms show mean overall facial muscle EMG reactivity (top) and EMG reactivity separately (below) for those trials on which viewed emotional expressions were identified correctly (corr) versus incorrectly (incorr); error bars indicate standard error of the mean (see also Table 2). bvFTD, patient group with behavioural variant frontotemporal dementia; Control, healthy control group; nfvPPA, patient group with nonfluent variant primary progressive aphasia; rtvFTD, patient subgroup with right temporal variant frontotemporal dementia; svPPA, patient group with semantic variant primary progressive aphasia.

Relationship between emotion identification and facial EMG reactivity. Across the participant cohort, overall EMG reactivity was significantly correlated with emotion identification accuracy (rho = 0.331, $p = 0.011$) and mean trial EMG reactivity was significantly higher for trials on which the emotion was correctly identified ($n = 1586$) than on error trials ($n = 1314$; $p = 0.002$). This differential effect of correct versus incorrect trials showed a significant interaction with participant group ($F_{(4)} = 4.18$, $p = 0.002$; see Fig. 2). Among healthy controls, there was a strong trend towards greater reactivity predicting correct identification ($p = 0.087$). Comparing trial types within patient groups, EMG reactivity was significantly higher on correct identification trials than error trials in the bvFTD group ($p = 0.009$) and the nfvPPA group ($p = 0.01$) but not the rtvFTD group ($p = 0.76$) or the svPPA group ($p = 0.06$, here signifying a trend towards greater EMG reactivity on incorrect trials).

Neuroanatomical associations. Significant grey matter associations of emotion identification and EMG reactivity for the patient cohort are summarised in Table 3 (all thresholded at $p_{FWE} < 0.05$ within pre-specified anatomical regions of interest); statistical parametric maps are presented in Fig. 3.

Accuracy identifying dynamic emotional expressions was correlated with regional grey matter volume in left supplementary motor cortex in all syndromic groups. Additional regional grey matter correlates of emotion identification were delineated for particular syndromic groups. The bvFTD, svPPA and nfvPPA groups showed syndromic grey matter correlates within a bi-hemispheric (predominantly left-lateralised) frontotemporal network including opercular inferior frontal gyrus, anterior cingulate, anterior insula and antero-inferior temporal lobe; while the svPPA group showed a further correlate in left posterior superior temporal cortex and the rtvFTD group showed a correlate in right temporo-occipital junctional cortex in the vicinity of MT/V5 complex[59].

Across the patient cohort, overall mean EMG reactivity was correlated with regional grey matter in an overlapping but more posteriorly directed and right-lateralised network, with variable emphasis in particular syndromic groups. The bvFTD and nfvPPA groups showed grey matter correlates of EMG reactivity in supplementary and primary motor cortices, while all syndromic groups showed grey matter associations in cortical areas implicated

Group	Region	Side	Cluster (voxels)	Peak (mm) x	y	z	T score	P_{FWE}
Emotion identification								
bvFTD	Anterior cingulate	L	196	−8	44	12	5.59	0.003
	Anterior insula	L	123	−30	27	0	4.07	0.047
	Supplementary motor area	L	5	−10	4	50	3.81	0.044
	Opercular IFG	L	32	−57	12	18	5.14	0.003
	Anteromedial temporal:							
	Temporal pole	L	2133	−32	8	−38	5.11	0.010
	Amygdala			−24	2	−38	4.94	0.015
	Fusiform gyrus			−30	−9	−38	4.82	0.019
rtvFTD	Supplementary motor area	L	34	−3	−10	57	4.15	0.022
	Temporo-occipital junction	R	18	66	−50	−8	4.06	0.038
svPPA	STG/STS	L	536	−58	−30	14	7.21	0.005
	Supplementary motor area	L	19	−4	−2	50	4.23	0.019
	Opercular IFG	L	25	−57	12	18	5.05	0.003
	Anterior cingulate	L	24	−2	44	3	4.11	0.042
	Fusiform gyrus	R	44	22	−4	−44	4.43	0.042
nfvPPA	Supplementary motor area	L	37	−4	−2	50	4.14	0.023
	Opercular IFG	L	9	−52	8	18	3.96	0.033
Facial EMG reactivity								
bvFTD	Supplementary motor area	L	12	−8	−9	56	3.99	0.030
	Temporo-occipital junction	L	25	−54	−45	−4	4.29	0.064
rtvFTD	Temporo-occipital junction	R	8	62	−62	2	3.96	0.046
svPPA	Parahippocampal gyrus	L	59	−20	−28	−24	4.25	0.028
	Parahippocampal gyrus	R	72	18	−33	−18	5.25	0.003
nfvPPA	Primary visual cortex	R	291	12	−80	3	5.92	0.001
	Primary motor cortex	R	521	56	8	27	5.43	0.007
	Supplementary motor area	R	18	8	8	68	4.42	0.012

Table 3. Neuroanatomical correlates of emotion identification and reactivity in patient groups. The table presents regional grey matter correlates of mean overall emotion identification score and facial EMG reactivity (as defined in Fig. 1) during viewing of facial expressions in the four patient groups, based on voxel-based morphometry. Coordinates of local maxima are in standard MNI space. P values are all significant after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-specified anatomical regions of interest (see text). bvFTD, patient group with behavioural variant frontotemporal dementia (excluding right temporal cases); IFG, inferior frontal gyrus; nfvPPA, patient group with nonfluent variant primary progressive aphasia; rtvFTD, patient subgroup with right temporal variant frontotemporal dementia; STG/S, superior temporal gyrus/sulcus; svPPA, patient group with semantic variant primary progressive aphasia.

in the analysis of visual signals, comprising primary visual cortex in the nfvPPA group; temporo-occipital. junction (MT/V5 complex) in the bvFTD and rtvFTD groups; and parahippocampal gyrus in the svPPA group.

Discussion

Here we have demonstrated facial motor signatures of emotional reactivity in the FTD spectrum. As anticipated, healthy older individuals showed characteristic profiles of facial muscle engagement by observed facial emotions; moreover, facial muscle reactivity predicted correct trial-by-trial identification of facial emotions. These findings provide further evidence that (in the healthy brain) facial mimesis is an automatic, involuntary mechanism supporting stimulus decoding and evaluation, rather than simply an accompaniment of conscious emotion recognition. In contrast, overall facial muscle reactivity and the normal coupling of muscle reactivity to facial emotion identification were altered differentially in the patient groups representing major FTD syndromes. As predicted, identification of facial expressions was impaired across the patient cohort: however, whereas the bvFTD group showed globally reduced facial muscle reactivity to observed emotional expressions, the svPPA group had preserved overall muscle reactivity but loss of the linkage between muscle response and correct expression identification. Among those patients with syndromes dominated by behavioural decline, the profile of facial muscle reactivity stratified cases with rtvFTD from other cases of bvFTD: the subgroup with rtvFTD had a particularly severe phenotype, exhibiting both globally reduced facial reactivity and also aberrant coupling of muscle reactivity to facial expression identification.

