SOCIAL SIGNAL DECODING IN FRONTOTEMPORAL LOBAR DEGENERATION

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Declaration

I, Camilla Neergaard Clark, confirm that the work presented in this thesis is my own. Where information is derived from other sources I confirm that this has been referenced accordingly.

ABSTRACT

Frontotemporal lobar degeneration (FTLD) is associated with progressive social cognitive impairment. Currently a comprehensive pathophysiological model allowing disease effects to be understood and anticipated at the level of the whole brain is lacking. In this thesis I explored candidate cognitive operations underpinning complex behaviours in patients with the canonical syndromes of FTLD; behavioural variant frontotemporal dementia (bvFTD) and semantic dementia (SD). I correlated behavioural deficits with brain network disintegration using the structural magnetic resonance imaging (MRI) technique, voxel based morphometry (VBM). I created synthetic scenes to manipulate congruity across semantic and emotional domains (Chapter 3) and showed deficits across both patient groups. The deficits have grey matter correlates in prefronto-parieto-temporo-insular network and a temporo-insulo-striatal network. I used music as a non-verbal syntactic probe to investigate reward anticipation and valuation (Chapter 4) and demonstrated dissociable deficits across dementias. Performance was associated with grey matter in a distributed network including anterior temporal cortex and orbitofrontal cortex (OFC), previously implicated in computing diverse rewards. I created a novel neuropsychological test of humorous intent (Chapter 5) to model incongruity processing. bvFTD demonstrates a particular difficulty decoding novel humorous situations while SD produces a more general deficit of humour detection. Humour detection accuracy was associated with temporoparietal junction (TPJ) and anterior superior temporal cortical volume which are hubs for processing incongruity and semantic associations. To assess the relevance of these findings (Chapter 5) to daily life behaviour I explored humour preferences across dementias (Chapter 6). Altered sense of humour is particularly salient in bvFTD and SD, but also frequent in AD and may predate more typical symptoms. In conclusion, impairment in incongruity processing and reward allocation was shown across paradigms. The neuroanatomical networks underpinning these processes overlapped with areas known to be targeted by FTLD. These processes have implications for our understanding of the social dysfunction that defines bvFTD.

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Abbreviations

$A\beta_{1-42}$	Amyloid-$Beta_{1-42}$ protein
AD	Alzheimer's disease
ACC	Anterior cingulate cortex
Am	Amygdala
ANOVA	Analysis of variance
Ant	Anterior
APP	Amyloid precursor protein
BPVS	British Picture Vocabulary Scale
bvFTD	Behavioural variant frontotemporal dementia
CBI	Cambridge Behavioural Inventory
CDR	Clinical Dementia Rating
CI	Confidence interval (expressed as standard 95% confidence interval)
CSF	Cerebrospinal fluid
CT	Computerised tomography
C9orf72	Pathogenic mutation in open reading frame 72 on chromosome 9
DMN	Default mode network
EcSc	Emotionally congruous, semantically congruous
EcSi	Emotionally congruous, semantically incongruous
FBI	Frontal Behavioural Inventory
fMRI	Functional magnetic resonance imaging
FTLD	Frontotemporal lobar degeneration
FUS	Fused in sarcoma
FWE	Family wise error
GDA	Graded difficulty arithmetic
GNT	Graded naming test
GRN	Progranulin
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobe
L	Left
LPA	Logopenic progressive aphasia
MAPT	pathogenic mutation in microtubule-associated protein tau
MFG	Medial frontal gyrus
MMSE	Mini mental state examination score
MNI	Montreal Neurological Institute
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
MTL	Medial temporal lobe
NART	National adult reading test
N/A	Not applicable

OFC	Orbitofrontal cortex
OR	Odds ratio
PAL	Camden Paired Associate Learning
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
PET	Positron Emission Tomography
PIQ	Performance IQ
PNFA	Progressive non fluent aphasia
Post	Posterior
PPA	Primary progressive aphasia
PS	Presenilin (1 or 2 is specified by number following abbreviation)
R	Right
rms	root-mean-square
RMT	Recognition Memory Test
ROI	Region(s) of interest
ScEc	Semantically congruous, emotionally congruous
ScEi	Semantically congruous, emotionally incongruous
s.d.	Standard deviation
SD	Semantic Dementia
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SN	Salience network
SPM	Statistical parametric map
STG	Superior temporal gyrus
Stroop D-KEFS	Delis Kaplan Executive System
STS	Superior temporal sulcus
TASIT	The Assessment of Social Inference test
TDP-43	Transactive response DNA binding protein 43 kD
TIV	Total intracranial volume
TPJ	Temporo-parietal junction
Trails B-A score	Trails-making task (B-A difference score)
VIQ	Verbal IQ
VOSP	Visual Object and Spatial Perception Battery
VBM	Voxel Based Morphometry
vmPFC	Ventromedial prefrontal cortex
WASI	Wechsler Abbreviated Scale of Intelligence
WMS-R	Wechsler Memory Scale Revised
18F	Fluorine-18

1 GENERAL INTRODUCTION

1.1 The challenge of social cognitive impairment in FTLD & rationale for the thesis

FTLD is a heterogeneous syndrome associated with progressive frontotemporal lobe atrophy. bvFTD is the most common subtype which typically presents with relentless decline in interpersonal conduct, with devastating consequences for affected individuals and families. Neurobiologically, it offers a unique window on pathophysiological processes translating brain network disintegration into the behavioural phenotype. Networks in the context of disease processes refer to anatomical signatures where certain diseases or pathogenic proteins appear to target specific structurally or functionally connected regions, often with a common function, that appear be specifically vulnerable to the disease process (Warren JD, JD Rohrer, JM Schott, et al. 2013). Currently, understanding of these cognitive mechanisms in bvFTD is limited.

FTLD collectively constitutes an important cause of young onset dementia (Ratnavalli E et al. 2002; Coyle-Gilchrist IT et al. 2016), however an increased disease prevalence in the over 65 year old population has become apparent (Onyike CU and J Diehl-Schmid 2013; Coyle-Gilchrist IT *et al.* 2016). There is evidence that in the two canonical forms of FTLD, bvFTD and SD, social and emotional deficits are an early indicator of disease (Seeley WW et al. 2005; Seeley WW, JM Allman, et al. 2007). Owing to the complexity of interpersonal behaviour and the multidimensionality of social cognition, the presenting symptoms of FTLD are poorly understood. This is an issue preventing early and accurate diagnosis (Davies RR et al. 2006; Kipps CM et al. 2007) and contributing to underdiagnosis at a population level. Furthermore, there is the potential for misdiagnosis as early in the disease course FTLD can mimic psychiatric diagnoses, and in one cohort as many as 50% were initially misdiagnosed with psychiatric illness (Woolley JD et al. 2011). These diagnostic difficulties are compounded by the fact that patients often present younger than the age range typical for neurodegenerative disease.

As molecularly targeted treatments begin to emerge, the emphasis is shifting towards earlier diagnosis using sensitive and dynamic biomarkers to enable disease tracking against potential symptomatic and disease modifying treatments. Although such biomarkers have yet to be robustly defined, they can be functional or physiological (Strimbu K and JA Tavel 2010) and

ideally should be a direct measure of a fundamental process key to the disease. One approach to this problem is to resolve complex symptoms into more basic and tractable component processes. The experimental designs in this thesis were intended to deconstruct key 'building blocks' of social cognition that might be engaged by more complex operations (such as theory of mind), rather than indexing those operations directly. The intention was to identify operations that more closely reflect pathophysiology.

The project of linking behaviour to psychology to neurobiology in the case of social cognition requires considering social cognition as a hierarchical construct. Each hierarchy captures regularities that are less economically described at other levels, and therefore all levels must be considered (Schaafsma SM et al. 2015). There has been headway made to this end; as reflected in recent mapping of phenotype to underlying structural and physiological changes in FTLD (Sturm VE et al. 2011; Balconi M et al. 2015; Fletcher PD, JM Nicholas, et al. 2015, 2015; Fletcher PD et al. 2016). Disordered valuation of biologically rewarding stimuli is a hallmark of bvFTD and is associated with alterations of autonomic and metabolic functions (Ahmed RM, V Iodice, et al. 2015; Ahmed RM et al. 2016) and physiological response to auditory semantic and salient stimuli is a marker of TDP-C pathology in SD (Sturm VE *et al.* 2011; Fletcher PD, JM Nicholas*, et al.* 2015, 2015). Physiological responses have been used to differentiate the FTLD syndromes from each other and from the most common neurodegenerative disease, Alzheimer's disease (AD) (Fletcher PD, JM Nicholas*, et al.* 2015).

There is currently no sensitive and specific way to predict molecular pathology from symptomatology or to determine the phenomenology from the culprit abnormal pathology (Rohrer JD et al. 2011; Rohrer JD and JD Warren 2011). Although SD is reliably associated with TDP-43 Type C pathology, bvFTD is a heterogeneous syndrome with no straightforward associations between clinical phenotype and underlying pathology (Knibb JA et al. 2006; Pressman PS and BL Miller 2014). The determination of which neurodegenerative disease underlies the syndromic diagnosis relies on identification of one of three main pathological proteins (Hodges JR et al. 2004; Josephs KA et al. 2011; Rohrer JD *et al.* 2011). The ultimate aim would be to use clinical or cognitive measures to help stratify underlying proteinopathies.

Approximately 20% of FTLD across syndromes is caused by an autosomal dominant inherited gene, and genetic subtypes are molecularly specified "models" for the sporadic phenotypes (Rohrer JD et al. 2015). Despite these associations, there is extensive overlap between the manifestations of behavioural symptoms across mutations, even within each genetic subgroup or within particular families, possibly secondary to genetic modifiers influencing phenotype (Rohrer JD *et al.* 2011; Rohrer JD and JD Warren 2011).

The need for accurate in vivo pathological identification is becoming increasingly urgent in the era of molecularly targeted treatments (Capell A et al. 2011; Cenik B et al. 2011) and ligand imaging and biomarkers (Mitsis EM et al. 2014; Rohrer JD *et al.* 2015; Brier MR et al. 2016). However, the detection of a pathogenic protein alone does not inform us of its functional consequences (Pikkarainen M et al. 2009), thus necessitating conjoint pathophysiological measures.

1.2 The nature of social signal processing and relevant brain substrates

Social cognition has been described as any cognitive process that is engaged to understand or interpret the self in relation to others (Forbes CE and J Grafman 2010) and in relation to the external environment (Fiske ST 1993). Many social behaviours are multidimensional and can be fractionated (Stuss DT 2011). Social cognition can be viewed in terms of the interacting component processes that can be recombined according to task demands (Mitchell JP 2006; Eslinger PJ et al. 2011).

Social situations tend to generate complex, multi-sensory signals. The Shallice model of frontal lobe function (Norman DA and T Shallice 1986) holds that the frontal lobes are necessary to solve tasks demanding considerable neural resources as a result of their novelty or complexity (Stuss DT 2011), an archetypal example of which is social cognition. The frontal lobes instantiate as a cognitive "buffer", which takes the available information offline and resolves any discrepancies in order to formulate an appropriate and coherent response. Selecting a unitary response is particularly challenging if the situation is ambiguous (multiple potential outcomes of equal probability) or incongruous (a signal mismatch with multiple conflicting responses) as is often the case with social signals. A normally functioning brain will maximise the available information from contextual cues in order to resolve these discrepancies

(Mesulam MM 1986). Consequently, heavy demands are placed on the neural networks decoding sensory data in social contexts.

The neural architecture of social cognition and its component subprocesses are increasingly well worked out in the healthy brain. In the normal brain, the specific cognitive mechanisms of salience allocation, expectation generation and prediction testing prior to incongruity and ambiguity resolution, allow the generation of a coherent behavioural response. The response is often directed toward the fundamental aims of reducing prediction error, obtaining reward or punishment avoidance. Predictive or generative models facilitate the processing of expected stimuli or planned actions (O'Reilly JX et al. 2013) and are the precursor to incongruity detection. A key motive of the free-energy hypothesis is increasing efficiency through decreasing redundancy and limiting surprise (Apps MA and M Tsakiris 2014). Under such models, surprising (low probability) stimuli or actions are deemed behaviourally relevant (salient) and are selected and prioritised to trigger reallocation of processing resources, whilst simultaneously signalling the need to update the underlying predictive model to reflect these changes (Dalton MA et al. 2012; O'Reilly JX *et al.* 2013; Schultz W 2013). This allocation of processing resources facilitates planning of responses to allow desired consequences beyond short term goals arising from automatic, stimulus-bound or prepotent responses. A free-energy account of brain function speaks to the fundamental role of the frontal lobes in integrating conflicting alternatives (Moran JM et al. 2004) and incongruity-ambiguity resolution (Friston K 2009). This may be a universal principle of brain operation.

The semantic appraisal network gives meaning to our experiences. Dynamic interactions of neural networks are key to this flexibility where different contexts trigger connectivity with amodal regions for attribution of meaning (Forbes CE and J Grafman 2010). The identification of self- and group-oriented goals is also created through this interaction of context dependent and independent regions. These interactions allow for greater flexibility of context to modulate emotional response despite the universal application of social values (Zahn R, J Moll, M Paiva, et al. 2009) generating for example context dependent social emotions and moral reasoning, or tactlessness versus sarcasm depending on associated sensory cues (Rankin KP et al. 2009). The context independent regions include an amodal hub of self-referential semantic knowledge centred in the superior temporal gyrus (STG) with regions for contextual and social

perceptive processing and assignment of emotional valence via frontolimbic circuitry (Zahn R, J Moll, M Paiva*, et al.* 2009; Green S et al. 2010). There is functional connectivity with distributed modality-selective primary and secondary association cortices (Guo CC et al. 2013).

The default mode network (DMN) governs the interface of our inner life with the external world including stimulus independent or internally directed thought (Leech R et al. 2011; Lehmann M et al. 2013). The DMN consists of at least two interacting subsystems: the mnemonic network centred on the medial temporal lobes (MTL) containing the hippocampal and parahippocampal structures and the self-referential mental simulation network centred on the posterior cingulate cortex (PCC) and including the ventromedial prefrontal cortex (vmPFC), and inferior parietal lobe (IPL) (Frith U and CD Frith 2003; Greicius MD et al. 2003; Buckner RL et al. 2008; Leech R and DJ Sharp 2013; Li W et al. 2014). The DMN constructs self-relevant mental simulations that are key to a number of cognitive functions including remembering the past, contemplating the future, emotion perception, theory of mind, empathy, inferring other's beliefs or intentions, and moral judgements (Baron-Cohen S et al. 1994; Castelli F et al. 2000; Addis DR et al. 2007; Leech R and DJ Sharp 2013; Li W *et al.* 2014; Irish M and P Piolino 2016). There is overlap seen between the DMN and regions activated in social cognitive tasks (Schilbach L et al. 2008). The PCC may further be involved in signalling salient external environmental changes to facilitate behavioural responses and subsequently update the predictive model of the world (Pearson JM et al. 2011).

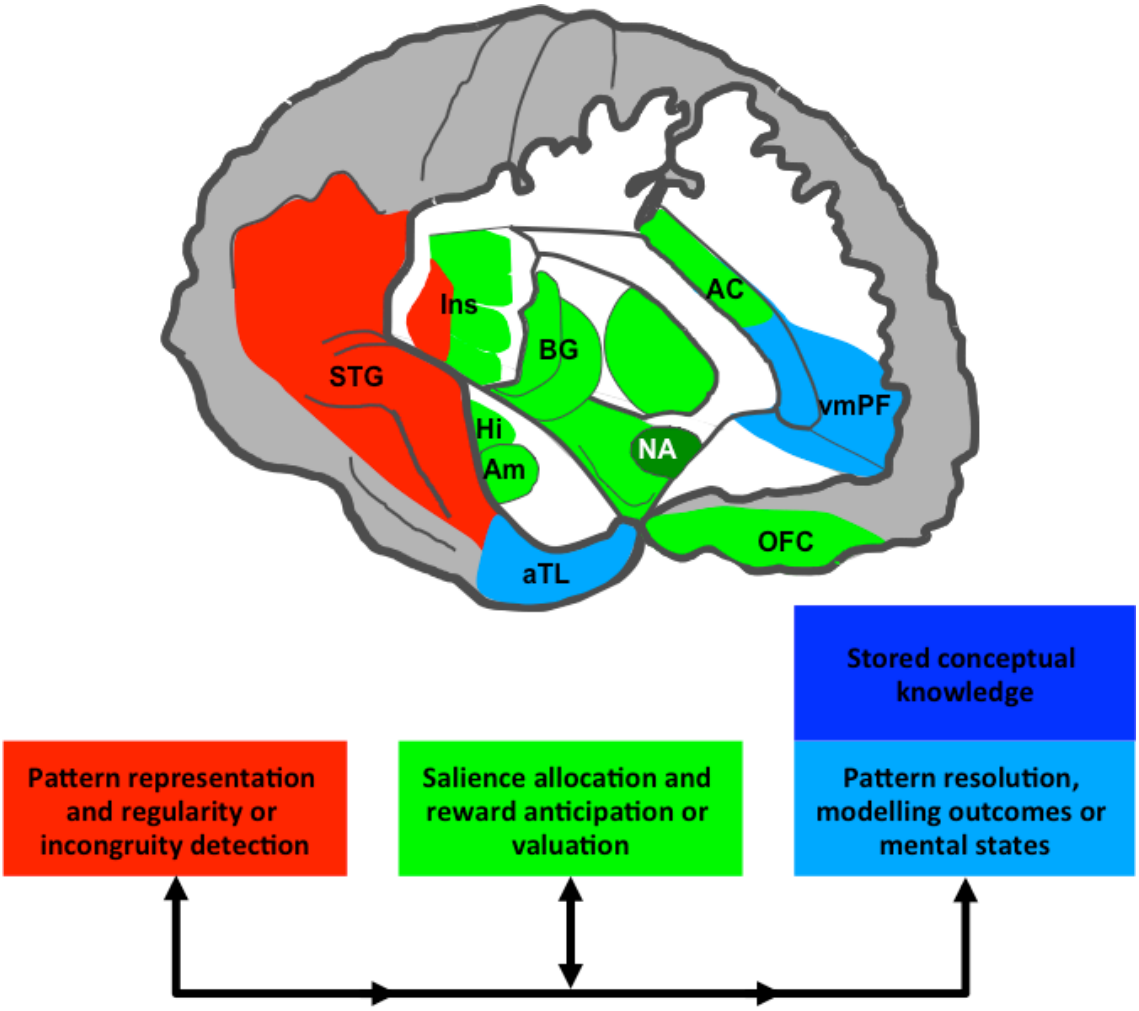
Distributed neuroanatomical networks process the salience of internal versus external cues through interactions with the limbic system (Wallis JD 2007; Lang S et al. 2009; Ibanez A and F Manes 2012; Zhou J and WW Seeley 2014). The 'salience' network (SN) comprises the insula, anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) and integrates environmental and internal homeostatic signals and their value in relation to behavioural goals. The ACC performs contingency, expectancy and salience coding and updates the underlying predictive model that allows efficient processing of expected events (O'Reilly JX *et al.* 2013). The co-activation of ACC and fronto-insular regions is in response to biologically significant stimuli such as social emotions (social rejection and embarrassment) to physical sensations (pain, thirst, and hunger) (Craig AD 2002; Critchley HD 2005; Singer T et al. 2009; Ibanez A et al. 2010). Integrating these competing interoceptive inputs with personal goals, hedonic

conditions, and social contextual information (Seeley WW et al. 2012) allows us to represent subjective feeling states and a 'global emotional moment' (Craig AD 2009).

A ventral striatal–mesolimbic dopaminergic network integrates cognitive and autonomic responses during reward anticipation, learning and the scheduling of goal-directed behaviours (Seeley WW, V Menon, et al. 2007; Pievani M et al. 2011; Halabi C et al. 2013; Perry DC et al. 2014; Zhou J and WW Seeley 2014; Bocchetta M et al. 2015; Perry DC et al. 2015). Reward (defined broadly as a biologically or cognitively desirable state or event) is a prime mover of human behaviour through facilitating associative learning and the seeking of repetition. Previously learnt association between reward and its context and the generation of reward prediction are functions encompassed by the OFC and ACC respectively (Wallis JD 2007; Kennerley SW et al. 2011; Rosenbloom MH et al. 2012).

The valence of social emotions is the result of whether the behaviour conforms to (e.g. pride) or violates (guilt and indignation) learnt social values (Sturm VE et al. 2008; Zahn R, J Moll, M Paiva*, et al.* 2009; Sturm VE, M Sollberger, et al. 2013). Social emotions and social values can be recast as processes requiring comparisons to set standards and may rely on common decoding mechanisms. In functional magnetic resonance imaging (fMRI) work, ventrolateral and dorsomedial prefrontal cortices respond when participants process events which violate contextual social expectations or norms (Berthoz S et al. 2002; Takahashi H et al. 2004; Finger EC et al. 2006). The right temporo-parietal junction (TPJ) plays a generic role in generating, testing, and correcting internal predictions about external sensory events which is a key function in such diverse cognitive processes as humour processing to theory of mind (Decety J and C Lamm 2007). When error or incongruency detection occurs the usual motivation is to re-establish coherence with the prediction. In the context of social emotions this could result in attempts at reparative or remedial action (Tangney JP et al. 1996). The prefrontal cortices (PFC) play a role in adherence to social norms (Frith U and CD Frith 2003; Moll J et al. 2012).

Figure 1 Components of socio-emotional signal decoding



Pattern representation (red) includes TPJ, posterior STG and STS; salience allocation and reward processing (green) includes the ACC, insula, basal ganglia and OFC; higher-order cognitive processing (blue) encompasses pattern resolution and modelling outcomes in the vmPFC (light blue); anterior temporal lobe (dark blue) where conceptual knowledge is stored. Social cognition accesses a distributed neural network including areas that code the perceptual components (red), limbic areas such as the insula that link interoceptive and exteroceptive emotionally salient experiences (green) and regions including the PFC and anterior temporal regions which are important for processing transgressions based on predictions or expectations including stored concepts (blue). See Table 1 for relevance to each thesis Chapter. The effect of FTLD on some of these links gives us insight into the processes in the normal brain. A proposed functional architecture for information exchange between these networks (based on empirical data) is shown below (arrows code primary direction of information flow). **AC**, anterior cingulate; **aTL**, anterior temporal lobe; **BG**, basal ganglia; **Ins**, insula

1.3 Issues with assessing social cognition

There are general difficulties in assessing cognitively impaired patients, in particular those patients with FTLD. This arises from difficulty in measuring complex social-emotional behaviours. Currently there is no diagnostic test for bvFTD, it remains largely a clinical diagnosis supported by neuropsychology and/ or imaging findings which meet established criteria (Rascovsky K et al. 2007). The patients tend to present at a younger age which means there can be a lack of age appropriate normal ranges for neuropsychology tests. bvFTD patients can perform within the normal range on standard cognitive tests early on in the disease process (Gregory CA and JR Hodges 1996; Torralva T et al. 2009) and there are few widely standardised specific tests for this group. There is a lack of uniformity between studies, perhaps in part attributable to methodological differences. There are further questions regarding to what extent research populations reflect the general disease population as they tend to be younger and by definition, able to comply with testing therefore excluding those most severely affected, as has been shown in populations of patients with comparable chronic progressive neurological conditions (Duquin JA et al. 2008).

Conventional neuropsychological instruments are insensitive to detect change in complex behavioural functions (Stuss DT 2011; Bertoux M et al. 2012). Widely validated standardised measures of social cognition are presently lacking. Part of the difficulty arises from finding tasks addressing specific components of the highest levels of the social cognitive processing hierarchy without inter-dependence between contributing subcomponents (Schaafsma SM *et al.* 2015).

At the earliest stage of disease detected using the Clinical Dementia Rating (CDR) scale, patients with FTLD show reduced sensitivity to errors, emotion naming and lexical fluency compared to patients with AD (Ranasinghe KG et al. 2016). However, verbally generated responses can be problematic in cases with accompanying aphasia or word retrieval impairment. Tests that have been constructed to assess higher order socially relevant cognitive processes are often reliant on verbal response procedures which could potentially result in underestimating the patient's ability on the task (McDonald S et al. 2006; Irish M et al. 2014). Alternative cross-modal, within-modality matching or procedures requiring classification according to a predetermined semantic criterion have been employed to circumvent this

problem (Omar R et al. 2010), but are not universal. Whereas recognition of emotions can be assessed using standard neuropsychological methods such as forced-choice labelling, assessment of emotional response is more difficult, relying on subjective ratings (such as pleasant / unpleasant: (Peretz I et al. 2001) or measurement of autonomic indices of arousal such as skin conductance (Johnsen EL et al. 2009; Balconi M *et al.* 2015).

Social behaviours are multidimensional and as a result neuropsychological tests can be difficult to interpret. Different patient groups may fail for varying reasons not necessarily differentiated by the test; as has been demonstrated in tests of insincere communication (McDonald S *et al.* 2006) or social faux pas (Torralva T *et al.* 2009). Those tasks which are directly accessing social cognitive processes are often reliant on complex decision making (Carr AR et al. 2015; Perry DC *et al.* 2015; O'Callaghan C et al. 2016). This allows the potential for confounds from executive, attentional or language deficits that are outside the intended remit of the test.

Assessment of theory of mind can be beneficial for early identification of bvFTD (Bora E et al. 2015). However, theory of mind is not a unitary construct. Lesion studies have demonstrated fractionated deficits (Duval C et al. 2012; Torralva T et al. 2015). Theory of mind impairment in bvFTD is of a similar magnitude to impairment on measures of more basic social cue perception such as emotion recognition (Bora E *et al.* 2015). Empathy and determination of intention are related, but not fully explained by performance on executive function (Bertoux M et al. 2016) or other social cognitive tests in bvFTD (Baez S et al. 2014). Patients with bvFTD are disproportionately impaired on tests of theory of mind compared to tests matched for cognitive demands other than mentalising (Gregory C et al. 2002; Henry JD et al. 2014). However, both patients with bvFTD and AD can perform at ceiling in first-order false-belief tasks despite minimal cognitive task demands, with strikingly discrepant social cognitive abilities, reflecting the complexity of attempting to capture social functioning in this manner (Fernandez-Duque D et al. 2009). Moreover, patients with neurodegenerative diseases and even healthy controls have failed the second-order false belief task owing to working memory demands (Gregory C *et al.* 2002; Fernandez-Duque D *et al.* 2009). Therefore it would be preferable for tests to directly assess the more basic operations or generic mechanisms. Theory of mind and social faux pas performance is preserved in patients with frontal lobe epilepsy despite deficits in emotion recognition, eyes gaze task and interpreting physical and

satirical humour (Farrant A et al. 2005). Taken together, this evidence demonstrates that potentially independent processes underpin these higher cognitive tasks and suggests that a conceptual deficit in theory of mind does not fully account for the difference in social functioning between bvFTD and AD.

Current evidence suggests that neurocognitive testing has limited practical benefit in distinguishing bvFTD from AD or from neuropsychiatric differentials such as major depressive disorder. Those tests demonstrating the most promise are reliant on social cognitive processes, appearing to differentiate bvFTD from AD even, for example, in the presence of concomitant episodic memory impairment in the bvFTD group (Bertoux M *et al.* 2012; Bertoux M et al. 2013; Buhl C et al. 2013). There is evidence that processes related to conflict monitoring and social judgement may occur early and outweigh executive dysfunction in bvFTD (Eslinger PJ et al. 2007; Libon DJ et al. 2007; Krueger CE et al. 2009) differentiating bvFTD from healthy controls (Torralva T *et al.* 2009; Gleichgerrcht E et al. 2010). Measures of mental flexibility were strongly predictive of performance in the social dilemmas task in bvFTD (Eslinger PJ *et al.* 2007). Tailored tests may detect deficits despite otherwise normal, standard psychology assessments by tapping into meta-cognitive processes such as context dependent memory and mentalising (McDonald S *et al.* 2006; Burgess PW et al. 2009; Fernandez-Duque D *et al.* 2009).

In essence, the dementias have profound consequences for complex behaviours that impact on the emotional and social functioning of patients in their daily lives. Such phenomena are notoriously difficult to capture using the conventional pencil-and-paper armamentarium of psychometric tests. The field of neurodegeneration research cries out for comprehensive pathophysiological models that will allow disease effects to be understood and anticipated at the level of the whole brain. A more fundamental difficulty has been the lack of a widely accepted information processing framework for understanding or capturing the social cognitive deficits seen in FTLD. An analogous development in the neurocognition of language has seen a move away from the approach of classical aphasiology toward cognitive information-processing techniques (Hickok G and D Poeppel 2007; Rauschecker JP and SK Scott 2009). An information processing model of social cognition states that we use implicitly learnt behavioural rules or cultural norms to make predictions about others' behaviour or to plan or

own (Mitchell JP 2006) and I would suggest that the key candidate processes for this are; expectation generation, pattern prediction, resolution of incongruity, ambiguity and determination of salience or reward. Tests directed to these information processing components of social cognition are largely lacking, this may be the route to tap into the underlying pathophysiology. There are tasks which address some of these key subprocesses, however the nature of the task is removed from socially relevant tasks (Dalton MA *et al.* 2012). This approach may address the nosological and diagnostic difficulties posed by FTLD stemming from the heterogeneity of symptoms which are often complex intractable behavioural changes. More direct measures reflecting pathophysiological processes would possibly allow the disease to be accurately tracked over time. This thesis will address candidate processes that underpin social cognition breakdown by trying to quantify metrics of social cognition in FTLD.

1.4 The nature of social cognitive deficits in FTLD

1.4.1 Scope of symptoms

FTLD describes a heterogeneous group of disorders (Pressman PS and BL Miller 2014). The main division is between the behavioural predominant type (bvFTD) and the language predominant types which are termed the primary progressive aphasias (PPA) (Seeley WW et al. 2009) and include the subtypes of SD and progressive nonfluent aphasia (PNFA). For further details of diagnostic criteria used for inclusion into the patient cohorts please see General Methods.

The canonical FTLD syndromes (bvFTD and SD) manifest clinically with diverse deficits of semantic, emotional and social signal decoding (Snowden JS et al. 2003; Kipps CM et al. 2009; Piwnica-Worms KE et al. 2010; Fumagalli M and A Priori 2012; Warren JD, JD Rohrer and MN Rossor 2013; Irish M *et al.* 2014; Downey LE et al. 2015; St Jacques PL et al. 2015). bvFTD is defined by a catastrophic decline in interpersonal skills and incoherent social behaviour encompassing many aspects of social functioning (Rascovsky K et al. 2011). The breadth of distinct social cognitive deficits seen in this disorder, illustrate the multidimensional nature of social cognition (Zahn R et al. 2007; Adolphs R 2009). I will focus on those deficits which are related to themes that I will expand upon in experimental work. The deficits that I will discuss include; the decoding of sensory or emotional signals (Rankin KP et al. 2005; Lough S et al.

2006; Mahoney CJ et al. 2011; Omar R, JD Rohrer, et al. 2011; Piguet O et al. 2011; Kumfor F et al. 2013; Torralva T *et al.* 2015), understanding others' behaviours (Le Bouc R et al. 2012; Downey LE et al. 2013), higher order social information processing using semantic knowledge (Chiong W et al. 2013), perception of insincere communication including attribution of social intent (Snowden JS *et al.* 2003; Kipps CM *et al.* 2009; Shany-Ur T et al. 2012; Mahoney CJ et al. 2015), conceptualising the self in relation to others (Irish M et al. 2011) and reward (Perry DC *et al.* 2015).

1.4.2 Separable socio-emotional phenotypes

FTLD impairs social cognition and emotional signal decoding (Snowden JS *et al.* 2003; Kipps CM *et al.* 2009; Irish M *et al.* 2014). I will partition the canonical FTLD syndromes into what I believe are their separable socio-emotional 'phenotypes'.

Theory of mind dysfunction, loss of empathy and the ability to infer intentions are robust features of bvFTD (Henry JD *et al.* 2014; Baez S et al. 2016). bvFTD has been regarded as a paradigm of acquired sociopathy (Mendez MF and JS Shapira 2009). The patients exhibit many hallmarks of social disintegration; disinhibition, impulsivity, emotional blunting, loss of empathy, mental flexibility and ability to think in the abstract, without any insight into these difficulties (Leyton CE and JR Hodges 2010; Rascovsky K *et al.* 2011). Reduced empathy may be secondary to this reduced ability to shift perspective in social situations (Rankin KP et al. 2006; Le Bouc R *et al.* 2012). Context dependent social emotions are affected (Sturm VE *et al.* 2008; Sturm VE, M Sollberger*, et al.* 2013). BvFTD patients fail to recognize when others violate social norms, and they are unable to identify instances in which their personal judgments transgress social conventions such as faux pas or embarrassment (Gregory C *et al.* 2002; Lough S *et al.* 2006; Sturm VE et al. 2006) or the gravity of transgression from moral expectations. These behavioural and emotional impairments tend to be early and prominent with later development of impaired conceptual understanding (Rascovsky K *et al.* 2011). Deciphering the semantic context of social situations is a key feature of successful interpersonal interactions (Kipps CM *et al.* 2009). bvFTD is associated with increased risk-taking (Rahman S et al. 1999) and aberrant hedonic processing manifesting as a reduced ability to delay seeking anticipated rewards (Bertoux M et al. 2015) and craving rewarding stimuli to excess, for example gluttony with a sweet food preference (Ahmed RM et al. 2014).

Sarcasm has proven a very useful probe of social cognition in bvFTD (Kipps CM *et al.* 2009). Sarcasm typifies incongruity resolution where the verbal content is at odds with intonational, prosodic and facial expressions (Uchiyama H et al. 2006) and contradicts the learnt assumption that all speech is truthful (Grice H 1975). Processing of sarcasm and these learnt assumptions are impaired in bvFTD (Shany-Ur T *et al.* 2012). Further described abnormalities of humour behaviours include compulsive punning ('Witzelsucht') which has been described (Ehrlé N et al. 2011; Ibanez A and F Manes 2012). There have been documented cases in moderately severe AD of a preserved ability to pun (Hawkins DB and NR Graff-Radford 2007). This may reflect a loosening of contextual constraints around the word allowing its ambiguous meaning to remain unresolved.

SD classically is defined by progressive, pan-modal impairment of semantic memory and subsequently personality and behavioural changes (Seeley WW et al. 2006; Kipps CM *et al.* 2009; Rascovsky K *et al.* 2011; Pressman PS and BL Miller 2014). Patients have deficient facial recognition which is a key part of social interactions (Kumfor F et al. 2015). The eroded conceptual knowledge in SD can include social conventions (Zahn R, J Moll, V Iyengar, et al. 2009). Emotion processing including when embodied in abstract stimuli such as music, and sarcasm detection are known to be affected in SD (Rosen HJ et al. 2004; Kipps CM *et al.* 2009; Rankin KP *et al.* 2009; Hsieh S et al. 2012; Shany-Ur T *et al.* 2012). Patients with SD also frequently exhibit abnormal processing of biological rewards (Perry DC *et al.* 2015; Ahmed RM *et al.* 2016).

PNFA patients do not tend to exhibit prominent social cognition deficits. However, impairments in emotion recognition, in particular linguistic prosody, (Kumfor F et al. 2011; Rohrer JD et al. 2012) and a dissociation of implicit and explicit emotional cue matching (Balconi M *et al.* 2015) are observed in this group. Although PNFA patients can have comparably severe deficits on tests of theory of mind as bvFTD patients, this is secondary to impaired face and emotion recognition rather than a defective ability to mentalise per se (Couto B et al. 2013).

1.4.3 AD in relation to FTLD

AD is an important comparator group to FTLD and a test case for the ideas proposed in earlier sections. AD is the most common dementia syndrome and typically presents with early prominent episodic memory decline (Dubois B et al. 2007). There is more variable impairment of semantic memory and relative preservation of procedural memory in the initial stages. Dementia is much more than failure of memory. AD and other neurodegenerative diseases often have profound consequences for complex behaviours that impact on the emotional and social functioning of patients in their daily lives. AD is distinct on clinico-anatomical and pathological grounds, but emerging evidence is that it does also have a social cognitive signature (Le Bouc R *et al.* 2012; Sturm VE, JS Yokoyama, et al. 2013; Bora E et al. 2016). The important question for this thesis is how this relates to FTLD.

Theory of mind has been shown to be impaired in both AD and bvFTD (Le Bouc R *et al.* 2012). In AD it is owing to a failure to infer an alternative person's mental state and in bvFTD arising from a failure to inhibit one's internal mental state. AD patients performed comparably to controls on an empathy and emotion recognition task whilst SD and bvFTD performed significantly worse (Hutchings R et al. 2015). Emotion recognition was preserved in AD and severely impaired in bvFTD patients, most apparent in the negatively valenced emotions (Bora E *et al.* 2016). Cognitive empathy or perspective taking was deficient in AD and bvFTD, related in the former directly to overall cognitive performance. Affective empathy was unimpaired in AD patients (Dermody N et al. 2016). Eroded emotional boundaries in AD are thought to result in empathy being invoked in a non-normative context (Sturm VE, JS Yokoyama*, et al.* 2013). Abnormalities of primary reward processing are frequent in AD, as in other neurodegenerative proteinopathies. Recent work has demonstrated that abnormalities of reward processing in neurodegenerative disease extend to non-biological stimuli and reward-based learning (Perry DC *et al.* 2015). Patients with bvFTD and AD show complementary profiles of altered reactivity to monetary and social reward and favourable versus adverse outcomes (Torralva T et al. 2007; Ha J et al. 2012; Perry DC *et al.* 2015).

The language variant of AD or Logopenic progressive aphasia (LPA) is distinct anatomically, pathologically and phenomenologically from the language variants of FTLD and therefore can be a useful comparator group with distinct deficits. LPA is associated with widespread atrophy

of a left hemispheric network involving the TPJ, which explains the core phonological processing deficit manifesting in word retrieval deficits and length-dependent repetition difficulty with relative preservation of semantic knowledge (Rohrer JD et al. 2010; Pressman PS and BL Miller 2014). LPA has no known distinct socio-emotional signature.

1.4.4 Neuroanatomy of social cognitive deficits within the FTLD / AD spectrum

Both AD and the diseases constituting the clinical FTLD spectrum have been associated with unique network breakdown that explains their symptomatology (Warren JD, JD Rohrer and MN Rossor 2013). Although anatomically distinct, the shared neural substrates can tell us about the neurobiology of social cognitive processes and the impact of disease on key network hubs (McGinnis SM 2012; Warren JD, JD Rohrer, JM Schott*, et al.* 2013; Downey LE *et al.* 2015).

bvFTD has a neuroanatomical substrate in vmPFC and anterior temporal lobe areas previously implicated in mentalising and social concept representation (Frith U and CD Frith 2003; Zahn R *et al.* 2007; Steinbeis N and S Koelsch 2009; Zahn R, J Moll, V Iyengar*, et al.* 2009). Patients with bvFTD, like those with focal lesions in vmPFC, show increased use of utilitarian or rule based principles in making decisions in moral dilemmas without being as swayed by emotive individual factors (Eslinger PJ *et al.* 2007; Koenigs M et al. 2007; Carr AR *et al.* 2015). Rule-based moral reasoning is also correlated with decreased cortical volume in the right OFC (Carr AR *et al.* 2015).

Alzheimer's pathology exhibits a predilection for the DMN (Buckner RL *et al.* 2008). AD changes may be reciprocal or complementary to bvFTD and therefore might potentially illuminate mechanisms of reciprocal activation and inhibition of networks in these diseases. Deficits in cognitive empathy in AD correlated with predominantly left-sided temporoparietal atrophy and global cognitive dysfunction (Irish M and P Piolino 2016). Through their dysregulation of the DMN and the upregulation of the SN, AD patients are thought to have heightened affect sharing (Sturm VE, JS Yokoyama*, et al.* 2013) whereas patients with bvFTD show the reverse pattern in that they are less susceptible to emotional contagion (Zhou J et al. 2010; Zhou J and WW Seeley 2014). This perhaps explains patients' apparent tendency to selfish behaviour (Bathgate D et al. 2001). Inhibition of interoceptive processing may benefit observation of social interactions (Le Bouc R *et al.* 2012; Blume C et al. 2015) and may explain

bvFTD patients' abnormal interpersonal behaviour. Right rostral ACC atrophy, an area targeted as part of the SN in bvFTD, is associated with attenuated physiological and behavioural self-conscious emotional reactivity (Sturm VE, M Sollberger*, et al.* 2013). Increased emotional expression (Snowden JS et al. 2001) shown in SD may be a consequence of increased limbic connectivity and decreased integration of medial temporal connections between the right insula and anterior temporal lobe. Increases in social interest and engagement have been reported in some cases of SD with bilateral temporal lobe involvement (Mendez et al., 2005).

There is substantial overlap, both clinically and neuroanatomically between SD and bvFTD (Hodges JR and K Patterson 2007; Gorno-Tempini ML et al. 2011; Rascovsky K *et al.* 2011; Warren JD, JD Rohrer and MN Rossor 2013). Cases meeting diagnostic criteria for SD have been reported with right temporal lobe predominant atrophy and social cognitive deficits more typical of bvFTD (Perry RJ et al. 2001; Rankin KP *et al.* 2005; Josephs KA et al. 2009; Rankin KP *et al.* 2009; Zahn R, J Moll, V Iyengar*, et al.* 2009; Kamminga J et al. 2015). Common areas of atrophy include vmPFC, posterior OFC, insula and ACC (Rosen HJ et al. 2002) with striatal atrophy postulated to play a particularly key role in socio-emotional deficits across syndromes (Halabi C *et al.* 2013). OFC dysfunction links the network disintegration across SD and bvFTD and is involved in affective decision making. It plays a role in social conformity, empathic concern, the identification of emotions including those evoked by music and selects the appropriate response by suppressing competing inappropriate responses (Blair RJ and L Cipolotti 2000; Omar R, SM Henley, et al. 2011; Hutchings R *et al.* 2015; Dermody N *et al.* 2016). Tasks incorporating social cognition often unfold over time and their processing is mediated by the precise temporal dynamics of OFC (Li Y et al. 2016).

Sarcasm detection is a paragon of incongruity resolution. Neuroanatomically, it is reliant on a circuit involving the lateral OFC, insula, amygdala and right temporal pole (Kipps CM *et al.* 2009; Mahoney CJ *et al.* 2015). The process of sarcasm detection activates brain networks engaged in mentalising (Uchiyama H *et al.* 2006; Kipps CM *et al.* 2009) and a deficit in this process is likely to contribute to degraded humour processing in FTLD. These fronto-temporal networks overlap with regions active in moral judgements and semantic knowledge of social norms, with additional activity in TPJ, right STS and medial frontal gyrus (MFG) (Shany-Ur T *et al.* 2012). STS and MFG are thought to be critical in linking emotional experience to moral

appraisals (Moll J et al. 2002), in addition to their role in prediction testing and detecting violation of prediction (Decety J and C Lamm 2007).

The network affected in PNFA involves; left frontal operculum, insula, perisylvian and precentral gyrus, supplementary motor cortices and bilateral IPL (Knibb JA *et al.* 2006; Hodges JR and K Patterson 2007; Seeley WW *et al.* 2009). Deficits seen in facial and emotion recognition have been localised to the insulo-temporal network (Couto B *et al.* 2013) and abnormal prosody processing for negatively valenced emotions was associated with grey matter volume in an overlapping distributed frontotemporo-parieto-limbic network (Rohrer JD *et al.* 2012).

It has recently been recognised that neurodegenerative proteinopathies (most notably, FTLD) target core brain networks that mediate reward-related behaviours of social or emotional relevance early in disease. The abnormal reward processing perhaps reflects abnormal reciprocal interactions between the SN and DMN encompassing the medial temporal lobe, PCC and parietal regions (Ismail Z et al. 2008; Seeley WW *et al.* 2009; Zhou J and WW Seeley 2014; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott, et al. 2015; Perry DC *et al.* 2015; Ahmed RM *et al.* 2016). Resting state activity in the SN, more specifically in the left insula, in affected patients significantly predicted changes in frontal behavioural inventory (FBI) scores (Day GS et al. 2013) amongst other prominent behavioural deficits (Rosen HJ *et al.* 2002; Seeley WW, R Crawford, et al. 2008). The semantic appraisal network centred in the dominant anterior temporal lobe is the focus of degeneration in SD (Rosen HJ *et al.* 2002; Pressman PS and BL Miller 2014; Coyle-Gilchrist IT *et al.* 2016).