Considered collectively, the motor signatures of emotional reactivity identified in our patient cohort amplify previous clinical, neuropsychological and physiological evidence in particular FTD syndromes. The generalised impairment of emotional mimesis in our bvFTD and rtvFTD groups is consistent with the clinical impression of facial impassivity[37,60], impaired intentional imitation[38] and blunting of autonomic responsiveness[30,31,33,35,36] in

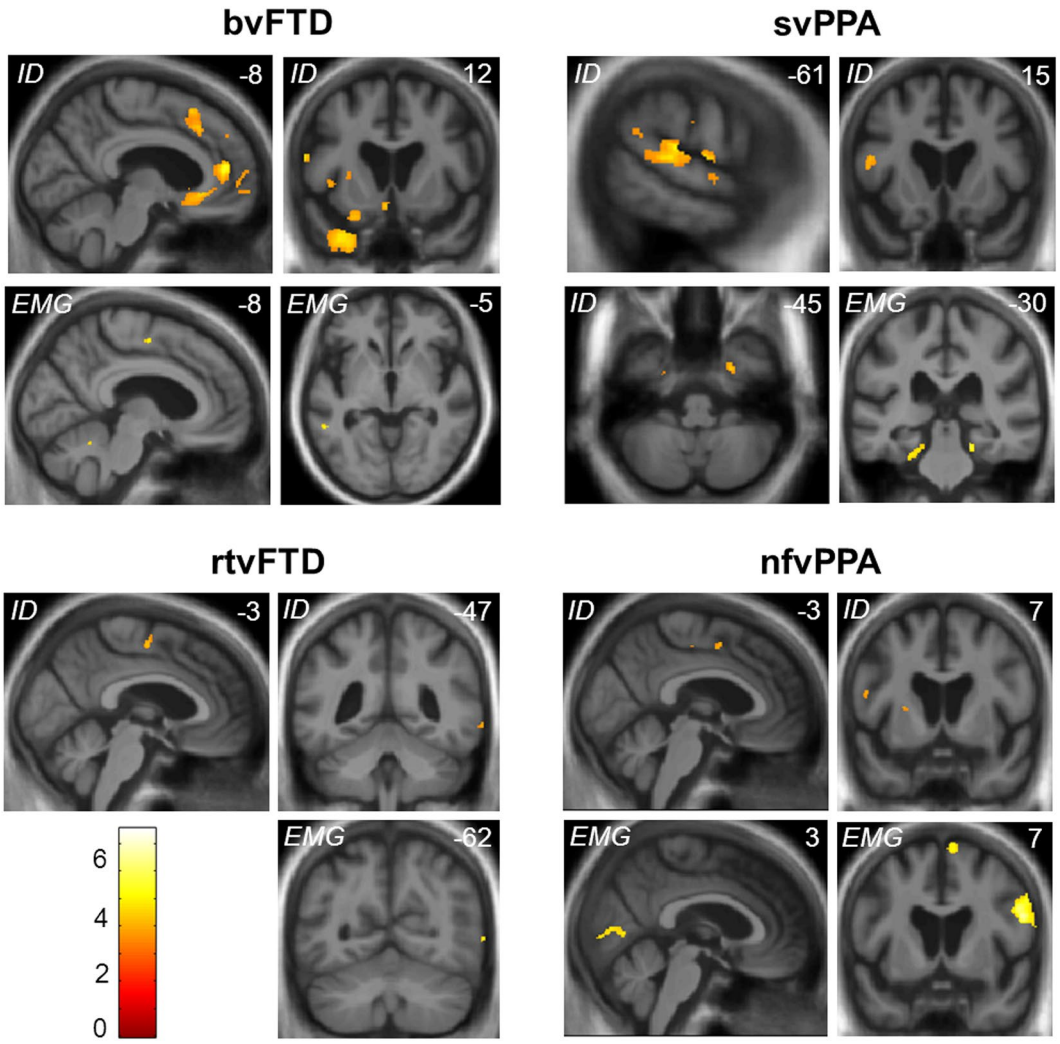

Figure 3. Neuroanatomical correlates of emotion identification and EMG reactivity for each syndromic group. Statistical parametric maps (SPMs) show regional grey matter volume positively associated with overall emotion identification accuracy and facial EMG reactivity during viewing of emotional facial expressions, based on voxel-based morphometry of patients' brain MR images (see also Table 3); T-scores are coded on the colour bar. SPMs are overlaid on sections of the normalised study-specific T1-weighted mean brain MR image; the MNI coordinate (mm) of the plane of each section is indicated (coronal and axial sections show the left hemisphere on the left). Panels code syndromic profiles of emotion identification (*ID*) or EMG reactivity (*EMG*). Note that the correlates of emotion identification and EMG reactivity in different syndromes overlapped in particular brain regions, including supplementary motor cortex and temporo-occipital junction (see Table 3). SPMs are thresholded for display purposes at $p < 0.001$ uncorrected over the whole brain, however local maxima of areas shown were each significant at $p < 0.05$ after family-wise error correction for multiple voxel-wise comparisons within pre-specified anatomical regions of interest (see Table 3). bvFTD, patient group with behavioural variant FTD; nfvPPA, patient group with nonfluent variant primary progressive aphasia; rtvFTD, patient subgroup with right temporal variant frontotemporal dementia; svPPA, patient group with semantic variant primary progressive aphasia.

these patients. Abnormal coupling of facial mimesis to facial expression identification in our svPPA group is in line with the disordered autonomic signalling of affective valuation previously documented in this syndrome[33,35], and suggests a method of dissociating emotional reactivity from the declarative, semantic categorisation of emotions. The present findings suggest that aberrant motor recoding of perceived expressions may constitute a core physiological mechanism for impaired emotion processing in FTD.

This mimetic mechanism may be particularly pertinent to the dynamically shifting and subtle emotions of everyday interpersonal encounters. Our own emotional expressions are normally subject to continual modulation by the expressed emotions of others, including tracking of transient 'micro-expressions'[61]; this modulation occurs over short timescales (a few hundred milliseconds) and contributes importantly to the regulation of social interactions, prosociality and empathy[28,62–64]. If facial mimesis plays a key role in tuning such responses, loss of this modulatory

mechanism (most notably in bvFTD and rtvFTD) might underpin not only impaired socio-emotional awareness in FTD but also the 'poker-faced' sense of unease these patients commonly provoke in others[37].

The neuroanatomical correlates we have identified speak to the coherent nature of dynamic emotion mimesis and identification. In line with previous evidence[38], these processes mapped onto a distributed cerebral network within which FTD syndromes showed separable profiles of grey matter atrophy. Involvement of supplementary motor cortex was a feature across syndromes and associated both with emotion identification and motor reactivity, though joint correlation was observed in the bvFTD and nfvPPA groups but not the rtvFTD and svPPA groups (see Table 3). Supplementary motor cortex is a candidate hub for the computation of sensorimotor representations unfolding over time, an integral function of the mirror neuron system: this region generates both facial sensory-evoked potentials and complex facial movements[65] and it is activated during facial imitation and empathy[66] as well as by dynamic auditory emotional signals[48]. Furthermore, transcranial magnetic stimulation of the supplementary motor region disrupts facial emotion recognition[67]. The uncoupling of motor reactivity from emotion identification in the rtvFTD and svPPA groups may reflect disconnection of this key hub from linked mechanisms for affective semantic appraisal[12], perhaps accounting for lack of an EMG reactivity correlate in supplementary motor cortex in these syndromic groups. Two further cortical hubs correlating both with emotion identification and mimesis were delineated in our patient cohort. In the svPPA and rtvFTD groups, a joint correlate was identified in the temporo-occipital junction zone, overlapping posterior superior temporal sulcus and MT/V5 visual motion cortices[59,68]: this region has been implicated in the imitation and decoding of dynamic facial expressions[15,49,69,70], integration of dynamic social percepts, action observation and theory of mind[71,72]. In the svPPA group, infero-medial temporal cortex was linked both to emotion identification and mimesis: this region has previously been shown to respond to dynamic facial stimuli[45].

Additional grey matter associations of facial expression identification accuracy were delineated in cingulo-insular, antero-medial temporal and inferior frontal areas previously implicated both in the detection and evaluation of salient affective stimuli and in canonical FTD syndromes[15,20,21,23,26,73,74]. Additional grey matter associations of facial motor reactivity were identified (for the nfvPPA group) in primary visual and motor cortices: enhanced responses to emotional facial expressions have previously been demonstrated in visual cortex[75], while motoric responses to social stimuli have been located in precentral gyrus[14]. However, it is noteworthy that certain grey matter associations emerging from this analysis - in particular, the 'hub regions' of supplementary motor cortex and temporo-occipital junction and (in the nfvPPA group) primary visual and motor cortices - lie beyond the brain regions canonically targeted in particular FTD syndromes or indeed, in previous studies of emotion processing in FTD[21]. It is likely that the dynamic expression stimuli employed here allowed a more complete picture of the cerebral mechanisms engaged in processing naturalistic emotions. Moreover, involvement of brain regions remote from zones of maximal atrophy may reflect distributed functional network effects (for example, visual cortical activity has been shown to be modulated by amygdala[75]) in conjunction with disease-related network connectivity changes, which are known to extend beyond the atrophy maps that conventionally define particular FTD syndromes[76]. Taken together, the present neuroanatomical findings are compatible with the previously proposed, hierarchical organisation of embodied representations supporting emotional decoding and empathy[13,48,77,78]: whereas early visual and motor areas may support automatic imitation via low-level visual and kinematic representations, higher levels of the processing hierarchy engage the human 'mirror' system and substrates for semantic, evaluative and mentalising processes that drive explicit emotion identification.

From a clinical perspective, this work suggests a pathophysiological framework for deconstructing the complex social and emotional symptoms that characterise FTD syndromes. Such symptoms are difficult to measure using conventional neuropsychological tests, and may only be elicited by naturalistic social interactions: dynamic motor physiological surrogates might index both the affective dysfunction of patients' daily lives and the underlying disintegration of culprit neural networks[38]. These physiological metrics might facilitate early disease detection and tracking over a wider spectrum of severity than is currently possible and enable socio-emotional assessment in challenging clinical settings (such as aphasia), especially since our results suggest that (in contrast to explicit emotion recognition) automatic motor reactivity may be relatively insensitive to semantic deficits. Our findings further suggest that such metrics are not simply ciphers of reduced cognitive capacity but may help stratify broad disease groupings (such as the heterogeneous bvFTD syndrome) and at the same time, may capture mechanisms that transcend traditional syndromic boundaries. We therefore propose that the paradigm of emotional sensorimotor reactivity may yield a fresh perspective on FTD nosology and candidate novel biomarkers of FTD syndromes. Looking forward, this paradigm suggests a potential strategy for biofeedback-based retraining of emotional responsiveness, perhaps in conjunction with disease-modifying therapies[79].

This study establishes a preliminary proof of principle but the findings require further corroboration. There are several clear limitations that suggest caution in interpreting our findings and directions for future work. We have studied a small, intensively phenotyped patient cohort: the most pressing issue will be to replicate the findings in larger clinical populations. Future studies should encompass a wider range of pathologies, in order to determine the general applicability of the paradigm and the specificity of syndromic motor profiles; it would be of interest, for example, to assess the heightened emotional contagion previously documented in Alzheimer's disease[80] in this context. Longitudinal cohorts including presymptomatic mutation carriers will be required in order to assess the diagnostic sensitivity of mimetic indices and their utility as biomarkers; ultimately, histopathological correlation will be necessary to establish any molecular correlates of the syndromic stratification suggested here. It will be relevant to explore the cognitive milieu of emotional motor responses in greater detail: for example, the effects of other sensory modalities (in particular, audition[48], micro-expressions[61], sincere versus social emotions[81] and emotional 'caricatures' in FTD[82]) and the correlation of mimetic markers with measures of social cognition and daily life empathy[38]. Emotional reciprocity might be modeled using virtual reality techniques to generate model social interactions[62]. Beyond mimesis, integration of somatic and cognitive mechanisms during social emotional exchanges demands the joint processing of autonomic and neuroendocrine signals under executive control[29,83,84]:

future work should assess other physiological modalities alongside EMG. Functional MRI and magnetoencephalography would amplify the present structural neuroanatomical correlates by capturing disease-related changes in underlying brain network connectivity and dynamics. Multimodal studies of this kind may set motor mimicry in the context of a comprehensive physiology of socio-emotional reactivity in neurodegenerative diseases. The ultimate goal will be to identify practical physiological markers that can be widely translated for the diagnosis and dynamic tracking of these diseases and the evaluation of new therapies.

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Author Contributions

Study conception and design: C.R.M., J.M.K., J.D.W. Data acquisition and analysis: C.R.M., C.J.D.H., L.L.R., C.N.C., R.L.B., K.M.D., E.V.B., C.J.M., J.M.S., J.D.R., J.M.K., J.D.W. Drafting of the manuscript: C.R.M., J.D.W.

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RESEARCH PAPER

Cardiac responses to viewing facial emotion differentiate frontotemporal dementias

Charles R. Marshall[1,2], Christopher J. D. Hardy[1], Micah Allen[3], Lucy L. Russell[1], Camilla N. Clark[1], Rebecca L. Bond[1], Katrina M. Dick[1], Emilie V. Brotherhood[1], Jonathan D. Rohrer[1], James M. Kilner[2] & Jason D. Warren[1]

[1]Dementia Research Centre, Department of Neurodegenerative Disease, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK
[2]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK
[3]Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK

Correspondence
Dr Charles Marshall, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK.
Tel.: 0203 448 3404;
E-mail: charles.marshall@ucl.ac.uk (or)
Jason Warren, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK. Tel.: 0845 155 5000;
E-mail: jason.warren@ucl.ac.uk

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Abstract

Objective: To establish proof-of-principle for the use of heart rate responses as objective measures of degraded emotional reactivity across the frontotemporal dementia spectrum, and to demonstrate specific relationships between cardiac autonomic responses and anatomical patterns of neurodegeneration. **Methods**: Thirty-two patients representing all major frontotemporal dementia syndromes and 19 healthy older controls performed an emotion recognition task, viewing dynamic, naturalistic videos of facial emotions while ECG was recorded. Cardiac reactivity was indexed as the increase in interbeat interval at the onset of facial emotions. Gray matter associations of emotional reactivity were assessed using voxel-based morphometry of patients' brain MR images. **Results**: Relative to healthy controls, all patient groups had impaired emotion identification, whereas cardiac reactivity was attenuated in those groups with predominant fronto-insular atrophy (behavioral variant frontotemporal dementia and nonfluent primary progressive aphasia), but preserved in syndromes focused on the anterior temporal lobes (right temporal variant frontotemporal dementia and semantic variant primary progressive aphasia). Impaired cardiac reactivity correlated with gray matter atrophy in a fronto-cingulo-insular network that overlapped correlates of cognitive emotion processing. **Interpretation**: Autonomic indices of emotional reactivity dissociate from emotion categorization ability, stratifying frontotemporal dementia syndromes and showing promise as novel biomarkers. Attenuated cardiac responses to the emotions of others suggest a core pathophysiological mechanism for emotional blunting and degraded interpersonal reactivity in these diseases.