It may be that more posterior and ventral temporal and parietal junctional cortices and their projections constitute a network substrate, via which more posterior cortical zones (not generally regarded as core targets of FTLD) may play a critical role in social cognition processing in these syndromes. bvFTD patients have increased task related activity in regions remote from those affected by disease which has been ascribed to abnormal DMN function (Greicius MD *et al.* 2003; Singh-Curry V and M Husain 2009; Cusack R et al. 2010). Updated integrated sensory models of the external world are fed forward to anterior regions for model evaluation and reconciliation (Critchley HD 2005).The anterior insula is a central hub linking

these networks, and is intimately and reciprocally connected with the thalamus and ascending brainstem pathways suggesting a mechanism for linking cortical with limbic or autonomic evaluations (Zhou J and WW Seeley 2014) (see Figure 1). This candidate mechanism has particular reference to the deficits of complex cognitive processes that FTLD patients display such as; impaired theory of mind, altered social emotions and moral reasoning which have been shown to arise from aberrant interaction of large-scale brain networks (Kipps CM *et al.* 2009; Chiong W *et al.* 2013; Schurz M et al. 2014). In addition these mechanisms of compensatory recruitment of posterior cortical regions may explain retained interest in abstract rewarding stimuli, for example in music and art despite known emotional impairment with the disease (Miller BL et al. 1998; Seeley WW, BR Matthews, et al. 2008; Cohen MH et al. 2016).

1.4.5 Common themes of deficit across syndrome

Decoding of sensory signals is a major component of social cognition and sensory signal processing stages are fairly well mapped out in classical neuropsychology. This is therefore a promising modus operandi with which to begin to deconstruct social cognitive deficits in dementia syndromes. In this thesis I will address mechanisms of impaired social cognition focusing on the two canonical syndromes of FTLD. Here I pose the core question; which key cognitive processes are impaired to cause this disintegration of social functioning? Improved understanding of these processes will be essential for accurate early diagnosis, disease tracking, and ultimately, effective interventions.

There are certain common categories of deficits within these diverse socio-emotional phenotypes. There is evidence of impaired reconciliation of ambiguity or incongruity in these disease groups (Krueger CE *et al.* 2009; Fong SS et al. 2016). Healthy people will maximise the use of available information such as learnt behavioural regularities or context to resolve this sensory signal mismatch (Ibanez A and F Manes 2012). Learnt templates of behavioural regularity allow prediction and incongruity detection (Zahn R *et al.* 2007; Salimpoor VN et al. 2015). Novel information will be assessed for its tendency to conform to these learnt associations (Michelon P et al. 2003; Brod G et al. 2015). This extends to social behaviour and mutually shared expectations constituting a common lexicon or template of learnt conduct (the terms lexicon or schema will be subsumed under the term template for the remainder of

the thesis) enables individuals to interact successfully with one another across a range of different scenarios (Zahn R, J Moll, M Paiva*, et al.* 2009). Bayesian probability relies on utilising context to increase the accuracy of probabilistic inference and therefore an inability to use contextual cues is likely to contribute to the social difficulties seen in bvFTD patients (Ibanez A and F Manes 2012). The failure of patients with bvFTD to do the normative response of attempting to re-establish coherence when experiencing deviation from their predictions may be one of the reasons their behaviour appears so socially inappropriate (Tangney JP *et al.* 1996).

Aberrant reward processing may be a fundamental mechanism of complex neuropsychiatric and other behavioural symptoms in neurodegenerative disease. They exhibit problems with processing emotional and behavioural salience (Ahmed RM *et al.* 2014; Ahmed RM, C Kaizik, et al. 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015; Perry DC *et al.* 2015). Emerging evidence suggests that patients with dementia may exhibit abnormal hedonic valuation of sensory stimuli (such as sounds) even where these lack or have oppositely-valenced reward potential for healthy older individuals (Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015; Fletcher PD *et al.* 2016). Foreseeing relevant outcomes within the relevant context is a general prerequisite for reward-directed and punishment avoiding decision-making, which is abnormal in AD and bvFTD (Ha J *et al.* 2012; O'Callaghan C *et al.* 2016). In addition, bvFTD, SD and AD may each have impaired anticipation and simulation of future events (Irish M et al. 2012; Irish M and P Piolino 2016) which contribute to these difficulties in appropriately allocating reward and predicting behaviours from learnt regularities.

1.4.6 Mapping the deficits to core operations and brain substrates

How the focal degeneration of the frontal and temporal lobes in FTLD translates into symptoms remains largely unknown (Boccardi M et al. 2005; Warren JD, JD Rohrer, JM Schott*, et al.* 2013). These generic candidate processes (see 1.4.5) can be mapped onto the core operations and brain substrates (see 1.4.4) of neurodegenerative disease. I would propose that this is a relevant experimental framework for deconstructing social cognitive deficits in the target diseases to expose more fundamental mechanisms.

Social cognitive abilities rely on implicit and explicit processing of socially relevant stimuli in relation to learnt conceptual knowledge leading to complex and flexible interpersonal behaviours that constitute interpersonal interactions (Schaafsma SM *et al.* 2015). The neural circuitry responsible for these candidate generic processes, encompass diverse networks of cortical and subcortical regions. The medial fronto-parietal cortices direct and control attention and the detection of salient sensory events according to the behavioural context; antero-medial temporal areas store previously learned knowledge and templates about sensory objects and regularities; insular and prefrontal cortices implement and assess violations in rule-based algorithms; and striatal and other subcortical structures code emotional and physiological value (Michelon P *et al.* 2003; Ridderinkhof KR et al. 2004; Nachev P 2006; Groussard M et al. 2010; Christensen TA et al. 2011; Klasen M et al. 2011; Rosenbloom MH *et al.* 2012; Uchiyama HT et al. 2012; Jakuszeit M et al. 2013; Nazimek JM et al. 2013; Balconi M and Y Canavesio 2014; Cohen MX 2014; Nelson AJ et al. 2014; Remy F et al. 2014; Silvetti M et al. 2014; Watanabe T et al. 2014; Brod G *et al.* 2015; Dieguez-Risco T et al. 2015; Merkel C et al. 2015; Salimpoor VN *et al.* 2015; Dzafic I et al. 2016; Gauvin HS et al. 2016; Henderson JM et al. 2016).

These align with the evidence from neurodegenerative diseases of when these processes become defective and the locations of the resultant anatomical correlations. It is known that those with frontotemporal lesions fail to recognise how context alters the meaning of stimuli (Milner B 1958; Mesulam MM 1986; Kipps CM *et al.* 2009). Oddball paradigms can yield useful information about rule acquisition and responses to salient unexpected events. In an auditory oddball paradigm, network connectivity among bilateral temporal, frontal and parietal sources in bvFTD have been shown to be abnormally extensive and inefficient (Hughes LE et al. 2013). Poor individual performance on a probabilistic learning task in FTLD correlated with reduced frontostriatal volume (Dalton MA *et al.* 2012).

Damage involving canonical reward networks has been linked to 'hedonic phenotypes' within FTLD (Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015). ACC and fronto-insula regions are key targets in FTLD and disordered valuation of biologically rewarding stimuli such as sweet foods and sex is a hallmark of bvFTD (Whitwell JL et al. 2007; Rascovsky K *et al.* 2011; Perry DC *et al.* 2014; Ahmed RM, C Kaizik*, et al.* 2015;

Ahmed RM *et al.* 2016). This abnormal processing of secondary rewards does not map simply onto other cognitive capacities, such as theory of mind (Torralva T *et al.* 2007), suggesting a more specific dysfunction of reward circuitry. Reward network dysfunction in these diseases is likely to underpin abnormal hedonic behaviours linked to negatively valenced homeostatic stimuli (such as pain and extremes of temperature) and specific phobias (Clark CN, LE Downey, HL Golden, et al. 2014; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JD Rohrer, et al. 2015).

1.5 Models of social signal decoding in FTLD

Neurodegeneration research needs comprehensive pathophysiological models that will allow disease effects to be understood and anticipated at the level of the whole brain. Certain phenomena are attractive model systems for assessing the signal information processing framework I am proposing, and these include; nonverbal sound scenes, music and humour processing. They have overlapping cognitive and emotional processing operations and neuroanatomical correlates which are central to this thesis (see Table 1). They are all key real-world models of social scenarios and reward processing. I will explore these themes in more detail in the experimental Chapters.

1.5.1 Nonverbal sound scenes

Nonverbal sound is one such attractive model sensory system, with particular resonance for FTLD and the potentially unifying theme of abnormal conflict and congruence signalling. For this thesis conflict can be defined as the simultaneous activation of incompatible or divergent representations in that dimension, or which requires alternative responses (Botvinick MM et al. 2001). Congruence is the antithesis, the simultaneous activation of compatible or coherent representations in that dimension. Processing of signal conflict versus congruence I here subsume under the more general term ‘signal relatedness’.

Every day our brains are required to extract meaning and respond coherently to the world around us. This requires multisensory integration of competing, often ambiguous or incongruous sensory inputs which are rich in meaning. Signal conflict often carries important information that may require modification of behavioural goals. A classical social situation such

as a 'cocktail party' is a particular demanding exemplar of multisensory integration and interpretation. An appropriate behavioural response depends on detecting salient signal mismatch and decoding its semantic and emotional significance. Equally, accurate determination of signal similarities and coherence is essential to establish regularities in the environment that can guide future adaptive behaviours. Accurate analysis of signal relatedness is key to a wide repertoire of behaviours, notably including social interactions; humour, for example, is a paradigm of incongruity decoding (Coulson S and M Kutas 2001; Moran JM *et al.* 2004; Chan YC, TL Chou, HC Chen, YC Yeh, et al. 2012) and more generic processes of incongruity resolution are integral to much complex decision making (Fumagalli M and A Priori 2012; Rosenbloom MH *et al.* 2012).

The auditory domain contains a rich diversity of environmental sounds that vary widely in perceptual characteristics and semantic and emotional associations, notwithstanding the specialised communication codes of speech and music,. According to information processing models derived from visual neuroscience (Marr D 1980), sensory objects ultimately acquire meaning as the result of a hierarchy of processing tasks that integrate particular aspects of information contained in the object. Neuropsychological models have been developed for the processing of nonverbal sounds both as individual 'auditory objects' and (as is typically the case under natural listening conditions) embedded as 'competing' sources in auditory scenes (Bregman AS 1990; Goll JC et al. 2010; Golden HL et al. 2015). Such models emphasise template based processing and close linkage between apperceptive and semantic levels of analysis of sound objects. These factors suggest that signal prediction and detection of violated predictions are likely to be intrinsic to the analysis of auditory scenes and resonate with the commonplace observation that sound events are often ambiguous and require active contextual decoding to prepare an appropriate behavioural response (Gygi B and V Shafiro 2013; Fletcher PD *et al.* 2016).

Minimising 'surprise' while maximising 'preparedness' through generating predictions may be a universal driver of brain operation (Moran JM *et al.* 2004; Friston K 2009). In neurobiological terms, behavioural responses to sensory signal relatedness reflect the operation of hierarchically organised generative models (Lieder F et al. 2013; Nazimek JM *et al.* 2013; Cohen MX 2014; Silvetti M *et al.* 2014) that form predictions about the environment based on current

and previous sensory experience, detect unexpected or 'surprising' events as prediction errors and adjust behavioural output to minimise those errors.

The underlying neural computations engage large-scale brain networks that encompass; posterior cortical areas that parse the auditory scene into component objects; medial fronto-parietal cortices that detect salient sensory events within their context; antero-medial temporal areas that store templates of learnt knowledge about objects and templates of environmental regularities; insular and prefrontal cortices that process deviations from these templates; and striatal and other subcortical structures that code emotional value (Michelon P *et al.* 2003; Ridderinkhof KR *et al.* 2004; Nachev P 2006; Groussard M *et al.* 2010; Christensen TA *et al.* 2011; Klasen M *et al.* 2011; Rosenbloom MH *et al.* 2012; Uchiyama HT *et al.* 2012; Jakuszeit M *et al.* 2013; Nazimek JM *et al.* 2013; Balconi M and Y Canavesio 2014; Cohen MX 2014; Nelson AJ *et al.* 2014; Remy F *et al.* 2014; Silvetti M *et al.* 2014; Watanabe T *et al.* 2014; Brod G *et al.* 2015; Dieguez-Risco T *et al.* 2015; Merkel C *et al.* 2015; Salimpoor VN *et al.* 2015; Dzafic I *et al.* 2016; Gauvin HS *et al.* 2016; Henderson JM *et al.* 2016). Within this distributed circuitry, there is normally extensive cooperativity and integration of component cognitive operations and neural substrates, however separable mechanisms have been identified for the processing of semantic and affective congruence (Dieguez-Risco T *et al.* 2015) and for elementary versus more abstract levels of incongruity decoding (Paavilainen P 2013).

1.5.2 Music

Using music as a model for social cognitive processes can allow us to connect pathophysiology to whole brain effects. As a neurobiological phenomenon, it is multidimensional and maps onto complex real-world behaviours. These dimensions range from the decoding of abstract sensory signals potentially lasting several hours, to physiological responses that shift from moment to moment. Furthermore, components of music lend themselves readily to analysis and can in turn be linked to distributed brain mechanisms that are also targeted by canonical dementia diseases.

The emotional content of music is for many (if not most) listeners its paramount attribute (Blood AJ and RJ Zatorre 2001). People listen to music to regulate arousal and mood, to achieve self-awareness, and as an expression of social relatedness (Schafer T et al. 2013).

Music can be thought of as a means of affect sharing or emotional contagion from stimulus to listeners, and is closely socially integrated in many listening contexts.

Intensely pleasurable responses to music, including musical chills or tears, are specifically and reliably triggered by particular musical features (Blood AJ and RJ Zatorre 2001), such as the resolution of tonal ambiguity (Huron D 2006; Salimpoor VN et al. 2011) and listeners typically seek to repeat the experience. Fundamentally, musical listening, like verbal humour, involves tracking a series of sound events over time and relating it to cognitive predictions (Salimpoor VN *et al.* 2015). These predictions are constantly generated and updated as each new acoustic event occurs (Winkler I et al. 1996) creating a sense of anticipation (Huron D 2006; Salimpoor VN *et al.* 2015).

The extensive linkages between the neural machinery of emotion, reward and auditory sequence analysis engaged during music processing provide an ample substrate for musical patterns to acquire biological resonance. In music, there are certain tensions between predictability and uncertainty. The high potential salience of music is based on the anticipated reward and pay-off. A larger mismatch between outcome and expectation may incur a greater dopamine release and greater consequent reward (Salimpoor VN *et al.* 2015). With repeated listening the intrinsic ambiguity of music allows our brain to rehearse the predictions whilst exploring different solutions (Pressnitzer D et al. 2011). The process continues until the melody becomes overlearned with no prediction error and no longer yields a pleasurable dopamine response (Schultz W 2013; Salimpoor VN *et al.* 2015), similar to a joke where reward is maximal at first exposure and diminishes once learnt.

Music appeals to the inherent fondness of our species for puzzle solving, engaging pattern prediction and completion mechanisms (Zatorre RJ and VN Salimpoor 2013) and activates resolution processes for perceptual ambiguity intrinsic to musical scenes (Pressnitzer D *et al.* 2011). However, this fails to explain why music, an abstract stimulus with no apparent survival advantage, has privileged access to our reward system. The solution may lie in the types of puzzles that music helps us to solve. Arguably, the most ambiguous and complex patterns that we routinely solve are the mental states and motivations of other people, with clear implications for individual social success. These decoding mechanisms may be a means of

rehearsal for deciphering social signals. Music provides a medium for representing 'floating intentionality' or apparent ambiguities and inconsistencies/incongruities in blended non-goal-directed emotional states (Trost W et al. 2012). Healthy listeners efficiently and reliably attribute mental states such as 'comforting' or 'seductive' to musical pieces (Downey LE *et al.* 2013). Understanding agency in music has a neuroanatomical correlate in a distributed anterior cortico-subcortical network which overlaps with that associated with other kinds of mentalising and social concept processing (Frith U and CD Frith 2003; Zahn R *et al.* 2007; Steinbeis N and S Koelsch 2009; Abu-Akel A and S Shamay-Tsoory 2011). Disambiguation of emotional states expressed in music may be based, in part, on learned associations or templates about emotional coding derived from other sensory modalities (Gosselin N et al. 2007). Rather than a single pre-eminent outcome (as, for example, with perceptual ambiguities), adaptive resolution of novel, ambiguous emotional states in music may require their conflicting elements to be kept on-line and 'harmonized' rather than selecting one pre-eminent constituent state. This has close links with cognitive demands during social scenario interpretation.

1.5.3 Humour

Humour is a multidimensional cognitive construct, among the most ubiquitous and highly valued of social phenomena and a basic source of empathy and social cohesion (McGhee PE 1979; Vrticka P et al. 2013). It is a surrogate index for social competence and illustrates the property of social contagion. Theories on humour comprehension are underpinned by the paradigm of incongruity resolution (Suls J 1972). Work has attempted to separate the phenomenon of incongruity resolution required for problem solving, from the additional experience of mirth when performed in the context of a joke (Amir O et al. 2015).

Humour engages generic cognitive processes that are useful probes for deconstructing social cognition. These include; incongruity detection and resolution of conflicting sensory and conceptual information (Suls J 1972; Bartolo A et al. 2006; Eslinger PJ *et al.* 2007; Krueger CE *et al.* 2009; Vrticka P *et al.* 2013; Hull R et al. 2016), processing of familiar objects and concepts from semantic memory against a putative stored template of humorous scenarios typified by slapstick humour (Zahn R, J Moll, V Iyengar*, et al.* 2009); cognitive flexibility and the signalling

of novelty (thwarted prediction) (Kramer JH et al. 2007; Irish M *et al.* 2011) with substantial associated reward (Berns GS 2004; Amir O *et al.* 2015).

Both slapstick and satirical humour rely on incongruity detection, however to comprehend a satirical joke this incongruity must additionally be resolved, often requiring a perspective shift and/or psychological insight (Suls J 1972; Vrticka P *et al.* 2013). Of the categories of humour, the most formulaic is slapstick or physical humour, the components of which are laid down in early childhood and the appreciation of which precedes satirical humour (Degabriele J and IP Walsh 2010; Hoicka E and N Akhtar 2012). This potential humour template of culturally sanctioned jokes acquired through exposure become sufficiently familiar that comedians such as Charlie Chaplin subvert these learned expectations to create novel jokes (e.g. stepping over a banana skin to have another disaster befall him). One could hypothesise that slapstick jokes become semanticised with lifelong exposure resulting in learned templates of a joke which are potentially eroded alongside other social concepts (Zahn R *et al.* 2007).

Table 1 Comparison table across cognitive models of cognitive processes and neuroanatomy

Cognitive Process	Environmental scenes	Music	Humour	Neuroanatomy
Pattern processing/ Perceptual decoding	Potential for multimodal integration	Auditory sequence	Verbal, visual routines	Association cortices (modality specific)
Prediction testing: novel stimuli matched to templates to enable violation detection	Parsing the auditory scene	Sequential pattern analysis & representation of higher order structures for musical expectation	Potentially humorous events. Slapstick humour can be detected at this stage.	Temporo-parietal/superior temporal cortex
Recognition of familiarity using semantic knowledge	Familiar scenes deemed semantically congruous	Template of melodies, tonal hierarchies	Template of social concepts utilised as jokes	Anterior superior and MTL
Pattern decoding/ resolution of incongruity in order to re-establish coherence	Rule decoding for coherence of scene (even if low probability explanation)	Completion of musical phrase	Humour comprehension/ 'getting the joke'. Key for satirical humour	OFC/mesial PFC & IFG
Mentalising. Perceiving cognitive, affective intent/belief	Understand intentions of those in scene	Modelling mental states	Perceiving mental states in humour	OFC/mesial PFC
Salience allocation & reward anticipation. Reward valuation links cognitive, autonomic & affective responses to anticipation	Emotional response to scene	Autonomic (shiver), affective (emotion) & responses to musical structure. Seek/crave to repeat experience, social contagion	Amusement & evaluative responses against social norms. Key to understanding sarcasm & humour appreciation. Seek/crave to repeat experience, social contagion.	Limbic circuitry: cingulo-insula, mesial temporal, OFC

Generic candidate cognitive processes with colour code as per Figure 1. These generic processes are then applied to the three cognitive models of environmental scenes, humour and music processing and these processes are mapped onto the common areas of involvement for these processes as shown in the normal brain

1.6 Key experimental questions motivating this thesis

In four linked experiments, this thesis addresses candidate, generic behavioural mechanisms of impaired social signal decoding and their neuroanatomical substrates in FTLD syndromes, based on my synthesis of key issues from the literature as outlined above. There would be considerable interest in identifying a model system that reflects important clinical deficits in these diseases, while at the same time allowing those deficits to be more easily understood, measured and tracked, with a view to the development and evaluation of therapies.

The experiments assess a well-defined cohort of patients with FTLD in relation to healthy older individuals and in Chapters 4 and 6 also in relation to patients with AD. Cognitive neuropsychological tools were used to define deficits and structural brain MRI and voxel-based morphometry (VBM) techniques to establish neuroanatomical associations (Chapters 3, 4 and 5). In these experiments, I investigate the processing of social signals of varying complexity (nonverbal sound scenes, music and humour) that depend fundamentally on the accurate decoding of incongruity and salience. In the final experiment (Chapter 6), I assess the potential for translating core cognitive mechanisms to daily life symptoms, using the paradigm of humour.

Experiment 1. INCONGRUITY PROCESSING IN FTLD: A BEHAVIOURAL & NEUROANATOMICAL ANALYSIS.

Hypotheses: bvFTD is associated with impaired decoding of emotional and semantic congruity and conflict in complex environments. SD is associated with a similar pattern of deficits, more markedly affecting semantic domains. These deficits have separable neuroanatomical substrates in semantic, affective and salience network circuitry. A capacity to evaluate and resolve conflicting signals is fundamental to successful negotiation of everyday sensory and social environments and loss of this capacity may be a generic mechanism of impaired socio-emotional functioning in FTLD. In this experiment, I use nonverbal sound as a model system to manipulate signal congruity in complex scenes, and assess neuroanatomical correlates in the target syndromes using VBM.

Experiment 2. MUSIC PROCESSING IN FTLD: A BEHAVIOURAL & NEUROANATOMICAL ANALYSIS.

Hypotheses: FTLD and other dementia syndromes show dissociable profiles of reward anticipation and valuation in music. Alterations of musical reward anticipation and valuation have separable neuroanatomical substrates in neural circuitry previously implicated in the processing of other biological and secondary rewards. Processing of salient stimuli is generally directed to the behavioural goals of obtaining rewards and avoiding punishment. Music is a ubiquitous, emotionally salient stimulus with potentially powerful reward value for most normal listeners. It is therefore an appropriate construct for probing aberrant reward valuation in dementia and has been shown to capture distinct behavioural hedonic phenotypes such as 'musicophilia' (frequent and intense craving for music in daily life), most notably in FTLD syndromes. In this experiment, I exploit the rule-based nature of music and its hedonic potential as a model system to compare generic alterations of reward processing in FTLD and AD syndromes. Manipulation of tonal expectancy in novel melodies is used to create musical stimuli that either finish or fail to finish congruously with harmonic expectation and the affective value of these conditions is quantified using a behavioural rating scale. Neuroanatomical correlates of altered musical reward processing are assessed using VBM in the patient cohort.

Experiment 3. **HUMOUR PROCESSING IN FTLD: A BEHAVIOURAL & NEUROANATOMICAL ANALYSIS**.

Hypotheses: Humour is a widely valued social construct that is vulnerable in common dementias. Abnormalities of humour processing in FTLD syndromes are underpinned by more generic deficits of situational incongruity detection and resolution. This particularly affects the perception of novel humour in bvFTD while SD is associated with a more global impairment of humour processing. The processing of incongruity and novelty in humour has separable neuroanatomical substrates in these syndromes, targeting brain networks previously implicated in decoding humour and other ambiguous social signals in the healthy brain. Fatuity and childlike humour are often prominent features of FTLD syndromes and sarcasm has been used a paradigm of abnormal social signal decoding in these syndromes. Neuropsychological

studies of humour have tended to emphasise theory of mind and related high-order cognitive processes. In this experiment, I address more fundamental operations of incongruity, template matching and novelty detection that are core to humour processing and vulnerable in FTLD syndromes, using a novel set of nonverbal cartoon stimuli manipulating these factors while controlling other perceptual and semantic features. Neuroanatomical correlates of these generic humour subprocesses are assessed using VBM in the patient cohort.

Experiment 4. ALTERED SENSE OF HUMOUR IN DEMENTIA.

Hypotheses: Abnormal cognitive mechanisms of humour decoding in FTD syndromes (defined in Experiment 3) translate to altered humour preferences and behaviours in daily life. Changes in humour emerge early in the course of disease. Humour is a compelling paradigm for assessing how cognitive mechanisms defined in this thesis might translate to daily life symptoms and disability. Clinical experience suggests that changes in patients' humour are a particular source of distress for families and caregivers and may emerge as an early feature of FTLD syndromes, with potential utility as a novel behavioural biomarker. In this experiment I use a bespoke caregiver questionnaire to quantify alterations in humour preferences and behaviours exhibited by patients with FTLD syndromes and AD, currently and (retrospectively) predating the onset of more typical clinical symptoms.

2 METHODS OVERVIEW

This Chapter will give an overview of the experimental methods employed in this thesis. Where individual experiments deviate from the procedures detailed here, further information will be provided in the specific Chapter.

2.1 Participants

Patients were recruited over a 3 year period (2012-2015) from the tertiary specialist cognitive clinic at the National Hospital for Neurology and Neurosurgery, London or consultant referrals for individuals who were previously affiliated to the clinic. All patients had neuroimaging findings compatible with their clinical syndromic diagnosis and conformed to consensus criteria for their respective diagnoses (see General Methods 2.1).

Any additional inclusion criteria are specified in the relevant Chapter. Ethical approval for all studies included in this thesis, were obtained from the local institutional ethics committee and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Demographic information was collected from each participant as follows; gender, handedness, age, and educational background. Patients' symptom duration was calculated from the date of symptom onset as reported by their principal caregiver. In the studies that included patients with likely Alzheimer's pathology, whether they were on cholinesterase inhibitors at the time of testing was recorded. Patients underwent a full neurological examination. Additional pertinent features detected during this examination e.g. parkinsonism, were noted if relevant for the task demands. A mini mental state examination score (MMSE) (Folstein MF et al. 1975) was recorded for patients.

An overview of overlap of individual participation by experiment and a table demonstrating cohort numbers by participant group are documented in the appendix. Syndromic group characteristics are summarised below.

2.1.1 bvFTD

All patients included in the bvFTD cohort fulfilled a diagnosis of 'probable' or 'definite bvFTD' if the presence of a known pathogenic causative mutation for FTLD (*C9orf72 or MAPT)* was detected (Rascovsky K *et al.* 2011). Clinically the syndrome of bvFTD is defined by a progressive decline in behaviour and/ or cognition. In addition patients exhibit three of the following early symptoms for diagnosis; behavioural disinhibition, apathy, loss of sympathy/empathy, perseveration, hyperorality or dietary changes which traditionally manifest as a preference for sweet foods.

2.1.2 PPA

PPA is the umbrella term for neurodegenerative diseases where the leading and most prominent symptom is language impairment which constitutes the principal cause of the patient's impairment (Gorno-Tempini ML *et al.* 2011). There are three canonical types (SD, PNFA and LPA) with differing consensus criteria for inclusion (Gorno-Tempini ML *et al.* 2011), which dictated whether they were included in the relevant disease cohort.

2.1.3 SD

SD is defined by breakdown in semantic memory, usually manifesting as anomia with a loss of vocabulary. Their speech production capabilities are spared.

2.1.4 PNFA

Patients with PNFA exhibit speech apraxia which encompasses phonemic errors, distortions and/or aggrammatism of language output and impaired comprehension of syntactically complex sentences. Semantic knowledge is initially preserved.

2.1.5 LPA

Patients with LPA exhibit marked word-finding pauses secondary to a word retrieval deficit. Phonological working memory is deficient and therefore these patients demonstrate phrasal repetition deficits with initially preserved single word repetition. They have relatively spared semantic and motor speech capabilities. They may have receptive agrammatism and syntax processing deficits. This patient group was only included in the experiments described in Chapter 4.

2.1.6 Typical Amnestic AD

All patients included in this cohort conformed to NINCDS-ADRDA consensus criteria for typical amnestic AD (Dubois B *et al.* 2007). The most prominent symptom at onset is episodic memory impairment which progresses over time.

2.1.7 Healthy control participants

Healthy older control participants were recruited from a research database held at the Dementia Research Centre. They were screened to ensure they had no history of neurological or psychiatric illness. For the auditory experiments they were excluded if they had reported difficulties with their hearing and/or determined by their performance on the chapter-specific screening tests (see Chapters 3 and 4).

2.2 Neuropsychological Assessment

Participants had a comprehensive general neuropsychological assessment including standard measures of visual perceptual, executive and semantic functions. Neuropsychological findings corroborated the clinical syndromic diagnosis in all cases. The most pertinent tests included in each chapter for comparison are represented in Table 2.

The battery of core neuropsychological tests incorporates tasks assessing general intellect. This includes the Wechsler Abbreviated Scale of Intelligence (Wechsler D 1999) which has both 'verbal' and 'performance' domains representing verbal (VIQ) and performance (PIQ) intelligence quotient measures respectively. Episodic memory was tested using long or short (Chapter 6) versions of the Recognition Memory Test (RMT) (Warrington EK 1984; Warrington EK 1996) and the Paired Associate Learning test (PAL) (Warrington EK 1996). Verbal working memory capacity was assessed via forward digit span from the Wechsler Memory Scale-Revised (Wechsler D 1987). A comprehensive assessment of executive function was captured with the following tests; verbal and category fluency for function in the verbal domain, the digit symbol task (Wechsler D 1999) and matrices (Wechsler D 1999) to determine function in the non-verbal domain, reverse digit span (Wechsler D 1987) additionally incorporating manipulation in auditory working memory, the Stroop task (Delis DC et al. 2001) particularly

the ink colour component which represents interference and trail-making A and B (Trails A and B) used to assess task-switching (difference score of B-A) (Reitan R 1992; Lezak M et al. 2004).

Verbal skills were assessed using the following tests; Graded Naming Test (GNT) (McKenna P and EK Warrington 1983), British Picture Vocabulary Scale (BPVS) (Dunn LM et al. 1982) which is a general cross-modal measure of semantic memory and the National Adult Reading Test (NART) (Nelson HE 1982). Posterior cortical skills were assessed using the Graded Difficulty Arithmetic (GDA) Test (Jackson M and EK Warrington 1986), the object decision subtest of the Visual Object and Spatial Perception battery (VOSP) (Warrington EK and M James 1991) and usual and unusual views of objects (Warrington EK and AM Taylor 1973, 1978).

The PPA patients were also assessed on in-house measures of graded difficulty word and sentence repetition and concrete and abstract synonyms (Warrington EK et al. 1998) to further characterise their language profile. The bvFTD patients underwent assessment using the TASIT (McDonald S *et al.* 2006) as a measure of their abilities to interpret social signals (see Chapters 5 and 6). The size-weight attributes test is a within-modality index of semantic memory which probes visual object knowledge about animals and objects (Warrington EK and SJ Crutch 2007). Participants were presented with 30 picture triads depicting familiar animals or inanimate objects; for animal stimuli, the task on each trial was to decide which member of the triad was largest and which smallest, while for object stimuli the task was to decide which was heaviest and which lightest.

2.3 Ancillary/Molecular Techniques

If cerebrospinal fluid (CSF) was obtained by lumbar puncture, the results were interpreted based on local laboratory reference ranges for known neurodegenerative markers; normal ranges of total tau<320, Amyloid-Beta$_{1\text{-}42}$ (A$\beta_{1\text{-}42}$) 220-2000 and tau/A$\beta_{1\text{-}42}$ ratio >0.8 were determined as predictive of underlying AD pathology.

The genetic screening performed at our centre consisted of a panel of mutations in major causative dementia genes which included; *C9orf72, MAPT*, *PGRN, presenilin 1 and 2 (PS1 and PS2)* and pathogenic mutations in amyloid precursor protein (*APP)*.

Table 2 Summary of demographic, clinical and general neuropsychological characteristics as included by Chapter

Chapter	3	4	5	6
General				
No., gender (M:F)	√	√	√	√
Handedness (L:R)	√	√	√	√
Age (yrs)	√	√	√	√
Musical training (yrs)		√		
Musical listening (hrs/week)		√		
Education (yrs)	√	√	√	√
Background (UK&Eire:other)[a]			√	√
Symptom duration (yrs)	√	√	√	√
MMSE (/30)	√	√	√	√
BACKGROUND NEUROPSYCHOLOGY				
General intellect				
VIQ	√	√	√	√
PIQ	√	√	√	√
NART estimated premorbid IQ		√		
WASI Vocabulary (/80)‡	√	√	√	√
WASI Block Design (/71)	√	√	√	√
WASI Similarities (/48)	√	√	√	√
WASI Matrices (/42)	√	√	√	√
Executive functions				
Verbal fluency (/min)	√	√	√	
Category fluency (animals:total)	√	√		
Stroop (ink colour)(sec)	√	√	√	√
Stroop (colour)(sec)	√	√		
Stroop (word)(sec)	√	√		
Trails (B-A difference) (sec)			√	√
Trails A (s)	√	√		
Trails B (s)	√	√		
WAIS-R Digit Symbol (total)	√	√		
Digit span reverse (/12)	√	√	√	√
Episodic memory				
Digit span forward (/12)	√	√	√	√
RMT Words (/50 or /25 for short version)	√	√	√	√
RMT Faces (/50 or /25 for short version)	√	√	√	√
Camden PAL (/24)	√	√		
Language and literacy functions				
GNT (/30)	√	√	√	√
Reading (NART) (/50)	√	√	√	√
Arithmetic (GDA) (/24)	√	√	√	√
Single Word Repetition (/45)		√		
Sentence Repetition (/10)		√		
Semantic memory				
BPVS (/150)	√	√	√	√
Synonyms concrete (/25)	√	√		
Synonyms abstract (/25)	√	√		
Size-weight attributes(/60)			√	

Chapter	1	2	3	4
Visuoperceptual functions				
VOSP object decision (/20)	√	√	√	√
Unusual views (20)			√	
Usual views (20)			√	
Social cognition				
TASIT (Emotion) (/14)			√	√
TASIT (Social Inference) (/36)			√	√

2.4 Presentation of Stimuli

Within each test used in the behavioural experiments (see Chapters 3, 4 and 5) trials representing each condition were presented in randomised order. Stimulus order was varied for each individual participant additionally in Chapters 4 and 5. Prior to commencing the experiments, practice examples (not used in the subsequent experiment) representing each condition were shown to familiarise participants with the stimuli, in order to establish that each participant understood the task and were able to comply reliably. No feedback about performance was given during the experiment and no time limits were imposed. Participant responses were recorded for offline analysis. A forced-choice response procedure was used in all tests unless otherwise specified. Further details regarding the details of specific stimuli are given in the relevant Chapters.

2.4.1 Presentation of Auditory Stimuli

All sound stimuli were presented binaurally via headphones (Audio-Technica®) through a notebook computer running Matlab7® using Cogent 2000 (http://www.vislab.ucl.ac.uk/cogent_2000.php) at a comfortable listening level (at least 70dB) in a quiet room (see Chapters 3 and 4).

2.4.2 Presentation of Visual Stimuli

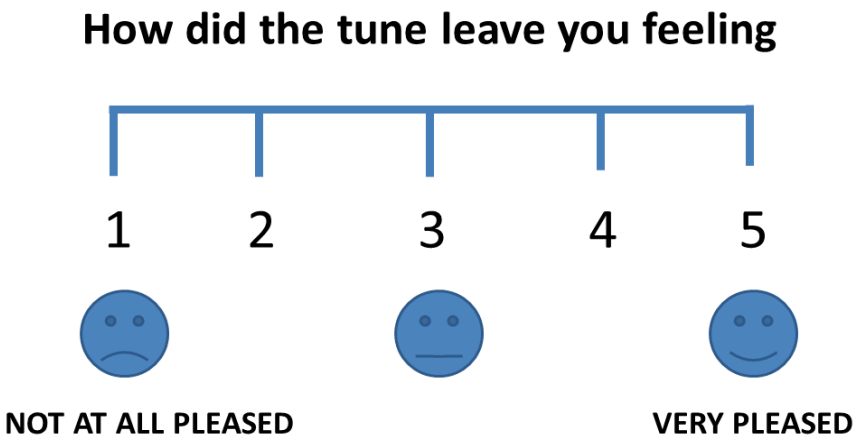
Stimuli were presented on the monitor screen of a notebook computer running Matlab7® using Cogent 2000 (http://www.vislab.ucl.ac.uk/cogent_2000.php) (see Chapters 3 and 5).

2.5 Likert scales

Likert scales were used for behavioural ratings for all participants (Chapters 3, 4 and 6) and in the pilot experiments in healthy controls (Chapters 3, 4 and 5). An example Likert scale used

for the implicit labelling of melody ending by emotional response (see Chapter 4) is shown in Figure 2. The scale is from 1-5 in order to cover a positively valenced (1-2) and a negatively valenced (4-5) response with an intermediate neutral response option (3).

Figure 2 Example of Likert scale (from Chapter 4)



2.6 Brain image acquisition

If there were no contraindications to MRI imaging, volumetric brain MR images were acquired on a Siemens Trio 3Tesla MRI scanner using a 32-channel phased array head-coil and a sagittal 3-D magnetization prepared rapid gradient echo T1 weighted volumetric sequence (echo time/repetition time/inversion time = 2.9/2200/900 ms, dimensions 256 x 256 x 208, voxel size 1.1 x 1.1 x 1.1 mm). Volumetric brain images were assessed visually in all planes to ensure adequate coverage and to exclude artefacts or significant motion. Patients with significant vascular disease demonstrated on their imaging were excluded. A small subset of patients participated in a fluorine-18 (18F) amyloid (Florbetapir) positron emission tomography (PET) imaging study (performed as part of another study; see Appendix Table 2 for further information), which was used to support or refute the diagnosis of AD in experimental participants.

2.7 Voxel Based Morphometry

Pre-processing of patient brain MR images was performed using the Segment routine and the DARTEL toolbox of SPM12 (fil.ion.ucl.ac.uk/spm/ 1994-2013; Ashburner J 2007) in MATLAB v2012a® (The Mathworks, Inc.). Normalisation, segmentation and modulation of grey and

white matter images used default parameter settings, with a smoothing Gaussian kernel of full-width-at-half-maximum 6mm. Smoothed segments were warped into Montreal Neurological Institute (MNI) space using the "Normalise to MNI" routine. In order to adjust for individual differences in global grey matter volume during subsequent analysis, total intracranial volume (TIV) was calculated for each participant by summing grey matter, white matter and cerebrospinal fluid volumes following segmentation of all three tissue classes. A study-specific mean brain image template, for displaying results, was created by warping all bias-corrected native space whole-brain images to the final DARTEL template in MNI space and calculating the average of the warped brain. To help protect against voxel drop-out due to marked local regional atrophy, a customised explicit brain mask was made based on a specified 'consensus' voxel threshold intensity criterion (Ridgway GR et al. 2009), whereby a particular voxel was included in the analysis if grey matter intensity at that voxel was > 0.1 in >70% of participants (rather than in all participants, as with the default statistical parametric map (SPM) mask). The mask was applied to the smoothed grey matter segments prior to statistical analysis.

Using the framework of the general linear model, multiple regression was used to examine associations between regional grey matter volume and the outcome of interest in the patient cohort (Chapters 3, 4 and 5). Outcomes of interest were only examined if they showed group behavioural difference between patients and healthy controls. Both positive and negative (inverse) associations were assessed. All contrasts are reported at a voxel-wise statistical significance threshold of $p<0.05$ either at whole brain (Chapters 3 and 4) and/or $p<0.05$ after family-wise error (FWE) correction for multiple comparisons within pre-specified anatomical small volumes (Chapters 3 and 5) according to our prior confidence in anatomical attributions of interest. Syndromic group was included as a variable of interest . Age, gender, TIV and an index of disease severity (reverse digit span for Chapters 3 and 4 and performance on the Trails task for Chapter 5) were included as nuisance covariates in all matrices.

2.7.1 Small Volume Generation

Anatomical small volumes were generated (see Chapters 3 and 5) to enable multiple voxel-wise comparisons corrections to occur within the region of interest (ROI). ROI were based on prior anatomical hypotheses and were derived from the Oxford-Harvard brain maps (Desikan

RS et al. 2006) in FSLview (Jenkinson M et al. 2012) and boundaries edited using MRIcron (mccauslandcenter.sc.edu/mricro/mricron/) to conform to the study-specific template (participant mean) brain image. Bi-hemispheric ROI are rendered on sections of the average normalised brain template for the patient cohort undergoing the VBM in that experimental chapter (Chapters 3 and 5) for display purposes in Figure 3 and Figure 4 respectively. The right hemisphere is shown on the right in the coronal sections of all SPM figures.

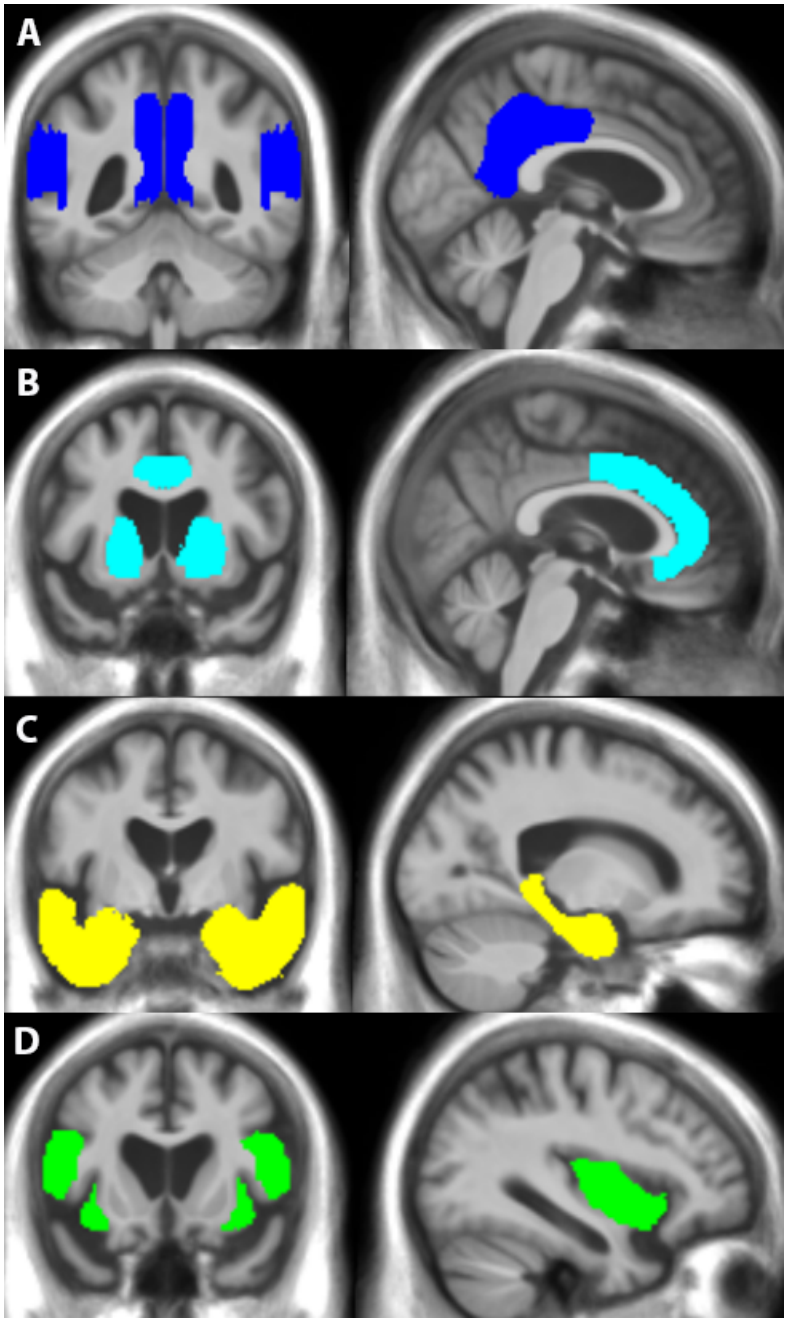
2.8 Statistical analysis

All behavioural data were analysed using Stata12® (Stata Corporation, College Station, TX, USA). A threshold $p<0.05$ was accepted as the criterion for statistical significance in all analyses. Primary analyses examined outcome variables within and between groups. Secondary analyses examined the association between the experimental outcome variable and the factors of interest including neuropsychology performance in key tests or indexes of disease severity for associations between primary outcome variables.