Introduction

Frontotemporal dementia (FTD) comprises a spectrum of neurodegenerative disorders with three major syndromes[1]; behavioral variant (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent variant primary progressive aphasia (nfvPPA). This classification admits considerable heterogeneity; in particular, bvFTD comprises several clinico-anatomical subsyndromes, of which the most distinctive is the variant with predominant right temporal lobe atrophy (right temporal variant; rtvFTD).[2,3] Deficits in emotion processing and empathy are prominent in all FTD syndromes,[4,5] but remain poorly characterized and difficult to quantify. Conventional neuropsychological instruments emphasize the cognitive categorization of emotions, which is potentially confounded by coexisting semantic deficits. Moreover, emotion labeling tasks do not capture the dynamic emotional reactivity that is central to interpersonal functioning in daily life.[6]

In health, responding to others' emotions comprises both cognitive and affective components, which are dissociable and have distinct anatomical bases.[7] Central to understanding affective empathy is the concept of interoceptive inference, which proposes that emotional awareness entails reciprocal feedback between somatic physiology and the cognitive interpretation of those signals.[8,9] Emotional stimuli produce autonomic effects including modulation of heart rate, but different emotions do not reliably produce specific individual patterns of autonomic responses, and they are therefore hypothesized to relate to arousal and intensity rather than emotion category.[10,11] Stimulus onset induces a cardiac orienting deceleration, which is modulated by affective content, with greater cardiac deceleration accompanying higher emotional valence.[12–14] This central regulation of cardiac function is mediated by a distributed brain network including anterior cingulate cortex (ACC), insula, and orbitofrontal cortex (OFC).[15,16] Cardiac afferent information informs affective valuation,[17] and visceral autonomic responses may support emotional contagion and empathy.[9]

If autonomic mechanisms contribute to aberrant emotion processing in FTD, one would anticipate associated changes in physiological reactivity, as has previously been documented in FTD syndromes. In particular, bvFTD has been associated with abnormal autonomic reactivity to affectively charged stimuli,[18–22] alterations of resting skin conductance and heart rate variability,[23,24] and abnormal brain-heart coupling,[24,25] while nfvPPA has been associated with reduced pupil responses to arousing stimuli.[20,26] Taken together, these findings are consistent with the known targeting of core cerebral autonomic fronto-cingulo-insular circuitry in bvFTD and nfvPPA.[27–30] svPPA has also been associated with deficits in afferent interoceptive signal processing.[20,26,31,32] Altered autonomic reactivity to others' emotions is a plausible pathophysiological basis for the socio-emotional symptoms exhibited by these patients. Moreover, autonomic responses and explicit identification of emotions are likely to be separably vulnerable in FTD syndromes.[18,22,27] However, these issues have not been addressed systematically across the FTD spectrum.

Here, we explored the potential for cardiac emotional reactivity to stratify FTD syndromes. We chose a simple heart rate response metric designed to incorporate both the cardiac orienting response and its potentiation by emotional content, with a view to easy replicability in future studies and potential clinical utility without the need for complex modeling of heart rate patterns. We hypothesized that cardiac modulation would be attenuated in bvFTD and nfvPPA due to degeneration of fronto-insular networks in these diseases, but relatively preserved (and separable from emotion identification) in syndromes targeting the anterior temporal lobes (svPPA and rtvFTD).[18,20,21] We further hypothesized that emotion recognition ability but not cardiac reactivity would be associated with semantic knowledge, while cardiac reactivity would correlate with atrophy in components of the central autonomic regulatory network (ACC, insula, OFC).[15,16,24]

Methods

Participants

Fifty-one participants were included in the experiment (mean age 67.6 years (range 51–84), 22 females), comprising 32 patients fulfilling consensus criteria for a syndrome of FTD[33,34] (10 bvFTD, 6 rtvFTD, 7 svPPA, 9 nfvPPA) recruited via our specialist cognitive disorders clinic, and 19 age-matched healthy individuals with no history of neurological or psychiatric illness recruited via our departmental research database. No participant had a history of cardiac arrhythmia, and none was taking cardiac rate-limiting medication. Brain MR imaging supported the syndromic diagnosis in all patients and none had any substantial burden of cerebrovascular disease. In all patients, the syndromic diagnosis was further corroborated in a comprehensive general neuropsychological assessment. Clinical, demographic, and neuropsychological characteristics of all participant groups are summarized in Table 1.

Standard protocol approvals, registrations, and patient consents

The study was approved by the local institutional ethics committee and all participants gave informed consent following Declaration of Helsinki guidelines.

Table 1. Demographic, clinical, and neuropsychological characteristics of participant groups

Characteristic	Healthy controls	bvFTD	rtvFTD	svPPA	nfvPPA
Demographic and clinical					
No. (m:f)	19 (8:11)	10 (7:3)	6 (6:0)	7 (5:2)	9 (4:5)
Age (yrs)	68.8 (5.5)	67 (6.3)	63.8 (9.1)	65.9 (7.5)	69.6 (6.5)
Handedness (R:L)	18:1	9:1:0	6:0:0	7:0:0	7:2:0
Education (yrs)	15.5 (2.9)	12.8 (2.5)[c]	18 (3.1)	15.3 (2.8)	15 (2.7)
MMSE (/30)	29.6 (0.6)	24.1 (4.9)[a]	25.3 (4.3)	22.6 (5.8)[a]	23.7 (6.0)[a]
Duration (yrs)	-	8.2 (5.3)	6.5 (3.5)	4.4 (2.1)	4.6 (2.2)
Mean heart rate	69.5 (10.2)	72.9 (14.2)	71.8 (11.8)	69.7 (5.2)	85.5 (17.1)[a]
Heart rate variance	0.23 (0.7)	0.21 (0.6)	0.05 (0.07)	0.08 (0.08)	0.03 (0.04)
Cardiac reactivity index	1.67 (1.5)	0.54 (0.4)[a,c]	2.42 (1.4)	1.61(1.6)	0.12 (1.1)[a,c]
Emotion recognition (%)	70.5 (9.2)	41.4 (18.9)[a]	40.0 (19.4)[a]	40.2(16.1)[a]	53.8 (18.5)[a]
Neuropsychological					
General intellect					
WASI verbal IQ	125.4 (7.0)	86.2 (23.7)[a]	86.7 (22.2)[a]	78.6(20.4)[a]	79.6 (17.3)[a]
WASI performance IQ	125.1 (9.7)	99.8 (20.2)[a]	106.8 (24.6)	112.3(10.1)	98.8 (21.5)[a]
Episodic memory					
RMT words (/50)	44.7 (3.7)	33.5 (7.9)[a]	34.8 (7.9)[a]	32.7 (6.4)[a]	39.5 (6.6)
RMT faces (/50)	49.3 (0.9)	35.6 (7.5)[a]	37.2 (9.3)[a]	30.3 (6.9)[a,e]	41.4 (9.5)[a]
Camden PAL (/24)	20.3 (3.5)	9.3 (8.2)[a]	12.5 (6.2)	2.7 (4.2)[a,c,e]	16.3 (7.8)
Executive skills					
WASI Block Design (/71)	46.0 (10.1)	29.9 (17.9)	37.2 (22.1)	41.6 (19.0)	25.1 (19.7)[a]
WASI Matrices (/32)	26.6 (4.1)	17.1 (9.6)[a]	19.0 (9.8)	21.7 (8.5)	17.4 (9.0)[a]
WMS-R digit span forward (max)	7.1 (1.2)	6.4 (1.3)	6.8 (1.2)	7.0 (1.2)	4.8 (0.8)[a,c,d]
WMS-R digit span reverse (max)	5.6 (1.3)	4.2 (1.5)	4.7 (1.4)	5.1 (2.0)	3.0 (0.7)[a]
D-KEFS Stroop color naming (s)	32.4 (6.4)[e]	49.9 (21.7)[e]	48.8 (21.4)[e]	50.3 (27.9)[e]	87.0 (6.7)
D-KEFS Stroop word reading (s)	23.5 (5.7)[e]	34.3 (20.9)[e]	38.7 (26.1)[e]	30.9 (19.2)[e]	85.4 (10.3)
D-KEFS Stroop interference (s)	56.2 (16.9)[b,e]	106.2 (50.7)[e]	98.3 (45.1)[e]	82.7 (50.5)[e]	165.0 (30.1)
Letter fluency (F: total)	18.1 (5.7)	6.8 (4.3)[a]	9.0 (4.7)[a]	9.7 (7.2)[a]	3.5 (1.7)[a]
Category fluency (animals: total)	24.7 (5.9)	12.4 (7.7)[a]	10.3 (2.3)[a]	6.7 (5.4)[a]	8.8 (3.5)[a]
Trails A (s)	32.2 (5.6)[e]	59.3 (35.5)	59.8 (32.9)	47.0 (21.0)	81.7 (48.4)
Trails B (s)	66.1 (20.5)[b,c,e]	182.5 (87.2)	186.7 (100.4)	133.6 (110.1)	211.1 (94.6)
Language skills					
WASI vocabulary (/80)	72.2 (3.4)	39.9 (23.8)[a]	47.0 (19.1)[a]	34.7 (22.7)[a]	31.7 (13.9)[a]
BPVS (/150)	148.5 (1.1)	112.9 (41.3)[a]	141.8 (7.2)	94.4 (49.4)[a,c,e]	142.6 (10.1)
GNT (/30)	26.3 (2.4)	9.4 (9.9)[a]	12.5 (10.1)[a]	2.0 (5.3)[a,c,e]	15.5 (6.6)[a]
Other skills					
GDA (/24)	15.8 (5.4)	7.9 (5.7)[a]	7.5 (6.3)[a]	11.3 (8.3)	5.4 (1.9)[a]
VOSP Object Decision (/20)	19.1 (1.6)	15.0 (3.3)[a]	16.7 (2.3)	15.7 (5.1)	15.3 (4.7)

Mean (standard deviation) scores are shown unless otherwise indicated; maximum scores are shown after tests (in parentheses). BPVS, British Picture Vocabulary Scale;[46] bvFTD, patient group with behavioral variant frontotemporal dementia; Category fluency for animal category and letter fluency for the letter F in 1 min;[47] GDA, Graded Difficulty Arithmetic;[48] GNT, Graded Naming Test;[49] MMSE, Mini-Mental State Examination score;[50] PAL, Paired Associate Learning test[51]; nfvPPA, patient group with nonfluent variant primary progressive aphasia; RMT, Recognition Memory Test;[52] rtvFTD, patient group with right temporal variant frontotemporal dementia (defined from inspection of individual brain MRI); svPPA, patient group with semantic variant primary progressive aphasia; Stroop D-KEFS, Delis Kaplan Executive System;[53] Trails-making task based on maximum time achievable 2.5 min on task A, 5 min on task B;[54] VOSP, Visual Object and Spatial Perception Battery;[55] WAIS-R, Wechsler Adult Intelligence Scale – Revised;[56] WASI, Wechsler Abbreviated Scale of Intelligence;[57] WMS, Wechsler Memory Scale.[58]

[a]Different from controls.

[b]Different from bvFTD.

[c]Different from rtvFTD.

[d]Different from svPPA.

[e]Different from nfvPPA (all at significance threshold $P < 0.05$).

Stimuli

Videos of emotional facial expressions were taken from the Face and Gesture Recognition Research Network database[35]; these videos are silent recordings of healthy young adults (further details about the stimuli are summarized in Table S1 in Supplementary Material online). These dynamic, naturalistic facial expressions are similar to those encountered in the unregulated social milieu of daily life; we anticipated that such stimuli should induce greater physiological responses than less ecological, static stimuli.[36] We selected 10 videos (minimizing emotional ambiguity and balancing for sex) to represent each of the "universal emotions" of anger, disgust, fear, happiness, and surprise for a total of 50 trials. We omitted the emotion of sadness, as naturalistic sadness has a more diffuse time course than other emotions, and is therefore less suitable for an analysis of event-related physiology. Each video stimulus lasted several seconds (mean 4.9 sec; range 4–8 sec), beginning with a neutral facial expression that evolved into an emotional expression. We did not include an "emotionally neutral" facial movement condition; there is currently no dynamic facial "baseline" stimulus widely accepted to be devoid of affective content. For each video, the frame in which each emotional expression began to emerge from the baseline neutral expression was identified manually; the timing of this frame (which occurred between 0.6 and 2.6 sec (mean 1.1 sec) after video onset) was used to align data traces between trials.

Stimuli were presented in randomized order via a notebook computer using Cogent presentation software in MatlabR2012b. On each trial, the participant was asked to identify the emotion by selecting one of the five alternative emotion names. Subjects were unable to provide an answer until after the stimulus had finished playing, and were then able to either select a response by pressing a number key, or pointing out the answer to the tester. The minimum interstimulus interval was 8 sec, and the typical duration of the testing session with cardiac recording was around 20 min. After sitting quietly at rest for at least 5 min, participants were initially familiarized with the stimuli to ensure they all understood the task and were monitored by the experimenter during the test to ensure they were able to comply.