2.9 Demographic and neuropsychological analysis

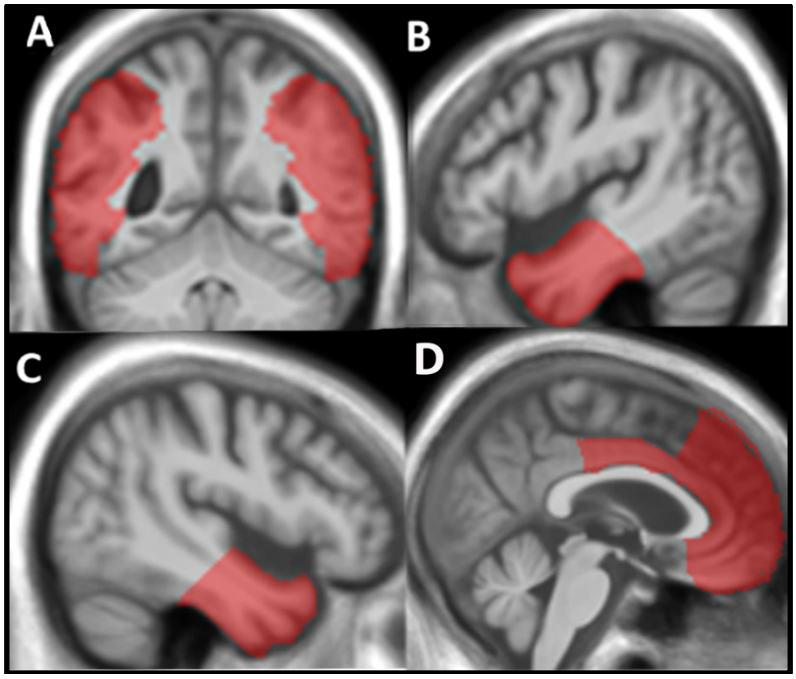
Demographic characteristics, neuropsychological and selected behavioural rating data (as indicated in the relevant Chapter) were compared between participant groups using Fisher's exact test for categorical variables, or for continuous variables either; analysis of variance (ANOVA)/two sample t-tests (according to the number of groups to be compared) on a group level before proceeding to pairwise differences, or where assumptions for the t-test were materially violated (for example, due to skewed data distribution) overall effects were tested with Kruskal-Wallis and between group differences assessed with Wilcoxon rank-sum tests.

Figure 3 Representative sections of anatomical ROI from Chapter 3



Representative coronal (left) and sagittal (right) sections of anatomical regions used for ROI analyses (see 2.7.1). Regions comprised: **A,** lateral temporo-parietal and posterior medial cortices (auditory scene perception); **B,** striatum and ACC (salience and reward evaluation); **C,** anterior and MTL (semantic processing); **D,** insula and IFG (auditory sequence and rule-based processing)

Figure 4 Representative sections of anatomical ROI from Chapter 5



Representative coronal and sagittal sections of anatomical regions used for ROI analyses (see 2.7.1). Regions comprised: **A,** right and left lateral temporo-occipital-parietal junctional cortex; **B,** left temporal lobe anterior to Heschl's gyrus; **C,** right temporal lobe anterior to Heschl's gyrus; **D,** vmPFC, OFC and ACC

2.9.1 Regression analyses

Linear regression is used for continuous predictors and has mathematical equivalence with ANOVA. Multiple linear regression is used to model the outcome variables where the relationship between explanatory input (mx) and output variables (y) is assumed to be linear (y=mx+c). The gradient of the slope represents the effect size or regression coefficient (m). The intersect (c) is the constant, equivalent to the output value for an input value of 0. Multiple linear regression models generate a proportion difference to compare performance between groups (pleasantness ratings in Chapter 3 and where data was corrected for guessing in Chapter 4). The following assumptions were checked prior to using the linear regression model; that the residuals are normally distributed and the variance is constant over levels of the predictor (e.g. between groups or ratings). Where the observations were not independent (violating an assumption of the linear regression model), appropriate statistical methods were used to deal with this; bootstrapping (see 2.9.3), mixed effect models and robust standard errors (see final paragraph of this section).

Logistic regression is a transformation of the linear regression model onto the log odds scale for binary outcomes. Logistic regression was used to model the scores (e.g. correct) on the post-scan behavioural tasks to analyse performance in the experimental groups (see Chapter 3 and dichotomised pleasantness scores in Chapter 4). The output is represented as an odds ratio (OR), or the odds that the outcome will occur given a particular exposure, compared with the odds of the outcome occurring in the absence of that exposure. For all OR, a 95% confidence interval (CI) including 1 indicates no significant difference between that patient group and the baseline group (usually healthy controls) for the parameter of interest. An OR> 1 represents an over-selection of that factor or a superior performance compared to the baseline group and OR<1 an inferior performance or under-selection of that factor compared to the baseline group.

Two methods were used to deal with data clustering or a clustering of responses for individuals. Clustered, robust standard error was used if the data conformed to normality assumptions, but with non-homogeneity of variance and/or if there was individual clustering of the data (see Chapters 3 and 4). Alternatively mixed effects models were used and participant level random effects were incorporated to account for the clustering by individual (see Chapter 5). Mixed effects logistic models were used to allow binary responses to be incorporated as the dependent variable.

Interactions with factors of interest were included to account for differential performance across conditions or stimulus type (correct score/ rating) by group. This enabled the investigation of factors that could plausibly affect outcome and the extent to which such effects were susceptible to disease.

2.9.2 Signal Detection Theory

Perceptual uncertainty or ambiguity is commonplace and outcomes are often uncertain. Signal detection theory refers to strategies of detecting the information carrying signal from the background noise or random distractor activity (Peterson WW et al. 1954). There are quantifiable measures of how signal detection theory thresholds are calculated (Stanislaw H and N Todorov 1999). There are four potential outcomes to consider; correctly identifying that the signal is present (hit) or absent (correct rejection). Alternatively errors are made if the

signal is incorrectly identified as being present when it is absent (false alarm) or as being absent when it is present (missed signal). These are quantified in the measure of sensitivity at stimulus detection and the response bias or the probability of giving certain responses.

Signal detection techniques were used (see Chapters 4 and 5) when the response options were not balanced (relatively infrequent 'hits') using two separate approaches. In Chapter 4 the task was to identify deviant notes by a button press. Participants were instructed to press the keyboard spacebar as quickly as possible whenever they heard a 'wrong note'. Presses within a pre-specified time window (1.5s) after deviant onset were counted as correct detections. As participants were free to respond at any time, it was necessary to account for potentially varying strategies: for example if only assessing 'correct' presses, a participant who only pressed in response to all the deviants (and never pressed outside the correct time windows) would perform equivalently to a participant who pressed continuously and indiscriminately throughout a trial. The observed 'hits' or presses falling within the target window was calculated, from this was deducted the probability of presses equivalently occurring inside this target window as a result of guessing alone. Misses were calculated as the rate of pressing that occurred outside the target window and was modelled using a Poisson distribution, represented by the following equation:

$$S = P - (1 - e^{-\lambda})$$

where S = score; P = proportion correct presses and λ = rate of incorrect presses x correct time window. This transformation resulted in a 'corrected-detection-score' for each participant.

In Chapter 5 a framework based on signal detection theory (deCarlo LT 1998) was used to fit a logistic regression model for the odds of labelling a hit against mis-hits represented as an OR. The dependent variable represented humour detection accuracy as a binary category indicating (for each cartoon) whether or not each participant in a group had labelled the cartoon as being a joke (rather than whether this label was correct). This comparative measure was represented as an OR. The model included a random intercept, representing the threshold for the log odds (if all other factors were equivalent) of labelling a stimulus as a joke, and a random coefficient for the stimulus type. This structure allowed us to take account of any bias introduced by patient factors owing to executive or frontal lobe impairment, which is

particularly relevant with an imbalance in response probabilities across conditions. For the VBM analysis, the incorporated behavioural outcome measure was the log OR of likelihood of labelling a stimulus as a joke, to be analogous with the behavioural analysis (rather than proportion correct). As the model in Chapter 5 was built on the likelihood of labelling a stimulus as a joke, the likelihood of being correct was added as an additional interaction effect.

2.9.3 Bootstrapping

Bootstrapping is the estimation of properties of an estimator (e.g. variance) by measuring those properties when sampling from an approximating distribution. The variability of the computed mean is quantified as a CI. Bootstrapping techniques were used if the data was non-parametric (see Chapters 3 (continuous modelling of categorical data for pleasantness ratings) and 4). Bias-corrected accelerated CI were generated from 2000 bootstrap replications. Where observations were not independent (see Chapters 3 and 4) bootstrap resampling was with clustering by individual. If a bootstrapped CI includes 0 it represents a non-significant difference between the target group and the comparator or baseline group for the parameter of interest. Conversely, if a bootstrapped CI excludes 0 it represents a significant difference between the target group and the comparator or baseline group for the parameter of interest.

2.9.4 Nuisance Covariates

Potentially confounding covariates of no interest were included in the model and mean-centred where appropriate. Age and gender were included as nuisance covariates in all the behavioural paradigms (Chapters 3, 4 and 5) with a relevant marker of disease severity and executive function (performance on Trails task in Chapter 5) or with additional capture of auditory working memory (e.g. reverse digit span in Chapters 3 and 4) for the auditory tasks. Any additional factors deemed to be potential confounds and thus included as nuisance covariates in specific behavioural paradigms are detailed further in the relevant Chapters.

2.9.5 Correlations

Post-hoc analyses were conducted to analyse correlations between the experimental outcome measure and factors of interest using the non-parametric Spearman correlation coefficient. Correlations were done between the behavioural outcome measure and general measures of disease severity (Chapters 5 and 6) and/or more specific neuropsychological markers of

executive dysfunction (Chapters 4, 5 and 6) in the combined patient cohort, semantic memory function in SD group (Chapters 5 and 6) or social inference in bvFTD group alone (Chapters 5 and 6), in addition to specific tests of correlation that were deemed to be pertinent as expressed in the relevant Chapter.

2.10 Data presentation

2.10.1 Tables

For all demographics tables in this thesis; mean (standard deviation (s.d.)) scores are shown unless otherwise indicated. Maximum scores are shown after tests (in parentheses). If tests were not deemed applicable and therefore not performed this was indicated with; N/A. Bold denotes significantly different ($p<0.05$) to the healthy control group in all tables.

Mean group raw scores are shown as proportion correct (s.d.). Maximum and chance scores are indicated in the table or legend. Where chance performance has not been specified, it can be presumed to be at 0.5.

Tables of group performance for the Chapters employing behavioural paradigms (Chapters 3, 4 and 5) show the data presented as OR (CI in parentheses) to allow the effect of covariates to be incorporated. The reference was the healthy control group's performance in Chapters 3 and 4 whereas the OR represented relative performance by group across humour category in Chapter 5. Pleasantness ratings are presented both as mean (s.d.) ratings and with the coefficients and bootstrapped confidence intervals for the effect of interacting constituent sound pleasantness ratings, within each group and for patient groups relative to the reference healthy control group (Chapter 3).

The neuroimaging tables present the data which showed significant grey matter associations of performance on all experimental tasks which demonstrated a difference between patient groups and healthy controls, identified using VBM techniques. Data for the combined patient cohort or additionally the bvFTD group (Chapter 5) is presented. Significance was defined as all local maxima exceeding a significance threshold of $p<0.05$ after FWE correction for multiple voxel-wise comparisons, either over the whole brain (see Chapters 3 and 5) or within pre-specified anatomical regions of interest (see 2.7.1, Figure 3 and Figure 4). Peak (local maxima)

coordinates are in MNI standard stereotactic space. Only positive grey matter associations are shown; no negative (inverse) associations were identified at the prescribed significance thresholds for the contrasts and groups of interest.

2.10.2 Figures

Individual raw scores are plotted as percentage or proportion correct by condition. If a proportion correct score is plotted, and chance performance is not specified, it can be presumed to be 0.5.

SPM figures are shown of regional grey matter volume associated with performance on experimental tasks for the combined patient cohort (Chapters 3, 4 and 5) or in the bvFTD group additionally (Chapter 5), as identified using VBM. SPMs are overlaid on representative 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 sections show the left hemisphere on the left, the axial section shows the left hemisphere at the top). Colour bars code T values for each SPM (Chapters 3 and 4). SPMs are thresholded at $p<0.001$ uncorrected over the whole brain for display purposes, however regional local maxima were significant at $p<0.05_{FWE}$ corrected for multiple comparisons at whole brain (Chapters 3 and 4) or within pre-specified anatomical ROI (Chapters 3 and 5).

3 INCONGRUITY PROCESSING IN NONVERBAL SOUND: A BEHAVIOURAL & NEUROANATOMICAL ANALYSIS

3.1 Chapter summary

Impaired analysis of signal conflict and congruence is fundamental to successful negotiation of sensory and social environments and loss of this capacity may underpin diverse socio-emotional symptoms in FTLD. However, the underlying mechanisms have yet to be defined. Here I addressed this issue in patients with bvFTD (n=19) and SD (n=10) relative to healthy older individuals (n=20). I created auditory scenes in which semantic and emotional congruity of constituent sounds were independently probed. Associated tasks controlled for auditory perceptual similarity, scene parsing and semantic competence. Neuroanatomical correlates of auditory congruity processing were assessed using VBM. Relative to healthy controls, both the bvFTD and SD groups had impaired semantic and emotional congruity processing (after taking auditory control task performance into account) and reduced affective integration of sounds into scenes. Grey matter correlates of auditory semantic congruity processing were identified in a distributed prefronto-parieto-temporo-insular network and correlates of auditory emotional congruity in a partly overlapping, temporo-insulo-striatal network. My findings provide support for the argument that decoding of auditory signal relatedness may probe a generic cognitive mechanism and neural architecture underpinning FTLD syndromes. The manipulation of signal relatedness engaged brain mechanisms similar to those engaged by complex social scenarios requiring incongruity evaluation and resolution.

3.2 Introduction

On clinical as well as neuroanatomical grounds, abnormal processing of conflict and congruence is a candidate generic mechanism of disease phenotypes in FTLD (Warren JD, JD Rohrer and MN Rossor 2013). Key deficits in both syndromes could plausibly reflect impaired integration of context and perspective taking (Ibanez A and F Manes 2012). An inability to reconcile different perspectives may contribute more specifically to loss of empathy and theory of mind (Kipps CM *et al.* 2009; Baez S *et al.* 2014; Irish M *et al.* 2014), reduced self-awareness (Sturm VE, M Sollberger*, et al.* 2013) and aberrant resolution of moral and social dilemmas (Eslinger PJ *et al.* 2007; Carr AR *et al.* 2015).

Defective recruitment of stored social and semantic templates may reduce adherence to social regularities (Zahn R *et al.* 2007; Schaafsma SM *et al.* 2015) while impaired ability to modify behaviour in response to 'surprising' events may contribute to dysfunctional reward seeking and valuation (Dalton MA *et al.* 2012; Perry DC *et al.* 2014). Abnormal conflict monitoring has been documented early in bvFTD (Krueger CE *et al.* 2009). It remains uncertain how far this reflects more general executive dysfunction (Seer C et al. 2015). Neuroanatomically, the candidate network substrates for processing signal relatedness overlap key areas of disease involvement in bvFTD and SD (Rosen HJ *et al.* 2002; Hodges JR and K Patterson 2007; Fletcher PD and JD Warren 2011; Halabi C *et al.* 2013; Warren JD, JD Rohrer and MN Rossor 2013; Perry DC *et al.* 2014). Despite much clinical and neurobiological interest, fundamental or generic models and mechanisms that can capture the clinical and neuroanatomical heterogeneity of FTLD are largely lacking.

The requirements for disambiguating competing sound sources, tracking of sound sources dynamically over time and linking sound percepts to stored semantic and emotional associations all impose heavy computational demands on neural processing mechanisms. Moreover, the fronto-temporo-parietal and subcortical brain networks that instantiate these mechanisms are selectively targeted by the disease process in FTLD (Warren JD, JD Rohrer and MN Rossor 2013; Hardy C et al. 2016). One might therefore predict abnormalities of sound signal decoding in these diseases and indeed, a range of a auditory deficits have been described, ranging from impaired electrophysiological responses to acoustic oddballs (Hughes LE *et al.* 2013) to complex cognitive and behavioural phenotypes (Downey LE *et al.* 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015; Fletcher PD, JM Nicholas*, et al.* 2015; Fletcher PD *et al.* 2016; Hardy C *et al.* 2016). From first principles, many of these phenotypic features might be underpinned by impaired integration of auditory signals and impaired processing of signal mismatch. However, the relevant cognitive and neuroanatomical mechanisms have not been defined.

The perception of auditory objects requires a parsing of the sound scene into, at minimum, the object of interest and the acoustic background (Bregman AS 1990). Sensory signals include those of high emotional or behavioural salience that unfold over time. It has been proposed that auditory scene analysis might involve a TPJ-mediated template matching process and top-

down predictions about regularities in the acoustic environment (Griffiths TD and JD Warren 2002; Warren JE et al. 2005; Gutschalk A and A Dykstra 2013). Performance in both auditory dimensions would potentially have a structural correlate in anterior temporal and insula cortical 'hubs' for processing signal salience based on prior expectations (Groussard M *et al.* 2010; Christensen TA *et al.* 2011; Nazimek JM *et al.* 2013; Remy F *et al.* 2014; Watanabe T *et al.* 2014; Merkel C *et al.* 2015); while the analysis of auditory semantic congruence would have an additional correlate in fronto-parietal cortices previously linked to processing of rule violations and conflict resolution (Ridderinkhof KR *et al.* 2004; Strelnikov KN et al. 2006; Groussard M *et al.* 2010; Chan YC, TL Chou, HC Chen, YC Yeh*, et al.* 2012; Rosenbloom MH *et al.* 2012; Jakuszeit M *et al.* 2013; Paavilainen P 2013; Remy F *et al.* 2014; Henderson JM *et al.* 2016) and the analysis of auditory emotional congruence would have an additional subcortical correlate in striatal and mesial temporal structures previously linked to the processing of emotional congruence and associated reward value (Klasen M *et al.* 2011; Schultz W 2013; Dzafic I *et al.* 2016).

Here I addressed the processing of signal conflict and congruence in auditory environments in bvFTD and SD relative to healthy older individuals. Auditory incongruity has been studied extensively as a perceptual factor. However, incongruity processing operates during semantic attribution. Semantic processing is of particular relevance to symptoms of bvFTD and SD. Therefore sound scenes are an attractive candidate system a priori for exposing deficits in FTLD. I designed a novel behavioural paradigm requiring decisions about auditory 'scenes', each comprising two competing sound sources in which the congruity or incongruity of the sources was varied along semantic (identity relatedness) and affective (emotional relatedness) dimensions independently. I constructed 'model' scenes that would simulate naturalistic processing of the kind entailed by real world listening while still allowing explicit manipulation of the stimulus parameters of interest. The stimulus dimensions of semantic and emotional congruity were anticipated to be particularly vulnerable to the target syndromes, based on an extensive clinical and neuropsychological literature in auditory and other cognitive domains (Hodges JR and K Patterson 2007; Warren JD, JD Rohrer and MN Rossor 2013; Hardy C *et al.* 2016). Structural neuroanatomical associations of experimental task performance were assessed using VBM in the patient cohort.

3.3 Experimental hypotheses

i) Both syndromes have impaired ability to detect auditory signal relatedness and abnormal affective valuation of signal conflict and congruence, relative to healthy individuals and taking into account background auditory perceptual and general cognitive competence.

ii) Based on the cardinal neuropsychological profiles of each syndrome (Hodges JR and K Patterson 2007; Gorno-Tempini ML *et al.* 2011; Rascovsky K *et al.* 2011; Warren JD, JD Rohrer and MN Rossor 2013), patients with bvFTD have a disproportionate deficit of emotional congruity processing and patients with SD have a disproportionate deficit of semantic congruity processing.

iii) These congruence dimensions have overlapping, but separable neuroanatomical substrates in brain networks previously implicated in decoding signal relatedness and salience in the healthy brain which would map onto a distributed fronto-temporo-parietal network with additional striatal correlates for signal relatedness and anterior temporal and insular volume correlating with salience.

3.4 Methods

3.4.1 Participants

For consensus criteria and general characteristics of syndromic groups please refer to General Methods (see 2.1). 29 patients with; bvFTD; n=19, mean age 64 years (s.d. 7.2 years), three female) or SD (n=10, mean age 66.2 (6.3) years, four female) were recruited. In addition 20 healthy older individuals (mean age 68.8 (5.3) years, 11 female) participated. For indication of participants' overlap across experimental Chapters please refer to Appendix (see Supplementary Table 2). None of the participants had a history of clinically relevant hearing loss. Demographic and general neuropsychological characteristics of the study cohort are summarised in Table 3 (for more information please see 2.2 and for overview of neuropsychology and demographic information across experimental Chapters please see Table 2). The bvFTD group included eight cases with confirmed pathogenic mutations (five *MAPT,* three *C9orf72*) (for further details see 2.3). CSF examination in six patients with sporadic bvFTD

Table 3 General demographic, clinical and neuropsychological characteristics of participant groups

Characteristic	Healthy controls	bvFTD	SD
General			
No. (m:f)	9:11	**16:3**	6:4
Handedness (R:L)	17:3[¥]	17:2	9:1
Age (yrs)	69 (5.3)	64 (7.2)	66 (6.3)
Education (yrs)	16.4 (2.0)	15.1 (2.8)	15.6 (2.6)
Symptom duration (yrs)	N/A	8.1 (6.3)	5.3 (2.9)
MMSE (/30)	29 (1.4)	24.3 (4.5)	21.3 (6.3)
Background Neuropsychology			
General intellect			
VIQ	126 (7.2)	**84 (22.2)**	**75 (17.0)**
PIQ	124 (9.6)	**102 (20.7)**	**106 (21.9)**
WASI Vocabulary (/80)	72.7 (3.27)	**39.7 (21.2)**	**31.8 (19.9)**
WASI Block Design (/71)	45.4(12.1)	32.5 (18.1)	36.8 (20.7)
WASI Similarities (/48)	41.5 (2.9)	**23 (12.0)**	**17.2 (11.0)**
WASI Matrices (/32)	26.5 (2.9)	**18.4 (9.0)**	**19.8 (9.8)**
Executive function			
Verbal fluency (/min)[§]	17.4 (4.4)	**7.7 (5.4)**	**10.0 (4.8)**
Category fluency (animals: total)	25.3 (5.0)	**10.5 (6.8)**	**6.2 (5.1)**
Stroop (ink colour) (s)	58.1 (17.0)	**88.4 (31.3)**	88.3 (48.8)
Stroop (colour) (s)	32.0 (6.3)	**46.9 (15.8)**	**60.7 (31.9)**
Stroop (word) (s)	23.7 (5.9)	32.2 (12.3)	36.2 (22.1)
Trails B (s)	67.1 (18.0)	**158 (81)**	**154 (112)**
Trails A (s)	32.5 (7.4)	**59.8 (34.4)**	**52.2 (17.8)**
WAIS-R Digit Symbol (total)	54.9 (11.1)	**35.6 (13.4)**	**39.7 (13.9)**
digit span reverse (/12)	7.8 (2.2)	**5.8 (2.5)**	**6.0 (3.0)**
Episodic memory			
digit span forward (/12)	9.2 (2.2)	8.6 (2.8)	8.2 (2.6)
RMT words (/50)	49.4 (0.9)	**37.1 (8.9)**	**37 (6.7)**
RMT faces (/50)	44.7 (3.6)	**34.5 (7.8)**	**32.3 (7.0)**
Camden PAL (/24)	20.5 (3.2)	**10.7 (7.5)**	**3.8 (3.9)†**
Language and literacy function			
GNT (/30)	26.6 (2.3)	**12.3 (9.6)**	**3.4 (6.1)†**
Reading (NART) (/50)	43.2 (4.9)	**30.4 (10.0)**	**19.2 (14.2)†**
GDA (/24)	14.8 (5.6)	**8.6 (6.8)**	11.1 (9.0)
Semantic memory			
BPVS (/150)	148.7 (1.1)	**122.5 (33.6)**	**95.1 (47.4)**
Synonyms concrete(/25)	24.1 (0.76)	N/A	**16.3 (3.5)**
Synonyms abstract(/25)	24.3 (0.91)	N/A	**18.8 (3.1)**
Visuoperceptual function			
VOSP Object Decision (/20)	18.9 (1.6)	**16.3 (2.6)**	**16.3 (4.3)**

For general rules of data presentation in tables in this thesis see 2.10.1. ¥ one patient in this group classified themselves as ambidextrous [c]mean difference between patient groups is statistically significant ($p<0.05$). § words generated in 1 minute beginning with letter F (Gladsjo JA et al. 1999); þ Time to complete Trails in seconds (maximum time achievable 2.5 minutes on task A, 5 minutes on task B) (Lezak M *et al.* 2004)

and five patients with SD provided no evidence for underlying AD pathology (for reference ranges see 2.3). Brain imaging (MRI/CT) revealed a compatible profile of atrophy in all patients (for further details of imaging acquisition see 2.6).

3.5 Experimental design

3.5.1 Auditory scene tests.

I created auditory scene stimuli based on overlaid pairs of sounds in which the congruity of the two sounds was varied independently along two dimensions: semantic (whether the sounds would be likely or unlikely to occur together) and emotional (whether the sounds had similar or contrasting affective valence). Individual sounds were obtained from on-line digital databases to sample semantic categories of human non-verbal sounds, animal sounds, natural environmental noises and artificial noises (machinery and tools). Sounds were selected from audio CDs (TMP computers sound effects, Digieffects, Warner Bros sound effects library (http://www.sound-ideas.coms) and a publically available online database: (http://www.findsounds.com). Sounds were digitally resampled where necessary to a fixed rate of 44.1kHz and mean sound intensity level (root-mean-square (rms) value) was equated across individual sounds using Matlab7.0®. To form stimuli for the semantic and emotional congruency tests, pairs of sounds were then superimposed and edited to fix overall duration (8 seconds) and rms value of the resulting auditory 'scenes' using Matlab7.0® and Goldwave®. Where necessary, brief or periodic sounds were concatenated and joined with intervening silent intervals to a total duration of 8 seconds. To form stimuli for the perceptual control test, individual (acoustically similar or dissimilar) sounds representing a given semantic category were concatenated to fixed duration (8 seconds) and rms level. The resulting auditory 'scenes' comprised four conditions (balanced for their constituent sounds), in a factorial matrix: semantically congruous – emotionally congruous, ScEc (e.g., alarm clock- snoring); semantically incongruous – emotionally congruous, SiEc (e.g., alarm clock – pig grunting); semantically congruous – emotionally incongruous (e.g., chiming clock – snoring); semantically incongruous – emotionally incongruous, SiEi (e.g., chiming clock – roaring lion).

Based on pilot data from 10 healthy older individuals (6 female; mean age 62.2 (s.d 3.9) years), where a series of 62 individual sounds was presented and participants were asked to identify

each sound and to rate it using a Likert scale (see General Methods 2.5 and Figure 2) along dimensions of pleasantness (1 = very unpleasant, to 5 = very pleasant) and how alerting was the sound (1 = not alerting, to 5 = very alerting). The same sounds were also presented rearranged as superimposed pairs in 193 auditory 'scenes'. Participants were asked to describe each scene and to rate on a Likert scale its overall pleasantness using the same scale as above and how often the constituent sounds would be likely to be heard together (1 = very rarely, to 5 = very often).

The final auditory scene stimuli were arranged to create two tests (comprising combinations of 46 individual sounds), each incorporating the four sound conditions (ScEc, SiEc, ScEi, SiEi), but requiring a decision on either the semantic congruity or the emotional congruity of the sound scenes. For details of stimuli presentation please see General Methods 2.4. Stimuli for each test are listed in Table 4 and Table 5.

An auditory scene was included in the final stimulus set if i) both constituent sounds were identified correctly by >80% of the pilot healthy control group and ii) the scene overall met an additional congruity criterion, based on pilot group ratings: for the semantic congruity test, likelihood of co-occurrence of the two sounds (semantically congruous, mean likelihood rating >3.5; semantically incongruous, mean likelihood rating <1.5) and for the emotional congruity test, pleasantness discrepancy of the two sounds (emotionally congruous, mean rated discrepancy <1; emotionally incongruous, mean rated discrepancy >2). In addition, scenes were selected such that each test was balanced wherever feasible for the 'nuisance' congruity parameter (for the semantic congruity test, the pleasantness discrepancy rating; for the emotional congruity test, the likelihood rating) and the individual sounds represented across conditions; and for the relative proportions of pleasant and unpleasant sound pairs comprising the congruous conditions. The semantic congruity test comprised 30 trials; the participant's task on each trial was to decide whether or not the sounds in the scene would usually be heard together. The emotional congruity test comprised 40 trials; the participant's task on each trial was to decide whether the sounds in the scene were both pleasant, both unpleasant or a mixture of pleasant and unpleasant. In addition, on each trial in the emotional congruity test the participant rated the overall pleasantness of the auditory scene (the sound combination)

on a Likert scale (1 = very unpleasant, to 5 = very pleasant) (see Figure 2 and General Methods 2.5 for further detail regarding Likert scales).

3.5.2 Control tests.

In order to interpret participants' performance on the auditory scene tests, I created control tests to probe auditory perceptual similarity processing, auditory scene analysis and semantic knowledge of individual sounds**.**

In the perceptual similarity control test, I assessed each participant's ability to perceive acoustic similarity and variation between two sounds. Concatenated sounds were presented such that the sequence of sounds either comprised a single sound source or two sound sources of a single kind (for example, a small dog and a large dog); the individual acoustic tokens comprising the sequence were always varied (for example, different barks from the same small or large dog). 30 trials (15 containing a change in source, 15 with no change in source) sampling different semantic categories were presented; the task on each trial was to decide if the thing making the sound changed or remained the same. This task served as a control both for the perceptual analysis of constituent sounds and the decision-making procedure used in the tests of semantic and emotional congruity judgment.

In the auditory scene control test, I assessed each participant's ability to parse superimposed sounds. I adapted an existing test (Golden HL *et al.* 2015) requiring identification of a personal name (e.g. 'Robert') spoken over multi-talker babble. 20 trials were presented; the task on each trial was to identify the spoken name.

In the auditory semantic (sound identification) control test, I assessed each participant's ability to identify and affectively evaluate individual sounds. All 46 constituent sounds composing the auditory scene stimulus set were presented individually; the task on each trial was to match the sound to one of three pictures representing the sound source (e.g., duck), a closely semantically related foil (e.g., gull) and a distantly semantically related foil (e.g., train). In addition, the participant was asked to rate the pleasantness of each sound on a Likert scale (1= very unpleasant, to 5 = very pleasant).

Semantically incongruous						
Woman crying	Pneumatic drill	SiEc	2	1.2	1.1	0.1
Wolf howling	Siren	SiEc	2	1.9	1.8	0.1
Wolf howling	Baby crying	SiEc	2	1.9	1.4	0.5
Cash register	Train crossing	SiEc	1.9	3	2.6	0.4
Surf	Typewriter	SiEc	1.8	3.9	3.6	0.3
Church bells	Lion roaring	SiEi	1.8	4.6	1.8	2.8
Alarm clock	Wolf howling	SiEc	1.7	2.4	1.9	0.5
Water lapping	Typewriter	SiEc	1.7	4.4	3.6	0.8
Applause	Scissors	SiEi	1.7	4.4	2.8	1.6
Baby laughing	Lion roaring	SiEi	1.7	4.8	1.8	3
Applause	Car alarm	SiEi	1.7	4.4	1.2	3.2
Applause	Pneumatic drill	SiEi	1.6	4.4	1.1	3.3
Pig grunting	Alarm clock	SiEc	1.5	2.7	2.4	0.3
Surf	Brushing teeth	SiEi	1.4	3.9	2.1	1.8
Chiming clock	Lion roaring	SiEi	1.3	4.3	1.8	2.5
		Mean	1.7	3.5	2.1	1.4

Sounds 1 and 2 are the constituent superimposed sounds composing each scene stimulus. Sound pairs are ordered here: primarily, in order of decreasing mean likelihood of co-occurrence (decreasing semantic congruity); secondarily, in order of increasing mean pleasantness discrepancy (decreasing emotional congruity), based on Likert ratings by the healthy pilot control group (see 3.5.1). Pilot group pleasantness ratings are shown for sound 1 and sound 2, respectively; the final column shows the modulus of the discrepancy rating for each pair

Table 4 Auditory scene stimulus characteristics: semantic congruity test

Sound 1	Sound 2	Category	Likelihood	Pleasant 1	Pleasant 2	Discrepancy
Semantically congruous						
Gulls	Surf	ScEc	5	4.1	3.9	0.2
Train tracks	Train crossing	ScEi	4.8	3.9	2.6	1.3
Babbling brook	Birds chirping	ScEc	4.7	4.4	4.3	0.1
Church organ	Church bell	ScEc	4.7	4.9	4.6	0.3
Baby laughing	Water splashing	ScEc	4.7	4.8	4.4	0.4
Sheep baa-ing	Rooster crowing	ScEc	4.7	4	3.6	0.4
Baby laughing	Carousel	ScEc	4.7	4.8	3.9	0.9
Sheep bleating	Pig grunting	ScEi	4.7	4	2.7	1.3
Alarm clock	Snoring	ScEc	4.5	2.4	1.8	0.6
Typewriter	Phone ringing	ScEc	4.3	3.6	3.2	0.4
Truck reversing	Pneumatic drill	ScEc	4.2	2.3	1.1	1.2
Water splashing	Baby crying	ScEi	4.1	4.4	1.4	3
Rain	Thunder	ScEi	3.8	3.3	2.3	1
Doorbell	Dog growling	ScEi	3.7	3.4	1.5	1.9
Chiming clock	Snoring	ScEi	3.7	4.3	1.8	2.5
		Mean	4.4	3.9	2.9	1

Emotionally incongruous

Baby gurgling	Alarm clock	ScEi	3.6	4.6	2.4	2.2
Carousel	Baby crying	ScEi	4	3.9	1.4	2.5
Chiming clock	Snoring	ScEi	3.7	4.3	1.8	2.5
Birds chirping	Snoring	ScEi	3.5	4.3	1.8	2.5
Birds chirping	Siren	ScEi	3.4	4.3	1.8	2.5
Birds chirping	Lion roaring	ScEi	3.2	4.3	1.8	2.5
Baby laughing	Dog yelping	ScEi	3.7	4.8	2.1	2.7
Chiming clock	Baby crying	ScEi	3.5	4.3	1.4	2.9
Water splashing	Baby crying	ScEi	4.1	4.4	1.4	3
Applause	Catfight	SiEi	2	4.4	1.4	3
Baby laughing	Lion roaring	SiEi	1.7	4.8	1.8	3
Church bells	Dog growling	SiEi	2.1	4.6	1.5	3.1
Church bells	Baby crying	ScEi	3.4	4.6	1.4	3.2
Applause	Adult crying	SiEi	2	4.4	1.2	3.2
Applause	Car alarm	SiEi	1.7	4.4	1.2	3.2
Baby laughing	Dog growling	SiEi	2.2	4.8	1.5	3.3
Applause	Pneumatic drill	SiEi	1.6	4.4	1.1	3.3
Baby laughing	Dentist drill	SiEi	2	4.8	1.2	3.6
Church bells	Vomiting	SiEi	1.8	4.6	1	3.6
Baby laughing	Vomiting	SiEi	1.8	4.8	1	3.8
		Mean	2.8	4.5	1.5	3

Sounds 1 and 2 are the constituent superimposed sounds composing each scene stimulus. Sound pairs are ordered here: primarily, in order of increasing mean pleasantness discrepancy (decreasing emotional congruity); secondarily, in order of decreasing mean likelihood of co-occurrence (decreasing semantic congruity), based on Likert ratings by the healthy pilot control group (see 3.5.1). Pilot group pleasantness ratings are shown for sound 1 and sound 2, respectively; the final column shows the modulus of the discrepancy rating for each pair

Table 5 Auditory scene stimulus characteristics: emotional congruity test

Sound 1	Sound 2	Category	Likelihood	Pleasant 1	Pleasant 2	Discrepancy
Emotionally congruous						
Babbling brook	Birds chirping	ScEc	4.7	4.4	4.3	0.1
Dog growling	Catfight	ScEc	3.2	1.5	1.4	0.1
Woman screaming	Dentist drill	SiEc	2.4	1.3	1.2	0.1
Woman crying	Pneumatic drill	SiEc	2	1.2	1.1	0.1
Gulls	Surf	ScEc	5	4.1	3.9	0.2
Baby laughing	Church bells	ScEc	3.9	4.8	4.6	0.2
Baby gurgling	Applause	ScEc	3.8	4.6	4.4	0.2
Siren	Glass smashing	ScEc	3.6	1.8	1.6	0.2
Woman screaming	Pneumatic drill	SiEc	1.9	1.3	1.1	0.2
Church organ	Church bell	ScEc	4.7	4.9	4.6	0.3
Baby gurgling	Chiming clock	ScEc	4.2	4.6	4.3	0.3
Ducks quacking	Doorbell ringing	SiEc	2.5	3.7	3.4	0.3
Dog growling	Dentist drill	SiEc	2.3	1.5	1.2	0.3
Baby laughing	Water splashing	ScEc	4.9	4.8	4.4	0.4
Chiming clock	Train tracks	SiEc	2.7	4.3	3.9	0.4
Lion roaring	Woman screaming	SiEc	1.9	1.8	1.3	0.5
Siren	Car alarm	ScEc	3.6	1.8	1.2	0.6
Lion roaring	Dentist drill	SiEc	2.2	1.8	1.2	0.6
Lion roaring	Car alarm	SiEc	2.1	1.8	1.2	0.6
Wolf howling	Pneumatic drill	SiEc	1.9	1.9	1.1	0.8
		Mean	3.1	2.9	2.6	0.3

3.6 General experimental procedure

For Presentation of Stimuli please refer to General Methods 2.4 and 2.4.1 .

3.7 Analysis of behavioural data

Please see General Methods 2.8 and 2.9 for further information. Auditory scene control data were compared between participant groups initially testing for an overall effect with Kruskal-Wallis before proceeding to pairwise differences with Wilcoxon rank-sum tests as the data had a skewed distribution.

On the perceptual similarity control test, participant groups were compared using logistic regression, with robust standard errors to account for clustering by participant (see 2.9.1). To compare participant groups on the auditory semantic control test, sound identification accuracy was assessed using a logistic regression model and pleasantness ratings of individual sounds were assessed using linear regression with bias corrected, accelerated confidence intervals from 2000 bootstrap replications (see 2.9.3). For nuisance covariates see 2.9.4.

Data for the semantic and emotional congruity decision tasks on auditory scene stimuli were pre-processed to take account of individual variation in constituent sound recognition, using data from the auditory semantic (sound identification) control test. For each participant, congruity decisions were scored for those scene stimuli containing sounds that were both identified correctly when presented in isolation in the auditory semantic control test. This analysis strategy allowed us to assess auditory scene semantic and affective processing independently of more elementary auditory semantic knowledge about particular sounds. As the subset of scene stimuli included in the final analysis could therefore potentially vary between individual participants and groups, scene parameters of likelihood and pleasantness (based on pilot data) were assessed to ensure there was no systematic bias that might have altered the effective difficulty of the stimulus subset for a particular participant group. For the subset of semantic scene stimuli containing sounds that were both recognised individually, the average likelihood of the constituent sounds being found together (based on ratings by the healthy pilot group) did not differ significantly between participant groups (healthy controls, 3.08 (s.d.=1.40); bvFTD 3.05 (1.38); SD 3.08 (1.38); $p>0.05$). For this same stimulus subset, the

average pleasantness discrepancy scores between the constituent sounds (based on pilot ratings) again did not differ between participant groups (healthy controls, 1.22 (1.05); bvFTD 1.20 (1.05); SD 1.23 (1.05); $p>0.05$). For the subset of emotional scene stimuli containing sounds that were both recognised individually, the average likelihood of the constituent sounds being found together (based on ratings by the healthy pilot group) did not differ significantly between participant groups (healthy controls, 3.41 (s.d. 1.41); bvFTD 3.40 (1.41); SD 3.36 (1.40); $p>0.05$). For this same stimulus subset, the average pleasantness discrepancy scores between the constituent sounds (based on pilot ratings) again did not differ between participant groups (healthy controls, 1.65 (1.37); bvFTD 1.66 (1.38); SD 1.69 (1.38); $p>0.05$).

Auditory scene congruity decision data for each test were compared between participant groups using logistic regression, allowing for a clustering of responses for individuals (see 2.9.1). In addition to the nuisance covariates used across experimental Chapters (see 2.9.4), scores on the perceptual similarity and auditory scene control tasks were incorporated.

Auditory scene pleasantness rating data in the emotional congruity test were compared between participant groups using a multiple linear regression model that allowed us to distinguish the effect of combining sounds into scenes from individual sound pleasantness (see 2.9.1). Overall auditory scene pleasantness might plausibly be biased by particular, strongly affectively laden constituent sounds and the extent of any such bias might itself be susceptible to disease; the model therefore incorporated separate terms for participant's own (potentially idiosyncratic) pleasantness ratings of both sounds individually and the interaction of the sounds in an auditory scene. This model allowed us to go beyond any abnormal rating of individual sound pleasantness in the disease groups, to assess group differences in the rating of sound combinations. Participant groups were compared using bias corrected, accelerated confidence intervals from 2000 bootstrap replications (see 2.9.3).

In separate post hoc analyses, we assessed the extent of any correlation between semantic and emotional congruity performance and between congruity decisions and performance on a standard test of nonverbal executive function (see 2.9.5). In addition, for each syndromic group separately we assessed any correlation between accuracy on the scene congruity tasks

and individual sound recognition and general executive performance respectively, and between accuracy in the emotional and semantic scene congruity tasks.

3.8 Brain image acquisition and analysis

Brain MRI data were acquired for 27 patients (18 bvFTD, nine SD) as per the procedure described in General Methods 2.6. Pre-processing of MR images was performed as described in 2.7.

In separate design matrices, voxel intensity was modelled as a function of participant scores on the semantic and emotional congruity tasks and the perceptual similarity, auditory scene and auditory semantic control tasks. For nuisance covariates and further detail regarding the analysis please refer to 2.7.

Anatomical small volumes were derived according to the techniques described in 2.7.1. These small volumes (see Figure 3) covered key areas in both hemispheres implicated in nonverbal sound and incongruity processing in the healthy brain, stratified for the contrasts of interest. ROI comprised: for all contrasts, a posterior temporo-parietal region combining posterior STG, lateral inferior parietal cortex and posterior medial cortex (previously implicated in auditory scene parsing and incongruity processing: (Groussard M *et al.* 2010; Chan YC, TL Chou, HC Chen, YC Yeh*, et al.* 2012; Gutschalk A and A Dykstra 2013; Zundorf IC et al. 2013; Pinhas M et al. 2015); and for the contrasts based on semantic and/or congruity processing (all contrasts apart from the auditory scene control contrast), additional regions combining anterior and MTL anterior to Heschl's gyrus, insula and IFG (previously implicated in auditory semantic and rule decoding: (Zahn R *et al.* 2007; Groussard M *et al.* 2010; Christensen TA *et al.* 2011; Jakuszeit M *et al.* 2013; Nazimek JM *et al.* 2013; Remy F *et al.* 2014; Watanabe T *et al.* 2014; Merkel C *et al.* 2015; Henderson JM *et al.* 2016), and ACC and striatum (previously implicated in salience, emotion and reward evaluation: (Ridderinkhof KR *et al.* 2004; Rosenbloom MH *et al.* 2012; Schultz W 2013; Watanabe T *et al.* 2014; Lake JI et al. 2016).

3.9 Results

3.9.1 General characteristics of participant groups

The participant groups did not differ for age (p=0.07) or educational background (p=0.25) and the syndromic groups did not differ in mean symptom duration (p=0.32). Gender distribution differed significantly between groups, males being significantly over-represented in the bvFTD group relative to the healthy control group (p=0.019); gender was incorporated as a nuisance covariate in all subsequent analyses. The patient groups' neuropsychological and demographic data is shown and demonstrated the anticipated profiles of general neuropsychological impairment (2.2 and Table 3).

3.9.2 Experimental behavioural data

3.9.3 Auditory control task performance.

Performance profiles of participant groups on the perceptual similarity, auditory scene and auditory semantic control tests are summarised in Table 6. Two patients with SD were excluded because they performed at chance on the individual sound identification task.

On the perceptual similarity control task, the bvFTD group performed significantly worse than both the healthy control group (p<0.0001) and the SD group (p=0.027), whereas the SD group performed similarly to healthy controls (p=0.153).