ECG recording and analysis

ECG was recorded continuously from electrodes over the right clavicle and left iliac crest. ECG data were high-pass filtered at 0.01 Hz to remove linear drift and establish a baseline from which the time point of each R wave local maximum was determined. Mean heart rate and heart rate variability (variance of RR intervals) during the period of recording were calculated for each participant. A simplified index of cardiac reactivity to viewing facial emotion was derived for each trial as the percentage change in RR interval for three heart beats before and after the onset of each facial expression, to capture both the orienting responses and its potentiation by affective content, using the formula:

$$([\text{mean of 3 RR intervals after onset}] - [\text{meanof3RRintervalsbeforeonset}]) \times 100/\text{mean RR interval}$$

Cardiac reactivity was calculated for each participant for each emotion separately and averaged across all five emotions to provide a measure of overall emotional autonomic reactivity.

The cardiac reactivity index (as defined above) was assessed for each emotion using one-sample Mann–Whitney *U*-tests versus zero (no heart rate response) and in a parametric model incorporating both cardiac reactivity and mean heart rate. Between-group differences were initially assessed using ANOVAs and post hoc *t*-tests were used to compare groups if a significant overall group effect was shown. For non-normally distributed data, equivalent non-parametric tests were used (Kruskal–Wallis rank and post hoc Mann–Whitney *U*). Between-group differences in categorical variables (i.e., sex and handedness) were assessed using chi-square contingency tests. We used a multiple regression model to test whether any relationship between group membership and cardiac reactivity persisted after covarying for emotion recognition ability and semantic knowledge. A threshold $P < 0.05$ was accepted as the criterion of statistical significance for all group comparisons.

Brain image acquisition and analysis

For each patient, a sagittal 3-D magnetization-prepared rapid-gradient-echo T1-weighted volumetric brain MR sequence (TE/TR/TI 2.9/2200/900 msec, dimensions 256 256 208, voxel volume 1.1^3 mm) was acquired on a Siemens Trio 3T MRI scanner using a 32-channel phased-array head-coil. Preprocessing of brain images was performed in SPM12 (www.fil.ion.ucl.ac.uk/spm) using an optimized protocol.[37] Normalization, segmentation and modulation of gray and white matter images were carried out using default parameter settings and gray matter images were smoothed using a 6 mm full width-at-half-maximum Gaussian kernel. For each patient, total intracranial volume was calculated by combining gray matter, white matter and cerebrospinal fluid volumes after segmentation of these tissue classes.

In the VBM analysis, associations between regional gray matter volume and both heart rate reactivity and emotion identification performance were assessed in a full factorial

model (see Figure S1 in Supplementary Material), looking for an interaction between syndromic group and cardiac reactivity for those patient groups showing altered heart rate reactivity relative to healthy controls and incorporating age, total intracranial volume, and group membership as covariates of no interest. Statistical parametric maps were evaluated at peak voxel threshold $P < 0.05$, after family-wise error (FWE) correction for multiple voxel-wise comparisons within prespecified anatomical regions of interest. These regions of interest were defined *a priori* based on the cortical components of the central autonomic control network delineated in the healthy brain,[15,16] and comprised ACC, insula and OFC as defined using the Harvard-Oxford Brain Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

Results

Clinical, behavioral, and heart rate reactivity data

Clinical, behavioral and heart rate reactivity data for the participant groups are summarized in Table 1. The participant groups did not differ in age, sex or handedness; patients and healthy controls did not differ in premorbid educational attainment and the patient groups had similar overall symptom duration (all $P > 0.05$).

Emotion identification was impaired in all syndromic groups relative to the healthy control group (overall group effect $F_{(4)} = 9.7$, $P < 0.001$, $\eta^2 = 0.459$; bvFTD, rtvFTD, svPPA all $P < 0.001$, nfvPPA $P = 0.01$). No differences were found between patient groups. Across the patient cohort, emotion identification score correlated strongly with performance on the British Picture Vocabulary Scale (a standard test of semantic knowledge; $r = 0.576$, $P < 0.001$).

Mean heart rate over the entire recording was higher in the nfvPPA group than in healthy controls ($P = 0.002$). No other differences between groups were identified for mean heart rate. Overall heart rate variability during the recording did not differ between participant groups ($P = 0.33$).

Cardiac reactivity indices for all participants are shown for each emotion, and the average over all emotions for each participant group in Figure 1. For the combined participant cohort, an increase in RR interval (cardiac deceleration) was found in response to viewing every emotion (all $P < 0.001$). ANOVA of cardiac reactivity incorporating all emotions showed a main effect of participant group ($P < 0.001$) but not emotion type ($P = 0.78$), nor any interaction of participant group and emotion type ($P = 0.58$). The data for average cardiac reactivity for each subject violated assumptions of homoscedasticity (Levene's test $P = 0.034$) and normality (evident from visualizing a Q-Q plot of residuals), and were therefore analyzed using nonparametric methods. There was a main effect of participant group on cardiac reactivity averaged over all emotions (Kruskal–Wallis rank test $\chi^2_{(4)} = 15.4$, $P = 0.004$, estimated $\eta^2 = 0.273$). Post hoc Mann–Whitney *U*-tests revealed attenuated heart rate responses relative to healthy controls in the bvFTD group ($P = 0.018$) and nfvPPA group ($P = 0.027$) but not the rtvFTD group ($P = 0.21$) or svPPA group ($P = 0.93$). Comparing patient groups, heart rate reactivity was reduced in the bvFTD group ($P < 0.001$) and nfvPPA group ($P = 0.002$) relative to the rtvFTD group; no other differences were identified between patient groups for overall emotion reactivity or reactivity to particular emotions. There was no effect of mean heart rate on cardiac reactivity ($r = -0.14$, $P = 0.32$) and the main effect of participant group on cardiac reactivity persisted after covarying for mean heart rate ($F_4 = 3.9$, $P = 0.008$). In a combined regression model with cardiac reactivity as the dependent variable, participant group as a fixed factor, and emotion recognition score and British Picture Vocabulary Scale as covariates, the main effect of participant group on cardiac reactivity persisted ($P = 0.005$), but there was no relationship between heart rate reactivity and emotion identification ($P = 0.79$) or general semantic performance ($P = 0.83$).

Voxel-based morphometric data

Neuroanatomical associations of heart rate reactivity and emotion identification are summarized in Table 2 and statistical parametric maps of the relevant contrasts are presented in Figure 2, thresholded at $P < 0.001$ uncorrected for display purposes (this threshold was chosen to aid visualization, provide an indication of the overall distribution of change, and avoid suggesting a higher degree of anatomical specificity than is possible with smoothed data). All reported anatomical associations were significant at peak-level $p_{FWE} < 0.05$ after correction for multiple voxel-wise comparisons within the prespecified regions of interest. In the bvFTD group, both reduced heart rate reactivity to viewing facial emotion and reduced emotion identification score were associated with gray matter loss in right dorsal anterior cingulate cortex and left orbitofrontal cortex. Emotion identification in the bvFTD group was additionally associated with gray matter loss in left anterior cingulate cortex and bilateral anterior insula. In the nfvPPA group, reduced heart rate reactivity was associated with gray matter loss in posterior right insula. No gray matter associations of emotion identification were identified in the nfvPPA group at the prescribed threshold.

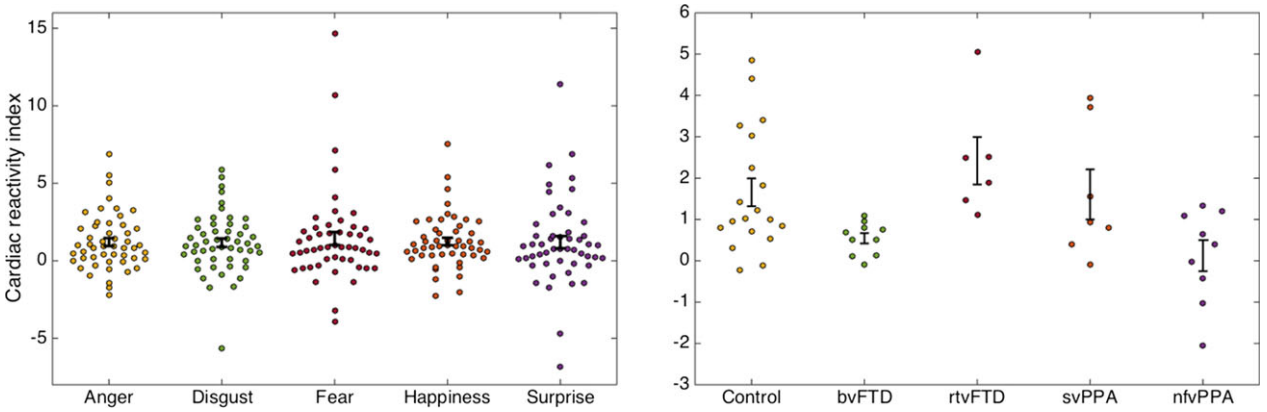

Figure 1. Cardiac reactivity indices by emotion and participant group. Plots show individual participants' mean cardiac reactivity index (mean percentage change in RR interval, see text) to viewing each of the assessed universal facial emotions (left) and mean overall cardiac reactivity index across viewed emotions, separately for each participant group (right; note change of scale on *y*-axis). Error bars represent standard error of the mean. bvFTD, patients with behavioral variant frontotemporal dementia; Control, healthy control group; nfvPPA, patients with nonfluent variant primary progressive aphasia; rtvFTD, patients with right temporal variant frontotemporal dementia; svPPA, patients with semantic variant primary progressive aphasia.

Table 2. Neuroanatomical associations of emotion reactivity and identification in patients

Parameter	Group	Region	Side	Cluster (voxels)	Peak (mm)			P_{FWE}
					x	*y*	*z*	
Cardiac reactivity index	bvFTD	Dorsal ACC	R	1040	8	33	33	0.007
		OFC	L	247	−36	27	−12	0.021
	nfvPPA	Posterior insula	R	38	36	−10	9	0.044
Emotion identification score	bvFTD	Dorsal ACC	R	852	8	28	45	<0.001
		OFC	L	875	−33	28	0	0.021
		ACC	L	245	−6	45	14	<0.001
		Anterior insula	L	44	−36	−4	15	0.006
		Anterior insula	R	32	40	15	0	0.043

The Table presents gray matter correlates of mean overall cardiac reactivity index (mean percentage change in RR interval, see text) in the bvFTD and nfvPPA groups and emotion identification score in the bvFTD group. Peak coordinates given are in mm in standard MNI space. *P* values are all significant at peak-level after family-wise error (FWE) correction for multiple comparisons within prespecified anatomical regions of interest. ACC, anterior cingulate cortex; bvFTD, patient group with behavioral variant frontotemporal dementia; nfvPPA, patient group with nonfluent variant primary progressive aphasia; OFC, orbitofrontal cortex.

Discussion

Here, we have shown differential impairment of cardiac reactivity to facial emotion across the FTD syndromic spectrum. Cardiac responses to emotional facial expressions, incorporating both orienting and affective components, were attenuated in patients with bvFTD and nfvPPA, relative both to healthy older individuals and to patients with rtvFTD. Patients with svPPA and rtvFTD showed preserved heart rate responses when viewing facial emotions. Across the patient cohort, the degree of heart rate modulation did not correlate with accuracy identifying facial emotions, which was impaired in all syndromic groups. In line with current models of visceral responses to emotion, this work has identified a physiological correlate of reduced emotional responsiveness in FTD, which dissociates from the ability to cognitively (and explicitly) categorize emotions. Our findings further suggest that FTD syndromes are stratified according to the profile of altered autonomic reactivity they exhibit. The findings are consistent with previous work showing reduced autonomic reactivity in bvFTD and nfvPPA[18,26] and preserved autonomic reactivity in svPPA.[31] The present work goes further in demonstrating a physiological basis for differentiating subsyndromes within the canonical diagnostic grouping of bvFTD: although a distinct syndrome of

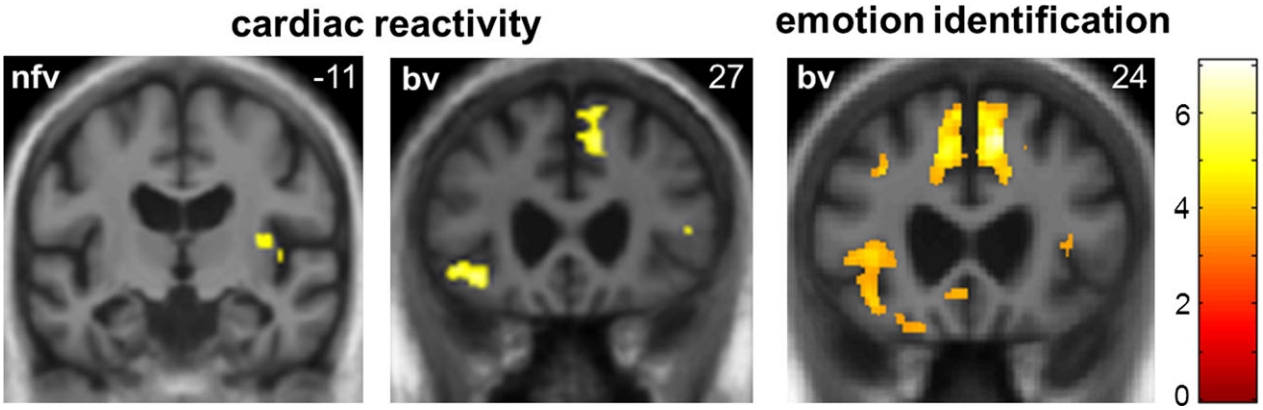

Figure 2. Neuroanatomical correlates of heart rate response to viewing facial emotion and emotion identification in patients. Statistical parametric maps of regional gray matter volume associated with change in RR interval and performance on a facial emotion identification task (derived from a voxel-based morphometric analysis) are shown for patients with behavioral variant frontotemporal dementia (bv) and nonfluent variant primary progressive aphasia (nfv; these syndromic groups showed an attenuated heart rate response relative to healthy controls). Maps have been overlaid on representative coronal sections of the normalized study-specific T1-weighted group mean brain MR image, thresholded at $P < 0.001$ uncorrected over the whole brain for the purpose of display; regional local maxima (see text) were significant at $P < 0.05_{FWE}$ corrected for multiple comparisons within prespecified anatomical regions of interest. The MNI coordinate (mm) of the plane of each section is indicated (the right hemisphere is on the right in each case) and the color bar codes T values.

rtvFTD has been proposed on neuroanatomical and clinical grounds,[2,3] these are to a degree arbitrary given the extensive clinico-anatomical overlap between patients and without mechanistic grounding. Autonomic profiling might establish a principled neurobiological rationale for subclassifying bvFTD, which has long presented nosological difficulties on account of its marked phenotypic and pathological heterogeneity.