On the auditory scene control task, both patient groups performed significantly worse than the healthy control group (bvFTD, p=0.0001; SD, p=0.0042). There was no significant performance difference between patient groups (p=0.96).

Table 6 Performance of participant groups on auditory control tests

Group	Perceptual similarity (/30)	Auditory scene analysis (/20)	Sound identification (/46)
Control	0.91 (0.29)	0.98 (0.04)	0.96 (0.06)
bvFTD	**0.69 (0.46)**	**0.86 (0.12)**	**0.85 (0.36)**
SD	0.83 (0.38)	**0.82 (0.20)**	**0.89 (0.31)**

For data presented in tables there is further information in 2.10.1. For the perceptual similarity task (two-alternative forced choice), a chance score corresponds to 0.5; for the sound identification task (three alternative forced choice), a chance score corresponds to 0.33. See 3.5.2 for details of tests

On the auditory semantic control (sound identification) task, both patient groups performed significantly worse ($p<0.0001$) than the healthy control group. There was no significant performance difference between patient groups ($p=0.50$). Overall pleasantness ratings of individual sounds did not differ significantly for either patient group versus healthy controls (bvFTD, $\beta = 0.07$ [95% confidence interval (CI) -0.30 to 0.47, $p>0.05$]; SD, $\beta = 0.33$ [95% CI -0.17 to 0.91, $p>0.05$]) nor between patient groups ($\beta = 0.26$ (95% CI -0.35 to 0.88, $p>0.05$]).

3.9.4 Auditory scene congruity decisions.

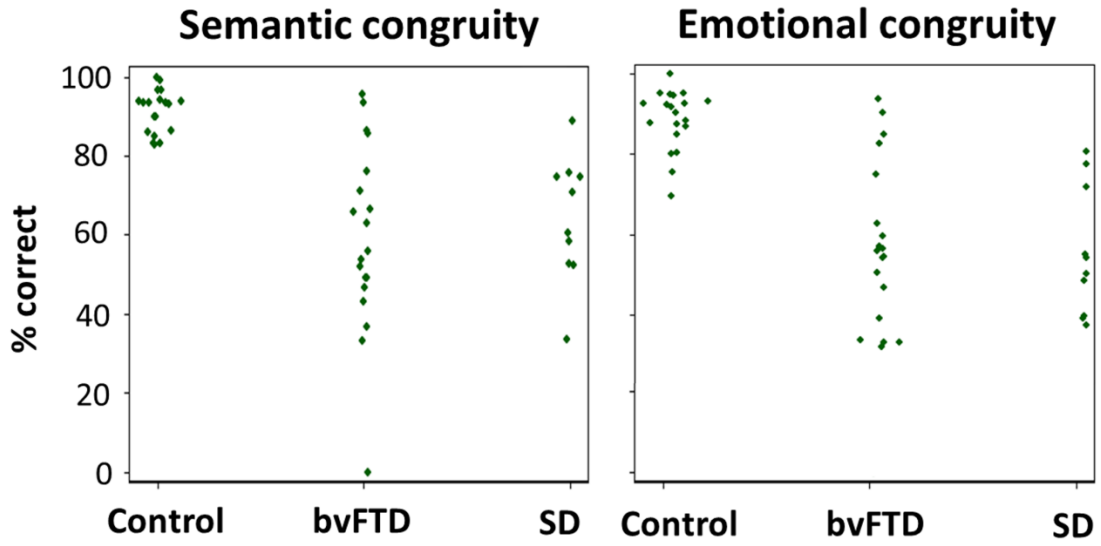
Individual raw scores are plotted in Figure 5 and group raw data is presented in Table 7.

Performance profiles of participant groups on the congruity decision tests are summarised in Table 8.

In the semantic scene congruity task (based on the scene stimulus subset with intact identification of constituent sounds, for each participant) there was an overall significant performance difference between participant groups ($p<0.0001$). Both the bvFTD and SD groups performed significantly worse than healthy controls ($p=<0.001$); there was no significant performance difference between patient groups nor evidence of an overall significant interaction between group and condition ($p=0.62$).

In the emotional scene congruity task (based on the scene stimulus subset with intact identification of constituent sounds, for each participant), there was again an overall significant performance difference between participant groups ($p=0.0001$), both the bvFTD and SD groups performing significantly worse than healthy controls in the congruous and incongruous conditions (all $p<0.005$) with no significant performance difference between patient groups. There was no evidence of an overall significant interaction between group and condition ($p=0.14$). However, the SD group trended toward a greater performance discrepancy between conditions than was shown by the healthy control group ($p=0.053$); this was driven by relatively more accurate performance for scenes containing emotionally congruous sounds.

Figure 5 Raw data for semantic and emotional congruity decisions on auditory scenes, for each participant group



Individual participant scores are plotted as proportion correct for those scene stimuli comprising sounds that were both individually recognised correctly by that participant

Table 7 Raw performance of participant groups on auditory scene congruity decisions

Group	ScEc	ScEi	SiEc	SiEi	All conditions	Total stimuli
Semantic congruity test						
Control	0.93 (0.25)	0.85 (0.36)*	0.89 (0.31)*	0.98 (0.15)	0.92 (0.28)	596 (600)
bvFTD	0.69 (0.46)	0.54 (0.50)	0.66 (0.48)	0.68 (0.47)	0.65 (0.48)	447 (570)
SD	0.60 (0.49)*	0.56 (0.50)*	0.70 (0.46)*	0.82 (0.39)	0.67 (0.47)	247 (300)
Emotional congruity test						
Control	0.87 (0.34)*	0.87 (0.33)*	0.86 (0.35)*	0.94 (0.23)	0.89 (0.32)	792 (800)
bvFTD	0.65 (0.48)	0.55 (0.50)	0.60 (0.49)	0.64 (0.48)	0.61 (0.49)	594 (760)
SD	0.74 (0.44)*	0.44 (0.50)*	0.53 (0.50)	0.55 (0.50)	0.57 (0.50)	331 (400)

For data presented in tables there is further information in 2.10.1. For each test see 3.5.1 for further details regarding criteria for inclusion. Data are based on scene stimuli containing sounds that that were both individually identified correctly by each participant. For the semantic congruity task (two-alternative forced choice), chance performance corresponds to 0.5; for the emotional congruity task (three alternative forced choice), chance performance corresponds to 0.33. *denotes significantly different from reference condition (SiEi). The final column shows the total numbers of stimuli included in this subanalysis (total number of stimuli presented in parentheses) across all participants in each group

Table 8 Performance of patient groups on auditory scene congruity decisions relative to the healthy control group

Group	ScEc	ScEi	SiEc	SiEi	All conditions
Semantic congruity test					
bvFTD	0.35 (0.15-0.81)	0.44 (0.19-1.03)	0.51 (0.21-1.19)	0.10 (0.02-0.52)	0.35 (0.19-0.67)
SD	0.17 (0.06-0.50)	0.37 (0.14-0.98)	0.45 (0.18-1.14)	0.19 (0.03-1.08)	0.30 (0.17-0.53)
Emotional congruity test					
bvFTD	0.58 (0.26-1.31)	0.18 (0.06-0.51)	0.52 (0.20-1.35)	0.21 (0.07-0.68)	0.41 (0.22-0.75)
SD	0.76. (0.37-1.55)	0.37 (0.16-0.85)	0.29 (0.11-0.78)	0.11 (0.03-0.39)	0.27 (0.14-0.52)

For data presented in tables there is further information in 2.10.1. For scene stimuli to be included the constituent sounds were both individually identified correctly by each participant. For further information regarding interpretation of OR see 2.9.1

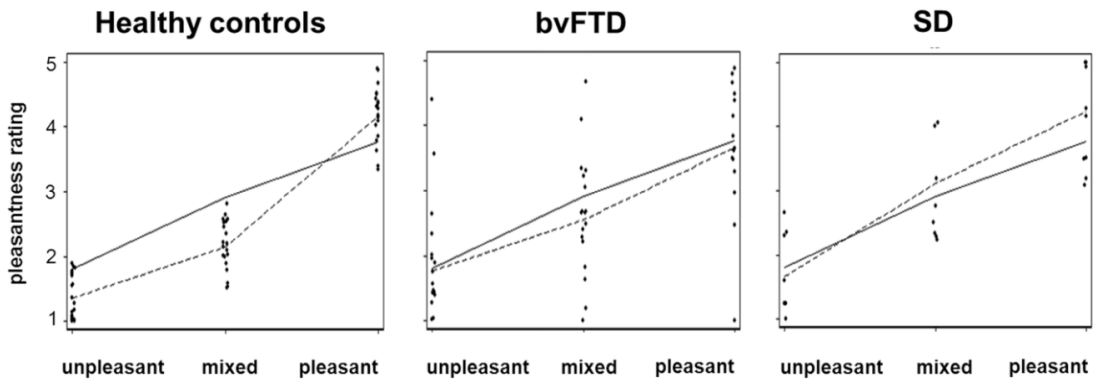
The control group performed significantly better when signals were matched in their congruency across both emotional and semantic dimensions when making semantic judgements. bvFTD behaved comparably across condition subsets, whereas SD patients had a superior performance for semantic congruency judgements if the scenes were incongruent across both dimensions.

3.9.5 Evaluation of auditory scene pleasantness

Individual raw scores are plotted in Figure 6. Behavioural profiles of participant groups for rating the pleasantness of auditory scene stimuli in the emotional congruity test are compared in Table 9.

The SD group rated auditory scenes overall as significantly more pleasant than did the healthy control group (β=0.73 [CI 0.25 to 1.29, $p<0.05$]) while the bvFTD group rated the overall pleasantness of the stimuli similarly to healthy controls (β=0.41 [CI -0.14 to 1.01, $p>0.05$]); the two patient groups rated sound scenes similarly for overall pleasantness (β=0.32 [CI -0.33 to 0.94, $p>0.05$]).

Figure 6 Individual data for rating pleasantness of auditory scene stimuli



For all individuals in each participant group, mean pleasantness ratings of auditory scene stimuli presented in the emotional congruity test (1, very unpleasant; 5, very pleasant) have been plotted against scene stimulus categories based on pilot healthy control group ratings of constituent sounds (**unpleasant**, pleasantness of both constituent sounds rated <3; **mixed**, pleasantness of one sound >3, other sound <3; **pleasant**, pleasantness of both sounds >3). On each plot, the solid line shows the calculated mean pleasantness rating of the two constituent sounds in each auditory scene, based on pilot healthy control group data; the dotted line shows the overall mean pleasantness of auditory scene stimuli in each category, as actually rated by participants in the main experiment

Table 9 Comparison of participant groups for rating pleasantness of auditory scene stimuli

Group	Scene pleasantness					Constituent sound pleasantness effect	
	ScEc	ScEi	SiEc	SiEi	Overall	Within group Coeff (95% CI)	Control comparison Coeff (95% CI)
Control	3.38 (1.45)	2.45 (0.84)	1.82 (1.02)	2.01 (0.80)	2.4 (1.2)	**0.13 (0.09 to 0.17)**	-
bvFTD	3.32 (1.50)	2.65 (1.28)	2.33 (1.39)	2.49 (1.24)	2.7 (1.4)	0.05 (-0.02 to 0.11)	**-0.09 (-0.15 to 0.003)**
SD	3.67 (1.47)	3.14 (1.37)	2.60 (1.49)	3.26 (1.41)	3.2 (1.5)	-0.002 (-0.07to 0.07)	**-0.14 (-0.22 to 0.06)**

For data presented in tables there is further information in 2.10.1. Raw mean (s.d.) scene pleasantness ratings of all auditory scene stimuli administered in the emotional congruity test are shown by sound scene condition (left) together with coefficients (Coeff) and CI for the effect of interacting constituent sound pleasantness ratings, within each group and for patient groups relative to the reference healthy control group (right; see text for details). For further information regarding bootstrapped confidence intervals see 2.9.3

The healthy control group exhibited an additive emotional effect of combining sounds into scenes (a significant positive interaction of sound pleasantness ratings) relative to individual sound pleasantness rated separately: emotionally incongruous auditory scenes were

significantly more likely to be rated as unpleasant than would be predicted from the individual sound ratings alone (β=0.13 [CI 0.09 to 0.17, p<0.05]). This interaction effect was significantly stronger in healthy controls than in either patient group (for bvFTD, β= -0.09 [CI-0.15 to -0.003, p<0.05]; for SD, β=-0.14 [CI -0.22 to -0.06, p<0.05]); indeed, neither patient group showed evidence of the effect (bvFTD, β= 0.05 [CI=-0.02 to 0.11, p>0.05]; SD, β= -0.003 [CI=-0.07 to 0.07, p>0.05]).

The healthy control group rated semantically congruous auditory scenes (within the emotional congruity test) as significantly more pleasant than semantically incongruous scenes (β=0.15 [CI 0.05 to 0.26, p<0.05]). This effect was replicated in the bvFTD group (β=0.21 [CI 0.05 to 0.34, p<0.05] but not in the SD group (β=0.19 [CI -0.005 to 0.46, p>0.05]). The effect was significantly stronger in healthy controls than in either patient group (for bvFTD, β=0.05 [CI -0.14 to 0.22, p>0.05]; for SD, β=0.04 [CI -0.19 to 0.31, p>0.05]) but did not differ significantly between patient groups (β=-0.01 [CI -0.26 to 0.28, p>0.05]).

In a separate subanalysis of the auditory scene pleasantness data, we assessed just those scene stimuli containing sounds that were both recognised by each participant (i.e., we applied the same procedure used in analysis of the congruity tasks). The group effects were substantially unaltered; these data are presented in Table 10.

Table 10 Comparison of participant groups for rating pleasantness of auditory scene stimuli: subset of scene stimuli for which both constituent sounds are recognised correctly

Group	Scene pleasantness					Constituent sound pleasantness effect	
	ScEc	ScEi	SiEc	SiEi	Overall	Within group Coeff (95% CI)	Control comparison Coeff (95% CI)
Control	3.38 (1.45)	2.46 (0.83)	1.82 (1.02)	2.01 (0.80)	2.4 (1.2)	**0.13 (0.09 to 0.17)**	-
bvFTD	3.32 (1.48)	2.69 (1.19)	2.21 (1.33)	2.48 (1.15)	2.7 (1.4)	0.04 (-0.014 to 0.10)	**-0.09 (-0.16 to 0.02)**
SD	3.66 (1.48)	3.01 (1.31)	2.60 (1.41)	3.11 (1.36)	3.1 (1.4)	-0.002 (-0.08 to 0.08)	**-0.13 (-0.22 to 0.04)**

For data presented in tables there is further information in 2.10.1. This table is equivalent to Table 9, except only sound scenes containing individually recognised sounds in the emotional congruity test are shown

3.9.6 Correlations between experimental and background measures

Accuracy of semantic and emotional auditory scene congruity decisions were significantly positively correlated in the bvFTD group (rho 0.80, $p<0.0001$), but not the SD group (rho 0.54, $p=0.11$). Accuracy of semantic scene congruity judgment and constituent sound identification (on the auditory semantic control task) were significantly positively correlated in the bvFTD group (rho 0.62, $p=0.005$) though not the SD group (rho 0.55, $p=0.10$). Semantic scene congruity judgment was significantly positively correlated with general executive capacity (WASI Matrices score) in the SD group (rho 0.91, $p=0.0002$) with a trend to a significant correlation in the bvFTD group (rho 0.40, $p=0.09$).

3.9.7 Neuroanatomical data

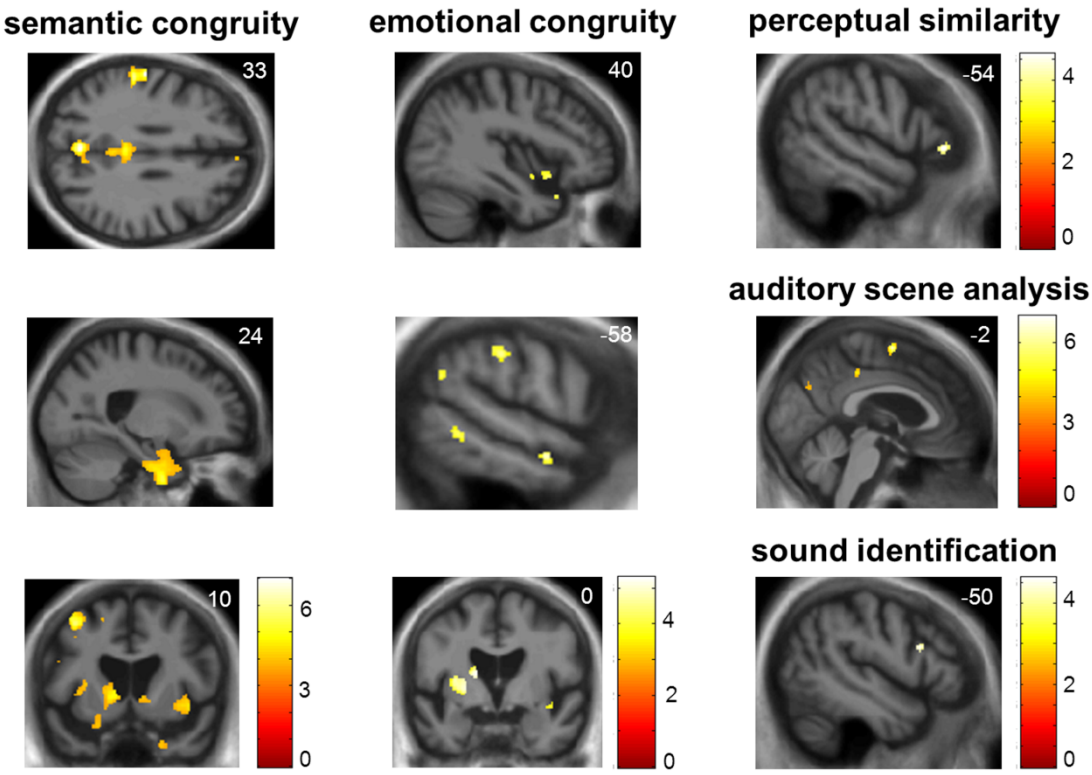
Significant grey matter associations of behavioural measures for the combined patient cohort are summarised in Table 11 and SPMs are presented in Figure 7.

Table 11 Summary of neuroanatomical associations of auditory task performance in the patient cohort

Regional association	Area	Side	Cluster (voxels)	Peak (mm)			Z score	P value
				x	y	z		
Semantic congruity								
Parieto-temporal	*Precuneus*	*L*	*609*	*-3*	*-70*	*33*	*4.86*	*0.032*
	SMG	*L*	*757*	*-58*	*-20*	*33*	*4.83*	*0.036*
	PCC	L	59	-10	-58	22	4.51	0.005
		L	497	-6	-34	34	4.33	0.009
		R	276	2	-34	34	3.91	0.038
	Retrosplenial	L	27	-12	-42	4	4.15	0.017
	Post STG/STS	L	327	-57	-48	22	4.48	0.005
Ant temporal	Ant STS	L	100	-62	-6	-15	4.11	0.018
	Temporal pole	R	908	24	-2	-45	4.14	0.030
Insula	Ant insula	L	428	-34	2	-2	3.84	0.025
		R	546	38	18	-14	3.90	0.014
	Post Insula	R	65	39	-15	8	3.79	0.021
Pre-frontal	*Premotor*	*L*	*351*	*-39*	*14*	*54*	*4.79*	*0.042*
	mPFC/ACC	R	42	3	48	3	4.20	0.014
	IFG	L	160	-50	15	21	4.43	0.003
Striatum	Caudate head	L	409	-12	10	-2	3.82	0.045
Emotional congruity								
Ant temporal	Ant STS	L	52	-58	-9	-16	3.82	0.039
Insula	Ant insula	R	64	40	14	-14	3.49	0.046
Striatum	Putamen	L	709	-24	-2	3	4.07	0.017
	Caudate head	L		-15	0	14	4.07	0.018
Perceptual similarity control								
Pre-frontal	IFG	L	24	-54	34	-2	3.73	0.029
Auditory scene control								
Parieto-temporal	PCC	L	105	-10	-58	22	4.44	0.004
		R	99	2	-33	44	4.03	0.024
	Post STS	L	21	-66	-44	4	3.86	0.039
Pre-frontal	*SMA*	*L*	*182*	*-3*	*-3*	*64*	*4.85*	*0.034*
Semantic control (sound identification)								
Pre-frontal	IFG	L	29	-50	15	21	3.61	0.047

For further information regarding data in tables see 2.10.1. *Italics* represent significant results corrected for multiple comparisons over the whole brain, rather than significant results within pre-specified ROI. Clusters > 20 voxels in size are presented. **Ant**, anterior; **L**, left; **mPFC**, medial prefrontal cortex; **Post**, posterior; **R**, right; See 3.5 for further details of experimental contrasts

Figure 7 SPMs of neuroanatomical associations of auditory task performance in the patient cohort



For further information about presentation of figures please see 2.10.2. Grey matter associations of semantic congruity processing in auditory scenes (left column), emotional congruity processing in auditory scenes (middle column) and auditory control tasks (right column) are presented (see 3.5 for details of contrasts). For further information see Table 11

Impaired accuracy of judging the semantic congruity of auditory scenes was associated with grey matter loss in a distributed, bi-hemispheric cerebral network including precuneus, left supramarginal and premotor cortices (all $p<0.05_{FWE}$ corrected for multiple comparisons over the whole brain), PCC, posterior and anterior superior temporal, insular, medial prefrontal and inferior frontal cortices and caudate nucleus (all $p<0.05_{FWE}$ corrected for multiple comparisons within pre-specified anatomical ROI). Impaired accuracy of judging the emotional congruity of auditory scenes was associated with grey matter loss in a bi-hemispheric, anterior cortico-striatal network including anterior STS, insula, putamen and caudate nucleus (all $p<0.05_{FWE}$ corrected for multiple comparisons within pre-specified anatomical ROI: see Figure 3).

Significant grey matter associations were additionally identified for each of the experimental auditory control tasks (Table 11). Accuracy of judging auditory perceptual similarity was associated with grey matter loss in left inferior frontal cortex. Impaired auditory scene analysis

(impaired identification of spoken names from background babble) was associated with grey matter loss in a prefronto-temporo-parietal network including SMA, ACC, PCC and posterior superior temporal cortices. Impaired sound identification was associated with grey matter loss in left inferior frontal cortex.

3.10 Discussion

Here I have shown that patients with bvFTD and SD have impaired processing of semantic and emotional congruence in auditory scenes relative to healthy older individuals. Both syndromic groups exhibited a similar profile of impaired congruence decisions. These deficits were evident after controlling for general executive, auditory semantic and auditory perceptual competence and did not correlate consistently with ability to identify constituent sounds composing the scene. Taken together the findings argue for specific difficulty processing the semantic and affective relatedness of nonverbal sounds in both these canonical FTLD syndromes. Though there was no strong evidence overall for a specific condition effect, the SD group showed a trend toward more accurate determination of emotional congruity than incongruity in auditory scenes, suggesting a partial retention of affective relatedness that was not evident in the bvFTD group. The findings corroborate a growing body of evidence for impaired processing of signal relatedness in the auditory and other domains in these syndromes, including striking impairments of socio-emotional signal decoding (Kipps CM *et al.* 2009; Krueger CE *et al.* 2009; Piwnica-Worms KE *et al.* 2010; Ibanez A and F Manes 2012; Hughes LE *et al.* 2013; Baez S *et al.* 2014; Irish M *et al.* 2014; Downey LE *et al.* 2015; Fletcher PD *et al.* 2016).

Consistent with previous work (Krueger CE *et al.* 2009; Seer C *et al.* 2015), the present study does not support a strong dissociation of congruence judgment from other aspects of executive function, but rather suggests this may be an ecologically relevant marker of failing executive processes. In this regard, it is of interest that the bvFTD group (but not the SD group) also showed a deficit on the auditory perceptual control task, in keeping with a more fundamental impairment of change detection or monitoring in this syndrome which may map onto social functions such as deviations from societal norms. However, any claim to syndromic specificity must be qualified. While the present findings broadly support the hypothesis of

impaired processing of auditory signal relatedness in bvFTD and SD, I found no strong support for distinctive syndromic profiles of auditory semantic and emotional congruity processing. On the other hand, performance in these two dimensions was correlated in the bvFTD group but not the SD group, suggesting that the underlying processing mechanisms are potentially dissociable. Additionally the SD group had a superior performance when making semantic congruency judgements if the scenes were incongruous across both the semantic and the emotional dimensions, possibly alluding to a pop-out effect which was partially replicated in control performance and absent in the bvFTD group.

In addition to impaired cognitive decoding, as anticipated both the bvFTD and SD groups here showed altered affective valuation of auditory scenes. The SD group (though not the bvFTD group) tended to rate auditory scenes overall as more pleasant than did healthy controls. While this appears somewhat at odds with the high reported frequency of daily life sound aversion in this syndrome (Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015) it is consistent with other evidence suggesting substantial modulation of affective responses by particular sounds in FTLD syndromes (Fletcher PD, JM Nicholas*, et al.* 2015). More informative in the current context was the emotional effect of embedding sounds into scenes. Healthy controls rated emotionally incongruous auditory scenes as less pleasant than predicted from their own constituent individual sound ratings (

Table 9, Figure 6) whereas neither patient group showed evidence of this effect. In addition, healthy individuals rated semantically incongruous auditory scenes as less pleasant than congruous scenes. This effect was also evident (albeit attenuated) in the bvFTD group, but not the SD group. In healthy individuals, affective integrative or 'binding' effects of combining emotional stimuli have been demonstrated previously in other modalities (Hietanen JK and JM Leppanen 2008; Muller VI et al. 2011) and incongruity has generally increased aversive potential compared with congruity in various contexts (Piwnica-Worms KE *et al.* 2010; Schouppe N et al. 2015). Information concerning the impact of neurodegenerative diseases on these processes remains very limited. The present findings suggest that both bvFTD and SD are associated with impaired sensitivity to contextual modulation of affective signals, consistent with the more pervasive impairments of emotion processing documented in these syndromes (Kumfor F and O Piguet 2012). Some sensitivity to the affective overtones of signal mismatch is

retained in bvFTD, but entirely lost in SD, consistent with the relative degree of semantic impairment in each syndrome.

The overlapping, but partly separable neuroanatomical correlates of semantic and emotional congruity processing identified here suggest a framework for understanding the brain mechanisms that process different dimensions of auditory signal relatedness. These neuroanatomical substrates are in line with my experimental hypotheses and with previous neuroanatomical work in auditory and other modalities. Processing of both semantic and emotional auditory congruence had a correlate in anterior temporal and insula cortices that are likely to constitute 'hubs' for processing signal patterns and salient deviations based on prior expectations or stored templates (Michelon P *et al.* 2003; Samson AC et al. 2009; Groussard M *et al.* 2010; Christensen TA *et al.* 2011; Nazimek JM *et al.* 2013; Remy F *et al.* 2014; Watanabe T *et al.* 2014; Merkel C *et al.* 2015; Gauvin HS *et al.* 2016). These regions are engaged during matching of incoming signals against previously learned semantic and affective templates (Zahn R, J Moll, M Paiva*, et al.* 2009; Groussard M *et al.* 2010; Leaver AM and JP Rauschecker 2010). The processing of auditory semantic congruence had additional correlates in a distributed medial and lateral prefronto-parietal network previously implicated in the processing of rule violations and reconciliation with previously established regularities, under a range of paradigms (Michelon P *et al.* 2003; Ridderinkhof KR *et al.* 2004; Strelnikov KN *et al.* 2006; Groussard M *et al.* 2010; Chan YC, TL Chou, HC Chen, YC Yeh*, et al.* 2012; Rosenbloom MH *et al.* 2012; Jakuszeit M *et al.* 2013; Paavilainen P 2013; Remy F *et al.* 2014; Watanabe T *et al.* 2014; Brod G *et al.* 2015; Pinhas M *et al.* 2015; Gauvin HS *et al.* 2016; Henderson JM *et al.* 2016). The processing of auditory emotional congruence had an additional correlate in striatal structures broadly implicated in the processing of emotional congruence and reward evaluation (Klasen M *et al.* 2011; Schultz W 2013; Dzafic I *et al.* 2016). Although emotion and reward processing have classically been associated with ventral striatum rather than the dorsal striatal structures identified here, it is increasingly recognised that these striatal subregions participate in intimately integrated functional networks. Moreover, dorsal striatum is particularly engaged during contingency monitoring and programming behavioural decisions on emotionally salient stimuli (Haber SN 2016). The salient events coded by the striatum necessitating the attentional switch can be non-rewarding, however, caudate activity increases

when distractors are behaviourally relevant (Zink CF et al. 2003). Increased activation in the caudate was seen in response to emotional speech where the valence of content and tone was incongruous (Kotz SA et al. 2015).

These neural network correlates of auditory semantic and emotional congruence decisions overlapped with cortical associations of performance on the auditory control tasks, suggesting that particular network components may play a more generic role in the analysis of stimulus relatedness. Performance on the auditory scene analysis control task had a substrate in TPJ and SMA, known to be fundamentally involved in parsing and monitoring of the auditory environment in healthy and clinical populations (Goll JC et al. 2012; Gutschalk A and A Dykstra 2013; Zundorf IC *et al.* 2013; Golden HL *et al.* 2015; Gauvin HS *et al.* 2016). The TPJ may serve as a domain-independent detector of salience associated with signal mismatch in diverse situations (Decety J and C Lamm 2007; Chan YC, TL Chou, HC Chen, YC Yeh*, et al.* 2012). Performance in both the perceptual similarity and sound identification control tasks here had a correlate in inferior frontal cortex. This region has been implicated previously in categorisation of sound stimuli, particularly under conditions of high perceptual or cognitive load (Engelien A et al. 2006; Du Y et al. 2014; Gauvin HS *et al.* 2016).

Auditory scene decoding may be a useful model paradigm for characterising the effects of dementias on signal processing in the more complex scenarios of daily life. From a clinical perspective, effective treatment of the dementias will likely depend on an accurate picture of the disability these diseases produce, particularly in domains such as social and emotional cognition that are most sensitive to patients' functioning in their daily lives (Franklin RG, Jr. and RB Adams, Jr. 2011; St Jacques PL *et al.* 2015; Sturm VE et al. 2015). This, in turn, will require an informed deconstruction of complex, ill-defined symptoms to more tractable building blocks that continue to mirror processes of clinical interest (Cicerone K et al. 2006).

This Chapter suggests one candidate approach relevant to symptoms arising from impaired processing of conflicting signals. Here, the manipulation of signal relatedness in simple auditory scenes engaged brain mechanisms similar to those engaged by complex social scenarios requiring conflict evaluation and resolution. More speculatively, analysis of signal relatedness may engage a fundamental cognitive mechanism that is co-opted to the analysis of

relatedness at different (sensory, perceptual, semantic, affective) levels of abstraction (Cohen MX 2014). In the next Chapter, I describe an analogous deconstruction exploiting the paradigm of music: a manipulation of the 'rules' governing simple melodies to capture generic brain mechanisms of anticipation and reward.

4 MUSIC PROCESSING IN FTLD: A BEHAVIOURAL & NEUROANATOMICAL ANALYSIS

4.1 Chapter summary

Here, I describe an analogous deconstruction to Chapter 3, exploiting the paradigm of music which generates emotional rewards based on internalised 'rules' and psychological expectancies. It therefore lends itself to evaluating the aberrant anticipation and valuation of reward exhibited by patients with FTLD and AD. I used music to assess cognitive and affective dimensions of musical reward processing in patients with canonical FTLD syndromes (bvFTD, n=11; SD, n=6; PNFA, n=8) in relation to patients with typical AD (n=14), LPA (n=5) and healthy age-matched individuals (n=22). Novel melodies were constructed in which cadence (tonal expectancy) was manipulated such that the melodies were either harmonically resolved or unresolved. The task was to classify each melody as 'finished'/'unfinished' (musical reward anticipation) and rate its pleasantness (musical reward valuation). Relative to healthy controls, patient groups showed separable profiles of musical reward processing: bvFTD and LPA were associated with abnormal musical reward anticipation and valuation; SD, with musical reward anticipation similar to healthy controls but abnormal reward valuation; typical AD with abnormal reward anticipation, but normal reward valuation and PNFA with the normal profile of reward anticipation and valuation. In a VBM analysis of patients' brain MR images, significant grey matter correlates of melody classification accuracy and pleasantness rating were identified in a distributed network including anterior temporal, medial and lateral OFC, previously implicated in computing diverse biological and secondary rewards. The syndromic profiles of altered musical reward anticipation and valuation shown here distil key features of abnormal risk taking, reward seeking and punishment avoidance behaviours exhibited by these patients in a range of experimental and social situations. Music is a useful model of expectation and reward processes that are relevant to complex, daily life behaviours in neurodegenerative diseases.

4.2 Introduction

Music occupies a unique place among hedonic stimuli. Music is biologically salient, a self-contained meaningful system, governed by implicitly learned rules acquired by all normal listeners which engage pattern completion or 'puzzle-solving' algorithms and associated

reward (Cuddy LL et al. 1981; Salimpoor VN et al. 2013; Salimpoor VN *et al.* 2015). These templates of musical structure are stored in the superior temporal cortex, from which musical expectations are generated (Salimpoor VN *et al.* 2015). The human brain is primed to rehearse and value particular musical 'codes'; examples include abnormally enhanced, intrusive and repetitive musical imagery or 'ear worms' (Levitin D 2007; Sacks O 2007; Beaman CP and TI Williams 2010).

Music recruits neural networks that process biological and secondary rewards in the healthy brain (Pressnitzer D *et al.* 2011; Salimpoor VN *et al.* 2013; Salimpoor VN *et al.* 2015). Music may be pleasurable because it engages our pattern completion algorithms, which hones our abilities to decode complex affective mental states (Salimpoor VN *et al.* 2013; Clark CN, LE Downey and JD Warren 2014; Clark CN et al. 2015; Salimpoor VN *et al.* 2015) (see 1.5.2).. It is therefore unsurprising that abnormalities of musical emotion and reward processing should accompany common dementias (Omar R, SM Henley*, et al.* 2011; Hsieh S *et al.* 2012; Perry DC *et al.* 2014; Agustus JL et al. 2015). In contrast to healthy age-matched controls, patients with bvFTD have specific difficulty in assigning surrogate mental states to music (Downey LE *et al.* 2013).

Those melodies that fulfil expectation or resolve ambiguity are perceived as subjectively pleasurable or rewarding (Huron D 2006; Pressnitzer D *et al.* 2011) while delayed resolution or lack of resolution (confounded expectation) is associated with subjective tension and negative affect (Steinbeis N et al. 2005; Gingras B et al. 2015; Tsai C-G and C-P Chen 2015). In normal listeners, the processing of tonal relationships and harmonic expectancy engages striatal, inferior frontal and anterior superior temporal regions (Koelsch S et al. 2000; Janata P et al. 2002; Steinbeis N *et al.* 2005; Tillmann B 2005; Seger CA et al. 2013).

An important determinant of music emotion processing is its temporal dynamics. The sense of tension and tonal resolution established via psychological expectancies conveys a potent emotional impact across musical genres (Huron D 2006) while more complex, abstract structural features may play a contributory role in particular genres (such as Western polyphony) (Pressnitzer D *et al.* 2011). Sequential activation occurs of OFC, amygdala and anterior cingulate gyrus during processing of musical dissonance (Dellacherie D et al. 2009).

Normal listeners exhibit a hierarchy of emotional responses to music and these responses have dissociable physiological (subjective experience culminating in intensely pleasurable musical chills) and cognitive (objective labelling) dimensions (Blood AJ and RJ Zatorre 2001; Juslin PN and D Vastfjall 2008; Salimpoor VN *et al.* 2011; Salimpoor VN *et al.* 2013). These features of musical reward and its anticipation tap neural mechanisms that are sensitive to dysfunction of culprit brain networks in dementia (Zhou J and WW Seeley 2014).

Functional imaging work in the healthy brain has demonstrated very extensive neuroanatomical correlates of musical emotion processing, including engagement of salience and evaluation systems in the insula, amygdala and their limbic connections (Blood AJ and RJ Zatorre 2001) and neurotransmitter (notably, dopaminergic) pathways that link cognitive and affective responses to music with mesolimbic and subcortical reward networks (Salimpoor VN *et al.* 2011) as well as prefrontal and somatosensory cortices (Koelsch S et al. 2006; Koelsch S, S Skouras, et al. 2013). It has been suggested that extra-temporal cortices may become engaged during evaluation of intrinsically ambiguous affective signals as embodied in music (Leitman DI et al. 2010). Pitch pattern analysis (for example, in melodies) engages the STG (Patterson RD et al. 2002; Warren JD and TD Griffiths 2003). Given that anterior superior temporal cortices are also engaged in processing higher order speech patterns, this region may have a generic role in the representation of higher order auditory structures (Patterson RD *et al.* 2002). Early anterior negativity changes occur after sound pattern violations to the higher order structure of music, such as harmonic expectations or inappropriate chord progressions (Garza Villarreal EA et al. 2011; Kim SG et al. 2011). Inferior frontal gyrus (IFG) has also been implicated in processing chord sequences (Tillmann B et al. 2003; Koelsch S et al. 2005) and melodies (Janata P *et al.* 2002) as well as more complex or ambiguous syntactic hierarchies in language (Grodzinsky Y and AD Friederici 2006) and actions (Fazio P et al. 2009).

This critical linkage between cortical mechanisms of musical pattern analysis and subcortical networks for processing reward and emotion (Pressnitzer D *et al.* 2011; Zatorre RJ and VN Salimpoor 2013) is shown by the loss of the ability to derive pleasure from the apprehension of coherent musical structures ('musical anhedonia') with lesions involving TPJ and parietal cortex (Mazzoni M et al. 1993; Peretz I *et al.* 2001; Griffiths TD et al. 2004; McDonald I 2006; Stewart L et al. 2006; Satoh M et al. 2011). Music frequently induces abnormal hedonic behaviour in

patients with bvFTD and SD (Fletcher PD et al. 2014). In the FTLD spectrum, selective disintegration of neuroanatomical and cognitive systems illustrates the involvement of temporal lobe structures in musical semantic memory, but also how it can sometimes be preserved despite pervasive semantic failure (Omar R *et al.* 2010; Omar R et al. 2012; Downey LE *et al.* 2015). Across this patient population, dichotomous behavioural responses to music occur in a high proportion of cases and encompass both avoidance and intense craving (musicophilia) (Agustus JL *et al.* 2015) and to a lesser extent are exhibited in AD patients (Fletcher PD et al. 2013; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015). Altered hedonic responses to music, correlate with abnormalities of homeostatic processing in patients with FTLD (Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015). Emerging evidence suggests that neurodegenerative syndromes may have separable profiles of abnormal musical reward processing (Omar R *et al.* 2010; Weinstein J et al. 2011; Hsieh S *et al.* 2012; Downey LE *et al.* 2013; Agustus JL *et al.* 2015).

As a stimulus with which to engage brain reward processing in cognitively impaired patients, music is relatively straightforward to manipulate and the abstract character of music creates an autonomous reward system that is independent of semantic knowledge (an important potential confound in interpreting the processing of primary biological rewards, such as foods (Piwnica-Worms KE *et al.* 2010; Omar R et al. 2013). In this Chapter, I used music as a novel paradigm of reward anticipation and valuation in patients with canonical syndromes of FTLD and AD. Music distils and codifies the computations that underpin such processes while remaining a close facsimile of emotionally salient events in the world at large (Zentner M et al. 2008). In order to exploit the 'rule-based' nature of musical expectancy and reward the harmonic structure of novel melodies was manipulated to create experimental conditions in which the melody either resolved as anticipated or lacked clear harmonic resolution. In this context, analysis of harmonic structure establishes an expectation or 'prediction' of reward (tonal resolution) and completion of the melody delivers a reward value according to whether or not resolution is achieved. I compared the cognitive and emotional responses corresponding to musical reward anticipation and valuation in patients and healthy older

individuals. Neuroanatomical correlates of these processes were assessed in the patient cohort using VBM.

4.3 Experimental Hypotheses

i) bvFTD patients have abnormalities of encoding long-range musical structure or musical reward anticipation (categorisation of tonally resolved versus unresolved melodies) and hedonic or reward valuation (emotional rating of these melodies)

ii) SD patients have abnormal musical reward valuation despite relatively preserved reward anticipation or structural encoding.

iii) PNFA patients have normal reward valuation

iv) AD patients have abnormal musical reward anticipation despite preserved reward valuation.

v) LPA patients have abnormal musical reward valuation

vi) Musical reward anticipation and valuation have separable neuroanatomical correlates in brain networks previously implicated in the structural analysis and affective processing of music and other sounds.

4.4 Methods

4.4.1 Participants

For consensus criteria and general characteristics of syndromic groups please refer to General Methods (see 2.1). 14 patients (six female) with typical amnestic AD, 11 patients (two female) with bvFTD, six patients (two female) with a diagnosis of SD, eight patients (six female) with PNFA and five patients (two female) with LPA were recruited. 22 healthy older individuals (11 female) also participated. None of the participants had a history of clinically significant hearing loss or congenital amusia. Two patients in the bvFTD group and five patients in the SD group had a history of musicophilia (Fletcher PD *et al.* 2013). For this experiment the operational definition of musicophilia was the caregiver responding yes to all four components of the

following question; does the patient have a new (1) obsessional interest (2) in music (3), the extent of which has an overall impact on their life (4)?

Ten of eleven patients in the AD group and four of four patients in the LPA group for whom CSF was available had a protein marker profile suggesting underlying AD pathology (see General Methods 2.3 and Table 2 in Appendix for further information). In contrast, CSF findings in eleven of thirteen patients with other syndromes provided no evidence for underlying AD pathology. The bvFTD group included nine cases with confirmed pathogenic mutations (six *MAPT,* three *C9orf72*) and one patient with PNFA had a pathogenic *C9orf72* mutation. At the time of testing, 13 patients in the AD group were receiving symptomatic treatment with donepezil and two with memantine; in the LPA group, four patients were receiving donepezil and two memantine; while in the PNFA group one patient was receiving donepezil.

4.4.2 Peripheral hearing assessment and analysis

The procedure was adapted from a commercial screening audiometry software package (AUDIO-CDTM®) (http://www.digitalrecordings.com/audiocd/audio/html) and was used to assess for a peripheral hearing impairment. Five frequency levels (500, 1000, 2000, 3000, 4000 Hz) were assessed. At each frequency, participants were presented with a continuous tone that slowly and linearly increased in intensity. Participants were instructed to indicate as soon as they were sure they could detect the tone and this response time was measured. Hearing was assessed in the right ear. Tone detection thresholds on audiometry screening were analysed using a multiple linear regression model with robust standard errors (see General Methods 2.9.1). The main effect of patient group was assessed whilst controlling for age. A combined log transformed (owing to a skewed non-normal distribution) audiometry score, using the sum of detection thresholds (for all frequencies) was derived as an overall measure of peripheral hearing function to test for associations with performance on the experimental tests of music processing. For further details of how this and all subsequent auditory tests were administered (see General Methods 2.4 and 2.4.1).

4.4.3 Pitch screening test

I used an elementary pitch discrimination screening test to establish that potential participants could comply with experimental tests involving the processing of musical sequences and

elementary pitch information. This screening test comprised 20 note pairs; 10 pairs had identical notes and 10 had notes that differed in pitch by an interval of one to six semitones (mean = 2.7 semitones). Notes were derived from a synthetic piano sound (Musescore®) and intervals corresponded to pitch values in traditional Western music. Each note had duration 1s and an inter-note gap of 1s. Participants were instructed to indicate whether note pairs were 'same' or 'different' after each pair was played. Participants were required to score >80% correct on this screening task in order to participate in the subsequent experiments included in this chapter. 20 patients (diagnoses distributed across syndromes) were excluded on the basis they failed to meet the screening criterion (>80% correct) on this test.

4.4.4 Demographics and neuropsychology

Demographic, clinical and general neuropsychological characteristics of the study cohort are summarised in Table 12. For further information regarding the statistical analyses please refer to General Methods (see 2.9). Tests which were deemed particularly important for this paradigm included; reverse digit span and WASI matrices. Additional information collected from participants specifically for this chapter was, years of musical training.

4.4.5 Assessment of music processing

4.4.6 Assessment of tonal expectancy

To assess processing of musical reward based on tonal expectancy, short monophonic melodies were composed in accord with the rules of Western harmony by an experienced musician (OM). Melodies were based on motifs that commenced on either the tonic or dominant degree of the scale to establish the tonal centre. For these motifs, melodies were constructed with harmonically altered endings such that the melody sounded 'finished' (tonally resolved) or 'unfinished' (tonally unresolved). 'Finished' melodies expressed perfect cadences (dominant – tonic) in the final bar whilst 'unfinished' melodies implied either imperfect cadences (ending on the dominant), interrupted cadences (dominant–submediant), or incomplete perfect cadences (dominant-leading note). Melodies were created with length sufficient to establish stylistically congruous harmonic progressions. Note sequences were synthesised with piano timbre as digital wavefiles using Logic Pro X®.