Profiles of cardiac reactivity were homogeneous across emotions and did not correlate with explicit emotion identification in our FTD cohort: we propose that autonomic mechanisms govern emotional arousal and intensity (rather than the cognitive categorization of emotions), and are potentially independent of semantic deficits. This interpretation is supported by work in the healthy brain.[10,11] The subjective experience of emotion is likely to be integral to the internalization of observed emotional states in others during emotional contagion. Our findings therefore provide a candidate neurobiological mechanism for the blunted emotional reactions and loss of empathy that characterize FTD syndromes[38,39] and amplify previous work linking altered cardiac vagal tone to reduced agreeableness in bvFTD.[24] Impaired awareness of heartbeat has also previously been demonstrated in FTD[25,32]: taken together with the present findings, this suggests that induction, awareness, and cognitive decoding of embodied emotional responses all contribute to emotional responsiveness and may be separably targeted in FTD syndromes. For example, in svPPA, despite the preserved heart rate response demonstrated here, diminished interpersonal reactivity may be due to reduced afferent processing of these cardiac signals.[32]

This work additionally delineates a neuroanatomical substrate for the differentiated profiles of physiological reactivity and explicit emotion identification in these syndromes. Gray matter associations of heart rate modulation in the bvFTD and nfvPPA groups comprised a predominantly right-lateralized fronto-cingulo-insular "salience" network previously implicated in autonomic regulation in functional neuroimaging studies of healthy individuals[15,40] and patients with bvFTD.[24] The components of this network are likely to play hierarchically organized roles in autonomic control, based on predictive integration of internal homeostatic and external affective signals[9]: according to this interoceptive inference formulation, the regulatory network compares incoming afferent information with predicted autonomic states and engages subcortical, modulatory autonomic reflexes in response to prediction errors (unexpected events).[9] This view emphasizes a reciprocal causality between autonomic responses and subjective emotional states, and suggests mechanisms by which aberrant processing of both afferent and efferent autonomic signals might contribute to reduced emotional reactivity. Posterior insula is the seat of primary interoceptive cortex[41]: noisy processing of cardiac along with other visceral afferent information in this region (as in the nfvPPA group here) would tend to reduce interoceptive sensory precision and therefore lead to reduced prediction errors in response to salient (unexpected) emotional stimuli. Higher stages of the processing hierarchy in ACC and OFC are likely to mediate top-down control of visceral states by integrating autonomic and cognitive state representations[9,42]; shared neuroanatomical

resources for cardiac reactivity and emotion identification in ACC and OFC (as illustrated by the bvFTD group here) would support such integration, as proposed in previous studies of the healthy brain and bvFTD.[19,43,44] It is also noteworthy that additional gray matter correlates of emotion identification were demonstrated in the bvFTD group (Table 2), suggesting a neuroanatomical substrate for dissociation of affective and cognitive processing over the FTD cohort.

These findings open a window on the pathophysiology of a complex neurodegenerative phenotype. It is of interest that this study employed dynamic emotional stimuli: whether in the domain of vision or sound,[20,31] stimuli that unfold in time more closely reflect the natural socioemotional milieu and may be more adequate for eliciting autonomic responses than the static stimuli that are currently widely used in clinical behavioral experiments. From a clinical perspective, the autonomic profiles reported here constitute simple, quantitative, and readily translatable indices of a behavioral hallmark of FTD (altered emotional responsiveness) that is largely inaccessible to conventional neuropsychological instruments. Indeed, in this study, autonomic metrics proved superior to an emotion identification task in differentiating FTD syndromes, and it is possible that metrics of this kind relate more closely to changes in interpersonal reactivity than does the ability to categorize emotional expressions cognitively. Autonomic indices of this kind warrant further evaluation as disease biomarkers in FTD, particularly with a view to stratifying heterogeneous and poorly demarcated syndromes such as bvFTD and the eventual creation of physiologically informed diagnostic criteria. This will be of considerable practical importance if we are to track disease evolution and the effect of disease modifying therapies dynamically. More immediately, the impaired emotional awareness of patients with FTD is a major determinant of caregiver distress[6]: improved understanding of this symptom would assist counseling and the design of nonpharmacological as well as pharmacological interventions.

This study provides proof-of-principle that should direct future work. There is a need for caution in interpreting our findings and, in particular, the practical utility of candidate physiological biomarkers such as cardiac reactivity is yet to be demonstrated. The cohort size here was relatively small, and our findings require corroboration in the wider FTD population. Larger patient cohorts representing a wider range of neurodegenerative pathologies and with additional psychophysiological markers would increase power to detect physiological disease signatures; ultimately, this will require histopathological and molecular correlation. There are successful precedents for large, multi-center studies of FTD syndromes informed by proof-of-principle work in intensively phenotyped patient cohorts.[45] Experiments to parse the roles played by sympathetic and parasympathetic nervous systems, and the relative contribution of more basic indices of psychophysiological reactivity (such as startle and orienting responses) would further elucidate the neurobiological basis for deficits in FTD. Relatedly, it remains unclear to what extent the cardiac reactivity profiles here are specifically elicited by perceiving facial emotion: in future, this might be resolved by comparing cardiac responses to facial emotional expressions with responses to "neutral" facial movements or emotional vocalizations, or by identifying the core stimulus parameters that convey facial emotion. A number of other factors (e.g., the circadian cycle and concomitant intake of alcohol and stimulants) could in principle modulate cardiac reactivity profiles and these could also be assessed in future studies. Autonomic techniques are potentially well suited for neurodegenerative disease staging and tracking of disease evolution, from the presymptomatic phase in genetic mutation carriers through advanced disease in which neuropsychological assessment may no longer be feasible; however, realizing this potential will require longitudinal analysis of autonomic reactivity indices in different neurodegenerative syndromes. Moreover, these techniques could be readily incorporated in functional neuroimaging studies to define network connectivity.

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Author Contributions

Marshall contributed to the study concept and design, acquisition of data, analysis and interpretation, initial drafting of the manuscript; Hardy contributed to the acquisition of data, analysis and interpretation, critical revision of the manuscript; Allen contributed to the

critical revision of the manuscript; Russell contributed to the acquisition of data; Clark contributed to the acquisition of data; Bond contributed to the acquisition of data, critical revision of the manuscript; Dick contributed to the acquisition of data; Brotherhood contributed to the acquisition of data; Rohrer contributed to the study supervision; Kilner contributed to the study concept and design, analysis and interpretation, study supervision; Prof Warren contributed to the study concept and design, analysis and interpretation, critical revision of the manuscript, and study supervision.

Conflict of Interest

No potential conflicts of interest are identified.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. The figure shows the SPM design matrix for the full factorial model used in the voxel-based morphometry analysis.

Table S1. The table presents gender balance and duration for video stimuli selected from the FG-NET database for presentation in the experiment.