Stroop (word) (s)	21 (3.7)	**27 (8.0)**	22 (5.3)	**52 (24.6)**	**35 (12.7)**	**37 (19.4)**
Trails B (s)	73 (20.4)	**148 (81.7)**	89 (48.0)	**233 (67.5)**	**232 (73.0)**	**175 (62.9)**
Trails A (s)[b]	32 (9.0)	**45 (17.3)**	35 (20.6)	**69 (37.2)**	**84 (38.5)**	**73 (48.0)**
WAIS-R Digit Symbol (total)	56 (10.7)	**34 (8.7)**	44 (11.2)	**27 (12.0)**	**38 (11.1)**	**20 (15.6)**
digit span reverse (/12)	8 (2.0)	7 (2.7)	10 (2.2)	**3 (2.2)**	**1.6 (1.4)**	**5 (1.7)**
Episodic memory						
digit span forward (/12)	9 (2.1)	9 (2.5)	11 (1.5)	**7 (2.0)**	**3 (2.5)**	**6 (2.2)**
RMT words (/50)	48 (1.8)	**37 (8.8)**	**33 (6.6)**	47 (3.7)	**32 (6.0)**	**30 (5.8)**
RMT faces (/50)	44 (4.1)	**33 (6.1)**	**32 (8.1)**	**37 (5.7)**	**34 (7.2)**	**33 (6.4)**
Camden PAL (/24)	20 (2.5)	**9 (6.6)**	**5 (4.5)**	17 (4.5)	**3 (2.5)**	**4 (4.0)**
Language and literacy function						
GNT (/30)	26 (2.2)	**8 (9.4)**	**0 (0.8)**	**17 (7.7)**	**7 (7.9)**	**16 (6.7)**
Reading (NART) (/50)	43 (3.6)	**31(11.5)**	**28 (10.5)**	**30 (12.8)**	**17 (10.8)**	**36 (7.2)**
GDA (/24)	16 (5.0)	13(6.6)	12(8. 4)	**5 (4.1)**	**4.4 (5.0)**	**5 (6.3)**
Single word repetition (/45)	N/A	N/A	45 (1.0)	33 (15.4)	40 (3.5)	N/A
Sentence repetition (/10)	N/A	N/A	10 (0.5)	6 (4.4)	7 (3.6)	N/A
Semantic memory						
BPVS (/150)	148 (1.9)	**128(21.2)**	**120 (14.8)**	**144 (4.8)**	**141 (6.8)**	**145 (3.0)**
Synonyms concrete(/25)	N/A	N/A	18 (2.6)	22 (2.9)	N/A	N/A
Synonyms abstract(/25)	N/A	N/A	17 (3.2)	21 (3.5)	N/A	N/A
Visuoperceptual functions						
VOSP Object Decision (/20)	19 (1.6)	**17(1.9)**	17 (2.7)	16 (5.6)	18 (2.2)	**16 (3.4)**

¥ One participant in this group identified as being ambidextrous **€** includes ratings by patients with musicophilia (five in SD group, two in bvFTD group); **§** words generated in 1 minute beginning with letter F (Gladsjo JA *et al.* 1999); **þ** Time to complete Trails in seconds (maximum time achievable 2.5 minutes on task A, 5 minutes on task B) (Lezak M *et al.* 2004). For further information regarding data in tables see 2.10.1 and for general information about neuropsychology and demographics tables please refer to Table 2 and General Methods 2.2

Table 12 General demographic, clinical and neuropsychological characteristics of participant groups

Characteristic	Healthy controls	bvFTD	SD	PNFA	LPA	AD
General						
No., gender (M:F)	11:11	9:2	4:2	2:6	3:2	8:6
Handedness (L:R)	17:3[¥]	1:10	0:6	1:7	1:4	3:11
Age (yrs)	68.5 (5.1)	65.8 (7.6)	66.2 (5.2)	71.5 (7.8)	63.6 (5.6)	68.6 (6.7)
Musical training (yrs)	4.5 (3.4)	4.8 (3.4)	4.3 (4.4)	3 (2.5)	3.2 (3.6)	4.4 (2.9)
Musical listening (hrs/week)	9.7 (10.1)	5.5 (4.7)€	8.8 (8.6)[€]	5.5 (7.4)	5.2 (3.1)	8.6 (11.0)
Education (yrs)	16.7 (2.0)	15.3 (3.4)	14.2 (3.1)	16.9 (2.2)	14.4 (3.0)	15 (2.4)
Symptom duration (yrs)	N/A	9.8 (5.5)	6.3 (1.8)	6.9 (3.7)	5.8 (2.8)	6.3 (1.9)
MMSE (/30)	N/A	25 (3.8)	27 (2.5)	23 (9.5)	16 (9.6)	21 (5.0)
Background Neuropsychology						
General intellect						
VIQ	119 (7.0)	**91 (16.5)**	**87 (11.5)**	**88 (16.1)**	**69 (12.4)**	**98 (14.4)**
PIQ	121 (10.6)	**104 (15.5)**	114 (19.1)	**103 (18.9)**	**94 (20.6)**	**90 (21.5)**
NART estimated premorbid IQ	122 (4.7)	**108 (12.2)**	**107 (12.1)**	**104 (15.8)**	**88 (12.2)**	**113 (9.0)**
WASI Vocabulary (/80)	71 (3.2)	**50(18.7)**	**42 (17.6)**	**39 (17.9)**	**23 (20.0)**	**56 (10.0)**
WASI Block Design (/71)	46 (13.0)	**33 (13.4)**	41 (19.8)	**21 (18.1)**	**26 (21.8)**	**18 (13.8)**
WASI Similarities (/48)	39 (4.8)	**26(8.4)**	**22 (8.7)**	**28 (7.2)**	**13 (7.3)**	**26 (11.4)**
WASI Matrices (/32)	25 (4.1)	**21 (5.6)**	24 (6.9)	**20 (6.7)**	**17 (9.0)**	**13 (7.8)**
Executive function						
Verbal fluency (/min)[§]	16 (5.5)	**9 (4.6)**	**11 (4.9)**	**4 (2.7)**	**7 (1.5)**	**11 (5.0)**
Category fluency (animals: total)	24 (5.4)	**12 (3.8)**	**6 (2.8)**	**10 (3.4)**	**9 (5.2)**	**12 (5.4)**
Stroop (ink colour) (s)	58 (17.1)	**81 (36.2)**	62 (27.5)	**149 (37.3)**	**115 (17.0)**	**107 (53.2)**
Stroop (colour) (s)	29 (4.2)	**40 (10.3)**	**37 (10.2)**	**67 (20.9)**	**62 (19.0)**	**54 (22.5)**

4.4.7 Pilot experiment

Novel melodies were presented according to the principles of General Methods (see 2.4 and 2.4.1). In the test of tonal expectancy processing, the task on each trial was to decide firstly, if the melody sounded 'finished' or 'unfinished'; and secondly, to rate how pleasing was the ending of the melody ('How did the tune leave you feeling?') on a 5–point Likert scale (1, not at all pleased; 5, very pleased; see Figure 2 in General Methods). Based on data in a pilot group of 15 healthy older individuals (mean age 61 years, range 51 to 74 years; 9 female), a subset of 24 melodies (12 pairs) from an initial set of 40 were selected to comprise the final stimulus set. The complete final set is notated in Figure 8.

The criterion for inclusion of a melody in the final set was >75% consensus agreement across the pilot control cohort as to whether that melody sounded 'finished' or 'unfinished'. Melodies in the 'finished' and 'unfinished' conditions were closely matched overall for key and length characteristics. Nine melody pairs were generated from harmonic motifs common to a given pair (rows I to IX from Figure 8), while the remaining six melodies were generated from unique harmonic motifs (rows X to XII from Figure 8). The final stimulus set covered a range of keys (19 major, 5 minor) and time signatures (17 in 4/4, four in 3/4, three in 5/4). Tempo was fixed at 120 beats/minute for all stimuli. Melodies varied in length between three and five bars.

4.4.8 Assessment of key processing.

In contrast to the tonal expectancy test, this test did not require a cognitive or emotional response based on anticipation of a musical structure, but simply detection of a musical event (a note) that deviated from the prevailing key. 'Key' constitutes a set of eight tones conforming to a Western diatonic scale. Tonal or harmonic expectancies are closely linked to musical scale or key hierarchies that govern the relations between individual notes comprising the scale. To provide a reference for interpreting the processing of tonal expectancy, we assessed participants' ability to detect key violations (yet remaining within the global melody contour) in five different major keys (A, G, D, F, B ♭). Deviant notes occurred with random onsets over the course of the trial. In order to establish the key of the trial, no deviants occurred before the fourth bar of the melody and the interval between deviants was at least 1.5 seconds. The five novel note sequences, containing a total of 20 deviant notes, were composed in

MuseScore® with a synthetic guitar carrier by an experienced musician (HLG). The melodies had a base tempo of 120 beats/minute with note durations ranging from a 'dotted minim' (1500ms) to a 'semiquaver' (125ms) and total sequence duration varying between 33.5 and 39.6 seconds across trials. Examples of stimulus sequences are presented in Figure 9. For further details of analysis please see 2.9.2.

Figure 8 Stimuli used to assess tonal expectancy

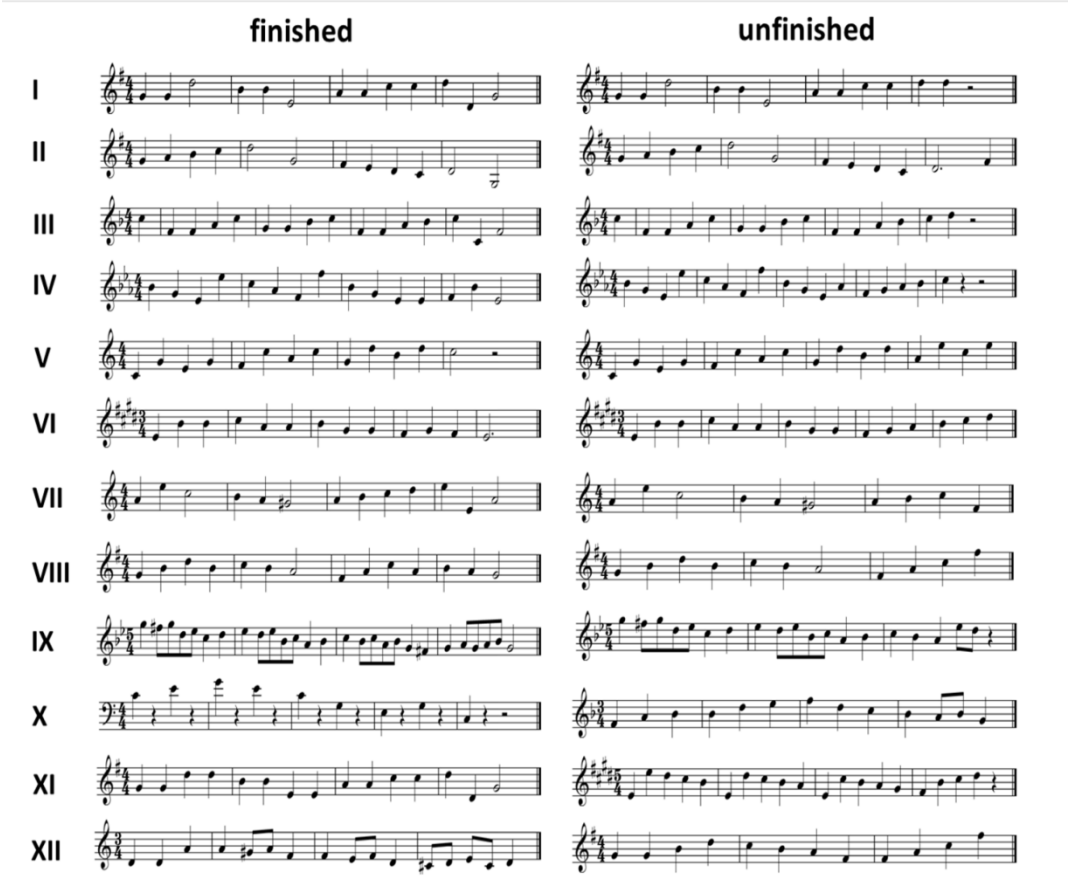
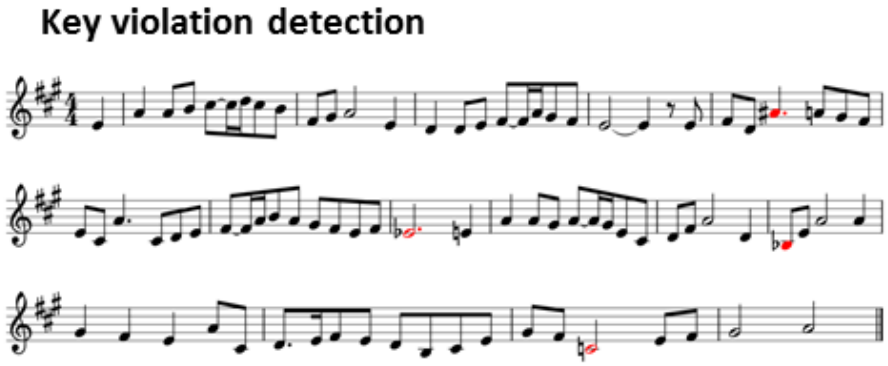


Figure 9 Examples of stimuli used in the key processing test



Note sequence presented in the key processing test with key-violating deviant notes shown in red (see 4.4.8 for further details)

4.4.9 Subject inclusion across tests

The tonal expectancy test was completed by all 66 participants who passed the pitch screen. The keys processing test was completed by 20 healthy control participants, 12 patients with AD, all patients with bvFTD, four patients with SD, six patients with PNFA and four patients with LPA.

4.4.10 Experimental procedure

For details of stimuli presentation, refer to General Methods (see 2.4 and 2.4.1)

4.4.11 Analysis of behavioural data

Please refer to General Methods (see 2.8) for details of statistical analyses used. For the tonal expectancy test, individual pleasantness ratings for melodies were first dichotomised based on a rating ≥3 ('pleasing') or <3 ('not pleasing') in order to avoid over-estimating the effect of gradations of pleasantness. Logistic regression was used to analyse accuracy of melody classification (correct versus incorrect) and pleasantness ratings ('not pleasing' versus 'pleasing'), first comparing groups overall and if significant overall effects were found, proceeding to pairwise group comparisons. An interaction term was included to examine whether there was differential performance between groups by melody type ('finished' versus 'unfinished').

For the key processing task, performance data were first transformed to individual corrected scores for detection of key violations (as detailed in General Methods (see 2.9.2)). Participant groups' deviation detection data were compared using a multiple linear regression model with robust standard errors as described in General Methods (see 2.9.1). The covariates of no interest which were included were those used in all chapters using auditory stimuli; as described in General Methods (see 2.9.4).

Post hoc analyses were performed as described in General Methods (see 2.9.5) to assess the extent of any correlation between tonal expectancy and key processing performance and any correlation of performance on each musical task with years of prior musical training and general executive function (WASI Matrices score, a measure of overall disease severity).

4.4.12 Brain image acquisition and analysis

Brain MRI data were acquired and preprocessed for 34 patients (12 AD, 11 bvFTD, five SD, six PNFA) according to General Methods (see 2.6 and 2.7).

In separate design matrices, voxel intensity (an index of grey matter volume) was modelled as a function of each music behavioural characteristic which showed a group difference in the behavioural analysis. The selection and incorporation of nuisance covariates in all matrices is described in General Methods (see 2.7).

4.5 Results

4.5.1 General participant characteristics

Patient and healthy control groups were well matched for age (p=0.30), gender (p = 0.25), educational background (χ^2 = 7.26, *P* = 0.2) and musical training (χ^2 =2.32, *P* = 0.8) and syndromic groups did not differ in mean symptom duration (χ^2 = 3.32, *P* = 0.5) (Table 12). Peripheral hearing function varied between participant groups (combined audiometric tone detection score, see Table 13; overall F[5, 57] =6.3, p<0.001), however the absolute value of the functional discrepancy was small and there was no significant correlation between peripheral hearing and accuracy on the tonal expectancy task over the entire participant group (rho=-0.13, p=0.31) nor within the combined patient cohort (rho = -0.09, p=0.56).

Table 13 Summary of peripheral hearing function in participant groups

Audiometry parameter	Healthy controls	bvFTD	SD	PNFA	LPA	AD
Summed score	10.8 (0.5)	11.5 (0.4)	11.1 (0.2)	11.3 (0.6)	11.5 (0.6)	10.8 (0.7)
Comparison with healthy controls: p value		**<0.001**	0.08	0.10	**0.02**	0.68

For further information regarding data in tables see 2.10.1. Overall mean (s.d.) natural log summed audiometry scores (see 4.4.2) for each participant group and pairwise regression comparisons (covaried for age) of patient groups versus the healthy control group are presented.

4.5.2 Tonal expectancy processing

Individual raw data are summarised in Figure 10 and Figure 11. Group raw data are shown in Table 14. Disease group performance profiles relative to healthy controls on tonal expectancy tasks are summarised in Table 15.

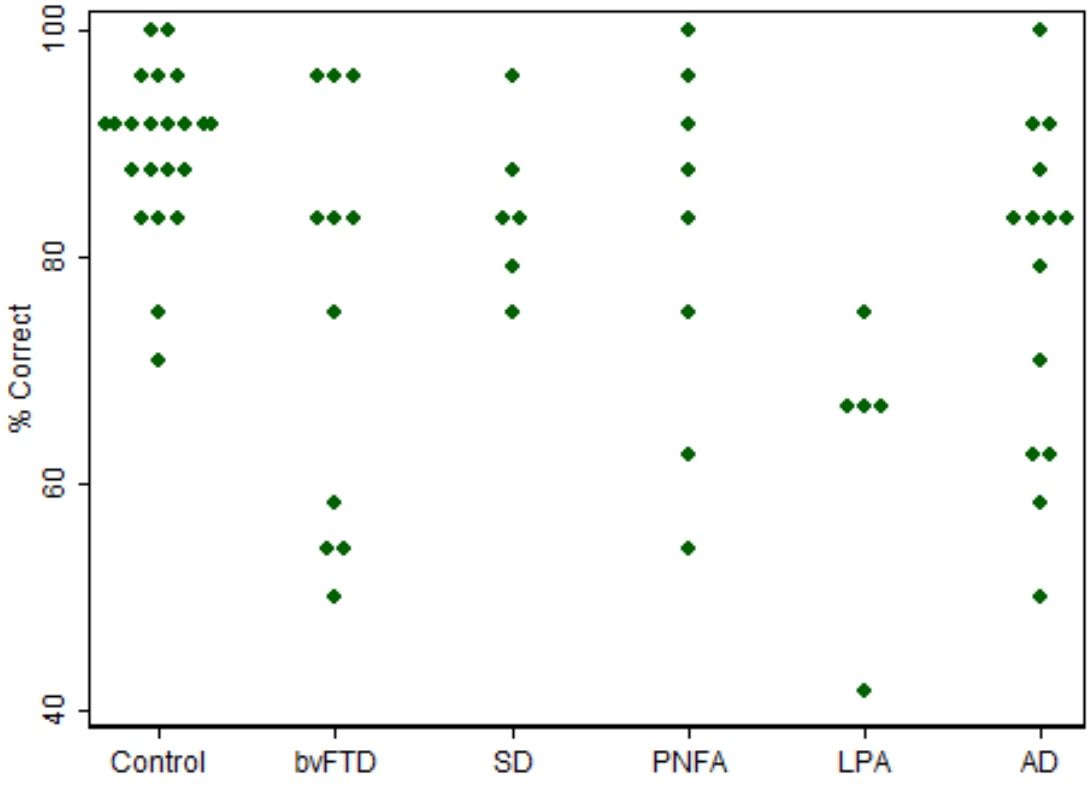
There was evidence of an overall group performance difference in the odds of correctly classifying melodies as 'finished' or 'unfinished' ($p=0.005$; Table 15, Figure 10). Relative to the healthy control group, the bvFTD, LPA and AD groups each showed overall significantly less accurate classification of melodies ($p<0.05$). Comparing syndromic groups, the LPA group showed significantly less accurate classification of melodies than the PNFA group ($p=0.04$). The differential accuracy of classifying melodies as 'finished' versus 'unfinished' also differed overall between groups ($p=0.006$). Whereas healthy controls were equivalently accurate in classifying 'finished' and 'unfinished' melodies (OR=1.4 [CI=0.7-2.9] $p=0.38$), classification of 'finished' (though not 'unfinished') melodies was significantly less accurate for the bvFTD group ($p=0.007$), the LPA group ($p=0.026$) and the AD group ($p=0.002$) than the healthy control group. The AD group was significantly less accurate classifying 'finished' than 'unfinished' melodies ($p<0.001$) and this performance discrepancy was significantly greater for the AD group than the healthy control group ($p=0.026$) and the PNFA group ($p=0.001$). Accuracy of melody classification by the patient cohort did not correlate with prior musical training (rho =0.2, $p=0.11$) or general executive function (WASI Matrices score, rho=-0.05, $p=0.69$).

There was evidence of an overall group difference in pleasantness ratings of 'unfinished' versus 'finished' melodies based on their endings ($p<0.0001$; Table 15, Figure 11). The healthy control group was significantly more likely to rate 'unfinished' than 'finished' melodies as 'not pleasing' OR 7.7 [CI 3.8-15.6]; the ranges of individual raw healthy control ratings for 'finished' and 'unfinished' melodies overlapped (Figure 11, Table 14), suggesting that controls did not simply rate melodies to align explicitly with their melody label. The bvFTD, SD and LPA groups rated 'finished' and 'unfinished' melodies more similarly than did healthy controls. Each of these syndromic groups showed significantly less discrepant pleasantness rating profiles than did the healthy control group ($p<0.05$). In addition, the SD group and the LPA group were each significantly less likely to rate 'unfinished' melodies as 'not pleasing' compared to healthy controls ($p<0.01$). The PNFA and AD groups showed a pleasantness rating profile similar to

healthy controls. Comparing syndromic groups, the bvFTD, SD and LPA groups each showed pleasantness rating profiles significantly different to the PNFA group ($p<0.02$) while the SD and LPA groups each showed pleasantness rating profiles significantly different to the AD group ($p<0.01$).

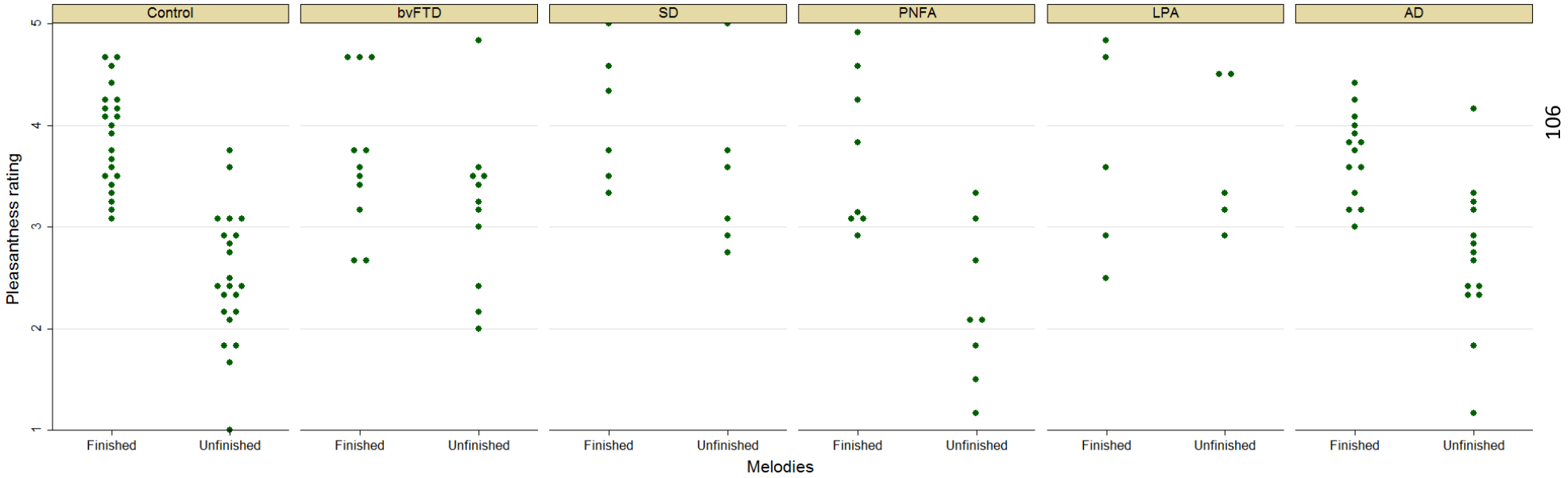
A post hoc analysis of the genetic subgroups with *MAPT* and *C9orf72* mutations using the same statistical models as the main analysis revealed abnormalities of melody classification and pleasantness rating in both subgroups relative to the healthy control group (Table 16). Direct comparison of the mutation subgroups revealed no significant differences, but a borderline significant trend ($p=0.054$) for the *C9orf72* mutation subgroup to rate unfinished melodies as more pleasing than did the *MAPT* mutation subgroup.

Figure 10 Individual accuracy scores for classifying melodies as 'finished or 'unfinished'



For further information about presentation of figures please see 2.10.2. Data is plotted as proportion of trials correct, for all participants (maximum score /24; proportion correct 0.5 corresponds to chance performance)

Figure 11 Individual pleasantness rating scores for 'finished' and 'unfinished' melodies are shown for all participants



For further information about presentation of figures please see 2.10.2. Melody pleasantness was scored on a Likert scale (1, not at all pleasing; 5, very pleasing; see Figure 2) and each point represents the mean rating for that participant for that melody ending type

Table 14 Summary of performance (raw data) on music cognition tests for all patient groups relative to healthy controls

Musical measure	Healthy controls	bvFTD	SD	PNFA	LPA	AD
Tonal expectancy task						
Accuracy classifying melodies						
All	0.89 (0.31)	**0.75 (0.43)**	0.84 (0.37)	0.81 (0.39)	**0.63 (0.48)**	**0.78 (0.42)**
Finished	0.88 (0.33)	**0.64 (0.48)**	0.82 (0.39)	0.84 (0.37)	**0.57 (0.50)**	**0.65 (0.48)**
Unfinished	0.91 (0.29)	0.87 (0.34)	0.86 (0.35)	0.78 (0.42)	0.70 (0.46)	0.90 (0.29)
Pleasantness rating of melodies						
All	3.2 (1.2)	3.4 (1.0)	**3.8 (1.0)**	3.0 (1.3)	**3.7 (1.2)**	3.2 (1.3)
Finished	3.9 (1.1)	3.7 (1.0)	4.1 (0.9)	3.7 (1.1)	3.7 (1.3)	3.7 (1.2)
Unfinished	2.5 (1.0)	3.2 (0.9)	**3.5 (1.0)**	2.1 (1.0)	**3.7 (1.2)**	2.7 (1.2)
Key violation detection task						
Corrected deviant detection score	0.83 (0.12)	**0.41 (0.35)**	**0.48 (0.36)**	0.51 (0.26)	**0.12 (0.29)**	0.57 (0.35)

For further information regarding data in tables see 2.10.1. maximum score /24); pleasantness ratings are mean (s.d.) Likert scores (see Figure 2). For key processing data, corrected scores for detection of key violations (see General Methods 2.9.2). See 4.4.5 for further details of conditions, Figure 10 and Figure 11 for individual data plots

Table 15 Summary of performance on music cognition tests for all patient groups relative to healthy controls

Test parameter	bvFTD	SD	PNFA	LPA	AD
Tonal expectancy task					
Accuracy classifying melodies					
All	**0.45 (0.25-0.82)**	0.59 (0.30-1.18)	0.64 (0.28-1.44)	**0.32 (0.16-0.63)**[a]	**0.54 (0.33-0.87)**
Interaction	2.9 (0.91-9.0)	1.0 (0.2-4.8)	0.50 (0.18-1.4)	1.3 (0.31-5.4)	**3.8 (1.2-12.4)a**
Finished	**0.3 (0.13-0.72)**	0.59 (0.19-1.87)	0.89 (0.41-1.94)	**0.28 (0.09-0.86)**	**0.33 (0.16-0.66)**
Unfinished	0.86 (0.41-1.82)	0.59 (0.23-1.49)	0.44 (0.14-1.40)	0.37 (0.15-2.96)	1.3 (0.53-2.96)
Rating of melodies as 'not pleasing'					
All	0.46 (0.14-1.5)	**0.17 (0.05-0.60)**[a,b]	1.18 (0.53-2.59)	**0.24 (0.06-0.95)**[a]	0.79 (0.37-1.7)
Interaction	0.30 (0.11-0.85)[a]	**0.19 (0.09-0.39)**[a,b]	1.78 (0.41-7.80)	**0.09 (0.026-0.33)**[a,b]	0.65 (0.24-1.7)
Finished	1.04 (0.31-3.48)	0.54 (0.16-1.87)	0.87 (0.35-2.18)	1.08 (0.28-4.17)	1.08 (0.44-2.64)
Unfinished	0.31 (0.09-1.12)	**0.10 (0.03-0.35)**	1.55 (0.48-5.03)	**0.10 (0.02-0.52)**	0.70 (0.28-1.71)
Key violation detection task					
Mean difference in proportion correct	**-0.47 (-0.68 to-0.25)**	**-0.31 (-0.55 to -0.08)**	-0.22 (-0.46 to 0.03)	-0.43 (-0.87 to 0.00)[£]	-0.19 (-0.40 to 0.02)

For further information regarding data in tables see 2.10.1. For tonal expectancy test data, OR (CI) are shown for correctly classifying melodies as 'finished' versus 'unfinished' and for rating the endings of melodies as 'not pleasing' versus 'pleasing' (see 4.4.6), relative to the healthy control group; 'interaction' here represents the odds of a rating difference for 'finished' versus 'unfinished' melodies, expressed for each patient group relative to healthy controls. For key processing data, mean difference scores for detection of key deviants (see 4.4.2) are shown for each patient group relative to healthy controls. **a**, significantly different ($p<0.05$) from PNFA group; **b**, significantly different ($p<0.05$) from AD group; **£** $p=0.05$ relative to healthy control group

Table 16 Music processing data for genetic mutation subgroups

Musical measure	Healthy controls n = 22	C9orf 72 n = 4	MAPT n = 6
Tonal expectancy task			
Accuracy classifying melodies			
All	0.89 (0.31)	**0.74 (0.44)**	**0.77 (0.42)**
Finished	0.88 (0.33)	0.70 (0.46)	**0.68 (0.47)**
Unfinished	0.91 (0.29)	0.79 (0.41)	0.86 (0.35)
Pleasantness rating of melodies			
All	3.2 (1.24)	**3.5 (0.85)**	3.5 (1.11)[£]
Finished	3.9 (1.1)	3.6 (0.96)	3.8 (1.06)
Unfinished	2.5 (1.01)	**3.3 (0.62)**[¤]	3.2 (1.09)
Key violation detection task			
Corrected deviant detection score	0.83 (0.12)	**0.41 (0.22)**	**0.36 (0.41)**

For further information regarding data in tables see 2.10.1. maximum score /24); pleasantness ratings are mean (s.d.) Likert scores (see Figure 2). For key processing data, corrected scores for detection of key violations are shown (see 2.9.2). **£,** p=0.05 relative healthy controls; **¤,** borderline significant difference between mutation subgroups (p=0.054). *C9orf72* group contained four patients with clinical syndrome of bvFTD, one with PNFA; *MAPT*, all patients had a syndrome of bvFTD

4.5.3 Key processing

There was evidence of an overall group performance difference in accuracy of detecting key violations (p=0.0004; Table 15). Relative to the healthy control group, the bvFTD and SD groups showed significantly less accurate detection of key deviants (p<0.05); the LPA group showed a borderline significant deficit (p=0.05) while the AD group showed a non-significant trend towards a deficit (p=0.078) in detecting key deviants. Comparing syndromic groups, the bvFTD group performed significantly worse than the AD group (p<0.05); no other differences between patient groups were identified. Accuracy of key processing by the patient cohort correlated significantly with accuracy on the tonal expectancy task (rho=0.42, p=0.01) and with prior musical training (rho=0.58, p=0.001), but not with general executive function (WASI matrices score, rho=0.26, p=0.18).

4.5.4 Neuroanatomical associations

In the VBM analysis, grey matter associations were assessed for the combined patient cohort for; accuracy of melody classification as 'finished' or 'unfinished' (raw proportion score), altered pleasantness rating of melodies (relative likelihood of rating unfinished melodies as

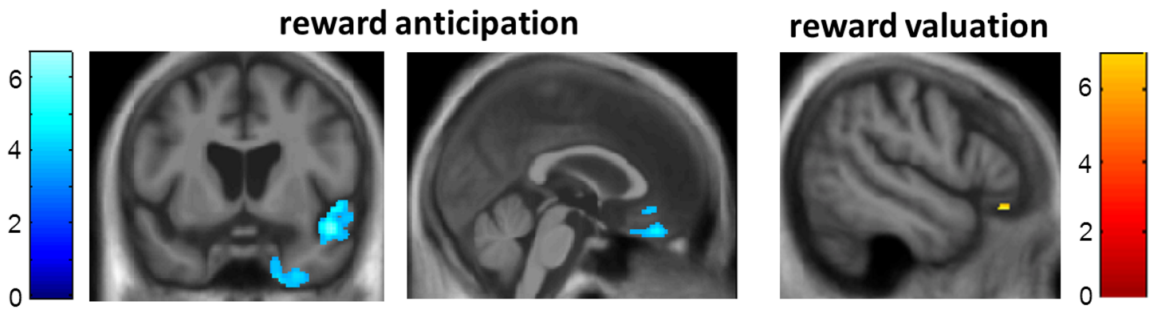
'not pleasing') and detection of key violations (corrected detection score, see 2.9.2). Significant neuroanatomical associations at the level of the whole brain (according to criteria specified in General Methods 2.7) are summarised in Table 17 and SPMs are presented in Figure 12.

Table 17 Summary of grey matter associations of tonal expectancy processing in patient cohort

Region	Peak coordinate (mm)			Z score	P value
	x	Y	z		
Accuracy of classifying melodies					
Entorhinal cortex	24	0	-50	5.22	0.008
Anterior STG	48	3	-18	4.94	0.025
Medial OFC	4	40	-22	4.92	0.028
Anterior superior temporal sulcus	56	-10	-8	4.91	0.029
Pleasantness rating of melodies					
IFG (pars orbitalis)	-51	33	-15	5.69	0.001

For further information regarding data in tables see 2.10.1. Statistically significant positive associations between grey matter volume and accuracy of classifying melodies ('finished' versus 'unfinished') and pleasantness rating of melodies (likelihood of rating unfinished melodies as 'not pleasing') are shown, based on a VBM analysis of brain MR images for the combined patient cohort (no patients with LPA were included in this analysis). No significant contrasts were identified for other musical processing tasks at the prescribed threshold

Figure 12 SPMs of regional grey matter volume positively associated with tonal expectancy parameters in the combined patient cohort



For further information about presentation of figures please see 2.10.2. T-scores are coded on the colour bars. Grey matter associations of accuracy of melody classification signify musical reward anticipation, coded in blue; grey matter associations of melody pleasantness rating signify musical reward valuation, coded in red-orange (see text for details). SPMs are overlaid on coronal (left) and sagittal (middle, right) sections of the mean brain MR image, selected to highlight right anterior superior temporal and entorhinal cortex (left), right medial OFC (middle) and left IFG or pars orbitalis (right) (see Table 17)

Significant positive associations between grey matter atrophy and impaired melody classification accuracy were identified in right entorhinal cortex, anterior STG, STS and medial OFC. A significant positive association between grey matter atrophy and abnormal pleasantness rating of melodies was identified in left IFG (pars orbitalis). No significant inverse associations were identified for either of these contrasts. No significant grey matter associations of key processing performance were identified for the combined patient cohort at the prescribed threshold.

4.6 Discussion

Here I have demonstrated profiles of reward anticipation and valuation based on the processing of tonal expectancy in music in patents with syndromes of FTLD and AD. These profiles varied between syndromic groups, in line with the experimental hypotheses. Relative to healthy controls, patients with bvFTD were less accurate in classifying melodies as resolved ('finished') or unresolved ('unfinished') based on tonal expectancy. I interpret this as evidence of impaired anticipation of musical reward. In addition, these patients rated unresolved and resolved melodies as more similar in overall pleasantness than did healthy controls. I interpret this as evidence of altered valuation of musical reward. In contrast, patients with SD showed melody classification performance (musical reward anticipation) similar to healthy controls but abnormal pleasantness ratings (musical reward valuation). Patients with typical AD showed the converse pattern of abnormal musical reward anticipation despite normal valuation, and patients with LPA showed a profile more similar to the bvFTD group. Patients with PNFA, considered as a group, showed a profile of musical reward processing similar to healthy controls. In line with previous work implicating orbitofrontal mechanisms in the processing of key relationships in the normal brain (Janata P *et al.* 2002), an additional deficit of key processing (detection of notes violating the prevailing key) was evident in the bvFTD and SD groups here. This test has some structural similarities to the perceptual incongruity test in Chapter 3 where SD patients performed as controls, indicating they have intact change detection in certain contexts. Accuracy of tonal expectancy (musical reward anticipation) was correlated with ability to detect key violations for the patient cohort as a whole. However, tonal expectancy was not correlated with prior musical expertise or general executive capacity. Taken together, these findings suggest that the tonal expectancy test indexed a relatively

specific impairment of musical reward processing. There was further qualified evidence for syndromic specificity of musical reward profiles, in that particular reward parameters differentiated PNFA and typical AD from other patient groups. Altered musical reward valuation in the bvFTD, SD and LPA groups here manifested as a blunting of the differential response to resolved and unresolved melodies. This effect was driven chiefly by the tendency of these patients to find unresolved (but not resolved) melodies relatively more pleasing than did healthy controls. In contrast, patients with bvFTD, LPA and typical AD classified resolved (but not unresolved) melodies less accurately than did healthy controls. Taken together, these profiles argue for dissociable cognitive profiles of musical reward anticipation and valuation across dementia syndromes.

These syndromic profiles for music resonate with reward processing behaviours exhibited by patients in various other experimental and social contexts. Patients with bvFTD show increased risk taking behaviour and reduced anticipation of future regret (aberrant reward prediction) (Rahman S *et al.* 1999; Torralva T *et al.* 2007; Bertoux M et al. 2014), and insensitivity to biological stimulus cues such as satiety after consuming carbohydrate-rich foods or somatic pain (abnormal reward valuation) (Ahmed RM *et al.* 2014; Ahmed RM, V Iodice*, et al.* 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JD Rohrer*, et al.* 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015; Ahmed RM *et al.* 2016). Patients with SD show abnormal valuation of biological stimuli (Ahmed RM *et al.* 2014; Ahmed RM, V Iodice*, et al.* 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JD Rohrer*, et al.* 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015; Ahmed RM *et al.* 2016) and musicophilia (Fletcher PD *et al.* 2013). Decision making based on anticipation of future alternatives (reward anticipation) in SD may be loaded on semantic task demands with evidence for preserved performance when semantic impairment is taken into account (Irish M *et al.* 2011; Irish M *et al.* 2012; Irish M and P Piolino 2016). In contrast to the situation in SD, and in line with their mirrored pattern of performance on the tonal expectancy task here, patients with AD have difficulty using rules to make decisions about future outcomes (deficient reward anticipation), but remain sensitive to affective outcomes (reward value), particularly where these are negatively valenced (Delazer M et al. 2007; Dohnel K et al. 2008; Sinz H et al. 2008). In

everyday life, this may translate to behaviour that is not obviously 'risky' or misdirected, but nevertheless dysfunctional and maladaptive (Irish M and P Piolino 2016).

While reward processing in PPA has not been studied in detail, our findings are consistent with limited previous evidence in these syndromes. Beyond the domain of music, complex abnormalities of emotional behaviour have been documented in LPA, and these patients appear to lack sensitivity to the reward value of biological (flavour) cues (Piwnica-Worms KE *et al.* 2010; Rohrer JD *et al.* 2010). However, PNFA appears to be associated with a lower frequency of daily life hedonic abnormalities than other dementia syndromes (Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JD Rohrer*, et al.* 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015).

Given wide individual variation (Figure 10 and Figure 11), caution is needed in attempting to generalise group profiles of musical reward processing, particularly in more heterogeneous syndromes. Some of this variation may have a molecular basis. Though case numbers were small, the present data raise the possibility of differential musical hedonic profiles associated with *C9orf72* and *MAPT* mutations, perhaps analogous to other hedonic domains (Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JD Rohrer*, et al.* 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015).

The neuroanatomical correlates of altered musical reward processing identified in the present patient cohort corroborate and extend other evidence for reward network breakdown in these diseases (Perry DC *et al.* 2014; Perry DC *et al.* 2015). Impaired accuracy of tonal expectancy judgments (classification of melodies) was associated with grey matter loss in right anterior superior and inferior temporal cortices and medial OFC, in line with previous work in the healthy and damaged brain (Peretz I *et al.* 2001; Koelsch S *et al.* 2006; Khalfa S et al. 2008; Fujisawa TX and ND Cook 2011; Hailstone JC et al. 2011; Omar R, SM Henley*, et al.* 2011; Hsieh S *et al.* 2012; Koelsch S, M Rohrmeier, et al. 2013; Salimpoor VN *et al.* 2013; Seger CA *et al.* 2013; Bonfiglio L et al. 2015). This brain network may link association cortical mechanisms mediating the structural analysis of melodies and harmonic hierarchies with paralimbic and orbitofrontal mechanisms mediating the cognitive representation and prediction of emotion and reward. Extracting regularities from the environment to make predictions for the future is

an underlying central mechanism of allowing us to predict other's behaviours and central to functions such as theory of mind. The impairment the bvFTD group show in anticipation here, may be a marker of a pervasive deficit in this generic cognitive process.

Altered pleasantness rating of melodies (a tendency to rate unresolved melodies as less unpleasant than did healthy controls) was here associated with grey matter loss in left IFG (pars orbitalis). Functionally, this region behaves as a subdivision of lateral OFC and links cortical mechanisms analysing hierarchical and rule-based patterns (such as linguistic and musical 'syntax') with mechanisms representing reward value. It has been implicated previously in representing musical tension associated with violation of harmonic expectancy (Lehne M et al. 2014) and musical rhythmic structures (Vuust P et al. 2014). Considered together, these neuroanatomical findings suggest that subregions of medial and lateral OFC are integrally involved in the anticipation and valuation of musical reward. The precise functions of these subregions continue to be defined. Under normal circumstances, these areas operate together in the anticipation, representation and valuation of reward across modalities and behavioural contexts (Li Y *et al.* 2016). Medial OFC has been particularly implicated in the obligatory integration of external stimulus features with homeostatic and behavioural goals in the computation of subjective value, while lateral OFC has been implicated in reward prediction and prediction error coding (Lehne M *et al.* 2014; Abitbol R et al. 2015; Li CW et al. 2015; Sachs ME et al. 2016; Tobler PN et al. 2016). I did not find neuroanatomical correlates in striatal or other subcortical structures previously implicated in processing musical reward (Omar R, SM Henley*, et al.* 2011; Salimpoor VN *et al.* 2013; Li CW *et al.* 2015). Previous studies have generally employed music holding personal significance for the participants, perhaps implying that other motivational, emotional or subjective factors engage these subcortical mechanisms. In addition, this study was not equipped to detect connectivity shifts between regions that signal musical reward in the healthy brain (Salimpoor VN *et al.* 2013; Sachs ME *et al.* 2016).

This study has several limitations and suggests a number of directions for future work. Larger patient cohorts will be required to characterise the specificity of musical reward phenotypes for particular diseases while taking account of intrinsic individual variation in the hedonic valuation of music (Clark CN, LE Downey and JD Warren 2014; Salimpoor VN *et al.* 2015; Sachs

ME *et al.* 2016). This may allow further stratification of pathologically and genetically diverse syndromes, such as bvFTD and PNFA. Acknowledging these caveats, the present findings provide a case for music as a useful probe of aberrant reward processing and associated complex behavioural disturbances in dementias.

This chapter proposes music as a model system to demonstrate abnormalities in reward anticipation and valuation across FTLD and AD. Here, the manipulation of tonal expectancy in simple melodies engaged brain mechanisms similar to those engaged by cognitive representation and prediction of emotion and reward. In the next chapter, I exploit the paradigm of humour to investigate generic processing of situational incongruity, template matching and novelty detection to capture brain mechanisms of incongruity detection and resolution.

5 HUMOUR PROCESSING IN FTLD: A BEHAVIOURAL & NEUROANATOMICAL ANALYSIS

5.1 Chapter Summary

Humour is a complex cognitive and emotional construct, which I have utilised to capture brain mechanisms of incongruity detection and resolution. Humour deficits can occur in FTLD, but have been poorly understood. Here I assessed humour processing in patients with bvFTD (n=22, mean age 67 years, four female) and SD (n=11, mean age 67 years, five female) relative to healthy individuals (n=21, mean age 66 years, 11 female), using a joint cognitive and neuroanatomical approach. I created a novel neuropsychological test requiring a decision about the humorous intent of nonverbal cartoons, in which I manipulated orthogonally humour content and familiarity of depicted scenarios. Structural neuroanatomical correlates of humour detection were assessed using VBM. Assessing performance in a signal detection framework and after adjusting for standard measures of cognitive function, both patient groups showed impaired accuracy of humour detection in familiar and novel scenarios relative to healthy older controls. Patient groups showed similar overall performance profiles; however the bvFTD group alone showed a significant advantage for detection of humour in familiar relative to novel scenarios, suggesting that bvFTD may lead to particular difficulty decoding novel situations for humour while SD produces a more general deficit of humour detection that extends to stock comedic situations. Humour detection accuracy was associated with grey matter volume in a distributed network including TPJ and anterior superior temporal cortices, with predominantly left-sided correlates of processing humour in familiar scenarios and right-sided correlates of processing novel humour. The findings quantify deficits of core cognitive operations underpinning humour processing in FTLD and suggest a candidate brain substrate in cortical hub regions processing incongruity and semantic associations.

5.2 Introduction

Humour is a multidimensional cognitive and emotional construct that is vulnerable in neurodegenerative diseases, notably FTLD, but incompletely understood (Warren JD, JD Rohrer and MN Rossor 2013). Aside from its relevance to clinical symptoms, humour is an attractive candidate model with which to analyse the neuropsychological and neurobiological

bases of social cognitive dysfunction in these syndromes. Difficulty with prediction generation and matching to learnt expectations (Chapter 3 and 4), shifting perspective and impaired use of context may underpin inter-personal difficulties of various kinds experienced by patients with FTLD (Ibanez A and F Manes 2012). Humour is likely *a priori* to be a sensitive index of these processes.

The literature includes a diversity of stimuli and paradigms that have been used to assess humour processing in health and disease (Coulson S and M Kutas 2001; Goel V and RJ Dolan 2001). Cartoon stimuli have been used to probe theory of mind processing and sarcasm in patients with bvFTD and SD (Snowden JS *et al.* 2003; Lough S *et al.* 2006; Ehrlé N *et al.* 2011; Irish M *et al.* 2014). However, such processes are themselves complex constructs and vulnerable to associated cognitive deficits (such as verbal semantic impairment) besides any specific impairment of humour processing *per se*.

There is presently no standard, widely accepted cognitive model of humour processing, nor any agreed terminology of the processes involved (Shammi P and DT Stuss 1999). Jokes and cartoons involve a surprising or apparently incongruous situation that has deviated from expectations, forcing a reappraisal of the situation and frame shifting to a previously neglected explanation which resolves the incongruity and re-establishes coherence. This resolution process has strong links to our reward system akin to novel problem solving in crosswords (Amir O *et al.* 2015) or music (Salimpoor VN *et al.* 2015).

In the healthy brain, anatomical correlates of humour cognition relate to a temporo-parietal-occipital network which shares extensive overlap with the fronto-temporo-parietal networks implicated in bvFTD and SD, a generic function of which could be deemed as detection and resolution of incongruity (Michelon P *et al.* 2003; Chan YC, TL Chou, HC Chen, YC Yeh*, et al.* 2012; Zhou J et al. 2012; Watanabe T *et al.* 2014). The region of the temporo-parieto-occipital junction (especially in the left cerebral hemisphere), may mediate humour detection and analysis of potentially humorous (in particular, incongruous) stimuli based on prior expectations and stored concepts (Goel V and RJ Dolan 2001; Moran JM *et al.* 2004; Franklin RG, Jr. and RB Adams, Jr. 2011; Neely MN et al. 2012). This may be particularly pertinent to the primitive humour associated with physical comedy (slapstick), which relies on the violation of

physical or social norms. Antero-medial and ventral temporal lobe areas and their inferior frontal lobe projections are likely to be engaged in humour comprehension, with accompanying incongruity resolution and semantic (including social conceptual) evaluation (Moran JM *et al.* 2004; Bartolo A *et al.* 2006; Samson AC *et al.* 2009; Zahn R, J Moll, V Iyengar*, et al.* 2009; Chan YC, TL Chou, HC Chen, YC Yeh*, et al.* 2012). ACC has been implicated in linking salient (especially, apparently incompatible or surprising) sensory and cognitive features of humorous stimuli with emotional coding of 'funniness' (Kohn N et al. 2011; Du X et al. 2013). vmPFC has shared functions with the ACC when processing, and more specifically analysing, mental states embodied in humour (Coulson S and M Kutas 2001; Kohn N *et al.* 2011; Du X *et al.* 2013). The striatal and mesolimbic forebrain may mediate the subjective amusement of a joke (Goel V and RJ Dolan 2001; Mobbs D et al. 2003; Franklin RG, Jr. and RB Adams, Jr. 2011).

Much early work on the neurology of humour in disease draws on a very broad anatomical distinction between the right and left cerebral hemispheres (Gardner H et al. 1975; Bihrle AM et al. 1986) which could loosely map onto bvFTD and SD respectively. Damage involving the non-dominant hemisphere (particularly the frontal cortex and anterior temporal lobe) often degrades the appreciation of humour (Gardner H *et al.* 1975; Shammi P and DT Stuss 1999). In these patients, amusement dissociates from comprehension of jokes, perhaps reflecting a more general deficit in linking cognitive appraisal with appropriate emotional responses. These patients may be unable to discriminate between punchlines (incongruity resolution) and *non sequitur* endings (incongruity detection without resolution) to jokes. Damage involving right frontal polar cortex impairs appreciation of more complex jokes while leaving responses to slapstick scenarios largely unscathed (Shammi P and DT Stuss 1999). This could perhaps reflect an inability to resolve incongruity in novel contexts. This contrasts to patients with dominant hemisphere damage who tended to prefer coherent, but unsurprising (and unfunny) endings (Bihrle AM *et al.* 1986). This reliance on decoding of incongruity, ambiguity and conflict may account for the fundamental role of humour processing during human social development (Gervais M and DS Wilson 2005; Neely MN *et al.* 2012).

The design was motivated by cognitive models of humour processing (Degabriele J and IP Walsh 2010; Vrticka P *et al.* 2013) that emphasise resolution of incongruity as a unifying principle of humour comprehension and work indicating that detection and resolution of

incongruity is a generic function of fronto-temporal parietal networks implicated in bvFTD and SD (Michelon 2003; Chan 2012; Zhou 2012, Watanabe 2014). I utilised the distinction between familiar and novel humorous scenarios; mapping broadly onto a distinction between scenarios that represent incongruous physical elements (a key characteristic of 'slapstick' humour) versus scenarios that juxtapose incongruous psychological elements such as concepts, beliefs or motivations (a characteristic of more complex humour) (Vrticka P *et al.* 2013). I did not in this study address the behavioural or brain correlates of amusement *per se,* as the cognitive analysis of humour and its emotional correlates are likely to be separately vulnerable to the effects of neurodegenerative disease (Bartolo A *et al.* 2006; Downey LE *et al.* 2013; Mensen A et al. 2014; Campbell DW et al. 2015).

5.3 Experimental Hypotheses

i) bvFTD patients have preserved recognition of slapstick humour (as represented in the familiar joke scenarios) and an impaired ability to recognise novel joke scenarios owing to a failure of incongruity resolution, given the known deficit in sarcasm processing in bvFTD (Kipps CM *et al.* 2009) and that right hemisphere damage prevents discrimination between punchlines (incongruity resolution) and *non sequitur* endings of jokes (incongruity detection) (Bihrle AM *et al.* 1986; Shammi P and DT Stuss 1999).

ii) SD patients have an impaired ability to detect joke scenarios across categories (novel and familiar) as patients with left hemisphere damage tend to prefer coherent but unsurprising (and unfunny) endings when completing the endings of jokes (Bihrle AM *et al.* 1986).

iii) The changes demonstrated in i) and ii) arise from distinct neuroanatomical correlates mediating these processes. Altered humour processing is associated with a distributed neuroanatomical network with key "hubs"; temporo-parieto-occipital junction (incongruity detection), anterior temporal lobe (category processing of familiar versus novel humour), vmPFC and ACC (novel cartoons requiring a psychological perspective shift).

5.4 Methods

5.4.1 Participants

22 patients with bvFTD (mean age 67 years, s.d. 7.7 years, four female), 11 patients with SD (mean age 67 years, s.d. 7.7 years, five female) and 21 healthy individuals (mean age 66 years, s.d. 5 years, 11 female) participated. All participants were recruited according to the specifications in General Methods (see 2.1). Participant characteristics are summarised in Table 18. All participants had lived most of their adult lives and the majority had also grown up (to age 16 years) in the United Kingdom. The patient cohort included 13 cases with confirmed pathogenic mutations (six *MAPT*, seven *C9orf72*). CSF analysis or 18F-amyloid PET imaging in 11 other cohort members provided no evidence for underlying AD (see General Methods 2.3 and Table 2 in Appendix for further information).

5.4.2 Neuropsychometry

Of the psychology tests administered to all participants (see General Methods 2.2) those that were deemed most pertinent for the humour paradigm included; the object decision subtest of the VOSP battery (visuoperceptual); the Trails test (task-switching) and BPVS (a general cross-modal measure of semantic memory); TASIT (decoding of sarcastic intent) (McDonald S *et al.* 2006) and the size-weight attribute test (see General Methods 2.2) (a control for semantic processing of cartoon stimuli in patients with SD).

5.4.3 Experimental design

To assess humour processing I designed a series of simple non-verbal cartoons, each requiring a forced-choice decision (whether or not the scenario was intended to be humorous). This design reflected the primary focus on the cognitive elements of humour rather than an indicator of subjective amusement. Four conditions were combined in a factorial design comprising cartoons that were intended to be either humorous or non-humorous and to represent familiar or novel scenarios (see Figure 13). The experimental design allowed me to control stimulus characteristics between cartoon conditions while minimising any dependence on language processing.

Table 18 Participant demographic, clinical and general neuropsychological characteristics

Characteristic	Healthy controls	bvFTD	SD
General			
No., gender (M:F)	21 (10:11)	22 (18:4)	11 (6:5)
Handedness (R:L)	18:3[¥]	20:1	10:1
Age (yrs)	66 (5)	67 (7.7)	67 (7.7)
Education (yrs)	15.7 (1.9)	**13.9 (3.0)**	**13.1 (2.5)**
Background (UK&Eire:other) [α]	19:2[β]	19:3[γ]	10:1[δ]
Symptom duration (yrs)	N/A	9 (5.4)	5.5 (3.0)
MMSE (/30)	N/A	25 (3.5)	18 (8.1)
Background neuropsychology			
General intellect			
VIQ	123 (6.4)	**84 (20.6)**	**69 (15.5)** [c]
PIQ	126 (9.7)	**98 (19.6)**	**107 (20.2)**
WASI Vocabulary (/80)[¥]	71.4 (3.8)	**38.5 (20.1)**	**23.1 (19.8)** [c]
WASI Block Design (/71)	33.4 (18.7)	40 (19.3)	38.2 (18.5)
WASI Similarities (/48)	42.1 (3.3)	**25.2 (11.1)**	**15.5 (10.6)** [c]
WASI Matrices (/42)	26.8 (2.9)	**17.1 (7.5)**	21.7 (6.9)
Executive functions			
Verbal fluency (/min)	16.3 (4.7)	**8 .3 (3.9)**	**7.4 (5.3)**
Stroop (ink colour)(sec)	53.7 (10.8)	**98.9 (41.2)**	**96.8 (54.1)**
Trails (B-A difference) (sec)	36 (24)	**140 (89)**	**113 (98)**
Digit span reverse (/12)	7.3 (1.9)	6.4 (2.2)	6.3 (3.0)
Episodic memory			
Digit span forward (/12)	8.9 (2.0)	7.9 (2.2)	6.6 (2.4)
RMT Words (/50)	47.6 (2.2)	**34.3 (7.3)**	**31.3 (7.2)**
RMT Faces (/50)	45.8 (5.0)	**32.8 (7.0)**	**34.3 (11.2)**
Language and literacy function			
GNT (/30)	27.8 (1.9)	**10.5 (9.3)**	**1.1 (2.2)** [c]
Reading (NART) (/50)	44.1 (3.0)	**29.2 (12.9)**	**22.4 (19.0)**
Arithmetic (GDA) (/24)	15.1 (4.4)	**10 (7.6)**	**9.3 (7.5)**
Semantic memory			
BPVS (/150)	147.9 (1.8)	**129.7 (17.7)**	**78.3 (46.3)** [c]
Size-weight attributes[ǂ](/60)	57.4 (2.3)	N/A	49.1 (11.6)[ǂǂ]
Visuoperceptual functions			
VOSP object decision (/20)	18.5 (1.7)	17.2 (1.8)	**16.9(2.4)**
Unusual views (20)	17 (2.3)	**10 (4.5)**	**7 (6.1)**
Usual views (20)	20 (0.3)	**17 (3.8)**	**17 (2.5)**
Social cognition			
TASIT (Emotion) (/14)	11.4 (0.7)	**6.8 (2.5)**	N/A
TASIT (Social Inference) (/36)	31.4 (2.2)	**20.9 (5.4)**	N/A

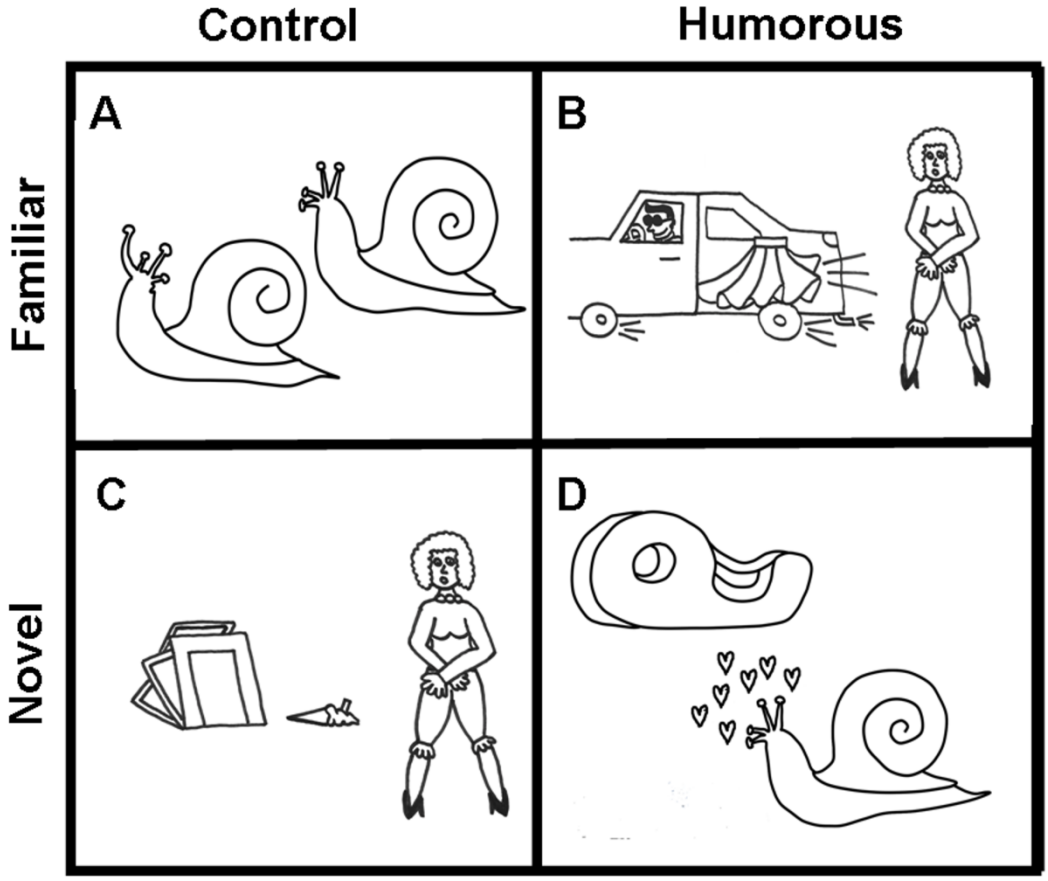
For further information regarding data in tables see 2.10.1, for demographics and neuropsychology (see 4.4.4 and Table 2). **¥**, one person from this group classified themselves as ambidextrous; **c**, mean difference between patient groups statistically significant ($p<0.05$); **ɣ,** scores referenced to separate historical healthy control group (n=40; age range 45-79 years; Professor EK Warrington, personal communication); **ǂ,** total score referenced to age range 56-83 years; **ǂǂ,** 7 patients completed this test; **α**, where lived to age 16; **β**, one North America, one other Western European country; **γ**, one North America, two other Western European countries; **δ**, one South Africa

Following review of published cartoon collections directed at adults or children, I adapted or generated de novo scenarios employing nonverbal humour in order to create an initial set of 180 new cartoons. All were line drawings without captions, each comprising a single frame depicting human and/or animal characters interacting with each other or with the physical environment. 'Familiar' humorous cartoons were designed to depict stock comedic situations, variants of which appear frequently in Western culture (e.g., the central character suffers some misadventure, such as slipping on a banana peel or having undergarments exposed in public; see panel B in Figure 13); while 'novel' humorous cartoons were designed to depict novel comedic scenarios relying on some active shift in viewer perspective (e.g., a snail declares his love for a tape dispenser; see panel D in Figure 13). Familiar humorous cartoons emphasised conventionally incongruous physical ('slapstick') elements; resolvable as humorous based on previously learned associations; whereas novel humorous cartoons emphasised resolution of apparently incongruous concepts as humorous based on interpretation of characters' beliefs or motives. Structural elements of humorous cartoons were rearranged to create matching non-humorous control cartoons balanced for perceptual features, semantic associations of individual elements and affective cues such as facial expressions. Control cartoons for familiar humorous scenarios depicted commonly-encountered, congruous everyday scenarios not normally considered humorous (see panel A in Figure 13), while control cartoons for novel humorous scenarios depicted bizarre incongruities that lack any clear resolution (see panel C in Figure 13).

5.4.4 Pilot experiment

14 healthy older individuals (mean age 60 (s.d. 4.1) years, eight female) of British or Western European cultural background participated in the initial pilot experiment. For each cartoon stimulus (n=180), participants were asked to decide whether or not it was intended to be humorous, whether or not the scenario depicted was familiar and the degree of amusement and physical humour on a Likert scale (see Figure 2 and General Methods 2.5). Based on these data a subset of 60 cartoons was selected such that each achieved >75% consensus on whether it represented a humorous or non-humorous scenario for presentation in the main experiment. Characteristics of the experimental stimulus set are summarised in Table 19.

Figure 13 Examples of captionless cartoon stimuli representing each experimental condition



Non-humorous control (A, C) and humorous (B, D) cartoon categories are shown. Features of humorous cartoons were rearranged to create familiar congruous (A) or unresolvably incongruous (C) non-humorous control scenarios (see 5.4.3 for further details)

Owing to a non-normative distribution of data, the analysis of pilot data was performed using the Wilcoxon rank-sum test.

Cartoons representing humorous scenarios were rated by pilot controls as significantly ($p<0.001$) more amusing than control cartoons representing non-humorous scenarios, while familiarity of the cartoon scenarios differed significantly between conditions ($p<0.001$, in ascending order of familiarity (corresponding panel in Figure 13): novel control (C) < novel humorous (D) < familiar control (A) < familiar humorous (B). In addition, cartoons depicting familiar humorous scenarios were rated as having significantly more prominent elements of physical humour generally associated with farce or 'slapstick' than cartoons depicting novel humorous scenarios ($p<0.001$). Subsequent *post hoc* testing established strong consensus

between this pilot control group and the main experimental healthy control group in classifying cartoon scenarios as humorous versus non-humorous (inter-group correlation Spearman's correlation coefficient = 0.70, p <0.001) and categorisation of joke stimuli as familiar versus unfamiliar (Spearman's correlation coefficient = 0.89, p < 0.001).

Table 19 Summary of characteristics of the experimental stimulus conditions

Cartoon condition	No.	Category[h]	Familiarity[j]	Amusement[k]	Physicality[k]
Humour familiar	10	1.94 (0.06)	1.86 (0.12)	2.69 (0.21)	3.96 (0.29)
Humour novel	10	1.92 (0.06)	1.52 (0.11)	3.06 (0.44)	3.29 (0.49)
Control familiar / congruous	20	1.06 (0.06)	1.68 (0.21)	1.14 (0.12)	N/A
Control novel / incongruous	20	1.08 (0.06)	1.35 (0.19)	1.14 (0.11)	N/A

For further information regarding data in tables see 2.10.1. Category ratings (1, not intended to be humorous; 2, intended to be humorous) and familiarity ratings (1, unfamiliar scenario 2, familiar scenario) were based on a binary classification; amusement ratings (1 = not at all amusing, 5 = very amusing) and physicality ratings (1 = humour not at all reliant on physical actions, 5 = humour very reliant on physical actions) were based on 5-point Likert scales (see Figure 2 and General Methods 2.5). **h**, humour and control condition ratings significantly different (p<0.001) **j**, ratings for each condition significantly different (p<0.001) from all other conditions; **k**, familiar and novel humour condition ratings significantly different (p<0.001)

5.4.5 Final Stimulus Set

The final experimental stimulus set of 60 cartoons comprised (corresponding panel in Figure 13):

i) familiar humorous scenarios (n=10; panel B)

ii) unfamiliar/novel, superficially incongruous, but resolvable humorous scenarios (n=10; panel D)

iii) familiar, congruous, everyday non-humorous control scenarios (n=20; panel A)

iv) novel, irresolvably bizarre incongruous, non-humorous control scenarios (n=20; panel C)

5.4.6 Procedure

Visual cartoon stimuli were administered according to General Methods (see 2.4.2). The task on each trial was to decide whether or not the cartoon was intended to show 'a joke'.

5.4.7 Behavioural Analysis

A mixed effects logistic regression model was used to model outcomes on the experimental humour decision task for each group (see General Methods 2.9.1 and 2.9.2). Here, an OR of 1 corresponds to chance level performance, i.e. the group had equal likelihood of labelling a humorous or control cartoon as humorous; an OR > 1 corresponds to increased accuracy discriminating humorous from control cartoons; and an OR < 1 corresponds to over-rejection of humorous cartoons as non-humorous or over-labelling of control cartoons as humorous.

An interaction of humour with familiarity across cartoon conditions was fitted to allow calculation of ORs of humour detection within familiar scenarios (between familiar humorous and familiar control cartoon conditions); within novel scenarios (between novel humorous and novel control conditions) and between humour conditions.

Nuisance covariates were included as detailed in General Methods (see 2.9.4). In addition the regression model incorporated the following covariates of no interest; years of education and the object decision subtest of the VOSP battery (as an index of visual perceptual ability).

5.4.7.1 Correlations

I assessed associations of humour detection score with MMSE score and symptom duration (see General Methods 2.9.5). Beyond these generic markers of disease severity, I assessed associations of humour detection score with measures of visual semantic memory functions (BPVS and within the SD group alone; size/ weight attribution test scores) and with social cognition function in the bvFTD group (as indexed by TASIT score).

5.4.8 Brain image acquisition and VBM analysis

Brain MRI data were acquired and processed for 28 patients (19 bvFTD, nine SD) according to the protocol described in General Methods (see 2.6 and 2.7).

In separate design matrices, voxel intensity (an index of grey matter volume) was modelled as a function of log-transformed ORs indexing overall accuracy of humour detection, accuracy of detection of humour in familiar scenarios and accuracy of detection of humour in novel scenarios with the incorporation of nuisance covariates according to General Methods (see 2.7). For each model, separate contrasts (one-tailed t-tests) assessed linear associations between grey matter and humour score of interest across the combined patient cohort and within the larger bvFTD group alone.

5.4.8.1 Small volume correction

Small volumes were derived as shown in General Methods (see 2.7.1). These small volumes included key areas implicated in humour processing in the healthy brain for the contrasts of interest (see Figure 4). Our small volume analysis was based on the prior assumption that neuroanatomical substrates for key cognitive operations underpinning humour processing are potentially dissociable (Campbell DW *et al.* 2015). Accordingly, contrasts on humour detection performance were separately assessed within small volumes comprising lateral temporo-occipital-parietal junctional cortex (previously implicated in detection of incongruity in potentially humorous stimuli: (Wild B et al. 2006; Neely MN *et al.* 2012; Amir O *et al.* 2015), temporal lobe anterior to Heschl's gyrus (previously implicated in semantic evaluation of humorous stimuli: (Mobbs D *et al.* 2003; Wild B *et al.* 2006; Samson AC et al. 2008) and vmPFC, OFC and ACC (previously implicated in processing behavioural and inter-personal relevance of humour (Goel V and RJ Dolan 2007; Samson AC *et al.* 2008; Samson AC *et al.* 2009).

5.5 Results

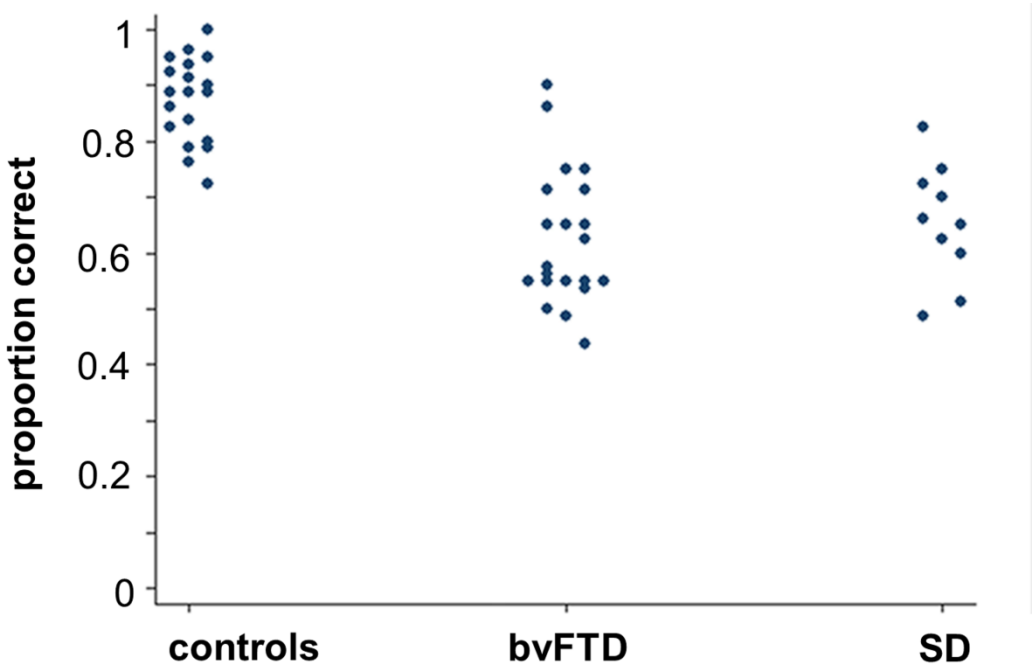
5.5.1 General characteristics of participant groups

Participant groups were matched for age, gender and socio-cultural background and patient groups did not differ significantly in clinical disease duration. Patients had, on average, significantly fewer years of education than healthy control participants (Table 18) and this factor was incorporated as a covariate in subsequent analyses (see 5.4.7); however, absolute differences in educational attainment were small and all participant groups were relatively highly educated.

5.5.2 Behavioural data: humour decision task

Individual raw data are summarised in Figure 14 and group raw data in Table 20. Performance on the humour decision task are summarised in Table 21.

Figure 14 Individual raw scores on the humour decision task



For further information about presentation of figures please see 2.10.2. Based on overall score /60

Table 20 Humour decision task performance data by condition for participant groups

Condition	Healthy controls	bvFTD	SD
Familiar humorous	0.78 (0.17)	0.65 (0.32)	0.57 (0.22)
Novel humorous	0.81 (0.15)	0.56 (0.28)	0.57 (0.17)
Familiar control	0.96 (0.05)	0.71 (0.24)	0.73 (0.21)
Novel control	0.95 (0.07)	0.59 (0.31)	0.73 (0.18)

For further information regarding data in tables see 2.10.1. Bold not used in this table as model not built from accuracy scores (see 2.9.2). See 5.4.3 for further details of conditions and Figure 14 for individual data plots

Table 21 Summary of humour decision task performance for all participant groups

Condition comparison		Healthy controls	bvFTD	SD
Humour detection: overall[m]	OR	90**	**4.9****	**5.7****
	CI	41 -193	2.1 -11	2.4 -13
Humour detection: familiar scenarios[n]	OR	93**	**7.3****	**5.6****
	CI	32 -267	2.6 -20	2.0 -15
Humour detection: novel scenarios[p]	OR	104**	**3.5****	**5.5****
	CI	38 -285	1.4 -8.9	2.1 – 15
Humour category[q]	OR	0.8	1.6*	1.0
	CI	0.5-1.4	1.01-2.5	0.6-1.7

For further information regarding data in tables see 2.10.1. Comparisons index participant performance on aspects of humour processing (see 5.4.7 for further details); *significantly different from chance ($p<0.05$); **significantly different from chance ($p<0.01$); **m**, OR>1 indicates increased accuracy in labelling any humorous cartoon as humorous compared with control cartoons; **n**, OR>1 indicates increased accuracy in labelling familiar humorous scenarios as humorous compared with control scenarios matched for familiarity; **p**, OR>1 indicates increased accuracy in labelling novel humorous scenarios as humorous compared with control scenarios matched for familiarity; **q**, OR>1 indicates greater accuracy in labelling familiar compared with novel humorous cartoons

5.5.3 Humour detection

On overall humour detection (discrimination of humorous from non-humorous cartoons), both the bvFTD group (OR 4.9 [CI 2.1 – 11]) and the SD group (OR 5.7 [CI 2.4 – 13]) performed above chance, but significantly worse ($p<0.001$) than the healthy control group. There was no significant performance difference between patient groups. However, comparing raw performance data in each condition between the patient groups (Table 20) revealed that patients with bvFTD tended to over-label novel control cartoons as humorous, whereas patients with SD tended to reject familiar humorous cartoons as non-humorous. Assessed in relation to general demographic and cognitive factors, humour detection accuracy over the combined participant cohort was not associated with age ($p=0.45$), gender ($p=0.71$), years of education ($p=0.37$) or VOSP score ($p=0.28$), but showed a significant positive association with executive function (Trails B-A score; $p=0.03$). Neither the healthy control group nor the combined patient cohort showed a significant correlation between humour detection accuracy and BPVS score (controls $p=0.31$, patients $p=0.24$); while the SD group additionally showed no correlation between humour detection accuracy and non-verbal semantic (size-weight attributes test) score; $p=0.14$). There was no significant correlation between humour detection accuracy and TASIT score in the bvFTD group ($p=0.68$). Humour detection accuracy was not

correlated with symptom duration (p=0.85), but was correlated with MMSE score (p=0.01) over the patient cohort.

On humour detection within familiar scenarios (discrimination of familiar humorous scenarios from familiar non-humorous scenarios), both the bvFTD group and the SD group performed above chance (OR for humour detection, 7.3 and 5.6 respectively), but were significantly worse ($p<0.001$) than the healthy control group. On humour detection within novel (incongruous) scenarios (discrimination of novel humorous scenarios from novel non-humorous scenarios), a similar pattern was again observed for both bvFTD and SD groups (OR for humour detection, 3.5 and 5.5 respectively; $p<0.001$ versus healthy control performance). There were no significant performance differences between the patient groups.

5.5.4 Humour category differentiation

For the comparison between humour categories, the healthy control group and SD group showed no significant performance discrepancy for humour detection in familiar versus novel scenarios; whereas the bvFTD group showed a significant advantage for detection of humour in familiar relative to novel scenarios (OR 1.57 [CI 1.01 – 2.45], p=0.045) and a trend toward a performance difference compared with the healthy control group (p=0.058). There was no significant performance difference between the patient groups.

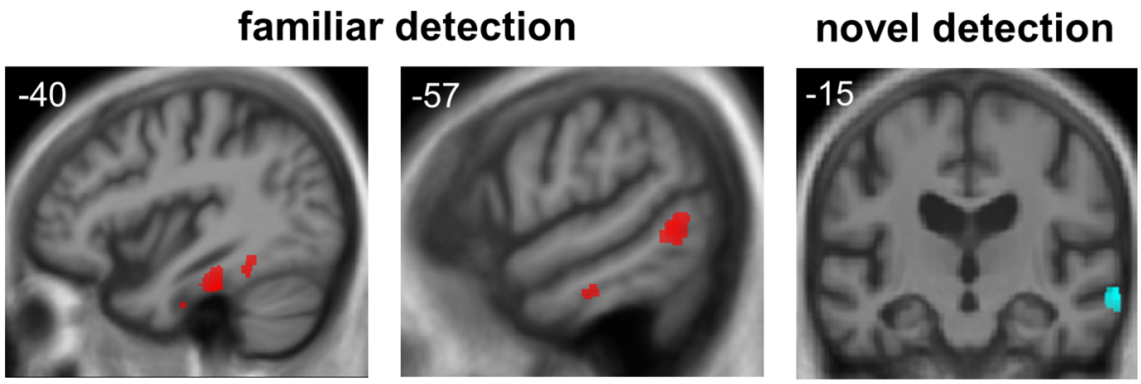
5.5.5 Neuroanatomical data

Associations between grey matter volume and humour processing in the patient cohort are summarised in Table 22; SPMs are presented in Figure 15 and data plots of correlations of peak voxel parameter values with humour indices are presented in Figure 16.

No significant associations between grey matter volume and experimental contrasts of interest were identified at threshold $p<0.05_{FWE}$ after correction for multiple comparisons over the whole brain. Examined at threshold $p<0.05$ after correction for multiple comparisons within the pre-specified anatomical ROI (see General Methods Figure 4), no significant associations were identified between grey matter volume and overall humour detection accuracy. However, humour detection accuracy within familiar scenarios was positively correlated with grey matter volume in the left fusiform gyrus in the combined patient cohort and additionally

with grey matter volume in lateral temporo-occipital junctional cortex within the bvFTD group. Humour detection accuracy within novel scenarios was positively correlated with grey matter volume in right anterior MTG and STS within the bvFTD group. No other significant grey matter associations were identified.

Figure 15 SPMs of regional grey matter volume associated with humour processing shown here for bvFTD



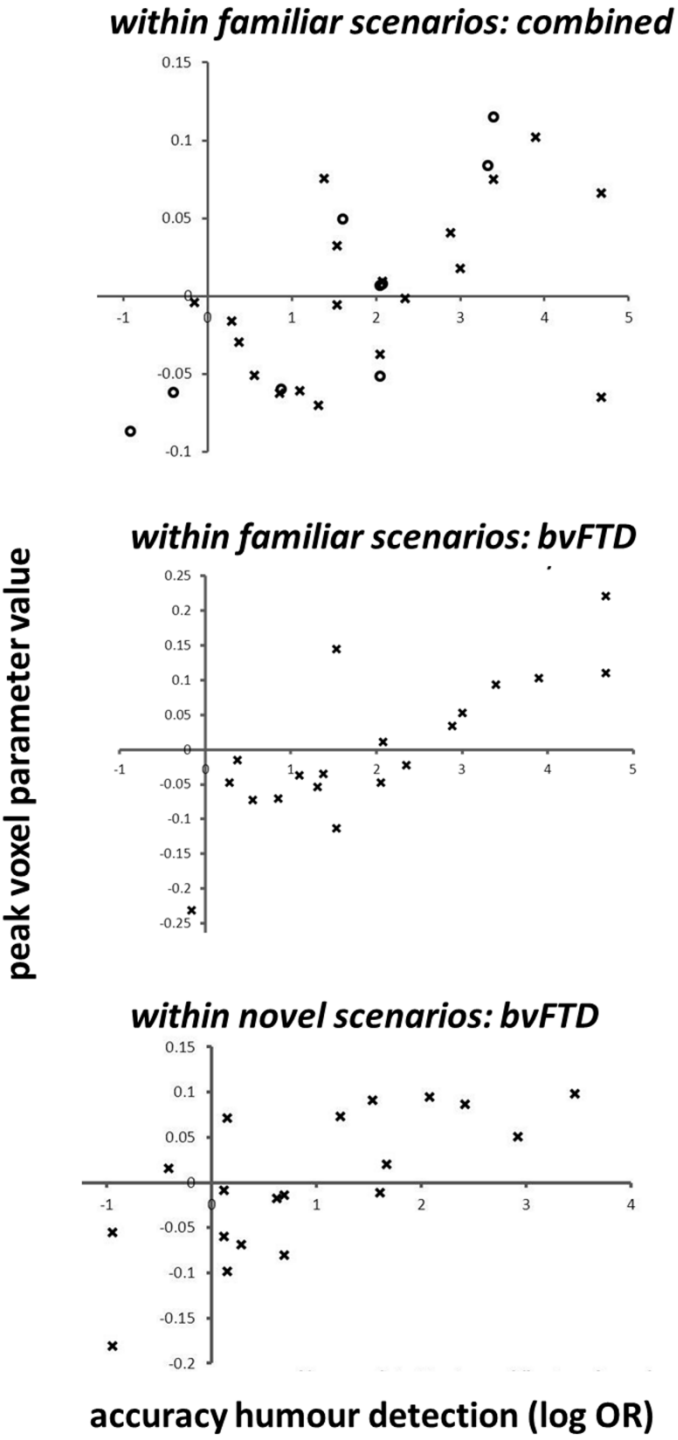
For further information about presentation of figures please see 2.10.2. Correlates of processing familiar humour (relying on recognition of stock comedy situations, exemplified by farce) are coded in red and correlates of processing novel humour (relying on a psychological perspective shift, exemplified by satire) are coded in cyan. **familiar detection**, grey matter volume positively correlated with accuracy of detecting humour in familiar scenarios from humour decision task (see Table 21); **novel detection**, grey matter volume positively correlated with accuracy of detecting humour in novel scenarios from humour decision task (see 5.4.7, Figure 4, in General Methods and Table 22)

Table 22 Summary of neuroanatomical associations of humour processing in the patient cohort

Contrast	Region	Side	Cluster (voxels)	Peak coordinates (mm)			Z score	P value	Group
				x	Y	Z			
Humour detection: familiar scenarios[r]	Fusiform gyrus	L	59	-40	-30	-29	3.87	0.048	Combined
	Fusiform gyrus	L	597	-40	-30	-29	4.25	0.013	bvFTD
	T - O junction	L	419	-57	-54	1	4.06	0.041	
Humour detection: novel scenarios[s]	Ant MTG/STS	R	315	68	-15	-12	4.47	0.008	bvFTD

For further information regarding data in tables see 2.10.1. '**combined**' refers to common associations across both patient groups. Contrasts index patient performance on aspects of humour processing, as follows (see also Table 21 and Figure 15): **r**, grey matter volume positively correlated with humour detection accuracy in familiar scenarios; **s**, grey matter volume positively correlated with humour detection accuracy in novel scenarios

Figure 16 Data plots derived from the VBM analysis showing correlations of peak voxel parameter estimate values (effect sizes)



Log-transformed OR were used for humour detection in familiar cartoon scenarios by the combined patient cohort (top panel) and within the bvFTD group alone (middle panel) and humour detection in novel cartoon scenarios by the bvFTD group alone. Corresponding peak voxel MNI coordinates are as follows; [-40 -30 -29] within familiar scenarios for the combined group; [-57 -54 1] within familiar for bvFTD alone; [68 -15 -12] within novel for bvFTD alone. For further details of regions please see Table 22. Crosses signify individual patients with bvFTD; open circles (top panel) signify individual patients with SD

5.6 Discussion

Here I have demonstrated deficits of humour comprehension in bvFTD and SD. Both syndromes showed impaired detection of humorous intent in both familiar and novel scenarios, corresponding broadly to farcical/ slapstick versus satirical humour, respectively. Patients with bvFTD showed a clear advantage for comprehension of familiar (slapstick) compared with novel (satirical) humorous scenarios. This contrasted with the equivalent performance of healthy older individuals and patients with SD across humour categories. There were additional, qualitative differences comparing the performance profiles of the two patient groups. Patients with bvFTD had greater difficulty distinguishing novel 'bizarre' scenarios from humorous ones, whereas patients with SD had greater difficulty detecting humour in stock comedic situations (slapstick). Taken together, these profiles suggest that bvFTD is particularly associated with impaired detection of humour where this relies on the active deconstruction of a novel incongruous situation. SD is associated with a more general defect of humour detection that extends to familiar scenarios that we normally 'learn' as humorous during social development (Degabriele J and IP Walsh 2010; Neely MN *et al.* 2012). This is analogous to the deterioration of language in SD patients reverses the normal development process. Perhaps the deconstruction of humour in FTLD recapitulates the developmental trajectory of humour.

A neuroanatomical analysis identified distributed anatomical networks of altered humour comprehension in the present patient cohort, many of which are known to relate to detection or resolution of incongruity as related to humour. Detection of humour in familiar scenarios was associated with relative preservation of grey matter in a left-sided cortical network including fusiform gyrus and lateral temporo-occipital cortex. This network is likely to represent fundamental attributes of humorous (or potentially humorous) stimuli, particularly if (as in the relevant contrast here) humour detection rests on detection of incongruity. Fusiform gyrus has previously been implicated for resolution of potentially conflicting elements in complex visual stimuli, coherent cross-modal linkage with stored semantic concepts (for example, stock comedic situations) and associated emotional resonance (Goel V and RJ Dolan 2001; Watanabe T *et al.* 2014). A closely related set of functions may be subserved by lateral temporo-occipital junctional cortex (Goel V and RJ Dolan 2001; Mobbs D *et al.* 2003; Bartolo A

et al. 2006; Samson AC *et al.* 2008; Amir O *et al.* 2015) including decoding of emotion from abstract visual art in FTLD patients (Cohen MH *et al.* 2016). The same region was activated in initial decoding of incongruities used by adults in perceiving slapstick humour (Wild B *et al.* 2006). Detection of humour in novel scenarios here was associated (in the bvFTD group) with relative preservation of grey matter in right-sided, antero-lateral superior temporal cortex. Anterior right superior and middle temporal cortex may engage social conceptual knowledge in a process of conflict resolution (Zahn R, J Moll, V Iyengar*, et al.* 2009; Zahn R, J Moll, M Paiva*, et al.* 2009), perhaps more specifically accessing learned associations or stored conceptual knowledge about potentially comedic situations (Goel V and RJ Dolan 2001; Mobbs D *et al.* 2003; Bartolo A *et al.* 2006; Samson AC *et al.* 2008). Activation of STS in healthy controls is shown to be associated with the social context in which an action occurs (Pelphrey KA et al. 2004).

Impaired ability to resolve incongruity might reflect generic deficits in maintaining and monitoring alternative possible resolutions (see Chapter 4) or in integrating the elements of a scene to achieve coherence (see Chapter 3), or a more specific deficit in engaging social semantic templates (Zahn R, J Moll, V Iyengar*, et al.* 2009; Barense MD et al. 2010). Cognitive flexibility and the capacity to shift perspective or cognitive set are also likely to be key vulnerabilities in FTLD and contribute to incongruity resolution in humour (Kramer JH *et al.* 2007; McMillan CT et al. 2012; Perri R et al. 2014). These findings in FTLD suggest an analogy with previous reports in patients undergoing temporal lobectomy who were no longer able to detect humour in cartoons due to impaired integration of situational elements and deficient perspective shifting (Ferguson SM et al. 1969).

Theory of mind has been emphasised in previous accounts of humour processing (Franklin RG, Jr. and RB Adams, Jr. 2011) and indeed, cartoons have been used to index theory of mind processes in FTLD (Snowden JS *et al.* 2003; Lough S *et al.* 2006; Irish M *et al.* 2014). While cartoons here (particularly within the novel humour set) incorporated elements of theory of mind, my emphasis here was on generic cognitive operations that might link humour to other neuropsychological and behavioural deficits. Moreover, theory of mind is difficult to assess reliably in patients (like those with SD) who have severe verbal deficits. It is noteworthy that a structural neuroanatomical analysis here revealed a relative dearth of classical theory of mind

correlates in PFC. It should also be emphasised that the cerebral correlates of theory of mind continue to be defined and these are likely to overlap extensively with temporal lobe regions involved in semantic and affective analysis (Irish M *et al.* 2014), including the anterior superior temporal cortical region identified here as a correlate of novelty processing in humour.

Although affective components of reward were not examined in this study these findings resonate with the complaints of caregivers of patients with FTLD, frequently indicating that they have lost the ability to appreciate more subtle comedy, that their tastes in comedy have shifted towards the farcical, that they have become humourless or more inclined to find humour in inappropriate contexts. While bvFTD and SD were both associated with extensive abnormalities of humour processing, our findings suggest that relatively greater affinity for more fatuous or childlike humour may be a marker of bvFTD while SD produces a more general impairment of humour processing (Ehrlé N *et al.* 2011; Ibanez A and F Manes 2012). These certain features may help differentiate syndromes at the bedside.

These findings extend previous work suggesting abnormalities of humour processing in FTLD (Chan D et al. 2009; Ehrlé N *et al.* 2011; Ibanez A and F Manes 2012; Warren JD, JD Rohrer and MN Rossor 2013; Irish M *et al.* 2014). I have shown the unique cultural and cognitive status humour enjoys might be exploited to probe complex behavioural deficits that would otherwise remain inaccessible. The potential for defining true humour universals for cross-cultural applicability of this work has yet to be established. Altered humour sensibility may constitute a distinct domain of social cognitive function that is not well captured by standard neuropsychological instruments, and impaired humour processing may contribute importantly to behavioural difficulties more generally, including the flouting of social norms (Barsuglia JP et al. 2014).

In this chapter I have demonstrated that humour can be reduced to cognitive building blocks and a potential template of scenarios that is likely to be resistant to the vagaries of taste, certainly within a cultural milieu. My experimental design allowed me to assess key elements in humour comprehension (novelty and incongruity) relatively independently of potentially confounding verbal, semantic and executive performance factors. Neuroanatomical correlates were in networks that resolved incongruity or conflict in the context of humour and other

social contexts. Humour has potential to be a novel, clinically and neurobiologically relevant model of complex social signal processing in neurodegenerative disease. Humour may act as a bridge between the cognitive deconstruction of social cognition and daily-life symptoms with the possibility of being used therefore as a biomarker. In the next chapter, I describe the potential implications for humour as a clinically relevant tool.

6 ALTERED SENSE OF HUMOUR IN DEMENTIA

6.1 Chapter Summary

Humour is important for successful inter-personal interactions, social functioning and quality of life. Humour is underpinned by incongruity resolution. I have shown humour detection to be impaired in bvFTD and SD (see Chapter 5). Humour is a vital part of successful interpersonal interactions and has observable real-world behaviours related to the reward component of humour processing, such as comedy preferences and laughter. I designed a semi-structured carer questionnaire to assess humour behaviour and preferences in patients with bvFTD (n=15), SD (n=7), PNFA (n=10), and AD (n=16) versus healthy age-matched individuals (n=21). Altered (including frankly inappropriate) humour responses were significantly more frequent in bvFTD and SD than PNFA or AD. All patient groups liked satirical and absurdist comedy significantly less than did healthy controls; this pattern was reported premorbidly for satirical comedy in bvFTD, PNFA and AD. Liking for slapstick comedy did not differ between groups. Altered sense of humour is particularly salient in bvFTD and SD, but also frequent in AD and PNFA. Humour may be a sensitive probe of social cognitive impairment in dementia, appearing to predate the onset of more typical symptoms. Humour may therefore be endowed with diagnostic, biomarker and social implications for FTLD.

6.2 Introduction

The emotional components of the humour response are at least partly separable from mechanisms of cognitive analysis as examined in Chapter 5 (Bartolo A *et al.* 2006; Mensen A *et al.* 2014; Campbell DW *et al.* 2015). Investigation into the subjective aspect of humour or amusement by jokes has implicated brain areas known to be affected by FTLD (Goel V and RJ Dolan 2001). Degree of amusement (funny contrasted with unfunny jokes) has been correlated with activation in ventral PFC, ACC, superior frontal gyrus (SFG), superior and mid temporal cortices and limbic and dopaminergic reward networks including ventral striatum and nucleus accumbens (Goel V and RJ Dolan 2001; Mobbs D *et al.* 2003; Watson KK et al. 2007; Campbell DW *et al.* 2015). Socially inappropriate humour was deemed 'unfunny' owing to reciprocal activation of the right hippocampus and inactivation and of the right vmPFC, implicated in contextual regulation of behaviour in relation to social norms (Goel V and RJ Dolan 2007).

Individual variation in sense of humour (ability to grasp one-liners) has been correlated with electrophysiological markers including lateralised frontal evoked potentials that may index frame-shifting and surprise (Coulson S and M Kutas 2001).

Affective responses to humour are likely to be critical for the normal integration of humour behaviours in daily life. Information concerning humour expression and awareness across neurodegenerative diseases remains limited. Using theory of mind tasks, affective changes are shown to lead cognitive change in bvFTD (Torralva T *et al.* 2015), however little is known about affective humour behaviours or preferences in relation to the cognitive understanding of humour in this group. Disturbances of humour may be an early features of disease (Warren JD, JD Rohrer and MN Rossor 2013; Dopper EG et al. 2014), but remain difficult to characterise. Early reviews of frontal lobe lesion studies function describes the patients becoming 'puerile' (Mesulam MM 1986). Some patients with right hemisphere damage find humour in intrinsically humourless situations (Gardner H *et al.* 1975), a potential analogy for bvFTD. Clinical experience suggests that altered sense of humour (particularly a predilection for the more fatuous comedic forms of farce, pranks and scatological jokes) commonly accompanies bvFTD while humourlessness may develop in association with syndromes of predominant temporal lobe atrophy (Chan D *et al.* 2009) (see Chapter 5).

Although humour abnormalities are not generally regarded as a cardinal feature of AD, emerging evidence suggests that the cognitive aspects of humour may be affected alongside social cognition (Irish M *et al.* 2014). AD patients have heightened affect sharing (Sturm VE, JS Yokoyama*, et al.* 2013) and this may result in their humour preferences shifting for fundamentally different reasons than in FTLD, for example, over-identification with characters' plights.

There is currently a lack of standardised instruments for assessing humour preferences. This partially stems from the lack of a formal definition of what constitutes a sense of humour (Martin GN and E Sullivan 2013) or a robust conceptual framework for understanding humour across all comedy genres. The most well defined genres are satirical and slapstick (as discussed in Chapter 5) and there have been attempts to interpret nonsense humour (Samson AC *et al.* 2009) as a paradigm of incompletely resolved incongruity being humorous.

Slapstick humour has potential cross-cultural applicability with its emphasis on physical humour and independence from language (as illustrated by Mr Bean or Charlie Chaplin) and therefore my hypothesis is that appreciation of this humour genre might be relatively preserved even in the presence of language impairment. Interestingly slapstick humour may be an enduring human universal as the world's oldest joke dated to Babylonian times relates to flatulence (Wolverhampton Uo 2008) and that Shakespearean audiences found humour in the infamous stage direction "Exit, pursued by a bear" (Shakespeare W 1914) speaks to shared slapstick comedic values with the present day. Therefore this genre of humour could (a priori) be preserved in FTLD, despite language deterioration.

The reward in humour is accompanied by the unique subjective experience of mirth, which is unlike solving a crossword or listening to music. Potential explanations include social imprinting, or related to the role of laughter and humour in social cohesion or the degree of surprise and cleverness in the unexpected resolution (Amir O *et al.* 2015). Contagion of mirth or laughter is a prominent feature of humour in daily life (Provine R 2004) and is responsible for the augmented experience of watching live comedy with an audience or the increased enjoyment when laughter is added to recorded comedy (Martin GN and CD Gray 1996). Contagion is vastly increased with stronger social bonds with the person who is laughing (Provine R 2004; Provine RR and K Emmorey 2006). Notably, deaf signers have similar social dynamics related to laughter in social interactions as hearing people do (Provine RR and K Emmorey 2006). Laughter is universally recognised (Sauter DA et al. 2010) and from an evolutionary perspective, is probably older than language (Hayworth D 1928). Laughter is a non-verbal vocalisation that is used to establish and maintain interpersonal bonds explaining its key role in social interactions (Provine R 2004; Provine RR and K Emmorey 2006). It is sensitive to modulation by context as genuine (as opposed to social), laughter is contagious, but mocking (albeit genuine) laughter, is extremely unpleasant for the individual who is the target. Behaviours such as laughter are complex constructs and offer a real world measure of social contagion and interpersonal interactions. Observable and potentially quantifiable humour behaviours include; laughter, generating jokes, seeking repetition of humour exposure in addition to autonomic alterations (Balconi M *et al.* 2015; Fletcher PD, JM Nicholas*, et al.* 2015).

In this chapter I assess how far the humour 'phenotypes' from Chapter 5 translate to real-world humour preferences with potential utility as a clinical biomarker. Work on frontal lobe function has emphasised the importance of utilising ecological scenarios in testing social abilities in bvFTD, because of greater sensitivity in detecting an effect (Mesulam MM 1986; Burgess PW *et al.* 2009; Baez S *et al.* 2014). I focused on the three genres of humour; satirical, slapstick and absurd which I felt were most representative of the spectrum of humour types and sample relevant cognitive and behavioural functions. I designed a semi-structured carer questionnaire to assess humour behaviour and preferences, both in the current phase of established disease and retrospectively prior to clinical onset, in comparison to healthy older individuals.

6.3 Experimental Hypotheses

These are direct consequences of the findings from the work presented in Chapter 5.

i) bvFTD have retained appreciation of slapstick comedy whilst losing their ability to appreciate satirical humour.

ii) bvFTD patients find humour in incongruous situations even if the context is non-humorous.

iii) SD and AD patients exhibit a blunting of humour sensibilities across comedy genre.

iv) PNFA patients have a preserved appreciation of humour across genre.

6.4 Methods

6.4.1 Participants

48 patients with dementia fulfilling current consensus criteria for their respective diagnoses as detailed in General Methods (see 2.1) were recruited. All participants had lived most of their adult lives and the majority had also grown up (to age 16 years) in the United Kingdom. The cohort comprised: bvFTD (n=15), SD (n=7), PNFA (n=10) or AD (n=16) and 21 healthy older individuals (from a similar socio-cultural milieu). Participant characteristics are summarised in Table 23 and General Methods 2.1. Nine patients (eight with bvFTD, one with PNFA) with FTLD

had confirmed pathogenic mutations (five *C9orf72*, four *MAPT*). Four of the five C9orf72 patients met criteria (Rascovsky K *et al.* 2011) for a diagnosis of bvFTD (see General Methods 2.1.1) and the remaining patient was diagnosed with PNFA (see General Methods 2.1.4). CSF analysis or 18F-amyloid PET imaging in 23 (10 = AD) cohort members corroborated their clinical diagnosis (see Supplementary Table 2 in Appendix).

Neuropsychological profiling was conducted on all participants (see Chapter 5, General Methods 2.1, 2.2 and Table 23). Of the core psychology tests administered to all participants those that were deemed most pertinent for the assessment of humour preferences included; non-verbal measures of executive impairment including task-switching, BPVS (a general cross-modal measure of semantic memory) and TASIT (decoding of sarcastic intent) (McDonald S *et al.* 2006).

Table 23 Summary of participant demographic, clinical and general neuropsychological characteristics

Characteristic	Controls	bvFTD	SD	PNFA	AD
GENERAL					
No., gender (M:F)	11:10	13:2	4:3	5:5	8:8
Handedness (R:L)	18:3[¥:]	15:0	6:1	9:1	14:2
Age (yrs)	65.9 (5.0)	65 (7.3)	66.9 (6.2)	69.4 (7.4)	66.1 (8.0)
Education (yrs)	16 (1.9)	15 (2.6)	14 (2.4)	16 (2.5)	14 (2.9)
Background (UK&Eire:other)	19:2[ω]	15:0	6:1[δ]	10:0	15:1[δ]
Symptom duration (yrs)	N/A	6.3 (3.4)	5.7 (3.3)	5.1 (2.6)	6.1 (2.7)
MMSE (/30)	N/A	25 (4)	22 (8)	21 (10)	20 (5)[t]
BACKGROUND NEUROPSYCHOLOGY					
General intellect					
VIQ	123 (6)	**85 (21)**	**76 (19)[u]**	**82 (19)**	**93 (22)**
PIQ	126 (10)	**96 (14)**	**109 (23)**	**98 (21)**	**85 (18)[v]**
WASI Vocabulary (/80)	71 (4)	**42 (21)**	**35 (22)**	**42 (17)**	**53 (17)**
WASI Block Design (/71)	51 (10)	**25 (15)**	**35 (20)**	**21 (17)**	**14 (14)[t,v]**
WASI Similarities (/48)	42 (3)	**25 (13)**	**22 (13)**	**28 (7)**	**25 (11)**
WASI Matrices (/42)	27 (3)	**17 (7)[v]**	23 (8)	**21 (6)**	**12 (7)[t,v,w]**
Executive function					
Stroop (ink colour) (sec)	54 (11)	**100 (41)**	**89 (50)**	**140 (33)**	**118 (47)**
Trails (B-A difference) (sec)	36 (24)	**131 (91)**	78 (76)[w]	**150 (58)**	**130 (84)**
Digit span reverse (/12)	7.3 (1.9)	6.5 (2.2)	8.4 (2.9[)]	**4.1 (2.7)[v]**	**6.3 (5.3)**
Episodic memory					
Digit span forward (/12)	8.9 (2.0)	8.4 (2.3)	9.4 (2.4)	7.6 (1.6)	**6.3 (2.5)[t,v]**
RMT Words (Z score) [ϕ]	0.6 (0.2)	-1.3 (1.3)	-1.5 (1.5)	-1.1 (1.4)	-1.6 (0.9)
RMT Faces (Z score) [ϕ]	0.2 (0.7)	-1.9 (1.1)	-0.6 (1.2)	0.4 (0.3)	-1.9 (0.9)
Language & literacy function					
GNT (/30)	28 (2)	**13 (8)**	**3 (4)[t,u,w]**	**18 (7)**	**16 (9)**
Reading (NART) (/50)	44 (3)	**31 (14)**	**24 (21)**	**34 (10)**	**29 (13)**
GDA (/24)	15 (4.4)	**10 (6.5)**	11 (9.7)	**5 (4.8)**	**11 (13.3)**
Semantic Memory					
BPVS (/150)	148 (2)	**136 (14)**	**97 (49)**	**142 (9)**	**119 (51)**
Visuoperceptual Function					
VOSP Object Decision (/20)	19 (1.7)	17 (1.9)	18 (2.4)	17 (2.8)	16 (3.8)
Social cognition					
TASIT emotion (/14)	12 (1.3)	**8.3 (2.6)**	N/A	N/A	N/A
TASIT social inference (/36)	31 (2.2)	**22 (6.0)**	N/A	N/A	N/A

For further information regarding data in tables see 2.10.1. ¥ one person from this group classified themselves as ambidextrous **δ,** one participant grew up in South Africa; **ω,** one participant grew up in Canada, one participant was subsequently found to have been brought up in Denmark; **ϕ**, floor performance -2.67 from age norms (long RMT) except AD floor performance -1.88 (short RMT); **t,** significantly different from bvFTD; **u,** significantly different from AD; **v,** significantly different from SD; **w,** significantly different from PNFA

6.4.2 Humour background questionnaire

In order to assess patients' sense of humour in daily life, I designed a semi-structured questionnaire comprising seven items (Figure 17). Questionnaires were completed for each patient by a normal informant who had known them well for at least 15 years. No time limit was imposed for questionnaire completion. In each case the informant knew the patient intimately, in most cases as their cohabiting spouse or a child or sibling they had been in long term regular contact (at least monthly). Although there are limitations to carer reporting; FTLD patients, even in the presence of profound social and executive impairments, lack self-awareness and self-knowledge of these deficits. They have been shown to significantly overrate themselves in multiple social, emotional, and cognitive domains, and fail to acknowledge that any behavioural change had occurred (Eslinger PJ et al. 2005). Healthy controls reported for themselves. While ideally control ratings might also have been based on third party ratings by other healthy individuals with an intimate knowledge of the person, this would be logistically cumbersome (as in most cases the healthy control's spouse was the patient) particularly in the absence of a prior suspicion of confounding effects.

The questionnaire recorded perceived changes in the patient's sense of humour over the course of the illness; an item adapted from the Cambridge Behavioural Inventory (CBI) was used to quantify any tendency to express humour in scenarios that others would not generally find funny (rated 0-4; 0 = never, 1 = a few times per month, 2 = a few times per week, 3 = daily, 4 = constantly). In addition, the questionnaire recorded patients' total daily life comedy exposure in broadcast and print media (estimated hours per week) and their liking for comedy (on a 10-point Likert scale), both currently and 15 years previously. This interval was chosen arbitrarily, but designed to capture any alterations in humour preferences before onset of typical clinical symptoms; while minimising potential confounding effects from normal cognitive ageing, informant knowledge and recall bias. Patients with disease duration longer than 15 years were accordingly not included in the study. The questionnaire assessed three broad comedy genres or categories: farcical or slapstick (e.g., *Mr Bean*); satirical (e.g., *Yes, Minister*); and absurdist (e.g., *Monty Python*). Informants were encouraged to seek clarification on examples of comedy genres to improve reliability and avoid bias. Healthy control participants completed a modified version of the questionnaire (comprising Questions 3, 6 and

7) to assess comedy exposure and preferences (questionnaire data for this group was based on self-report).

Figure 17 Questionnaire to assess patients' daily life humour preferences

DAILY LIFE HUMOUR QUESTIONNAIRE

ID code: **Date of assessment:**

1. Care-giver's relationship to patient:
2. How long have you known the patient? (years):
3. What country did s/he mainly grow up in? (to age 16)
4. Has s/he exhibited a change in sense of humour in the course of the illness?'
   If so, in what way?

5. Does s/he find humour or laugh at things others do not find funny? Please rate:

   0, never; 1, a few times per month; 2, a few times per week; 3, daily; 4, constantly

6. Please estimate the total hours in a typical week that s/he spends watching comedy programmes (TV or films) or looking at humorous cartoons:

   Currently: **15 years ago:**

7. Please rate his/her liking for comedy of the following kinds, according to the scale shown below

   1 **10**
   Dislikes very much **Likes very much**

7.1 Slapstick or farcical comedy, e.g. Mr Bean, Benny Hill, Tom and Jerry

   Currently: **15 years ago:**

7.2 Satirical comedy, e.g. Yes, Minister; Punch; The New Yorker

   Currently: **15 years ago:**

7.3 Absurdist comedy, e.g. Monty Python, The Goon Show

   Currently: **15 years ago:**

6.4.3 Statistical analyses

Demographic characteristics and neuropsychological and behavioural rating data were compared between groups as described in General Methods (see 2.9). Data on participant gender, country of origin (UK/Eire versus other) and altered sense of humour (present/absent) were analysed using two-tailed Fisher's exact tests. Kruskal Wallis tests were used to compare other demographic characteristics, comedy exposure and liking for particular comedy genres between groups. Relations between humour preference ratings and gender were assessed in the healthy control cohort using the Wilcoxon rank-sum test. Spearman's tests were used to assess correlations of humour measures with general disease measures (symptom duration and MMSE) and WASI Matrices score in the combined patient cohort, BPVS score in the SD group and TASIT scores in the bvFTD group.

6.5 Results

Participant groups did not differ significantly in mean age ($p=0.54$) or education ($p=0.25$; see Table 23). Males were significantly over-represented in the bvFTD group compared with the healthy control group ($p=0.04$); gender was not significantly correlated with any humour measure (all $p>0.05$) in the healthy control reference group and accordingly was not analysed further. Patient groups did not differ in estimated symptom duration ($p=0.77$); the AD group had a significantly lower MMSE score than the bvFTD group ($p=0.03$).

Humour questionnaire data are summarised in Table 24 and representative informant comments are in Table 25. Three patients with bvFTD – one with a pathogenic C9orf72 mutation, one with a MAPT mutation and one with no identified mutation on screening – were not entered into the study because estimated symptom duration was >15 years in these cases. In each case, the patient's caregiver described alterations in their sense of humour similar to other patients with bvFTD. Most participants had grown up in the United Kingdom; a few had spent part of their childhoods abroad in countries affiliated with Britain (Table 24). One patient with bvFTD and no identified mutation on screening was excluded owing to the fact he was a French national (his spouse did not recognise any of the comedy exemplars given and it was apparent they had experienced a comedy milieu not shared by the rest of the cohort).

Table 24 Humour questionnaire data for the participant groups

Characteristic	Healthy controls	bvFTD	SD	PNFA	AD
Background					
Informant's relationship to patient (spouse:other)	N/A	13:2[μ]	5:2[Ψ]	7:3[Ω]	15:1[λ]
Duration of relationship (yrs)	N/A	44.7 (11.5)	40.1 (9.1)	44.2 (9)	43.4 (10.6)
Participant country of origin (UK/Eire: other)	19:2[ω]	15:0	6:1[δ]	10:0	15:1[δ]
Humour: Over course of illness					
Altered sense of humour? (Y:N)	NA	15:0[x]	7:0[y]	4:6	7:9
Inappropriate humour (Y:N)¶	NA	8:7[z]	4:3[A]	0:10	0:16
Tendency to laugh: frequency¶¶	NA	1.8 (1.2)[B]	0.4 (0.2)	0.1 (0.3)	1 (1.4)
Humour: Currently					
Total comedy exposure[Ӿ] (hrs / wk)	1.5(1.2)	5.8 (13.3)	0.4(0.6)	2.1(1.7)	1.6(1.7)
Liking[Ж]: slapstick	4.9 (2.1)	4.1 (2.8)	3.6 (2.0)	4.5 (2.5)	3.7 (1.6)
Liking: satirical	7.7 (1.5)	**3.1 (1.7)**	**4.1 (3.7)**	**5.9 (1.9)[C]**	**3.8 (1.8)**
Liking: absurd	6.3 (2.1)	**3.3 (2.5)**	**3.5 (3.2)**	**4.6 (2.7)**	**4.1 (2.0)**
Humour: 15 years ago					
Total comedy exposure (hrs / wk)	3.3 (2.6)	5.4 (7.1)	2.8 (2.8)	1.8 (1.4)	2.7 (2.0)
Liking: slapstick	5.5 (2.1)	5.7 (2.0)	4.5 (2.3)	4.3 (2.0)	4.5 (1.9)
Liking: satirical	7.7 (1.4)	**6.2 (1.9)**	7.0 (2.1)	**6.2 (1.8)**	**5.2 (2.2)**
Liking: absurd	6.4 (2.2)	5.9 (2.2)	5.0 (3.4)	4.7 (2.7)	5.1 (2.4)

For further information regarding data in tables see 2.10.1. **μ** two siblings; **Ψ** two children **Ω** two children **λ** one child; **δ** one participant grew up in South Africa; **ω** one participant grew up in Canada, one participant was subsequently found to have been brought up in Denmark; ¶based on post hoc analysis of informant reports (see text); ¶¶from CBI (data available for 15 patients with bvFTD, six patients with SD, nine patients with PNFA, 15 patients with AD), scaled as: 0 (never), 1 (a few times a month), 2 (a few times a week), 3 (most days) or 4 (constantly); Ӿ broadcast and print media; Ж 10 point Likert scale (1, dislikes very much to 10, likes very much); [x]significantly different from PNFA (p=0.001) and AD (p=0.001); [y]significantly different from PNFA (p=0.035) and AD (p=0.019); [z]significantly different from PNFA (p=0.008) and AD (p=0.001); [A]significantly different from PNFA (p=0.015) and AD (p=0.004); [B]significantly different from SD (p=0.004) and PNFA (p=0.0004), borderline significantly different from AD (p=0.051); [C]significantly different from bvFTD (p=0.002) and AD (p=0.02)

Participant groups did not differ significantly according to country of origin (p=0.62; see Table 24). Altered sense of humour was reported significantly more frequently in bvFTD (p<0.01) and SD (p<0.05) (all patients) than PNFA or AD (around 40% of patients). Patients with bvFTD were significantly more likely to express humour in situations not generally considered humorous than patients with SD or PNFA (p<0.01; borderline significant versus AD, p=0.051); other patient groups did not differ with respect to expressed humour.

The CBI measure of increased tendency to show humour was significantly correlated with executive impairment (WASI Matrices) for the combined patient cohort (rho=-0.36, p=0.018), but additionally correlated with symptom duration only in AD (rho=0.62, p=0.014). No other significant within-group correlations were identified between humour measures and general disease severity or executive performance measures (all p>0.05). In the SD group no humour measure showed a significant correlation with semantic performance as assessed using BPVS score (all p>0.05). In the bvFTD group no humour measure showed a significant correlation with social cognitive performance as assessed from TASIT scores (total score, emotion subscore, sarcasm subscore all p>0.05).

Informant comments (Table 25) revealed a number of instances in which patients were reported to show frankly inappropriate humour responses such as laughter over others' misadventure (e.g., watching news stories about natural disasters, witnessing a spouse injure herself) or impersonal stimuli (e.g. a badly parked car, a barking dog). In a post hoc analysis, such inappropriate humour responses were significantly over-represented in bvFTD (p<0.01) and SD (p<0.05), occurring in around half these patients, but not at all in PNFA or AD. Informant reports indicated a shift in patients' comedy preferences toward the fatuous and farcical as the clinical syndrome became established (Table 25). Estimated overall comedy exposure (hours/week) did not differ significantly between participant groups either currently (p=0.07) or premorbidly (p=0.24; Table 24). However, current liking for satirical and absurdist comedy was significantly less in all patient groups compared with healthy controls (p<0.05) and liking for satirical comedy (though not other comedy genres) was significantly less in bvFTD and AD compared with PNFA (p<0.05). Premorbidly, liking for satirical comedy was significantly less in bvFTD, PNFA and AD (though not SD) compared with healthy controls (p<0.05). This change was estimated to have been evident between two to 13 years (on average, nine years) prior to onset of more typical symptoms. Patient groups did not differ premorbidly in their liking for satirical comedy and no patient group showed premorbid alterations in liking for other comedy genres.

Table 25 Representative informant comments recording instances of altered humour exhibited by patients

Case	Group	Informant comment
1	bvFTD: C9orf72	Has developed a dark and misplaced sense of humour; relishes other people's mishaps or upset
2		Rarely laughs heartily at a joke like before. Tells a filthy joke, wonders why others don't laugh
3		Previous dry and entertaining sense of humour has completely disappeared; rarely laughs now
4		Still sees humour in some things- particularly those of a more visual nature (eg slapstick); **will laugh at things inappropriately eg. after messy eating**; inclined to mimic others who smile or laugh
5	bvFTD: MAPT	Very rarely laughs these days, laughs when see a disaster on the news
6		Rarely laughs at jokes now except own, **often inappropriately**. Jokes taken literally, misses the point
7		Used to be very witty but that has all gone; humour has to be more obvious, laughs if others laugh
8		Almost zero sense of humour
9	bvFTD: sporadic	Idea of humour now very rude and graphic, everything is now 'funny'
10		Was very sharp and clever with words, now finds slapstick/childlike humour very funny; **frequently laughs at a disaster on the news or a child falling off their bike**
11		Early on laughed very loudly at things that were only mildly funny, flippant or 'over the top'; now laughs all the time at things that are not particularly funny and will say "I'm laughing and I'm not sure why I'm laughing". **When I badly scalded myself the other year, thought it was hilarious**
12		Has little sense of humour at all, does not really find anything funny but will give a silly laugh or sneer **when totally inappropriate.** Does not find any humour in our new puppy
13		Tends not to laugh as much at things previously thought funny (e.g. *Dad's Army)*, **sometimes laughs inappropriately at news items**
14		Has always been a joker, but this has increased- **not always appropriately**
15		Cannot understand nuances, irony
16	SD	Sense of humour now simpler, or more basic, no longer comprehends complex jokes, more likely to laugh at slapstick comedy or **things that seem out of place (e.g. car parked on pavement), coincidences**
17		Doesn't seem to know when someone is joking and tends to take everything at face value
18		Much more likely to make 'silly' comments (eg. "it won't suit you" if I say "I'll put the kettle on")
19		Now rarely laughs unless more obvious, slapstick humour but no longer e.g. *Monty Python*; **often laughs at things that are not funny, e.g. personal misfortune**, TV programmes used to find puerile
20		Now virtually devoid of humour; cannot appreciate word based jokes or visually based jokes, will laugh if others are laughing or things that **aren't funny, e.g a barking dog**
21		Doesn't get subtleties, e.g. used to read *Private Eye*, but now needs jokes explained
22		I have asthma - **laughs sometimes when I am fighting to get my breath**
23	PNFA	More keen on slapstick and farce

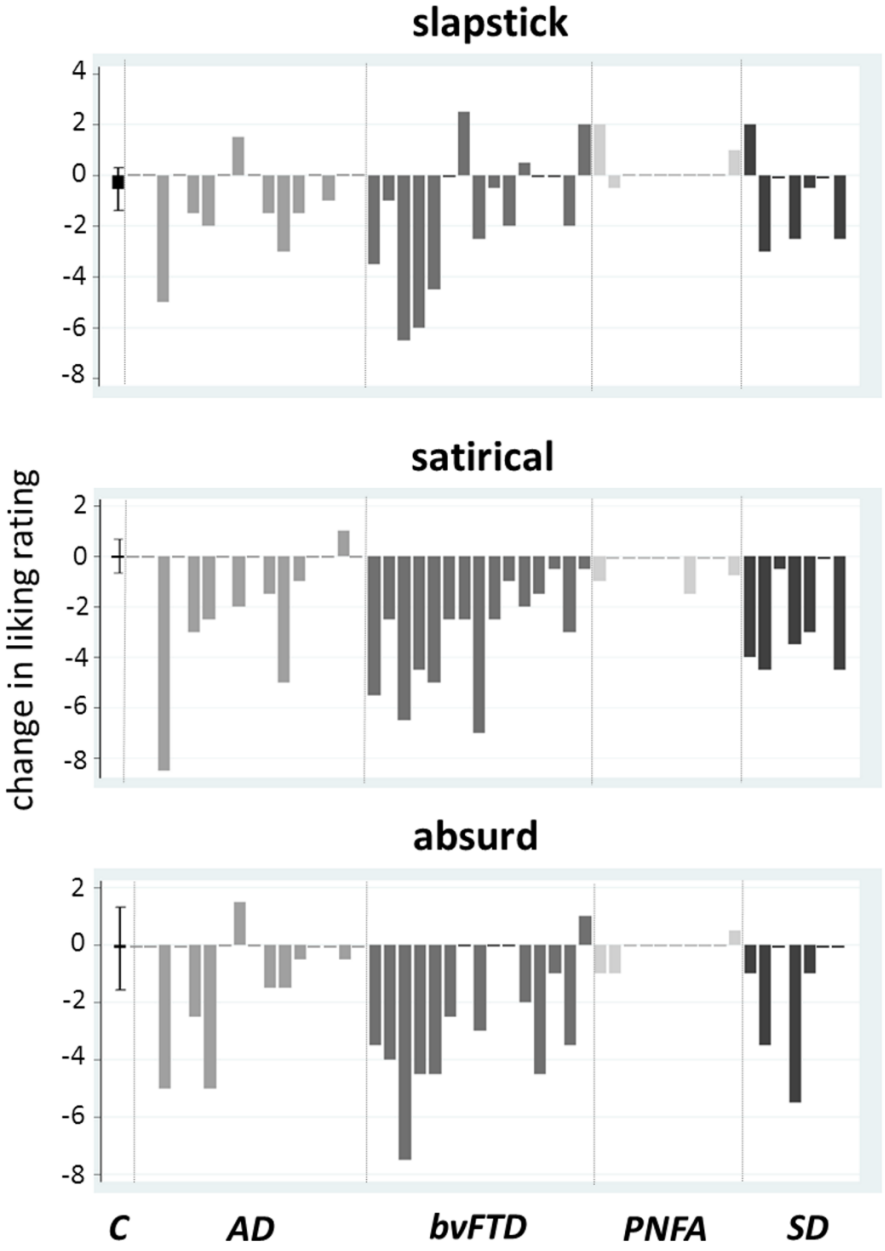
24		Laughs more at black humour but less into comedy
25		Sometimes laughs at things others don't
26		More childish and immature; laughs in a loud and embarrassing way[ø]
27	AD	Makes several "non" jokes per day, mostly verbal plays and puns, compulsive
28		Now finds childish humour funny
29		Does not tell as many jokes as before, more smutty humour
30		Doesn't laugh very often, humour needs to be very simplistic
31		Doesn't understand jokes even when explained, may become angry when others laugh at something
32		A bit more vulgar, will tell jokes that really aren't funny, laughs at own remarks a lot.
33		Slower to detect humour as looks for literal meaning, less humour than before

(Case identifier numbers are used here for convenience only). References to inappropriate humour are in bold. **ø** This patient had a *C9orf72* mutation

Questionnaire data on liking for particular comedy genres in individual patients in each disease group are presented in Figure 18. These data show that the majority of patients with bvFTD and SD showed reduced liking for comedy while most patients with PNFA showed no change in liking for comedy across genres following the onset of their illness. However, a few patients in each group showed increased liking for comedy; this occurred most frequently for slapstick comedy and in patients with bvFTD and PNFA (20% of patients in each of these groups).

Post-hoc analyses of genetic bvFTD subgroups revealed no differences with respect to any humour characteristic compared with the sporadic bvFTD subgroup. One patient with predominant right temporal lobe atrophy was included in the SD cohort; this patient had a profile of humour alterations that was qualitatively similar to other bvFTD cases.

Figure 18 Questionnaire data on changes in liking of comedy over a 15 year interval



Questionnaire data are shown for individual patients alongside the mean change in liking for the healthy control group (***C***), with error bars indicating s.d. from the mean in controls. Data for each comedy genre are plotted in separate panels. In each plot, the zero line indicates no change over the interval; values below the line indicate reduced liking and values above the line increased liking for that comedy genre, on a 10-point Likert scale (see 6.4.2, Figure 17 and Table 24 for details)

6.6 Discussion

Here I have shown that canonical dementia syndromes commonly produce an altered sense of humour and this alteration differs qualitatively and quantitatively across syndrome. Altered humour was universal in bvFTD and SD, and occurred in a substantial minority of patients with PNFA and AD. Increased fatuity and relative predilection for childlike or slapstick humour with reduced enjoyment of other comedy genres were features of all dementia syndromes. Frankly inappropriate humour in response to unpleasant or impersonal stimuli was a hallmark of bvFTD and SD. Moreover, selectively altered humour responsiveness was reported to have occurred well before the onset of more typical symptoms in association with both FTLD and AD, manifest as less pleasure in satirical comedy premorbidly. The clinical duration was estimated based on a standard clinical history probing for symptoms according to the established criteria (Rascovsky K *et al.* 2011), which do not include alterations in sense of humour therefore this change in humour preference preceded these more typical symptoms. Development of abnormal humour expression correlated with executive impairment across syndromes and with clinical disease duration in AD, but not FTLD syndromes, supporting the clinical impression that sense of humour is often impoverished early in FTLD, but relatively preserved initially in AD.

The most striking alterations of humour responsiveness here occurred in FTLD syndromes characterised by impaired interpersonal functioning and for comedy genres (satirical, absurdist) most reliant on social cognition processes such as incongruity resolution. This corroborates cognitive profiling of these syndromes (see Chapter 5). Both bvFTD and SD were associated with impaired detection of humorous intent in cartoon scenarios requiring psychological insight. Whereas the appreciation of slapstick humour typically entails detection of surface and physical incongruities, appreciation of satirical and absurd comedic scenarios requires a model of our place in the world with an understanding of social norms and often, others' beliefs and intentions (Irish M *et al.* 2014). Comedy relying on incongruity resolution has analogues with the incongruous scenes where bvFTD and SD patients were shown to be impaired in judging the signal relatedness or congruity of constituent sounds in a scene (Chapter 3). Although slapstick scenarios are reliant on incongruity detection, it was demonstrated that bvFTD patients were unable to detect change in the perceptual similarity

task (Chapter 3), or the key deviation task (Chapter 4) although for the latter condition this likely relates to melody processing within OFC being fundamental to this task.

From the comments presented in Table 24 recording instances of altered humour exhibited by patients, one could define the boundary for inappropriate humour demonstrated in FLD to be around laughing at other's misfortunes. Work on physical comedy has shown the facial expression of the protagonist can provide the context for a shift from interpreting an incident as a misfortune to a humorous event (Manfredi M et al. 2014). bvFTD may be unable to take advantage of this cue, owing to impaired facial (particularly if negatively valenced) expression identification (Blair RJ and L Cipolotti 2000; Omar R, SM Henley*, et al.* 2011; Kumfor F *et al.* 2013). Without an ability to recognise negative facial emotions, a situation of horrific injury could potentially be interpreted as a slapstick joke.

The lack of correlation here between humour measures and the TASIT in the bvFTD group might appear initially somewhat counterintuitive. Arguments to a negative finding must be cautious, particularly in the face of small case numbers. This might reflect the modularity of social cognitive subcomponents and suggests that substrates for humour decoding may be at least partly separable from other social cognition processes. It is also noteworthy that only a minority of patients with bvFTD were reported as showing enhanced liking for slapstick comedy (Figure 18) despite a clear tendency to increased fatuity and inability to suppress humour responses. This might indicate that humour behaviours in these patients become 'mirthless' (dissociated from subjective pleasure) or alternatively, that the behavioural correlates of such pleasure are harder for normal informants to decode, although this could only be fully clarified with associated autonomic measures to check for a dissociation. The case with PNFA that carries the pathological mutation C9orf72 was described to "laugh in a loud and embarrassing way". This may be describing gelastic laughter which has been observed in PNFA patients and is probably a separable phenomenon (Rohrer JD et al. 2009).

Impaired detection of sarcasm has been shown to predict and to track progression of disease hinting at the potential for social cognition to be used as a potential biomarker (Kipps CM *et al.* 2009; Kumfor F et al. 2014). The richness and complexity of humour, both regarding individual preferences and the wealth and breadth of genres of humour allow potential customisation of

humour batteries on both an individual basis and potential development of bespoke batteries for use across different pathologically, anatomically or phenotypically defined groups. Humour is embedded in our daily lives and humour behaviour may have advantages over current social cognition tests (McDonald S *et al.* 2006) as it incorporates reward, which is a field of emerging importance for understanding FTLD (Ahmed RM *et al.* 2014; Ahmed RM, C Kaizik*, et al.* 2015; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015; Perry DC *et al.* 2015)

In this thesis I have alluded to the free-energy hypothesis being a model of incongruity resolution and as such, frontal lobe function. The underlying premise of the free-energy hypothesis is a desire to establish and maintain homestatically stable states. Therefore the inherent reward in the unexpected nature of humourous punchlines may appear, at first glance, at odds with this. However, the mesolimbic activation in humour arises from re-establishing coherence or a stable state (Suls J 1972) and under specific contexts, pre-exposing the person to elements from the punchline and therefore reducing the unexpectedness, increases its funniness (Topolinski S 2013). This aligns with predictions derived from the free-energy hypothesis. It has been argued that humour and music may serve to debug inferential errors in our comprehension of the world (Hurley MM et al. 2011; Juslin PN 2013; Schwartenbeck P et al. 2013). The corrollary of this is, if the process becomes defective, the model of the world can no longer be updated as new events occur. This would prevent maximal learning from our environment. Their reward is linked to the successful resolution of violations of the predictive code or learnt templates. Humour, like music, is a paradigm of incongruity and ambiguity resolution with potent abilities to link these psychological expectancies to reward (Suls J 1972; Chan YC, TL Chou, HC Chen and KC Liang 2012; Chan YC, TL Chou, HC Chen, YC Yeh*, et al.* 2012; Lehne M et al. 2013; Clark CN *et al.* 2015). Without adequate resolution of the incongruities, the normal amusement or mirth in response to 'getting the joke' will not occur. Consequently this may contribute to the loss of appreciation of comedy genres reliant on incongruity resolution.

Alteration in humour preferences and behaviours may allow us to capture these dynamics and has potential to be a real world biomarker. Beyond the biomarker potential, exposure to humour has tangible outcomes for quality of life measures. Using humour as a coping strategy

when caring for those with dementia correlates with higher caregiver quality of life and higher satisfaction scores for patients with dementia (Saunders PA et al. 2016). Elder clowns (slapstick comedy) performing in nursing homes significantly reduced behavioural disturbance and increased quality of life scores for moderately to severely demented individuals (Low LF et al. 2014; Kontos P et al. 2016).

This study has several limitations that should guide future work. Patients were assessed using third-person reports while control data were based on self-report, both potentially subject to recall bias. Future work using participants from other ethnic and cultural backgrounds should be used to validate the questionnaire. Humour abnormalities have probably been under-recognised across the neurodegenerative disease spectrum and the finer details of which remain to be clarified. In particular, there is a need to investigate the relations between humour alterations and other components of social cognition in these diseases. More broadly, the present findings have implications for the social functioning and quality of life of patients and those who care for them and this should be explored explicitly in the future.

From a clinical perspective, the results provide a basis for understanding the altered humour behaviours exhibited by patients with FTLD and align these neurodegenerative disorders with diseases causing focal brain damage in which abnormalities of humour processing and behaviour (including humourlessness and context-inappropriate humour) have been previously described (Ferguson SM *et al.* 1969; Gardner H *et al.* 1975; Bihrle AM *et al.* 1986; Shammi P and DT Stuss 1999).

7 GENERAL DISCUSSIONS

7.1 Summary of Findings

The work presented in this thesis has addressed candidate, generic mechanisms of impaired social signal decoding and their neuroanatomical substrates in FTLD syndromes, using the model of altered incongruity processing. The results may be of wider relevance to the phenomenology of FTLD syndromes. They give support for FTLD displaying deficits in a number of subprocesses pertinent to social cognition, including expectation generation, pattern prediction, resolution of incongruity and allocation of salience and reward. The associated neuroanatomical correlates are known components of networks targeted in FTLD.

Chapter 3 used the model of nonverbal auditory scenes to capture congruency processing and showed that bvFTD and SD patients have impaired processing of semantic and emotional congruence with associated altered affective valuation. From a neuroanatomical perspective, I have shown that processing of signal relatedness (congruence versus incongruence) in these simple scenes was shown to engage an extensive brain circuitry of scene analysis, rule decoding and reward valuation. In Chapter 4, the model of music was used to probe processes of expectation generation, hedonic anticipation and valuation. Dementia syndromes showed a range of different profiles of affective responses to meeting versus violating expectancies. The neuroanatomical correlates of altered musical reward processing were shown to map onto established reward areas known to be important in processing harmonic expectancy. In Chapter 5, I demonstrated that impaired appreciation of humour is a feature of neurodegenerative disease and have related this to deficits of incongruity and novelty processing. These deficits correlated with regions known to engage social conceptual knowledge and conflict resolution**.** The findings were extended to the realm of patients' daily lives, by demonstrating humourlessness and the converse, indiscriminate humour extending to inappropriate contexts in Chapter 6. My findings further indicate that changes in music and humour processing are not exclusive to FTLD syndromes, but also evident in AD which is not traditionally regarded as a behavioural syndrome. Taken together the findings provide a case for music and humour as useful probes of aberrant reward processing and associated complex behavioural disturbances in a range of dementia syndromes.

This concluding chapter draws together the main findings of the thesis, and evaluates these in relation to previous work and concepts put forward in the thesis introduction.

7.2 Evidence for generic impairment social cognition

7.2.1 Prediction

Perception of sound stimuli unfolding over time depends on anticipating the future (sounds still to come), no less than tracking the past (sounds that have happened) (Salimpoor VN *et al.* 2015). Anticipation is therefore inherent to processing sound patterns, whether embedded in environmental scenes (Chapter 3), music (Chapter 4), verbal humour (Chapter 6), or in other cognitive processes with characteristic temporal architectures. Humour relies on prediction that is violated in a surprising and ultimately rewarding way when we resolve the incongruity and get the joke. Our emotional and physiological reactions to such predictive phenomena are likely to contribute importantly to our sense of continuity across time (Huron D 2006). Self-projection is known to be vulnerable in the neurodegenerative diseases (Irish M *et al.* 2011; Irish M *et al.* 2012; Irish M and P Piolino 2016). Music and humour may be very well equipped to model this and suggest parallels with more fundamental sources of reward, such as the extension of one's self in time.

7.2.2 Schemas

Prediction relies on efficient utilisation of regularities learned from our past experience of the world. These extracted regularities form stored neural templates that are used to generate expectations (and subsequent associated reward). Examples include implicit learning from lifetime exposure to canonical sound scenes (Chapter 3), the 'rules' of one's dominant musical culture (Chapter 4) and slapstick humour (Chapter 5 and 6) (Goel V and RJ Dolan 2007; Gygi B and V Shafiro 2013; Salimpoor VN *et al.* 2015). Targeted degeneration of the anterior temporal lobes could feasibly degrade these stored templates along with more generic semantic knowledge (Zahn R, J Moll, V Iyengar*, et al.* 2009; Groussard M *et al.* 2010). If disintegrating templates consequently become less specific, the potential consequences include the triggering of inappropriate behaviours that align with the experimental findings described in this thesis and manifest as faulty social behaviours.

7.2.3 Hedonic valuation

The study in FTLD of pleasure from real world stimuli such as sound scenes (Chapter 3), music (Chapter 4) and humour (Chapter 6) offers a unique window on the processes that degrade hedonic value and behaviour in neurodegenerative disease. My work builds on previous evidence (Fletcher PD *et al.* 2014) by showing that abnormal valuation can extend to abstract sensory stimuli such as music (see Chapter 4) and humour (Chapter 6) in addition to primary biological reinforcers such as food and sex (Perry DC *et al.* 2014). This work begins to explain why bvFTD patients may find humour in a funeral (detection of incongruity from normative events where people are alive and continuous in time), yet detect no humour in an ordinary joke or sarcastic remark (inability to resolve incongruity).

7.3 Neuroanatomical substrates

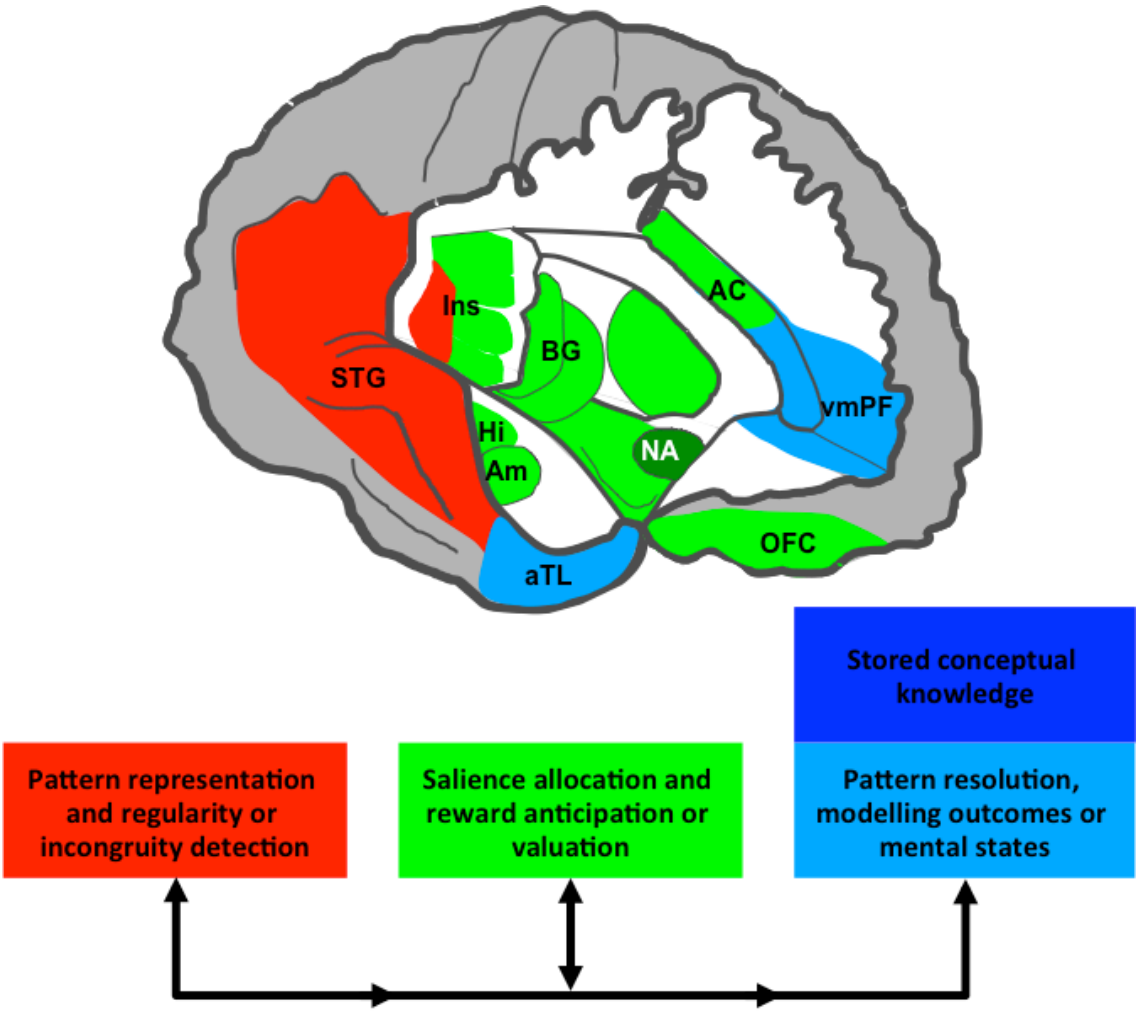
In this thesis behavioural measures were correlated with distributed neuroanatomical networks responsible for perceptual analysis, expectation generation, incongruity detection against learnt templates, re-establishing coherence through incongruity resolution and determination of salience and reward. There is extensive overlap between the anatomical correlates across candidate models (see Table 26, Chapters 3, 4, and 5), which adds credence to the concept of underlying shared generic processes. Perceptual decoding in sound scenes correlated with SMA volume (Chapter 3). The temporal pole appears to be a hub processing signal patterns and salient deviations based on prior expectations including stored semantic or affective templates (Chapter 3). The MTL seemed to represent the fundamental aspects of humorous (Chapter 5) or musical (Chapter 4) stimuli to be linked with cortical mechanisms for structural analysis and incongruity detection. Superior temporal lobe volume appears to be associated with template matching of potentially comedic scenarios (Chapter 5) and of musical structure (Chapter 4) to novel stimuli which aligns with previous work on semantic conceptual knowledge (Zahn R *et al.* 2007; Salimpoor VN *et al.* 2015). Prediction testing for incongruity in the context of signal and/or salience mismatch was localised to insula and TPJ for sound scenes (Chapter 3) and TOJ for humorous stimuli reliant on incongruity detection alone (slapstick) (Chapter 5). PFC grey matter appears to code regularities, rule violations and re-establishing coherence in auditory scenes (Chapter 3).

Table 26 Key grey matter associations demonstrated in experimental Chapters

Lobe	Neuroanatomy	Model	Chapter	Cognitive process
Parietal	SMA	Sound scenes	3	Parsing auditory scene. Perceptual decoding
Insula	Insula			Processing patterns & salient deviations based on prior expectations (semantic & affective). Prediction testing
Temporal junctional	TPJ			Signal and salience mismatch. Prediction testing
	TOJ	Humour	5	Incongruity detection linked to emotional response. Prediction testing
Temporal lobe	Ant MTG/STS			Novel stimuli matched to templates of humorous scenarios
	Ant STG	Music	4	Musical expectation/anticipation for melody structural analysis
	MTL	Humour	5	Fusiform cortex represents fundamental aspects of humorous stimuli & incongruity detection
		Music	4	Musical expectation/anticipation. Entorhinal cortex links cortical mechanisms for melody structural analysis
	Temporal pole	Sound scenes	3	Processing salient deviations based on prior expectations (semantic/affective)
Frontal	mPFC			Rule violations & reconciliation
	IFG			Categorisation of sound stimuli
		Music	4	Musical reward/valuation. Links rule based processing with reward
	Medial OFC			Musical expectation/anticipation. Integration of external stimulus features with paralimbic response & behavioural goals
Subcortical	Striatum	Sound scenes	3	Emotional congruity and associated reward

For further details regarding colour coding and anatomical hypotheses see Table 1, Figure 1 and Figure 19

Figure 19 Schematic dissected brain shows generic cognitive processes implicated in experimental Chapters



See **Table 26** for relevance to each of thesis Chapters. See Table 1 and Figure 1 for further details regarding functions of regions associated with colour codes (relevant Chapters indicated in brackets). **AC**, Anterior cingulate; **Am**, amygdala; **aTL**, anterior temporal lobe (Chapter 3); **BG**, basal ganglia (Chapter 3); **Hi**, hippocampus (entorhinal cortex; Chapter 4); **IFG**, inferior frontal gyrus (Chapters 3 and 4); **Ins**, insula (Chapter 3); **MTL**, medial temporal lobe (fusiform; Chapter 5); **OFC**, orbitofrontal cortex (Chapter 4); **SMA**, supplementary motor area (Chapter 3); **STG**, superior temporal gyrus (Chapter 4); **STS**, superior temporal sulcus (Chapter 5); **TOJ**, temporo-occipital junction (Chapter 5); **vmPFC**, ventromedial prefrontal cortex (Chapter 3)

IFG volume is associated with the ability to categorise sound stimuli under a high perceptual load (Chapter 3) and with musical expectations, it may link rule based processing and cortical analysis of hierarchical structure to reward (Chapter 4). OFC may integrate external stimulus features with the paralimbic response and behavioural goals in musical expectation (Chapter

4). The striatum appears to code contingency monitoring, emotional congruity and associated reward in the sound scenes (Chapter 3).

Targeting of large-scale intrinsic brain networks by neurodegenerative proteinopathies has proven to be a concept of considerable explanatory power (Seeley WW *et al.* 2009; Zhou J *et al.* 2010). The correlates of incongruity decoding identified here do not respect conventional demarcations of the 'salience', 'default-mode' and other such networks. Rather, the data suggest that congruence analysis may depend on neural components distributed between intrinsically-connected networks. This interpretation is in line with an emerging paradigm emphasising network interactions in the processing of real-world, dynamic signal arrays that direct adaptive behaviours (Chiong W *et al.* 2013; Mattar MG et al. 2015).

7.4 FTLD as a disease of aberrant template matching

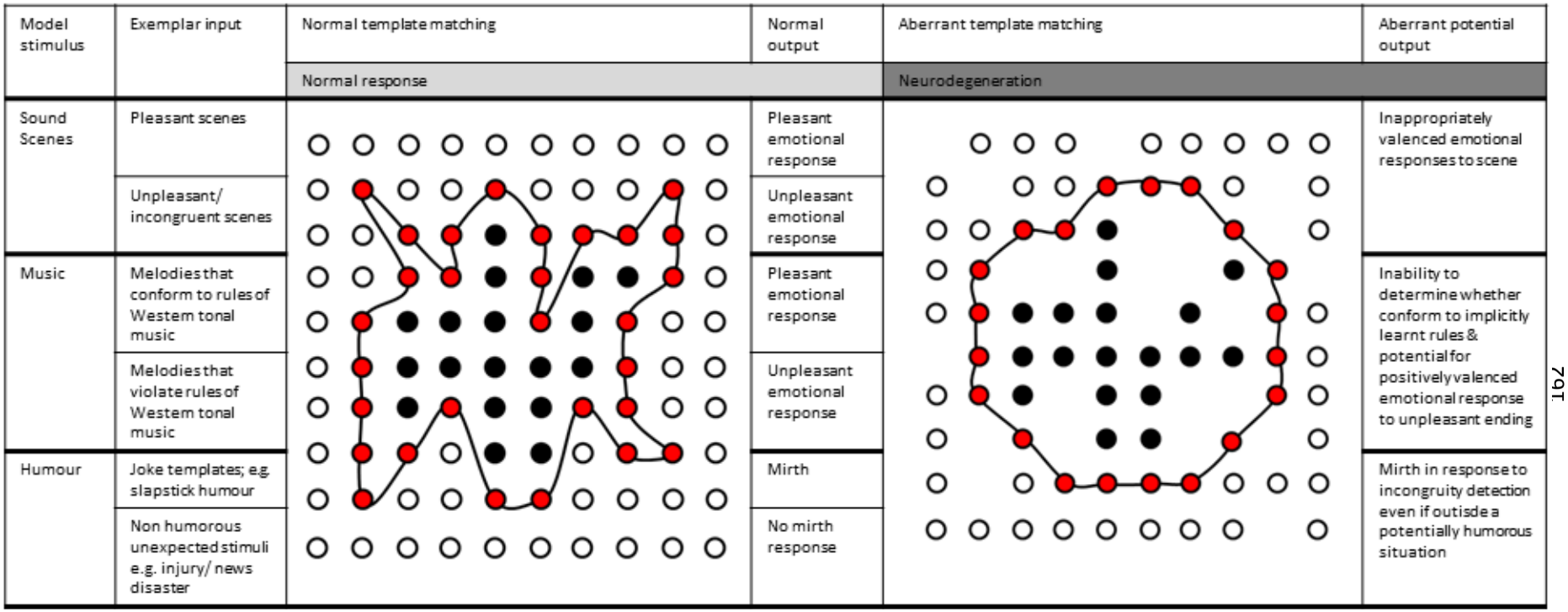
The experiments presented in this thesis (nonverbal sound scenes in Chapter 3, music in Chapter 4 and humour in Chapter 5) suggest a framework of generic (see 7.2) impairments of prediction, template engagement and hedonic valuation, which are of relevance to complex behavioural changes in FTLD. These generic mechanism contribute to decoding of social signals in natural environments that might underpin a range of difficulties that patients experience in the more complex scenarios of daily life (for example, those surrounding ambiguous emotional communication, violation of social norms or conflicted moral choices (Lough S *et al.* 2006; Eslinger PJ *et al.* 2007; Zahn R *et al.* 2007; Kipps CM *et al.* 2009; Carr AR *et al.* 2015; Downey LE *et al.* 2015). Whereas defective detection of unexpected salient events would tend to promote the rigid and maladaptive behaviours that typify bvFTD and SD (Snowden JS *et al.* 2003; Fumagalli M and A Priori 2012; Warren JD, JD Rohrer and MN Rossor 2013), inability to determine signal congruence could preclude the extraction of environmental regularities required for probabilistic learning and appropriate reward seeking (Dalton MA *et al.* 2012; Perry DC *et al.* 2014).

These generic cognitive operations might be linked together in a neural algorithm of template matching where stored schemas are used to build predictions. This draws on a model neural

architecture that has previously been proposed to underpin concept erosion with the 'simplified' semantic classification responses exhibited by patients with SD (Lambon Ralph MA et al. 2009). According to the proposed scheme, stored neural templates are normally used to match representations of the sensory and social environment to output behavioural routines (see Figure 20). A template constitutes a specific pattern of activation within a neural network that links representations of sensory data with output behaviours or experienced sensations. The configuration of the template determines the fidelity of the template matching algorithm. These templates are then used to evaluate error with associated hedonic potential, which in turn motivates behaviour to minimise future prediction error. This aligns naturally with the concept of generative models articulated in the free-energy formulation, according to which free-energy or prediction error minimisation is a fundamental organising principle of brain function (Friston K 2009; Schwartenbeck P *et al.* 2013).

A candidate generic neural architecture can be envisaged (Figure 20) (Clark CN and JD Warren 2016) according to which neurodegenerative pathologies promote network disintegration, leading to eroded (simplified or 'bevelled') template boundaries. In patients with bvFTD and SD, this puzzle-solving behavioural algorithm appears to be defective, and less precise in its application. Such patients are apt to assign value to stimuli in highly inappropriate contexts. One could consider a preference for less ambiguous or more immediately rewarding comedy as having a parallel to developing a sweet food preference or an interest in catchy music or 'earworms' (as opposed to classical music preferences), perhaps indicating common underlying mechanisms. This in turn both limits template activation in response to appropriate sensory representations and allows loose or inappropriate matches to be achieved at a given intensity of sensory input or behavioural set. In terms of output emotional behaviour, this could manifest as hypo-emotionality in response to an adequate stimulus, exaggerated emotionality in response to a trivial stimulus or a mixture of these.

Figure 20 A schematic substrate for bivalent behaviours in FTLD and other neurodegenerative syndromes.



According to the scheme I am proposing here, a template constitutes a specific pattern of activation within a neural network (rendered under title of 'normal template matching' as a grid of circles) that links representations of sensory data with output behaviours or experienced sensations (filled circles). The configuration of the template (linked red circles) determines the fidelity of the template matching algorithm. Neurodegenerative pathologies promote network disintegration, leading to eroded (simplified or bevelled) template boundaries. This in turn both limits template activation in response to appropriate sensory representations and allows loose or inappropriate matches to be achieved at a given intensity of sensory input or behavioural set (represented under title of 'aberrant template matching' as black circles). In terms of output emotional behaviour, this could manifest as hypo-emotionality in response to an adequate stimulus, exaggerated emotionality in response to a trivial stimulus or a mixture of these (see column 'aberrant potential output'). See 7.4 for specific examples of hyper and hypo-emotional behaviours documented in FTLD

One prediction from this is the occurrence of behavioural dichotomies or bivalent behavioural responses (excessive as well as deficient valuations). Although the prevailing view has been that bvFTD patients exhibit hypoemotionality, there were some striking instances of hyperemotionality which was inappropriate in its magnitude or context exhibited during the experiments for this thesis, for example one of the patients was moved to tears by the simple melodies used in Chapter 4. Examples of bivalent and aberrant hedonic responses that potentially define the phenotypic spectrum of dementia can be tracked through signal relatedness in sound scenes (Chapter 3), or affective responses to music (Chapter 4) and humour (Chapter 5).

The dimension of hyperemotional inter-personal conduct is largely absent in published case series of FTLD (Snowden JS *et al.* 2001; Ikeda M et al. 2002; Ahmed RM, C Kaizik*, et al.* 2015), however exaggerated emotional displays involving basic emotions such as surprise have been reported in association with both bvFTD and SD (Snowden JS *et al.* 2001). There have even been instances of emotional warmth, the display of emotional expressions, and instances of seeking out social interactions in this group (Snowden JS *et al.* 2001). Viewed alongside the typical syndromic pattern of hypoemotionality and blunted empathy, the existence of hyperemotional responses suggests a dichotomisation of abnormal prosocial emotional behaviours within the FTLD spectrum. However, the hyperemotional states appear to not be appropriately calibrated and often excessive, for their context. The valence of the response may be appropriate, but not its intensity. This could be thought of as an analogue to inappropriate context-sensitive gain, as has been demonstrated in other network based diseases (Phillips WA and SM Silverstein 2013).

The traditional symptoms of FTLD could be re-appraised in the context of bivalent abnormal reward processing secondary to the erosion of neural templates for emotional behaviours (as demonstrated in Figure 20); for example to biologically rewarding stimuli; hyperphagia and food aversion (Ahmed RM *et al.* 2014), musicophilia and musical anhedonia (Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015), hyper and hyposexual behaviours (Ahmed RM, C Kaizik*, et al.* 2015) in addition to internally generated salient or homeostatic stimuli with increased or decreased sensitivity to pain and temperature (Snowden JS *et al.* 2001; Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW

Paterson, JD Rohrer*, et al.* 2015). There may be associated shifts of taste towards less ambiguous or more immediately rewarding stimuli as the template becomes less specific or nuanced in its selection, examples include their predilection for slapstick or less complex jokes (Chapters 5 and 6) and other changes in patient preferences such as a craving of sweet food.

To date template matching has been invoked mainly in the domain of perception (Griffiths TD and JD Warren 2002), but might be iterated at different levels of abstraction including semantic and affective (Chapters 3, 4 and 5). The concept of template matching to detect deviations or incongruency has relevance to even more complex cognitive operations such as moral dilemmas or social norm violations including guilt, and theory of mind (Eslinger PJ *et al.* 2007; Zahn R, J Moll, V Iyengar*, et al.* 2009; Carr AR *et al.* 2015; Ondobaka S et al. 2015). Moral and social dilemmas represent an inherent conflict about the correct course of action (Eslinger PJ *et al.* 2007; Carr AR *et al.* 2015). Guilt can be considered as a deviation from socially expected conduct (Tangney JP *et al.* 1996). Theory of mind allows us to explain and predict behaviour in others by perceiving intention and motivation to maintain alternative models of others' mental states in relation to one's own (Fletcher PC et al. 1995; Lough S et al. 2001).

Abnormal template matching could represent a generic pathophysiological network mechanism or universal algorithm of generative decoding (Friston K 2009) with powerful links to the means of generating predictions of direct relevance to the work presented in this thesis. In particular, by studying the effects of pattern prediction, template matching, the allocation of reward and salience in FTLD, we can establish the extent to which the targeted brain systems are critical for generic higher level processes. The impairments demonstrated by the FTLD population with respect to processing incongruity may index an impaired ability to detect and resolve ambiguity and conflict in the world at large. This may map onto deficits of social understanding in the face of ambiguous or conflicting information (Kipps CM *et al.* 2009; Krueger CE *et al.* 2009; Chiong W *et al.* 2013) and may track social cognitive deterioration. A candidate brain substrate has been identified in the distributed fronto-insular, anterior temporal and subcortical circuitry that links social concepts and representations with reward, cognitive evaluation and behavioural responses which aligns with previous work in health and disease (see Figure 14) (Green S et al. 2013; Sturm VE *et al.* 2015) and is targeted by neurodegenerative pathologies (Warren JD, JD Rohrer and MN Rossor 2013; Clark CN and JD

Warren 2016). Given the patterns of targeted network vulnerabilities across syndrome, one could speculate that particular proteinopathies might also represent selective vulnerabilities in particular neural networks or levels of processing with a corollary of pathogenic protein destruction selectively targeting specific template matching architecture (Warren JD et al. 2012).

In this thesis I have investigated sensory object processing of high clinical relevance to real world behaviours using different model systems with a common cognitive framework. The examples explored indicate the value of extending conventional neuropsychological models to investigate apparently less tractable, but essential aspects of social cognitive experience.

7.5 Clinical translation

Findings from the thesis experiments could be extended clinically in several ways. The experiments presented builds on our understanding of general mechanisms underlying various abnormal behaviours; including abnormal anticipation, template matching, aberrant hedonic responses to music (Chapter 4) and humour (Chapter 6) with the potential for bivalent reward responses. By analogy the general principles can be applied to a much wider spectrum of other aspects of social cognition. Complex social behaviours which are key for interpersonal interactions include; moral and economic reasoning, empathy, theory of mind and self-prospection (Irish M *et al.* 2011; Irish M *et al.* 2012; Irish M and P Piolino 2016) and are underpinned by the generic processes of incongruity processing (exemplified in sarcasm and faux pas) and the mental simulation of future events. The applicability could extend beyond FTLD; for example, AD and its variants, might be expected to show a quite different profile of auditory conflict signalling based on available neuropsychological and neuroanatomical evidence (Seeley WW, JM Allman*, et al.* 2007; Fong SS *et al.* 2016).

The extent to which music and humour share a dynamic hedonic signature with other sources of primary and secondary reward could illuminate the neurobiology of reward more generally. Perhaps the same patient could have differential access to the reward system with different primary and secondary reward stimuli and differing consequences to their clinical behaviour. Further exploration as to what extent these effects are primarily due to impaired cognition or altered reward biology, is necessary. Further unanswered questions remain around the effects

of anhedonia versus hyper-hedonia on the daily life of patients and their families. Managing abnormal reward behaviour will be reliant on answers as to whether the patients are able to downregulate their response if given frequent exposure to the rewarding stimulus to become satiated or even whether they can exhibit aversion to excessive quantities of reward.

Potential anatomical and dynamic behavioural biomarkers might be quantified more easily than complex socio-emotional behavioural symptoms, with future applications for disease diagnosis and tracking. Relevant hub regions such as the insula have been shown to be involved prior to clinical symptom onset in mutation carriers (Rohrer JD *et al.* 2015). Behavioural correlation might yield a novel biomarker of imminent clinical conversion. This is an area of early promise based on the present behavioural data and observations in the presymptomatic phase in the genetically enriched FTLD cohort (Dopper EG *et al.* 2014). More detailed stratification in larger cohorts will be required to account for wide individual variation in processing and to assess the clinical value of metrics such as ambiguity, incongruity and hedonic processing. The potential use of anticipation and reward valuation should be studied prospectively. Adjunctive autonomic, structural and functional neuroanatomical correlation should be used to capture alterations in the experience of reward beyond the ability of patients to subjectively report their internal states. There is now an emerging body of empirical evidence for altered emotional, salience, semantic processing and auditory hedonic phenotypes in the target neurodegenerative diseases which have been linked closely to autonomic or physiological responses (Fletcher PD, LE Downey, HL Golden, CN Clark, CF Slattery, RW Paterson, JM Schott*, et al.* 2015; Fletcher PD, JM Nicholas*, et al.* 2015, 2015; Fletcher PD *et al.* 2016). The results of Chapter 6 suggest that humour preferences may be a sensitive index of behavioural change. If this is validated it should be built into future practice guidelines and diagnostic statements as currently altered humour is not mentioned explicitly in the current consensus criteria for diagnosis (Rascovsky K *et al.* 2011).

Themes of this thesis may inform non-pharmacological interventions. Established behavioural interventions already address some aspects related to this work (Kortte KB and EJ Rogalski 2013). One such intervention is addressing unmet needs in FTLD and monitoring for hunger and physiological requirements which are known triggers of behavioural disturbance (increased salience of internal sensations). FTLD patients' behaviour has been described as

being unrelated to the emotional and social context, with suggested interventions to counteract that using environmental cues (unable to integrate multiple competing cues therefore appear to behave in a context independent fashion). Notwithstanding the fact that the models explored here could provide potential targets for intervention or means to evaluate candidate interventions, understanding the rationale that drives the abnormal behaviour will be an important part of counselling families when the behaviour otherwise seems incomprehensible.

There are emerging symptomatic drug therapies in FTLD with apparent effects on social cognition (Finger EC 2011). Oxytocin may exert its action through regulating the salience of social cues (Shamay-Tsoory SG and A Abu-Akel 2016) and has shown promise in clinical trials (Finger EC et al. 2015). Incidentally, oxytocin levels are shown to rise during improvised singing with a concomitant fall in cortisol precursors as social flow measures increase (Keeler JR et al. 2015).

The aim would be for the brain mechanisms that support social cognition information processing to eventually illuminate the specific neural architectures that underpin particular proteinopathies (Warren JD, JD Rohrer, JM Schott*, et al.* 2013). This would direct target individuals for disease modifying treatments as molecularly targeted treatments are beginning to emerge (Capell A *et al.* 2011; Cenik B *et al.* 2011).

7.6 Limitations

The studies contained in this thesis have several limitations and suggest a number of directions for future work. In the world at large, signal integration and mismatch detection are rarely confined to a single sensory modality or time-point. Therefore for more realistic representations of congruency processing, cross-modality or audio-visual multisensory integration should be explored.

There are cultural, social and idiosyncratic influences on comprehension and appreciation of humour and music. Identifying true universals of humour and music in order to define cross-cultural applicability is a major challenge that would need to be investigated prior to any wider translation as biomarkers. There is a need to validate the humour questionnaire (Chapter 6) in

participants from other ethnic and cultural backgrounds and to correlate subjective measures with more objective (e.g. autonomic) indices that might encompass a wider spectrum of disease.

All the experimental work described in this thesis is cross-sectional. Longitudinal analyses are particularly called for to assess the biomarker potential of novel behavioural and neuroanatomical metrics, to assess their potential in detecting and tracking disease. The usage of, for example, Likert scales precludes the inclusion of severely cognitively impaired patients who are no longer able to give verbal responses.

Anatomical ROI analyses are potentially susceptible to bias. Structural neuroanatomical methods like those used here cannot capture dynamic processing and interactions between neural network components. Derivation of network-level effects using metrics such as tractography, connectivity and activation imaging should capture a more complete picture of these phenotypes. The mechanisms of ambiguity and incongruity resolution and reward are generally intertwined and difficult to separate by using structural imaging techniques alone (Bartolo A *et al.* 2006), but they appear to be dissociable (Mas-Herrero E et al. 2013; Campbell DW *et al.* 2015). Complementary approaches may give a more complete picture of such dynamic integrated processes.

My experimental paradigms incorporated subjective measures, for example caregiver or third person questionnaire data and subject reporting of emotional response. This is potentially problematic in a group known to have implicit/explicit emotional mismatch (Balconi M *et al.* 2015) and abnormal behavioural responses may be misinterpreted by observers. Patients were assessed using third-person reports while control data were based on self-report, both are potentially subject to recall bias.

Group sizes were relatively small. Larger patient cohorts (recruited for example by collaborating specialist centres) should improve power to detect further effects at the level of the whole brain and to stratify syndromic groups. It would be interesting to examine to what extent these effects are sensitive and specific to particular neurodegenerative pathologies. Ideally, they should also be assessed in the setting of disorders that spare cognitive function or disease mimics of FTLD, for example major psychiatric illness and developmental disorders

such as autism and congenital amusia (Stewart L 2016) as well as chronic neurological disorders, in order to disambiguate cognitive from nonspecific chronic disease effects.

7.7 Future Directions

The experiments presented in this thesis raise a number of key questions that might motivate future work. This section will be structured as a series of pertinent questions for future exploration that are posed by this work.

7.7.1 To what extent can the mechanisms identified be generalised to other domains and modalities?

The work on incongruity could be extended to other domains (e.g. visual) and examined at both the perceptual and the semantic levels of processing. Multi- and cross-modal paradigms will likely amplify the findings here.

This could be explored in novel experimental paradigms. For each processing level, separate subtests could manipulate congruity. On the perceptual level this could involve impossible (Escher-like) versus naturalistic visual scenes and on the semantic level, visual objects embedded in contextually appropriate or inappropriate scenes.

Ambiguity could equivalently be tested on both levels of processing. The perceptual test could involve bistable percepts (visual and auditory) with or without disambiguating perceptual cues and on the semantic level, non-canonical views of target visual objects or degraded sounds embedded in a disambiguating or non-disambiguating semantic context. The a priori hypothesis would be that bvFTD patients would have an impaired ability to resolve incongruity and ambiguity in visual and auditory signals that is not-modality specific, but is relatively selective for semantic versus perceptual levels of processing. These deficits would be relatively specific to bvFTD, as compared to AD (representing another canonical neurodegenerative disorder). It will also be of interest to assess the extent to which patients are able to learn new rules and adapt responses accordingly (Michelon P *et al.* 2003; Dalton MA *et al.* 2012).

Other model systems of primary biological reinforcers could be investigated; for example sexual behaviour (Ahmed RM, C Kaizik*, et al.* 2015). There appears to be questions raised about the bivalent reward phenotypes encompassing hyper- and hyposexual tendencies. An

enlightening comparator group could be the dopamine dysregulation syndrome of Parkinson's disease where the hypersexual behaviour is of a different character in FTLD, where there appears to be a dissociation between sexual gestures of references (libidinous comments or obsession with pornography) without an active interest in partaking in sexual intercourse (Ahmed RM, C Kaizik*, et al.* 2015). There are alternative socially relevant concepts which would be amenable to paradigms being constructed incorporating incongruity detection and resolution and potential associated reward, for example morality.

The importance of assessing ecological paradigms with real world resonance, is of direct relevance to this work. Ultimately techniques are being developed in order to recreate more naturalistic social settings (Franklin RG, Jr. and RB Adams, Jr. 2011) which will offer the potential to replicate social situations and to manipulate isolated factors within social scenes to monitor their effects. This does not detract from the merit of assessing physiological correlates of behaviour or focusing on information processing techniques, but will be used as a complementary research technique.

7.7.2 What are their physiological correlates?

Further experiments could explore the extent to which abnormal behaviours in FTLD are truly dichotomous rather than bivalent extremes on a behavioural continuum. Experiments should be constructed to investigate whether the primary fault lie with the representation of emotional signals *per se*, with the 'gain' of the behavioural response or with the linkage between them.

The next question is whether the behavioural routines are disingenuous or they are accompanied by the physiological markers of real emotions which are inappropriately directed. Perhaps they are extremes or caricatures of the templates of learnt behavioural outputs suggesting an inappropriate gain of the output (Phillips WA and SM Silverstein 2013). The means by which to dissociate these would be through physiological correlates such as functional imaging or autonomic recordings. The physiological correlates of defective social signal analysis in bvFTD will likely map onto specific brain networks including polymodal cortex in the anterior temporal lobe and insula, and evaluative areas in OFC and ACC. Autonomic recordings would provide complementary information about the arousal potential of cognitive and affective decisions about these social and sensory signals and may be a useful means of

objectifying affective valuation. This would likely help define disease phenotypes more fully (Fletcher PD, JM Nicholas*, et al.* 2015; Fletcher PD *et al.* 2016; Fong SS *et al.* 2016). Autonomic and other physiological metrics may reveal disease-associated dissociations between implicit and explicit coding of reward (Balconi M *et al.* 2015; Fletcher PD, JM Nicholas*, et al.* 2015; Sturm VE *et al.* 2015).

Future work should employ electrophysiological modalities with high temporal resolution sufficient to track the dynamic signature of music, humour, signal conflict and salience processing (Strelnikov KN *et al.* 2006; Marinkovic K et al. 2011; Koelsch S, M Rohrmeier*, et al.* 2013; Meyer GF et al. 2013). Electrophysiological methods such as magnetoencephalography or abnormal saccadic exploration of visual scenes can capture temporal dynamics inaccessible to patient reporting. To define brain mechanisms of aberrant incongruity and ambiguity processing in social signals more fully will require correlation of cognitive and behavioural measures with connectivity based anatomical techniques such as fMRI. Furthermore, macro-anatomical convergence between lesions or processes does not eliminate the possibility of distinct functional mechanisms on a microscopic level.

7.7.3 What is their disease specificity and sensitivity?

The potential relevance of reward as a biomarker will only be defined by longitudinal studies. Studying larger cohorts would increase power to detect effects and there would also be considerable interest in comparing these FTLD syndromes with other syndromes and diseases. This would allow assessment of the specificity of behavioural and neuroanatomical profiles including reward phenotypes for particular neurodegenerative pathologies while taking account of intrinsic individual variation (Salimpoor VN *et al.* 2015; Sachs ME *et al.* 2016). Further stratification of pathologically and genetically diverse syndromes within FTLD may be possible as there would be merit in comparing candidate biomarker profiles across proteinopathies in larger cohorts. Of equal relevance would be to use longitudinal analyses to assess how the deficits identified here evolve over the course of illness, including in presymptomatic carriers of defined genetic mutations (Rohrer JD *et al.* 2015).

Ultimately mapping the behavioural phenotypes and physiological changes will need to be corroborated with histopathology. However histopathological identification of protein alone

would not clarify function and therefore careful pathophysiological phenotyping in vivo is vital to truly understand these complex diseases.

7.7.4 Can these results inform future clinical practice?

There is a need to identify and evaluate suitable, relatively simple, robust candidate biomarkers with appropriate sensitivity and specificity to differentiate the disease of interest from its mimics early in the course, and allow tracking of the target disease over time (Strimbu K and JA Tavel 2010). Chapter 6 examines humour preferences which would potentially be amenable for use as a clinical biomarker, but needs further prospective validation. A robust biomarker would not only allow the diagnosis to be made more definitively, but will enable accurate sample size calculations to be made for future trials to quantify and monitor therapeutic effects. To establish whether these markers are superior to existing or emerging biomarkers will require head to head comparisons against more conventional biomarkers. It may be that no single biomarker is used in isolation, but a combination of biomarkers and physiological measures are used which together generate a phenotypic signature of underlying proteinopathy.

Although impairments in incongruity processing alone are unlikely to explain all of the social cognitive deficits demonstrated in FTLD, the aim of this thesis is to understand some of the fundamental contributing processes to the deterioration in social functioning. This provides a framework for behavioural treatments and assessments to address directly the defective processes (Cicerone K *et al.* 2006). In a disease defined by changes in social functioning, the most direct approach to unravelling the mechanism of disease is using socially relevant stimuli. It could be argued that social cognition has been relatively constrained by anchoring it to a single concept, such as impaired theory of mind (Schaafsma SM *et al.* 2015), without easy translation downwards to molecular phenotyping. Systems neuroscience and information processing accounts may allow us to close this gap from behavioural phenotypes to the underlying molecular physiology via the selective dysfunction of brain networks. In this thesis, I have identified novel, generic mechanisms underpinning cardinal symptoms in FTLD and their brain substrates. As a clinical neurologist, my hope is that this work will ultimately help to inform future diagnostic techniques, track disease and suggest targets for therapeutic interventions.

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9 APPENDIX

Supplementary Table 1 Number of participants by cohort across Chapters

Chapter	Controls	bvFTD	SD	PNFA	AD	LPA
3: Incongruity processing in FTLD	20	19	10			
4: Music processing in FTLD	22	11	6	8	14	5
5: Humour processing in FTLD	21	22	11			
6: Altered sense of humour in dementia	21	15	7	10	16	

Shaded boxes denote this patient group was not recruited for that Chapter

Supplementary Table 2 Participation by subject across Chapters

Subject	Group	Genetic	Age	Gender	Handed-ness	Symptom duration	CSF	Amyloid scan	MRI	CT	Chapter			
											3	4	5	6
1	Control		70	M	A						√		√	√
2	Control		73	M	R								√	√
3	Control		72	M	R							√		
4	Control		71	F	R							√		
5	Control		63	M	L							√		
6	Control		69	M	R						√	√		
7	Control		59	F	R						√		√	√
8	Control		67	M	R						√		√	√
9	Control		64	F	R						√	√	√	√
10	Control		72	F	R								√	√
11	Control		66	F	R							√	√	√
12	Control		68	F	R							√	√	√
13	Control		70	M	R						√	√	√	√
14	Control		66	F	L						√		√	√
15	Control		67	F	R						√			
16	Control		75	F	R							√		
17	Control		69	F	R						√	√	√	√
18	Control		69	F	R						√		√	√
19	Control		78	F	R						√			
20	Control		72	F	R						√	√		
21	Control		71	M	R						√	√	√	√
22	Control		59	F	L								√	√
23	Control		64	M	R							√		
24	Control		69	M	R							√		
25	Control		67	F	R						√			
26	Control		68	M	R								√	√
27	Control		73	M	R						√		√	√

28	Control		74	F	L							√		
29	Control		57	M	R							√	√	√
30	Control		71	M	R							√		
31	Control		69	M	R						√		√	√
32	Control		66	M	R								√	√
33	Control		56	F	R						√			
34	Control		60	M	R							√		
35	Control		59	F	R							√	√	√
36	Control		70	M	R						√	√		
37	Control		79	F	R						√	√	√	√
38	Control		70	M	L						√			
39	Control		59	F	A							√		
40	bvFTD		79	M	R	8			√				√	√
41	bvFTD	C9	55	M	R	15	√		√		√		√	√
42	bvFTD		76	M	L	16	√		√		√			
43	bvFTD	MT	53	M	R	6	√		√		√	√		
44	bvFTD		84	M	R	19			√				√	
45	bvFTD	MT	66	M	R	12			√				√	√
46	bvFTD	MT	64	M	R	7			√			√	√	
47	bvFTD		66	M	R	8			√		√			
48	bvFTD		61	M	R	8			√				√	√
49	bvFTD	C9	73	M	R	4			√			√	√	√
50	bvFTD		63	M	R	3			√				√	√
51	bvFTD	C9	68	F	R	8			√		√			
52	bvFTD		58	M	R	4	√		√				√	√
53	bvFTD		60	M	L	2	√		√		√			
54	bvFTD		77	M	R	7	√		√		√	√	√	√
55	bvFTD		52	M	R	3			√		√			
56	bvFTD		73	M	R	4			√		√			√
57	bvFTD		73	M	R	8			√				√	
58	bvFTD	MT	65	M	R	10			√		√	√	√	√
59	bvFTD	MT	59	F	R	5			√		√	√	√	√
60	bvFTD	C9	68	M	R	13	√		√				√	
61	bvFTD		72	F	R	11	√		√				√	
62	bvFTD		59	M	R	3			√		√			
63	bvFTD	MT	65	F	R	20	√		√		√	√	√	
64	bvFTD		65	M	R	4			√		√			
65	bvFTD	C9	61	M	R	6	√		√			√	√	√
66	bvFTD		62	M	R	4	√		√		√			
67	bvFTD	C9	64	F	R	5	√		√				√	√
68	bvFTD		77	M	L	12			√			√	√	
69	bvFTD	MT	63	M	R	8			√		√	√	√	√
70	bvFTD		58	M	R	6	√		√		√			
71	bvFTD	C9	70	M	R	4			√				√	
72	bvFTD	C9	71	M	R	23			√		√	√	√	
73	bvFTD		69	M	R	3	√		√		√			√

74	SD		57	F	R	5	√		√		√			
75	SD		72	F	R	3			√				√	
76	SD		59	F	R	6			√		√		√	√
77	SD		64	M	R	9	√		√		√	√		√
78	SD		58	F	R	3	√		√			√	√	
79	SD		64	M	R	6	√		√		√	√	√	√
80	SD		72	F	R	11			√			√	√	√
81	SD		69	F	L	8	√	√	√				√	√
82	SD		73	M	R	8			√		√	√		
83	SD		71	M	R	3			√		√			
84	SD		65	M	R	4	√		√		√			
85	SD		63	F	R	3	√		√		√			
86	SD		69	M	R	3		√	√				√	√
87	SD		69	M	L	11			√		√			
88	SD		77	F	R	3	√		√		√			
89	SD		67	F	R	8	√		√			√	√	
90	SD		80	M	R	10		√	√				√	
91	SD		75	M	R	4				√			√	√
92	SD		60	M	R	4		√	√				√	
93	PNFA		66	M	R	4	√	√	√			√		√
94	PNFA		73	F	R	3	√		√			√		√
95	PNFA		70	M	L	2	√		√					√
96	PNFA		77	F	L	2			√			√		
97	PNFA		76	F	R	10	√		√			√		√
98	PNFA		80	F	R	7			√			√		√
99	PNFA		66	F	R	2			√			√		√
100	PNFA		62	M	R	5	√		√					√
101	PNFA		71	F	R	8	√	√	√			√		√
102	PNFA		75	M	R	5			√					√
103	PNFA	C9	55	M	R	5	√		√			√		√
104	AD		59	F	R	3	√		√					√
105	AD		79	F	R	7				√		√		√
106	AD		64	M	R	9	√		√			√		√
107	AD		69	M	R	4			√					√
108	AD		71	M	R	10	√		√			√		√
109	AD		66	M	R	6	√		√			√		√
110	AD		63	F	R	10	√		√			√		√
111	AD		74	F	R	11			√					√
112	AD		52	M	R	3	√		√					√
113	AD		80	M	L	3	√		√			√		
114	AD		63	M	R	5	√		√			√		√
115	AD		65	F	R	7	√		√			√		
116	AD		73	M	R	5	√		√			√		
117	AD		60	M	R	5	√		√			√		√
118	AD		67	M	L	7	√		√			√		
119	AD		81	F	L	3			√			√		√

120	AD		74	M	R	5			√					√
121	AD		62	F	R	7			√			√		√
122	AD		57	F	L	4	√		√					√
123	AD		64	F	R	6	√		√			√		√
124	LPA		56	M	R	8	√		√			√		
125	LPA		61	M	R	5	√		√			√		
126	LPA		66	F	L	11	√	√	√			√		
127	LPA		65	M	R	3			√			√		
128	LPA		63	F	R	10	√		√			√		

Subjects are ordered by group. The shaded boxes indicate which patient groups were not recruited to the experimental cohort represented by the column heading. A tick denotes that subject was recruited to that experimental cohort or had the investigation as shown by the column heading. **A**, ambidextrous**; C,** C9orf72**; F**, female; **L**, left; **M,** male**; MT,** MAPT**; R,** right

9.1 Division of Labour

The work described in this thesis was conducted by CNC in collaboration with other researchers based at the Dementia Research Centre, University College London. Contributions made by others for each experimental Chapter are detailed below.

9.1.1 Chapter 3 – Incongruity processing in FTLD: a behavioural & neuroanatomical analysis

Experimental design: CNC, JDW

Construction of tests: CNC, HLG

Data collection: CNC, HLG

Data analysis: CNC in consultation with JMN

9.1.2 Chapter 4 – Music processing in FTLD: a behavioural & neuroanatomical analysis

Experimental design: CNC, HLG, JDW

Construction of tests: CNC, OM, HLG

Data collection: CNC, HLG, MHC

Data analysis: CNC in consultation with JMN

9.1.3 Chapter 5– Humour processing in FTLD: a behavioural & neuroanatomical analysis

Experimental design: CNC, JDW, SJC, SMDH

Construction of tests: CNC

Data collection: CNC, LED, IOW, HLG, PDF

Data analysis: CNC in consultation with JMN and SMDH

9.1.4 Chapter 6 – Altered sense of humour in dementia

Experimental design: CNC, JDW, SJC, SMDH

Construction of tests: CNC

Data collection: CNC, EG, HLG, MHC, FJW, KM

Data analysis: CNC in consultation with JMN